Diseases of the Nervous System

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Journal of Neurology, Neurosurgery and Psychiatry

Diseases of the Nervous System

Clinical Neuroscience and Therapeutic Principles

Third Edition

VOLUME 2

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This text is dedicated to our many friends and colleagues who wrote the chapters, for their diligence, for their intellectual rigour, and for their belief in the vision of scientific and clinical excellence on which these volumes are predicated.

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Preface

In the 10 years since the second edition of *Diseases of the Nervous System* appeared, extraordinary change has taken place in the field of neurosciences, both basic and clinical. In accordance with what is happening in the neurosciences, major changes have occurred with this third edition. Organization of subject matter and ordering of topics has changed substantially, in some cases dramatically. Of the contributors, a number of the authors for the previous two editions have written again in their special fields of expertise, but overall, more than three-quarters of the contributors are new to these pages. Two new editors have been added, Peter J. Goadsby and Justin C. McArthur; Cambridge University Press is the new publisher; and a new subtitle, *Clinical Neuroscience and Therapeutic Principles* has supplanted the previous one.

Despite these changes, the purpose of these reference volumes remains the same, namely to summarize what the scientific method, as applied to problems of neurological dysfunction, has taught us about the pathophysiology of neurological disorders. To say it differently, our purpose is not to focus on incidence, natural history, phenomenology and semeiology of neurological disorders, although these aspects are touched upon, but rather to focus on the mechanisms of neurological disease and the principles that form the basis for management and therapeutics. In addition to the emphasis on pathophysiology and principles of therapy, three other axioms guided the planning of this edition, just as they did for the previous editions. First, contributors were chosen who brought clinical expertise to bear as well as scientific authoritativeness. Second, we tried to assure that the depth with which each topic covered was relatively uniform from one chapter to the next. There is a corollary to this principle of uniformity. Given that these volumes are a general reference covering the entire field of neurological disorders, each chapter is, by necessity, a relatively brief summary of where matters

stand in that particular disorder or area of interest. This level of detail will be insufficient for some readers. When this is the case, readers are urged to consult the primary literature listed in the references.

The third point has to do with the intended readership. It is assumed that the reader will have a grasp of the terminology of everyday neurology and of the neurological examination, and will have a working knowledge of the basic concepts of nervous system anatomy and physiology. With this proviso, these volumes are designed to be of use to medical students, physicians in training, physicians trained in fields other than the nervous system, and of course to those trained or training in the fields of neurology, psychiatry, neurosurgery and related specialties. Neuroscientists of any background or level of training should have no difficulty using these volumes, and indeed it is this readership whom we particularly have in mind.

A project of this size requires many hands. The editors owe a debt of gratitude to the many who worked so diligently to make these volumes a reality. Particular thanks go to Ms Barbara C. Williams, the overall coordinator, Ms Theresa Daly at the School of Medicine, University of Pennsylvania, Ms Nancy Rosenberg at Johns Hopkins Hospital, Ms Olga Shapeero and Ms Sophie Ryan at the Institute of Neurology Queen Square, and Ms Susan Soohoo at the Krieger Mind-Brain Institute, Johns Hopkins University. Ms Mary Sanders performed the copy editing thoroughly and skilfully. Dr Richard Barling, director of medical and professional publishing at the Cambridge University Press, provided excellent guidance and support. But it is the chapter authors to whom we most deeply indebted, and to whom these volumes are dedicated. The publisher provided the loom, the editors made the design, but it was the 213 contributors who wove the fabric.

Arthur K. Asbury
Guy M. McKhann
W. Ian McDonald
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Part I

Introduction and general principles

1

Pathophysiology of nervous system diseases

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Since the last edition of this textbook, the field of Neurology and the Neurosciences has witnessed remarkable advances in the technologies available for the study of the brain and our concepts about the nervous system and its diseases. There has been progress in our ability to modify, prevent or treat these disease processes and to evaluate clinical outcomes, and in the resources available to handle and disperse data. There is, however, always a competition between the advancement of knowledge and the challenges of disease. We face challenges that demand that we put these advances to good use.

This introduction provides a brief, and necessarily incomplete, overview of some of the advances, and the many remaining challenges, for the study and treatment of diseases of the nervous system. A number of new therapeutic strategies have already been developed, and are already impacting on the quality of life of those with neurological disease. Many new treatments, both symptomatic and disease-modifying, are in the developmental pipeline. With the delineation of the human genome in 2001, a particular problem has emerged: the need to delineate protein production (proteomics) and protein modifications on a cellular basis. 'The emerging challenge in understanding the pathogenesis of the neurodegenerative disorders will be to characterize and elucidate aberrant protein interactions in the affected cells' (Martin, 1999). Future efforts will be focused on determining the tertiary structure of proteins which is currently determined using X-ray crystallography and nuclear magnetic resonance. Because of their relatively low through-put, complexity and high cost, these techniques have not generally been used for therapeutic targeting in drug discovery programmes. Recent technological advances, coupled with the information from human genome sequencing, are beginning to enable construction of a database to predict protein structure from sequence, and may be relevant for up to one-third of all gene targets (Christendat et al., 2000).

Global challenges in the developed and developing world

The world's aging population is increasingly affected by both acute and chronic neurological diseases. These include cerebrovascular disease, Alzheimer's disease and other dementias and Parkinson's disease. In the USA, the number of the very old (older than 85) is expected to increase sevenfold, from 2 million in 1990 to 14 million in 2040 and is increasingly vulnerable to chronic neurodegenerative disorders.

Since the original descriptions in the 1870s that microbes caused infections, specifically the discovery by Koch that *Bacillus anthracis* caused anthrax, major neurological complications of systemic infections continue to affect millions annually, particularly in developing nations. These infections include malaria, HIV-1 infection, tuberculosis, and leprosy, as well as 'new' infections that have emerged in previously unaffected areas. Malaria remains a major scourge across the world, with approximately 1.5 million deaths annually, many from cerebral involvement. Until recently, research efforts have been scattered and underfunded, with little coordinated effort for the development of a vaccine. In sub-Saharan Africa, the AIDS epidemic has produced an enormous sociopolitical crisis because it has literally decimated a generation, with seroprevalence rates exceeding 25% of the population, and an estimated 13.2 million 'AIDS orphans' (UNAIDS, 2000). Despite the availability of effective treatment, leprosy remains the commonest cause of peripheral neuropathy worldwide. Increasingly, developed and developing countries are linked by diseases which have spread because of the ease and speed of global travel. As

one recently developing example of 'emerging' infections, the appearance of West Nile encephalitis in the eastern USA in the past few years is thought to reflect the introduction of infected *Anopheles* mosquitoes from increased air travel (Lanciotti et al., 1999).

One of the major challenges facing our society will be how to equitably distribute therapeutic advances, many of which may be both costly and complex, particularly to underserved populations. The AIDS epidemic provides a stark warning of how an inadequate global response can fail to deliver currently available and effective treatments to millions. It serves as an example to avoid as improved pathogenesis-based treatments for neurological diseases such as Alzheimer's are developed (Steinbrook & Drazen, 2001).

The impact of imaging on neurosciences

No technology has changed the practice of the clinical neurosciences more than cranial imaging. Within the past two decades we have witnessed the development first of structural imaging (CT and MRI), then functional imaging (PET and fMRI), and now refined morphological and physiological imaging (diffusion-weighted and perfusion-weighted imaging), and biochemical characterization with magnetic resonance spectroscopy (MRS). Advances in imaging techniques during the past two decades have literally revolutionized our ability to localize pathology within the nervous system, establish diagnoses, and guide therapies. Rather than devalue the role of neuropathology in the clinical neurosciences, the improvements in imaging have facilitated an even closer integration of clinical neurology with pathology. We can now see the brain, ask what part is involved in neural and cognitive processing, evaluate the extent and distribution of injury, and characterize mechanisms of plasticity and recovery.

Of all of the various imaging modalities: computerized tomography, positron emission tomography, angiography, arguably magnetic resonance imaging (MRI) has become the most widely used modality because of its sensitivity, and lack of radiation risk. The field of MRI has now taken on two new functions: (i) magnetic resonance spectroscopy, identifying the biochemical profile of the living brain through the identification of specific chemical spectra and (ii) the development of functional MRI using changes in deoxyhemoglobin to detect regional brain activation. Both of these techniques are non-invasive, repeatable, and involve no radiation risk. Specialized MR techniques such as diffusion-weighted imaging and perfusion-imaging have pushed forward our understanding of cerebrovascular pathophysiology. They allow for the identification of 'vulnerable' brain tissue within the first few hours after onset of stroke. The identification of diffusion–perfusion 'mismatch' can now lead directly to treatment with thrombolytic therapies or induced hypertension.

Table 1.1. Physiologic processes accessible in humans by functional and metabolic imaging

Physiologic processes	Methods
Glucose metabolism	FDG-PET[a]
Blood flow or volume	[^{15}O]H_2O-PET, perfusion MRI
Tissue oxygenation	nitroimidazole-PET, fMRI
Tissue pH	^{31}P-MRS
Protein synthesis	Amino acid-PET
Cell proliferation (mitotic rate)	Thymidine-PET
Receptor concentration or occupancy	PET
Enzyme kinetics	PET
Endogenous metabolite concentration	MRS(I)[a]
Water diffusion	DWI
Tissue anisotropy	DTI
Drug pharmacokinetics/dynamics	PET, MRS
Vascular permeability	Dynamic MR

Notes:
DTI, diffuse tensor imaging; DWI, diffusion-weighted MR imaging; FDG, [^{18}F]fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; MR, magnetic resonance; MRS(I), magnetic resonance spectroscopy–spectroscopic imaging; PET, positron emission tomography. [a] Technique used routinely in clinical practice for oncology.
Source: From Pomper, M.G. (2000). Table 27.3–1, p. 680. Reproduced with permission from the publisher.

These remarkable advances are incomplete. We are still not 'online' with the timing of the brain's processing of information. The dependence of current methods of functional imaging, both PET and fMRI, on changes in blood oxygenation and blood flow associated with neural activity remains a limiting factor. Other imaging techniques based on electrophysiological or magnetophysiological principles may provide further advances. Nonetheless, current physiological imaging as detailed in Table 1.1 can now permit the detection of a variety of metabolic alterations within the living brain, including blood flow, metabolism and perturbations in neurotransmitters (Fig. 1.1, see colour plate section). The recent development of the National Institute of Biomedical Imaging and Bioengineering (NIBIB) at the National Institutes of Health will probably further facilitate and accelerate the progress of imaging research.

Neuropsychiatric disorders have been extensively studied using both structural and functional neuroimaging. Mood disorders have a neurochemical origin, but may also be associated with regionally selective alterations in brain structure. For example, a 40% reduction has been found in grey matter volume in prefrontal cortex in patients with bipolar disorders or familiar recurrent unipolar depression (Drevets et al., 1997). As an example of an investigative approach which combines genetic studies, neuropsychological testing and functional imaging, a specific gene variant in the dopamine-degrading enzyme, catechol-*o*-methyltransferase, is more common in schizophrenics and the prefrontal cortex appears to be metabolically more active (Egan et al., 2001). Positron emission tomography scans during reading tasks showed reduced activity in the left hemisphere in dyslexics from three different countries, suggesting that there is a universal neurocognitive basis for dyslexia (Paulesu et al., 2001). Multidisciplinary studies such as these will become more common and will undoubtedly facilitate an improved understanding of how genetic variation may influence brain behaviour in health and disease.

The genetics of neurological diseases

Over 50% of genetic disorders affect the nervous system and are detailed in the online textbook *Online Mendelian Inheritance in Man (OMIM)*. This database is a catalogue of human genes and genetic disorders authored and edited by Dr Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere, and developed for the World Wide Web by NCBI, the National Center for Biotechnology Information. OMIM contains 12 749 genetic disorders and 9365 established gene locations.

The elucidation of the genetic mechanisms of disease using molecular techniques has advanced rapidly, in large part because most neurogenetic disorders are inherited in a simple Mendelian fashion. Linkage analysis, positional cloning and searches for mutations in candidate genes have led to the identification of mutant genes in more than 50 disorders. The elucidation of the human genome through the Human Genome Project and the surprising observation that the number of identifiable human genes (26 000) is only a few thousand more than the number identified for a much smaller organism, the round worm, sets the stage for a detailed exploration of genes and proteins associated with specific neurological diseases.

Extraordinary progress has been made in identifying specific genes that pose risk factors for many common neurodegenerative disorders and the ways in which proteins coded by these genes are associated with loss of function or gain of adverse properties (Price et al., 1998a; Hardy & Gwinn-Hardy, 1998; Price et al., 1998b). Even before the Human Genome Project was completed in 2001, the mapping and cloning of genes involved in inherited neurological disorders had been performed. It is now anticipated that the genomes of given individuals will be highly variable, as compared to the reference human sequence. Thus, it should be possible to analyse disease genes from studies of a single individual, rather than large kindreds, as has been required up to now. For a number of disorders long considered 'sporadic', the findings from genetics have changed our ways of thinking. Advances in Alzheimer's disease (AD) are illustrative, but we could equally have chosen Parkinson's disease (PD), frontotemporal dementia, or amyotrophic lateral sclerosis. It has been known for some time that rare families existed with an early onset of Alzheimer's disease (under age 60) and an apparently dominant pattern of inheritance. Evaluation of these families has yielded four genetic loci with numerous mutations, all involved in the processing of the protein beta amyloid. These findings not only strengthened the amyloid hypothesis as the underlying mechanism of Alzheimer's disease, but provided information leading to the development of transgenic mouse models. Allelic variation in apo-E appears to act as a time dependent susceptibility gene (Price et al., 1998a).

In an example of a multidisciplinary approach to improve the sensitivity of preventive treatment trials for AD, genetic testing has been combined with functional imaging in an innovative approach to more efficiently test preventive treatments. Positron emission tomography is used in cognitively normal apolipoprotein E4 heterozygotes to identify those with decreased glucose metabolism in several brain regions typically affected in AD. Those with PET abnormalities are considered to be at greatest risk for the development of AD and participate in the clinical trial (Reiman et al., 2001).

Alzheimer's disease also provides an example of the identification of genes associated with an increased risk of disease, rather than disease mechanisms. The first such genotype, Apo-E4, is associated with a fourfold increased risk of late-onset AD and appears to act as a time-dependent susceptibility gene (Price et al., 1998a). Two other genetic loci, A2M and LRPAP1 have also recently been reported as risk-associated genes (Sanchez et al., 2001; Nicosia et al., 2001), and perhaps only operate in selected populations. The concept of risk factor genes has been proposed for some time, but finally there is specific evidence for such a phenomenon. Manipulation of transgenic mice models has suggested therapeutic strategies for the much

larger group of patients with late-onset Alzheimer's disease through manipulation of the secretases involved in processing amyloid, or vaccines aimed against possibly toxic fragments of amyloid. As outlined in Chapter 115, similar strategies have been used to explore the role of the protein alpha synuclein in Parkinson's disease, and the protein tau in frontotemporal dementia.

The mechanisms of cellular injury for most neurogenetic disorders remain uncertain, even when a gene product can be identified. Another genetic abnormality, the triplet repeat mechanism for diseases such as Huntington's disease, fragile X syndrome, and various spinocerebellar ataxias, has focused attention on how proteins determine abnormal cellular function and ultimately cell death. There has been a shift away from thinking about enzymatic abnormalities to abnormalities of protein structure and function. This consideration of proteins as mechanisms of disease applies not only to the triplet repeat diseases, but also to other diseases involving proteins such as prion diseases and neurodegenerative diseases.

Common mechanisms may exist for a number of neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. Most neurodegenerative diseases have been linked to abnormal protein aggregates interfering with neuronal function and viability. Genetic errors and mutations may produce misfolded proteins which tend to accumulate within neurons and may impair the function of proteasomes, which is normally critical in the ubiquitin proteasome system for breaking down proteins. Further accumulation, over a prolonged period, may lead to additional accumulation and even more proteasomal dysfunction (Bence et al., 2001). In Huntington's disease, polyglutamine expansions in the huntingtin and atrophin-1 proteins can be identified, and have been proposed to lead to neuronal toxicity by interference with gene transcription (Fig. 1.2) (Nucifora, Jr. et al., 2001). Mitochondrial disorders can affect almost every tissue and organ system, typically with maternal transmission. Mitochondrial genetics have become increasingly important since the first descriptions of mutations in mitochondrial DNA in 1988 (Holt et al., 1988). A wide range of systemic and neurological diseases have now been linked to specific mutations, including chronic progressive external ophthalmoplegia (CPEO), Leber's optic atrophy, MELAS and MERRF. In addition, mutations in mtDNA may contribute to aging and neurodegenerative diseases.

The accurate diagnosis of many neurogenetic disorders is now possible; and both antenatal and presymptomatic disease diagnosis is also feasible. Genotypic diagnosis by DNA testing allows for precision in diagnosis, and facilitates genetic counselling and predictive testing. It can also identify patients with specific genetic disorders for natural history studies, and ultimately, for therapeutic interventions. These technological advances bring their own set of ethical concerns, however, including the potential misuse of genetic testing to screen 'at risk' individuals for employment or health insurance.

The field of gene therapy was introduced with tremendous fanfare over a decade ago, and had the potential to introduce functional genes into a diseased cell. There have been persistent technical challenges with the delivery systems used to deliver the genes, and the entire field suffered a major setback following an unanticipated patient death in one gene therapy trial. Nonetheless, the recent demonstration of a non-viral gene-transfer therapy for hemophilia A has generated renewed excitement at the potential to cure selected genetic diseases (Roth et al., 2001).

Ion channels and neurotransmitters in neurological disease

The study of ion channels and their distribution in muscle and nerve has expanded tremendously in the past decade, and has led to an improved understanding of the molecular basis for a collection of disorders termed 'channelopathies', including the familial myotonias and periodic paralyses. In epilepsy, different types of rare seizure disorders are now known to be inherited in either an autosomal dominant or autosomal recessive pattern. Mutations have recently been identified in a widely distributed sodium channel, SCN1A in an inherited form of epilepsy, Generalized Epilepsy with Febrile Seizures Plus type 2 (Escayg et al., 2000). The underlying mechanisms have now been clarified for febrile seizures inherited in an autosomal dominant pattern and have been linked to a point mutation in the beta subunit of voltage-gated sodium channel (Wallace et al., 1998). Identification of the mutant genes underlying rare forms of human epilepsy could facilitate recognition of molecular targets and the development of new treatments, for example, drugs acting on potassium channels to enhance potassium current and inhibit seizures. In other areas, the study of genetically determined dysfunction in ion channels has been productive. Several channelopathies with know genetic alterations have been identified in diseases as phenotypically diverse as familial hemiplegic migraine, episodic ataxia, benign neonatal epilepsy type I, and congenital myotonia. These can affect calcium, potassium or chloride channels, with molecular alterations ranging from point mutations, to prematurely truncated proteins, to pathological expansion of terminal sequences (Nappi et al., 2000).

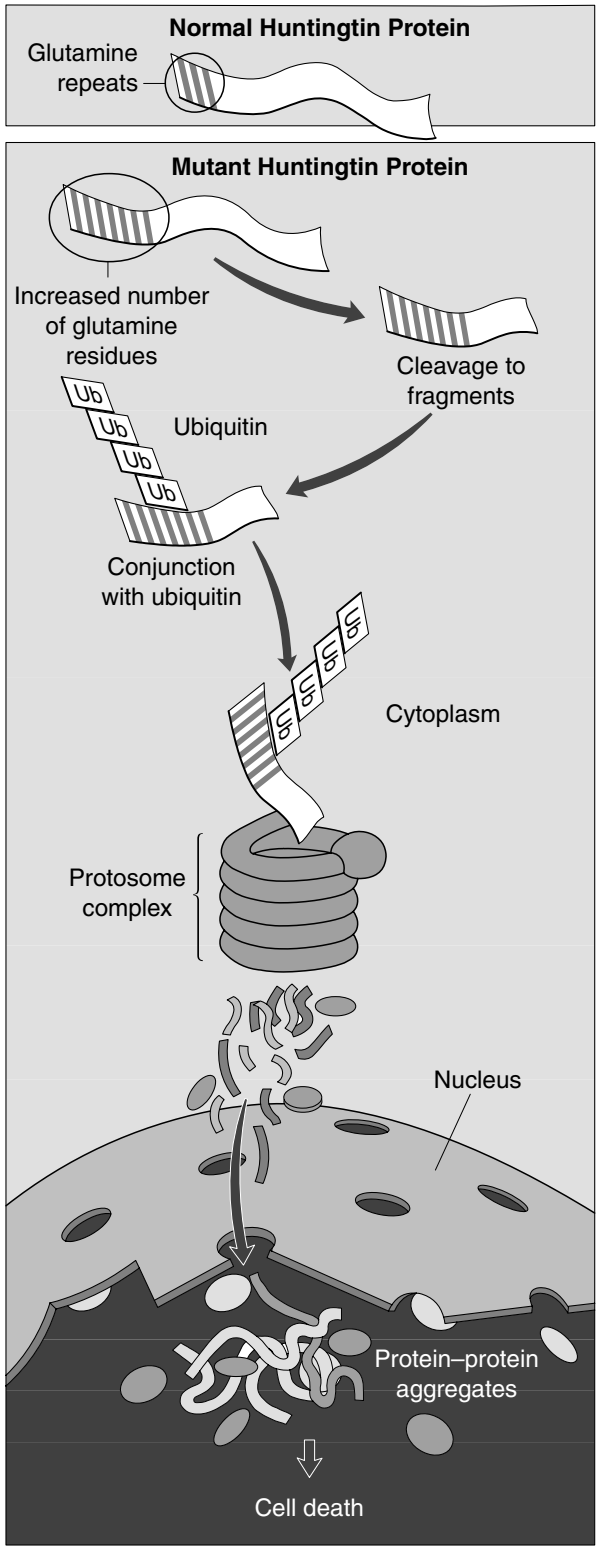


Fig. 1.2. Proposed mechanism of huntingtin-induced death of neuronal cells. The mutant huntingtin protein produced by an increase in the number of CAG repeats in the DH gene is cleaved to fragments that retain the increased number of glutamine residues. These fragments are conjugated with ubiquitin and carried to the proteasome complex. Subsequent cleavage is incomplete, and components of both huntingtin and the proteasome are translocated to the nucleus, where aggregates form, resulting in intranuclear inclusions. Over time, this process leads to cell death. (From Martin, 1999.)

With the description of the neurotoxicity of glutamate in 1957, there has been an explosion in our understanding of the biology of neurotransmitters in the CNS. Much of this work has focused on glutamate, the principal excitatory neurotransmitter, and its inhibitory counterpart gamma-amino butyric acid (GABA). To date, five high-affinity glutamate transporters have been cloned, with differential cellular and anatomical localization. In addition to its neurotoxicity, glutamate plays important roles in synaptic plasticity, learning, and development (Maragakis & Rothstein, 2001).

The molecular pathways underlying learning, memory and drug addiction have begun to converge with the recognition that drugs of abuse can cause long-lasting neural changes in the brain (Nestler, 2001).

The impact of stem cells for neurological diseases

Most of us were brought up with the concept that individuals are born with all of the neurons that they are ever going to have, and that neurons are gradually lost with aging. This concept has now been clearly proven wrong, at least for specific areas of brain such as the hippocampus. The adult brain and spinal cord contain neural stem cells that have the capacity to form neurons, astrocytes, and oligodendrocytes from cells in the ependyma and subventricular zone. Although widely viewed as a 'new' observation, in fact progenitor cells were identified in the periventricular zones in the 1950s. What functional significance this neurogenesis has in later life for the processing of memories or in response to injury remains to be determined. In addition, marrow stroma cells transplanted to the brain are able to generate astrocytes (Kopen et al., 1999). Cell lines developed from pluripotent human fetal or embryonic stem cells have now been developed (Shihabuddin et al., 1999), and successful transplantation has been achieved in animal models of Parkinson's disease, motor neuron disease, and spinal cord injury. The

long-term efficacy of such treatments, particularly in Parkinson's disease, is a particularly active area of investigation. Stem cells are usually derived from aborted fetuses or embryos, and in the USA, ethical concerns have effectively halted the public funding of stem cell research using these embryonic stem cells. The field of stem cell transplant has achieved even greater promise, both scientifically and politically, through the recognition that pluripotential embryonic stems cells can develop into a wide range of differentiated tissues, including neurons and muscle cells. Although embryonic stem cells appear to proliferate much more efficiently than adult stem cells, these cells are being actively developed and may avoid some of the ethical issues of the use of embryonic tissue. There are many questions still to be answered regarding the relative potential of embryonic stem cells and adult-derived progenitor cells. The exciting possibility exists, however, that these cells could be used as therapeutic agents, either as cell transplants, as sources of trophic factors or gene products to modify neurodegenerative processes in the brain or spinal cord. Functional recovery has been achieved in damaged spinal cords with some restoration of neurological function after injury (Kocsis, 1999) and early human trials have been completed in stroke with positive results.

The development of animal models

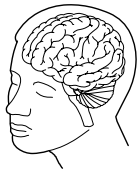
Animal models have, of course, been available for the study of neurological diseases for many years. These models usually occurred spontaneously and were utilized when an astute observer realized their implications for neuroscience research. The development of molecular biological techniques has allowed the insertion and removal of genes at the will of the investigator, particularly in easily manipulated species like the mouse and the fruit fly. This has permitted the development of reproducible animal models of common neurological diseases. Transgenic animals engineered to express human genes linked to Alzheimer's disease, amyotrophic lateral sclerosis and Huntington's disease have produced critically valuable advances in our understanding of the pathophysiological mechanisms. Although the exact pathophysiological mechanisms of Alzheimer's disease remain unclear, several transgenic animal models have already been used to delineate discrete pathways of injury. The application of transgenic technology should allow us to modify tumour-suppressor genes and to test pharmacological, biological, or genetic manipulations to prevent progression or even reverse the neurological disease. Small animal models will also allow for the efficient testing of new therapies for PD and other chronic neurodegenerative disorders. For example, in Parkinson's disease, animal models have been developed in the fly and mouse, which duplicate many of the cardinal features of Parkinson's disease (Fig. 1.3) (Dawson, 2000). Transgenic mice or flies over-expressing alpha synuclein develop pathology within dopamine neurons and age-dependent motor deficits (Masliah et al., 2000; Feany & Bender, 2000). Shimura et al. (2001) showed that the products of two genes, Parkin and alpha-synuclein, functionally interact and may lead to Parkinsonian degeneration.

A genetic model of Tauopathies has been developed by expressing human wild type and mutant Tau in the nervous system of the fruit fly. Transgenic flies die early after developing progressive neurodegeneration, but, at least in this model, show no signs of the large filamentous aggregates of Tau that compose neurofibrillary tangles (Wittmann et al., 2001).

Even more complex functions and neurological disorders can now be evaluated in large animal models. These have traditionally been used for physiological experiments, but are now being developed for the study of neuropsychiatric disorders such as schizophrenia. For example, by disrupting the development of fetal pigs brains chemically with a toxin that impedes cell division, pathological changes can be induced that mimic the abnormalities evident in the brains of some schizophrenics (Anon, 2001).

Mechanisms of cellular injury

Work since the last edition of this book has delineated more clearly how neurons and astrocytes may be injured during neurological diseases. The role of excitotoxic substances including glutamate has been studied extensively and the 'traditional' dichotomous model of two forms of cell death (necrotic or apoptotic) has been challenged. Substantial advances have been made in understanding the pathophysiological mechanisms underlying neuronal cell death in diverse neurological disorders. Great efforts have been made both in dissecting the cellular mechanisms mediating neuronal death, and in developing therapeutic strategies to prevent this, broadly defined as 'neuroprotection'. The two basic mechanisms of neuronal death, necrosis and apoptosis (or programmed cell death), have been extensively researched. In excitotoxic cell death, exposure to exogenous toxic substances, including glutamate, leads to an energy-independent cell destruction. Glutamate exposure can trigger neuronal death within the brain and has been implicated in the pathogenesis of numerous CNS diseases, including ischemic brain injury,



Human	Mouse	Fly
Age-dependent onset with chronic progression	Age-dependent onset – unknown	Age-dependent onset with chronic progression
	Inclusions get larger with age	
Dopamine neuronal cell loss in select brain regions	Dopamine neuronal cell injury	Dopamine neuronal cell loss
Lewy bodies (cytoplasmic inclusions containing α-synuclein and ubiquitin with a core and radiating fibrils)	Cytoplasmic inclusions (containing α-synuclein and some ubiquitin without fibrils); nuclear inclusions	Cytoplasmic inclusions (containing α-synuclein with fibrils; ubiquitin not determined)
Motor deficits	Motor deficits	Motor deficits
Mitochondrial complex 1 deficits	Unknown	Unknown
Increased markers of oxidative stress	Unknown	Unknown

Fig. 1.3. A comparison of animal models of PD. Recent molecular advances have enabled the engineering of mice and flies that carry wild-type or mutant versions of the protein α-synuclein, which is implicated in PD. A comparison of the features of the fly and mouse animal models of PD and how they correlate with the characteristics of the disease in human patients is shown. (From Dawson, 2000.)

amyotrophic lateral sclerosis, trauma, and seizures (Choi, 1988). NMDA receptors appear to be critical in acute glutamate neurotoxicity, for example, in ischemic brain injury. Hypoxic–ischemic brain injury may lead not only to excitotoxic cell death, but also to apoptosis or programmed cell death wherein cells die with negligible inflammation. Lee and Choi (Lee et al., 1999) have proposed that ischemic brain injury most likely represents an 'admixture' of morphologic features of both excitotoxicity and apoptosis. In apoptosis, caspase activation results in cell death through the destruction of critical molecules and the activation of others which mediate an energy-dependent 'suicide programme'. Mediators of apoptosis have been defined and several genes identified, including a family of 'cell death' sustained proteases, the caspases. Activation of caspase1 occurs in diverse models including cerebral ischemia, cerebral trauma, and neurodegenerative diseases such as ALS and Huntington's disease (Hara et al., 1997; Ona et al., 1999). Caspase inhibition may therefore be yet another avenue for targeted therapies, both for acute and chronic neurological disorders. Caspase activation also occurs in cerebral trauma, amyotrophic lateral sclerosis and Huntington's disease. Caspase pathways are activated in territories subjected to moderate hypoxia and lead to apoptotic cell death over a more prolonged period than that occurring with necrotic cell death. The importance of this is that apoptosis can be aborted either by timely reperfusion of the brain or by caspase inhibition (Friedlander, 2000). Despite the clear effectiveness of NMDA antagonists in experimental models of stroke, numerous clinical trials have unfortunately failed to show any clinical efficacy. Rather than being the result of faulty trial design or poor outcome measures, it seems more likely that other forms of cellular injury may play critical roles in ischemic brain injury. These may include AMPA/kainate receptor-mediated toxicity and extracellular zinc.

An important new concept in pathology is the description of the role of inflammation in diseases previously thought not to involve an inflammatory component. For example, in Alzheimer's disease there are now clear descriptions of local microglial activation, cytokine release, reactive astrocytosis and a multiprotein inflammatory response (McGeer & McGeer, 1995; Eikelenboom et al., 1994). Whether these responses are critical, or simply reflect an epiphenomenon, remains to be determined, but

already clinical trials of anti-inflammatory agents are in progress, and their results eagerly awaited.

Multiple sclerosis has traditionally been referred to as an inflammatory demyelinating disease and most of us were taught in medical school that it 'spared CNS axons'. Though degeneration of axons in multiple sclerosis lesions was first recognized by Charcot in 1877, recent elegant work has reinforced the frequency with which axonal transection and both neuronal and axonal loss occurs in multiple sclerosis. Axonal pathology has been identified as a determinant of irreversible disability (Matthews et al., 1998; Davie et al., 1995). This has led directly to change in treatment philosophy, ie, to begin treatment early before there is irreversible axonal injury. Refinement of non-invasive MR-based techniques to quantify underlying pathological lesions in MS will be relevant to the rational development of new treatments.

Plasticity in adult brains

In the past three decades, there has been an increased understanding of the synaptic and molecular basis of plasticity within the adult human brain. Current research indicates that experience-dependent plasticity may not decrease dramatically with age, as had previously been thought. This research may produce effective remediation for neurological impairments following trauma, stroke, or surgery. Functional magnetic resonance imaging has been widely used to examine the neural mechanisms underlying the acquisition of skilled behaviours. In epilepsy, the development of circuitry with recurrent excitatory synapses has emerged as common to numerous experimental models of epilepsy and could potentially occur within the sclerotic hippocampus of humans (McNamara, 1999).

Dendrites may have the capacity to synthesize proteins, thus could modulate the strength of connections between neurons, ultimately influencing neural activities including learning and memory. Protein synthesis occurs in intact dendrites, and this local protein synthesis could facilitate the ability of synapses to make synapse-specific changes (Aakalu et al., 2001).

Information processing and computational neuroscience

The ability to store, integrate and rapidly analyse large amounts of data has been a crucial advance in facilitating the progress in areas such as genomics and imaging. Data management, data handling, and statistics have all advanced to a point where more than adequate computational power is available on the average laptop computer. In addition, the Internet has revolutionized how most neuroscientists access, publish and disperse information, making use of large publicly available databases. One exciting application is the potential for the Internet to enhance remote or long-distance collaborations, without the need for travel or telephone communications. Systems are now in place which can permit the control of experimental equipment remotely in real time. For example, the Great Lakes Regional Center for AIDS Research facilitates telemicroscopy, distance learning, and video conferencing with real-time document and image sharing (Teasley & Wolinsky, 2001).

The objectives of computational neuroscience span the development of alternative test systems to model biological processes to the working of physiological systems, such as explaining how the brain might process information. This field has obviously been advanced by the revolution in affordable computers, which can be applied to produce neural networks and artificial intelligence, or systems which 'learn' how to address a neurobiological problem. The concept of neural networks has increasingly focused on attempts to understand complex human behaviour. For example, complex human memory is likely mediated by assemblies of interconnected neural networks with different components contributing towards memory function and dysfunction. At the same time, our patients and non-scientists have become our partners because they have the potential to tap into the same information sources as clinicians and scientists. In this new era, there is increasing need for clinicians and investigators to be sources of understandable, accurate and unbiased information.

Advances in neuroepidemiology and clinical trials

Here, neurological clinical trials research has advanced on several different fronts. At a national level in the USA, programmes and resources sponsored by the NIH to train and develop well-trained clinical researchers have been expanded. One example of this is the NIH-funded K23 programme, which is designed to foster the career development of clinician–investigators in patient-oriented research. The widespread application of evidence-based neurology in the past two decades has greatly improved clinical practice, the quality of patient-oriented neurology publications and the education of neurologists. Many neurological therapies and interventions have been submitted to rigorous and systematic analyses and meta-

analyses to examine both the efficacy and effectiveness of therapies. Detailed literature reviews and practice guidelines have been developed for most neurological disorders and their treatments through mechanisms such as the *Cochrane Review* and the *American Academy of Neurology*.

The design of clinical trials has improved markedly with the more accurate modelling of sample size calculations to ensure that clinical trials are adequately powered to show statistically significant differences, where they exist. The interactions of neuroscientists and statisticians have led to new strategies to more efficiently test new therapies in controlled clinical trials. As an example, it is now recognized by clinical trialists that even small overestimates in the efficacy of an intervention can lead to a significant reduction in the statistical power of a trial. Cost-effectiveness modelling techniques can be used to better define minimum clinically important differences (Samsa & Matchar, 2001). Finally, new outcome measures have been developed and refined both for the study of central and peripheral nervous system disorders in clinical trials. For example, in multiple sclerosis, clinical trials now routinely incorporate magnetic resonance imaging as one of the important outcome measures. In the study of painful peripheral neuropathies, skin biopsy, a technique originally developed in the 1960s has now been 'rediscovered' and is now being used as an outcome measure in trials of regenerative agents for sensory neuropathies.

Some of the great successes in clinical neurosciences have actually been in prevention with the development of effective vaccines. Thus, we rarely encounter poliomyelitis, postrubella mental retardation, or postinfectious demyelination after measles (at least in the developed world). Recognition of risk factors and changes in life style have led to a significant decline in cardiovascular and cerebrovascular diseases, but strategies for preventing or delaying neurodegenerative diseases are still lacking. Possible protective effects of estrogens, antioxidants, and non-steroidal anti-inflammatory agents for neurodegenerative diseases are promising, but firm recommendations can still not be made.

The ultimate value of deciphering pathophysiological processes at a molecular level will arise in the development of targeted therapies. These should both reduce toxicity and permit a direct attack on disease process. Examples include the development of Herceptin, a 'monoclonal antibody', which has been proved useful for treatment of metastatic breast cancer which has been linked to the over-expression of the HER-2 allele. More recently, a targeted treatment for CML has been approved which blocks the expression of AB-1, a 'tumour promoting gene' (Druker et al., 2001). Gene and cell-based therapies are being developed for stroke, anoxic brain injury and other neurological disorders. In global ischemia models in gerbils, it appears that new neurons are produced within the hippocampus, raising the possibility that recovery after brain ischemia may, in part, reflect neurogenesis (Frank R. Sharp, University of Cincinnati, personal communication 2001). Fetal stem cells have been implanted in rodent models and continue dividing for several weeks. Cell lines in a marmocet model of stroke have restored some functional recovery (Svendsen & Smith, 1999; Ostenfeld et al., 2000).

At the same time, clinical research has come under closer scrutiny. Potential conflicts of interest by investigators, adequacy of informed consent procedures and the adequacy of monitoring of ongoing studies are subjects of concern, not only among investigators, but among the general public as well. As we proceed into the intervention phase of neurologic disease research and care, it is essential that investigators maintain their credibility for accurate, unbiased clinical research trial design, implementation and interpretation.

Therapeutic impact of translational neurosciences research

The concept of translational research, the delivery of laboratory discoveries to patient-oriented applications has many examples in neurological diseases. One increasingly important aspect of translational research is the development of new therapies, focused on pathogenic mechanisms. There are now FDA-approved agents for neurological diseases for which, until recently, we had no therapeutic options. These include Alzheimer's disease, amyotrophic lateral sclerosis, and multiple sclerosis, with agents that, at least for ALS and MS, are truly 'disease modifying', rather than symptomatic. One intervention which has changed clinical practice substantially is the introduction of TPA in appropriately selected patients with acute ischemic stroke. Acute ischemic strokes are now considered, like myocardial infarction, as 'brain attacks' requiring urgent evaluation and consideration for specific treatment. In stroke, the concept of neuroprotection has been tested successfully in ischemic animal models, but has failed to translate successfully to human trials. In fact, the last 15 years have seen a series of failures for a variety of treatments for ischemic stroke. Some of these failures may have been due to underpowered trials, or incorrect estimates of treatment effect (Samsa & Matchar, 2001) In Alzheimer's disease, transgenic models have been used to probe possible effectiveness of disease-modifying therapies, including inhibitors of beta secretase, the enzyme

critical for A-production, vaccination strategies directed against A-beta, neuroprotective strategies with antioxidants or estrogens to protect neurons from the downstream effects of A-beta accumulation, and other strategies. In other neurodegenerative diseases, such as Parkinson's disease, strategies to replace critical neurotransmitters have been attempted. Disappointingly, fetal neuronal grafts into the basal ganglia have as yet produced only modest effect on symptoms of Parkinson's disease with the added concern that dyskinesias developed in a proportion of patients (Freed et al., 2001)

In the tremendous potential of the basic and clinical neurosciences to permit an ever finer dissection of disease processes, we must never lose sight that these same processes affect a person, a family, a mind.

Ask not what disease the person has, rather what person the disease has. ***William Osler, 1889***

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2

Genetics of common neurological disorders

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There is growing appreciation of the influence of genetic constitution on predisposition to disease, even that not usually considered 'genetic'. Approximately 40% of the estimated 30 000 human genes are expressed in the nervous system, the majority of these exclusively (Hurko, 1997; International Human Genome Sequencing Consortium, 2001; Sutcliffe, 1988; Venter et al., 2001). Neurological and psychiatric health might thus be especially susceptible to genetic influence. Furthermore, the nervous system can be uniquely vulnerable to mutations in genes expressed ubiquitously, as with huntingtin (Trottier et al., 1995), and to primary metabolic derangements in non-neural tissue, as with hepatic porphyrias (Strand et al., 1970) or diabetes mellitus. A disproportionate number of single gene disorders manifest as neurological or psychiatric dysfunction (Hurko, 2001).

Many of the successes of human molecular genetics have come from study of neurological disease. Neurological patients suffering from monogenic disorders have thus far only benefited from improved diagnosis. Identification of pathogenic genes has provided powerful reagents, transgenic animals, lessons from homologues in lower organisms and other insights into pathophysiology. These will hasten the development of effective therapies. However, most of these benefits, both realized and anticipated, have been confined to monogenic disorders. Such single gene, or Mendelian, disorders are rare.

Complexity in single gene disorders

Furthermore, even in monogenic disorders the relationship to clinical phenotype is not always straightforward (Estivill 1996). A given phenotype can result from mutation of any of a number of genes. Genetic heterogeneity exists in early-onset Alzheimer's disease (Dartigues & Letenneur, 2000), autosomal dominant spinocerebellar atrophies (Durr & Brice, 2000), limb-girdle muscular dystrophies (Beckmann, 1999; Bushby, 1999; Kissel & Mendell, 1999) and X-linked mental retardation (Toniolo & D'Adamo, 2000), among others.

Allelic heterogeneity

Different mutations within a single gene also contribute complexity. Frame-shift mutations abolish activity of dystrophin, causing Duchenne muscular dystrophy (DMD); mutations that do not shift reading frame compromise function only partially, resulting in milder Becker dystrophy or just subclinical elevation of serum creatine kinase (England et al., 1990; Matsuo et al., 1990). Similarly, variations in the length of triplet repeat expansions underlying Huntington disease (Reddy et al.,1999; Trottier et al., 1994), several of the spinocerebellar atrophies (Cummings & Zoghbi, 2000; Stevanin et al., 2000), fragile-X mental retardation, (Jin & Warren, 2000; Kooy et al., 2000), and myotonic dystrophy (Lieberman & Fischbeck, 2000) determine the severity of the neurological disorder. Allelic differences can be qualitative as well as quantitative. For example, some mutations of the ryanodine receptor result in central core myopathy (Zhang et al., 1993); others confer susceptibility to malignant hyperthermia without clinically evident myopathy (Gillard et al., 1992; McCarthy et al., 2000).

Mosaicism, the presence or expression of more than one genotype in an individual, results either from lyonization in X-linked disorders (Lupski et al., 1991), heteroplasmy in mitochondrial disorders (Hurko, 2001), or somatic mutations, as in tumours. In mosaics, clinical phenotype depends not only on which gene is mutant, but also on distribution and frequency. Parental imprinting adds further complexity. Inheritance of a certain mutation from father results in the Prader–Willi syndrome, whereas inheritance

of a similar mutation from mother causes the very different Angelman syndrome (Fridman & Koiffmann, 2000; Greenstein, 1990; Hulten et al., 1991).

Further complexity results from interaction of a pathogenic gene with the environment and with other genes. Mutation of the ryanodine receptor gene may be inapparent until exposure to halothane; mutations underlying hepatic porphyria inapparent until exposure to barbiturates. No gene is expressed in isolation. 'Monogenic' disorders can be modified by epistatic interactions with other genes (Maestri & Beaty 1992).

Genetically complex disorders

Even more complicated genetic and environmental interactions determine susceptibility to many common neurological and psychiatric disorders. Because of this complexity, delineation of genetic factors for common diseases has lagged behind those of rare Mendelian traits (Risch & Botstein, 1996). Analyses suitable for monogenic disorders are often suboptimal for complex traits. However, recent technical and analytical advances promise identification of susceptibility genes for several common neurological and psychiatric disorders.

Is a disease genetic?

Before turning to specific examples, it is useful to consider the meaning of genetic disorder. All biological phenomena result from complex interactions of thousands of genes and innumerable environmental factors. Diseases are no exception. In a given setting, some factors are more important than others. As a start, it is useful to estimate the relative contribution of genetic and environmental factors.

For many genetic diseases familial grouping is inapparent, particularly given the small size of modern nuclear families. These days, most cases of autosomal recessive disorders, such as metabolic disorders and progressive neurodegenerations of infancy like Tay–Sachs disease, occur as singletons in families with no previous history. Even if 1/100 healthy individuals carry a single copy of recessive mutation, there is only 1/10 000 chance that two such heterozygotes will marry, and only 1/4 of their offspring will fall ill because of homozygosity for the mutant gene. With a typical family size of two children, the overwhelming likelihood is that there will not be additional cases in siblings or in other generations. Only systematic analyses of large populations or consideration of biological data will reveal the genetic nature of such disorders. Similar considerations apply to new autosomal dominant mutations (Rudnik-Schoneborn et al., 1994), mitochondrial disorders like Kearns–Sayre syndrome (Butler & Gadoth, 1976), and chromosomal anomalies like Down's syndrome (Antonarakis, 1993).

Furthermore, not all diseases that 'run in families' are genetic. Members of a family share environmental factors: diet, socioeconomic class, as well as exposure to infectious, physical and chemical pathogens. A classic method for estimating the relative contributions of genetic and environmental factors has been the adoption study. Significantly higher similarity to biological rather than adoptive parents was the seminal indicator of the importance of genetics in schizophrenia (Heston, 1996) and alcoholism (Goodwin et al., 1974). However, the adoption method is limited. It will not detect recessive disorders or new mutations, and it also suffers from selective placement of adopted children into environments similar to those into which they were born. Adoption studies have not been used extensively in the study of neurological diseases.

A useful alternative is the comparison of concordance rates in monozygotic (MZ) and dizygotic (DZ) twins (Hawkes, 1997; Maher & Reik, 2000; Martin et al., 1997). MZ twins share all their genes, whereas DZ twins share only half. Therefore, a higher concordance rate in MZ than DZ twins is evidence of a genetic contribution. The higher the ratio of MZ concordance to DZ concordance, the higher the estimate of heritability. In the simplest case of a genetically determined disease, one would expect that all MZ twins would be perfectly concordant. For complex disorders this is usually not the case, for reasons only partially understood. There may be genetic heterogeneity: some twin pairs may have a highly heritable form of the disease, whereas others have a nonheritable phenocopy. In part, discordance may be an artefact of disease definition: MZ concordance for an expanded definition that includes schizoids is an almost perfect 1.0, twice that for classic schizophrenia. Furthermore, twin discordance has been seen even in well-defined single gene disorders. In X-linked DMD, dramatic discordance between MZ twin carriers is the rule rather than the exception, because of asymmetries in X-inactivation (Lupski et al., 1991). Not only environmental but also other developmental factors such as gene imprinting, may contribute to twin discordance, as has been shown for the Beckwith–Wiedemann tumour and mental retardation syndrome (Maher & Reik, 2000). In theory, the twin method is subject to the possible criticism that MZ twins share more environmental factors both prenatally and postnatally than do DZ twins. However, many of these concerns have proven more apparent than real (Kendler, 1993).

Although not perfect, twin studies have provided useful initial evidence of genetic factors in neurological and

Table 2.1. Comparative heritabilities

Disorder	λ	MZ	DZ	Heritability (%)
Autism	84–210	73%	7%	93
Schizophrenia	11	46%	14%	89
Anorexia nervosa	41			80
Multiple sclerosis	30	25.9%	2.3	
Febrile seizures	6–12	39%	12	
Alzheimer's disease	5			
ADHD	2–4	58%	31%	79
Lacunar stroke volume	2.5	61%	38%	73
Obsessive compulsive disorder				47–68
Bipolar depression	7	62%	8%	59
Migraine		34%	21%	52
Panic disorder	2.4–4.75			35–46
Unipolar depression		40%	17%	21–45
Sciatica		18%	12%	21
Pressure pain threshhold		57%	51%	10

psychiatric diseases, among them, multiple sclerosis (Ebers et al., 1986, 1995; James, 1996), autism (Bailey et al., 1995; Folstein & Rutter, 1977), schizophrenia (Gottesman, 1994), and attention deficit hyperactivity disorder (ADHD) (Sherman et al., 1997; Sutcliffe, 1988).

Other types of segregation analysis consider the relative risk among first-, second- and third-degree relatives of affected probands. The ratio of the risk to each class of relative is compared to the general population risk, expressed as the statistic λ_x. For example, λ_1 of 10 indicates that a first-degree relative of an affected individual has a tenfold higher risk of developing the disorder than does an unrelated individual in the same population. The more heritable the disorder the higher the value of λ_1. The more common the disorder in the general population, the lower is λ_1. This statistic serves as a rough guide to the tractability of a complex disorder for genetic analysis. Modest successes have now been achieved for complex human disorders such as schizophrenia, with λ_1 of about 10 (Table 2.1).

Genetic models

Further evidence of a genetic contribution can be provided by a distinctive pattern of transmission. For example, transmission of DMD from unaffected mothers to half of their sons strongly implicated the X chromosome, long before the dystrophin gene, or, for that matter, anything about DNA or the physical structure of any gene, were known. Identification of genetic patterns of transmission requires an explicit model against which to test data. There are two fundamentally different types of genetic model (Murphy & Chase, 1975). Neurologists are most familiar with the qualitative Mendelian model. An alternative Galtonian model has been used to describe quantitative traits, largely by agricultural and behavioural geneticists. Both models are simplifications, but are demonstrably useful in certain circumstances. Analysis of complex neurological and psychiatric diseases may require a synthesis of the two.

The Mendelian model posits that each phenoype is dichotomous. Either a bean is wrinkled or smooth, green or yellow. In Mendelian disorders, an individual either has the disease or is well. The Mendelian model further posits that each trait is determined exclusively by a single gene represented by two alleles, which can be either identical (homozygous) or different (heterozygous) in a given individual. Each allele is either recessive or dominant with respect to expression of a given trait. Segregation of a mendelian dominant disorder such as Huntington disease can be be modelled by a single coin toss representing the allele a child receives from her affected parent, heads for the wild-type allele, tails for the mutation (Murphy & Chase, 1975). If one scores 1 for heads, there are only two possible outcomes: a score of 1 and she will be healthy, a score of 0 and she will get Huntington disease.

The Galtonian genetic model has been used for metric rather than dichotomous traits. For example, the weight of livestock is more accurately described as a continuum

rather than as a simple dichotomy of heavy or light. Genetic transmission of many metric traits behaves as if there were a large number of genes contributing to the phenotype (Falconer, 1960). An appropriate analogy is a coin tossing game with a hundred equally weighted coins, again scoring 1 for heads and 0 for tails (Murphy & Chase, 1975). In this game there are a large variety of possible outcomes ranging from 0 to 100. The distribution of expected winnings will approximate a normal distribution with a mean of 50. From the score, one is able to tell how many times one flipped heads, but one wouldn't be able to tell which particular coins did so. The agricultural geneticist studying the weight of livestock will be able to estimate the aggregate number of heavy alleles inherited by a given animal, but will be unable to determine in which genes these heavy alleles reside. Some disease states, such as hypertension, are more accurately modelled as a continuum rather than as dichotomous states. Even when diseases can be considered dichotomous, such as stroke, the severity, age of onset and susceptibility may be modelled along a continuum.

For many complex traits, reality is somewhere in between the extreme Mendelian and Galtonian models. Even though multiple genes affect susceptibility, they are unlikely to be of equal effect. A single gene of dominant effect, as occurs in a Mendelian disorder, would be represented by a silver dollar, ten genes of low effect modifying the course of the illness would each be represented by a penny. Possible winnings would be represented by two nonoverlapping normal distributions with means of 5 cents and $1.05. If disease threshold were 50 cents, only the toss of the silver dollar would determine if the person became ill. Furthermore, even though refined measurements might provide an estimate of the total number of modifying genes mutant in an individual, only the presence or absence of mutation in the single gene of major effect could be determined unequivocally.

It is likely that many complex genetic disorders result from alterations of a small number of genes with different degrees of influence. An appropriate analogy is a coin tossing game with pennies, nickels, dimes and quarters. The total score could be determined, but the outcome of any particular toss may be indeterminate. Similarly, mutation of a given susceptibility gene could be present in an unaffected individual or absent in someone affected by virtue of the remainder of the genome. Furthermore, the relative importance of a given gene may vary according to the environment. A gene affecting lipid metabolism may be an importantant determinant of stroke in those consuming a lot of animal fat, but have only negligible significance for vegetarians.

Gene identification

Gene identification in single gene disorders

Definitive proof of monogenic determination requires identification of a gene mutant in affected individuals and normal in those that are healthy. Pathogenic mutations have been identified by one of two general methods: one beginning with biology, the other with genetics. In certain disorders, biochemical definition of abnormal patterns of metabolites or storage products in diseased individuals led to identification of a defective enzyme and subsequent analysis of the encoding gene. This method has been most successful in the delineation of autosomal recessive neurological disorders occurring in infants and children (Online Mendelian Inheritance in Man, 2001).

Many neurological disorders occuring later in life do not leave leave a sufficiently clear biological signature for unambiguous identification of a mutant protein. This calls for an alternative strategy based on identification of the chromosomal location of the mutant gene. This approach of 'reverse genetics' was appropriately renamed 'positional cloning' (Collins, 1990). The favoured method has been linkage analysis in large families segregating the disorder in a Mendelian pattern (Ott, 1985). Naturally occuring variants in the DNA sequence are used as markers. Originally, these markers were polymorphisms of surface antigens or electrophoretic patterns of proteins, then restriction fragment length polymorphisms (RFLPs) (Botstein et al., 1980) and later more ubiquitous microsatellites or short tandem repeats (Bently & Durham, 1995). The chromosomal locations of these markers had previously been determined and assembled into maps. One by one the segregation of these markers is compared to the segregation of the disease phenotype in large families. Unlinked markers are transmitted from affected parent to affected offspring at random, on average, 50% of the time. Those markers in the immediate vicinity of the disease gene are transmitted to affected offspring more often than expected by chance, and are thereby linked.

The observed frequency of recombination, separation of the marker and the disease in offspring, is an estimate of the genetic distance between the two loci. This value is expressed as θ. Because estimates of genetic distance are subject to sampling error, the accuracy of the estimate is given as a likelihood, expressed as a lod score, logarithm of odds. For example, a family study reporting a maximum lod score of 3 for $\theta = 0.04$ to a marker means that it is 1000 times more likely that the true genetic distance between that marker and the pathogenic mutation is 4 centiMorgans (cM), than is the null hypothesis that the two

are unlinked. The larger the number of informative family members observed, the more accurate the estimate.

With current technology, most genome-wide scans are undertaken with about 300 markers, spaced roughly every 10 cM (Brzustowicz et al., 2000; Kehoe et al., 1999b; Morissette et al., 1999; Weeks et al., 2000). Areas of the genome that give positive signals are then re-examined with a denser array of markers confined to that region. In theory, it should be possible to resolve any genetic distance given a sufficient number of observed transmissions and informative meioses. However, there are practical limitations. Accuracy improves by a square of the number of informative meioses sampled. Precise definition of a disease-causing mutation by strictly genetic methods requires analysis of hundreds of thousands of meioses. In actual practice, the accuracy of human linkage studies is limited to about 2–3 cM, roughly 2–3 million base pairs. Current estimates of the total number of human genes have converged on about 30 000 (International Human Genome Sequencing Consortium, 2001; Venter et al., 2001), having previously ranged from 35 000 to 140 000 (Aparicio, 2000; Liang et al., 2000), distributed over the 3300 cM of the human genome. Therefore linkage analysis on practicable human sample sizes can only resolve down to the 20 to 30 genes within that region. Each of these genes becomes a 'positional candidate'. Sometimes this number can be whittled down further by identification of deletions or translocations, overlaps of which define a narrower critical region. In the absence of such physical rearrangements, biological clues such as tissue distribution and predicted gene function guide a series of guesses until a gene mutant only in affected individuals is found. The majority of monogenic disorders have been resolved by a combination of genetic and biological information.

When large families are unavailable, multiple smaller kinships are analysed under the assumption that the gene responsible for the disorder is the same in each family. This assumption proved valid for many neurological disorders, a tribute to the diagnostic precision afforded by clinical neurology. However, for many others, the assumption does not hold. Notably, the demyelinating forms of Charcot Marie Tooth disease, the limb–girdle muscular dystrophies, the adult-onset spinocerebellar degenerations as well as many other Mendelian neurological disorders proved to be genetically heterogeneous (Online Mendelian Inheritance in Man, 2001). Results from linkage data from several small families each segregating a phenotypically indistinguishable but genetically distinct spinocerebellar atrophy would cancel each other out. Ideally, this problem is avoided by the use of a single large family. However, if only small families are available, allowances for heterogeneity can be made, but only by increasing sample size (Lander & Botstein, 1986). Allowances also have to be made for age-dependent penetrance, with care taken not to score individuals as unaffected if below likely age of onset. These considerations, and others, also apply to complex disorders.

Gene identification in complex disorders

Linkage approaches similar to those for monogenic disorders have also been applied to genetically complex diseases, chiefly diabetes, asthma and psychiatric disorders (Brzustowicz et al., 2000; Morissette et al., 1999). However, despite many successes with monogenics, linkage analysis of complex traits has proven much more difficult. Even with strict diagnostic criteria and large samples, most of these linkage analyses have yielded only weak and irreproducible findings (Risch & Botstein, 1996). This failure could mean that even highly heritable common disorders are influenced by a very large number of genes, each of small effect, approaching a Galtonian model. If so, then their identification would be impossible by any feasible linkage study. However, the failures may simply be methodological.

If most of the susceptibility for a given disease results from a small number of genes with large or moderate effect, modifications of the linkage approach may prove successful. One such modification is a non-parametric technique, not requiring specification of a pattern of inheritance (Kruglyak et al., 1996). In the standard parametric linkage analyses used for monogenic disorders, one must specify whether the disease mutation segregates as a dominant or a recessive. In many complex disorders, this is not known. Furthermore, many gene effects are semidominant, a heterozygote is phenotypically distinguishable from either homozygote, unlike the classic Mendelian model (Falconer, 1960). One nonparametric linkage approach is the method of affected sibling pairs. Regardless of mode of inheritance, any marker shared by affected siblings more often than expected by chance must be linked to a susceptibility gene. The closer the marker to the disease gene, the more frequently will it be shared by affected individuals in a given family. The utility of this approach depends not only on the distance between the marker and the disease gene but also on the frequency of the disease allele in the population and the magnitude of its effect on disease susceptibility. In a favourable situation, for example, if individuals with a copy of a susceptibility allele were at four-fold or greater risk of developing

the disorder than were those without that allele, then several hundred sibling pairs are sufficient to establish linkage in a genome-wide search (Risch & Merikangas, 1996).

However, if the disease allele confers less susceptibility or is unusually rare or frequent in the population, linkage can only be established by analysis of tens or hundreds of thousands of sibling pairs. For this reason, alternatives to linkage analysis have to be considered.

The major alternative to linkage analysis in families is allelic association in populations: the presence of a marker allele more frequently in affected individuals than in matched controls from the same population. In properly designed studies, allelic association is more powerful than linkage analysis, detecting associations with genes of only modest effect (genotype relative risk of 1.5) in samples of only a few hundred individuals. In an association study, the goal is to find linkage disequilibrium (not to be confused with linkage analysis) between a marker and a disease-susceptibility gene. Linkage disquilibrium is based on the assumption that a significant proportion of disease susceptibility attributable to a given gene results from an ancestral mutation in a single individual (Jorde, 1995; Kruglyak, 1997). Markers are usually nucleotide polymorphisms in the immediate vicinity of an ancestral mutation, rather than the pathogenic mutation itself. Such markers are transmitted together with the disease allele until separated by recombination. Unless the marker happens to be a unique disease susceptibility mutation, the correlation between it and disease would not be perfect in present-day populations.

In present-day populations, some unaffected individuals with the marker will be descendants of the diseased ancestor, but will have had the marker and disease allele separated by recombination. Such an event can be recognised by the use of multiple markers arranged in a haplotype that brackets the disease susceptibility locus. Other unaffected individuals will have inherited the marker not from the diseased ancestor but from her unaffected sibling. Some affected individuals may not have the marker, either because of recombination or by virtue of having inherited a disease allele from another ancestor with a different background set of markers. For these reasons, the success of association studies depends not only on the proximity of the markers to the actual disease susceptibility locus, but also on the history of the population.

There are two major limitations to association studies, population stratification and the inability to survey beyond the immediate vicinity of the marker. Spurious associations can arise if the ethnicity of affected and control individuals is not matched carefully. For example, both sickle cell anemia and G6PD deficiency are more common in individuals of African and Mediterranean descent than they are in Northern Europeans. In a sample that included both Europeans and Africans, a G6PD marker would show a strong association with sickle cell disease even though the genes are on separate chromosomes. In such a case, allelic association is not an indication of linkage disquilbrium. An identical association study in sub-Saharan Africa would show no association.

A number of methods have been suggested to guard against spurious associations from population stratification (Pritchard & Rosenberg, 1999). However, their utility in population-based case control studies of allelic association of complex disorders resulting from genes of small to modest effect is still untested. An alternative to case-controlled population-based allelic association studies is the transmission/disequilibrium test (TDT) (Spielman et al., 1993), which is immune to errors of population stratification. In this test, nonrandom distribution of a marker from heterozygous parents to an affected offspring provides robust evidence of linkage disequilibrium to a disease susceptibility gene. A thousand trios of affected offspring with both parents should be sufficient in a genome-wide scan to identify markers in linkage disequilibrium with genes of modest effect (Risch & Merikangas, 1996).

The remaining limitation of TDT, as of all association studies, is that in most populations, linkage disquilibrium only extends for very short distances, tens of thousands of bases. Linkage analysis can be undertaken with markers separated by tens of centiMorgans, tens of millions of base pairs, from the disease locus, because the experiment only requires detection of cross-overs in a few generations. A complete linkage scan can therefore be accomplished with 300 markers. In contrast, association studies for linkage disequilibrium depend on the absence of recombination between marker and disease loci in the many generations that separate the study population from the ancestral mutation (Kruglyak, 1997). Thus, even a marker within the same gene but 100 kilobases distant from a pathogenic mutation may fail to show an association. A complete survey of the human genome by association might require testing of as many as 1 000 000 markers (Risch & Merikangas, 1996). The technology to accomplish this will likely require the use of a different type of marker, the single nucleotide polymorphism [SNP], detection of which is amenable to automation. A consortium to develop the necessary SNP markers is already under way (Gray et al., 2000). The technical and statistical problems posed by this

number of assays on hundreds of individuals are formidable, but soluble. Pooling of DNA from affected and unaffected individuals in case control studies followed by quantitation of allele frequencies in each of the two pools requires that an assay need only be done twice, rather than separately for each of hundreds of individuals (Germer et al., 2000; Shaw et al., 1998) Genotyping using dense oligonucleotide arrays on solid supports or other technologies will significantly increase throughput and reduce costs (Fan et al., 2000).

Presently, association studies are limited to analysis of a few candidate genes, selected because of a biological rationale. Many association studies will be mentioned in the sections on specific neurological diseases, but most of them have used single markers and a case-control rather than TDT design. Both negative and positive studies are thus suspect. Ideally, association studies should use TDT with a dense array of multiple markers spanning the gene of interest, something not yet done in most neurological studies. An excellent example of the candidate gene TDT approach has been the robust demonstration of association of ADHD with polymorphisms in the dopamine D4 gene (Muglia et al., 2000; Smalley et al., 1998; Tahir et al., 2000). The recent completion of a first rough draft of the human genome (Bentley, 2000; Butler & Smaglik, 2000; International Human Genome Sequencing Consortium, 2001; Venter et al., 2001) and increased understanding of pathophysiology of neurological diseases will aid in the selection of candidates for allelic association studies as will reference to tissue- or disease-specific patterns of gene expression made possible by high-density nucleotide arrays (Gaasterland & Bekiranov, 2000; Lee et al., 2000).

In addition to the top-down allelic association methods used in case-controlled population studies and TDT, the bottom-up approach of cladistic analysis may prove useful (Haviland et al., 1997; Templeton et al., 1987). In this approach, haplotypes constructed for a randomly selected population sample are used to construct trees, where each branchpoint represents an alteration of one marker. Comparisons of disease frequency are then made on either side of each branchpoint. A significant difference implies that the individuals on either side of the branchpoint must differ by the presence of a mutation affecting susceptibility. Although this method is mathematically more powerful than conventional association studies, it has not been used widely, in part because of the difficulties with accurate estimation of haplotypes and the use of population-based samples in which only a minority of individuals have a clinical phenotype of interest. However, cladistics may prove useful in very common neurological disorders such as stroke or migraine.

Neurological disorders with complex inheritance

In contrast to psychiatric and autoimmune disorders, the emphasis on neurological genetics has been on monogenic disorders. In the last two decades, in excess of 650 monogenic neurological disorders have been mapped. Of these, the responsible gene has been identified for over 460 (Hurko, 2001; Online Mendelian Inheritance in Man, 2001). Over two-thirds of these mapped disorders present in childhood, many of them autosomal recessive disorders such as Tay–Sachs disease for which biochemical analysis revealed an a enzymatic deficiency that was subsequently confirmed by sequencing of a mapped gene in affected individuals. Since homozygosity for many of these mutations precludes reproduction, the mutant alleles survive in the gene pool in the much larger reservoir of asymptomatic heterozygous carriers. Although the total burden of heritable neurological disease in children is low compared to that of adults, the number of discrete diagnoses is considerably higher (Childs, 1998).

In both single-gene and complex disorders, deleterious alleles can survive in the gene pool as dominants if serious disease only becomes manifest after child-bearing years. In contrast to the many rare, single-gene, autosomal recessive neurological diseases in childhood, the number of neurological diagnoses are in adults are fewer even though the total burden of neurological disease is higher. The genetic propensity for most of these diseases is complex. Some neurological diseases are grouped under the same diagnosis, such as Alzheimer's disease, even though they may result from any of a number of distinct genetic abnormalities.

As a general rule, genetic diseases of chidhood are rare, many and monogenic, those of adults are common, few and polygenic (Childs, 1998).

Adult-onset dementias

Some of the heterogeneity of adult-onset dementia is readily apparent clinically, as with multi-infarct dementia, vitamin B12 deficiency, hypothyroidism, Creutzfeld–Jacob disease or late syphilis. More careful clinical and pathological analysis further subdivides late-onset dementia into frontotemporal dementia, Lewy body dementia, Alzheimer's disease, and multiple rarer disorders. The genetic contribution to each of these disorders ranges from negligible to major. As shown in Table 2.2 several of these segregate as single-gene disorders. Allelic heterogeneity has been demonstrated for the amyloid precursor protein and tau genes, mutations of which can cause a variety of clinical phenotypes (Table 2.2).

Table 2.2. Single-gene adult-onset dementias

Disorder	MIM	Location	Gene product
(Early-onset) Alzheimer's disease 1, APP related	104300	21q21.3–q22.05	amyloid beta 4 precursor
Dementia, presenile, and cerebroarterial amyloidosis	104760 0.0005	21q21.3–q22.05	amyloid beta A4 precursor
Amyloid angiopathy (Dutch)	104760	21q21.3–q22.05	amyloid beta A4 precursor
(Early-onset) Alzheimer's disease 3	104311	14q24.3	presenilin-1, seven transmembrane domain protein
Alzheimer's disease, familial, with spastic paraparesis and unusual plaques	104311 0.0017	14q24.3	presenilin-1, seven transmembrane domain protein
(Early-onset) Alzheimer's disease 4	600759	1q31–q42	presenilin-2, seven transmembrane domain protein
Alzheimer's disease, familial, Type 5	602096	12p11.23–q13.12	association with transcription factor CP2; TFCP2 (189889)
Alzheimer's disease without neurofibrillary tangles	604154	3	
Hereditary frontotemporal dementia (FTD)	601630	17q21–q22	microtubule-associated protein tau; MAPT (157140)
Disinhibition–dementia–Parkinsonism–amyotrophy complex (DDPAC)	600274	17q21–q22	tau
Progressive subcortical gliosis (PSG) of Neumann	221820	17q21–q22	?
Parkinsonism-dementia with pallido-ponto-nigral degeneration (PPND)	168610	17q21–q22	tau
Multiple system tauopathy with presenile dementia	601875	17q21	tau
Familial British dementia; presenile dementia with spastic ataxia cerebral amyloid angiopathy, British type	176500	13q14	BRI 603904, integral membrane protein 2B; ITM2B
Creutzfeld–Jakob disease	123400	20pter–p12	prion protein (176640)
Cerebral autosomal dominant angiopathy with subcortical infarctions and leukoariosis [CADASIL]	125310	19q12	Homologue 3 of Drosophila NOTCH (600276)
Dementia, familial nonspecific	600795	3p11.1–q11.2	
Atherosclerosis, premature, with deafness, nephropathy, diabetes mellitus, photomyoclonus, and degenerative neurologic disease	209010		
Lewy body dysphasic dementia	127750		associated with allele of debrisoquine 4-hydroxylase (CYP2D6B)
ALS-Parkinson–Dementia complex	105500		
Ceroid lipofuscinosis, adult type (Kufs disease) (CLN4)	204300		

Autosomal dominant Alzheimer's disease is rare, accounting for only 0.3% of cases (Campion et al., 1999). Mutations of any of three genes account for the majority of these autosomal dominant cases (Table 2.2). All of these lead to early onset, by age 60 (Dartigues & Letenneur, 2000). The prevalence of early-onset Alzheimer's disease has been estimated to be 41.2/100 000 of which only 12.9% were autosomal dominant. In the same population survey, 56% of these autosomal dominant families were found to have a mutation of presenilin-1, and another 15% to have a mutation in amyloid precursor protein APP. Although the vast majority of Alzheimer cases have not been associated with mutations in either presenilins-1, -2 or APP, these rare families have

had great heuristic value in supporting a primary role for amyloid pathology.

In contrast, no simple inheritance pattern is evident in the more common late-onset Alzheimer's disease (AD). That notwithstanding, genetic factors play a major role in predisposition to AD, which has a λ_1 of 5. The only major susceptibility gene unequivocally identified to date is apolipoprotein E, with the presence of the E4 allele increasing the relative risk for AD by a factor of 4.5 in the heterozygous state (Scott et al., 1999). Although this was discovered in the course of linkage analysis, the positive marker was in linkage disquilibrium with apoE, and might not have been detected had a slightly more distant marker been used (Martin et al., 2000; Risch & Merikangas, 1997). However, the E4 allele is neither necessary nor sufficient for Alzheimer's disease: most apoE4 carriers do not dement and about one-half of Alzheimer's disease is not associated with apoE4 (Myers et al., 1996).

Furthermore, the effect of apoE is not specific for Alzheimer's disease, associations with ApoE 4 having been observed for susceptibility to Creutzfeld–Jakob disease (Amouyel et al., 1994), age of onset and susceptibility to Pick's disease (Farrer et al., 1995), susceptibility to schizophrenia (Harrington et al., 1995), age of onset of Huntington's disease in males (Kehoe et al., 1999a) though not disease susceptibility (Kalman et al., 2000), as well as poor outcomes after head trauma and intracerebral hemorrhage (Friedman et al., 1999; Horsburgh et al., 2000).

Although the total λ_1 for AD is 5, the gene-specific λ_1 for apoE is only 2, implying that a substantial part the genetic risk for AD results from other genes. It appears likely that there may be as many as 4 additional susceptibility genes for late-onset AD with effect comparable or greater than that of apoE (Martinez et al., 1998; Warwick Daw et al., 2000). Candidates include an alpha-2-macroglublin in 12p13.3–p12.3, supported in some studies (Blacker et al., 1998; Liao et al., 1998), but not others (Shibata et al., 2000); a perhaps unrelated gene in 12p11.23–q13.12 (Scott et al., 2000); very low density lipoprotein receptor encoded on 9p24 (Okuizumi et al., 1995); bleomycin hydrolase on 17q11.2 (Papassotiropoulos et al., 2000); interleukin 1α (Du et al., 2000); and certain variations of the mitochondrial genome (Hutchin & Cortopassi, 1995). Genetic studies with these candidates have either given mixed results or await confirmation.

Multiple sclerosis

Unlike the adult-onset dementias, no monogenic forms of multiple sclerosis have been reported. Although there may be initial diagnostic confusion presented by the clinical features of adult-onset spinocerebellar atrophies and hereditary spastic paraplegias (Durr & Brice, 2000) or with the radiographic appearance of CADASIL or some of the leukodystrophies, routine clinical evaluation easily distinguishes these Mendelian disorders from multiple sclerosis (Hutchin & Cortopassi, 1995).

Neverthess, this disorder is highly heritable, with a λ_1 of 30, five times that of late-onset Alzheimer's disease. Six per cent of MS probands have an affected first-degree relative, considerably in excess of that predicted by a population frequency of 3/10000. Monozygotic twins have a concordance rate of 25.9% compared to a 2.3% concordance rate in dizygotic twins, suggesting polygenic inheritance. The number of concordant twins in these studies is low, however, and the twin data need to be viewed with some circumspection (Ebers et al., 1995). Despite this apparently high heritability, three recently completed genome-wide linkage scans have failed to identify a susceptibility locus unequivocally (Ebers et al., 1995; Multiple Sclerosis Genetics Group, 1996; Sawcer et al., 1996). The strongest signals from these linkage studies clustered around the HLA region on chromosome 6p21. Even though the HLA locus contributes little to overall susceptibility, it has been clearly identified in a number of case-controlled and TDT studies that have demonstrated an association with HLA-DR2 alleles (Haines et al., 1998).

Weaker positive associations have been observed with interferon gamma in patients at low risk because of their HLA status (Goris et al., 1999; Vandenbroeck et al., 1998) and the I-cell adhesion molecule (Mycko et al., 1998). Severity of but not susceptibility to MS (Reboul et al., 2000) has been reported to be associated with a certain combination of interleukin-1beta and interleukin-1 receptor antagonist genes. An association has been reported with TNF-α, independent of the association with the nearby HLA region (Fernandez-Arquero et al., 1999) as has an association with the immunogobulin heavy chain region (Walter et al., 1991). Association studies with myelin basic protein (Wood et al., 1994) and complement factors 6 and 7 (Chataway et al., 1999) have been negative. Both the negative and positive associations deserve to be re-examined and other regions of the genome examined in larger populations with denser marker arrays. However, at present, there is no strong evidence to support the existence of any susceptibility genes of moderate or major effect other than HLA.

Parkinson's disease

Although there is little evidence for substantial genetic contribution to typical late-onset Parkinson's disease,

some early-onset disease is attributable to either monogenic or polygenic disorders. A rare autosomal dominant form of parkinsonism associated with dysautonomia and dementia has been associated with mutations of the alpha-synuclein gene (Polymeropoulos et al., 1996). An autosomal recessive juvenile-onset parkinsonian syndrome with atypical clinical features has been associated with mutations in the parkin gene (Kitada et al., 1998). Parkinsonian features can sometimes be seen in several other Mendelian disorders, including some of the dominantly inherited spinocerebellar atrophies associated with triplet repeat expansions (Durr & Brice, 2000); the X-linked Segawa syndrome resulting from mutations in GTP cyclohydrolase (Ischinose et al., 1994; Nygaard & Duvoisin, 1986); Filipino dystonia syndrome (Muller et al., 1990); as part of the phenotype of a single infant with tyrosine hydroxylase deficiency (Ludecke et al., 1996); in several of the syndromes associated with mutations in the microtubule tau gene (Lynch et al., 1994; Wijker et al., 1996); and in the X-linked Waisman syndrome of early-onset parkinsonism, megaencephaly and seizures (Gregg et al., 1991).

However, these rare Mendelian disorders can be distinguished readily from classic Parkinson's disease, a common disorder of late adult life with incidence of about 1/10000 (Bower et al., 1999; Tanner et al., 1999). A large twin study demonstrated no difference in concordance for monozygotic or dizygotic twins with late-onset Parkinson's disease (Tanner et al., 1999). The same study demonstrated a sixfold higher monozygotic concordance rate in those twins for whom disease onset was before age 50. These data imply that there is a significant genetic risk for early-onset disease, but none for typical late-onset Parkinson's disease. Segregation analysis has ruled out Mendelian inheritance as an explanation for occasional familial clustering of Parkinson's disease (Zareparsi et al., 1998). Biochemical and cell fusion studies have suggested that a non-Mendelian susceptibility factor might be mitochondrial DNA (Swerdlow et al., 1996), a plausible hypothesis for which the evidence remains inconclusive.

Epilepsy

Although described by Hippocrates as a familial disease, epilepsy is present in siblings in only a minority of families (Baraitser, 1982). Heritability differs by seizure type and age of onset. For idiopathic grand mal epilepsy beginning before age 35, the concordance rate for MZ twins is 0.30 and for DZ twins it is only 0.13 (Miller et al., 1999) whereas for late-onset cases there is no significant difference. Overall, the frequency in close relatives ranges from 3 to 6%, compared to a general population risk of 0.5% (Alstrom, 1950). Febrile seizures have a recurrence rate of 0.39 in MZ twins and 0.12 in DZ twins, indicating significant heritability. The frequency of febrile seizures in siblings is 20% (Frantzen et al., 1970), compared to a general population risk of 3% (Baraitser, 1982). Other studies suggest common genetic factors for febrile convulsions, temporal lobe epilepsy and early status epilepticus (Baraitser, 1982).

Some of this familial clustering results from rare monogenic disorders that segregate as simple Mendelian traits (Table 2.3). However, a larger number of cases appear to result from multigenic inheritance. Susceptibility loci have been mapped, but genes not yet identified. (Table 2.4). In some types of epilepsy, there are a few genes of major effect, none of which is either necessary or sufficient to cause the disorder. In nocturnal frontal lobe epilepsy the effects of two single genes were so strong that they were located with a modified Mendelian model, with allowances for low penetrance (Phillips et al., 1995) (Table 2.3). In contrast juvenile myoclonic epilepsy proved more difficult to map using a Mendelian model, but more tractable using a complex genetic model (Elmslie et al., 1997; Greenberg et al., 2000) using which, two susceptibility loci have been identified. Reduced penetrance in a Mendelian model and complex genetics can simply be different ways of modelling the same reality.

Migraine

The genetics of migraine has proven difficult in part because of the high prevalence of this disorder, with a lifetime incidence of 33% in women and 13.3% in men (Launer et al., 1999). Studies in monozygotic and dizygotic twins raised either together or apart, have yielded heritability estimates of 52% (Ziegler et al., 1998). Twin studies of migraine with aura show a concordance rate of 34% in MZ twins and only 21% in DZ twins, similar to that of non-twin siblings (Ulrich et al., 2000). In migraine without aura, the concordance ratios were similar: 28% in MZ and 18% in DZ twin pairs (Gervil et al., 1999). Although many MZ twin migraineurs are concordant for the presence or absence of aura, a significant proportion are not (Kallela et al., 1999). Rare severe forms of migraine with aura, familial hemiplegic migraine, have been shown to be monogenic disorders. Fifty per cent of these families have mutations of the CACNL1A4 gene on chromosome 19p13 (Ophoff et al., 1996). The same locus appears to contribute to some cases of non-hemiplegic migraine, either with or without aura. There are at least two other monogenic forms of hemiplegic migraine, one of which has been mapped to chromosome 1q31 (Gardner et al., 1997). There is evidence

Table 2.3. 'Monogenic' epilepsy syndromes

Disorder	OMIM	Locus	Gene
Benign adult familial myoclonus epilepsy (BAFME; FAME) (autosomal dominant)	601068	8q23.3–q24.11	
Benign neonatal convulsions, type I (BFNC1) (autosomal dominant)	121200	20q13.3	potassium channel, voltage-gated, subfamily Q, member 2; KCNQ2 (602235)
Benign neonatal convulsions, type II (EBN2; BFNC2) (autosomal dominant)	121201	8q24	potassium channel, voltage-gated, subfamily Q, member 3 KCNQ3 gene (602232
Idiopathic generalized epilepsy (EGI)	600669	8q24	? allelic to EBN2
Benign familial infantile convulsions BFIC (autosomal dominant)	601764	19q	
Benign Rolandic epilepsy; Centrotemporal epilepsy	117100		(mouse gene found on 9)
Childhood Absence Epilepsy 1 (ECA1)	600131	8q24	
Childhood Absence Epilepsy 2 (ECA2)	600131	5q31.1–q33.1	gamma-aminobutyric acid receptor, gamma-2 (GABRG2) (137164)
Febrile convulsions, familial, 1 FEB1 (autosomal dominant, penetrance 60%)	602476	8q13–q21	
Febrile convulsions, familial, 2 FEB2 (autosomal dominant)	602477	19p13.3	
Febrile convulsions, familial, 3 FEB3 (autosomal dominant)	604403	2q23–q24	
Generalized epilepsy with febrile seizures plus; GEFS+, TYPE 1 (autosomal dominant)	604236	19q13	voltage-gated sodium channel beta-1 subunit gene (SCN1B) (600235)
Generalized epilepsy with febrile seizures plus, type 2; GEFS+, TYPE 2 (GEFSP2)(autosomal dominant)	604233	2q21–q33	alpha-subunit voltage-gated sodium channels (SCN1A)(182389)
Generalized epilepsy with febrile seizures plus, type 3; GEFS+, TYPE 3 (GEFSP3)	614233	5q31.1–q33.1	gamma-aminobutyric acid receptor, gamma-2 (GABRG2) (137164)
Nocturnal frontal lobe epilepsy ENFL 1 (autosomal dominant, low penetrance)	600513	20q13.2	neuronal nicotinic acetylcholine receptor, alpha polypeptide 4 (CHRNA4) (118504)
Nocturnal frontal lobe epilepsy ENFL 2 (autosomal dominant, low penetrance)	603204	15q24	close to the CHRNA3 (118503)/CHRNA5 (118505)/CHRNB4 (118509) cluster.
Nocturnal frontal lobe epilepsy ENFL 3 (autosomal dominant, low penetrance)	605375	1p21	Acetylcholine receptor, neuronal nicotinic, beta-2 subunit (CHRNB2) (118507)
Partial epilepsy (autosomal dominant)	600512	10q23.3–q24.1	
Reading epilepsy	132300		
Rolandic epilepsy and speech dyspraxia	601085		

Table 2.4. Susceptibility loci for epilepsy

Disorder	Susceptibility locus
Febrile convulsions, familial, 4 (FEB4)	5q14–q15
Idiopathic generalized epilepsy EGI	8q24
Idiopathic generalized epilepsy EGI	2q22–q23
Juvenile myoclonic epilepsy EJM1, Janz syndrome	6p
Juvenile myoclonic epilepsy EJM2	15q14

Table 2.5. Heritability of stroke

Aneurysm/SAH	$\lambda = 4.2$	(2.2–8.0)
Intraparenchymal hemorrhage	$\lambda = 2.39$	
Dissection	$\lambda = 6.3$	(2.2–18.3)
All ischemic	$\lambda = 1.4$	(1.1–2.0)
Large artery	$\lambda = 1.85$	
Lacunar	$\lambda = 2.53$	
heritability = 73%		
twin concordance = 61% MZ, 38% DZ		

for susceptibility loci on the X chromosome and elsewhere for non-hemiplegic migraine (Nyholt et al., 1998)

Genetic analyses have been undertaken not only for susceptibility but also for specific characteristics of the migraine syndrome. For example, preliminary observations suggest that predisposition to aura in migraineurs may be influenced by a locus on chromosome 6p (Gardner et al., 1997), predisposition to migraine-related strokes by variations in the mitochondrial genome (Nyholt et al., 1998), and the frequency of migraine attacks by a gene in the vicinity of angiotensin-converting enzyme (Martelletti et al., 1999).

Stroke

Although individually rare, there are a large number of Mendelian disorders associated with stroke, which have been reviewed extensively (Hassan & Markus, 2000; Natowicz & Kelley, 1987). Of particular interest is CADASIL, resulting from mutations of the notch3 gene (Viitanen & Kalimo, 2000) and homocystinuria, which can result from deficiency of any of several enzymes (Mudd et al., 1998). Although homozygotes for classic homocystinuria are very rare, heterozygotes are relatively common. An elevated plasma level of homocystine is a significant risk factor for stroke in the general population (Giles et al., 1998) but the relationship to specific genes has not yet been established (Kiely et al., 1993).

Except for these rare Mendelian disorders it is difficult to demonstrate a significant degree of heritability for stroke, in large part because of the high incidence in the general population. The sex-averaged relative risk of having a stroke by virtue of having an affected parent is only 1.9 (Kiely et al., 1993). Population studies demonstrate ethnic differences, which could either be genetic or environmental (Kiely et al., 1993; Reed, 1993). Although a twin concordance study has suggested an influence of genetic factors, generalizations from this small sample must be made with caution (Howard et al., 1994).

However, if stroke is subdivided by type, certain groupings appear to have a higher heritability than others (Table 2.5). A large number of association studies have been undertaken in an effort to identify susceptibility genes underlying ischemic stroke in the general population. Of these, studies with the fibrinogen gene have been positive, showing a modest but consistent effect, whereas studies with genes encoding other clotting factors have been either negative or irreproducible (Hassan & Markus, 2000). Complex genetic analyses of the stroke-prone spontaneously hypertensive rat have identified three distinct quantitative trait loci that account for most of the variance in incidence and severity of stroke (Jeffs et al., 1997; Rubattu et al., 1996) in these laboratory strains. The genes underlying such susceptibility remain to be identified, as does its relevance to human disease (Rubattu et al., 1999).

Myasthenia gravis

About 4% of myasthenics have an affected relative, higher than would be expected from a population prevalence of 2 to 4/100000. There is a sharp dichotomy in heritability between early- and late-onset forms (Online Mendelian Inheritance in Man, 2001). Forty-two per cent of familial cases have onset before 2 years of age, and perhaps are more appropriately described as myasthenic syndromes. Some of this familial clustering is not genetic, but results from maternal transmission of antibody, whereas others result from rare mutations affecting end-plate acetylcholinesterase or the alpha, beta or gamma subunit of nicotinic receptor. Infantile cases only account for 1% of all myasthenics.

Genetic susceptibility to the more common adult-onset form is complex. Some of this genetic susceptibility resides in the HLA region, particularly HLA-DR3 and -B8 (Janer et al., 1999), especially for females. The predisposing haplotypes are the same as for juvenile-onset diabetes mellitus, systemic lupus erythematosus and susceptibility to HIV

(Price et al., 1999). Other HLA associations have been reported for polymyositis and dermatomyositis (Rider et al., 1998). An association with myasthenia gravis has also been reported for the beta-adrenergic receptor (Xu et al., 2000). Although there has been no association independent of HLA between TNFβ and myasthenia (Manz et al., 1998), differences in this site may discriminate myasthenics with thymic hyperplasia from those with thymomas (Zelano et al., 1998). Similarly, there may be an allelic association between interleukin-10 and levels of circulating antinicotinic receptor antibodies in myasthenics but no association with disease susceptibility (Huang et al., 1999).

Pain

Weak associations with the HLA locus have been demonstrated for susceptibility to reflex sympathetic dystrophy (Huang et al., 1999) now renamed the complex regional pain syndrome. Rare instances of monogenic congenital insensitivity to pain have been mapped (Online Mendelian Inheritance in Man, 2001), and, in one instance, the mutant gene identified (Kemler et al., 1999).

However, the heritability of overall pain sensitivity in the general population is a low 10%, with MZ and DZ concordances almost identical. Genetic studies with inbred rodents tested for specific pain mechanisms have shown much higher heritability, attributable in most instances to a small number of genes of major effect (Mogil et al., 1999). Susceptibility to one type of painful stimulus can be either positively or negatively correlated with responses to other stimuli. Genetic analysis of mechanism-based pain susceptibility has yet to be undertaken in humans.

Sleep disorders

Several types of sleep disorder have been described, of which narcolepsy is the best understood. Strong association with the HLA region on chromosome 6 p21.3 has long been known (Mignot et al., 1997). The segregation pattern is complex. Mutations of orexin receptor 2, encoded by a gene on human chromosome 6p21, give rise to a monogenic narcolepsy in dogs (Lin et al., 1999). To date, mutations in the orexin receptor 2 gene have not been reported in humans with narcolepsy although low CSF levels of orexin are common (Nishino et al., 2000). It appears that the proximity of the two genes is fortuitous, and orexin deficiency in most cases of narcolepsy may be the result of immune attack on the hypothalamus. A mutation in the preproorexin gene has been reported in a single case of atypical narcolepsy (Peyron et al., 2000), but this mutation appears exceptional.

Other types of sleep disorder have been shown to segregate as simple Mendelians traits: rare instances of fatal familial insomnia, an autosomal dominant disease resulting from mutations of the prion protein gene (Harder et al., 1999) and a circadian rhythm disturbance (Toh et al., 2000). Genetic definition of other sleep disorders will depend in part on a better definition of phenotype.

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3

Repeat expansion and neurological disease

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Repetitive DNA sequences are abundant in the human genome, scattered throughout the regions between genes and, in some cases, within genes. They take the form of minisatellites (repeat sequences ranging in length from tens to hundreds of nucleotides) and microsatellites (repeat sequences consisting of one to several nucleotides in length) and have an intrinsic genetic instability that results in frequent length changes (Charlesworth et al., 1994; Tautz & Schlotterer, 1994). Thus, mini- and microsatellites are highly polymorphic between individuals, a feature which has led to their extensive use in genetic research as markers in positional cloning of genes and also in forensic medicine for DNA-based identification, so-called 'DNA fingerprinting'. While the normal role of these sequences, if any, remains unclear, repeat sequences have gained a great deal of attention over the past decade because of their emerging role in human disease. In particular, expansions of repetitive sequences within genes are increasingly found to underlie hereditary neurological diseases. In this chapter we discuss mechanisms that have been proposed to generate repeat expansion, the relationship between repeat length and disease manifestations, and present a classification scheme for organizing trinucleotide expansion diseases. Finally, we discuss the clinical features, genetics, pathology and molecular pathogenesis of 16 currently recognized trinucleotide expansion diseases.

Anticipation

Neurologists have long recognized the clinical phenomenon of anticipation, the tendency of certain inherited neurological diseases to appear earlier in successive generations, often with more severe clinical manifestations. This phenomenon, which was described as early as 1918 in myotonic dystrophy (Fleischer, 1918) and subsequently observed in other neurodegenerative diseases, was at odds with the classical Mendelian genetic principle that mutations are stably passed on to offspring. Thus, for many years the phenomenon of anticipation was attributed to ascertainment bias. Then, in 1991, spinobulbar muscular atrophy and the fragile X syndrome were found to result from expanded trinucleotide repeats in their respective genes. Furthermore, these expanded repeats were found to be unstable, frequently becoming longer in successive generations. Since longer repeat expansions are generally associated with earlier disease onset and more severe disease, this provided a molecular basis for anticipation. Since then, this dynamic form of genetic mutation has been found to underlie an increasing number of inherited neurological diseases, most of which exhibit anticipation. In general, there is an inverse relationship between age of onset and length of the repeat expansion, and a direct relationship between expansion length and disease severity. In disorders with incomplete penetrance, such as fragile X syndrome, penetrance is also related to length of the expansion.

While anticipation is frequently associated with diseases caused by unstable repeat expansion, it varies markedly in degree, and in some diseases may not occur at all. Anticipation is most pronounced in myotonic dystrophy, but also readily observed in the spinocerebellar ataxias and Huntington's disease. Anticipation is generally not seen in spinobulbar muscular atrophy and oculopharyngeal muscular dystrophy. One feature of anticipation is the 'parent of origin effect'. This is the tendency for anticipation to be observed when the gene is passed on through a specific gender. The tendency may be greater with paternal transmission (e.g. Huntington's disease) or maternal transmission (e.g. myotonic dystrophy), a phenomenon that probably reflects the nature of the expansions underlying the respective diseases.

Mechanisms of repeat expansion

There is an emerging consensus that unusual secondary structures adopted by trinucleotide repeats are responsible for their inherent instability, provoking errors at multiple levels of DNA metabolism (Bowater & Wells, 2000). Errors introduced during DNA replication, DNA repair, and homologous recombination have been implicated as contributing to trinucleotide repeat expansion. The propensity of repetitive DNA sequences to adopt unusual secondary structures (hairpin loops for CAG, CTG, and CGG repeats; triple helices for GAA repeats) provides an explanation for two features of trinucleotide repeat expansion: (i) the threshold effect for repeat instability, and (ii) a greater tendency towards expansion of some trinucleotide repeats than others.

Replication-dependent strand slippage during DNA replication is the mechanism of repeat sequence instability most strongly supported by both in vitro and in vivo evidence. Strand slippage is believed to occur when transient dissociation of the primer and template strands is followed by misaligned reassociation of the complementary strands, resulting in 'slippage' of the nascent DNA to a new position on the template (Wells, 1996). Unusual secondary structures promote primer/template dissociation, probably by causing the DNA replication complex to pause in the vicinity of repeat sequences (Kang et al., 1995).

Nucleotide excision repair systems recognize DNA damage by sensing distortion of helical structure (Wood, 1996). The unusual secondary structures adopted by some trinucleotide repeat sequences are likely to induce this repair pathway. In addition, these structures may be recognized by the mismatch repair system (Modrich & Lahue, 1996). Studies carried out in prokaryotic systems provide evidence that these pathways may contribute to trinucleotide repeat instability (Bowater & Wells, 2000).

An additional mechanism that may contribute to repeat instability is the introduction of errors during homologous recombination. Several human haplotype studies implicated gene conversion and unequal crossing-over as mechanisms that may contribute to the expansions and contractions of CTG trinucleotide repeats observed in myotonic dystrophy (Tsilfidis et al., 1992; O'Hoy et al., 1993; Tishkoff et al., 1998). Three studies investigating the loss of a fragile X mutation between parent and offspring concluded that gene conversion was responsible, suggesting that CGG repeats may also promote errors in homologous recombination (Van den Ouweland et al., 1994; Losekoot et al., 1997; Brown et al., 1996).

Classification of repeat expansion diseases

Trinucleotide repeat expansion disorders may be divided into two types based on the location of the mutation within their respective genes (Paulson & Fischbeck, 1996; see Fig. 3.1). This classification is useful because the location of the mutation may have implications regarding the mechanism of pathogenesis. Type I disorders are those in which the expansion occurs in-frame within the coding region and results in an expanded stretch of amino acids within the gene product. Type II disorders are those in which the expansion occurs outside the coding region: either upstream of the coding sequence, downstream of the coding sequence, or within an intron.

In type I disorders the mutant gene is transcribed and translated normally but leads to production of a protein harboring an expanded repeat of a particular amino acid. The trinucleotide expansions in type I disorders tend to be modest, with a similar threshold for disease (36–40 trinucleotide repeats, with limited exceptions). To date, nine type I diseases have been identified, and in each case the mutant protein is endowed with a toxic 'gain of function'. In general, type I diseases are dominantly inherited (except spinobulbar muscular atrophy), tend to be of late onset, and manifestations are mostly limited to the nervous system.

Conversely, in type II disorders, the coding sequence remains unchanged and the protein product is normal, yet mutations in untranslated regions of the gene lead to abnormal transcription or RNA processing, often resulting in altered levels of gene expression. The trinucleotide expansions leading to type II disorders tend to be large, with hundreds to over one thousand trinucleotides. These mutations often result in 'loss of function' of the relevant gene. To date, seven type II disorders have been identified; most are multisystem disorders and tend to have younger ages of onset than type I disorders.

Type I trinucleotide expansion disorders

Polyglutamine diseases

We currently recognize nine neurodegenerative disorders that result from the same kind of mutation: expansion of a CAG trinuceotide repeat within the coding region of the disease gene. Since CAG is the codon for glutamine, the proteins encoded by these genes carry an expanded polyglutamine tract; thus, these nine disorders are known as the polyglutamine diseases. This list includes Huntington's disease (HD), dentatorubro-pallidoluysian

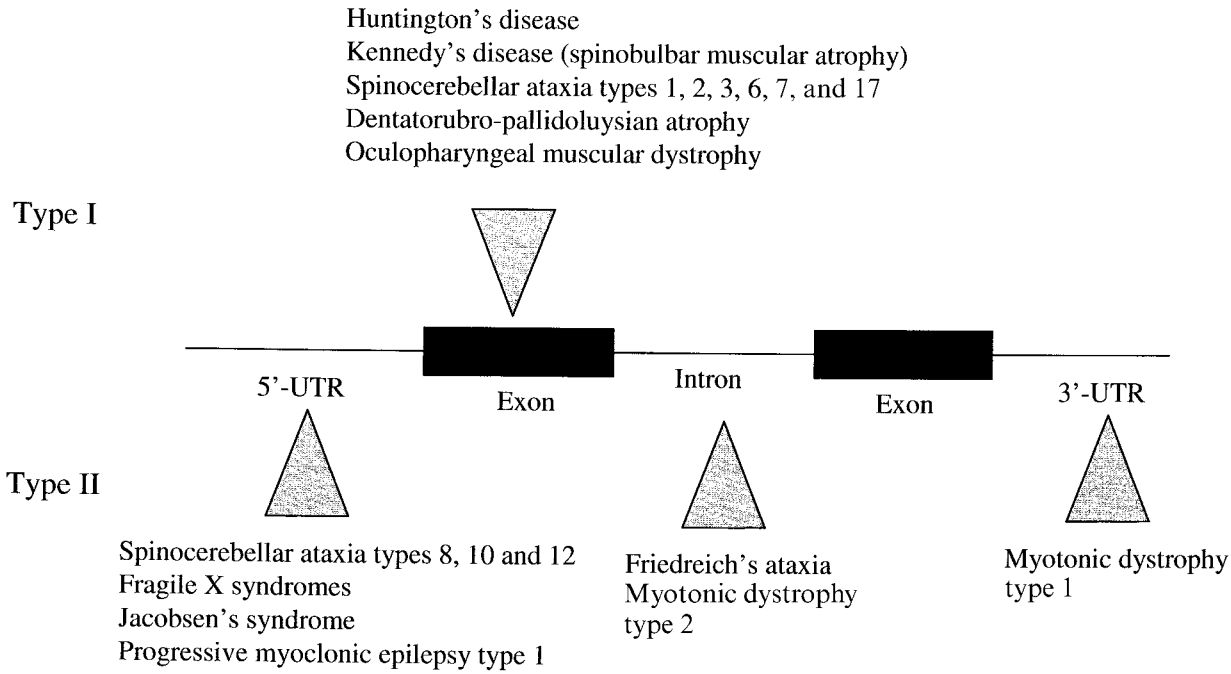

Fig. 3.1. Type I and type II repeat expansion diseases. In type I diseases, the expansion occurs within the coding region (exons) and results in an expanded stretch of amino acids in the mutant protein. In type II diseases, the expansion occurs outside of the coding region in introns, 3′ untranslated, or 5′ untranslated regions. (Adapted from Paulson & Fischbeck, 1996.)

atrophy (DRPLA), Kennedy's disease (also known as spinobulbar muscular atrophy, SBMA), and six spinocerebellar ataxias (SCAs 1, 2, 3, 6, 7 and 17). Evidence indicates that these eight diseases share a common pathogenic mechanism involving a toxic gain of function by the mutant gene product. Below, we present the clinical features and genetic basis of each of these disorders, followed by a general discussion of polyglutamine disease pathogenesis. The clinical features of HD and the SCAs are covered elsewhere in this book.

Huntington's disease

Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disease characterized by disordered movement, intellectual impairment, and emotional disturbance. HD is typically a late-onset illness, and it is invariably fatal (Myers et al., 1988). HD was the first autosomal disorder in which the gene was mapped using polymorphic DNA markers. The initial mapping to chromosome 4p16 was followed by a decade of intensive collaborative research that culminated in the identification of a novel gene (*IT15*, for 'interesting transcript 15') of unknown function containing a CAG trinucleotide repeat sequence in the first exon (Huntington's Disease Collaborative Research Group, 1993). The length of this CAG repeat sequence is polymorphic, with 6 to 35 CAGs in normal individuals, and 36 to 121 CAGs in individuals affected by HD. Examination of a large number of individuals carrying 30–40 repeats within *IT15* demonstrated that rare individuals become symptomatic with as few as 36 repeats while others show no sign of disease despite two alleles with 40 repeats (Rubinstein et al., 1996). This evidence demonstrates the incomplete penetrance of HD in the range of 35–40 repeats, while repeat lengths greater than 40 are invariably associated with disease.

Huntington's disease frequently demonstrates anticipation, with successive generations experiencing earlier age of onset and more severe disease than their parents. Anticipation is a consequence of intergenerational instability leading to further expansion of CAG repeat in *IT15* and is particularly associated with paternal transmission. Eighty per cent of patients with juvenile-onset HD, generally associated with alleles of more than 70 repeats, inherit the mutant gene from their father. A likely explanation for greater repeat instability associated with paternal transmission is the larger number of cellular divisions that take place during spermatogenesis.

Ultrastructural studies of HD brain tissue demonstrate both cytoplasmic and nuclear abnormalities in neurons.

The most notable features are ubiquitinated inclusions that are present in neuronal nuclei and dystrophic neurites throughout the brain regions most affected in HD, including the cortex and neostriatum but not in unaffected regions such as the globus pallidus or cerebellum (DiFiglia et al., 1997). These neuronal inclusions stain with antibodies directed to the amino-terminal portion of huntingtin, the protein product of *IT15*, but not with antibodies to the carboxy-terminus. Moreover, an amino terminal fragment of huntingtin of about 40 kD is detectable in nuclear extracts from patient brain and not in an extract prepared from normal brain (DiFiglia et al., 1997). Huntingtin is cleaved by caspases, cysteine proteases that play a significant role in mediating apoptosis. This observation led to the suggestion that low-grade caspase activation may generate toxic, amino-terminal fragments of mutant huntingtin that aggregate in the nucleus (Wellington et al., 2000).

Dentatorubro-pallidoluysian atrophy

In 1958, Smith et al., described a syndrome of progressive myoclonic epilepsy, ataxia, choreoathetosis, and dementia. They used the term 'dentatorubro-pallidoluysian atrophy' (DRPLA) to describe the most prominent neuropathological features; namely, extensive degeneration of the dentate nucleus, red nucleus, globus pallidus, and subthalamic nucleus of Luys. Rare in most parts of the world, a pocket of relatively high incidence of DRPLA is found in Japan (Naito & Oyanagi, 1982). The gene responsible for DRPLA was mapped to chromosome 12p by linkage analysis. Subsequently, because of phenotypic similarities to HD, genes from chromosome 12 were screened for CAG repeat expansions, a novel approach that culminated in identification of the *DRPLA* gene (Li et al., 1993; Koide et al., 1994; Nagafuchi et al., 1994).

Normal *DRPLA* alleles have 6–36 CAGs, while expanded alleles with 49–84 CAGs have been identified in symptomatic patients. Like Huntington's disease, intergenerational instability is more pronounced with paternal transmission (Koide et al., 1994). The product of the DRPLA gene is a widely expressed protein of approximately 190 kD named 'atrophin-1'. Atrophin-1 shares no homology with other known proteins, and its normal function remains unclear. Like huntingtin, atrophin-1 is cleaved by caspases, producing an amino-terminal fragment. Atrophin-1 is distributed through the cytoplasm in neurons and peripheral tissues of both unaffected and affected individuals (Knight et al., 1997; Yazawa et al., 1995). In addition, nuclear inclusions containing mutant atrophin-1 are found in neurons and glia of affected individuals, especially in degenerating regions of the brain (Hayashi et al., 1998; Igarashi et al., 1998).

Spinobulbar muscular atrophy

Spinobulbar muscular atrophy (SBMA), also known as Kennedy's disease, is an X-linked, slowly progressive disorder resulting from degeneration of motor neurons of the brainstem and spinal cord. Patients with SBMA also frequently exhibit mild signs of feminization (Arbizu et al., 1983). Gynecomastia is present in about half of patients, and some degree of infertility may occur. Pathologically, SBMA is characterized by degeneration of motor neurons in the anterior horn of the spinal cord and lower brainstem motor nuclei. Additionally, there is degeneration of sensory neurons in the dorsal root ganglia. Electrophysiological studies on SBMA patients demonstrate sensory neuropathy as well as neurogenic atrophy with fibrillations and fasciculations. Muscle biopsies show evidence of chronic denervation, often with collateral reinervation (Sobue et al., 1981, 1989; Harding et al., 1982).

In 1991, the cause of SBMA was found to be CAG trinucleotide repeat expansion within the first exon of the androgen receptor (AR) gene (La Spada et al., 1991). Normal alleles exhibit polymorphism with repeat length ranging from 9 to 36, while patients with SBMA have been identified with repeat sizes ranging from 40 to 62. In SBMA, anticipation is usually not observed. There is a correlation between repeat length and clinical manifestations, although as with other repeat expansion diseases, repeat length is not a reliable indicator of age of onset and disease severity (Doyu et al., 1992).

The AR is a member of the nuclear receptor superfamily. Like other steroid hormone receptors, it contains distinct domains for hormone and DNA binding. Upon binding of androgen in the cytoplasm, the receptor/ligand complex is transported to the nucleus where it activates the transcription of hormone responsive genes (Zhou et al., 1994). The AR is expressed widely in the brain, but most extensively in motor neurons of the spinal cord and brainstem where it may mediate a neurotrophic response to androgen (Ogata et al., 1994).

The polyglutamine tract is located at the amino-terminus of AR in a region distinct from the hormone and DNA binding regions. The function of the polyglutamine tract is not known, and it is dispensable for transactivation of hormone responsive genes (Jenster et al., 1991). Expansion of the polyglutamine tract may cause partial loss of receptor function and perhaps underlies the mild androgen insensitivity observed in SBMA. However, loss of function alone cannot account for the neurological features of SBMA, because complete absence of AR leads to androgen insensitivity (testicular feminization) syndrome, with no weakness or motor neuron degeneration. This

observation contributes to the argument that SBMA results from a toxic gain of function by mutant AR due to polyglutamine expansion. Heterozygous females carrying a single expanded allele sometimes report mild weakness or muscle cramps and may have subclinical electrophysiological abnormalities. These female carriers may be protected by low androgen levels (if the toxic effect is ligand dependent) or by X-inactivation. Similar to the observations in HD and DRPLA, intranuclear inclusions of mutant AR are found in motor neurons within regions affected by SBMA (Li et al., 1998).

Autosomal dominant spinocerebellar ataxia

The spinocerebellar ataxias (SCAs) are a genetically heterogeneous group of disorders that exhibit substantial overlap in clinical and neuropathological features. We currently recognize 14 genetically distinct forms of autosomal dominant spinocerebellar ataxia (SCA), five of which are caused by CAG repeat expansion and discussed in this section. SCA types 8, 10 and 12 are type II trinucleotide repeat disorders and are presented below. At least five additional genetic loci associated with the SCA phenotype have been identified (SCAs 4, 5, 11, 13 and 14), but the genes and their mutations remain to be determined. The designation SCA 9 remains unassigned.

Degeneration of the cerebellum and brainstem is common to all of the SCAs; consequently, cerebellar ataxia and dysarthria are the hallmark clinical features of these diseases (Zoghbi & Orr, 2000). Additional, variable features may lead the clinician to suspect a particular SCA subtype. For example, SCA1 patients show hyperreflexia, extensor plantar responses, and an increased amplitude of saccadic eye movements, while SCA2 is characterized by reduced saccadic eye movements and depressed or absent reflexes. Protuberant eyes, faciolingual fasciculations, and extrapyramidal signs are features of SCA type 3 (Durr et al., 1996a). SCA type 6 is generally a late-onset, pure cerebellar ataxia. SCA type 7 typically features a pigmentary macular degeneration that accompanies spinocerebellar degeneration. Nevertheless, definitive diagnosis of a particular SCA subtype requires genetic confirmation.

Spinocerebellar ataxia type 1

The SCA1 locus was narrowed by linkage analysis to 6p22–p23 (Zoghbi et al., 1991). When subsequently identified, the *SCA1* gene was found to contain a polymorphic CAG trinucleotide repeat within its coding region (Orr et al., 1993). Normal *SCA1* alleles carry from 6 to as many as 44 CAGs, but those with greater than 20 are interrupted by several repeats of CAT (Chung et al., 1993). Disease alleles, in contrast, contain longer CAG repeat stretches (39–82) and are uninterrupted by CAT sequences (Goldfarb et al., 1996). Marked intergenerational instability is observed, with paternal transmissions tending to produce expansions, whereas maternal transmissions actually tend to show contractions (Chung et al., 1993; Jodice et al., 1994; Ranum et al., 1994).

The *SCA1* gene encodes a ubiquitously expressed protein named 'ataxin-1' that shares no homology with other known proteins and is normally found in the nucleus and the cytoplasm. Ataxin-1 is highly expressed in the central nervous system including Purkinje cells and brain stem nuclei (Servadio et al., 1995). In SCA1 patients, mutant ataxin-1 localizes to large, solitary, nuclear inclusions in Purkinje cells and brainstem neurons (Skinner et al., 1997; Cummings et al., 1998). These inclusions stain positively for ubiquitin, components of the proteasome, and the molecular chaperone HDJ-2/HSDJ. Ataxin-1 likely plays a role in synaptic plasticity, because mice in which the *SCA1* gene has been disrupted have impaired spatial and motor learning, and decreased paired-pulse facilitation in the CA1 area of the hippocampus (Matilla et al., 1998). These *SCA1* 'knockout' mice do not develop ataxia, supporting the contention that *SCA1* is not caused by loss of normal ataxin-1 function. In an analogous observation in humans, large deletions spanning the *SCA1* gene lead to a syndrome of mental retardation and seizures, but do not result in an ataxic phenotype (Davies et al., 1999).

Spinocerebellar ataxia type 2

The *SCA2* gene was mapped by linkage analysis to chromosome 12q23–24.1 (Gispert et al., 1993), and the gene was subsequently identified by three independent groups and found to contain a CAG repeat (Pulst et al., 1996; Imbert et al., 1996; Sanpei et al., 1996). The CAG repeat in *SCA2* is less polymorphic than in the other genes that are involved in polyglutamine disease. Normal *SCA2* alleles have 15–31 CAGs, but 94% of alleles have 22 CAGs. *SCA2* disease alleles have 36–63 CAGs.

SCA2 encodes a widely expressed protein named 'ataxin-2' of approximately 140 kD that shares no homology with proteins of known function, although an ataxin-2– related protein has been identified (Pulst et al., 1996). Immunostaining of SCA2 brain specimens reveals cytoplasmic inclusions containing the mutant protein in Purkinje cells and dentate neurons, an observation that has also been made in a transgenic mouse model (Huynh et al., 2000).

Spinocerebellar ataxia type 3

Spinocerebellar ataxia type 3 (SCA3), also known as Machado–Joseph disease, was initially described among Portuguese–Azorean emigrants who settled in New England. Since then, this disease has been found worldwide in a variety of ethnic backgrounds, but it is especially prevalent in two islands in the Portuguese Azores (Nakano et al., 1972). The presence of SCA3 in regions with historically active sea-trade such as India, China, and Japan led to speculation that the worldwide distribution of the disease may be attributed to the travels of Azorean sailors in the late fifteenth and sixteenth centuries. In support of this suggestion, a worldwide haplotype study has demonstrated a founder effect, with the majority of non-Portuguese families sharing a disease haplotype with families from one Azorean island (Gaspar et al., 2001).

The *MJD1* gene was mapped to chromosome 14q (Takiyama et al., 1993) and subsequently identified by scanning a human brain library using an oligonucleotide probe designed to detect expanded CAG repeats (Kawaguchi et al., 1994). In normal alleles, the CAG repeat length ranges from 12 to 41, while disease alleles have 62 to 84 CAGs (Durr et al., 1996a; Maruyama et al., 1995). *MJD1* is somewhat unusual among the polyglutamine disease genes in that there is a distinct gap between normal and affected repeat sizes. Intergenerational instability is common and more pronounced with paternal transmission.

The *MJD1* gene encodes an approximately 42 kD protein of unknown function named 'ataxin-3' (Kawaguchi et al., 1994). Ataxin-3 is widely expressed in the brain, and regions of greatest susceptibility to degeneration do not show significantly higher ataxin-3 expression. In SCA3 brain specimens, ataxin-3 localizes to ubiquitinated nuclear inclusions in neurons from affected brain regions (Paulson et al., 1997). In addition, these inclusions are found to colocalize with components of the proteasome and cellular chaperones (Chai et al., 1999).

Spinocerebellar ataxia type 6

The mutation responsible for SCA6 is CAG repeat expansion in the *CACNA14* gene, which encodes the α_{1a}-voltage-dependent Ca^{2+} channel (Zhuchenko et al., 1997). The calcium channels formed by α_{1a} are abundant in the central nervous system, with highest levels in the cerebellum (Fletcher et al., 1996). While the seven other known polyglutamine diseases are associated with expansion beyond 36–40 CAGs, SCA6 has a lower disease threshold. Normal alleles of the *CACNA14* gene have 6–18 CAGs, and disease alleles have 21–33 CAGs (Matsuyama et al., 1997; Zoghbi 1997). SCA6 also differs from the other polyglutamine diseases in that the repeat expansion shows little intergenerational instability and anticipation is not observed.

Other mutations in the *CACNA14* gene are associated with two paroxysmal neurological disorders, episodic ataxia type 2 (EA2) and familial hemiplegic migraine (FHM) (Ophoff et al., 1996). Interestingly, both EA2 and FHM are sometimes associated with persistant, slowly progressive ataxia. In addition, naturally occurring mouse mutants known as *tottering* and *leaner*, which exhibit cerebellar atrophy, ataxia and seizures, have point mutations in the orthologous mouse *Cacna1a* gene (Fletcher et al., 1996). The autosomal dominant nature of these disorders suggests that a toxic gain of function may be responsible, but the mechanistic relationship of these disorders to SCA6 remains to be determined. It is also unclear whether altered function of the voltage-gated Ca^{2+} channel contributes to the pathogenesis.

Spinocerebellar ataxia type 7

Using a technique called 'repeat expansion detection' (RED) in which the polymerase chain reaction is used to scan genomic DNA for large trinucleotide repeats, a candidate region for SCA7 was located at chromosome 3p21.1–p12 (Lindblad et al., 1996). Subsequent positional cloning revealed the genetic basis of SCA7 to be expansion of a CAG repeat in a gene of unknown function (David et al., 1997). In normal *SCA7* alleles, CAG repeat lengths range from 7 to 35; and mutant alleles carry 38–200 CAGs (David et al., 1997; Johansson et al., 1998). SCA7 shows anticipation, with greater genetic instability associated with paternal transmission (Johansson et al., 1998). The protein encoded by the *SCA7* gene has been designated 'ataxin-7' and normally consists of 890 amino acids with a nuclear localization motif. Ataxin-7 is widely expressed in the brain and some peripheral tissues, but it is particularly enriched in regions susceptible to degeneration in SCA7 (Cancel et al., 2000; Lindenberg et al., 2000). Two studies have reported ubiquitinated neuronal intranuclear inclusions in the brain and retina of SCA7 patients (Holmberg et al., 1998; Mauger et al., 1999).

Polyglutamine expansion in TATA-binding protein (*SCA17*)

In addition to the eight genes responsible for the polyglutamine diseases listed above, a number of other human genes are known to contain polymorphic stretches of CAG

within the coding region. Many of these genes encode transcription factors in which the polyglutamine tract may mediate protein–protein interactions. The recognition that expanded stretches of polyglutamine can cause neurodegeneration has prompted examination of these genes in otherwise unexplained neurodegenerative disorders. In one Japanese patient, a young girl with progressive cerebellar ataxia, hyperreflexia, extensor plantar responses, atypical absence seizures and intellectual impairment, an expanded series of CAG and CAA repeats was identified in the gene encoding TATA-binding protein (Koide et al., 1999). The mutant allele from this patient encodes a stretch of 63 glutamines. In contrast, the patient's parents, who were neurologically normal, carried alleles encoding 35–39 glutamines. This disorder has now been identified in additional families and has been given the designation *SCA17* (Nakamura et al., 2001).

The molecular pathogenesis of polyglutamine disease

A common mechanism?

Four major lines of evidence suggest that the polyglutamine diseases share a common pathogenesis resulting from gain of function in the disease gene product, i.e. that the expanded polyglutamine confers upon the mutant protein a new property that is toxic to neurons. (i) The expanded polyglutamine tract is the only common feature among the genes responsible for these diseases. They share no other sequence homology, no common subcellular localization, and appear to be functionally unrelated. Yet, the phenotype of each disease is characterized by late-onset, slowly progressive neurodegeneration with clinical overlap. Furthermore, they share common pathological features, most notably ubiquitinated neuronal inclusions containing the mutant protein in brain regions susceptible to neurodegeneration. (ii) With the exception of SBMA, which is X-linked, all of these diseases exhibit dominant inheritance. In SBMA, female carriers may complain of cramps and be found to manifest subclinical electrophysiogical abnormalities suggestive of mild motor neuron disease. As mentioned above, female carriers of SBMA may be protected by X chromosome inactivation or low levels of androgen. (iii) A wide array of model systems has been developed, including cell culture and transgenic animal models, in which expression of the disease genes with repeat expansion recapitulates features of the diseases. Furthermore, transgenic expression of expanded polyglutamine in an unrelated protein (hypoxanthine phosphoribosyl-transferase) also results in neurodegeneration (Ordway et al., 1997). (iv) Naturally occurring and experimentally introduced mutations that cause loss of function in these genes do not recapitulate features of the diseases.

Targets of expanded polyglutamine

Examination of patient tissue, animal models, and in vitro systems has revealed a variety of biochemical pathways and cellular functions that may be altered by expanded polyglutamine (Fig. 3.2). A major challenge is to distinguish primary biochemical derangements caused by expanded polyglutamine from the secondary effects that surely follow. An added difficulty is to discern which alterations are fundamentally related to neuronal dysfunction and death. A primary molecular target of polyglutamine toxicity would be expected to have a novel or altered interaction with the mutant protein, due to altered physical properties resulting from the expanded polyglutamine. Two cellular processes stand out as particular candidates for primary disruption by expanded polyglutamine: transcription and the ubiquitin-proteasome pathway.

The inclusions formed by expanded polyglutamine recruit and sequester additional proteins, particularly proteins that normally contain polyglutamine tracts. One appealing hypothesis suggests that inclusions in the nucleus sequester and deplete factors critical to neuronal function and survival. Candidate targets in this model are transcription factors that are present in limiting quantities and contain polyglutamine tracts. Various transcription factors have been found to colocalize with nuclear inclusions, including CREB-binding protein (CBP), p53, TATA-binding protein, and nuclear receptor co-repressors (Perez et al., 1998; Boutell et al., 1999; McCampbell et al., 2000; Steffan et al., 2000). Furthermore, cell culture studies suggest that sequestration of CBP and p53 has functional consequences on transcriptional regulation. Depletion or altered function of transcription factors in human disease or animal models has yet to be demonstrated directly. Nonetheless, expression-profiling studies on brain tissue from HD and SCA1 mice suggest that altered transcription is an early event in polyglutamine pathogenesis (Luthi-Carter et al., 2000; Lin et al., 2000).

The ubiquitin–proteasome pathway is the primary biochemical means by which cells eliminate unwanted proteins. Proteins are targeted for degradation by covalent linkage to ubiquitin. Ubiquitination is the molecular signature enabling recognition by a family of chaperone proteins which facilitate the targeted protein's access to, and degra-

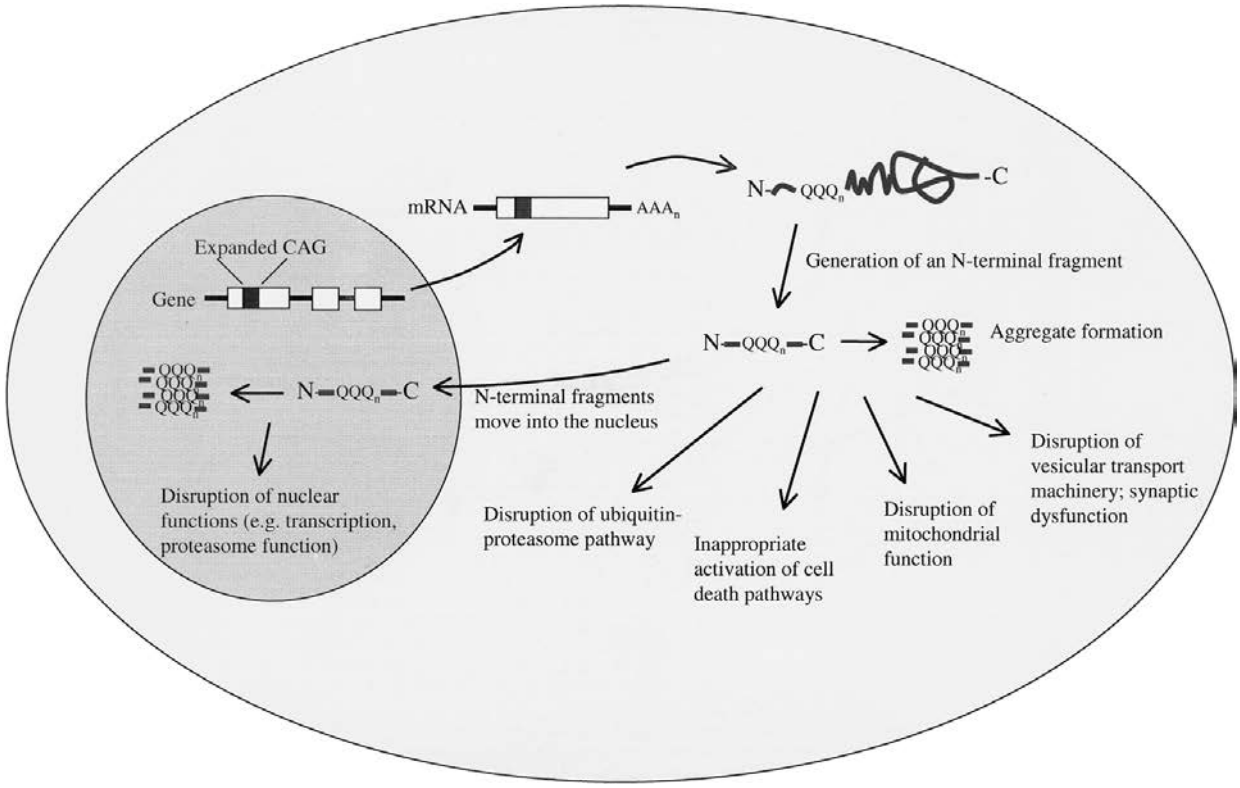

Fig. 3.2. Molecular pathogenesis of polyglutamine disease. The mutant gene with an expanded stretch of CAGs undergoes normal transcription and translation. The mutant gene product contains an expanded polyglutamine tract that confers a toxic gain of function. The mutant protein is susceptible to cleavage, releasing a polyglutamine-containing fragment. The polyglutamine-containing fragments form intracellular aggregates in the cytoplasm and nucleus. It remains unclear whether polyglutamine is toxic as full-length protein, as monomeric fragments, or as aggregate. An array of possible cellular targets is shown and discussed in the text.

dation by, the proteasome, a large macromolecular proteolytic apparatus (Ciechanover, 1997). Normal function of the ubiquitin–proteasome pathway is critical to determining the steady-state levels of many proteins. Additionally, this pathway is charged with rapidly eliminating nascent proteins that fail to adopt their correct structure, thereby protecting the cell from deleterious effects of misfolded proteins. Polyglutamine inclusions in brain specimens from human disease and animal models stain positively for components of the ubiquitin-proteasome pathway, including ubiquitin, chaperone proteins, and proteasome subunits (Paulson et al., 1997; Davies et al., 1997; Hackam et al., 1998). It remains unclear which components of the inclusions are ubiquitinated. The mutant proteins themselves may be ubiquitinated, but resist degradation because of a particular conformation adopted by expanded polyglutamine. Expanded polyglutamine may inhibit the proteasome, resulting in a global accumulation of ubiquitinated substrate with dire consequences for the cell. Neurons may be particularly susceptible to proteasome dysfunction because they are limited in their ability to dilute accumulating toxic proteins with cell division. Experimental evidence supporting a role for the ubiquitin–proteasome pathway in polyglutamine disease comes from a transgenic mouse study of SCA1. A genetic cross between a SCA1 mouse and a mouse with dysfunctional E6–AP ubiquitin ligase, and impairment of the ubiquitin–proteasome pathway, resulted in exacerbation of the neurodegeneration despite fewer inclusions (Cummings et al., 1999). There are precedents for neurological disease resulting from disruption to the ubiquitin–proteasome pathway: juvenile-onset Parkinson's disease, an autosomal recessive disease, is caused by mutations in the gene for parkin, an E3 ubiquitin ligase (Polymeropoulos, 2000). Angelman's syndrome, a developmental disorder that is characterized by motor and intellectual retardation, ataxia, hypotonia, epilepsy, and dysmorphic features, results from mutation in the gene for E6–AP, which is also an E3 ubiquitin ligase.

Other targets have been proposed for expanded polyglutamine. Ultrastructural examination of brain tissue from Huntington's patients shows mitochondrial abnormalities, and patients with HD have altered energy metabolism in brain and muscle, suggesting a role for mitochondrial dysfunction in this disease (Murphy et al., 2000). Mutant huntingtin has been found to associate with synaptic vesicles and vesicular transport machinery, implicating vesicular transport as a potential target of polyglutamine toxicity (Li et al., 2000). Electrophysiological studies of neurons from HD mice demonstrate abnormalities in synaptic transmission (Murphy et al., 2000). Much attention has focused on the potential role of apoptosis in mediating polyglutamine toxicity. Aside from a single report suggesting that mutant huntingtin activates caspase-8 (Sanchez et al., 1999), evidence is scant that components of the apoptotic machinery serve as a primary target for expanded polyglutamine. On the other hand, evidence is accumulating that caspases may play a role in mediating early events in toxicity. Many of the disease proteins contain consensus caspase cleavage sites. Evidence suggests that an important step in the pathogenesis of HD, SBMA, and DRPLA is caspase-mediated generation of polyglutamine-containing fragments that are more toxic than the parent protein (Ellerby et al., 1999; Wellington et al., 2000).

The deposition of misfolded proteins into neuronal inclusions is a central feature of many neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and the prion diseases. The importance of aggregation in these disorders has been underscored by the identification of three additional dominantly inherited neurodegenerative disorders that are characterized by intracellular aggregation of mutant α-synuclein (Polymeropoulos, 2000), neuroserpin (Davis et al., 1999), and tau proteins (Lee & Trojanowski, 1999). Deposition of misfolded protein in neuronal inclusions has emerged as a common theme in neurodegenerative diseases, perhaps indicating that these diseases also share common mechanisms.

What is the role of aggregation in the polyglutamine diseases?

One pathological feature shared by the polyglutamine diseases is the presence of intraneuronal, ubiquitinated inclusions in brain regions susceptible to degeneration. At the subcellular level, inclusions may be found in the nucleus (e.g. SCA1), cytoplasm (e.g. SCA2), or both (e.g. Huntington's disease). These inclusions consist of insoluble aggregates of polyglutamine-containing fragments in association with a host of additional proteins. Tracts of polyglutamine aggregate as antiparallel ß-strands linked by additional hydrogen bonding: so-called 'polar zipper' formation. There is a remarkable correlation between the threshold polyglutamine length for aggregation in experimental systems and the CAG repeat length that leads to human disease. These observations form the basis of the argument that self-aggregation by expanded polyglutamine is the acquired property underlying neurodegeneration (Perutz et al., 1994).

But are the inclusions themselves toxic? The dissociation of toxicity from inclusion formation observed in cell culture suggests that they are not (Saudou et al., 1998). A dissociation between inclusion formation and the development of pathology has also been demonstrated in transgenic mice (Klement et al., 1998; Leavitt et al., 1999). Some have suggested that inclusion formation may be a protective mechanism employed by the cell to cope with excess, misfolded polyglutamine, perhaps analogous to so-called 'aggresomes' which form in vitro in response to overexpression of misfolded protein (Johnston et al., 1998).

Oculopharyngeal muscular dystrophy

Oculopharyngeal muscular dystrophy (OPMD) has been recognized as a distinct entity since a report by Victor et al., in 1962, although case reports can be found in the literature dating from the early twentieth century. OPMD is an inherited myopathy that shares with the CAG repeat expansion diseases a similar type of genetic mutation and certain pathologic features. OPMD is inherited as an autosomal dominant disease of late onset. It occurs worldwide, although it is particularly prevalent among French Canadians. Patients typically present in the fifth or sixth decade with bilateral ptosis and dysphagia (Tome & Fardeau, 1994). In an attempt to compensate for severe ptosis, patients may contract the frontalis muscle and throw their head back, a position known as Hutchinson's or astrologist's posture. Unfortunately, this posture often has the unwanted affect of worsening the dysphagia. In late stages of the disease, the eyelids are very thin and transparent, the eyebrows are raised, and the supraorbital ridges are prominent. The disease is slowly progressive, and may eventually impair eye movements, occasionally causing diplopia. Instrinsic eye muscles are always spared. Along with dysphagia, patients may experience decreased palatal mobility, an impaired gag reflex, and laryngeal weakness with dysphonia. Skeletal muscles of the extremities may be affected by the disease, often resulting in shoulder-girdle weakness and atrophy. Involvement of limb muscles is symmetric and is not associated with fasciculations.

Tendon reflexes are typically decreased. Dysphagia predisposes patients to malnutrition and aspiration pneumonia.

The pathologic changes in skeletal muscle are progressive, and parallel the worsening clinical features. Biopsy reveals myopathic features, including increased variation in fibre size, internal nuclei, and interstitial fibrosis. There are often scattered small, angulated fibres that are strongly NADH positive. Two pathologic features help distinguish OPMD. Rimmed vacuoles, first described by Dubowitz and Brooke in 1973, appear as clear spaces lined by a granular basophilic rim. While these spaces are not membrane bound, they are likely derived from autophagic vacuoles. Ultrastructural examination has also revealed the presence of intranuclear inclusions (Tome & Fardeau, 1980). These inclusions are composed of aggregated tubular filaments that measure 8.5 nm in outer diameter and up to 0.25 μm in length. They contain the poly(A)-binding protein 2, the protein mutated in the disease (see below), and sequestered poly(A) RNA (Becher et al., 2000; Calado et al., 2000).

The French Canadian population provided a rich source of OPMD families that was important for the identification of the defective gene. After studying these families, Andre Barbeau concluded that the causative mutation was likely introduced into Quebec by ancestors who emigrated from France in 1634 (Barbeau, 1969). A genome-wide scan pointed to a critical region on 14q11 (Brais et al., 1995), which was further narrowed to a 0.26 cM candidate interval (Brais et al., 1998). Within this interval is the gene encoding poly(A)-binding protein 2 (PABP2), a nuclear protein that increases the efficiency of polyadenylation and specifies the length of the mRNA poly(A) tail (Barabino & Keller, 1999). The first exon of the PABP2 gene encodes a stretch of ten alanines, the first six of which are encoded by a GCG repeat. Rouleau and colleagues (Brais et al., 1998) demonstrated an expansion of this repeat in 144 families with OPMD, with the mutated tract containing 8 to 13 GCG triplets. This group of families came from 15 different countries, indicating that cases of OPMD occurring worldwide are caused by the same genetic mutation. Rare cases with two pathologically expanded alleles presented with an earlier onset of the disease (Blumen et al., 1999). This short repeat expansion differs from the longer CAG expansions in SBMA and other polyglutamine diseases in that it is meiotically stable, and therefore families with OPMD do not show genetic anticipation.

Two per cent of the French Canadian population carry a $(GCG)_7$ allele. This allele acts as a modifier of the disease phenotype by worsening symptoms in heterozygotes carrying one pathologically expanded allele. The $(GCG)_7$ allele also functions as a recessive mutation, causing late-onset disease in homozygotes (Brais et al., 1998). Thus, changes in GCG repeat length in the PABP2 gene account for cases of OPMD that are inherited in both a dominant and a recessive fashion.

The mechanism by which an expanded alanine tract leads to OPMD is unknown. One attractive hypothesis is that the mutated protein is prone to form insoluble aggregates, particularly in the nucleus where PABP2 is normally located. These aggregates may then disrupt cell function by mechanisms similar to those proposed for the polyglutamine disorders. Alternatively, as with the polyglutamine disorders, these intranuclear aggregates may be markers of disease that are not mechanistically related to cell injury. It may be that dominantly inherited cases of OPMD are due to haploinsufficiency. Intranuclear aggregates and rimmed vacuoles are also present in other muscle diseases that occur without a GCG expansion in the PABP2 gene, such as inclusion body myositis (Mezei et al., 1999). This may indicate that similar pathways leading to muscle injury are triggered in these diseases, although further studies are required to define this relationship.

Type II repeat expansion disorders

We currently recognize seven type II trinucleotide expansion disorders (see Table 3.1). These are inherited neurological diseases in which a trinucleotide repeat expansion occurs outside the coding region of the mutated gene. The expansions in this diverse group tend to be longer than those observed in the Type 1 diseases. Most often, these repeat expansions lead to reduced expression of the affected genes resulting in loss of gene function and a recessively inherited phenotype that may present early in life. In other instances, the disease phenotype is dominantly inherited, likely reflecting a toxic gain of function. The molecular mechanisms by which these expansions exert their effects are varied and complex.

Myotonic dystrophy

Myotonic dystrophy (DM) is a dominantly inherited multisystem disorder that was first described in the early twentieth century. It has a prevalence of approximately 1 in 8000 worldwide. The clinical presentation is highly variable, reflecting the diverse effects that the underlying mutation has on gene expression. Adult patients with DM often present in the second or third decade with slowly progressive disease. Typical cases are characterized by muscle weakness and wasting particularly involving the face and distal limbs, and by myotonia. Patients may have

Table 3.1. Trinucleotide repeat expansion diseases

Disorder	Gene/locus	Chromosomal location	Protein	Repeat Sequence	Repeat location	Inheritance
Type I						
Huntington's disease	IT15	4p16.3	Huntingtin	CAG	Coding	AD
Dentatorubro-pallidoluysian atrophy	DRPLA	12p13.31	Atrophin-1	CAG	Coding	AD
Spinobulbar muscular Atrophy (Kennedy's disease)	AR	Xq13–21	Androgen receptor	CAG	Coding	X-linked
Spinocerebellar ataxia Type 1	SCA1	6p23	Ataxin-1	CAG	Coding	AD
Spinocerebellar ataxia Type 2	SCA2	12.24.1	Ataxin-2	CAG	Coding	AD
Spinocerebellar ataxia Type 3	SCA3/MJD1	14q32.1	Ataxin-3	CAG	Coding	AD
Spinocerebellar ataxia Type 6	CACNA14	19p13	α_{1A} Subunit of voltage-dependent calcium channel	CAG	Coding	AD
Spinocerebellar ataxia Type 7	SCA7	3p12–13	Ataxin-7	CAG	Coding	AD
Spinocerebellar ataxis Type 17	SCA17	6q27	TATA binding protein	CAG	Coding	AD
Oculopharyngeal dystrophy	PABP2	14q11	Poly-A binding protein	GCG	Coding	AD
Type II						
Fragile X syndrome	FMR1 (FRAXA)	Xq27.3	FMRP	CGG	5′-UTR	X-linked
Fragile XE mental retardation	FMR2 (FRAXE)	Xq28	FMR2	GCC	5′-UTR	X-linked
Spinocerebellar ataxia Type 8	SCA8	13q21	KLH1	CTG	5′-UTR	AD
Spinocerebellar ataxia Type 10	SCA10	22q13	Ataxin-10	ATTCT	9th intron	AD
Spinocerebellar ataxia Type 12	PPP2R2B	5q31–33	PP2A regulatory protein	CAG	5′-UTR	AD
Friedreich's ataxia	X25	9q13–21.1	Frataxin	GAA	1st intron	AR
Myotonic dystrophy	DMPK	19q13.3	Myotonic dystrophy protein kinase	CTG	3′-UTR	AD
Myotonic dystrophy Type 2	ZNF9	3q13–24	Zinc finger protein 9	CCTG	1st intron	AD

a characteristic facial appearance due to atrophy of the masseters, sternocleidomastiods, and temporalis muscle, with involvement of the extraocular muscles that produces ptosis, weakness of eyelid closure, and limited extraocular movements. In addition, the disease often has systemic manifestations, including cataracts, cardiac conduction defects, male frontal balding, testicular atrophy, insulin resistance, pilomatrixomas, and intellectual impairment. Congenital myotonic dystrophy has a more severe presentation with profound hypotonia and weakness from birth, poor feeding and respiratory distress. Cataracts and clinical myotonia are not evident at presentation. Congenital cases typically occur in the setting of maternal transmission from mildly to moderately affected female patients (Harper & Rudel, 1994). Muscle biopsies show an increased number of internal nuclei that are often arrayed in chains, sarcoplasmic masses, ring fibres, and type 1 fibre atrophy. Other myopathic changes may be present, especially in biopsies from patients with advanced disease.

DM is caused by a CTG repeat expansion in the 3′ untranslated region of a cAMP-dependent serine–threonine protein kinase, named 'DM protein kinase' (DMPK) or 'myotonin', one of several genes found at the disease locus 19q13.3 (Brook et al., 1992; Buxton et al., 1992; Fu et al., 1993; Mahadevan et al., 1992). The CTG repeat length is polymorphic in the normal population, varying between 5 and 37 CTGs. Patients with DM have between 50 and several thousand CTGs. The age of onset is inversely correlated with repeat length (Brook et al., 1992; Harley et al., 1992; Hunter et al., 1992; Mahadevan et al., 1992).

The mechanism by which this repeat expansion leads to disease is complex. It was initially hypothesized that loss of DMPK function led to DM, but mice with null mutations in the *DMPK* gene did not replicate the disease phenotype (Jansen et al., 1996; Reddy et al., 1996). When knockout mice were bred to homozygosity, complete loss of expression did result in a mild myopathy and cardiac conduction abnormalities, but not other features of DM, such as the hallmark myotonia (Berul et al., 1999). Several studies have found that expression levels of DMPK protein and mRNA are also decreased in patient muscle (Carango et al., 1993; Fu et al., 1992; Hofmann-Radvanyi et al., 1993). These data suggest that loss of DMPK function contributes to the disease, but is insufficient to account for the full spectrum of clinical manifestations observed in DM.

In addition to loss of DMPK function, the CTG repeat expansion alters the expression of other genes by various mechanisms, including disruption of RNA processing. *DMPK* transcripts that harbour expanded repeats accumulate in intranuclear clusters (Davis et al., 1997; Hamshere et al., 1997; Taneja et al., 1995). This abnormal retention of transcripts is associated with decreased DMPK RNA splicing and polyadenylation (Hamshere et al., 1997; Krahe et al., 1995; Wang et al., 1995). Defects in RNA processing may be caused by altered function of RNA-binding proteins that normally recognize CUG repeats. Several CUG-binding proteins have been identified (Timchenko et al., 1996). One of these proteins, CUGBP1, is involved in pre-mRNA splicing and has altered function in DM (Philips et al., 1998). Sequestration of this, or other RNA-binding proteins, may have widespread effects on gene expression, possibly contributing to the varied manifestations of the disease. In support of this RNA gain of function model, mice in which an untranslated CUG repeat is expressed as a transgene develop certain features of DM, including myotonia and myopathy (Mankodi et al., 2000).

The CTG expansion may also interfere with expression of genes near *DMPK* on chromosome 19. DM-locus-associated homeodomain protein (DMAHP/Six5) is a homeobox gene located close to the expanded repeat in exon 15 of the *DMPK* gene. DMAHP/Six5 mRNA expression in fibroblasts and myoblasts from DM patients is significantly decreased (Klesert et al., 1997; Thornton et al., 1997). This decreased expression may be mediated by methylation of a CpG island adjacent to the expanded repeat (Steinbach et al., 1998). Mice in which the *DMAHP/Six5* gene is disrupted develop cataracts but no apparent skeletal muscle abnormalities (Klesert et al., 2000; Sarkar et al., 2000), suggesting that DM is a contiguous gene disorder caused by altered expression of more than one gene. The CTG repeat expansion may also influence the expression of other nearby genes, including *DMR-N9/59*, a WD-repeat gene located telomeric to *DMPK* (Alwazzan et al., 1999; Jansen et al., 1995).

A phenocopy of myotonic dystrophy was described in a large family that lacks a CTG expansion in the *DMPK* gene (David et al., 1997; Ranum et al., 1998). This disease locus, called DM2, maps to chromosome 3q. Other patients with disease manifestations similar to DM but lacking an expansion in the *DMPK* gene also have been described (Ricker et al., 1994; Thornton et al., 1994). Some of these patients have been classified as having proximal myotonic myopathy (PROMM) to highlight clinical differences with DM (Ricker et al., 1994). The gene mutated in this disorder was recently identified as the zinc finger protein 9 gene (Liquori et al., 2001). The responsible mutation is an intronic tetranucleotide CCTG repeat expansion that results in RNA sequestration, consistent with a messenger RNA gain of function mechanism for both DM and DM2.

Fragile X syndrome

Fragile X syndrome, one of the most common forms of inherited mental retardation, has an estimated incidence of 1 in 4000 males and 1 in 8000 females (Warren & Nelson, 1994). It is inherited as an X-linked dominant trait with reduced penetrance. Those affected have mild to moderate mental retardation, with IQ scores ranging as low as 20 to 60. Clinical features may include hyperkinetic behaviour and concentration problems, and systemic manifestations such as macro-orchidism in males, and abnormal facial features with large ears and a prominent jaw.

Fragile X syndrome is associated with a folate sensitive fragile site at Xq27.3 (Giraud et al., 1976; Harvey et al., 1977; Sutherland, 1977). This cytogenetically defined alteration is caused by an expansion of a CGG trinucleotide repeat. The repeat falls within the 5′ untranslated region of the gene *fragile X mental retardation-1* (*FMR1*) (Kremer et al., 1991; Yu et al., 1991; Verkerk et al., 1991; Oberle et al., 1991). The *FMR1* gene, encompassing 17 exons and spanning

approximately 38 kb of DNA, is widely expressed in mammalian tissues (Ashley et al, 1993; Eichler et al., 1994b). In the normal population, the CGG repeat is polymorphic both in length, ranging from seven to 60 triplets, and in content, as it is variably punctuated by AGG triplets. These AGG interruptions contribute to the stability of the CGG repeat length, and their loss is associated with tracts that are prone to expansion (Fu et al., 1991; Eichler et al., 1994a, b; Kunst & Warren, 1994; Snow et al., 1993, 1994).

Full mutations in patients with fragile X syndrome contain over 230 CGG triplets. These large expansions are associated with DNA hypermethylation and decreased expression of the *FMR1* gene. Somatic mosaicism may affect both repeat length and methylation status. That loss of FMR1 protein (FMRP) is causative of fragile X syndrome is supported by the identification of patients who lack a cytogenetically identified fragile site, and who have deletions or point mutations in the *FMR1* gene (De Boulle et al., 1993; Wohrle et al., 1992). Full mutations are generally inherited through maternal transmission and arise from expansion of an unstable premutation that contains 60 to 230 repeats. These premutations expand during gametogenesis or very early embryonic development (Malter et al., 1997). In carrier females, premutations are unmethylated and give rise to normal levels of *FMR1* transcript and protein. The risk of premutation expansion to full mutation increases exponentially as the number of repeats increases from 65 to 100. Males with full mutations do not, as a rule, transmit alleles with very long expansions, and sperm from these patients have premutation length repeat expansions. These unusual genetics provide a mechanistic explanation of the Sherman paradox (Sherman et al., 1984, 1985; Fu et al., 1991), which states that fragile X transmission occurs through normal males, that their heterozygous daughters are not mentally retarded and have few or no fragile sites, but that by the next generation, a third of heterozygous females are mentally subnormal and contain fragile sites.

Loss of FMRP causes fragile X syndrome in humans, and its targeted deletion causes macro-orchidism and subtle learning and memory deficits in mice (Dutch–Belgian Fragile X Consortium, 1994). FMRP is located primarily in the cytoplasm, but it contains both a nuclear localization signal and a nuclear export signal, suggesting that it shuttles between these two compartments (Eberhart et al., 1996). The protein contains two types of RNA-binding protein motifs, two ribonucleotide K homology domains (KH domains), and clusters of arginine and glycine residues known as RGG boxes (Ashley et al., 1993; Siomi et al., 1993). These RNA-binding domains enable the binding of FMRP to RNA, as demonstrated by in vitro assays where it preferentially associates with poly(G) or poly(U). Its in vivo binding specificity and native targets remain unknown.

FMRP associates with ribosomes as a component of messenger ribonucleoprotein (mRNP) particles. Additional components of these mRNP particles include two autosomal homologues of FMRP, designated FXR1P and FXR2P, nucleolin, and at least three other proteins (Siomi et al, 1995; Zhang et al., 1995). In this context, FMRP may play a role in the export of specific mRNAs from the nucleus to the cytoplasm. Alternatively, FMRP may regulate the stability or translation of the mRNAs with which it associates. In either case, FMRP likely plays an important role in protein synthesis, and its loss may severely impact neuronal function during development and learning.

FRAXE, FRAXF, and Jacobsen syndrome

In addition to the folate-sensitive fragile site associated with fragile X syndrome (FRAXA), two other fragile sites are present distally on Xq. FRAXE at Xq28 is caused by amplification of a CCG repeat (Knight et al., 1993). In normal individuals, this region contains 6 to 25 triplets, whereas in FRAXE-positive mentally retarded patients there are more than 200 triplets. The expansion is associated with methylation of a nearby CpG island, and decreased expression of a putative transcription factor, designated FMR2 (Gu et al., 1996; Gecz et al., 1996). Distal to both FRAXA and FRAXE is a third folate-sensitive fragile site, designated FRAXF (Hirst et al., 1993). This site results from the expansion of a GCC repeat that is polymorphic in the normal population, ranging from 6 to 29 triplets (Parrish et al., 1994). Rarely, an expansion to several hundred triplets has been associated with developmental delay (Ritchie et al., 1994), but there is not a well-established correlation between FRAXF and human disease.

Mental retardation may be associated with fragile sites on autosomes as well. One such example is Jacobsen syndrome, a clinically complex disorder with manifestations that include psychomotor retardation and trigonocephaly (Jacobsen et al., 1973). The disorder is due to deletions of the long arm of chromosome 11, typically from 11q23 to the telomere, with subsequent loss of numerous genes. Jacobsen syndrome is associated with a folate-sensitive fragile site at 11q23.3, designated FRA11B. As with other fragile sites, this cytogenetic abnormality is caused by the expansion and hypermethylation of CCG repeats. For Jacobsen syndrome, the triplets fall within the 5′ end of the gene encoding the proto-oncogene *CBL2* (Jones et al., 1995). Here, the fragile site may predispose to chromosome breakage, resulting in profound clinical consequences.

Progressive myoclonus epilepsy type 1

Progressive myoclonus epilepsy type 1 (EPM1), also known as Unverricht–Lundborg disease or Baltic myoclonus, was separately described by Unverricht and Lundborg in cases from Estonia and Sweden, respectively, near the turn of the last century. It is an autosomal recessive disorder that occurs worldwide, but is particularly prevalent in the Baltic and western Mediterranean regions. EPM1 is also the major cause of progressive myoclonus epilepsy in North America (Lehesjoki & Koskiniemi, 1998).

EPM1 has its onset in childhood, typically between the ages of 6 and 13 years (Lehesjoki & Koskiniemi, 1998). The myoclonus may generalize to shaking attacks and usually progresses to tonic–clonic seizures. Later in the course of the disease, patients may exhibit ataxia, intention tremor, and dysarthria. A slow cognitive decline and emotional lability are often seen. EEG abnormalities are present in patients even before the onset of symptoms, and characteristically manifest as symmetric, generalized and high-voltage spike and wave and polyspike and wave paroxysms. Other laboratory tests are generally unrevealing, except for increased urinary excretion of indican.

EPM1 is associated with severe diffuse Purkinje cell loss and Bergmann's gliosis (Hanovar & Meldrum, 1997). Surviving Purkinje cells are swollen and vacuolated. Mild to moderate neuron loss also occurs in the cerebral cortex, striatum, medial thalamic nucleus, brainstem nuclei, and spinal motor neurons. No Lafora bodies are present, indicating that EPM1 and Lafora disease are both pathologically and genetically distinct (Labauge et al., 1995).

EPM1 is caused by mutations in the *CSTB* gene, which encodes cystatin B, a cysteine protease inhibitor. Uncommonly, point mutations in the coding region result in protein truncation (Pennacchio et al., 1996). More often, expansions of a 12-nucleotide repeat in the 5′ untranslated region result in reduced mRNA expression (Lalioti et al., 1997; Lefreniere et al., 1997, Virtaneva et al., 1997). While normal alleles contain two to three copies of this 12-mer repeat unit, mutant alleles contain more than 60 copies. Unstable premutations containing 12–17 repeats are prone to expansion but do not cause clinical symptoms. That EPM1 is caused by the loss of cystatin B expression is further supported by the targeted disruption of this gene in mice, which causes progressive ataxia and myclonic epilepsy (Pennacchio et al., 1998).

Spinocerebellar ataxia type 8

The spinocerebellar ataxia type 8 (SCA8) locus at 13q21 was identified in a family with an undefined form of adult-onset, autosomal dominant spinocerebellar ataxia (Koob et al., 1998, 1999). The identified expansion consisted of 80 CAG triplets followed by 11 TAG triplets. DNA from a collection of ataxia families was then screened, leading to the identification of seven other affected kindreds carrying this expansion. The largest of these families, with 7 generations and 84 members, was evaluated clinically and genetically. All affected family members were found to have the expansion, yielding a maximum lod score for linkage between ataxia and the expansion of 6.8 at $\theta = 0.00$. In this and other kindreds (Ikeda et al., 2000), disease onset was in adulthood, ranging from 18 to 73 years, with symptoms including limb and truncal ataxia, ataxic dysarthria, and horizontal nystagmus. Disease manifestations were slowly progressive, and only severely affected individuals were non-ambulatory by the fourth to sixth decades. MRI scans revealed marked cerebellar atrophy.

Characterization of transcripts from the SCA8 locus indicate that the repeat expansion is near the 3′ end of an RNA that lacks an extended open reading frame (Nemes et al., 2000). The expansion is transcribed in the CTG orientation, complementary to the CAG repeat found in other spinocerebellar ataxias and reminiscent of the expansion in myotonic dystrophy (Koob et al., 1999). The 5′ exon of the SCA8 transcript is complementary to the first exon of another gene that is transcribed in the opposite orientation. This gene encodes a novel actin-binding protein that is primarily expressed in brain, named Kelch-like 1 (KLH1). The arrangement of these two genes suggests that the SCA8 transcript may be an endogenous antisense RNA that regulates the expression of KLH1.

Caution should be observed in interpreting whether expansion at the SCA8 locus is causative for the disease. In the large SCA8 kindred originally described, both the CTG and adjacent CTA repeats were polymorphic, and were expanded to 110–130 combined repeats in affected individuals. Normal alleles were found to carry 16–91 combined repeats. Several studies (Stevanin et al., 2000; Worth et al., 2000; Vincent et al., 2000) have since confirmed that the vast majority of control alleles (over 97%) have a small combined CTG/CTA repeat length, ranging from 3–31. However, in each of these studies, rare expanded alleles were also identified in the control population and in patients with other neurologic disorders. Very large expansions to hundreds of repeats were also observed in unaffected members of SCA8 kindreds and in a CEPH reference family. These data have raised the question whether the repeat expansion is causative for the disease or only linked to the causative mutation. If the expansion is involved in disease pathogenesis, then the reduced penetrance of the SCA8 phenotype and ranges for normal and pathologic expansions need to be explained.

Spinocerebellar ataxia type 10

Spinocerebellar ataxia type 10 (SCA10) is an autosomal dominant form of spinocerebellar ataxia associated with seizures. The disease locus was originally mapped to a 15 cM region at 22q13 (Zu et al., 1999). Matsuura et al., (2000) identified large expansions of an ATTCT pentanucleotide repeat in five Mexican SCA10 families. This pentanucleotide repeat is polymorphic in normal controls of European, Japanese and Mexican descent, and ranges in length from 10 to 22. In patients with the disease, there is a marked expansion to upwards of 4500 repeats. The pentanucleotide repeat is present within intron 9 of a gene of unknown function, designated *SCA10*, that is widely expressed within the mammalian brain. The mechanism by which the repeat expansion causes the diseases is unknown, and the possibility that it represents a rare polymorphism in linkage disequilibrium to the true pathogenic mutation has not been formally excluded.

Spinocerebellar ataxia type 12

Spinocerebellar ataxia type 12 (SCA12) is an autosomal dominant form of spinocerebellar ataxia identified in a single, large pedigree of German descent (Holmes et al., 1999). Clinical onset ranged from 8 to 55 years. Most patients presented in the fourth decade with a slowly progressive illness initially characterized by upper extremity tremor. The disease typically progressed to include head tremor, gait ataxia, dysmetria, dysdiadokinesis, hyperreflexia, paucity of movement, abnormal eye movements, and, in the oldest patients, dementia. MRI and CT scans of five cases revealed cortical and cerebellar atrophy. No pathological studies have been reported.

Like other autosomal dominant spinocerebellar ataxias, SCA12 is defined based on the involvement of a distinct genetic locus. Using a PCR-based strategy (Schalling et al., 1993; Koob et al., 1998; Holmes et al., 1999), a novel CAG repeat expansion was identified in the proband and other affected family members of the German pedigree. The range of expansion was relatively narrow (66–78 CAGs), and distinct from that observed in 394 normal subjects and 1099 disease controls (7–28 CAGs). In affected individuals, there was no apparent correlation between repeat length and age of onset, although the precise age of onset was often difficult to define and the expansion range in this pedigree was narrow.

The SCA12 CAG repeat is located 133 nucleotides 5′ of the apparent transcriptional start site of the gene encoding a brain-specific regulatory subunit of protein phosphatase PP2A, known as *PPP2R2B*, which has been mapped to 5q31–5q33. The use of an alternative transcriptional start site 5′ of the CAG repeat was suggested by the identification of a mouse brain EST derived from this region, and by the identification of promoter elements upstream of the repeat. As such, the repeat expansion may affect expression of this PP2A regulatory subunit, thereby altering PP2A function in the brain. Alternatively, the repeat may lie within an as yet unidentified overlapping or adjacent gene, or it may be in linkage disequilibrium with the causative mutation.

Friedreich's ataxia

Friedreich's ataxia (FRDA) is an autosomal recessive, multisystem degenerative disorder affecting approximately 1 in 40 000 individuals in the United States. The principal feature of FRDA is progressive gait and limb ataxia (Harding, 1981). Other commonly associated neurological features include cerebellar dysarthria, sensory loss, distal weakness, pyramidal signs, and absent reflexes in the lower limbs (Durr et al., 1996b). Disease onset is usually before age 25, and the symptoms are progressive. Skeletal deformities, diabetes, and progressive hypertrophic cardiomyopathy are found in many patients (Sanchez-Casis et al., 1977). This later aspect of the disease often contributes to mortality.

The neurological manifestations of FRDA reflect the distribution of pathology within the nervous system. FRDA is characterized by widespread neuronal degeneration within the central nervous system, but the hallmarks are atrophy of the posterior columns of the spinal cord, loss of deep cerebellar nuclei and efferent cerebellar pathways and degeneration of distal corticospinal tracts. In the peripheral nervous system, loss of sensory neurons is observed in the dorsal root ganglia (Hewer, 1968; Lamarche et al., 1993).

FRDA results from mutations causing loss of function of the *FRDA* gene at chromosome 9q13 (Campuzano et al., 1996). The vast majority of these mutations (more than 95%) are expansions of a guanine–adenine–adenine (GAA) trinucleotide repeat in the first intron of *FRDA*. The causative nature of *FRDA* mutations was verified by the identification of patients carrying one expanded allele and one allele with a point mutation (Campuzano et al., 1996; Durr et al., 1996b). No patients with point mutations in both alleles have yet been reported. The length of the GAA trinucleotide repeat in the *FRDA* gene is polymorphic, with normal chromosomes carrying fewer than 42 triplets (Cossee et al., 1997). FRDA chromosomes, in contrast,

carry from 80 up to 1200 GAA repeats. Through a mechanism that remains unclear, but which likely involves defective transcriptional elongation, the expanded GAA repeat results in reduced *FRDA* expression.

The *FRDA* gene encodes a widely expressed 210-amino acid protein, frataxin, which localizes to the mitochondria (Campuzano et al., 1996, 1997) and likely contributes to iron homeostasis (Koutnikova et al., 1997; Babcock et al., 1997). In model systems, loss of frataxin results in overload of mitochondrial iron accompanied by reduced activity of key mitochondrial enzymes, hypersensitivity to oxidative stress, and defective oxidative phosphorylation (Wilson & Roof, 1997; Babcock et al., 1997; Rotig, 1997; Radisky et al., 1999). Mitochondria are a major source of reactive oxygen species, catalysed by iron via the Fenton reaction. These reactive oxygen species are believed to be the principal mediators of mitochondrial injury.

In patients with FRDA, loss of frataxin expression and function also results in accumulation of iron within mitochondria. This iron overload is especially pronounced in the tissues that are most severely affected in FRDA, including cardiac muscle, pancreatic islet cells, and the nervous system (Sanchez-Casis et al., 1977; Campuzano et al., 1997). Examination of tissues from patients with FRDA confirms that excess iron accumulation is associated with a reduction in mitochondrial enzyme function, increased susceptibility to oxidative stress, and defective oxidative phosphorylation (Lamarche et al., 1993; Waldvogel et al., 1999; Lodi et al., 1999; Delatycki et al., 1999; Rotig, 1999). Iron-induced injury in FRDA tissues is diminished by free radical scavengers such as ubiquinone (coenzyme Q_{10}) and idebenone, supporting the contention that the injury is mediated by reactive oxygen species (Wong et al., 1999). Elevated levels of urinary 8-hydroxy-2′-deoxyguanosine (a byproduct of oxidative damage to DNA) and plasma malondialdehyde (a byproduct of lipid peroxidation) are found in patients with FRDA, lending further support to the hypothesis that iron overload is associated with oxidative injury (Schultz et al., 2000; Edmond et al., 2000). The emerging consensus regarding the pathogenesis of FRDA is that loss of frataxin expression leads to a loss of iron homeostasis. The resulting overload of iron in mitochondria, in turn, results in increased steady-state levels of reactive oxygen species which cause oxidative damage and decreased ATP production causing injury to tissues – particularly those with a high energy demand (Beal, 2000).

In conclusion, the last decade of research in neurology has resulted in recognition of an entirely new class of hereditary disease. Progress in understanding these diseases will probably proceed hand in hand with a better understanding of underlying biochemical and cellular processes. Beyond the specific mechanisms at work in each of these disorders, there are a number of shared characteristics. First, all known repeat expansion diseases affect the nervous system. This may be related to specific molecular targets that are expressed only in neurons, or to a deficiency in some compensatory mechanism relative to non-neuronal cells. That neurons are long-lived cells with limited regenerative capacity probably contributes to their selective vulnerability. Secondly, naturally occurring repeat expansion diseases have thus far only been found in humans. Perhaps this is related to the long duration between birth and age of procreation in humans, which allows a large numbers of cell divisions in spermatogenesis, resulting in a greater opportunity for these dynamic mutations to occur. Also, since many of these diseases appear late in life, it is likely that the long lifespan of humans favours a higher incidence of disease. Ascertainment probably also plays a role. Finally, the repeat expansion diseases may be related to other non-expansion neurodegenerative diseases. Parallels exist between the polyglutamine diseases and more common neurodegenerative proteinopathies such as Parkinson's disease, Alzheimer's disease, prion diseases and amyotrophic lateral sclerosis. It is possible that protein deposition is an epiphenomenon representative of a morbid state in neurons. But the recent recognition of additional dominantly inherited neurodegenerative disorders that are characterized by intraneuronal aggregation of the mutant gene product, and the emerging evidence that defects in the ubiquitin–proteasome pathway may underlie neurodegenerative disease, argue that many of these diseases share a common pathogenesis. If the next decade of neurological research is as productive as the last, then a better understanding of this pathogenesis may lead to effective treatment for these disorders.

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4

Cell birth and cell death in the central nervous system

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Formation of the neural tube and control of cell fate by dorsal–ventral signalling centres

One of the most remarkable features of mammalian neural development is the production of the complicated end product, the brain, spinal cord and peripheral nervous system, from a simple one-cell layer thick sheet of neuroepithelial cells. The first step in this process is the formation and patterning of the neural tube through a process termed neural induction (Kandel et al., 2000). This involves the formation of a specialized region of columnar epithelium, called the neural plate, from the embryonic dorsal ectoderm. Soon after its formation the neural plate folds and becomes a tube (Fig. 4.1). In this process the most medial regions of the neural plate form the ventral neural tube and the more lateral regions of the neural plate form the dorsal neural tube. At the neural plate stage, signals from the mesoderm underlying it pattern the neural plate so that there are molecular differences between the rostral and caudal regions of the neural plate. Therefore, these early patterning events are fundamental to the later production of specialized regions and cells of the nervous system from the neural tube.

Neural induction is not completely understood at the molecular level but significant recent progress has been made (Harland, 2000). Current thinking is that the ectoderm at this stage of embryogenesis has a default neural fate except that the action of bone morphogenetic proteins (BMPs) and Wnts (a family of secreted glycoproteins similar to the *wingless* gene in *Drosophila*) expressed widely in the embryo suppress the acquisition of neural fate. Neural induction then occurs in the neural plate because of the release of soluble BMP and Wnt inhibitors from the underlying mesoderm. The inhibition of BMP and Wnt effects allows the default neural fate pathway to operate and the neural plate forms. The rostral–caudal patterning of the neural plate is further affected by the actions of molecules such as retinoic acid (which induces a caudal neural pattern).

After the neural tube forms, the rostral–caudal subdivisions (that will become the telencephalon, diencephalon, mesencephalon, metencephalon and spinal cord) become visible anatomically. At this stage, at each level from rostral to caudal, the fate of individual neural precursors begins to be controlled by dorsal and ventral signalling centres present in the neural tube called the roofplate and the floorplate, respectively. The roofplate produces a variety of molecules in the Wnt and BMP families, while the floorplate produces sonic hedgehog (SHH). There is now persuasive evidence that signaling by BMPs and Wnts regulates the proliferation, differentiation and migration of derivatives of the dorsal neural tube (Lee & Jessell, 1999). These include dorsal spinal interneurons and neural crest cells, which go on to generate the entire peripheral nervous system. Similarly, the differentiation of spinal motor neurons and ventral spinal interneurons is directly controlled by SHH secreted from the floorplate (Kandel et al., 2000). The roofplate and floorplate also secrete a host of other factors that regulate later events such as axon guidance decisions made by cells at all levels of the developing nervous system. Structures analogous to the roofplate and floorplate are present at rostral levels of the nervous system as well but their role in differentiation is much less completely understood in these more morphologically complex regions. Failure of the proper dorsal–ventral patterning events in the developing prosencephalon leads to major brain malformations such as holoprosencephaly. A number of hereditary cases of this syndrome have been linked to genes involved in dorsal–ventral patterning, including mutations in SHH itself (Wallis & Muenke, 2000). Cyclopamine, a teratogenic chemical, appears to cause holoprosencephaly by interfering with SHH signalling (Cooper et al., 1998).

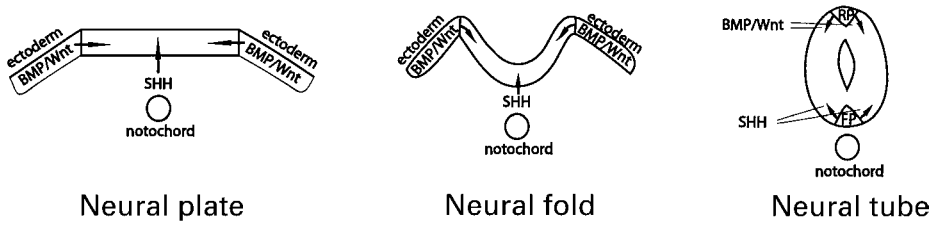

Fig. 4.1. Schematic diagram of the stages of formation of the neural tube from the neural plate. Initially the neuroectoderm is specified from the ectoderm and is a flat sheet of epithelial cells. It begins to fold and finally forms a tube. During this entire time the medial neural plate (which becomes the ventral neural tube) and the lateral neural plate (which becomes the dorsal neural tube) are patterned by secreted molecules. Abbreviations – SHH = sonic hedgehog, RP = roofplate; FP = floorplate.

Cellular and molecular correlates of neurogenesis and gliogenesis during development

Once the neural tube forms and the actions of the dorsal–ventral signalling centres have had their initial effects on the patterning of the neural tube, the process of cellular differentiation begins. Within the ventricular zone, mitotic multipotential cells begin to produce differentiated neuronal and glial cell types following a sequential programme. This process is best understood in the six-layered neocortex. Initially, mitotic stem cells undergo repeated cycles of so-called 'symmetric' cell divisions that yield two daughter cells with the same potential as the parent cell (Lu et al., 2000). These mitoses occur in a characteristic to-and-fro migratory pattern termed interkinetic migration. In this pattern stem cells have cellular processes that span the cortical wall from ventricular to pial surface, and their soma is in an intermediate position. As the stem cell prepares to divide, its cell body descends to the ventricular surface where mitosis occurs. At the appropriate stage of development for the production of differentiated neurons, neural stem cells begin to undergo 'asymmetric' cell divisions that yield a daughter cell that goes on to further differentiate and a daughter cell that remains a stem cell (Lu et al., 2000). The differentiated daughter cell then migrates radially into the cortical plate. As development goes on, progressively more cell divisions are asymmetric and waves of differentiated cells are produced, and less and less stem cells remain in the ventricular zone. Disorders such as tuberous sclerosis and focal cortical dysplasia may arise because of dysfunction in the processes regulating the decision whether to adopt a neuronal or glial fate within the ventricular zone (Walsh, 1999).

In the ventricular zone, neurons with particular laminar fates are produced in a characteristic 'inside-out' manner so that cells destined for the deeper cortical layers are born first and cells destined for superficial cortical layers are born later and migrate past the earlier born cells. The migrating of cells from the ventricular zone using radial glial cells as the scaffolding to reach their final laminar position in a so-called radial pattern of migration. Lissencephalies, periventricular nodular heterotopias and periventricular band heterotopias are all disorders of this process of radial migration and are caused by mutations in genes controlling various steps of migration (Walsh, 1999; Gleeson & Walsh, 2000).

The molecular regulation of the events occurring in the ventricular zone during this period is starting to be elucidated. The decisions made by neural stem cells are controlled in part by the actions of the Notch family of transmembrane receptors. These receptors interact with their ligands, the Delta and Jagged proteins, in a cell contact-dependent manner. Activation of the Notch receptor leads to a decision to remain an undifferentiated stem cell or to become a radial glial cell (Lu et al., 2000). Inhibition of Notch signalling occurs in part by the inheritance of a protein called Numb that is asymmetrically distributed between daughter cells of asymmetric cell divisions. Numb blocks the downstream effects of the Notch receptor and releases the cell to differentiate into a neuron (Lu et al., 2000).

The differentiation of glial progenitors to mature oligodendroglia and astroglia in the developing CNS is also subject to extrinsic regulation. Basic fibroblast growth factor (bFGF) inhibits maturation of glial progenitors to either oligodendroglia or astroglia (McKinnon et al., 1990; Grinspan et al., 2000). Platelet-derived growth factor-alpha (PDGFα) drives recruitment into the oligodendroglial lineage (Fruttiger et al, 1999), whereas the BMPs enhance differentiation of glial progenitors to glial fibrillary acidic protein (GFAP) positive astroglia (Grinspan et al., 2000).

Apoptosis during normal brain development

Immature animals remodel CNS and other tissues by apoptotic removal of redundant cells. Morphological features of apoptosis include nuclear fragmentation, cell shrinkage, membrane blebbing, and phagocytosis by macrophages. Apoptosis is triggered by activation of target cell plasma membrane death receptors (e.g. CD95, the tumor necrosis factor (TNF) receptors, and the low affinity neurotrophin receptor, p75NTR), by unsuccessful competition of the target cell for critical survival factors, or by inability of the target cell to establish and maintain contact with critical extracellular matrix constituents ('anoikis') (Savill & Fadok, 2000; Meier et al., 2000).

A superfamily of cysteine proteases, the caspases, are responsible for apoptotic execution. These proteins are synthesized as procaspases, which require proteolytic clipping in order to activate their catalytic sites. This activation can be initiated by their aggregation with a plasma membrane death receptor or with proteins (cytochrome c and Apaf-1) released through mitochondrial membrane pores. Once begun, a chain reaction of proteolytic caspase activation follows. The caspases cleave target proteins at aspartate residues. In some instances, this cleavage results in protein activation (e.g. other members of the caspase family, and interleukin-1). More commonly, the target protein (e.g. gelsolin, and an inhibitor of a nuclease capable of intranuclear double-stranded DNA nicking) is inactivated. Together, these proteolytic events are responsible for the DNA nicking and cytoplasmic and plasma membrane remodelling that characterize apoptosis, and culminate in cell digestion by macrophages (Hengartner, 2000).

The Bcl-2 family of proteins modulate caspase activation. Pro-apoptotic members of this family (e.g. Bax and Bak) facilitate release of cytochrome c and Apaf-1 from target cell mitochondria, whereas anti-apoptotic members (e.g. Bcl-2 and Bcl-x_L) inhibit this release. Expression of this Bcl-2 family of proteins is developmentally regulated in the CNS (Kelekar & Thompson, 1998; Hengarter, 2000).

Apoptosis is prominent in both neuronal and macroglial lineages in the CNS. In the cat retina, for example, more than 80% of the ganglion cells do not survive long after birth (Meier et al., 2000), and more than 50% of the late oligodendroglial progenitors formed in perinatal rat optic nerve do not survive to maturity (Barres & Raff, 1994). This apoptotic culling of neural cells unable to obtain the survival factors they require provides a powerful and precise means by which normal CNS tissue structure and function can be ensured. An illuminating example of this is provided by examination of transgenic mice that overexpress $PDGF_{AA}$ in CNS. $PDGF_{AA}$ is a growth factor for oligodendroglial progenitors, and these mice accumulate many more oligodendroglial progenitors in the perinatal period than do their normal littermates. Yet, as these transgenic mice mature, the numbers of oligodendroglia and their levels of myelination in the CNS are normal (Calver et al., 1998). Conversely, in mice in which CNS apoptosis is prevented by knocking out caspase-9 or caspase-3, there are ectopic accumulations of supernumerary neurons (Yuan & Yankner, 2000).

Neurogenesis in the normal adult brain

Up to this point only the mechanisms of developmental production of cells have been discussed. It has been known for many years that continued production of glial cells occurs in the adult brain. Most of these are thought to be generated from the striatal and cortical subventricular zones. What has been less widely appreciated, although also well established in the 1960s, is that there is continued production of neurons in the adult brain of mammals in two locations, the dentate gyrus and olfactory bulb (Gage, 2000).

In the dentate gyrus of the hippocampal formation there is a layer of mitotically active cells at the border of the hilus and dentate granule cell layers that has been proven to produce new neurons throughout life in both rodents and primates (Gage, 2000) (Fig. 4.2). The function of the newly born granule cells is unknown, but it is known that at least some of these cells extend axons that integrate into the normal circuitry of the hippocampus. Recent studies have shown that environmental stimuli, including visuospatial learning and physical activity, can have substantial effects on the birth and survival of new dentate granule cells in adult rodents (Kempermann et al., 1997a; Gould et al., 1999a, b; van Praag et al., 1999). Also, there is an age-related decrease in the production of new neurons in the dentate gyrus (Kuhn et al., 1996).

The phenomenon of dentate granule neurogenesis in the adult is being intensively studied since it is a paradigm for the regulation of new neuron production in adult mammals. Many studies have addressed exogenous influences that regulate the rate of proliferation of granule cell precursors, and have shown that granule cell neurogenesis is inhibited by excess glucocorticoids and by excitotoxins (Cameron & Gould, 1994; Cameron et al., 1995). A particularly interesting set of studies has characterized the balance of cell production and granule cell number in inbred strains of mice. These studies demonstrated that various inbred strains of mice may have a low or high basal

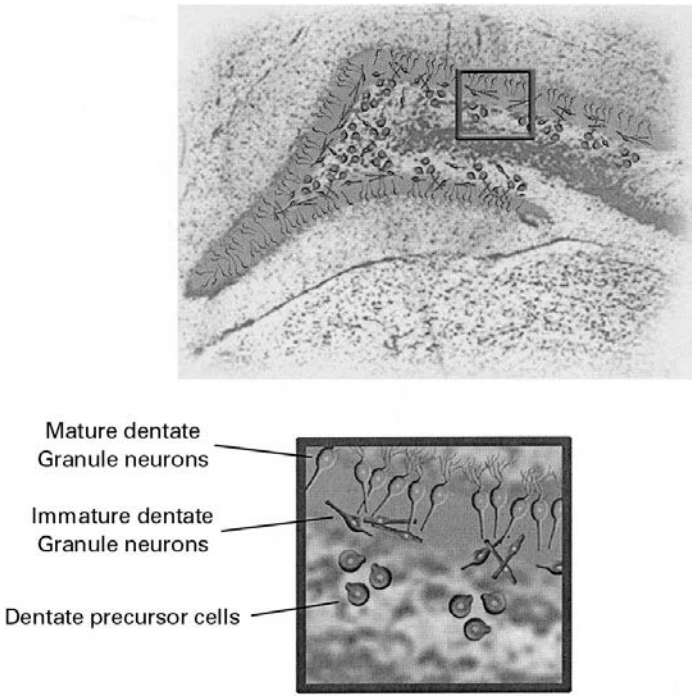

Fig. 4.2. Schematic diagram showing the organization of neurogenesis in the adult dentate gyrus. Mitotic dentate precursor cells are located in the zone just under the granule cell layer. Newborn immature cells are at the inner border and more mature granule cells are in the outer domains of the granule cell layer. (Artwork by Erin Browne.)

rate of new granule cell production (Kempermann et al., 1997b). Some strains have basal rates of granule cell death that match the production of granule cells very closely, while others have a lower rate of death leading to an increasing number of granule neurons as the animals mature (Kempermann et al., 1997b).

The granule and periglomerular interneurons of the olfactory bulb are also produced in adult mammals. These cells are generated in a small region of the anterior subventricular zone. They reach the olfactory bulb by migrating long distances in a direction tangential to the radial migration seen during development (Gage, 2000). Once in the bulb, they appose themselves to radial glial-like cells and migrate radially to take up their final position. What functional role the production of new neurons has in the olfactory bulb is currently unknown. In non-human primates, a recent controversial study demonstrated ongoing neurogenesis from the subventricular zone of neurons that migrated to association areas of neocortex (Gould et al., 1999b). This type of adult neurogenesis has never been seen in rodents and thus may be a primate specialization. Again, the function of these new cells is unknown presently but, if this type of neurogenesis is ongoing in humans, it may have important implications for plasticity of higher cortical functions.

Neurogenesis and gliogenesis in pathologic states

The production of neurons from the dentate subgranular zone and the subventricular zone in the adult nervous system of rodents has been studied in a number of pathologic contexts. The most extensively studied of these is following status epilepticus (Bengzon et al., 1997; Parent et al., 1997). In rodent models of status epilepticus following systemic administration of pilocarpine or kainic acid, there is a dramatic up-regulation of granule cell neurogenesis starting several days after the prolonged seizure and continuing for about 2 weeks. Similar increases in neurogenesis have been seen in the dentate gyrus following transient global ischemia in gerbils (Liu et al., 1998). The functional significance of this response is unclear, but there is some reason to believe that the increased neurogenesis is somehow coupled to increased cell death of granule cells following the same insults (Bengzon et al., 1997). If there is a mechanism for linking the birth of new neurons in the dentate gyrus to cell death, it may also be possible to activate this mechanism in other brain regions that suffer extensive cell death in response to pathologic stimuli like excitotoxicity or neurodegenerative processes. This might serve as a basis for novel therapeutic strategies to help repair the effects of these pathologic insults.

Focal traumatic lesions in the cortex have been shown to up-regulate the rate of proliferation of astrocyte precursors in the subventricular zone. It is possible that this represents the main source of cells contributing to gliosis in the cortex following focal or diffuse injuries (Szele & Chesselet, 1996). In the subventricular zone, increased cell birth of cells with properties of glial cells has been demonstrated in response to experimental allergic encephalomyelitis (Calza et al., 1998). Oligodendroglial progenitors are also identifiable in chronic multiple sclerosis plaques, but often have exited the mitotic cycle (Wolswijk, 1998). Treatment strategies need to be developed that enhance proliferation of these progenitors, and their differentiation to myelin-forming oligodendroglia.

Apoptosis and necrosis in pathologic states

The death of neurons and macroglia caused by deprivation of oxygen and glucose (e.g. in an ischemic infarction)

occurs by two apparently distinct mechanisms. Where oxygen/glucose deprivation is most severe, ATP generation is blocked, and the cells lose the capacity to regulate intracellular Ca^{2+} and Na^{+} concentrations. Cell necrosis results, characterized by perikaryal swelling, loss of plasma membrane integrity, and cell fragmentation. Ionotropic glutamate receptors (GluR), activated by increased extracellular glutamate concentrations, are of central importance in the pathophysiology of ischemic necrosis of neurons and oligodendroglia, and inhibitors of these GluR minimize the extent of ischemic necrosis (Dugan & Choi, 1999). Where oxygen/glucose deprivation is less severe (e.g. in the 'ischemic penumbra'), neurons and macroglia die by apoptosis, and can be rescued by caspase inhibitors (Yuan & Yankner, 2000).

The contribution of apoptosis to neural cell loss in chronic neurological diseases is less clearcut. While cells undergoing apoptosis are common in active multiple sclerosis plaques, most are lymphocytes rather than cells of the oligodendroglial lineage (Bonetti & Raine, 1997). In respect of Alzheimer's disease, amyloid-β can activate neuronal caspases, but most degenerating neurons in this disorder do not show apoptotic features. In mice expressing the human mutant superoxide dismutase-1 gene that causes a familial form of amyotrophic lateral sclerosis (ALS), inhibition of caspase-1 or overexpression of Bcl-2 delays disease progression, and caspase inhibition also delays disease progression in a transgenic model of human Huntington's disease, but neuronal apoptosis is difficult to demonstrate morphologically in these mouse models (Yuan & Yankner, 2000)

Stem cells in the adult brain

The existence of neurogenesis and gliogenesis in the subventricular zone and dentate gyrus of adult animals implies that there must be precursors for these cells (Gage, 2000). The usual terminology applied to progenitor cells for neurons and glia divides them into stem cells and committed precursor cells. A stem cell is multipotential and capable of numerous self-renewing mitoses. A committed precursor cell will be limited to one or a small number of ultimate fates and has a limited capacity for self-renewal. The clear presence of neurogenesis and gliogenesis and the in situ and in vitro demonstration of dividing precursor cells have led to the search for the elusive multipotential neural stem cells that are assumed to be present in the adult nervous system.

In the early 1990s, several cell culture systems that are capable of maintaining multipotential (cells capable of making neurons and glia) stem cells were described. Following these initial studies, there have been a great number of studies that have demonstrated the properties of these cells and their requirements for trophic factors and mitotic factors (such as basic FGF and epidermal growth factor (EGF)) to be maintained in culture (Gage, 2000). Other studies have demonstrated that treating these cultures with factors like retinoic acid can force these cells into producing neurons, while serum and ciliary neurotrophic factor (CNTF) induce the cells to become astrocytes (Gage, 2000). The use of these culture systems has demonstrated that there are quiescent stem cells in all regions of the nervous system rather that just in the areas known to produce new neurons (Gage, 2000). Are these cells placed in a distributed manner in order to produce new glial cells in areas away from the germinative zones? Are there ways to induce them to become neurons in situ and replace neurons killed or injured by pathologic insults?

The scientific question of the location and identity of the neural stem cells in vivo has recently been addressed. Several laboratories have reported that either the ependymal cells lining the adult ventricles or astrocyte-like glial cells adjacent to them are likely to be the in vivo stem cells responsible for the production of olfactory interneurons and glial cells in the adult subventricular zone (Doetsch et al., 1999; Johansson et al., 1999). The relationship of these two populations of stem cells to each other (e.g. are they transitional forms of the same population?), and their relationship to the multipotential cells in the dentate gyrus and elsewhere in the CNS are unknown.

Until recently it was believed that neural stem cells were capable of producing exclusively neurons and glia. Recent exciting experiments have shown that this view may be too limited. In one set of studies, investigators transplanted mouse neural stem cells that were marked with an enzymatic tag to other mice whose bone marrow had been destroyed by irradiation. In these mice, amazingly, the neural stem cells were able to generate hematopoetic stem cells that populated the bone marrow and produced differentiated blood elements and immune cells that expressed the enzymatic tag (Bjornson et al., 1999). Another, even more startling result was obtained when neural stem cells were injected into mouse blastocysts and were able to contribute differentiated cells to all three germ layers of the developing embryo, albeit less efficiently than true embryonic stem cells (Clarke et al., 2000). These experiments blur the distinctions between neural stem cells and other stem cells in the body and perhaps imply that the immediate molecular milieu may be as important as any developmental history in contributing to the multipotentiality of stem cells.

Therapeutic approaches based on neurogenesis

How can we utilize the new understanding of neurogenesis and gliogenesis in the nervous system to treat neurological diseases? One approach is to generate cells for therapeutic purposes in vitro and transplant them into the diseased host (Bjorklund & Lindvall, 2000a). The other approach is to attempt to harness the regenerative capacity of the nervous system to facilitate functional recovery from insults (Lowenstein & Parent, 1999; Bjorklund & Lindvall, 2000b). In the future it is likely that both approaches will be useful.

The approaches that are based on the in vitro production of neural cells are being investigated most intensively for the treatment of Parkinson's disease, Huntington's disease, stroke and epilepsy (Bjorklund & Lindvall, 2000a). In each of these cases the approach depends on the ability to culture pure populations of the appropriate neurons from identified sources. The sources being investigated include xenografts from porcine sources, expanded human neural stem cells, human bone marrow stromal stem cells, and immortalized human cell lines (Bjorklund & Lindvall, 2000a). Each of these sources has its own perils and promises. Xenotransplants may have a higher potential for rejection or infection with zoonotic organisms. Expanded human neural stem cells are still incapable of producing sufficient quantities of pure cells to meet clinical needs. All immortalized cell lines have the potential to lead to neoplasm. The next 10 years will almost certainly lead to solutions to these problems and will allow the clinical efficacy of these treatments to be tested.

The potential for harnessing the native regenerative capacity of the nervous system is perhaps the most exciting future possibility. A recent series of experiments utilizing a clever technique to deliver focal cell type specific injury to the nervous system has emphasized the heretofore unrecognized ability of the nervous system to replace certain types of cells (Snyder et al., 1997). This technique allows the selective photoablation of cells in the cortex in a layer specific manner. These experiments reveal that, after the selective ablation of cortical pyramidal neurons, the rodent brain is capable of using endogenous precursors to replace these cells, despite the fact that these cells are never normally produced in the adult animal (Magavi et al., 2000). If we can understand the cues that regulate these events then these signals may allow regulatable repairs to be performed in the nervous system (Lowenstein & Parent, 1999; Bjorklund & Lindvall, 2000b).

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5

Neuroprotection in cerebral ischemia

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Ischemic stroke is a consequence of transient or permanent reduction of blood flow to a focal region of the brain, usually caused by the occlusion of an artery by an embolus or thrombus. Cerebral ischemia may also occur globally in the setting of cardiac arrest and resuscitation. While historically brain damage has been considered to be an inexorable consequence of focal or global ischemic insults, in recent years a growing understanding of the underlying mechanisms responsible for brain cell death has led to the identification of new therapeutic approaches. Two main approaches have emerged. The first aims to restore lost blood flow by dissolving the thrombus responsible for cerebral artery obstruction (in ischemic stroke). Thrombolysis has become an established treatment for ischemic stroke after the efficacy of intravenous tissue plasminogen activator (tPA) was demonstrated in a landmark study (The NINDS rt-PA Stroke Study Group, 1995). Promising results have also been reported for the thrombolytic agent pro-urokinase, delivered by intra-arterial catheter directly to the site of intravascular thrombus (Furlan et al., 1999). The second approach, neuroprotection, aims to reduce the intrinsic vulnerability of brain tissue to ischemia; it will be the topic of this chapter.

Mechanisms of ischemic neuronal death

The brain is more vulnerable to ischemia than many other tissues, so it seems plausible that the cellular mechanisms of this heightened vulnerability could be delineated and blocked. Over the last 15 years evidence has accumulated indicating that normal brain signaling and immune defense mechanisms may become harmful after ischemic insults (Rothman & Olney, 1986; Choi, 1988; del Zoppo et al., 2000). In particular, substantial evidence now implicates excitotoxicity, programmed cell death, and inflammation in the pathogenesis of ischemic neuronal death.

Excitotoxicity

The excitatory transmitter glutamate normally mediates most fast synaptic transmission throughout the CNS, but it also has a surprising ability to trigger central neuronal death upon prolonged exposure, a phenomenon called 'excitotoxicity' by Olney (1969). Excitotoxicity now appears to be involved in the pathogenesis of several CNS diseases including ischemic brain injury (Rothman & Olney, 1986; Choi, 1988). Under ischemic conditions, neurons deprived of oxygen and glucose rapidly lose ATP and become depolarized, leading to abnormally high levels of glutamate release (initially mediated by vesicular release from nerve terminals, and later by reverse transport from astrocytes). Once in the extracellular space, glutamate activates three major families of ionophore-linked receptors identified by their preferred agonists: *N*-methyl-D-aspartate (NMDA) alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate. The channels gated by all three receptors subtypes are permeable to both Na^+ and K^+. Channels gated by NMDA receptors, but only a small number of channels gated by AMPA or kainate receptors (see below), additionally possess high permeability to Ca^{2+}. Marked neuronal cell body and dendrite swelling occur, as Na^+ and Ca^{2+} enters the cell joined by the influx of Cl^- and water. Excessive Ca^{2+} influx mediated predominately by NMDA receptors (but also triggered secondarily by Na^+ influx through AMPA-, kainate-, and NMDA-receptor-gated channels via activation of voltage-gated Ca^{2+} channels and reverse operation of the Na^+/Ca^{2+} exchanger), leads to elevated intracellular free Ca^{2+} concentrations and lethal metabolic derangements (Choi, 1988; Kim et al., 2001).

In neuronal cultures, selective NMDA-receptor blockade prevents most of the Ca^{2+} influx and cell death induced by brief intense glutamate exposures, and also markedly attenuates the death of cultured neurons subjected to oxygen and/or glucose deprivation. These observations are consistent with studies conducted with selective agonists: exposure to NMDA for as little as 3–5 minutes triggers widespread necrosis of cultured cortical neurons ('rapidly triggered excitotoxicity'), whereas exposure to high concentrations of kainate typically requires hours to do the same ('slowly triggered excitotoxicity'). NMDA antagonists are also highly neuroprotective in animal models of focal brain ischemia (Albers et al., 1992), but not consistently in models of transient global ischemia (Buchan, 1990).

Profoundly elevated intracellular Ca^{2+} concentrations, resulting from ischemia and excitotoxicity, are thought to initiate many potentially lethal derangements in cellular processes. Work in recent years has assigned particular responsibility for ensuing cellular death to the Ca^{2+}-dependent activation of catabolic enzymes, generation of free radicals including nitric oxide (NO), impairment of mitochondrial function, and excessive utilization of energy by the DNA repair enzyme poly(ADP–ribose) polymerase (PARP) (see below).

Ca^{2+} may not be the only divalent cation whose excessive entry mediates excitotoxic neuronal death after ischemic insults. The excessive influx of Mg^{2+} through NMDA–receptor-gated channels and its toxic intracellular accumulation has been proposed as a potential component of excitotoxic injury (Hartnett et al., 1997). Furthermore, growing evidence suggests that glutamate receptor overactivation may promote the toxicity of neurotransmitter Zn^{2+} (Choi & Koh, 1998). Zn^{2+} is concentrated in synaptic vesicles at excitatory terminals throughout the forebrain and is released upon neuronal stimulation; it can alter the behaviour of several transmitter receptors and voltage-gated channels, including the NMDA receptor (Frederickson, 1989). Cell culture experiments showed that exposure to concentrations of extracellular Zn^{2+} plausibly attained in the ischemic brain could kill central neurons, especially if the neurons were depolarized. Subsequent studies have indicated that the first step in Zn^{2+}-mediated neuronal death, like Ca^{2+}-mediated neuronal death, is excess entry across the plasma membrane, facilitated by membrane depolarization and consequently enhanced influx through several routes, in particular, voltage-gated Ca^{2+} channels (see below). The idea that Zn^{2+} neurotoxicity might contribute specifically to ischemic brain damage was raised by Tonder et al. (1990), who showed that transient global ischemia in rats was associated with depletion of Zn^{2+} from hippocampal mossy fibres, and the abnormal appearance of Zn^{2+} in the cell bodies of degenerating target CA3 or hilar neurons (dubbed 'zinc translocation', Frederickson et al., 1989). This idea was strengthened by the observation that Zn^{2+} translocated into selectively vulnerable postsynaptic neuronal cell bodies throughout the forebrain, and did so prior to neuronal degeneration. Furthermore, intracerebroventricular injection of the membrane-impermeant chelator CaEDTA (EDTA saturated with equimolar Ca^{2+}, so that it does not affect extracellular Ca^{2+} or Mg^{2+} but still avidly binds Zn^{2+}) before transient global ischemia in rats markedly reduced Zn^{2+} translocation into selectively vulnerable neurons throughout the hippocampus, cortex, thalamus and amygdala, and also reduced the delayed death of these neurons (Koh et al., 1996).

Recently, the idea that toxic Zn^{2+} originates primarily from synaptic vesicles has been challenged by intriguing observations suggesting that Zn^{2+}-mediated neuronal death may still occur after kainate-induced seizures in Zn^{2+} transporter 3 gene (*znt-3*)-null mice, which lack histochemically reactive vesicular Zn^{2+} in nerve terminals (Lee et al., 2000; Cole et al., 1999). These observations raise the possibility that at least some of the toxic Zn^{2+} may originate from intracellular sources, perhaps released from protein binding sites by oxidative stress (Aizenman et al., 2000).

The morphology of cells dying after intense glutamate receptor overactivation and Ca^{2+} and/or Zn^{2+} influx typically has characteristics of necrosis, a fulminant form of cell death associated with failure of the plasma membrane and swelling of both the cell and internal organelles. However, milder levels of toxic glutamate receptor stimulation on cells with preserved energy metabolism may lead to an alternative, more orderly death: apoptosis (Ankarcrona et al., 1995).

Apoptosis

Cerebral ischemia seems an obvious example of a violent 'environmental perturbation' capable of producing necrosis; however, growing evidence indicates that many brain cells undergo apoptosis after ischemic insults (Choi, 1996; Dirnagl et al., 1999). Apoptosis is the end result of a genetically regulated program that induces cells to die in an 'altruistic' fashion, with minimal release of genetic material and other proinflammatory intracellular constituents (Kondo, 1988). In normal physiological settings such as during development, apoptosis has a characteristic morphological appearance, featuring chromatin condensation and aggregation to the nuclear margin, cell and internal organelle shrinkage, and fragmentation of the

nucleus and cytoplasm into membrane-bound vesicles (apoptotic bodies, Kerr et al., 1972). In the past, it has been characterized biochemically by internucleosomal fragmentation of genomic DNA in 185–200 base pair intervals, resulting in 'DNA laddering' detected on agarose gel electrophoresis, or by TdT-mediated biotinylated dUTP nick end-labeling (TUNEL) of nuclei. It is now becoming clear that DNA fragmentation and TUNEL of nuclei also occurs in cells undergoing necrosis, and thus cannot be the sole criterion for identifying apoptosis.

Recent investigations have yielded insights into the molecular mechanisms underlying programmed cell death. It is now apparent that this process is under tight regulatory control at several checkpoints. One checkpoint occurs on the outer membrane of mitochondria and is regulated by a group of proteins belonging to the bcl-2 family, composed of three groups based on structural and functional similarities. Members of group 1 (including bcl-2 and bcl-x_L) which share four conserved bcl-2 homology domains (BH) BH1–4 and a C-terminal hydrophobic tail (anchoring the protein to the outer mitochondrial membrane), are anti-apoptotic, whereas members of group 2 (including bax and bak), which contain BH1–3 and the hydrophobic tail, are proapoptotic. Members of group 3, which share only the BH3 domain, are pro-apoptotic and include bid and bik (Adams & Cory, 1998). Through a process that is currently poorly understood, pro- and anti-apoptotic members of the bcl-2 family interact on the outer mitochondrial membrane to regulate the release of the electron carrier cytochrome c from the intramembranous compartment (Jurgensmeier et al., 1998). Once in the cytoplasm, cytochrome c binds with another apoptosis regulator, Apaf-1, and dATP to form part of the 'apoptosome' (Cecconi, 1999), which activates the effector arm of programmed cell death carried out by a class of cysteine proteases, termed caspases. Caspases can also be activated by cell surface death receptors such as TNF receptors via caspase-8 (see below). Evidence is also emerging for a caspase-independent pathway of mammalian cell apoptosis, mediated by the mitochondrial release of apoptosis-inducing factor (Joza et al., 2001).

Highly conserved through evolution, more than a dozen caspases have been identified; a majority appear to participate in apoptosis, while others are responsible for the proteolytic activation of proinflammatory cytokines. Caspases are activated by proteolytic cleavage at caspase recognition sites. Thus, activation can occur autocatalytically, or through proteolysis by another caspase family member (Thornberry & Lazebnik, 1998). The apoptosome complex provides the initial stimulus for the autocatalytic activation of apical caspase-9, which subsequently cleaves and activates other downstream caspases including caspase-3, -6, and -7; these in turn cleave several proteins vital to survival (Slee et al., 1999). For example, caspase-3-mediated cleavage of the inhibitory subunit of caspase-activated DNase (CAD) results in internucleosomal DNA cleavage and 'DNA laddering' (Nagata, 2000). In addition, cleavage of nuclear lamins results in nuclear shrinking and budding (Buendia et al., 1999), and cleavage of cytoskeletal proteins such as fodrin and gelsolin result in loss of overall cell shape (Kothakota et al., 1997), characteristic of apoptotic cellular morphology.

Potassium efflux and resultant cell shrinkage may also play an important role in apoptosis. It is well established that raising extracellular K^+ inhibits neuronal apoptosis in vitro, an observation attributed historically to the activation of voltage-gated Ca^{2+} channels (Johnson & Deckwerth, 1993). However, the protective effect of raising extracellular K^+ against cortical neuronal apoptosis induced by staurosporine or serum deprivation was not eliminated by blocking voltage gate Ca^{2+} channels and associated increases in intracellular Ca^{2+} concentrations (Yu et al., 1997). Furthermore, these forms of neuronal apoptosis were associated with an early enhancement of the delayed rectifier current I_K, and depletion of cellular K^+ content; and blocking I_K with tetraethylammonium (TEA) attenuated subsequent neurodegeneration (Yu et al., 1997). Similarly, lymphocytes undergoing apoptosis were found to have intracellular K^+ concentrations of 50 mM (normally 140 mM), and blockade of K^+ efflux by raising extracellular K^+ inhibited apoptosis in these cells (Hughes et al., 1997). Such reductions in the concentration of intracellular K^+ may promote apoptosis by facilitating the proteolytic activation of caspase-3 and Ca^{2+}-activated endonuclease (Bortner et al., 1997).

Early evidence implicating apoptosis in the pathogenesis of brain damage after ischemic insults included findings of condensed nuclei with sharply delineated chromatin, apoptotic bodies, and evidence of internucleosomal DNA fragmentation (Li et al., 1995; Linnik et al., 1993; MacManus et al., 1993). While the precise morphology of ischemic neuronal death does not correspond exactly to that of pure apoptosis, for example, seen during development, it is quite plausible that contributions from excitotoxicity and other concurrent pathogenic events would lead to mixed morphological patterns. More recently, specific molecular markers of apoptosis have been identified in ischemic brain tissue. For example, increased expression of anti-apoptotic regulators bcl-2, bcl-x and bcl-w was shown in neurons that survived focal ischemia (Chen et al., 1995; Isenmann et al., 1998; Minami et al., 2000), while proapoptotic bax expression was

increased selectively in vulnerable CA1 neurons following transient global ischemia (Krajewski et al., 1995). The activation of caspase-3 was demonstrated in cortical neurons several hours after a focal ischemic insult (Namura et al., 1998) and after transient global ischemia (Chen et al., 1998). Furthermore, as will be discussed further below, genetic or pharmacological interventions designed to block apoptosis can reduce cell death in cell culture or animal models of brain ischemia.

Inflammation

Cerebral ischemia induces an inflammatory reaction that may exacerbate initial levels of tissue injury in the hours to days after the initial insult. Within hours after transient global ischemia in gerbils, the expression of several proinflammatory cytokines is increased within the hippocampus and thalamus, including tumor necrosis factor (TNF)-α, primarily secreted by microglia, and IL-1β, primarily released from astrocytes. Mounting evidence suggests that the acute expression of these cytokines contributes to brain injury after ischemia, as blockade of their receptors or neutralization with antibodies reduces infarct volumes in rodent models of focal ischemia (for review see Barone & Feuerstein, 1999, and see below). Several actions of TNF-α may contribute to its deleterious effects in the ischemic brain, including a constrictive effect on pial arteries that can exacerbate ischemia, stimulation of matrix-degrading metalloproteinase activity, oligodendrocyte toxicity, and activation of leukocytes (Beutler & Cerami, 1987). However, the effects of TNF-α following cerebral ischemia are not all injurious, as rather surprisingly, mice lacking TNF receptors developed larger infarcts than wild-type controls (Bruce et al., 1996). It has been proposed that this cytokine has dual roles in brain injury, exacerbating toxicity at early time points, but promoting recovery at later times (Shohami et al., 1999).

TNF-α belongs to a family of ligands that activate the TNF superfamily of receptors (so called death receptors), which includes fas ligand (fasL, aka CD-95–L or APO-1–L) and TNF-related apoptosis-inducing ligand (TRAIL). In some cell-types, activation of these death receptors leads to the cleavage and activation of apical pro-caspase-8 (Ashkenazi & Dixit, 1998), which then can activate downstream effector caspases including caspase-3, leading to apoptosis independent of bcl-2-regulated cytochrome c release (Srinivasula et al., 1996). Recent evidence implicates this death receptor pathway of apoptosis in ischemic neuronal death, as fasL and TRAIL were found to be upregulated after transient focal ischemia. Furthermore, *lpr* mice expressing dysfunctional fasL receptors (fas) had smaller infarct volumes than wild-type animals after transient focal ischemia (Martin-Villalba et al., 1999).

TNF-α and IL-1 also have important effects on leukocyte infiltration. Both cytokines 'prime' endothelium for cellular adherence, probably by increasing the expression of adhesion molecules (e.g. intercellular adhesion molecule 1 [ICAM-1], P-selectins, and E-selectins), enhancing neutrophil adhesion and subsequent infiltration (Barone & Feuerstein, 1999). Macrophages and monocytes follow, guided by chemokines such as IL-8, monocyte chemoattractant protein-1 (MCP-1), and interferon inducible protein-10 (IP-10), which are upregulated in the ischemic brain (del Zoppo et al., 2000). The infiltrating leukocytes probably contribute to ischemic brain injury through several mechanisms, including microvascular occlusion and release of cytotoxic products. One particularly damaging product of infiltrating macrophages is nitric oxide (NO), synthesized inside these cells by inducible NO synthase (iNOS or type II NOS). Under ischemic conditions NO can react with superoxide anion to form the powerfully destructrive free radical, peroxynitrite. Other deleterious consequences of NO production include DNA damage (and subsequent activation of PARP, with resultant energy failure), and inhibition of DNA synthesis; both apoptosis and excitotoxic necrosis may be enhanced as a result (Iadecola, 1997; Hewett et al., 1994). Neuronal NOS (nNOS or type I NOS), a second isoform of NOS which is activated by elevated intracellular Ca^{2+}, may be a major mediator of brain cell death following ischemia (see below). In contrast, NO synthesized by a third isoform of NOS in endothelial cells (eNOS or type III NOS) may play a protective role early after ischemia onset, relaxing vascular smooth muscle cells and helping to preserve blood flow (Samdani et al., 1997).

Postischemic inflammation is further augmented by the excessive activation of the Ca^{2+}-activated catabolic enzymes, phospholipase A2 and C (PLA2 and PLC) in neurons, endothelial cells and leukocytes, which promote membrane phospholipid breakdown, producing platelet activating factor (PAF) and arachidonic acid. PAF exerts a variety of deleterious actions in ischemic brain including platelet and leukocyte activation, breakdown of the blood–brain barrier with resultant edema, and direct neurotoxicity at high concentrations (Stanimirovic & Satoh, 2000). Cyclooxygenase-2 (COX-2) is also upregulated following ischemia in close proximity to cells expressing iNOS, probably stimulated by NO (Nogawa et al., 1998), and further metabolizes arachidonic acid to a variety of toxic prostanoids; free radicals are also produced by arachidonic acid metabolism.

Neuroprotective interventions

Antiexcitotoxic approaches

Reducing extracellular glutamate

One approach to decreasing ischemic injury may be to reduce glutamate efflux from presynaptic nerve terminals and astrocytes. The most powerful method of accomplishing this so far may be mild hypothermia, which sharply limits the build-up of extracellular glutamate induced by ischemia (Busto et al., 1989). Both intra- and postischemic hypothermia produce lasting neuroprotective effects in animal cerebral ischemia studies (Barone et al., 1997b). At present, the clinical use of hypothermia is limited to surgical procedures that require concomitant cardiac arrest and neurosurgical procedures such as cerebral aneurysm clipping (Tommasino & Picozzi, 1998). Although hypothermia in patients with traumatic brain injury has been reported to improve outcomes in small clinical studies, a recent randomized trial of hypothermia after acute brain injury initiated within 6 hours did not demonstrate improved outcomes (Clifton et al., 2001).

Neurotransmitters (other than glutamate) released to the extracellular space during ischemia can also influence resultant brain injury, in part by altering circuit excitability and vesicular glutamate release from nerve terminals. GABA is the major inhibitory neurotransmitter in the mammalian brain; agonists at postsynaptic GABA receptors activating Cl^- channels ($GABA_A$ receptors) such as muscimol or benzodiazepines attenuate brain injury in rodent models (Sternau et al., 1989; Lyden & Hedges, 1992; Schwartz-Bloom et al., 1998). However, a phase III trial of the GABA agonist, clomethiazole, failed to show efficacy in patients with acute ischemic stroke (Lyden et al., 2002). One possible explanation for this disappointment might be a surprising ability of $GABA_A$ receptor activation to promote neuronal death induced by oxygen-glucose deprivation, perhaps because it hyperpolarizes neuronal cell membranes and thus enhances the voltage gradient for Ca^{2+} entry (Muir et al., 1996). In addition, it may well be that much of the glutamate accumulating in the extracellular space after ischemic insults is not mediated by circuit activation and vesicular release, but rather by transport from tonically de-energized and depolarized astrocytes (Szatkowski et al., 1990). Agonists of the $5\text{-}HT_{1A}$ serotonin receptor subtype have also been reported to reduce brain injury in rodent models of focal and global ischemia (Prehn et al., 1993; Piera et al., 1995), and a phase III clinical trial of the agonist, Bay x 3702, is currently under way (Goldberg, 2001).

A second general approach to reducing membrane excitability and vesicular glutamate release would be to manipulate various membrane ion channels. For example, several K^+ channel openers reduced endogenous glutamate release following brief ischemia in hippocampal slices (Zini et al., 1993) and have shown some promising effects in animal studies (Takaba et al., 1997; Heurteaux et al., 1993). However, BMS-204352, an opener of large-conductance Ca^{2+}-activated K^+ channels (BK channels) failed to show efficacy in a clinical trial for acute ischemic stroke (Goldberg, 2001). A possible explanation for this failure is raised by the potential of K^+ efflux to promote apoptosis (see above). Blocking voltage-gated Na^+ channels may provide another strategy to reduce circuit excitation. Na^+ channel blockers such as tetrodotoxin, phenytoin, and riluzole exhibit neuroprotective effects in vitro against both excitotoxic neuronal cell death (Lustig et al., 1992) and axonal damage (see below), as well as in vivo in both focal and global ischemia models (Yamasaki et al., 1991; Cullen et al., 1979; Pratt et al., 1992), but a recent clinical trial of fosphenytoin failed (Goldberg, 2001). Newer Na^+ channel blockers such as BIII 890 CL, that demonstrate increased activity in depolarized tissue and reduced interference with normal physiologic function, remain promising (Carter et al., 2000). Lastly, blocking voltage-gated Ca^{2+} channels would be a way to reduce glutamate release, as well as postsynaptic Ca^{2+} or Zn^{2+} influx, although more postsynaptic Ca^{2+} influx into neurons is probably mediated by NMDA receptors, and there might also be risk of potentiating apoptosis (see below). In any case, clinical trials with dihydropyridines in ischemic stroke have so far not been encouraging (American Nimodipine Study Group, 1992; Horn et al., 2001).

Manipulating glutamate receptors

Once released into the extracellular space, glutamate activates its ionophore-linked receptors, in addition to a family of metabotropic receptors linked to second messenger systems. These different glutamate receptors subtypes do not participate equally in excitotoxicity, but several receptor subtypes may be manipulated to reduce glutamate-induced Ca^{2+} overload in the ischemic brain.

Consistent with the prominent role of NMDA receptors in mediating glutamate-induced Ca^{2+} overload and rapidly triggered excitotoxic neurodegeneration in vitro, NMDA antagonists can reduce the death of cultured cortical neurons induced by hypoxia and glucose deprivation (Choi, 1992), and a substantial literature indicates that NMDA antagonists can reduce neuronal death in ischemic brain injury in vivo (Simon et al., 1984; McCulloch, 1992). Unfortunately, several recent clinical trials of NMDA antagonists in stroke patients have been disappointing (see Table 5.1); side effects including hallucinations, ataxia, or hypertension were prominent with several drugs (Lees,

Table 5.1. Agents recently tested as acute treatments for brain ischemia

Drug Category	Mechanism	Drug Name	Trial Status
Manipulate glutamate receptors			
Glutamate antagonists	AMPA antagonists	YM872	Phase III: ongoing
		ZK-200775 (MPQX)	Phase IIa: abandoned
	Competitive NMDA antagonists	CGS 19755 (Selfotel®)	Phase III: no efficacy
	NMDA channel blockers	aptiganel (Cerestat®)	Phase III: no efficacy
		dextrorphan	Phase II: abandoned
		dextromethorphan	abandoned
		magnesium	Phase III: ongoing
		NPS 1506	Phase Ib/IIa: suspended
		remacemide	Phase III in cardiopulmonary bypass: borderline efficacy
	NMDA glycine site antagonist	ACEA 1021 (Licostinel®)	Phase I: abandoned
		GV 150526	Phase III: no efficacy
	NMDA polyamine site antagonist	SL 82-0715 (eliprodil)	Phase III: abandoned
Reduce extracellular glutamate			
GABA agonists	↓ excitation, ↓ glutamate release	clomethiazole (Zendra®)	Phase III: no efficacy
Opiate antagonists		nalmefene (Cervene®)	Phase III: no efficacy
Serotonin agonists		Bay x 3702 (Repinotan®)	Phase III: ongoing
Sodium channel antagonists		Fosphenytoin (Cerebryx®)	Phase III: no efficacy
		BW619C89	Phase II: abandoned
Voltage-gated calcium channel antagonists	↓ Ca^{2+} influx, ↓ glutamate release	nimodipine (Nimotop®)	Phase III: no efficacy
		flunarizine (Sibelium®)	Phase III: no efficacy
Voltage-dependent potassium channel agonists		BMS-204352	Phase III: no efficacy
Unknown	↓ glutamate release, ↓ neuronal excitability, or ↓ NO-mediated injury	lubeluzole (Prosynap®)	Phase III: no efficacy
Block downstream mediators			
Free radical scavengers	↓ free radical-mediated injury	tirilazad mesylate (Freedox®)	Phase III: abandoned
		ebselen	Phase III: borderline efficacy
Phosphatidylcholine precursor	Membrane stabilizer	citicoline (Ceraxon®)	Phase III: no efficacy
Anti-apoptotic			
Growth factor	Anti-apoptotic?, ↑ NMDA receptor inactivation	Fibroblast growth factor (Fiblast®)	Phase II / III: abandoned
Anti-inflammatory			
Leukocyte adhesion inhibitor	Reduction of leukocyte infiltration	anti-ICAM antibody (Enlimomab®)	Phase III: no efficacy
		Hu23F2G	Phase III: no efficacy

Source: From Goldberg (2001).

1997). It remains to be seen whether efficacy can be established with this strategy, perhaps with the aid of enhancements in dosage regimens or drug characteristics, or whether utility in human stroke will prove to be fundamentally constrained (see below).

NMDA receptor blockade can be achieved in a variety of ways, using agents that act at distinct molecular sites within the receptor complex. Competitive antagonists bind the glutamate recognition site; channel blockers (or uncompetitive antagonists), bind sites within the channel pore; glycine antagonists bind the glycine recognition site; and noncompetitive antagonists bind other sites on NMDA receptors (e.g. polyamines, Zn^{2+}, redox site), downmodulating receptor activation via remote actions, for example, via allosteric changes. One might envision trying to improve the therapeutic index of NMDA antagonists in several ways. One strategy might be to find compounds capable of preferentially blocking overactivated NMDA receptors relative to physiologically activated receptors. Memantine, such an activity-dependent NMDA channel blocker, has shown promise in attenuating excitotoxic neuronal loss in vitro as well as brain damage in a rodent model of stroke, at potentially tolerable concentrations (Chen et al., 1992). Another approach might be to limit antagonism with partial antagonists, such as cycloserine (Hood et al., 1989), or by partial reduction in the endogenous glycine-site agonist D-serine (Snyder & Kim, 2000). A third approach might be to develop NMDA receptor subunit-selective antagonists along the lines of ifenprodil, an NR2B-selective antagonist with neuroprotective efficacy in vivo against focal ischemia (Gotti et al., 1988; Kemp et al., 1999). NR2B-containing NMDA receptors are expressed preferentially in the adult forebrain, so blocking these may give adequate neuroprotection against forebrain ischemia with relatively fewer side effects mediated by antagonism of hindbrain receptors. A novel approach to NMDA receptor antagonism was explored using an oral adeno-associated virus vaccine against the NR1 subunit; strong neuroprotection was demonstrated against focal ischemia-induced injury after a single-dose vaccine (During et al., 2000). This strategy could presumably be adapted to yield subtype-selective NMDA receptor blockade; but on the other hand, the resulting blockade cannot be easily controlled, and there is a risk of developing compensatory changes in the NMDA receptor system.

While NMDA antagonists may reduce the toxic influx of Ca^{2+} following cerebral ischemia in certain neurons, there is a risk that NMDA blockade may concurrently increase the likelihood of apoptosis in other neurons (Lee et al., 1999). Several studies have indicated that there can be an inverse relationship between intracellular Ca^{2+} concentration and the propensity to undergo apoptosis (Ca^{2+} set-point hypothesis, Koike & Tanaka, 1991). One unsettling corollary of this hypothesis is that NMDA-antagonist drugs may act as double-edged swords, attenuating excitotoxic necrosis in cells that are in a state of relative Ca^{2+} overload, but promoting apoptosis in Ca^{2+}-starved neurons. While Ca^{2+} overload and Ca^{2+} starvation are opposite states, both could be triggered by the same ischemic event, separated in space or time: for example, excitotoxic Ca^{2+} overload might predominate acutely, close to the ischemic core, whereas at later time intervals and further from the core, Ca^{2+} starvation and apoptosis might predominate. Supporting this idea is the recent observation that NMDA antagonists reduced primary excitotoxic injury in a rodent head trauma model at the impact site, but increased the severity of secondary apoptotic injury at distant sites (Pohl et al., 1999).

As discussed above, AMPA/kainate receptors can directly mediate excitotoxic cell death, albeit less powerfully than NMDA receptors. Besides promoting toxic Ca^{2+} entry, depolarization mediated by AMPA/kainate receptor activation may be a key factor promoting toxic levels of Zn^{2+} entry (see above). The competitive AMPA/kainate receptor antagonist NBQX is effective in reducing neuronal loss following both global (Sheardown et al., 1990) and focal (Buchan et al., 1991) cerebral ischemia. Likewise, the noncompetitive antagonist GYKI-52466 has also exhibited neuroprotective effects in studies of global (Le-Peillet et al., 1992) or focal (Smith & Meldrum, 1992) ischemia. Several factors that operate in the ischemic brain, in particular a shift towards acid pH due to buildup of lactic acid, may attenuate NMDA-receptor function and so reduce the prominence of NMDA-receptor-mediated neurotoxicity relative to AMPA- or kainate-receptor-mediated neurotoxicity. Acid pH may also enhance AMPA receptor-mediated neurotoxicity, perhaps by slowing recovery of cellular calcium homeostasis (McDonald et al., 1998b).

Another mechanism that has been proposed to enhance the contribution of AMPA/kainate receptor-mediated toxicity to ischemic neuronal death is an ischemia-induced enhancement of the expression of Ca^{2+} (and Zn^{2+}) permeable AMPA receptors, due to an alteration in subunit composition (reduced expression of AMPA receptor subunit GluR2/GluR-B (Pellegrini-Giampietro et al., 1997). However, on the downside, AMPA/kainate receptor blockade may be inadequate to reduce calcium overload on neurons where NMDA receptors have been strongly activated, and conversely, AMPA/kainate receptor blockade also has some potential to enhance apoptosis in the setting

of relative calcium starvation. Will the strategy work? A phase III trial of the AMPA antagonist YM872 in acute ischemic stroke is currently ongoing.

Although not directly mediating excitotoxicity, the metabotropic glutamate receptors can modify excitotoxicity and thus may be useful targets for therapeutic manipulation. These receptors, which are linked to G-proteins rather than ion channels, have been identified and segregated into three groups based on sequence similarity and mechanisms of signal transduction (Nakanishi & Masu, 1994; Conn & Pin, 1997). The first clue to neuroprotective actions was the demonstration that the nonselective mGluR agonist, trans-1-aminocyclopentane-1, 3-dicarboxylic acid (tACPD), could attenuate glutamate-induced neuronal death (Koh et al., 1991); non-selective activation of mGluRs also reduced infarct volume in vivo after focal ischemia (Chiamulera et al., 1992). Growing evidence suggests that activation of mGluR group II and III receptors, which typically have inhibitory effects on circuit excitation and glutamate release (Conn & Pin, 1997; Cartmell & Schoepp, 2000), may have more powerful antiexcitotoxic effects than non-selective agonists. A recent study suggests that the excitatory effects of group I mGluR activation may be harnessed to reduce neuronal apoptosis (Allen et al., 2000).

Blocking downstream mediators

Many enzymes including proteases, endonucleases, kinases, and phosphatases are activated directly or indirectly by increases in intracellular Ca^{2+} concentration and may contribute to cellular damage after ischemic insult. Compared with glutamate-receptor antagonists, interventions directed at blocking the downstream intracellular mediators of excitotoxicity may have a longer therapeutic window. For example, calpain inhibition by MDL 28170 decreased infarct volume after transient focal ischemia even when administered 6 hours after ischemia onset (Markgraf et al., 1998). Cytoplasmic phospholipase A2 ($cPLA_2$) is activated following NMDA receptor stimulation and promotes membrane phospholipid breakdown, liberating arachidonic acid (Dumuis et al., 1988) and producing free radicals. Pharmacological inhibition (Phillis, 1996) or genetic ablation (Bonventre et al., 1997) of $cPLA_2$ reduced brain injury in animal models of cerebral ischemia. Blocking PAF, a product of phospholipid breakdown, with gingkolide B or BN 52021 also reduced ischemic injury (Lindsberg et al., 1991).

Adding to the injury occurring during a given ischemic insult, postischemic reperfusion induces further tissue damage in the brain, probably mediated by the accelerated formation of several reactive oxygen species including superoxide, hydroxyl, and NO radicals (Kuroda & Siesjo, 1997). Free radical production is likely a specific downstream mediator of glutamate-induced neuronal death. As noted above, nNOS which is activated by elevated intracellular Ca^{2+} forms the weak oxidant, NO (Dawson & Snyder, 1994), but in the presence of superoxide anion can be converted to peroxynitrite (Beckman & Koppenol, 1996). Inhibiting nNOS either pharmacologically or genetically (via gene deletion) renders cultured neurons resistant to NMDA-induced death, and also reduces infarct volume in rodent models of transient focal ischemia (Samdani et al., 1997). Blockade of iNOS in inflammatory cells after ischemia will be discussed below. COX-mediated metabolism of arachidonic acid to a prostaglandin intermediate can also lead to the production of toxic superoxide anion (Chan et al., 1985). In cortical neuronal cultures, NMDA-induced excitotoxicity was decreased by a specific COX-2 inhibitor (Hewett et al., 2000) which also afforded neuroprotection against focal ischemia when administered to rats post-occlusion (Nogawa et al., 1997). Another link between excitotoxicity and free radicals is through excessive Ca^{2+} accumulation in mitochondria which uncouples energy production from electron transport and the formation of toxic levels of free radicals (Dugan et al., 1995; Reynolds & Hastings, 1995).

Beneficial results have been obtained with several free radical scavenger drugs in animal studies of ischemic or traumatic brain injury (Clemens et al., 1994), although the magnitude of neuroprotection observed has typically not been very large. Two phase III clinical trials involving free radical scavengers in acute ischemic stroke were conducted recently. One trial testing the lipid peroxidation inhibitor tirilazad mesylate was prematurely terminated due to concerns about the safety of the drug (Haley, 1998). The second trial involved treatment with ebselen, a selenoorganic compound with antioxidant activity, and did not demonstrate definitive efficacy (Yamaguchi et al., 1998). It is possible that more powerful antioxidant agents may yield greater therapeutic benefits. The spin trapping agent α-phenyl-*N*-tert-butyl nitrone (PBN) reduced infarct volume following focal ischemia in rats even when administered up to 3 hours after ischemia onset (Zhao et al., 1994).

One especially important consequence of reactive oxygen species formation may be single-stranded DNA breakage, leading to activation of the repair enzyme, PARP, and consequent depletion of cellular NAD^+ and energy stores (Szabo & Dawson, 1998). Pharmacological inhibition or gene deletion of PARP attenuated neuronal death induced by glutamate receptor agonists in vitro (Zhang et al., 1994; Eliasson et al., 1997), and decreased infarct size in

rodent focal ischemia studies (Zhang et al., 1994; Eliasson et al., 1997; Endres et al., 1997).

Antiapoptotic strategies

As noted above, accumulating evidence suggests that many brain cells undergo apoptosis following ischemic insults, including evidence that blocking apoptosis reduces ischemic brain damage in vivo or in vitro. Transgenic overexpression of *bcl-2* (Martinou et al., 1994) or its delivery via herpes virus vector (Linnik et al., 1995) were both found to reduce infarct volume in mice subjected to focal ischemia; and the survival of hippocampal CA1 neurons after transient global ischemia was enhanced in transgenic mice overexpressing bcl-2 (Kitagawa et al., 1998). Likewise, overexpression of *bcl-*x_L in transgenic mice reduced infarct volume following permanent focal ischemia (Wiessner et al., 1999). In experiments in our laboratory, mice lacking the *bax* gene exhibited reduced infarct volumes after transient focal ischemia (F. Gottron & D.W.C., unpublished data). While genetic manipulation of the Bcl-2 family of genes may not be a practical approach to antiapoptotic therapy in the human, future development of strategies to suppress or enhance this family of proteins (e.g. using antisense oligonucleotides) or to disrupt interactions between family members may prove beneficial (Nicholson, 2000).

A more immediately viable approach to antiapoptotic therapy might be via pharmacological caspase inhibitors. Intracerebroventricular (icv) infusion of the relatively non-specific caspase-3 inhibitor (*N*-benzyloxycarbonyl-Asp(OMe)-Glu(OMe)-Val-Asp(OMe)-fluoromethylketone or z-DEVD.FMK) decreased infarct size after transient focal ischemia (Hara et al., 1997) and reduced hippocampal CA1 cell death in transient global ischemia (Chen et al., 1998). In addition, the pan-caspase inhibitor, boc-aspartyl(OMe)-fluoromethylketone (BAF) given icv or systemically, was markedly neuroprotective in a rat model of neonatal hypoxia-ischemia even when administered 3 hours after the insult (Cheng et al., 1998). It is plausible that non-specific caspase inhibitors may be more effective at stopping the effector arm of apoptosis, owing to the broad-spectrum inhibition of all caspases in the cascade. Several caspases other than effector caspase-3 have been implicated in ischemic brain injury including the upstream caspases, caspase-9 (Krajewski et al., 1999), and caspase-8 which is activated via the death receptor pathway (Martin-Villalba et al., 1999). In addition, recent work suggests that caspase-11, a novel upstream caspase activated only under pathological conditions, is also activated after cerebral ischemia (Kang et al., 2000). Although concerns about the systemic blockade of all caspase activity are warranted, given the importance of apoptosis in normal physiologic processes, short-term administration after acute stroke may be tolerable. Another approach to inhibiting caspases may be modelled by the inhibitor of apoptosis (IAP) family of proteins, which bind and inhibit both initiator and effector caspases (Reed & Tomaselli, 2000). Included in this family is neuronal AIP (NAIP); inactivation by a hereditary mutation underlies motor neuron degeneration in spinal muscular atrophy (Roy et al., 1995). While antiapoptotic caspase inhibitors have not yet reached the clinic, drugs that block caspase-1 (or interleukin-1 converting enzyme, ICE) have recently been introduced for the treatment of rheumatoid arthritis (Nicholson, 2000).

The recent finding that the death receptor-mediated pathway to apoptosis may be involved in ischemic injury opens other potential targets for intervention. Development of means to suppress fasL or to block its receptor fas may be of benefit. The immunosuppressant FK506, a known neuroprotective agent following focal ischemia, suppresses the upregulation of fasL following ischemia (Martin-Villalba et al., 1999). In addition, one might try to mimic or augment the action of a naturally occurring protein known as FLICE-inhibitory protein (FLIP), which blocks the recruitment and activation of caspase-8 (formerly known as FLICE) and inhibits apoptosis induced by several death ligands (Thome et al., 1997).

As outlined above, transmembrane ionic fluxes may play a role in the regulation of programmed cell death, with Ca^{2+} starvation and K^+ efflux promoting apoptosis. Addressing these derangements through therapeutic intervention is plausible, but will have to be done in such a way that death due to excitotoxic calcium overload is not augmented. We have speculatively suggested a 'pull–push' approach to manipulating neuronal calcium homeostasis during ischemic insults: initially reducing calcium influx, with drugs like NMDA antagonists, to reduce excitotoxicity, and then later enhancing calcium influx to reduce calcium starvation and apoptosis (Lee et al., 1999). Similarly, targeting K^+ depletion in cells at risk for apoptosis, for example by augmenting K^+ influx or blocking upregulation of the neuronal delayed rectifier current, has to be accomplished with specificity, as this may also enhance circuit excitability and excitotoxicity.

Growth factors may be valuable in reducing apoptosis following cerebral ischemia. The expression of several growth factors increases in ischemic tissue, likely as a protective response. In addition, exogenous administration of growth factors including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophins 4/5 (NT-4/5), basic fibroblast growth factor (bFGF), and type-1

insulin-like growth factor (IGF-1) reduces brain damage in rats subjected to cerebral ischemia (Hefti, 1997). Some growth factors may also enhance nerve fibre sprouting and synapse formation after ischemic injury, thereby promoting functional recovery. Delivery issues are substantial obstacles to practical use, but may be surmountable through the development of small-molecule agonists that bind immunophilins, and have neurotrophic and neuroprotective actions that can be separated from immunosuppressant effects (Snyder et al., 1998). Unfortunately, the first trial of a growth factor for treatment of ischemia, bFGF in acute ischemic stroke, was unsuccessful (Goldberg, 2001). In addition, in a fashion akin to the situation with manipulation of calcium homeostasis, a downside risk of at least the neurotrophins and IGF-1 may be the enhancement of excitotoxic necrosis (Koh et al., 1995).

Anti-inflammatory approaches

Interference with inflammatory cascades is another general approach likely to aid neural cell survival. A key early event amenable to therapeutic intervention may be the suppression of key cytokines which are induced shortly after ischemia onset. For example, delivery of the IL-1 receptor antagonist (IL-1ra, which is a naturally occurring inhibitor in the brain) by intracerebroventricular injection (Loddick & Rothwell, 1996) or by adenoviral vector (Betz et al., 1995) reduced brain injury following focal ischemia in rats. Although clinically impractical, these interventions underscore the potential of this pathway as a target for neuroprotection. The peripheral administration of IL-1ra (a more clinically relevant route) reduced infarct volume in a rodent focal ischemia model (Relton et al., 1996). Likewise, interfering with TNF-α signalling using an anti-TNF-α monoclonal antibody or soluble TNF-α receptor I (which acts by competing with membrane receptors) resulted in attenuation of brain injury after focal ischemia (Barone et al., 1997a), likely by improving microvascular perfusion in ischemic cortex (Dawson et al., 1996). These effects must be interpreted with caution, as cerebral ischemia in mice lacking TNF receptors demonstrated larger infarct volumes than their wild-type counterparts (Bruce et al., 1996).

One of the detrimental effects of TNF-α is the upregulation of endothelial cell adhesion molecules and leukocyte adherence to blood vessels, another potential target for intervention. Administration of antibodies to either ICAM-1 or the β-integrins (CD11a/CD18) expressed on leukocytes decreased infarct size in rodent transient (Chopp et al., 1996), but not permanent focal ischemia (Zhang et al., 1995). In addition, mice lacking the ICAM-1 gene were less susceptible to ischemia-reperfusion injury (Connolly et al., 1996). A phase III clinical trial using anti-ICAM antibodies failed, possibly due to murine antibody-induced complications; however, another trial using humanized antibodies directed against CD11/CD18 also failed to show efficacy in patients with acute ischemic stroke (Enlimomab Acute Stroke Trial Investigators and Sherman, 1997; Goldberg, 2001).

Following cerebral ischemia infiltrating leukocytes increase expression of iNOS, peaking 12–48 hours after ischemia onset (del Zoppo et al., 2000). The relatively selective iNOS inhibitor, aminoguanidine, reduced infarct volume following focal ischemia even if given 24 hours after MCA occlusion (Nagayama et al., 1998). Confirming the pharmacological effect, mice lacking the iNOS gene also had smaller infarcts than their wild-type littermates (Iadecola et al., 1997). The delayed expression of iNOS following cerebral ischemia makes it an attractive target for intervention in human stroke with a potentially long therapeutic window.

The secretion of vasoactive mediators by endothelial cells is another consequence of ischemia-induced inflammation, and may lead to vasoconstriction and microvascular thrombosis, resulting in further exacerbation of ischemic damage (del Zoppo et al., 2000). Two classes of agents, attractive because they are currently in clinical use, may be able to reduce ischemic brain damage by altering vasoactive mediators. The cholesterol-lowering agents, 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors (or statins) decreased cerebral infarct size in mice by upregulating eNOS, resulting in increased cerebral blood flow (CBF) during ischemia (Endres et al., 1998). In addition, the estrogens have been shown to have neuroprotective properties in rodent cerebral ischemia models. Although the mechanism of action is not as well defined as that of the statins, it is believed that improvement in CBF may contribute, in part by up-regulation of NOS. Other proposed neuroprotective mechanisms include antioxidant actions, induction of *bcl-2* and neurotrophic factors, and modulation of excitotoxicity (Hurn & Macrae, 2000).

White matter injury

While much of the current work in neuroprotection has focused on blocking injury mechanisms relevant to dendrites and neuronal perikarya (grey matter), myelinated fibre tracts (white matter) are also damaged by ischemic insults and could benefit from targeted neuroprotective approaches. Many antiexcitotoxic treatments, such as NMDA receptor antagonists, would not be expected to

protect white matter. Experiments using isolated rat optic nerve as an in vitro model for myelinated CNS tracts have revealed that compound action potentials disappear after 8–10 minutes of anoxia, evidence that white matter tracts are critically dependent on oxidative metabolism to maintain energy for excitability (Waxman et al., 1991). Hypoxic–ischemic energy depletion leads to failure of the membrane Na^+–K^+-ATPase, leading to membrane depolarization and accumulation of axoplasmic free Na^+, largely due to influx through tetrodotoxin-sensitive, voltage-gated Na^+ channels subserving action potentials. This elevation in axonal $[Na^+]_i$ stimulates the Na^+/Ca^{2+} exchanger, resulting in Ca^{2+} influx and toxic elevations in $[Ca^{2+}]_i$ (Stys, 1998), leading to consequences presumably similar to those outlined in studies of cultured neurons. Agents that block voltage-gated Na^+ channels, including local anesthetics, antiarrhythmics and certain anticonvulsants, are protective in the optic nerve anoxia model, as are the Na^+/Ca^{2+} exchange inhibitors, bepridil and benzamil (Stys, 1998).

Oligodendrocytes, responsible for myelinating nerve fibres in the CNS, express Ca^{2+}-permeable AMPA receptors and are highly vulnerable to AMPA-receptor-mediated injury in vitro (Matute et al., 1997). In addition, cultured oligodendrocytes deprived of oxygen and glucose were protected by an AMPA receptor antagonist, and injection of AMPA into rat brain white matter induced widespread oligodendrocyte death (McDonald et al., 1998a). Although most oligodendrocytes are remote from synapses, they may be exposed to excess extracellular glutamate, released by adjacent neurons or astrocytes following ischemic insults. Glutamate may also be released along axons through a non-synaptic process mediated by reversal of the Na^+/K^+-glutamate transporter (Nicholls & Attwell, 1990).

Clinical trials and future directions

Despite the wealth of preclinical data supporting the efficacy of many neuroprotective agents, why have these agents failed so far in human trials? The answer to this vexing question probably lies partly in the difficulty of conducting human clinical trials of neuroprotective agents, and partly in limitations of neuroprotective efficacy in the agents tested to date. Clinical trials have many more variables than studies with experimental animals in controlled laboratory settings. While most laboratory investigations are conducted on young healthy animals, patients suffering strokes or cardiac arrest typically are elderly and have concomitant diseases such as hypertension or diabetes; etiology, severity, and lesion location (cortical vs. subcortical infarction) typically vary widely. The endpoint used to determine efficacy is another important difference between human and experimental studies: most animal studies have utilized lesion size measured hours to days after ischemia, whereas human clinical studies have relied upon functional outcome as measured by clinical assessment scales (Barthel Index, Rankin Score, etc.) usually several months after ischemia. A drug that reduces lesion size may or may not produce a detectable improvement in functional outcome, depending upon multiple other factors, in particular lesion location. In the future, enhanced neuroimaging techniques may be able to provide sufficient quantitation of lesion volume to be able to serve as surrogate outcome measures for assessing neuroprotective interventions. Furthermore, techniques for imaging at-risk tissue, such as diffusion- and perfusion-weighted magnetic resonance imaging, may permit each patient to serve as his/her own control (comparing the brain volume initially at risk, to the volume of damage that ultimately evolves with or without intervention).

Most clinical trials of neuroprotective agents to date share, at least in part, a common rationale of reducing excitotoxicity. The future of neuroprotective approaches for brain ischemia will likely lie in broader aims, specifically encompassing strategies to limit ischemic apoptosis and post-ischemic inflammation. Indeed, as discussed above, the postulate that the prominence of apoptosis in the brain after ischemic insults approximates that of excitotoxicity, supported by substantial emerging evidence, places many anti-excitotoxic treatments on a dangerous balance point (Fig. 5.1). Many approaches useful in limiting excitotoxicity, reducing circuit activation, glutamate release, membrane depolarization, calcium entry, etc., may have a downside, enhancement of apoptosis. Perhaps the key difference between experimental studies, for the most part conducted with lissencephalic rodent brains and sharply controlled ischemic insults, and human stroke, involving a gyrencephalic brain and sometimes fluctuating levels of ischemia, is a greater prominence of mild ischemia and apoptosis in the latter setting.

One path ahead may thus be to combine approaches, so that excitotoxicity and apoptosis might be simultaneously reduced. Two experimental studies have so far tested the concurrent administration of NMDA antagonists and inhibitors of apoptosis. Coadministration of dextrorphan and cycloheximide produced greater than 80% reduction of infarct volume after transient focal ischemia in rats, better than the effect of optimal doses of either agent alone (Du et al., 1996). Furthermore, the combination of MK-801 and z-VAD.fmk demonstrated neuroprotective synergy in reducing infarction, and an extended therapeu-

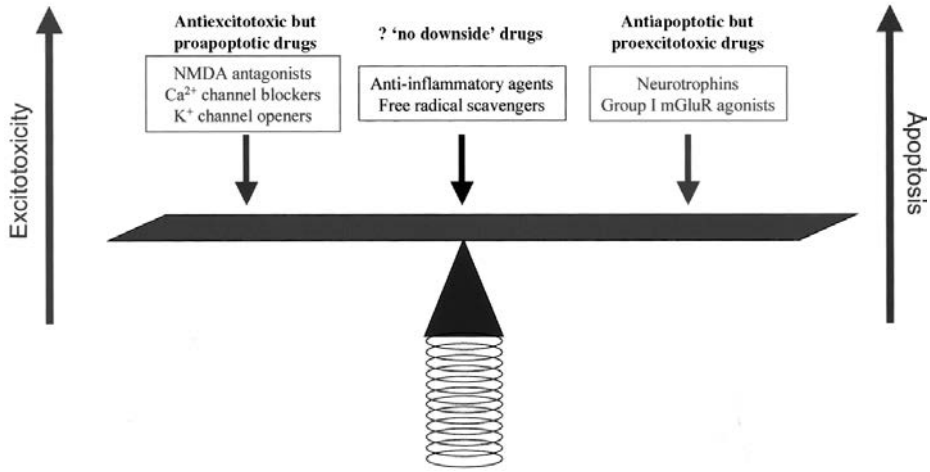

Fig. 5.1. Balancing antiexcitotoxic and antiapoptotic approaches to neuroprotection in the ischemic brain. Speculative diagram depicting the possibility that some approaches may reduce excitotoxicity but enhance apoptosis, or vice-versa; whereas some 'no downside' approaches may reduce both forms of death (or at least reduce one without enhancing the other).

tic window compared to that of either drug alone (Ma et al., 1998).

Alternatively, it may be possible to target antiexcitotoxic and anti- apoptotic approaches in time or space to maximize benefits and minimize deleterious consequences. With progressive enhancements in brain imaging, both in terms of resolution and in terms of yielding information about functional state, one can envision a time when imaging techniques are used to select and direct the optimal neuroprotective strategies for a given specific clinical situation. For example, the development of methods for identifying the early activation of the apoptosis cascades, or levels of intracellular free calcium, might enable clinicians to know when to stop delivery of acutely initiated NMDA antagonist drugs, and begin treatment with caspase inhibitors or neurotrophins.

A third path ahead might be to prioritize the deployment of 'no downside' drugs: capable of limiting excitotoxicity or apoptosis, but lacking concurrent ability to enhance the other form of death. Examples of such drugs might be PARP inhibitors for excitotoxicity or caspase inhibitors for apoptosis; antioxidants or anti-inflammatory drugs might be able to reduce both forms of death (Fig. 5.1).

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6

Promoting recovery of neurological function

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This chapter focuses on the biologically driven strategies that are being developed to enhance that recovery following neural injury. It is beyond the scope of this chapter to review the entire field of neurologic rehabilitation, much of which involves orthotic, prosthetic, behavioural, psychological and sociological approaches. Many of these approaches are accumulating substantial evidence for their effectiveness and their omission here should not be interpreted as an indication of lack of importance. Several recent monographs on neurologic rehabilitation cover them in greater detail (Dobkin, 1996; Lazar, 1998; Ozer, 2000). Here, the behavioural, physiological and structural mechanisms by which the nervous system adapts spontaneously to injury will be reviewed. Then some promising current approaches to optimizing recovery by utilizing the nervous system's own adaptive processes will be discussed. Finally the mechanisms that limit the ability of the nervous system to reconstitute the lost neural circuitry will be examined, and strategies that are being developed to overcome these limitations will be summarized.

Mechanisms of spontaneous recovery

Following injury to the nervous system, it is usual for patients to recover to a variable degree. This is a consequence of three processes. First, depending on the type of injury, an ischemic/traumatic penumbra (Heiss & Graf, 1994; Tator, 1995) results in temporary dysfunction of neuronal elements due to pressure from edema, excitotoxicity with intracellular (intramitochondrial) calcium accumulation (Stout et al., 1998), extracellular accumulation of potassium and magnesium, and inflammation (Carlson et al., 1998) (Fig. 6.1). If they do not kill the neurons, these changes eventually resolve and neuronal function is restored. Secondly, patients can employ a variety of behavioural adaptations to restore equivalent functions to those lost as a consequence of the structural and physiological alterations brought about by the injury. Thirdly, physiological changes and short distance anatomic rearrangements in spared neural pathways may result in compensatory enhancement in transmission through those pathways to reproduce or substitute for lost functions. A fourth mechanism, frank regeneration of injured axons and replacement of lost neurons to reconstitute the interrupted synaptic circuits, is currently believed not to occur to a significant degree in the mammalian CNS. Strategies to promote such neural repair are discussed later in the chapter.

Behavioural adaptation

Behavioural adaptation refers to the conscious substitution of behaviours, based on spared physiological functions for the lost more natural or commonly utilized functions, aimed at producing the same desired result. For example, a right-handed person who has suffered a left hemispheric stroke might begin using his left hand to perform functions previously performed with the right hand. To a large extent, occupational therapy is involved in teaching patients to utilize effective behavioural adaptations (see below). To the extent that the newly acquired behaviours must be learned and learning involves physiological plasticity, most behavioural adaptations involve physiological plasticity as well.

Cortical remodelling

Experiments utilizing electrophysiological, stimulation and imaging techniques have demonstrated that injuries to both the peripheral and central nervous systems result in alterations in the central representations of sensory and motor functions in such a way as to suggest effective

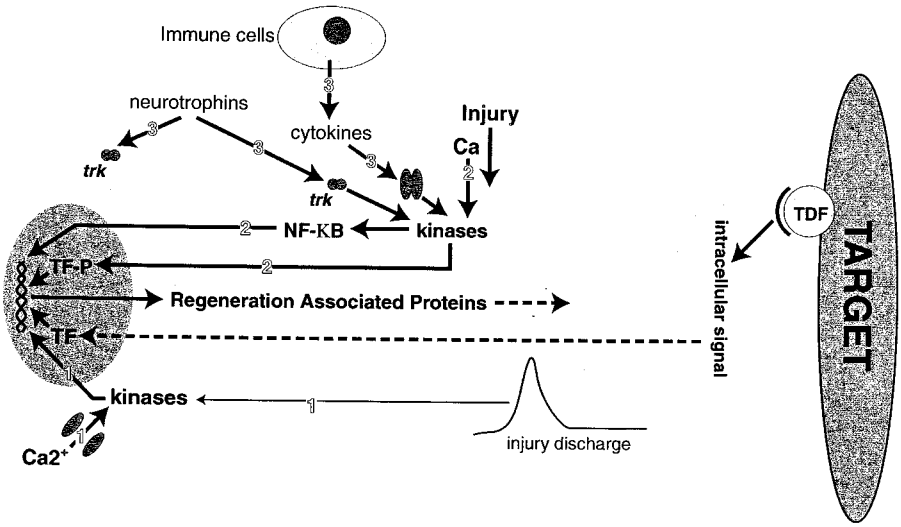

Fig. 6.1. Molecular responses to axon injury leading to regeneration. Neural injury gives rise to an injury-related discharge (1) that back-propagates towards the cell body where it leads to the opening of voltage-dependent calcium channels. This calcium influx activates kinases, including CaMKII, PKA, PKA and MAP kinase, that phosphorylate a variety of target proteins. Especially important targets of these kinases are transcription factors such as CREB and NF-κB. These transcription factors induce the expression of regeneration-associated proteins such as GAP-43, CAP-23 and several cytoskeletal proteins. Injury also results in bulk calcium influx at the site of injury (2). The longer-term response to injury involves the release of neurotrophins (NGF, BDNF, NT-3, NT-4/5) and cytokines (CNTF, LIF, IGF, IL-6) that activate intracellular signalling pathways via specific receptors (3).

compensation for the injury. These changes following injury resemble in many ways the cortical changes that are observed following learning or other experiences. A common term used to describe these altered physiological responses following injury and training is 'neural plasticity'. Many plastic processes result from alterations in intracellular signalling cascades but, in many cases, ultrastructural or immunohistological alterations also are observed.

Reorganization of synaptic contacts is especially prevalent in the cortex, where sensory and motor maps undergo extensive reorganization and remapping as a result of experience (Buonomano & Merzenich, 1998). One well-known example of neural plasticity within the cortex is the rearrangement of hand representation in the somatosensory cortex following injury to a peripheral nerve or amputation of a digit. Following such deafferentation, the cortical representation of adjacent regions expands over the surface of the cortex for a distance of approximately 1.5 mm, an area that encompasses the distribution of terminals of thalamocortical neurons (Rausell & Jones, 1995). Because this initial expansion occurs rapidly, it might be the result of the unmasking of formerly inactive synaptic connections that were previously masked by inhibition from the lost afferent pathway (Jones, 1993). At longer recovery times, the area covered by the shifting sensory map increases substantially beyond that covered by the distribution of thalamic afferents (Pons et al., 1991).

Cortical plasticity may contribute to functional recovery following a CNS injury such as stroke. A region of the sensory cortex to which behaviourally important portions of the finger tips project was destroyed by microlesions, the behaviour of monkeys in a learned sensorimotor task at first deteriorated, but then improved (Xerri et al., 1998). Concomitantly, the central projection for those finger tips shifted to neighbouring regions of cortex. These findings are consistent with 'substitution' and 'vicariation' models of recovery from brain damage and stroke. In these models, adaptive reorganization of the cortex takes place following a lesion in such a way that other regions of the cortex that may not have been originally involved in the function of the injured area now directly compensate for the dysfunctional area (Xerri et al., 1998).

Afferent input to the cortex can also be modulated by experience, including environmental enrichment and training. Increases in dendritic arbourization and synaptic contacts in the cerebellar and cerebral cortices have been observed in many environmental enrichment studies and after extensive training (van Praag et al., 2000). These alterations are thought to result from the induction of use-

dependent patterns of neural activity that lead to the selective reshaping of neuronal connections. Whether similar mechanisms act following injury is not known, but the similarity between the two processes suggests that they may share overlapping molecular mechanisms. Repeated sensory overstimulation and training on digital dexterity tasks can increase the receptive fields of the involved digits within the primary somatosensory cortex in primates (Buonomano & Merzenich, 1998). Enlarged representation of relevant movements is also observed in the primary motor cortex after training (Buonomano & Merzenich, 1998). Such remapping results in a much finer representational grain than normal. Thus, for both sensory and motor cortices, experience alters the cortical map in a way that correlates with the behavioural demands of the task.

Using transcranial magnetic stimulation (TMS), functional imaging, magnetoencephalography or high resolution electroencephalography, many examples have been documented of cortical remapping in normal human subjects as well as in patients with peripheral or central nervous system lesions (Classen et al., 1998; Karni et al., 1995). For example, focal stimulation of the motor cortex using TMS was used to evoke thumb movements before and after the practising of thumb movements. Focal TMS more often evoked movements in the recently practised direction than in other directions (Classen et al., 1998). Thus, in humans, training rapidly and transiently induces a change in the cortical network representing the movement of the thumb, thereby encoding the details of the practised movement.

What molecular mechanisms are responsible for this newly emergent representation of sensory information or motor maps within the cortex? There are several mechanisms that might be responsible for the neural plasticity that underlies the long-term alterations in cortical maps that follow injury or training. Two major mechanisms are the restructuring of neuronal morphology and changes in the strength of synaptic connections. It is important to note that these mechanisms may be inter-related. The induction of synaptic plasticity is accompanied by morphological changes in neurons (Segal & Andersen, 2000). Morphological changes might result from the sprouting of collateral axon branches, the extension of dendritic arbours, the creation of dendritic spines, and the creation of new synapses. The expansions of sensory receptive fields produced by long-term alterations in afferent input are probably due to physiological and/or anatomical plastic changes (Buonomano & Merzenich, 1998). Activity-dependent modifications in synaptic strength may play a critical role in cortical remapping, perhaps via NMDA receptor mediated long-term potentiation (Garraghty & Muja, 1996), as has been described for synaptic plasticity in the hippocampus (Bliss & Collingridge, 1993).

To investigate the hypothesis that synaptic plasticity underlies cortical map reorganization, researchers have used pharmacological, electrophysiological and genetic approaches. Recent experiments in humans have used the changes in TMS-evoked thumb movements after training (Classen et al., 1998) to explore the effects of drugs that block synaptic plasticity in the motor cortex in vitro on cortical map plasticity in vivo. An NMDA receptor antagonist, dextromethorphan, and a GABA-A receptor modulator, lorazepam, both of which block the induction of long-term potentiation (LTP) in the motor cortex in vitro, block the use-dependent reorganization of the cortical thumb representation in human subjects (Butefisch et al., 2000). By contrast, lamotrigine, a drug that modifies sodium and calcium channels without altering LTP induction, does not alter cortical map reorganization. Thus, these findings point to a striking similarity between use-dependent cortical plasticity and the cellular mechanisms of LTP, which is thought to underlie learning and memory (Martin et al., 2000; Rioult-Pedotti et al., 2000). Genetic approaches in mice have been used to study plasticity in the barrel (somatosensory) cortex, which receives input from the whiskers. Removal of all facial whiskers (vibrissae) except for one results in the expansion of the spared whisker's functional representation in the somatosensory cortex. Mutant mice with impairments in LTP, including those with alterations in CaMKII or CREB, exhibit impairments in this form of experience dependent cortical plasticity (e.g. Glazewski et al., 2000). Thus, understanding the molecular mechanisms underlying forms of synaptic plasticity, such as LTP, may provide insights into the molecular basis of cortical remodelling following injury.

Physiological plasticity

Since its introduction over a century ago by Santiago Ramón y Cajal, the word 'plasticity' has been used in many ways by neuroscientists studying a variety of processes ranging from recovery from neural injury to learning and memory to drug addiction and psychiatric disorders (Nestler & Hyman, 1999). We will focus our discussion on two broad forms of plasticity: physiological plasticity, in which patterns of use and disuse modify synaptic strength (synaptic plasticity) and modulate neuronal firing (neural plasticity), and anatomical plasticity, which involves structural alterations (e.g. sprouting, pruning, regeneration) following injury or use. Many of these forms of plasticity share

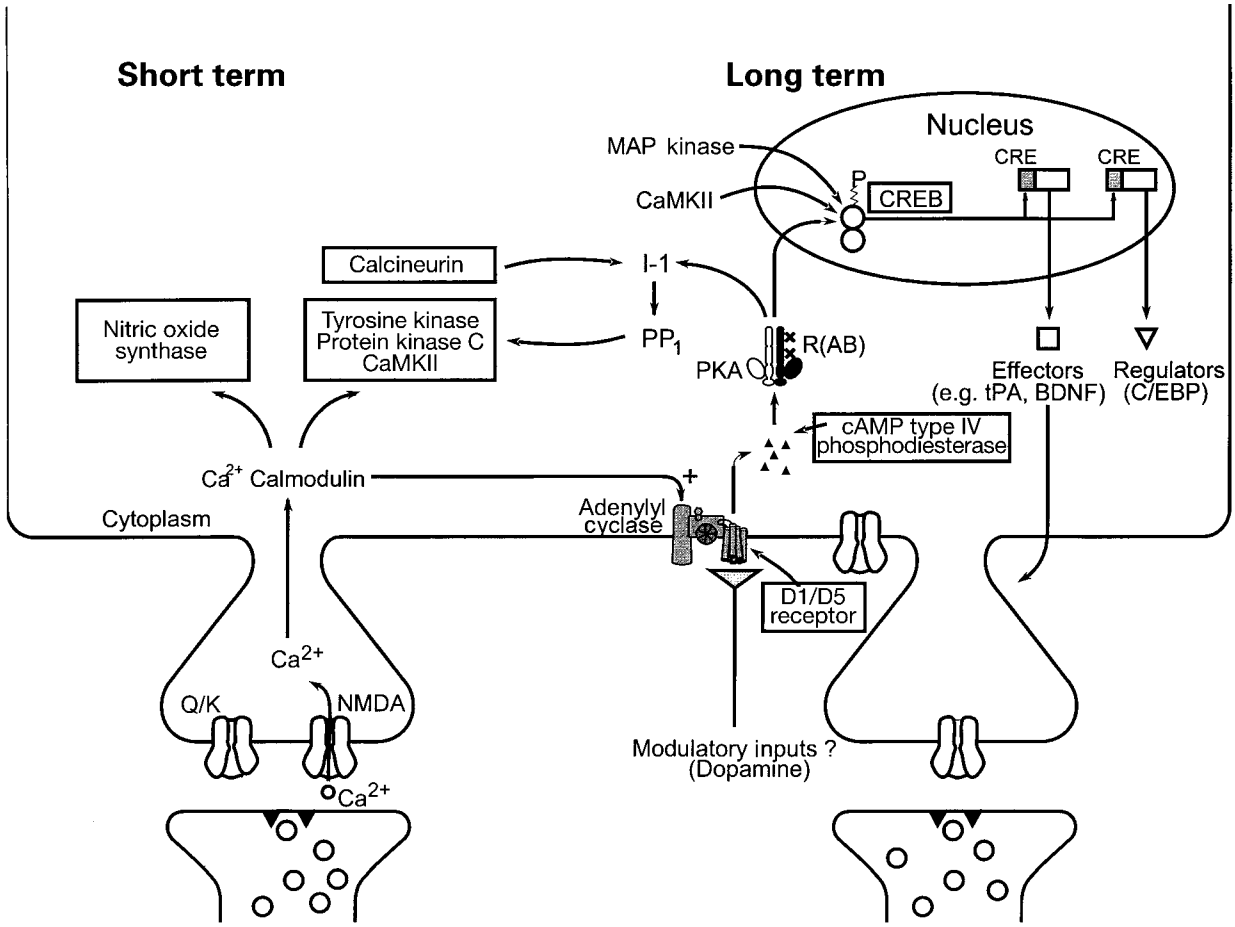

Fig. 6.2. Molecular mechanisms of synaptic plasticity. Studies of long-term potentiation in the hippocampus have revealed the signaling pathways that mediate changes in synaptic strength. Activation of the NMDA type of glutamate receptor leads to calcium influx and the activation of calcium sensitive enzymes such as CaMKII, PKC and calcineurin. Other signaling pathways involved in the early phase of LTP include tyrosine kinases and nitric oxide synthase, which may give rise to a retrograde messenger in the form of the diffusible gas NO. Long-term changes in synaptic strength result from the activation of adenylyl cyclase by calcium or modulatory neurotransmitters that stimulate G protein coupled receptors. This activation of adenylyl cyclase leads to the synthesis of the second messenger cAMP, which, in turn, activates PKA. PKA plays a central role in initiating the events that lead to long-lasting changes in synaptic strength by acting on a variety of targets, including the transcription factor CREB. CREB, which is also the target of other kinases such as CaMKIV and MAP kinase, turns on a variety of effector and regulatory genes whose gene products include tPA and BDNF. (Adapted with permission from Abel et al., 1997.)

common underlying molecular mechanisms mediated by intracellular signal transduction cascades (Girault and Greengard, 1999). The responses of a neuron to neurotransmitters or neuromodulators, or to neural injury are mediated by intracellular signal transduction pathways that include a large variety of protein kinases, protein phosphatases and adapter molecules (Fig. 6.2). Kinases play a particularly important role in signalling cascades that respond to alterations in synaptic input. These kinases include tyrosine kinase receptors that are activated by the binding of a growth factor or a neurotrophic factor such as BDNF or NGF, as well as cytoplasmic Src family tyrosine kinases, such as Fyn. In other cases, serine/threonine kinases, such as protein kinase A (PKA) or protein kinase C (PKC), may be activated by second messenger molecules, such as cAMP or IP_3, respectively. These second messengers are formed when a neurotransmitter (e.g. norepinephrine or dopamine) or hormone (e.g. insulin) binds to a receptor that is linked by a GTP-binding-protein. These G proteins activate enzymes such as adenylyl cyclase or phospholipase C, thus leading to the production of cAMP or IP_3. Calcium is another second messenger molecule that

activates calcium-dependent enzymes, including certain isoforms of adenylyl cyclase and PKC. Once kinases are activated, they modulate the activity of a number of target proteins ranging from ion channels to metabolic enzymes to transcription factors. These transcription factors are potentially important candidates to mediate long-term changes in neural function that might occur following injury and during the recovery from neural injury. Transcription factors bind to DNA and regulate the expression of one or more genes, whose protein products may mediate long-term changes in the physiology and structure of the neuron, including processes such as programmed cell death (apoptosis), increased synthesis and release of neurotransmitter, or the sprouting of extra branches by spared axons.

Although we will consider physiological and anatomical plasticity in separate sections, it is worth noting that there has been a convergence of these two processes in recent years (Squire & Kandel, 1999). Kandel's work on the mollusk *Aplysia* has revealed that long-term memory for sensitization is accompanied by the increased strength of particular synaptic connections as well as the growth of new synaptic connections between neurons mediating the reflex that has undergone sensitization (Abel & Kandel, 1998). These long-term changes in behaviour, neural anatomy and synaptic function are mediated by the activation of genes containing cAMP response elements (CRE) through the phosphorylation of the transcription factor CRE-binding protein (CREB). A critical challenge is to see if such transcription-mediated changes in neural function and structure underlie the recovery from neural injury.

Long-term potentiation

Synaptic plasticity, the use-dependent change in the strength of neuronal connections in the brain, is thought to underlie memory storage and may play a crucial role in a variety of neurological and mental disorders, including Alzheimer's disease, mental retardation, epilepsy and depression. During recovery following neural injury, the changed pattern of activity in the remaining synaptic connections may alter the strength of these connections and perhaps contribute to recovery. Repeated high frequency stimulation of excitatory glutamatergic pathways to the pyramidal cells of the CA1 region of hippocampus results in a large increase in synaptic efficacy of those pathways that may last hours or even days, a phenomenon termed LTP (Martin et al., 2000). LTP has been observed in many locations in the brain, and the cellular mechanism may vary from location to location. Further, some synapses in the brain undergo long-term depression, depending on the pattern and intensity of stimulation (Linden & Connor, 1995). Our discussion will focus on LTP in the CA1 region of the hippocampus because of the extensive knowledge of the signal transduction mechanisms that mediate this form of synaptic plasticity (Fig. 6.2). This form of LTP depends critically on the NMDA subtype of glutamate receptor, a receptor that serves as a 'coincidence detector' because it is activated in response to both neurotransmitter and membrane depolarization. Once activated, the NMDA receptor is permeant to calcium, and thus calcium is a critical second messenger mediating LTP in hippocampal area CA1.

Genetically modified mice have been particularly useful in the study of the molecular basis of hippocampal LTP. The analysis of genetically modified mice provides a way to test whether a particular gene product is important for synaptic plasticity and provides a useful bridge between molecules and synaptic plasticity, on the one hand, and systems of neurons and behaviour, on the other. Many of these studies have focused on an early, transient phase of LTP (E-LTP) that lasts 1 to 2 hours in hippocampal slices. These studies have shown that genetic manipulation of any one of several kinases, including calcium/calmodulin-dependent protein kinase II (CaMKII) and fyn, interferes with E-LTP, and also often results in impaired short-term memory (Fig. 6.2; Martin et al., 2000). The influx of calcium that occurs during the induction of LTP also appears to result in the creation of a retrograde chemical signal directed back to the presynaptic terminal, where it may regulate neurotransmitter release. The nature of the retrograde signal is not known, but both nitric oxide and carbon monoxide have been suggested as candidate retrograde signals (Zhuo et al., 1999).

The study of amnesic patients and experimental animals has revealed, however, that the role of the hippocampus in memory storage extends from weeks to months (Squire & Alvarez, 1995), suggesting that longer lasting forms of hippocampal synaptic plasticity may be required. LTP in the CA1 region of hippocampal slices, like many other forms of synaptic plasticity and memory, has distinct temporal phases (Huang et al., 1996). In contrast to E-LTP, the late phase of LTP (L-LTP) lasts for up to 8 hours in hippocampal slices and for days in the intact animal. Long-term memory storage is sensitive to disruption by inhibitors of protein synthesis, and L-LTP in the CA1 region of hippocampal slices, unlike E-LTP, shares with long-term memory a requirement for translation and transcription (Huang et al., 1996; Silva et al., 1998).

Although extensive information is available about E-LTP and its relation to behaviour, less is known about L-LTP. Pharmacological experiments have suggested that PKA

plays a critical role in L-LTP (Fig. 6.2) (Huang et al., 1996). One of the nuclear targets of PKA is CREB, and CRE-mediated gene expression is induced in response to stimuli that generate L-LTP and long-term memory. Behavioural studies of mice lacking the α and Δ isoforms of CREB have suggested that this transcription factor plays a role in long-term memory storage (Silva et al., 1998). The deficits in long-lasting forms of LTP and in long-term memory observed in transgenic mice with alterations in PKA suggest that this signal transduction pathway plays a role in initiating the molecular events leading to long-lasting changes in neuronal function in mammals (Abel et al., 1997). The importance of the cAMP/PKA pathway is further underscored by recent work examining mutant mice lacking calcium/calmodulin activated isoforms of adenylyl cyclases, AC1 and AC8 (Wong et al., 1999). These mutant mice exhibit deficits in long-lasting forms of LTP and in long-term memory that are strikingly similar to those observed in the R(AB) transgenics.

Alterations in the subunit composition of NMDA receptors in the hippocampus can also modulate synaptic strength and hippocampal function. This is shown by the study of mice overexpressing the 2B subtype of NMDA receptor (Tang et al., 1999). In these transgenic mice, the NMDAR2B subunit is expressed in neurons within the forebrain using the CaMKIIα promoter, resulting in increased activation of the NMDA receptor and increased long-term potentiation. These mice also exhibit increased performance on a number of behavioural tasks. This study has received much attention, both in the scientific literature and in the popular press and it would seem to suggest that the 2B subunit of the NMDA receptor would be an interesting candidate for enhancing neuronal function.

Memory suppressor genes

The study of synaptic plasticity in a number of systems has revealed the existence of proteins that act as inhibitory constraints to block increases in synaptic strength and impede memory storage. These inhibitory constraints have been termed memory suppressor genes by analogy to tumour suppressor genes that restrict cell proliferation (Abel et al., 1998; Cardin & Abel, 1999). The study of memory suppressor genes is important not only for understanding the link between synaptic plasticity and learning, but also for identifying potential targets for future pharmaceuticals to treat memory disorders. In *Aplysia*, memory suppressor gene products act at each step in long-term facilitation: in the cytoplasm to regulate kinase activity, in the nucleus to alter the activity of transcriptional regulatory proteins, and on the cell surface to modulate cell–cell interactions. During long-term facilitation following serotonin treatment, the activity of PKA is constitutively enhanced as a result of the proteasome-mediated degradation of the regulatory subunit of PKA. A cell adhesion molecule, apCAM, is internalized via a MAP kinase-mediated process thus allowing for defasiculation and synaptic growth. In the nucleus, a transcriptional repressor, CREB-2, is inactivated, thus enabling the induced expression of a number of effector genes.

One potential memory suppressor gene product in mammalian systems is cAMP phosphodiesterase. Rolipram, an inhibitor of type IV cAMP phosphodiesterase, induces persistent long-term potentiation in hippocampal area CA1 after a single tetanic train of stimulation, which normally gives rise to a transient potentiation in untreated slices (Barad et al., 1998). Behaviourally, rolipram treatment prior to training increased long-term memory for contextual fear conditioning, without altering short-term memory. Further, rolipram is able to overcome the deficits in synaptic plasticity and spatial memory that are observed with aging in rodents (Bach et al., 1999). Thus, memory suppressor genes may be particularly attractive targets for therapies designed to enhance neural function.

Denervation supersensitivity

Following the loss of a synaptic input, a neuron generally becomes more responsive to that transmitter, a phenomenon termed 'denervation supersensitivity'. This supersensitivity is usually specific to the neurotransmitter at that synapse. At the neuromuscular junction, an increase in the number of extrajunctional acetylcholine receptors is observed due to loss of electrical activity in the muscle (Lomo & Rosenthal, 1972). In the CNS, the depletion of dopamine in the nigra-striatal tract results in supersensitivity to dopamine in the basal ganglia (Rioux et al., 1991). A similar receptor hyperactivity has been observed in some patients with Parkinson's disease and this may explain some of the dyskinesias observed after chronic L-dopa treatment of Parkinson's disease patients (Nguyen et al., 2000). Such changes in receptor responsiveness may also play a role in the response of schizophrenics to neuroleptics (Seeman & Van Tol, 1995). The upregulation of receptors or the signal transduction pathways that they activate may also be the basis for the behavioural changes induced by chronic exposure to drugs of abuse such as cocaine or morphine (Nestler, 1997). Denervation supersensitivity appears to be a widespread phenomenon seen in many neurotransmitter and neuromodulator systems. Thus, it may play a role in the response to injury and the subse-

quent recovery of function. Such supersensitivity of α-adrenergic receptors in peripheral nociceptors has been proposed as a mechanism for the causalgic pain that follows partial nerve injuries (Perl, 1999). Whether supersensitivity plays a role in the hyper-reflexia or functional recovery seen after partial spinal cord injury represents an important direction of future research.

Anatomical plasticity

Some of the molecular mechanisms of neural plasticity result in changes of neuron structure, such as axonal sprouting and dendritic remodelling. These changes are important, not only because they have functional consequences; they may represent a potential for more profound regenerative responses.

Collateral sprouting

Ideally, injured axons would regenerate towards their appropriate targets and form functional synapses, thereby restoring the connection severed by the lesion. This type of regeneration is seen in the CNS of amphibia, fish and lampreys (Cohen et al., 1998), but is not seen in birds and mammals. However, during development and during regeneration of peripheral nerve, the sprouting of collateral branches of axons plays an important role in the establishment and refinement of neuronal circuitry. This sprouting occurs when new motile structures, filopodia and lamellae, form along previously quiescent regions of the axon. In the peripheral nervous system (PNS), partial denervation of muscle is followed by sprouting of neurites from neighbouring spared axons and reinnervation of the denervated muscle fibres by the sprouts (Brown et al., 1981). Collateral sprouting is different in several ways from regenerative growth. First, collateral sprouting occurs from unlesioned axon fibres near the lesioned axons. Secondly, collateral sprouting occurs close to the denervated target cells, so axon fibres do not have to extend over long distances. In this way, collateral sprouting in response to injury is similar to the terminal branching that occurs near the target region during development. Thirdly, the regions near targets are often less myelinated and thus provide less impedance to axon elongation. As discussed below, myelin associated neurite growth inhibitors appear to be present in the CNS. Thus collateral sprouting is increased in rats in which myelination has been suppressed by neonatal X-irradiation (Schwegler et al., 1995). Fourthly, at the neuromuscular junction, Schwann cells that cap degenerated nerve terminals send out processes to adjacent neuromuscular junctions that may also serve to guide sprouts to the denervated muscle and thus help establish a new neuromuscular junction (Son et al., 1996).

Collateral sprouting has been observed in the spinal cord (Liu & Chambers, 1958) and in several locations within the brain, including the septal nucleus, the CA3 region of hippocampus and the dentate gyrus, where it has been studied most extensively. Entorhinal cortical lesions result in sprouting of as much as 2–3 mm within the contralateral entorhinal cortical projection to the dentate gyrus (Steward et al., 1974). Sprouting of the mossy fibre projection from the dentate gyrus to hippocampal area CA3 has been observed following electroconvulsive, pharmacological or kindling induced seizures (McKinney et al., 1997).

The functional role of sprouting remains unclear. In the spinal cord, the time course of sprouting correlates with the development of hyper-reflexia and increased muscle tone following spinal transection, suggesting that sprouting might be of functional benefit in spinal cord injured animals by enhancing their ability to support their weight (Goldberger & Murray, 1974; Murray & Goldberger, 1974). Sprouting in the spinal cord after peripheral nerve lesions may also underlie chronic pain conditions. Here, sprouting often involves the expansion of axons into inappropriate target areas, perhaps leading to severe pain syndromes because sprouting axons derive from low threshold mechanoreceptors (Woolf & Doubell, 1994). In the hippocampus, mossy fibre sprouting develops in parallel with recurrent seizures. It has been suggested that sprouting contributes to post-traumatic epileptogenesis in the hippocampus by eliciting 'reactive synaptogenesis', which may contribute to the formation of a functional excitatory feedback circuit (McKinney et al., 1997). Alternatively, sprouting might be protective against seizures as a result of sprouting mossy fibres synapsing onto inhibitory interneurons.

The molecular mechanisms underlying sprouting in the CNS are not known, but as at the neuromuscular junction, sprouting appears to involve interactions between cells in the region of axon terminal degeneration and the neighbouring spared axons. In addition to inhibitory proteins in myelin, the intrinsic growth potential of the axon also appears to be a determinant of the extent of axonal outgrowth. Axonal sprouting is increased in the peripheral and central nervous system in adult mice that overexpress the growth associated protein GAP-43 (Aigner et al., 1995). Moreover, the neurotrophins nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) are often up-regulated following seizures (Ernfors et al., 1991) and may provide a signal for collateral sprouting of mossy

fibres (Patel & McNamara, 1995). Neurotrophins promote axon collateral formation in vivo, modulate growth cone morphology in culture and mediate developmental processes involving collateral sprouting (Cohen-Cory & Fraser, 1995). Further, neurotrophins produced by target tissues can modulate axon branching (Hoyle et al., 1993). During regeneration of DRG cell axons, NGF promotes the formation of collateral branches (Diamond et al., 1987). Neurotrophins act directly on the axon of DRG cells to promote the formation of collaterals (Gallo & Letourneau, 1998). This sprouting is mediated by the activation of actin-dependent motility via a phosphoinositide-3 kinase pathway initiated by the trk A receptor. Although neurotrophins can initiate and stabilize branching, other factors may be responsible for stabilizing collaterals and allowing them to mature (Bastmeyer & O'Leary, 1996).

Cell adhesion molecules (CAMs) may also regulate axon outgrowth and synapse formation. In *Aplysia*, long-term memory storage and long-term changes in synaptic strength are accompanied by increases in axonal branching and in the number of synaptic contacts (Abel et al., 1998). This is paralleled by a decrease in the levels of apCAM as a result of endocytosis of this molecule. This downregulation of apCAM suggests that cell adhesion molecules may normally act to block synaptic growth. Thus a CAM may act as a 'memory suppressor' gene product, normally inhibiting memory storage (Abel et al., 1998). The removal of these inhibitory constraints may provide a mechanism to enhance axon outgrowth and new synapse formation during memory storage and recovery from neural injury.

Dendritic remodelling

The loss of input to a postsynaptic neuron leads to changes in neuronal morphology, including the loss of dendritic spines, the simplification of the dendritic arbour and atrophy of the postsynaptic neuron, processes that are termed dendritic pruning. The mechanisms underlying this dendritic plasticity are unknown but changes in intracellular calcium may play a crucial role (Segal, 2001). Calcium may act to regulate protein synthesis within the spines because clusters of polyribosomes have been demonstrated associated with cysternae at the base of dendritic spines (Steward & Reeves, 1988). Denervation results in loss of these polyribosomes, whereas reinnervation is associated with their return (Steward & Fass, 1983). Thus synaptic activity localized to one spine could rapidly influence protein synthesis in that portion of dendrite and thereby affect the size, shape and function of the dendritic tree.

The communication between the dendritic spine, the dendrite itself and the soma are crucial issues. The dendritic spine is often thought of as a relatively isolated environment in which calcium can reach sufficient levels to activate intracellular signal transduction pathways, but this depends critically on spine head and spine neck geometry. Further, the activation of calcium release from intracellular stores can have dramatic effects on calcium levels throughout the cell, leading to the activation of transcriptional processes (Berridge, 1988). This complexity of calcium signalling may potentially explain the many contradictory findings in studies of dendritic morphology (Segal, 2001): at very low calcium levels, spines are eventually eliminated, moderate increases in calcium cause the elongation of spines and the formation of new ones and large increases in calcium, such as occur during trauma or an epileptic seizure, cause the shrinkage and collapse of spines.

A crucial issue is how new dendritic processes form in response to collateral sprouting and axonal outgrowth. The formation of new synapses has been observed after environmental enrichment, learning and long-term potentiation (Segal, 2001). Recent studies have used organotypic cultures of hippocampal slices combined with a local superfusion technique to restrict the site of LTP induction to a small dendritic region. Using two-photon laser scanning microscopy, three-dimensional images of the postsynaptic neuron can be obtained. In these studies, new spines are observed on the postsynaptic dendrite of the CA1 pyramidal cell after the induction of long-term synaptic potentiation (Engert & Bonhoeffer, 1999). No changes in dendritic morphology are observed after short-lasting potentiation or in control regions that were not potentiated. Are such newly formed dendritic spines functional? This is a difficult and important question. Quantal analysis of synaptic transmission does suggest that cAMP-induced long-lasting forms of LTP are accompanied by an increase in the number of quanta released in response to a single presynaptic action potential (Bolshakov et al., 1997). This increase may be due to an increase in the number of sites of synaptic transmission, an idea supported by studies using the fluorescent dye FM 1–43, which suggest that cAMP-induced synaptic potentiation is accompanied by an increase in the number of active presynaptic terminals (Ma et al., 1999).

Although much of the discussion of anatomical plasticity has focused on morphological changes in axonal arbourization or dendritic spines, it is important to note that molecular changes can make previously 'silent' (or, perhaps more precisely, 'deaf') synapses functional. Studies of LTP in hippocampal area CA1 have revealed intracellular trafficking processes in the postsynaptic

neuron by which AMPA receptors are rapidly redistributed after NMDA receptor activation (Shi et al., 1999). The redistribution of AMPA receptors provides a striking mechanism by which synapses may be strengthened.

Therapeutic approaches to recovery

In order to promote recovery from neural injury, it is necessary to optimize the nervous system's own adaptive responses as well as to intervene in those mechanisms that inhibit full neurophysiological restoration. Promising approaches include: (i) teaching patients adaptive behaviours; (ii) harnessing the physiological plasticity of the CNS through cutting edge physical therapies; (iii) promoting regeneration of axons by neutralizing environmental inhibitory influences, upregulating the intraneuronal molecular regeneration program and supplying growth promoting factors; (iv) replacing lost neurons. By using one or a combination of these approaches, researchers have already made progress in eliciting functional recovery in animals, and even in some human patients.

Behavioural adaptation (occupational therapy)

The field of occupational therapy is targeted toward promoting recovery of vocational, recreational and self-care functions by teaching patients adaptive strategies to substitute for lost physiologic functions. The focus is mostly on upper extremity and cognitive/perceptual functions. For example, a person with a homonymous hemianopia can be taught to scan the written page to be certain that she is not ignoring written material on the hemianopic side. Much of conventional practice in occupational therapy has been based on common empirical experience, *a priori* reasoning and theories that have not been subjected to controlled clinical trials. Increasingly, the practices in the field are coming under experimental test. In any case, there is little doubt that retraining of patients with neurological injuries and diseases, by any number of strategies, results in significant functional improvement (Cheung & Broman, 2000). A generalization that can be drawn from a variety of studies is that functional improvement is most likely to occur when the training is task specific. Thus, relearning words after an aphasic injury requires that the words to be learned be repeated. Learning one word has little effect on the ability to learn another word. Similarly, the effect of exercise in improving a particular function is greatest when the exercise task closely resembles the function (Kwakkel et al., 1999; Taub et al., 1999).

Physical therapies

Conventional practice methods

Although there is considerable overlap in the potential roles of occupational therapists and physical therapists in the rehabilitation of patients with neurological impairments, physical therapists tend to be concerned more with issues of gait retraining, strengthening and cardiovascular conditioning. Thus they more often address lower extremity functions than upper extremity functions or cognition. The comments made above regarding occupational therapy are also true for the therapist-assisted, staged retraining of gait following stroke, spinal cord injury and other CNS injuries using parallel bars, walkers, canes and braces. However, specific types of training targeted at inducing plastic changes in the motor output warrant special consideration.

Constraint-induced forced use

In an attempt to test the theory that learned non-use contributes to upper limb disability in stroke patients, Ostendorf and Wolf constrained the unaffected left arm in a sling in a patient 18 months after a right hemiplegic stroke, forcing her to use the affected right arm (Ostendorf & Wolf, 1981). During a 1-week trial, there was no change in the function of the restrained arm but the patient used the affected arm more frequently and more effectively. Subsequently, several studies of patients with chronic hemiparesis due to stroke or head trauma confirmed that constraint-induced, forced use of the impaired arm for a period of 2 weeks or less results in functional improvement of that arm for many months (Miltner et al., 1999; Wolf et al., 1989). A recent randomized, single blind, controlled study of constraint-induced forced use vs. conventional rehabilitation was carried out on 20 patients within 14 days of an ischemic stroke (Dromerick et al., 2000). Measurements during acute inpatient rehabilitation suggested that the constraint technique provides improved recovery on some tests of arm function. How this would affect long-term recovery remains to be determined. Electrophysiological studies have shown that forced use of the limb results in long-lasting plastic changes in the CNS. In four hemiparetic stroke patients, movement-related cortical potentials before and immediately after training and at 3 months follow-up suggested that movement of the affected hand was associated with activation not only of the contralateral hemisphere but also the ipsilateral hemisphere in the absence of mirror movements of the unaffected hand (Kopp et al., 1999). By contrast, TMS before and after a 12-day-period of constraint-induced movement therapy in 13 chronic stroke patients showed an

increase in the motor representation of the test muscle on the affected side and a displacement of the center of the motor output area of that muscle to adjacent cortex (Liepert et al., 2000). As with the changes seen in functional imaging of recovery from stroke, the significance of the shifts, particularly the activation of cortex ipsilateral to the affected arm, is not clear. However, these studies do suggest that functional recovery by application of constraint-induced forced use of a paretic limb is associated with electrophysiological evidence of cortical plasticity.

Partial body weight supported treadmill training

The spinal cord of all vertebrates studied thus far contains intrinsic circuitry, called central pattern generators (CPGs), that produce rhythmic locomotor efferent discharges to synergistic groups of muscles (Cazalets et al., 1995; Grillner, 1975). There is evidence that the spinal CPG is subject to experience-induced plastic changes, i.e. the spinal cord is capable of a form of learning that is now under investigation as a possible means by which impaired locomotion due to stroke or spinal cord injury may be improved (Dobkin, 1999). Experiments in thoracic spinal transected cats indicated that treadmill training with early support of the hindlimbs could permit the animals to develop rhythmic stepping of the previously paralysed hindlimbs, and eventually to do so while supporting their own weight (Barbeau & Rossignol, 1987; Lovely et al., 1986). Although the hindlimb stepping was not coordinated with that of the forelimbs, the hindlimb stepping persisted for 6 weeks after cessation of training, declining by 12 weeks (De Leon et al., 1999a). Retraining resulted in an accelerated acquisition of full weight-bearing stepping. These observations suggest that the spinal cord pattern generator for locomotion is subject to a form of learning. Of interest, training for weight bearing caused a loss of previously attained ability to step. This loss could be reversed immediately by strychnine, suggesting a role for glycinergic inhibition in the ability of locomotor circuits to interpret sensory input to drive stepping (De Leon et al., 1999b).

There is also EMG and visual observation evidence for spinal cord rhythmic motor output in paralysed humans (Bussel et al., 1996; Calancie et al., 1994), suggesting that a locomotor central pattern generator exists in the human lumbosacral enlargement. As in animals, the human pattern generator appears to be subject to modulation by sensory input (Harkema et al., 1997). If so, then the human pattern generating circuitry might also be subject to use-dependent and pharmacological enhancement (Fung et al., 1990). Given the widespread acceptance of the principle of task-specific training, a difficulty with attempting to retrain the central pattern generator in paralysed patients is that weakness in patients' antigravity muscles prevents them from practising the task (locomotion) that is to be recovered. In order to get around this problem patients have been placed in harnesses that partially support their weight, permitting them to practise locomotion on a treadmill. Preliminary clinical trials have suggested that such training can enhance recovery in chronic and acute patients with incomplete spinal cord injury (Dietz et al., 1995; Gazzani et al., 1999; Wernig et al., 1995) and hemiparetic stroke (Hesse et al., 1995; Visintin et al., 1998). In one follow-up study on spinal cord injured patients, improvement persisted for 6 months to 6 years (Wernig et al., 1998). While promising, all these studies have been limited in some degree by small sample size, lack of prospective design, non-randomization of controls, lack of blinding in outcomes measurements or non-uniformity of rehabilitation protocol, including time of intervention after injury (for critical review, see Dobkin, 1999). An NIH-supported, prospective, randomized, multicenter trial of body weight supported treadmill training in spinal cord injured patients is currently under way (Dobkin, 1999).

Promotion of regeneration

Although there is great promise in approaches that harness the endogenous plasticity of the CNS, maximal recovery will require reconstitution of lost neuronal connections. The peripheral and central nervous systems both show evidence for regenerative potential but they have different strengths and limitations in this regard.

Spontaneous axonal regeneration in PNS

Wallerian degeneration

Injury to peripheral nerve results in variable effectiveness of regeneration, depending on the type of injury, the distance from the perikaryon and the distance from the target. Proximal lesions result in faster regeneration (3–6 mm/day) than distal lesions (1 mm/day; reviewed in Selzer, 1987). When an axon is interrupted by physical trauma, a process called 'Wallerian degeneration' ensues (Scherer & Salzer, 2001). This consists of breakdown of the axon distal to the lesion, and the separation of myelin sheaths at the incisures of Schmidt–Lanterman into ovoids that are phagocytosed primarily by macrophages that invade the degenerating nerve. Schwann cells also participate in the phagocytosis and proliferate within the denervated connective tissue sheath, forming linear arrays called 'bands of Büngner'. The molecular signals that trigger the Schwann cell proliferation are not known, but

correlative data suggest involvement of neuregulin-1, a constituent of axons that is a potent Schwann cell mitogen in vitro. Denervated Schwann cells express a receptor for neuregulin 1, consisting of a heterodimer of ErbB2/ErbB3. During Schwann cell proliferation, ErbB2 is activated by phosphorylation (Kwon et al., 1997).

The degenerated distal nerve stump supports regeneration

The bands of Büngner form a particularly fertile environment for regeneration of the peripheral axons. This appears to be due to a combination of complex factors including the nature of the basal lamina sheath, which includes extracellular matrix molecules such as laminin-2, fibronectin and type IV collagen and several others that are excellent substrates for axon elongation in vitro (Fu & Gordon, 1997). Denervated Schwann cells contribute importantly to the regenerative ability of peripheral nerve fibres by synthesizing these extracellular matrix molecules and a variety of cell adhesion molecules, including the Ig-like cell adhesion molecules (CAMs) N-CAM, P_0, L1 and MAG. The axon binds to extracellular matrix molecules by expressing a family of heterodimeric receptors called integrins, which connect the extracellular matrix molecules to the axon cytoskeleton (Helmke et al., 1998; Schmidt et al., 1995) and may mediate activation of intracellular signaling cascades, as suggested primarily by studies in non-neuronal cells (Boudreau & Jones, 1999; Clark & Brugge, 1995). However, the axon growth cone appears to grow along Schwann cells in preference to the basal lamina, when given a choice in vitro (reviewed by Martini, 1994). As with extracellular matrix molecules, CAMs not only provide an adhesive surface for axons to grow along, but also mediate the activation of intracellular signalling pathways (Walsh et al., 1997). In this way, the extracellular matrix and cell adhesion molecules synthesized by denervated Schwann cells may contribute to the elongation and navigation of growing axon tips during regeneration. These conclusions are based primarily on studies of embryonic neurons growing in vitro. The degree to which they apply to regeneration of peripheral nerve in vivo is not clear.

Denervated Schwann cells, together with macrophages and fibroblasts in the denervated nerve, also manufacture a variety of trophic molecules and their receptors, many of which appear to be important for both axonal regeneration and Schwann cell proliferation. Among these factors are the neurotrophins NGF, BDNF, neurotrophin 3 (NT-3) and NT-4, transforming growth factors β (TGF-βs), glial cell line derived neurotrophic factors (GDNFs), the cytokines ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), interleukin 6 (IL-6), and the insulin-like growth factors (IGFs) and fibroblast growth factors (FGFs). Their possible role in regeneration of peripheral nerve has recently been reviewed (Scherer & Salzer, 2001).

Specificity of regeneration

Although the precise roles of all of these molecules in regeneration are not known, the denervated distal stump of injured peripheral nerve provides an especially welcoming environment for regenerating axons to grow in. Yet, many injuries to peripheral nerve are not followed by regeneration that is adequate to result in satisfactory functional recovery. The distance of regeneration might be further enhanced by the application of extrinsic trophic factors but the main reason for incomplete functional restoration is that the degree to which regenerating axons find their correct targets is limited (Lee & Farel, 1988; Scherer, 1986). The anasthomotic fascicular structure of peripheral nerve is such that the individual axons of a severed nerve do not regenerate to their original destinations unless they find their original endoneurial tubes. Even if the fascicles are matched perfectly by microsurgical repair, the preponderance of experimental evidence (Aldskogius et al., 1987) and clinical experience has indicated that the specificity of reinnervation is still limited. The further the injury from the target, the greater the number of nerve branches the regenerating axons might enter and the more likely that a mismatch will occur between the axon and its eventual target. On the other hand, when the axon is interrupted by a compressive injury that does not interrupt the Schwann cell basal lamina endoneurial sheath, the nerve can regenerate along its original path and innervate its original muscle or sensory target (Brown & Hardman, 1987; Selzer, 1987).

Despite the above observations of inaccuracy in regeneration of severed peripheral nerve, more recent studies suggest that a certain degree of specificity does occur. In tadpoles before the Schwann cells have elaborated a basal lamina tube, severed motor axons tended to reinnervate their correct muscles selectively. It is only after a basal lamina tube is formed that axons are forced to innervate incorrect muscles if the axons enter an incorrect tube (Meeker & Farel, 1993). In neonatal but not adult rats, transection of facial nerve is followed by selective reinnervation of correct muscles (Aldskogius & Thomander, 1986). Even in adult rats, transected nerves reinnervate portions of the serratus anterior and diaphragm muscles in a somatotopically correct, though imperfect way (Laskowski & Sanes, 1988). This positional selectivity may involve the expression of ephrins by muscle fibres (and presumably complementary receptors on the motor axons) (Feng et al., 2000) and competition among regenerating axons for

correct synaptic targets (Laskowski et al., 1998). Thus, in some circumstances, synaptic competition and pruning of incorrectly regenerated axons may compensate for randomness in reinnervation of Schwann cell tubes. A form of secondary pruning also accounts for selective reinnervation of motor and sensory branches by motor and sensory axons respectively, during regeneration of severed rat femoral nerve (Brushart et al., 1998; Madison et al., 1996). Unlike the selectivity in the reinnervation of the serratus anterior, the selectivity of motor vs. sensory nerve reinnervation appears to involve guidance signals associated with the Schwann cells (Martini, 1994). Unfortunately, the specificity in regeneration of some peripheral nerve axons is not absolute but reflects statistical trends that still are not robust enough to result in functional recovery in most cases.

Spontaneous axonal regeneration in CNS

By contrast with the PNS, regeneration is quantitatively much less successful. Paradoxically, where regeneration does occur, it appears much more specific. Thus if ways can be found to enhance the probability and distance of regeneration in CNS, sufficient specificity in pathway selection and synapse formation would occur that the regeneration would yield functional recovery. Some of the molecular mechanisms that block regeneration in CNS and also contribute to its specificity are summarized below. For additional details, see Chapter 47 by J. McDonald.

Extracellular determinants

Growth cone collapsing factors

During regeneration, axons come in contact with molecules in their environment that inhibit their growth. An understanding of this phenomenon requires an understanding of the mechanisms of axon elongation.

Mechanisms of axon growth in the regenerating CNS

The leading edge of axons belonging to embryonic or invertebrate neurons grown on conventional adhesive substrates such as laminin or polo-L-lysine takes the form of a specialized structure, the 'growth cone' (Gordon-Weeks, 1989; Lankford et al., 1990; Lin et al., 1994; Rivas et al., 1992). The proximal flattened portion of the growth cone is the 'lamellipodium', which contains microtubules and short actin and myosin filaments in a relatively disorganized orientation. Extending along the leading edge of the lamellipodium are fine projections called 'filopodia'. These contain bundles of fibrous actin (f-actin) microfilaments and elongate on the extracellular matrix through target activated polymerization of the actin filaments at their distal end (Lin & Forscher, 1993). The elongation of filopodia translates into tension on the more proximal growth cone by actin-myosin linkages to the microtubules (Lin et al., 1996). This results in the rapid (1–3 mm/day) growth that characterizes early embryonic development. While much of the thinking about mechanisms underlying axon regeneration assumes that this mechanism obtains in axonal regeneration in the mature CNS, work in the lamprey suggests that this may not be true (Conti & Selzer, 2000). In this species, the growth cones of cut spinal cord axons lack filopodia (Lurie et al., 1994), have little f-actin (Hall et al., 1997) and regenerate more slowly (Yin & Selzer, 1983) than vertebrate and invertebrate embryonic axons. Observations on the morphology and cytoskeletal contents of growth cones regenerating in the CNS of mammals and other vertebrates in vivo have been scant. Thus it is not known whether the differences between regenerating lamprey growth cones and growth cones of embryonic neurons are due to species differences or to differences between axon development and regeneration.

Myelin associated growth inhibitors

Cells in the mature CNS express several molecules that inhibit axon growth in tissue culture by causing collapse of the growth cone. Because most knowledge concerning axon elongation has been derived from studies in vitro, work on the molecular mechanisms involved in growth inhibition have usually employed tissue culture assays. Perhaps most well known of these growth inhibitors was described by Caroni and Schwab (1988a, b), who observed that neurons can grow long processes when cultured on peripheral myelin fractions but not on fractions of CNS myelin. They identified two molecules with MW 35 000 and 250 000 (NI-35/NI-250) on the surfaces of oligodendrocytes, but not Schwann cells, that cause growth cones to collapse on contact (Caroni & Schwab, 1988b). Both molecules were bound by a single mAb, IN-1 (Caroni & Schwab, 1988a). These molecules appear to cause growth cone collapse by activating a G protein (Igarashi et al., 1993) and releasing calcium from intracellular stores (Bandtlow et al., 1993). The excess calcium might activate breakdown of microtubules and actin microfilaments and thus turn off growth cone motility. For years, the identities of NI-35/250 remained a mystery. However, similar molecules have now been sequenced from rats (Chen et al., 2000) and humans (GrandPre et al., 2000) and renamed 'Nogo'. Three members of the Nogo family have been identified, of which Nogo A appears to be the one responsible for the oligodendrite associated growth inhibition (Chen et

al., 2000). Several lines of in vivo experimentation suggest that neutralizing Nogo with IN-1 can enhance the regenerative capacity of CNS axons but the role of Nogo as the main cause of regenerative failure in the CNS is still debated (see below and Chapter 47 by McDonald).

Myelin-associated glycoprotein (MAG) has also been shown to have neurite outgrowth inhibiting and growth cone collapsing activity in vitro (McKerracher et al., 1994; Mukhopadhyay et al., 1994). This activity can be overcome by prior administration of neurotrophins or dibutyryl cAMP, which is elevated by neurotrophins (Cai et al., 1999). It has been suggested that in the presence of appropriate neurotrophins, cAMP levels in neurons are elevated, activating PKA, which blocks subsequent inhibition of regeneration. MAG activates a Gai protein, which blocks increases in cAMP, thus voiding the neurotrophin effect (Cai et al., 1999). The significance of MAG for regeneration in vivo has been questioned because axon outgrowth was not better on CNS myelin of MAG-deficient mice than on myelin of wild-type mice (Bartsch et al., 1995).

Two chondroitin sulfate proteoglycans, each having neurite growth inhibiting properties, have been demonstrated on the surfaces of bovine spinal cord oligodendrocytes (Niederost et al., 1999). Treatment with beta-xylosides, which inhibited synthesis of both proteoglycans, reversed the growth cone collapse seen during encounters of neurites with oligodendrocytes. Since chondroitin sulfate proteoglycans had previously been suggested to be inhibitors of regeneration associated with glial scars (Bovolenta et al., 1997) (see below), these molecules might also account for part of the regeneration inhibiting effect of CNS myelin.

Another molecule that has neurite growth inhibiting properties in vitro and is produced by oligodendrocytes is tenascin-R. In the salamander, optic nerves regenerate after they are cut, even though the myelinated optic nerve contains tenascin-R and retinal ganglion cells of salamander do not grow on a surface of tenascin-R in vitro. This may be explained by the disappearance of myelin, MAG and tenascin-R from the optic nerve by phagocytosing cells within 8 days after transection (Becker et al., 1999). In rats, optic nerves do not regenerate and tenascin-R is not removed after optic nerve transection (Becker et al., 2000). Thus tenascin-R may be a significant inhibitor of axonal regeneration in CNS, but thus far the evidence is only correlational.

It is not clear how universal the inhibitory effect of oligodendrocytes is. Contact with oligodendrocytes in vitro inhibited the growth of dorsal root ganglion (DRG) cell axons but not those of retinal cells (Kobayashi et al., 1995). Growth cone collapsing activities require not only the presence of an inhibitory molecule but also the presence of receptors on the surfaces of susceptible neurons. It is assumed that axons grow readily during embryogenesis because the late development of myelin delays contact with myelin-associated growth inhibitors. However, embryonic neurons from hippocampus, neocortex and superior colliculus were able to grow long axons when transplanted by atraumatic microinjection into various white matter tracts in the adult mouse (Davies et al., 1994). This may reflect an absence in these immature neurons of receptors for myelin-associated inhibitory molecules. On the other hand, myelin-associated growth inhibitors might not be as potent when encountered by growing axons in vivo as in vitro and other molecules normally introduced at the site of injury might be more important (Davies et al., 1997).

Neuron-associated growth inhibitors

Growth cone collapsing activity is also associated with neuronal membranes (Kapfhammer & Raper, 1987). Axons from the nasal side of the developing retina grow selectively to the posterior part of the optic tectum, while temporal retinal axons grow to the anterior tectum. This is due to a growth cone collapsing activity on cell membranes from the posterior tectum that act only on temporal but not nasal retinal axons (Cox et al., 1990). This is now ascribed to the interaction between ephrins on the surfaces of posterior tectal membranes and Eph receptors on the surfaces of growth cones of temporal retinal neurons (Ciossek et al., 1998). Ephrin signalling may also be involved in the development of the spinal cord (Yue et al., 1999). Re-expression of Eph B3 after spinal cord injury (Miranda et al., 1999) suggests the possibility that ephrin signalling may inhibit regeneration of some spinal cord axons (see section on Specificity of Regeneration below). Similarly, the persistence of netrins and their chemorepellent receptor molecule UNC-5 in the CNS of postembryonic animals suggests that netrin may act as a chemorepellent to some growth cones during regeneration (Shifman & Selzer, 2000).

Astrocyte-derived extracellular matrix molecules

It was long assumed that axons did not regenerate through an astrocytic injury scar because of the scar's hard consistency and other mechanical features. However, although membrane fractions from grey matter support axon growth in vitro, membrane fractions from astrocytic scars do not (Bovolenta et al., 1993). This growth-inhibiting activity appears to be associated with one or more cell surface sulfated glycoproteins, especially chondroitin sulfate proteoglycans. Secretion of proteoglycans by reactive astrocytes is

one proposed mechanism by which the glial scar inhibits axonal regeneration in the CNS (McKeon et al., 1991). Thus adult DRG cells grew long processes when microinjected atraumatically into spinal cord white matter (Davies et al., 1997). In a few cases, the injection was traumatic enough to activate secretion of proteoglycans, and this was associated with failure of axon growth. Such observations have suggested that CNS myelin is not significantly inhibitory to regeneration in vivo, but rather it is the proteoglycans secreted at the site of injury that inhibits regeneration. Until now, it has not been possible to repeat the microinjection experiments with adult neurons other than DRG cells.

Intraneuronal determinants

Within a species, the ability of axons to regenerate decreases with age. For example, spinal axons regenerate in tadpoles, but not in postmetamorphic frogs (Beattie et al., 1990; Clarke et al., 1986; Forehand & Farel, 1982). Fetal spinal cord transplants are more successful in restoring anatomic connectivity and locomotor function to a spinal cord injury when performed in neonatal mammals than in adults (Miya et al., 1997). Most explanations for the failure of regeneration in the mature CNS have focused on the delayed appearance of myelin and its growth inhibiting molecules discussed above. The importance of environmental causes for failure of regeneration may have been overemphasized as a result of the striking observations that some axons of mature CNS can regenerate into peripheral nerve grafts (David & Aguayo, 1981; Richardson et al., 1980; Vidal-Sanz et al., 1987). However, in these and subsequent experiments on retinal ganglion cells, environmental influences were insufficient to explain the decline in regenerative ability in postembryonic mammals. For example, only a minority of injured axons regenerate into peripheral nerve grafts (Villegas-Perez et al., 1988). This issue has been investigated in cocultures of retina and optic tectum in rat (Chen et al., 1995). Embryonic retinal cells were able to extend axons into adult tectum, but postnatal retinas were unable to send axons into embryonic tecta. Thus the age of the neuron rather than that of its host environment most influenced the regenerative ability of axons. Similar conclusions were drawn when cocultures of entorhinal cortex and hippocampus were used to test the influence of postnatal age on regeneration of the entorhino-dentate pathway of rats (Li et al., 1995). Perhaps the most convincing evidence for the importance of intraneuronal factors is the great heterogeneity in regenerative abilities of axons growing in the same part of the CNS in the same animal. Following spinal cord transection in the lamprey, identified reticulospinal neurons vary greatly in their ability to regenerate through the same spinal cord environment (Davis & McClelland, 1994; Jacobs et al., 1997; Yin & Selzer, 1983). The same axons regenerated better following axotomy close to the perikaryon than more distally (Yin & Selzer, 1983). Similarly in the rat, supraspinal axons did not regenerate as well into peripheral nerve grafts inserted into the spinal cord at thoracic or lumbar levels as into cervical levels (Richardson et al., 1984). It is also well known that adult neurons are difficult to grow in culture in the absence of myelin and on the same substrates that support extensive survival and neurite outgrowth in embryonic neurons. Thus neuron intrinsic factors must contribute greatly to the limitations on regeneration in the CNS. Recent therapeutic approaches have attempted to enhance the intrinsic regenerative abilities of neurons through the use of supplemental trophic factors. Several examples of neuron intrinsic influences on regeneration and of the effects of trophic factors are reviewed below.

Conditioning lesion effects

A conditioning axotomy can accelerate regeneration after a second lesion (Lanners & Grafstein, 1980). Although environmental changes at the injury site may contribute, the conditioning lesion effect is attributed mainly to intracellular changes of the injured neuron (Lankford et al., 1998). That this is true can be deduced from experiments using DRG neurons, which have two processes originating from a unipolar axon. One process travels with the peripheral nerve and the second enters the spinal cord with the dorsal root. Injury of the peripheral process initiates a robust metabolic response that leads to regeneration. The regenerative response to injury of the central process in the dorsal root is weaker (Chong et al., 1994; Oblinger & Lasek, 1988). Although the axons regenerate within the dorsal root, they do not penetrate the spinal cord at the dorsal root entry zone (Liuzzi & Lasek, 1987; Pindzola et al., 1993). Nor do the central processes ascending in the dorsal columns regenerate after spinal cord injury. However, regeneration of the central processes of DRG cells can be enhanced by a preceding peripheral nerve injury that boosts the growth-associated metabolic response in the cell body (Neumann & Woolf, 1999; Richardson & Issa, 1984). The conditioning lesion may upregulate the expression of growth-associated genes and decrease the synthesis of receptors for inhibitory molecules within the spinal cord (for review see Chong et al., 1999).

GAP-43

An early strategy to identify molecules that may be important in regeneration was to look for proteins whose con-

centrations are greatly increased in neurons during regeneration of their axon. The best known of these proteins, growth-associated protein of 43 kDa (GAP-43), was discovered in the frog retina during regeneration of the optic nerve (Skene & Willard, 1981). GAP-43 is transported to the growth cone, where it is preferentially concentrated during development and synaptic remodelling (Goslin et al., 1988). Although the precise mechanism is still unknown, GAP-43 may mediate signal transduction for the reorganization of the cytoskeleton in growth cones and synaptic terminals in response to extrinsic stimuli (Igarashi et al., 1995) that activate axon growth and synaptic plasticity, e.g. LTP (Namgung et al., 1997). There is also correlative evidence for a role of GAP-43 in regeneration (Chong et al., 1996; Kobayashi et al., 1997; Ng et al., 1995; Schaden et al., 1994). Direct evidence for a role of GAP-43 in axon regeneration has been difficult to obtain, although a role in axon development has been fairly well supported. Some of the ambiguities concerning the role of GAP-43 in regeneration may ultimately be cleared up by recent studies suggesting that a second growth associated protein, CAP-23, acts in concert with GAP-43 in promoting subplasmalemmal accumulation of actin in the growth cone (Frey et al., 2000). Thus, although overexpressing GAP-43 alone does not enhance regeneration of DRG axons, coexpression of GAP-43 and CAP-23 in DRG cells resulted in enhanced process outgrowth in vitro and increased regeneration of DRG axons after spinal cord injury (Bomze et al., 2001).

Cytoskeletal proteins

The neuronal cytoskeleton consists of three major elements: (i) microtubules, molecularly complex structures that mediate axonal transport of molecules and organelles; (ii) microfilaments, f-actin strands composed of polymers of g-actin; and (iii) intermediate filaments, heteropolymers of three neurofilament subunits NF-L, NF-M and NF-H. Axotomy of motoneurons in peripheral nerve results in decreased synthesis of neurofilament and increased synthesis of actin and tubulin (for review see Bisby & Tetzlaff, 1992; Conti & Selzer, 2000). After the nerve has regenerated to its target, the changes are reversed (Muma et al., 1990; Oblinger & Lasek, 1988), but they are permanent if regeneration is prevented (Tetzlaff et al., 1988). Thus regeneration of peripheral nerve may depend on the transport and assembly of actin and microtubules, while neurofilaments are important to the subsequent maturation and enlargement of the regenerated fibres.

Even less is known about the role of cytoskeletal proteins in regeneration of axons in the CNS. Arguments against the applicability of developmental growth cone mechanisms to regeneration in the CNS have been made in the lamprey, which recover normal appearing swimming and other behaviours after spinal transection (Selzer, 1978). Unlike growth cones of embryonic neurons, the growth cones of regenerating lamprey axons lack lamellipodia and filopodia (Lurie et al., 1994) and contain densely packed neurofilaments (Pijak et al., 1996) but little f-actin (Hall et al., 1997). Moreover, neurons whose axons regenerate well showed only a transient downregulation of neurofilament mRNA expression, while neurons that regenerate poorly showed a permanent downregulation (Jacobs et al., 1997). This has suggested a hypothesis that regeneration involves a protrusive force generated by the transport of cytoskeletal elements such as neurofilaments into the growing tip (Jacobs et al., 1997; Pijak et al., 1996). However, it will be necessary to manipulate expression of cytoskeletal proteins in vivo in order to test any specific hypothesis concerning their roles in regeneration.

Specificity of axonal regeneration

In recent years, substantial progress has been made in understanding how developing axons choose their paths (Goodman, 1996). Much less is known about the degree to which axons are guided during regeneration, the specificity with which they form synapses, or the molecular mechanisms of any specificity that they show. Regeneration in the CNS of several lower vertebrates does appear to be specific to a significant degree. The severed optic nerves of fish and frogs regenerate to their proper target regions of the optic tectum, restoring accurate vision (Gaze & Jacobson, 1963; Sperry, 1948). Retinotectal regeneration in reptiles is much less specific and does not restore correct vision (Dunlop et al., 2000). Cut or crushed dorsal roots in the frog regenerate into the spinal cord and muscle sensory neurons form synaptic contacts selectively with appropriate agonist motoneurons (Sah & Frank, 1984). In the lamprey, axons cut by a spinal transection regenerate selectively in their original paths (Lurie & Selzer, 1991; Yin et al., 1984). During regeneration, these axons behave as if they were following local environmental guidance cues (Mackler et al., 1986). Moreover, they form functioning synapses selectively with correct neurons distal to the lesion (Mackler & Selzer, 1987).

Much less is known about the specificity of axonal regeneration in mammalian CNS. Rat retinal ganglion cell axons regenerate through peripheral nerve grafts into the superior colliculus and terminate in correct layers, forming synapses with normal ultrastructural features (Vidal-Sanz et al., 1991). In similar experiments, peripheral nerve grafts connected the cut optic nerve with the rostral brainstem or diencephalon. In one-third of such animals, retinal axons

had regenerated up to 6 mm within the brainstem, terminating selectively in normally retinorecipient pretectal nuclei, i.e. the nucleus of the optic tract and the olivary pretectal nucleus (Aviles-Trigueros et al., 2000). Thus even in mammals, there is evidence for at least limited specificity in the regeneration of optic nerve when inhibitory effects of the adult CNS environment are circumvented by peripheral nerve grafts.

The molecular mechanisms underlying specificity in CNS axon regeneration are still unknown. Several developmental guidance molecules are expressed in postembryonic CNS of lower vertebrates and mammals (Aubert et al., 1995; Shifman & Selzer, 2001). Expression of some guidance molecules is upregulated in the spinal cord or supraspinal projecting neurons following spinal cord injury. These include: Eph B3 (Miranda et al., 1999), a member of the Eph family of protein tyrosine kinase receptors for the chemorepellent molecules of the ephrin family; netrins (Shifman & Selzer, 2000), molecules that can act as either chemorepellents or chemoattractants, depending on the receptor with which they interact; and the chemorepellent netrin receptor UNC-5 (Shifman & Selzer, 2000). In the lamprey, netrin mRNA expression has been demonstrated widely throughout the spinal cord, while UNC-5 is expressed by some reticulospinal neurons. Following spinal cord transection, UNC-5 may be upregulated selectively in neurons that are bad regenerators, suggesting that netrin signaling might be involved in modulating the regeneration of these axons (Shifman & Selzer, 2000). In adult zebrafish, rostral-low to caudal-high gradients of ephrine-A2 and ephrin-A5b mRNA expression have been found in the tecta of normal animals and during retinotopically correct regeneration of optic nerve (Becker & Becker, 2000). It has not yet been established that the retinal ganglion cells express the corresponding Eph receptors. Thus far, evidence that guidance molecules influence the pathfinding of regenerating axons in the CNS is only correlative.

Potential therapeutic approaches based on repairing the injured nervous system

Substantial progress has been made in developing methods to repair the injured nervous system. These are reviewed briefly below. Additional details may be found in Chapter 47 by McDonald.

Enhance neuronal survival and regenerative capacity

Secondary neuronal death in acute CNS injury

Part of the functional loss that follows CNS injury is attributable to the secondary death of neurons near the site of injury due to a complex interplay among glutamate excitotoxicity, edema, vascular changes and possibly cytokine toxicity (for reviews see Martin et al., 1998; Schwab & Bartholdi, 1996; Tator & Koyanagi, 1997). This is especially problematic in spinal cord injury, where the process of secondary neuronal damage is especially virulent. Despite a large number of interventions that have been successful in reducing excitotoxic and other modes of secondary neuronal injury in experimental animals (Anderson et al., 1985), the only treatment of acute spinal cord injury that has proven successful in humans is high dose methylprednisolone (Bracken et al., 1992), which is thought to act primarily by suppressing lipid peroxidation and opposing the effects of free radicals (Anderson et al., 1988).

Neurotrophic factors

Additional functional loss is attributable to atrophy or apoptotic death of axotomized neurons due to loss of target derived trophic support (Himes & Tessler, 2000; Martin et al., 1998). In addition to eliminating the possible involvement of surviving neurons in compensatory neuronal circuits, neuron death precludes the application of strategies designed to promote regeneration. Thus there is a rationale for developing pharmacological strategies to sustain the viability and vigor of axotomized neurons until a more definitive reparative manipulation can be instituted.

Peripheral nerve bridges

The ability of some CNS axons to regenerate in peripheral nerve grafts has been employed to reconnect transected optic nerve to the superior colliculus (Carter et al., 1989; Vidal-Sanz et al., 1987). Schwann cells in the nerve grafts produce growth-permissive extracellular matrix molecules such as laminin. The grafts also release trophic factors necessary for the survival of the injured neurons, in particular brain-derived neurotrophic factor (BDNF) and neurotrophin 4/5 (NT-4/5) (Cohen et al., 1994; Jelsma et al., 1993; Mansour-Robaey et al., 1994). The neurotrophic effect was enhanced when the nerve grafts predegenerated for 7 days (Golka et al., 2001), presumably because the denervated Schwann cells upregulate their production of trophic factors and extracellular matrix. These nerve grafts were reported to mediate light–dark discrimination in hamsters (Sasaki et al., 1993) and pupillary light reflexes in rats (Whiteley et al., 1998). Peripheral nerve grafts might be used to enhance recovery in spinal cord injury and other cases of interruption of compact long white matter tracts.

However, peripheral nerve grafts attract axons primarily from neurons situated close to the grafts (Richardson et al., 1984), as opposed to axons of supraspinal projection neurons such as the corticospinal or rubrospinal tracts.

Neutralize inhibitory factors

Antibodies directed at oligodendrocyte-associated growth cone collapsing factors have been used to promote regeneration (Schnell & Schwab, 1990). IN-1 secreting hybridomas were transplanted into the parietal lobes of rats, which were then subjected to spinal cord dorsal over-hemisection, interrupting both corticospinal tracts. Corticospinal axons grew up to 15 mm around and beyond the hemisection. Contact placing reflexes were restored in the hindlimbs and stride length was partly normalized (Bregman et al., 1995). In control rats, regeneration did not exceed 1 mm. Similar regeneration has been achieved by infusion of a partially humanized, recombinant Fab fragment derived from IN-1 directly into the injury site (Brosamle et al., 2000). However, in such experiments, only approximately 10% of corticospinal axons regenerate, possibly due to the presence of additional myelin-associated growth inhibitory molecules. A novel approach to dealing with this limitation has been developed by immunizing mice against myelin, using incomplete Freund's adjuvent to avoid the development of experimental allergic encephalomyelitis (Huang et al., 1999). This presumably resulted in neutralizing several inhibitory molecules. Immunized animals showed regeneration of large numbers of corticospinal axons and recovery of hindlimb motor functions after spinal cord dorsal over-hemisection.

Fetal tissue transplants

Transplants of fetal spinal cord can reduce both retrograde death of axotomized neurons (Himes et al., 1994; Shibayama et al., 1998) and the amount of glial scarring that occurs at the site of a spinal cord injury (Houle, 1992). The axons of corticospinal and bulbospinal neurons regenerate through fetal spinal cord transplants and into caudal host spinal cord, where they enhance the development of locomotion and other motor functions in newborn animals (Bregman et al., 1993; Diener & Bregman, 1998; Kim et al., 1999; Miya et al., 1997). By contrast, in adult hosts long axon tracts regenerate poorly through the transplant and regeneration of CNS axons is almost exclusively from neurons close to the transplants. Even these axons do not extend into the distal host spinal cord (Jakeman & Reier, 1991). Administration of exogenous neurotrophic factors increases growth of supraspinal axons into the transplant (Bregman et al., 1997). By combining fetal spinal cord transplants with exogenous neurotrophic factors or with the IN-1 antibody against Nogo, it was possible to increase sprouting adjacent to the transplants, enhance long distance regeneration and promote recovery of hindlimb locomotor function (for review see Bregman et al., 1998).

Modulate intraneuronal factors

As we learn more about the neuron-intrinsic factors that modulate axonal regeneration, it will become possible to manipulate expression of these factors such as growth associated and cytoskeletal proteins, as well as the proteins important for synaptic plasticity. However, intraneuronal growth programs are modulated by environmental factors such as guidance molecules and neurotrophic factors. For the moment, most manipulations of the intrinsic regenerative capacities of neurons has been achieved through extrinsic application of trophic factors, as described above.

Neuronal replacement

Fetal neurons

Embryonic neurons have been used to promote recovery by transplanting them into the brains of patients with neurodegenerative diseases (Bjorklund & Lindvall, 2000). The most extensive experience has been with Parkinson's disease (Lindvall, 1998; Olanow et al., 1996). This approach is reviewed in more detail in chapters on the relevant diseases. Challenges associated with this approach include (i) addressing the ethical and practical difficulties associated with the use of human fetal tissue; (ii) enhancing survival of grafted cells; (iii) enhancing the degree of innervation of the host striatum. Theoretically, the difficulties associated with the use of human fetal tissues can be addressed by the substitution of stem cells and immortalized cell lines. In practice, using xenografts of fetal porcine dopaminergic neurons has already shown promise (Schumacher et al., 2000), with clinical improvement comparable to that reported with human allografts. On the basis of animal studies, survival of the graft may be improved by the use of trophic factors, antiapoptotic drugs, calcium channel blockers and inhibitors of lipid peroxidation (Brundin et al., 2000). Porcine xenografts of striatal cells have now been inserted into several patients with Huntington's disease (Fink et al., 2000). It is too soon to know whether there will be a therapeutic response.

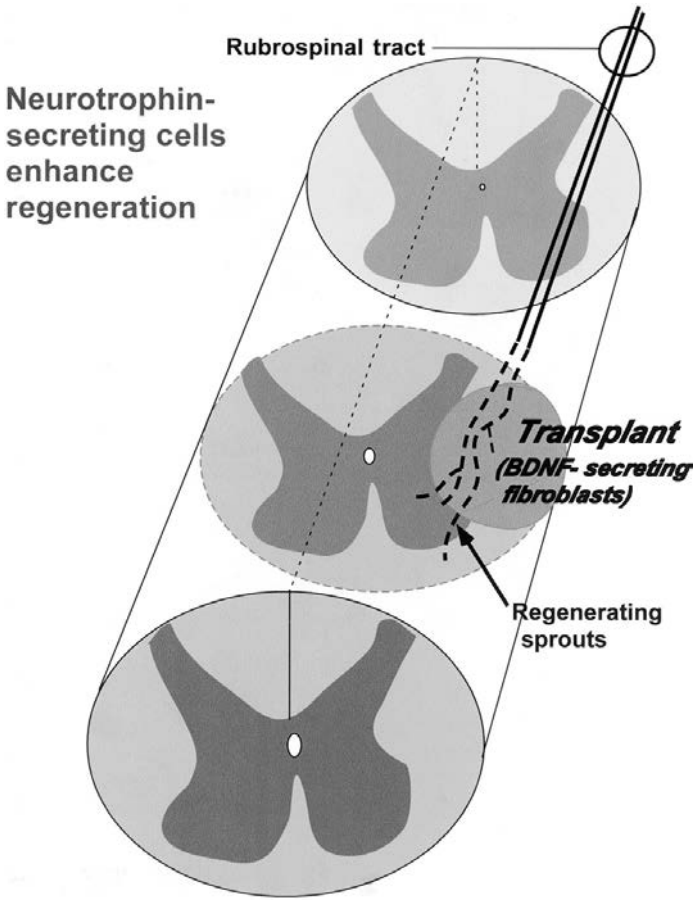

Fig. 6.3. Use of genetically modified cell lines to deliver trophic factors. Fibroblasts can be genetically modified to release molecules that enhance regeneration and clonally expanded (Blesch et al., 1999). This would have the advantage that a patient's own fibroblasts could be used for transplantation into the CNS, thus reducing the risk of immune rejection. An example of this strategy is illustrated in the work of Liu et al. (1999a), who transplanted BDNF-expressing fibroblasts into a spinal hemisection lesion that severed the rubrospinal tract, among others. Anterograde tracing from the red nucleus revealed regeneration of rubrospinal axons through the transplant into the spinal cord caudal to the lesion. This was accompanied by evidence of enhanced functional recovery.

Stem cells, neuronal progenitors and other cell lines

Because of the limited effectiveness of fetal transplants in many circumstances, the limited availability of human fetal tissue and the ethical considerations that their use has raised, alternative sources of neurons have been explored. The most promising approaches are based on cell lines that can be genetically modified to express desirable molecules, such as trophic factors. One attractive approach is to use cells from the patient's own body. Fibroblasts and Schwann cells engineered to synthesize trophic factors have been transplanted in rats to rescue axotomized neurons, promote regeneration and remyelination, and even enhance functional recovery (*c.f.* Blesch et al., 1999; Jin et al., 2000; Liu et al., 1999a; McTigue et al., 1998) (Fig. 6.3).

Neural stem cells and progenitor cells are particularly attractive for use as transplants (McKay, 1997). They have been isolated from the brain and spinal cord of adult as well as developing animals (Gage, 1998), including humans (Eriksson et al., 1998). Neural progenitors can be genetically modified to make neurotrophic factors (Liu et al., 1999b) and may be able to generate neurons to replace those lost to trauma and to furnish oligodendrocytes (Liu et al., 2000) that can remyelinate surviving and regenerating axons.

The olfactory nerve is constantly regenerating in life. Adult olfactory bulb ensheathing glia, which form the environment for this natural regeneration, can be transplanted into the injured spinal cord to promote axonal regeneration (Ramon-Cueto et al., 1998) and even functional recovery (Li et al., 1997).

Combination approaches

It is unlikely that any individual treatment will restore function completely and combinations of therapeutic approaches will probably be required. For example, Schnell and Schwab combined the IN-1 antibody and fetal spinal cord tissue inserted into the lesion to enhance the distance and profusion of regeneration (Schnell & Schwab, 1993). Local injections of NGF, BDNF or NT-3 were effective substitutes for the fetal transplants (Schnell et al., 1994). Olson's group in Sweden combined multiple peripheral nerve grafts, fibrin tissue glue, acidic fibroblast growth factor (aFGF) and compressive wiring of the dorsal spines in dorsiflexion to bridge a gap of 5 mm of spinal cord produced in rats by excision of the T_8 segment. Anterograde tracing demonstrated evidence for anatomic regeneration of ascending and descending pathways (Cheng et al., 1996) and improvement in open-field walking scores and in more elaborate measures of gait coordination (Cheng et al., 1997). These striking observations and other recent experiments suggest that combinations of surgical manipulations, trophic factors and growth inhibitor neutralization measures may be more effective than single therapies. Moreover, as the mechanisms of spontaneous recovery are better understood, new therapeutic approaches will incorporate strategies that optimize these mechanisms into the combination approach.

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7

Measurement of neurological outcomes

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Increasingly, clinical trials in neurology are using rating scales of patient-based outcomes to evaluate the effectiveness of therapeutic interventions and, therefore, influence patient care and the expenditure of public funds. To justify this important role in research and clinical practice, these measurement methods must demonstrate that they are rigorous indicators of abstract and unobservable variables such as disability and health-related quality of life.

This chapter, divided into five major sections, is about rating scales for measuring health. The first section examines the history underpinning the science of health measurement and psychometrics, demonstrates that the scientific foundations of this new medical discipline are deeply rooted in education and psychology, and discusses how clinical variables can be rigorously measured. Sections two to four discuss frameworks for evaluating, choosing and developing measures. This approach, rather than recommending a list of instruments, has been chosen because the clinical neurologist is often faced with a choice of instruments. No instrument has universal usefulness, it is therefore important to identify the strengths and weaknesses of individual measures. Section five introduces some of the new developments in health measurement.

Health measurement and psychometrics

History

Although health measurement as a distinct discipline emerged in the 1980s (Ware et al., 1980; McDowell & Newell, 1987; Streiner & Norman, 1989), it is derived from well-established theories and methods of measurement in the field of social sciences whose origins can be traced to the mid-1800s. The basic scientific principles of measurement were established by mathematical psychologists interested in the human being as a measuring instrument. By studying how people make subjective judgements about measurable physical stimuli (e.g. length, weight, loudness), they developed the science of psychophysics: the precise and quantitative study of how human judgements are made (Guilford, 1954). The investigation of overt responses to physical stimuli requires precise methods, referred to as psychophysical methods, for presenting the stimuli and for measuring responses (Nunnally, 1959).

The work of psychophysicists seems far removed from health measurement. It established the fundamental principles of subjective measurement which are as equally relevant to judgements about health as to judgements about physical stimuli. The psychophysicists demonstrated that: subjective judgement is a valid approach to measurement; humans make judgements about abstract comparisons in an internally consistent manner; and accurate judgements can be made on ratio rather than simple ordinal scales. It is notable that psychophysical methods are still used in neurology; thermal threshold testing is based on the principle of the just noticeable differences in temperature detection and audiometry on a person's response to different sound frequencies.

Whilst the psychophysicists were measuring subjective judgements about physical stimuli that could be independently and objectively measured and verified, experimental psychologists were attempting to measure human attributes for which there were no independent physical scales of measurement (e.g. intelligence, personality, attitudes) (Nunnally, 1959). Darwin's empirical demonstration of evolution in the *Origin of Species* in 1859 was the impetus behind the study of individual differences in psychology (Rogers, 1995). It was reasoned that, if animals inherit ancestral characteristics, and if individual differences influence their ability to adapt and survive, so individual differences in humans would have functional

significance and could be inherited. Galton, who followed Darwin and believed that the human race could be bettered through controlled mating (eugenics), realized that human characteristics must be measured in a standardized manner before their inheritance could be studied. He coined the term 'mental test' for any measure of a human attribute (this explains why this term appears in the original literature, e.g. Gulliksen (1950), Lord & Novick (1968), and set about the large-scale testing of sensory discrimination and motor function in the belief that people with the most acute senses would be the most gifted and most knowledgeable (Rogers, 1995). However, when Galton's colleague Pearson developed and applied the correlation coefficient, it became clear that results from these simple sensory and motor tests bore almost no relationship to measures of intellectual achievement, such as school grades (Nunnally, 1970). This finding prompted the development of the mental test movement, i.e. the widespread interest in the development and application of mental testing, and the measurement of individual differences.

A major advance in mental testing (Torgerson, 1958) was made when Thurstone demonstrated that psychophysical scaling methods could be used to accurately measure psychological attributes (Thurstone, 1925; Thurstone & Chave, 1929). This finding prompted the development of psychological (or psychometric) scaling methods, which are defined as procedures for constructing scales for the measurement of psychological attributes (Guilford, 1954). Spurred on by the practical need to measure diverse outcomes, the mental test movement flourished between 1930 and 1950 with the spread of standardized testing for assessing educational achievement, measuring attitudes and personality and selecting and screening personnel. In addition, scientific interest in methods of testing led to the development of psychometrics as a prominent discipline within psychology and established the cornerstones of the scientific evaluation of measuring instruments based on reliability and validity testing (Guilford, 1954; Nunnally, 1967).

Thus, when health care evaluation needed methods for measuring patient-oriented outcomes, the technology already existed. Since the 1970s, the focus of health care evaluation has moved to the measurement of function (the ability of patients to perform the daily activities of their lives), how patients feel, and their own personal evaluation of their health in general (Stewart & Ware, 1992). The primary source of this information is standardized surveys (Ware et al., 1980), for which psychometric techniques of scale construction are highly appropriate (Stewart & Ware, 1992). Two studies in the US confirmed the value of psychometric methods for measuring health variables. The Health Insurance Experiment (Brook et al., 1979), a randomized experiment conducted by The RAND Corporation between 1974 and 1981, demonstrated that psychometric methods can be used to generate reliable and valid measures for assessing changes in health status for both adults and children in the general population. Following on from this, the Medical Outcomes Study (Stewart et al., 1989; Stewart & Ware, 1992) demonstrated that psychometric methods of scale construction and data collection were successful for measuring health status in samples of sick and elderly people. This study also demonstrated that psychometrically equivalent short-form measures could be constructed from the original longer-forms (McHorney et al., 1992), thereby reducing respondent and administrative burden and improving measurement efficiency. These two pivotal studies confirmed that psychometric methods, borrowed from the social sciences, generated scientifically sound and clinically useful health measures.

Psychometric methods, however, have been slow to transfer to clinical practice. Perhaps because many clinicians do not have the time to learn about instrument development and evaluation, and the literature, which is directed primarily towards educationalists and psychologists, is incomprehensible (Streiner & Norman, 1995). Consequently, awareness of psychometric methods is limited, despite a rapid expansion of the health measurement literature since the mid-1980s. Although the principles and standards developed in psychology and education are highly applicable to health, it is important to note that they may not be wholly appropriate as measurement of health differs from measurement of psychological and educational constructs (McDowell & Jenkinson, 1996). McDowell and Jenkinson argue that 'as health is based on biological processes it includes a factual element and a consistent internal logical structure that is absent in ratings of political opinions or economic preferences' (McDowell & Jenkinson, 1996, page 238). Important health-specific methodological work is still needed (Hunt, 1997).

Measuring clinical variables

Traditionally, medicine has evaluated the effectiveness of therapeutic interventions using measurements made by machines or by documenting simple clinical end points. For example, studies of interferons in MS have measured MRI abnormalities and relapse rates; studies of interventions in stroke have measured mortality rates, recurrence of stroke rates, and incidence of cerebral haemorrage as a complication of treatments; studies in epilepsy have meas-

0 No increase in tone

1 Slight increase in tone giving a "catch" when the limb is moved in flexion or extension

[1+* Slight increase in tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of movement]

2 More marked increase in tone but the limb easily flexed

3 Considerable increase in tone, passive movement difficult

4 Limb rigid in flexion or extension

* The modified Ashworth scale includes the 1+ rating

Fig. 7.1. Ashworth scale of spasticity.

ured seizure frequency; studies of neurological cancers have measured mortality rates, duration of survival and 5-year survival rates.

Two limitations of traditional outcomes have recently been highlighted. They provide little information about the diverse consequences of disease, and they fail to incorporate the patient perspective. Consequently, there is a need to measure more pertinent but abstract health status concepts such as disability/activities, handicap/participations, and health-related quality of life. As neurology is a specialty with few cures and a large proportion of chronic disorders, this change in focus from measuring quantity of life towards assessing aspects of the quality of life is particularly appropriate. However, this change has brought new challenges because abstract health status concepts, unlike concrete physical entities such as height, weight, and blood pressure, are impossible to measure explicitly because they are unobservable (Bland & Altman, 1997). In the social sciences unobservable variables are know as theoretical constructs or latent variables. Reliable and valid rating scales must be devised to measure these variables. (A construct is a variable that is relatively abstract as opposed to concrete, and is defined or operationalized in terms of observed indicators (Stewart & Ware, 1992)).

Latent variables can be measured indirectly by asking questions intended to capture empirically the essential meaning of the construct. The simplest way to do this is to ask a single straightforward question (item). For example, rate patient X's degree of disability on a scale of 1 (no disability) to 5 (extremely disabled). The Ashworth scale (Fig. 7.1), which grades spasticity from 0 (no increase in tone) to 4 (limb rigid in flexion or extension), is an example of a single item measure (Ashworth, 1964; Bohannon & Smith, 1987). Although single item measures are simple, user friendly, and appropriate for measuring some individual properties, they have a number of scientific limitations when measuring complex clinical variables. Single items are unlikely to represent well the broad scope of a complex theoretical construct and, are likely to interpreted in many different ways by respondents. In addition, single items are imprecise as they cannot discriminate fine degree of an attribute (the Ashworth scale categorises patients into five levels only), and are notoriously unreliable (prone to random error) as they do not produce consistent answers over time (Nunnally, 1978). Finally, it is difficult to estimate the measurement properties of single item measures (McIver & Carmines, 1981).

Multi-item instruments, where each item addresses a different aspect of the same underlying construct, are able to overcome the scientific limitations of single items and are superior methods of measuring latent variables. More items increase the scope of the measure, are less open to variable interpretation, enable better precision, and improve reliability by allowing random errors of measurement to average out (Nunnally, 1978). The Barthel Index (Mahoney & Barthel, 1965) is an example of a multi-item measure. Its ten items measure feeding, grooming, dressing, bathing, walking, transfers, stairs, toilet use, bladder, and bowels. Item scores are summed to generate a total score, which is an estimate of dependency in activities of daily living.

There are many methods, termed scaling models, for combining multiple items into scales depending on the purpose the resulting scale is to serve (Thurstone, 1925; Guttman, 1945; Gulliksen, 1950; Edwards, 1957; Torgerson, 1958). The most widely used scaling model in health measurement is the method of summated rating proposed by

Likert in 1932 (Likert, 1932; Likert et al., 1934). Four characteristics constitute a summated rating scale. First, there are multiple items whose scores are summed, without weighting, to generate a total score. Secondly, each item measures a property that can vary quantitatively (e.g. difficulty walking ranges from none to unable to walk). Thirdly, each item has no right answer. Fourthly, each item in the scale can be rated independently. Examples of Likert scales in health measurement are: the Barthel Index (BI) (Mahoney & Barthel, 1965), functional independence measure (FIM) (Granger et al., 1986), Medical Outcomes Study 36-item Short Form Health Survey (SF-36) (Ware et al., 1993, 1994), General Health Questionnaire (GHQ) (Goldberg, 1978), Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983), and the Parkinson's Disease Questionnaire (PDQ-39) (Peto et al., 1995). Likert scales are popular because they are simple, easy to administer, user friendly, cheap, relatively straightforward to develop, and can be reliable and valid.

Evaluating health rating scales

In this section we discuss the process of evaluating rating scales. We make the assumption that a neurologist has chosen to use a particular scale but there is no published evidence concerning its measurement properties. This is a common scenario…what should be done?

There are two compelling reasons why it is important for clinicians to consider formally evaluating health rating scales. First, the properties of a scale are sample dependent (not simply disease dependent) and, therefore, the performance of a measure in a specific application is more important than its performance generally (McHorney et al., 1994). Secondly, data are only as strong as the instruments used to collect them. Sophisticated statistical methods and advances in study design will do little to overcome the damage done by poor quality measures (Fleiss, 1986; Cone & Foster, 1991), despite opinions to the contrary (Wade, 1999). It is sobering to think that vast amounts of money have been spent evaluating the impact of interferons on disability in MS using a measure, the Expanded Disability Status Scale (Kurtzke, 1983). Prior to these studies there had been limited evaluation of the EDSS using formal psychometric methods. Subsequently, evaluations have demonstrated its limited ability to discriminate between individuals and groups known to differ in their levels of disability and poor responsiveness (Sharrack et al., 1999; Hobart et al., 2000).

The aim of scale evaluation is to determine whether an instrument satisfies criteria for rigorous measurement. Much of this information can be gained from the retrospective analysis of data if they have already have been collected. However, prospective studies are often required. We recommend evaluating five measurement properties: data quality, scaling assumptions, acceptability, reliability, validity and responsiveness.

Data quality

Indicators of data quality, such as percentage item nonresponse and percentage computable scores, determine the extent to which an instrument can be incorporated into a clinical setting. These indicators, like all psychometric properties, vary across samples (McHorney et al., 1994). If the measure is patient report, these indicators reflect respondents' understanding and acceptance of a measure and help to identify items that may be irrelevant, confusing, or upsetting to patients (McHorney et al., 1994). If the measure is clinician report, these indicators reflect the ability to incorporate a measure into a clinical setting. When there are large amounts of missing data for items, scores for scales cannot be reliably estimated.

Scaling assumptions

Tests of scaling assumptions determine whether it is legitimate to generate scores for an instrument using the algorithms proposed by the developers. For example, the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36; Ware et al., 1993), a generic measure of health status, has 36 items grouped into eight scales. A score is generated for each SF-36 scale by summing scores across groups of items. However, few investigators examine whether the assumptions that underpin the summing of items to generate scores are satisfied. Items can be summed without weighting or standardization when they measure at the same point on the scale (have similar mean scores), contribute similarly to the variance of the total score (have similar variances), measure a common underlying construct (the items must be internally consistent), and are correctly grouped into scales (hypothesized item groupings are supported by techniques including factor analysis and examination of item convergent and discriminant validity).

Acceptability

Acceptability is the extent to which the spectrum of health measured by a scale matches the distribution of health in the study sample and is determined simply by examining score distributions (Lohr et al., 1996). Ideally, the observed scores from a sample should span the entire range of the

Table 7.1. Score ranges, means, standard deviations, floor and ceiling effects for EDSS[a], Barthel Index, and FIM[b] ($n = 64$)

	Admission score				
	Range			Floor effect	Ceiling effect
Instrument	Scale	Sample	Mean (SD)	*n* (%)	*n* (%)
EDSS	0–10	5.0–9.0	7.1 (0.9)	0 (0)	0 (0)
Barthel Index	0–20	0–20	12.02 (5.7)	5 (2.5)	10 (5.4)
FIM	18–126	24–122	89.42 (23.6)	0 (0)	0 (0)

Notes:
[a] EDSS = Kurtzke Expanded Disability Status Scale.
[b] FIM = Functional Independence Measure.

scale, the mean score should be near the scale midpoint, and floor and ceiling effects (percentage of the sample having the minimum and maximum score, respectively) should be small. McHorney recommends floor and ceiling effects should be <15% (McHorney & Tarlov, 1995).

Table 7.1 presents results from an unpublished study and illustrates the importance of examining score distributions. Score distributions for 64 MS patients undergoing inpatient neuro-rehabilitation are presented for three disability measures, the EDSS, Barthel Index, and Functional Independence Measure (FIM). Neither scale has floor or ceiling effects. These results indicate that the range of disability in the sample is adequately covered by all three instruments. However, the sample spans the whole range of the Barthel Index and FIM but only 50% of the EDSS scale range. These results indicate that the EDSS covers a greater range of disability than the Barthel and FIM. More importantly, these findings indicate that the EDSS does not discriminate as well as the Barthel Index and FIM between different levels of disability. This is further exemplified by examining Table 7.2, which reports the range of Barthel and FIM scores for each EDSS score in the study sample.

Table 7.2. Barthel Index and FIM score ranges and means for each EDSS score ($n = 311$)

		Barthel Index score		FIM score	
EDSS score	*n*	Range	Mean	Range	Mean
5.0	3	19–20	N/A[a]	114–122	NA
5.5	6	14–19	17.7	99–119	112.0
6.0	49	8–20	17.9	80–122	110.3
6.5	80	8–20	15.6	71–122	103.8
7.0	48	5–20	12.3	64–117	93.6
7.5	37	2–18	10.1	37–114	83.3
8.0	54	2–16	8.1	38–113	75.9
8.5	23	0–11	3.7	33–93	56.5
9.0	11	0–5	N/A	24–57	n/A

Notes:
[a] Not applicable due to small sample.

Reliability

Reliability is defined as the extent to which a measure is free from random error, and is expressed as a reliability coefficient. However, reliability is a generic term, multiple types (and therefore many reliability coefficients) exist for each instrument. Each type of reliability addresses a different source (or sources) of random error. Ideally, all relevant types of reliability should be quantified.

For health measures the most important (but not the only) types of reliability are internal consistency and reproducibility (test–retest, inter-rater, and intrarater). Other types of reliability are beyond the scope of this chapter but are detailed in standard texts (Cronbach, 1949; Nunnally, 1978; Anastasi & Urbina, 1997). Internal consistency is the extent to which items within a scale are reliable measures of the same construct. This type of reliability only applies to multi-item measures like the SF-36 and Barthel Index and is determined using Cronbach's alpha coefficient (Cronbach, 1951). Reproducibility is the agreement between two or more ratings on the same person. Test–retest reliability is the agreement between two or more self-report ratings for the same patient. Intrarater reproducibility is the agreement between two or more ratings for the same patient made by the same observer. Inter-rater reproducibility is the agreement between two or more ratings for the same patient made by the different

Table 7.3. Product–moment correlations between the FIM, other measures of disability, and measures of handicap, psychological well-being, health status and age

	Barthel Index	EDSS[a]	LHS[b]	GHQ[c]	SF-36 PCS[d]	SF-36 MCS[e]	Age
FIM[f]	0.94	0.87	0.42	0.13	0.14	0.28	−0.05

Notes:
[a] EDSS = Kurtzke expanded disability status scale.
[b] LHS = London handicap scale.
[c] GHQ = general health questionnaire.
[d] SF-36 PCS = medical outcomes study 36-item short form health survey physical component summary score.
[e] SF-36 MCS = medical outcomes study 36-item short form health survey mental component summary score.
[f] FIM = functional independence measure.

observers. Reproducibility should be reported as an intra-class correlation coefficient for continuous data (Shrout & Fleiss, 1979), and Kappa coefficients for dichotomous data (Cohen, 1960).

Validity

The validity of a health measure is the extent to which it measures what it purports to measure (Nunnally, 1978). Determining the validity of a health measure is difficult for three reasons: validity cannot be proven it can only be supported, there is no consensus as to the minimum requirement of evidence to satisfy validity, and evidence supporting validity in one context does not guarantee validity for another.

Although any evidence that an instrument measures the construct it is purported to measure supports its validity, the strongest evidence is provided by examining its correlations with other measures collected at the same time (convergent and discriminant construct validity; Cronbach & Meehl, 1955). Validity is supported by the extent to which correlations conform with the direction, pattern, and magnitude of predictions. For example, Table 7.3 presents correlations between the FIM and a selection of other scales in 64 MS patients undergoing inpatient rehabilitation. If the FIM measures disability, we would predict: high correlations with other measures of physical disability (BI, EDSS); higher correlation with measures of disability than with measures of handicap (LHS), and psychological well-being (GHQ); low correlations with age. The data in Table 7.3 conform with these predictions and therefore provide strong evidence for the validity of the FIM as a measure of disability in MS patients. Studies of convergent and discriminant construct validity are limited if the validating instruments themselves have not been comprehensively validated. Consequently, it is important to have results from multiple studies.

Responsiveness

Responsiveness is the ability of an instrument to detect clinically significant change in the attribute measured (Guyatt et al., 1987). Responsiveness methodology is less well advanced than that for reliability and validity, and whilst several methods have been proposed for determining the responsiveness of health measures there is no clear consensus as to which method is optimal (Liang, 1995). Most methods examine scores at two points in time, usually before and after an intervention thought to alter the attribute being measured. Responsiveness is reflected by the magnitude of the standardised change score (effect size). Simply reporting raw change scores as indices of responsiveness is limited because these do not take into account the sample studied nor allow comparison between different instruments. Only reporting the statistical significance of change scores as an index of instrument responsiveness is also limited because this is heavily dependent upon the sample size. Moreover, statistical significance doesn't guarantee clinical significance (Cohen, 1994; Cortina & Dunlap, 1997). For these reasons it is recommended that responsiveness is reported in the form of an effect size (standardized change score). The formula for the most commonly reported effect size is: mean change score divided by the standard deviation of the baseline scores (Kazis et al., 1989). The larger the effect size, the greater the responsiveness of an instrument. To aid the clinical interpretation of effect size values it has been recommended that Cohen's arbitrary criteria are applied: 0.20 = small; 0.50 = medium; 0.80 = large (Cohen, 1988; Kazis et al., 1989). However, when comparing instruments, the strongest evidence for the superior responsiveness of an instrument comes from head-to-head comparisons of instruments.

Practical aspects of scale evaluation

Data quality, scaling assumptions, and internal consistency reliability can be examined from a single administration of a rating scale to a sample of people. Some aspects of validity, for example intercorrelations between scales and group differences validity, can also be examined. Convergent and discriminant validity can be examined from a single administration when other scales are administered at the same time.

Reproducibility (test–retest, inter-rater, intrarater) and responsiveness require an instrument to be administered on two or more occasions. The time interval between the two administrations for reproducibility estimation is important. Whilst some authors recommend around two weeks (Streiner & Norman, 1995), the most appropriate interval is study dependent. The aim is to achieve the optimum balance between raters (patient of clinicians) remembering their answers and therefore observed reliability being an overestimate, and true change occurring in the person being rated. Memory effect leads to overestimates of reliability and change results in underestimates of reliability. Nevertheless, more conservative estimates are best. Responsiveness studies require that an instrument is re-administered after change has occurred.

As many measurement properties can be evaluated from the single administration of a scale, psychometric studies can often be undertaken on the data arising from clinical trials. Whilst we do not encourage the retrospective evaluation of scales as the primary approach to determining the psychometric properties of an instrument, such data are important evidence of the value of a rating scale in a given clinical setting.

There is no consensus or even published guidelines for sample size calculations for psychometric studies. However, there are two rules of thumb. First, the sample studied should be representative of the population in whom the rating scale is going to be used. Secondly, the larger the sample the greater the confidence of the results. It is also important to consider clinical practicality. It may be impossible to study large samples of people with rare or uncommon diseases. Finally, some evidence is better than none.

Choosing a rating scale

Clinical trialists often have to choose one scale from among many potential candidates (Bowling, 1991, 1995; Wade, 1992; Wilkin et al., 1992; McDowell & Newell, 1996; Herndon, 1997). Unfortunately, no one scale exhibits all desirable qualities, different scales have different virtues, and instruments that are useful for one clinical trialist may not be useful for others. Therefore, scales must be selected for the particular purpose for which they are to be used and the scale user must be able to choose measures intelligently based on their needs.

For success in clinical trials, instruments must be clinically useful and scientifically sound. Clinical usefulness refers to the successful incorporation of an instrument into clinical practice and its appropriateness to the study sample. Scientific soundness refers to the demonstration of reliable, valid, and responsive measurement of the outcome of interest. Clinical usefulness does not guarantee scientific soundness, and vice versa. Below is a list of questions that we think should be addressed when selecting a rating scale.

Does the scale measure the appropriate health entity?

This is a fundamental question that must be addressed head on. Instruments selection should be based on a clear hypothesis of the impact of the intervention under study. Choosing scales simply because of their popularity, or because they were developed locally, is likely to result in the measurement of outcomes that are distal to the ideal. Under these circumstances the effectiveness of an intervention may be misrepresented.

Is the method of administration appropriate for the study?

The method of administration of an instrument should not be changed from that recommended by the instrument developers in order to suit the needs of a study. This is because altering the method of administration may affect the scientific properties (reliability and validity) of a measure. If an alternative method of administration is considered necessary, the validity of this method needs to be evaluated before the instrument is used. This can be achieved by correlating scores for patients obtained by the two methods, the higher the correlation the greater the validity of the alternative method of administration.

Is the rating scale acceptable to patients?

User acceptability is important in obtaining the cooperation of persons in the study. Patients in clinical trials are often ill or disabled and their tolerance for completing long and complex questionnaires may be limited. Seemingly irrelevant items arouse criticism. Busy clinicians with no ownership of a study have little personal gain from the

results. These factors influence the interest of patients and clinicians in participating in clinical trials, affect the reliability and validity of scores, and also the relationships between the investigators, clinicians and patients.

Does the spectrum of health measured by the scale match the level of health in the study sample?

The range of health addressed by a rating scale needs to match the distribution of scores in the sample otherwise there will be notable floor and ceiling effects (percentage of subjects scoring the minimum and maximum possible scores, respectively). Floor and ceiling effects represent subsamples of patients for whom actual changes in health will be underestimated (floor) or not recorded (ceiling) by a rating scale. The acceptability of a scale can be determined by examining score distributions for the sample of interest. Ideally, scores should span the entire scale range, means scores should be near the scale midpoint, and floor and ceiling effects should be small (<15%) (McHorney & Tarlov, 1995).

Does the rating scale generate reliable estimates?

When evaluating reliability data available for instruments, investigators should try and answer three questions:

Have the appropriate types of reliability been assessed?

Internal consistency can be examined in all multi-item measures. Test–retest reproducibility should be examined for self-report measures. Inter-rater and intrarater reproducibility should be examined for observer report measures. It is unusual to find instruments were the assessment of reliability is comprehensive. For multi-item measures the most useful index of reliability is the internal consistency because the major source of error is item sampling. A full explanation of this can be found in standard texts (Nunnally, 1978). Also, there is good evidence that estimates of internal consistency and reproducibility are similar (Ware et al., 1978, 1979) and that Cronbach's alpha tends to provide a conservative reliability estimate (Bravo & Potvin, 1991). Finally, high test–retest reliability with low internal consistency is much more likely than low internal consistency with high test–retest reliability.

Were the reliability studies conducted in appropriate samples?

All psychometric properties are dependent upon the samples from which they were determined. Therefore, results can only be generalised from one sample to another if the reliability in the two samples is expected to be similar. For example, demonstration of high reliability for a self-report health measure in persons with cervical myelopathy cannot be assumed to indicate high reliability in persons with dementia. However, evidence of reliability from multiple studies in different groups suggests reliability is a stable property for the instrument. There is no consensus as to the sizes of samples for reliability studies. However, it is important that the sample is representative of the larger sample in which the rating scale is to be used.

Has adequate reliability been demonstrated?

Widely recommended minimum requirements are 0 .80 (ideally 0.85 (Nunnally & Bernstein, 1994)) for group comparison studies, and 0.90 (ideally >0.95) for individual comparison studies (Nuyens et al., 1994; Lohr et al., 1996). The need for high reliability in individual comparison studies is clear when confidence intervals around individual scores are calculated using the standard error of measurement (SEM). This estimates the standard deviation of scores obtained if an instrument were administered repeatedly to the same individual using the following formula:

$\text{SEM} = \text{SD} \times \sqrt{(1 - \text{reliability})}$;
95% confidence intervals (+/− 1.96 SEM).

Table 7.4 illustrates the effect of decreasing reliability on the confidence intervals of Barthel Index scores and demonstrates why scores for individual patients should be interpreted with extreme caution.

Is the rating scale valid?

To determine whether an instrument is valid for a specific purpose, clinical trialists must assess the strength of empirical evidence available. Evidence for content validity

Table 7.4. Effect of different levels of reliability on the confidence intervals around individual patient scores for the Barthel Index

Reliability	95% confidence interval
0.95	+/−2.6
0.90	+/−3.7
0.80	+/−5.2
0.70	+/−6.3
0.60	+/−7.3
0.50	+/−8.2

Notes:
Barthel Index scores: $n = 149$; mean score = 11.5; SD = 5.9; sample range 0–20; floor effect = 2.5%; ceiling effect = 5.4%.

is weak validity evidence. Stronger evidence is provided by studies of group differences. Even stronger validity evidence is provided by studies of convergent and discriminant construct validity.

Is there evidence that the scale will detect change?

When evaluating responsiveness data, the most useful studies are head-to-head comparisons of instruments purported to measure the same health construct. These data are rare. The most likely scenario, if responsiveness has been examined, is that the statistical significance of the change scores is reported. These results can be misleading as *P* values are sample size dependent. Are the raw data available to compute effect sizes?

Developing scales

Developing clinical scales is a labour-intensive process requiring considerable expertise in health measurement (Spector, 1992). Therefore, clinical trialists are advised to carefully evaluate available measures before abandoning them. The psychometric properties of available measures can be determined more quickly. Here, we present an overview on instrument development.

Development of a measurement instrument in accordance with psychometric theory involves four stages: first, defining a conceptual model; secondly, generation of an item pool; thirdly, reduction the item pool to form an instrument; fourthly, testing the reliability, validity and responsiveness of the final instrument.

A conceptual model is the rationale for, and description of the concept(s) that the measure is intended to assess (Lohr et al., 1996). The importance of a conceptual basis for the measurement of latent variables cannot be overemphasized (DeVellis, 1991; Kopec et al., 1995). However, this is often absent or poorly defined for health measurement instruments (McDowell & Newell, 1996). For example, a clinical trialist may wish to develop a measure of disability for MS. The trialist must first define disability in MS and decide which aspects to measure. Only when this has been done can a comprehensive approach to item generation be undertaken.

There are four sources from which candidate items can be generated: semistructured interviews of patients with the disorder under study, consensus opinion of experts in the field, literature review, and examination of available measures. Patient interviews are very valuable as they help to identify areas that are important to them, a process that maximizes the validity of an instrument. From these four sources, items are devised aiming to address the appropriate range and depth of concept/s to be measured. These items are then pretested on a small sample to assess how easily they can be understood and completed. Appropriate alterations are made and this version is used in the preliminary field test.

The purpose of the preliminary field test phase is to reduce the number of items and to develop a scale. The instrument is administered to a large sample of patients and the results are analysed using standard psychometric techniques for item analysis (Nunnally & Bernstein, 1994; Streiner & Norman, 1995). The aim of item reduction is to select, on an empirical basis, the items that measure the construct of interest, that is items that discriminate between individuals, are stable over time, and measure the same underlying construct. The importance of selecting items on an empirical basis is that approaches to measurement on an intuitive basis often fail to produce the desired empirical results (Nunnally, 1970). After items have been reduced, they may need to be grouped into scales if it is anticipated that the instrument may measure more than one related but different construct. Items can be grouped in two ways: first, on a theoretical basis and, secondly on an empirical basis using item-level exploratory factor analysis. Item groupings, both hypothesized and empirically defined, are then tested using multitrait scaling techniques to define which method of grouping items produces the best empirical measurement instrument (Ware et al., 1997). When items have been reduced and scales formed, the final instrument must be tested on an independent sample for its clinical usefulness and scientific soundness (reliability, validity and responsiveness) using the techniques outlined above.

It is encouraging to see that traditional psychometric methods are being used increasingly in the neurosciences (Peto et al., 1995; Jenkinson et al., 1999; Williams et al., 1999; Hobart et al., 2001).

New development in psychometrics

The methods we have described above are termed traditional psychometric methods. These methods have been used successfully to develop reliable and valid patient-based health outcome measures (Stewart & Ware, 1992). Most of these measures are multi-item rating scales in which scores across several items or questions are summed to generate a total (raw) score that quantifies the health variable of interest (e.g. physical function). Nevertheless, the raw scores generated by these rating scales have important limitations that restrict the impact

of patient-based outcomes on clinical trials, epidemiological studies and routine clinical practice.

The first limitation is that raw scores are non-linear counts and not interval measures. This potentially biases the interpretation of scores and score changes, and may result in treatment effectiveness being underestimated (Wright & Linacre, 1989; Wright, 1997). A second limitation is that raw scores are scale dependent. Therefore, different scales purporting to measure the same health construct cannot be accurately equated, or their results combined for systematic reviews and meta-analyses (Bjorner & Ware, 1998). A third limitation is that the psychometric properties of scales are sample dependent and, therefore, not necessarily stable across different samples (McHorney et al., 1994). A fourth limitation is that rating scales tend to cover a limited spectrum of health. Samples in clinical studies often extent outside of the range of the scale resulting in floor and ceiling effects. These represent subsamples of patients for whom health changes will not be detected, or be underestimated by scales. A final limitation is that raw scores are not precise enough for individual patient clinical decision-making. Therefore, rating scales cannot be used in routine clinical practice (McHorney & Tarlov, 1995).

These limitations of summed rating scales were recognized years ago in education and psychology. Research led to the development of Rasch item analysis (Rasch, 1960) and Item Response Theory (IRT; Lord & Novick, 1968) models. These new psychometric methods convert raw scores into interval measures using a log odds-ratio transformation (Wright & Stone, 1979). Moreover, these methods claim to generate sample-free item calibrations and scale-free person measures, thereby enabling the accurate cocalibration of measures of the same health construct and the formation of calibrated item banks from which any subsets of items can be chosen to solve measurement problems (Wright, 1977). Calibrated item banks lay the foundation for rapid and efficient individual-patient measurement using computer algorithms (Wainer et al., 1990).

Since 1990 there has been considerable interest in applying Rasch analysis and IRT to health measurement. Initially, studies concentrated on using these methods to evaluate (Linacre et al., 1994; Tennant et al., 1996a, b), and refine (Prieto et al., 1998) existing rating scales. More recently, studies have successfully used Rasch and IRT to equate rating scales in oncology (Chang & Cella, 1997), elderly adults (McHorney & Cohen, 2000), and headache (Ware et al., 2000). Although many believe that Rasch item analysis and IRT have the potential to take the health outcomes field to a new plateau (Cella & Chang, 2000; Hambleton, 2000; Hays et al., 2000; McHorney & Cohen, 2000; Ware et al., 2000), these methods have been criticized (Divgi, 1986; Rust & Golombok, 1999) and are not as widely used as their apparent advantages would suggest they should be (Embretson & Hershberger, 1999). These facts have been attributed, in part, to a misunderstanding of the models and ill-considered applications (Linacre, 2000). Nevertheless, there have been surprisingly few empirical studies critically evaluating these methods in health measurement and comparing them with traditional psychometric approaches.

Conclusions

Latent variables can be measured rigorously using Likert scales and should be used as outcomes in the evaluation of therapeutic interventions in neurology. When assessing available instruments, clinical trialists must evaluate their clinical usefulness and scientific soundness with respect to a particular study. First, find instruments that can be incorporated into the study design, whose items look like they measure the required constructs for the study (don't be misled by instrument names), and are appropriate to the study sample. Next, examine the empirical evidence that these measures are reliable, valid and responsive in the study sample. Start with evidence for reliability as this is a prerequisite for (but not sufficient for) validity and responsiveness. Have the important types of reliability been determined in appropriate samples, and have minimum criteria for the type of study (group or individual comparisons) been satisfied? Next, examine the empirical evidence that the instrument measures what it purports to measure. What type of evidence supports the instrument's validity and how strong is this evidence? Finally, what evidence is there that the instrument has the ability to detect change over time?

The trialist is commonly left with no instrument fulfilling all the above criteria. Can further evaluative studies be undertaken on available instruments, or does the study design need to be reconsidered? If no instrument exists and no compromise is acceptable, a new instrument may need to be developed. Be sure to collaborate with a health measurement expert, but also be sure that they have one foot in clinical reality (Aaronson, 1988). Finally, new methods of data analysis have the potential to overcome the limitations of summed rating scales and improve the value of health measurement to clinical practice.

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8

Principles of clinical neuro-epidemiology

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Epidemiology is 'the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems' (Last, 1995). Historically, the science of epidemiology began with the study of outbreaks of infectious disease. It has since progressed in parallel with a shift, in the Western world, from infectious disease to chronic diseases as the major causes of morbidity and mortality. New branches have developed, such as clinical epidemiology, which again have spawned the concept of evidence-based medicine. The modern neurologist must now have both an understanding of the traditional concepts of epidemiology, such as incidence and prevalence of major diseases, and also a solid understanding of clinical research methods and how results of clinical trials apply to their patients. This chapter is designed, with brevity in mind, to provide an initial overview of these fundamentals.

Population-based research in neurological disease

Populations and sampling

There is no substitute for good natural history data. In some cases, society has legislated that all instances of a disease be reported. Both rare diseases, such as rabies or previously more common diseases such as poliomyelitis, are reportable in most jurisdictions in the western world. Legislated data collection results in population-based information. It is no coincidence that these examples are both infectious diseases. With the shift to chronic or degenerative diseases such as atherosclerosis, cancer, arthritis as the leading killing and disabling illnesses, we have not made the same commitments to collecting data as with infectious diseases. We rely upon extrapolation from much smaller samples drawn from the population.

If one could study every human being, it would be unnecessary to understand sampling. Even in very large studies, researchers can only study a tiny proportion of the population; pragmatism dictates it. The principle of sampling is to select from the population a truly representative group for study. A population is any group of persons described as generally or as specifically as appropriate. One may study the entire population of the Western hemisphere, the population of North American First Nations peoples, or the population born in a particular year or years, e.g. the 'baby boomers'. A sampling unit is the basic unit of sampling, e.g. individual, family, city, etc. This entire list of sampling units is called the sampling frame. The sample is derived from the sampling frame.

Samples may, or may not, be random. For example, in studying individual patients, a simple random sample is one in which each person in the population has an equal probability of being chosen for the sample. Sampling may be stratified according to some characteristic or done in a clustered fashion, e.g. by household. The choice of sampling methodology is governed by such things as cost, convenience, generalizability and has an important bearing on the interpretation of the results of the study.

Causation and causal inference

Determination of the causative factors in human disease is not a facile exercise. This is particularly true in the western world where diseases with long latency between exposure and disease onset have replaced shorter latency infectious diseases as the major causes of morbidity and mortality. Koch postulated that in determining the cause of disease, the following conditions should be met: (i) the agent must be found in every case, i.e. it was a necessary

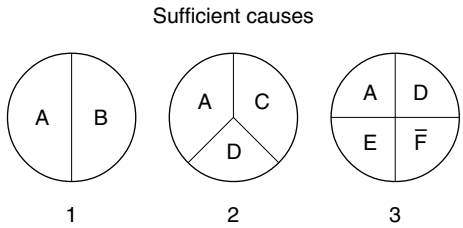

Fig. 8.1.

cause; (ii) the agent should occur in no other situation; and (iii) the agent must be isolated from a case and induce disease when transferred to a susceptible host. These were reasonable for the time but, in fact, do not apply even to most infectious diseases. For instance, the tubercle bacillus does not necessarily comply with postulates 2 or 3. It is a necessary but not sufficient cause. Disease causes are multifactorial.

Rothman described a modern deterministic model of disease causation, suggesting that sets of one or more factors act as sufficient causes (Rothman & Greenland, 1998). Each sufficient cause has an independent effect on disease causation, being responsible for a number of cases. Consider, for example, that there are six factors involved in the cause of a disease, and that these combine to form three sufficient causes (Fig. 8.1).

The effects of each component cause within each sufficient cause are mutually interdependent. For instance, in sufficient cause 2, A does not cause the disease unless C and D are present. If the sufficient cause is complete, the disease becomes inevitable, and the latent period begins. A component cause which appears in each sufficient cause, is known as a necessary cause. For instance, herpes simplex virus type 1 is a necessary but not sufficient cause for herpes simplex encephalitis. That is, many people carry the virus but some additional factor (s) is necessary to produce a sufficient cause. Because of the impossibility of determining the component causes in individuals, it is necessary to study samples of populations and use a probabilistic approach to determine causal relationships between exposure and disease. Factors shown to have a causal relationship with a disease are known as risk factors.

Several criteria have been proposed to strengthen the concept of causal inference, since the probabilistic approach lacks the finality of a true experiment, such as a clinical trial. Doll and Hill (1950) proposed six criteria based upon their work examining cigarette smoking and lung cancer. To conclude that an exposure is a causative factor in human illness, they suggested that the following be considered:

(i) the strength of the statistical association
(ii) the biological credibility
(iii) the consistency with other investigations
(iv) the temporal relationship between exposure and disease
(v) the dose–response relationship
(vi) the effect of removal of exposure

The two most important statistical ratio measures of association are the odds ratio (OR) and the relative risk (RR). These describe, in different ways, the difference in the risk of disease occurrence between those exposed and not exposed. Thus, the higher the RR or OR, the stronger the association. Because inferring causation for many of the determinants of health and disease is not simplistic, many so-called 'causes' of disease are really only associations. Based upon the above criteria, we assume with a leap of faith, that they are causative.

Study designs and interpretation

Epidemiologic studies can be descriptive, examining the distribution of disease or analytic, uncovering the determinants of disease. Descriptive epidemiology encompasses both individual level studies and population level research. Analytic epidemiology involves highly selected groups of subjects and exposures.

Descriptive: case reports, case series, cross-sectional studies and ecologic studies

The simplest observational studies are case reports and case series. These represent clinical observations and may be the first step toward an important understanding of neurological disease. Cross-sectional studies are designed usually to assess prevalence. They may examine the burden of disease, prevalence of risk factors, resource utilization, demographics, etc. They do not provide evidence for causation. The fallacy of reverse causality may occur when two factors A and B are identified in a cross-sectional survey and A is imputed to be the cause of the B. This may be a false deduction as B could just as easily be the cause of A, or both could be influenced by something else. Similarly, one must recognize that all prevalence studies are a reflection of disease duration as well as disease incidence. Nevertheless, these study designs are useful as hypothesis generating tools.

Ecological studies generally analyse groups, such as regions or worksites. Administrative and/or public health data such as mortality data are often used. Comparison of the incidence of multiple sclerosis and rate of seropositivity to HHV-6 across several cities would be an example of an ecological study. It would be erroneous to link a possible

exposure, e.g. HHV-6, with the disease (MS) on an individual basis in this kind of study since it is impossible to control for confounding. This error of logic is named the ecological fallacy. Similarly, temporal association between putative risk factors cannot be assessed by this study design.

Analytic: case-control and cohort studies and clinical trials

Case-control methodology was devised in response to a shift from acute to chronic diseases as major causes of morbidity and mortality in the western world. A case-control study is best used to study rare diseases or events. Subjects are classified according to disease status. The cases and non-cases (controls) are sampled separately and the proportions of subjects with a given exposure in each group are compared. From this type of analysis, an odds ratio (OR) can be derived as an expression of the magnitude of association between the disease and the exposure (risk factor).

The advantages of case control studies include low cost, rapid completion, suitability for studying rare outcomes, the possibility of examining multiple exposures and the quantification of the magnitude of association. Case-control studies are subject to selection bias. It is imperative that the controls be chosen, preferably randomly, from the same population as the cases. Similarly, the information collected and setting should be the same for both cases and controls. Research personnel should be blinded to case or control status and if possible, to the study hypothesis. It may be difficult to establish temporal relationships and it may not be possible to derive incidence rates unless the study is population based.

A recent case-control study assessed the risk of a rare outcome – hemorrhagic stroke – in association with a common exposure – phenylpropanolamine in commonly available cold remedies and appetite suppressants (Kernan et al., 2000). There was an increased odds of hemorrhagic stroke in women (OR = 16.6) but not in men.

Cohort studies are longitudinal studies of a defined group or population, stratified on the basis of exposure status. A well-known example of a prospective cohort study is the Framingham study. In this study, an inception cohort was defined from one geographic location (Framingham, MA) and subjects, divided into groups on the basis of exposures such as hypertension, were studied at baseline and sequentially over time. This type of study is expensive, lengthy and labour intensive; it is not easy to follow people prospectively over time. Undertaking representative sampling, minimizing loss to follow-up, standardizing follow-up and blinding outcome assessment are important measures to be taken in reducing potential bias. This type of study design is robust in that it can assess risk factors which were measured premorbidly, allowing the calculation of relative risk (RR).

Clinical trials

A clinical trial is an interventional cohort study. This is a prospective study in which the subjects are randomly assigned to the exposure (treatment) at the outset, with blinded follow-up for the measurement of outcome. This design is thought to be the ideal method of eliminating selection bias and unknown confounding factors. Successful randomization should result in equal distribution of any premorbid factors in each group or groups. Several design variations on the clinical trial include cross-over vs. parallel group design, factorial design and pseudo-randomization. Most clinical trials are analysed on an intention-to-treat basis. This implies that outcomes are assessed based upon the initial assignment of exposure group, regardless of whether patients dropped out or switched treatment regimens. Such studies are expensive and labour intensive. Additionally, it is not clear that results of randomized trials can be generalized to the usual situation in day-to-day medical practice, since the study subjects are not necessarily representative of the population. Nevertheless, because it is the epidemiological gold standard methodology, the randomized clinical trial has been adopted as the standard by which new pharmacotherapies and surgical interventions are tested.

Several important issues arise at the inception of any intervention trial. Perhaps, the most important is ethical. Is there sufficient uncertainty to withhold a treatment from one half of the cohort? The ethical underpinnings of RCTs have been recently readdressed in the literature (Weijer et al., 2000; Shapiro & Glass, 2000; Ellenberg & Temple, 2000a, b).

Neurology has become a specialty in which therapy plays an increasing role. New treatments for stroke, Guillain–Barré syndrome, multiple sclerosis, amyotrophic lateral sclerosis, and Alzheimer's disease have all been proven to have efficacy based upon randomized clinical trials (National Institute, 1995; Plasma Exchange, 1997; IFNB Multiple Sclerosis Study Group, 1995; Lacomblez et al., 1996; Rogers et al., 1998).The clinician needs to be able to understand the clinical trial and how it might apply to his/her patients and the neurology community must assess the effectiveness of a given therapy in the community once it has passed the test of a clinical trial. The magnitude of effect of tested agent or procedure in a clinical trial can be measured in several ways. Both ratio measures and difference measures can be used (Table 8.1).

Table 8.1.

		Outcome		
		+	−	
Treated	+	a	b	a + b
Placebo	−	c	d	c + d
		a + c	b + d	a + b + c + d

The relative risk (RR) is the risk of disease in the exposed (treated) group compared to the non-exposed (placebo or usual care) group.

$RR = [a/(a+b)]/[c/(c+d)]$

The risk difference (RD) is the incidence of the outcome in the exposed group less the incidence in the non-exposed group. This difference is also called the absolute risk reduction (ARR) and should be carefully distinguished from the relative risk reduction (RRR).

$ARR = a/(a+b) - c/(c+d)$

These are known as measures of efficacy. Where the exposure and outcome are causal, the ARR can be interpreted as the attributable risk – the risk attributable to the exposure.

$NNT = 1/ARR$

In understanding clinical trial results, the reciprocal of the absolute risk reduction (1/ARR) is used to derive the number need to treat (NNT) to prevent one occurrence of the outcome. For example, in the NASCET study (1991) of carotid endarterectomy to prevent stroke, the ARR in favour of surgery for symptomatic carotid stenosis with 70% or greater narrowing measured on angiography was 0.17 or 17%. This results in an NNT of 6 implying that, in order to prevent one ipsilateral stroke or death over 2 years of follow-up, six patients must be treated with endarterectomy compared to medical therapy. Alternatively, the number of patients who benefit per 1000 patients can be expressed at the ARR% × 10. Both methods of understanding the ARR are useful but limited by what they measure. They only provide an indication of the benefit or lack of it according to the outcome measure chosen by the study designers. For instance, an NNT of 9 for tPA treatment of acute ischemic stroke does not imply that the eight patients who did not achieve an excellent functional outcome did not benefit. Additionally, one must consider the time of follow-up. The NASCET study was instructive in showing that the event rate in the medical group waned considerably after 2 years. Extrapolating constant event rates from short term follow-up data may not be valid. In Table 8.2, we have listed some examples of major trials in clinical neurosciences and the NNT.

Guyatt et al. (1993, 1994) have provided criteria for reviewing and interpreting the results of clinical trials as part of a series on evidence-based medicine, published in the *JAMA*. The reader is encouraged to review the series.

The concept of effectiveness is beginning to gain credence in contemporary medicine. Despite solid evidence that the treatment of hypertension reduces the risk of stroke, MI and vascular death, it is common parlance (without tongue in cheek), that only half of hypertensives know they are hypertensive, half of those who know are treated and half of those who are treated actually comply with their prescribed medicine. Similarly, the rate of treatment of atrial fibrillation with anticoagulation is poor (Leckey et al., 2000). Two recent reports suggest that carotid endarterectomy for both asymptomatic and even symptomatic carotid stenosis may be vastly overused because community-based effectiveness does not measure up to the standard established in clinical trials (Chaturvedi et al., 2000; O'Neill et al., 2000). These are examples where the benefit established as efficacy of therapy in tightly controlled clinical trials has not been generalisable to the community as effectiveness of therapy. This distinction becomes particularly relevant where the risk–benefit ratio of any given therapy is close to one. Often, in 'real-life' the risks are higher and the benefit achieved lower than in clinical trials. If the demonstrated benefit is obliterated by the elevated risk observed in community practice, the treatment cannot be routinely justified. This may be the case for carotid endarterectomy for asymptomatic carotid stenosis in many jurisdictions in North America (Perry et al., 1997; Feasby, 2000).

Diagnostic and screening tests for neurologic diseases

Sensitivity, specificity, positive-predictive value (PPV) and negative-predictive value (NPV) are conditional probabilities and are best understood using a 2 × 2 table (Table 8.3).

The sensitivity of a test is the probability that the test is positive given that the patient has the disease $[a/(a+c)]$. Specificity is the probability that the test is negative, given that the patient does not have the disease $[d/(b+d)]$. The positive predictive value is the probability that the patient has the disease given that the test is positive $[a/(a+b)]$ and the negative predictive value is the probability that the patient does not have the disease given that the test is negative $[d/(c+d)]$.

Table 8.2.

Trial	Outcome measure	Absolute RR	NNT
Carotid endarterectomy for ≥70% symptomatic stenosis (NASCET Collaborators, 1991)	Ipsilateral stroke or death over 2 years	17%	6 – treat 6 pts and follow for 2 years to prevent 1 outcome
Carotid endarterectomy for ≥60% asymptomatic stenosis (Exec. Comm. ACAS, 1995)	Ipsilateral stroke or death over 5 years	5.9%	17 – treat 17 patients and follow for 5 years to prevent 1 outcome
Intravenous tPA for acute ischemic stroke (Nat. Inst., 1995)	Excellent functional outcome at 90 days	11%	9 – treat 9 patients and follow for 3 months to get 1 outcome
β-interferon for relapsing–remitting MS (IFNB MS Study Group, 1993)	Proportion of symptom-free subjects in the high-dose treatment group at 2 years	15%	7 – treat 7 patients for 2 years to prevent 1 outcome
Treatment of isolated systolic hypertension in the elderly (SHEP) (1991)	Incidence of total stroke over 5 years	3%	33 – treat 33 patients for 5 years to prevent 1 outcome

Table 8.3.

		Disease (truth)		
		+	−	
Test	+	a	b	a+b
	−	c	d	c+d
		a+c	b+d	a+b+c+d

Table 8.4.

		Disease (truth)		
		+	−	
Test	+	2	4	6
	−	1	93	94
		3	97	100

In clinical practice, the interpretation of diagnostic testing is most informed by the use of PPV and NPV. This is because one does not know whether the patient has the disease or not, while one does know the test result. Both sensitivity and specificity are functions of the test itself. However, PPV and NPV depend upon the patients and the population from which they arise and therefore will vary as the prevalence of disease within a population. Calculation of PPV and NPV when the characteristics of a test are known (sensitivity and specificity), is a function of Bayesian theory (Table 8.4).

In the foregoing example, the prevalence of the disease is only 3%. The result is that the PPV = 0.5 and NPV = 0.99. Therefore, when the prevalence of a disease is low, a positive test may not be helpful since there may be a significant probability that the test is a false positive. A negative test adds only minimally to the diagnostic process since the prior probability of the diagnosis was only 3%.

The usefulness of any test depends very much upon what its intended use is. One can deduce from the above explanations of sensitivity and specificity that increased sensitivity comes at the expense of decreased specificity and vice versa. For example, when selecting a test for the diagnosis of a disease, a test with high specificity, which results in the highest positive predictive value, will be most useful. Alternately, if you wish to exclude a disease then a test with high sensitivity is best. For tests used in screening, similar considerations apply.

Graphically, this relationship is shown in a receiver–operator characteristic (ROC) curve. A ROC curve provides a visual method to examine the sensitivity and specificity of a diagnostic or screening tool at every possible cut-off point (Murphy et al., 1987). It is created by plotting the sensitivity of a diagnostic or screening tool as a function of (1 − specificity). This reveals a function that, at each point in the distribution of the screening test, yields a sensitivity and specificity for identifying those with disease. For tests where no clear cut-off for identification exists, the point of maximal sensitivity and specificity can be found.

Burden of neurologic disease

Major neurologic diseases

Neurological illness routinely creates long-term disability; it is therefore important to understand the differences between incidence and prevalence. Incidence is the number of new cases of a disease in a specified time in a population. Prevalence is the number of existing cases of a disease in a population. When a disease has either a high mortality or high resolution rate, the prevalence and incidence will be approximately equal. For example the incidence of Bell's palsy is 15–40 cases per 100 000 population. The prevalence is the same because mortality from Bell's palsy is nil and there is a high rate of spontaneous resolution. For chronic illnesses, such as multiple sclerosis, which have low mortality and low spontaneous cure rates and therefore long durations, the prevalence will be higher than the incidence.

Stroke is numerically the most important neurological disease. The incidence and prevalence are significantly higher than any of the other major neurological diseases and neurological mortality is highest for stroke. Stroke may increasingly account for the rising incidence of epilepsy in the older population. Indeed, as the population ages, brain neoplasms and dementia will play an increasing role in population neurological morbidity and mortality.

In the developing world AIDS plays an increasingly devastating role. Much of the continent of Africa continues to be and will be for the foreseeable future, bludgeoned by the virus. Neurological manifestations of AIDS resulting both from the virus (e.g. progressive multifocal leukoencephalopathy, primary CNS lymphoma, HIV dementia) and from the treatment (e.g. myopathy, painful neuropathy) are very important components of the overall morbidity and mortality from the virus.

Stroke

Stroke is a major cause of both mortality and morbidity. It is the third leading cause of death in North America and Canada and a leading cause of acquired adult disability. US data suggests that there are seven to eight times more stroke survivors than stroke deaths. The age-adjusted incidence of stroke, determined from the Framingham study, is 603 per 100 000 men and 453 per 100 000 women. There is a clear association of increasing stroke incidence with increasing age. As with other diseases, there is substantial regional variability in stroke incidence.

Of interest in stroke epidemiology has been the dramatic decline in age-adjusted mortality rates from stroke. Parallel declines have been seen in other atherosclerotic diseases such as coronary heart diseases. However, the impending aging of the population in many countries will more than make up for the declining mortality and we will see increasing numbers of patients with stroke over the next several decades.

The cost and burden of stroke are enormous because of the sheer numbers of persons affected. Estimates of societal cost in the US approach tens of billions of dollars per annum (Taylor et al., 1996). This is therefore an exciting period, with the introduction of the first new and cost-effective therapy (tPA) for acute ischemic stroke, bringing the potential for reduced cost and suffering (Kwiatkowski et al., 1999; Fagan et al., 1998).

Brain cancer

Brain tumours are second after stroke as a cause of neurological death. There are wide geographical variations in incidence ranging from 1.0 to 14.3 per 100 000 population (Bahemuka, 1988). However, older studies are marred by incomplete ascertainment due to the lack of modern imaging techniques. Indeed, an ongoing issue in the epidemiology of brain tumours is lead-time bias. Studies that suggest longer survival after brain tumour therapy may be biased by earlier diagnosis due to increased use of CT and MRI scanning. A corollary to this concept is that more asymptomatic tumours are uncovered in life rather than as incidental findings at autopsy (Nakasu et al., 1987).

The age-adjusted incidence of brain neoplasms was 14.1 in Olmstead County, Minnesota (Annegers et al., 1981). Incidence of primary brain neoplasms clearly rises with age. Types of brain tumours vary by gender. For example, meningiomas are more common in females and glioma more common in males (Preston-Martin, 1989).

Despite several reports suggesting that the incidence of primary brain tumours is rising rapidly, it appears that, with the exception of primary CNS lymphoma, brain tumour incidence is stable. The dissemination and widespread use of CT and MR imaging has resulted in greater diagnostic accuracy and increased case recognition rates (Radhakrishnan et al., 1995).

Primary CNS lymphoma, accounting for only 1% of CNS neoplasms, has shown an increasing incidence (threefold) over the last several decades. Although the AIDS epidemic has dramatically increased the absolute number of cases, it appears that the trends to increasing numbers began before the AIDS epidemic accelerated. Increased case acquisition also does not explain the rising incidence (Eby et al., 1988).

Dementia

Dementia, like stroke, is an enlarging public health issue because of aging populations in many parts of the world. Dementia, of which Alzheimer's disease is the most common, occurs with steeply increasing incidence and prevalence with age. Data on the descriptive epidemiology of dementia is quite consistent across the world, where it has been gathered. However, the prevalence of the disease in older age groups is more variable because small sample sizes in the oldest old produce more variation in these age brackets (Fratiglioni et al., 1999).

While Alzheimer's disease is the most common form of dementia, differing case definitions of vascular dementia allow for variations in the proportion of cases attributable to each and in which age brackets (Hebert & Brayne, 1995). Recent work suggests that there is a very strong synergy between cerebrovascular disease and Alzheimer's disease (Snowdon et al., 1997). Because of difficulties in premorbid clinical diagnosis, it remains unclear how commonly other forms of dementia, e.g. diffuse Lewy body disease, the fronto-temporal dementias, progressive supranuclear palsy, etc., are found across the world.

Multiple sclerosis (MS)

Interest in the epidemiology of MS is piqued by the non-random distribution of the disease with increasing prevalence according to increasing latitude in both hemispheres (Kurtze, 1975, 1977; Hammond et al., 1988). In addition, smaller migration studies have suggested that migrants take on the prevalence of the disease in the indigenous population of the new country. These observations 'favour an environmentally-based latitude effect' upon MS prevalence (Ebers & Sadornick, 1998). Genetic influences have generally not been controlled for in these studies such that, despite enthusiasm for viral and other infectious causes of MS, genetic predisposition with a non-specific inciting environmental agent may be the most plausible ontogenic theory of MS.

The prevalence of MS varies from 5/100 000 to as high as 120/100 000 population. The incidence of the disease is much harder to estimate for several reasons. The biology of the disease suggests that it exists well before a clinically definite diagnosis can be reached, and this lag time may be quite variable among patients. Improving diagnostic strategies may improve this situation but they also cast doubt upon research done prior to routine magnetic resonance imaging. Data from Olmstead County, Minnesota suggest an annual incidence rate of 3.6 per 100 000 (Percy et al., 1971).

The burden of MS upon patients, families and society is tremendous. A majority of patients are unemployed either inside or outside of the home after 10 years. Depression and other psychiatric conditions occur in MS due to both the disease itself and its effects upon the psyche. Cost estimates including both direct and indirect medical care as well as lost wages suggest that MS is an expensive disease. Although there is excess mortality from MS, particularly the malignant, rapidly progressive forms (e.g. Marburg variant) and from suicide, the societal impact is due to chronic morbidity and reduced quality of life rather than increased mortality (Swingler & Compston, 1992).

Table 8.5.

Disease[a]	Estimated age-adjusted annual incidence per 100 000 population
Stroke	603 (men); 453 (women)
Dementia[b]	80–400 for the age-group 60–64 4980–13 570 for the age group >95
Epilepsy	24–53
Primary brain neoplasms	9.0
MS	3.6
Guillain–Barré syndrome	1–2

Notes:

[a] Referenced in the text.

[b] Not age adjusted.

Epilepsy

Epilepsy is a disease of the extremes of age in the developed world. While the overall incidence varies between 34 and 53/100 000/y, children (<20 y) and older adults (>60 y) have two to four times that incidence. In Africa and South America, this U-shaped curve is flatter and an increase in incidence in the elderly has not been observed (Rwiza et al., 1992; Lavados et al., 1992). The prevalence of epilepsy worldwide is much higher, ranging from 400–800 per 100 000 population (Hauser & Hesdorffer, 1990).

Epilepsy is slightly more common in males and its overall incidence in the western world has been stable. However, data from Rochester suggest that overall stability reflects significant declines in the pediatric age group and increases in incidence in the group over 60 y (Hauser et al., 1993) (Table 8.5).

In conclusion, a solid comprehension of basic clinical epidemiology is invaluable to the practicing clinician. Particularly as clinical neuroscience practice becomes more and more subject to the results of clinical trials, clinicians will need to know how to interpret the literature for both therapeutic and diagnostic modalities. The concepts

outlined here are only the tip of the iceberg and further exploration is suggested (Sackett et al., 1991).

Review of some of the major neurological diseases is helpful in placing both ourselves as treating physicians and our patients in context. From a public policy point of view, interventions to prevent stroke will have the most chance of reducing neurological morbidity and mortality. From the viewpoint of physicians and patients, knowledge of disease prevalence aids in the interpretation of diagnostic testing and awareness of risk factors aids preventative management. Understanding from where and how these data are derived can only further the practice of good clinical medicine.

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9

Principles of therapeutics

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Traditional neurology has been dominated by a focus on diagnosis with accurate neuroanatomical localization of the lesion or pathophysiological definition of the underlying disease process. With some notable exceptions, such as changes in the pattern of infectious diseases in the Western world, neurological diseases have not altered much since Gowers (1888) set out the problem. The process of diagnosis, certainly for structurally based conditions, has been immeasurably served by brain imaging, first with X-ray computerized tomography and most recently with magnetic resonance imaging. Pathological study remains a cornerstone of accurate disease classification for some brain disorders, notably tumours, while the pathophysiological basis of many diseases has been elucidated by techniques including molecular biology, clinical neurophysiology and functional brain imaging. However, therapeutics in neurology can be barren, indeed neurology has often suffered the tag of being expert on diagnosis and wanting in treatment. While there can be no doubt that patients seek a label, or explanation, for their problems, treatments, indeed cures, for neurological maladies must be our aim.

Several areas of neurology have seen substantial advances in their therapeutic armamentarium in recent times and it seems appropriate to consider some of the underlying principles that drive neurological therapy and how new therapies may fit such a framework. First, some principles will be covered, after which some specific generic issues will be considered, clinical trial evaluation, dose selection, drug metabolism and interactions, and some issues of special populations.

Some principles

While everything in neurology, indeed medicine, can be individualized there are some underlying themes. The emphasis on these themes will vary with the condition being considered, and the needs of the patient. However, some part of these principles can be applied in many clinical conditions.

- Patients need an explanation of the condition from which they suffer and how their symptoms fit that diagnosis.
- Patients need to know the natural history of their condition so they can judge the likely benefit of treatments.
- Patients need to know the treatment options, both complementary if they exist, and orthodox.
- It should be made clear whether a treatment will address symptoms or the underlying disease process.
- Realistic goals need to be set for treatment: if the best that can be expected is a 50% improvement this needs to be stated clearly.
- Commonly expected or potentially serious side effects need to be stated and explained.

Naturally, these principles simply state what most neurologists do, coming as no surprise to the clinician. In the modern, ever more technologically driven and litigious environment in which we practice one might add some expectations of patients. Therapeutics should not be a battle, with tension between treatments and side effects, but a partnership. Most practitioners seek to do good and it is a shame that this is not the starting point in all clinical interactions. Notwithstanding the best intentions an adequate record of the management plan, including side effects explained and options offered needs to be recorded in the case notes for the many good reasons that such records are made.

Evaluating clinical trials

The cornerstone of modern neurotherapeutics is the controlled trial. The importance of proper, scientifically sound

clinical studies cannot be overemphasized. Many neurological disorders have such remarkable variability with time or between ictal events that uncontrolled studies are unacceptable. This does not imply that good clinical observation has no place in modern therapeutics; indeed many important developments come from the careful observer notingchange where it was not expected, but this approach generates hypotheses not textbook advice. Some conditions lend themselves to clinical study and some do not. For rare conditions the *N*-of-1 approach (Jones & Kenward, 1989) deserves more exploration, often overcoming the problem of recruitment.

Ideally therapeutic studies need a control group and must be randomized and double-blinded. Clinicians need to understand the many biases of single blinding, of the patient without the clinician, and generally reject such designs. If it is undesirable to offer treatments without evidence, it is even more unhelpful to conduct studies that cannot by their design yield useful information. The control group needs careful consideration, it should be contemporaneous, not historical, carefully matched for obvious variables: age, sex and disease, and consider other issues of matching, such as weight, that may effect the study outcome. Often a placebo control group is desirable but for some indications in which there are established treatments an active control group, in addition or instead of the placebo group, may be desirable. An active control group can help clinicians position a new treatment, whereas a placebo control can facilitate comparison with previous studies in a therapeutic area.

A special problem arises when, as in the case of multiple sclerosis, several treatments are licensed to modify the course of the disease but none is more than modestly effective and better treatments are clearly needed. Because there are licensed treatments available, it may no longer be ethically justified to perform large, double blind, placebo controlled, randomized clinical trials. In this context historical controls may be necessary; mathematical modelling of disease course utilizing data from the placebo arms of previous clinical trials and from epidemiological studies may provide a basis for comparison of the effects of new agents. The Sylvia Lawry Centre for Multiple Sclerosis Research in Munich set up by the Multiple Sclerosis Federation is an attempt to develop such an approach.

Study analysis and data presentation is an area that is often found lacking when new data are published. Study size is crucial; how was the study powered and to what endpoint? When new treatments are being evaluated against established therapies and equivalence is claimed, was the study powered adequately for equivalence? What clinical difference is being evaluated? Is a difference of 5% of any clinical relevance? What was the primary end-point and was it significant? How many hypotheses have been tested to obtain a positive result? In our clinical desire to have new treatments it is important that substandard studies do not end up driving clinical practice inappropriately.

Some principles in evaluating clinical trials

These include:

- Has the therapy been studied in randomized controlled double-blinded studies?
- Is the control group appropriate and suitably matched?
- Is the primary end-point clear and was it statistically significant?
- Was the study adequately powered?
- Are the reported differences and benefits clinically important?
- Were the adverse events clearly stated, and were there any serious adverse events that will be important to mention in clinical practice?

Dose selection

The pharmaceutical industry has often taken the view that simplicity is best and one dose should fit all patients. It is borne of the perception that anything too complex will not be used and dose titration is too much trouble. It is a nonsense to expect that a treatment studied in 70–80 kg patients would necessarily be of any use to those weighing 100 kg, or that tolerability will not be a problem in those weighing 40 kg. Weight is a simple but clear example of the need to consider dose carefully. Patients can often be engaged in such a process of dose selection understanding that one is trying to do what is best for the individual rather than applying a *herd-based* therapeutic approach.

If individualization, where possible, is one guiding principle, the other must be the often-quoted medicinal aphorism: start low and go slow. Patient responses may be idiosyncratic, indeed side effects may be unpredictable on the base of dose so that giving a low dose and making small increments will greatly aid compliance and alert the clinician to a problem when the drug load is low. Many drugs that are used in neurology have significant central nervous system side effects that can be tolerated if patients are gradually exposed. It is a shame to lose a useful treatment in the rush for a response. Again, it is important to make it clear to the patient why one is taking this approach so that their expectations for a response are suitably modified.

An obvious general exception to the slow and steady principle is the neurological emergency. In some situa-

tions, such as acute stroke or giant cell arteritis, dosing must reflect the significant morbidity, indeed mortality, of the condition being treated.

Pharmacokinetics: giving drugs safely and effectively

When prescribing a treatment, the clinician needs to consider how the substance might interact with the patient, in terms of metabolism and drug interactions. Such interactions vary from trivial alterations in drug metabolism to profound change, as may be seen with some of the older anticonvulsants.

Issues of drug metabolism have become more complex as our treatment options expand, and those of other specialties conspire to make administration much harder in some individuals. It is beyond the scope of this chapter to discuss every aspect of pharmacokinetics but as a checklist one might consider:

- absorption issues in oral medications vs. other routes of administration;
- bioavailability and the effect of feeding or interactions with the disease on absorption, such as impaired oral absorption in acute migraine;
- drug metabolism involving monoamine oxidase (MAO) or cytochrome P450 pathways that can cause potential interactions with other medications;
- drug delivery issues, such a protein binding or special brain issues, such as whether a medication is a substrate for the brain P-glycoprotein (PGP) pump (Wacher *et al.*, 1995), which can specifically promote efflux of medicines out of the brain, or the state of blood–brain barrier itself;
- drug half-life issues that may drive dosing considerations, and thus affect compliance;
- drug elimination issues such as those seen in hepatic impairment or renal failure.

The list is not exhaustive, but illustrates the challenges we face as we seek to employ new medications into daily practice. On-line and various electronic PDA solutions will help alert clinicians to potentially fatal interactions but will not replace the thoughtful, well-trained neurologist who plays the pivotal role in bringing innovative medicines to daily clinical practice.

Special populations

Some populations are so special that therapeutics can be a particular challenge, which deserves particular attention.

Females of child-bearing age and pregnancy

For very good reasons females of child-bearing age and pregnant women are generally excluded from clinical studies of new therapeutic agents. While it is easier to include females in the child-bearing age by adequate screening and discussion, pregnant women are a complex therapeutic proposition. Generally, females of child-bearing age should not be denied the potential benefits of treatments for their neurological conditions. Contraceptive issues can be discussed and the lack of experience of any treatment in pregnancy explained. Indeed clinical trials should seek actively to include patients in the demographic distribution of the target condition. Pregnancy is a more complex issue.

Given that most therapeutics studies will exclude pregnant females, there can be no data concerning the effects of a new agent on the pregnant female or the fetus. The possibility of teratogenicity or abortion must be mentioned even though it is effectively impossible to give any reliable estimates of the chance of an adverse event. Often the clinical condition will assist in making these decisions in that the disease itself may adversely affect the fetus; situations such as a prolonged seizure or acute migraine with vomiting and dehydration, weigh into the risk–benefit of treating pregnant females. Ideally treatments whose risks are minimal, or at least clearly understood, can be presented to the patient. It is attractive and often helpful to have both parents, when possible, hear the same information and certainly to document what is said.

It is worth remarking that effects of the pregnancy on a treatment should be considered. Metabolic, hormonal or simply blood volume changes should be considered when dosing the pregnant female. Having taken a decision to treat, that treatment must be adequate to prevent or control symptoms, as desired.

Younger patients and the elderly

Neurological disorders clearly affect children and adolescents, as well as the elderly. The general issues surround dosing and desirability to treat these groups. Dosing is an obvious issue with simple weight adjustments being a minimal consideration in the young, while in the elderly drug metabolism needs to be factored into dosing considerations. The route of elimination of a compound is important, particularly for renal excretion in the elderly, and if dose adjustment is recommended this needs action.

Some conditions, perhaps most notably stroke and degenerative diseases, affect the population more with time, and development programmes for new treatments

will reflect this reality. However, some conditions of younger patients also affect the elderly, and are no less disabling. Where the age cut-off for studies should be, and what constitutes elderly, is no simple decision. Many patients over 65 years, and particularly under the age of 75, are remarkably biologically agile, while many adolescents acquire both the physiology and responsibility of adulthood before their 18th birthday. Lack of exposure of a new therapy to an older or younger age must be weighed against the disability that is attendant the disease process. For the young, perhaps school attendance and performance, and for the elderly issues of quality of life need to be considered when planning treatment. For children careful involvement of the parents or care-givers is essential.

In conclusion, neurotherapeutics is likely to be the next great change to neurological practice. Increasingly neurologists will be required to treat what has been untreatable, to palliate where only suffering was previously on offer, and eventually to alter the course of neurological diseases as modifying and curative approaches become available. The challenges are substantial and the rewards considerable. Neurotherapeutics will drive subspecialization in neurology as patient expectations grow and the number of options becomes more complex. Careful attention to the principles will help the clinician bring the fruits of the post-human genome translational therapeutic revolution to the group of diseases that neurologists are charged with managing.

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10

Windows on the working brain: functional imaging

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Functional imaging encompasses methods used for visualizing a variety of aspects of cerebral physiology ranging from cerebral blood flow and metabolism to neurotransmitter binding and turnover. Functional imaging has numerous applications in basic and clinical neuroscience, many of which are now in routine clinical use. These techniques may be used to image physiological alterations in the brain that cannot be detected by structural assessment, or to elucidate metabolic changes which underlie structural lesions. The major modalities used for functional imaging of the brain include positron emission tomography (PET), single photon emission tomography (SPECT), and magnetic resonance imaging (MRI). PET and SPECT methods measure the distribution of exogenously administered radioactive tracers, while functional MRI (fMRI) studies primarily utilize endogenous contrast and as such are completely non-invasive. For this reason, over the past 5 years fMRI has begun to replace PET as the technique of choice for mapping regional brain function in response to sensorimotor and cognitive tasks, as well as for imaging alterations in cerebral blood flow and metabolism. However, because of the extreme sensitivity of radioactive tracer techniques, PET and SPECT remain the only means of mapping changes occurring at very low concentrations, such as receptor binding. This chapter will provide an overview of these approaches to physiological imaging of the brain. Applications to neurological diagnosis and management as well as to cognitive neuroscience will also be addressed.

Physiology of regional brain function

A number of cellular and metabolic processes in the brain can be monitored using functional imaging methods, and have relevance to basic and clinical neuroscience. Figure 10.1 illustrates these processes which include neurotransmitter binding and reuptake, glucose utilization (CMRGlu), oxygen metabolism ($CMRO_2$), and hemodynamic parameters of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) and time to peak (TTP) for intravascular tracers. Depending on the specific application, some of these parameters may be more relevant than others. For example, studies in cerebrovascular disease have focused on hemodynamic parameters and their effects on oxidative metabolism, as well as on the apparent diffusion coefficient (ADC) in brain, a biophysical parameter available in MRI that reflects early cytotoxic injury. By contrast, functional imaging studies in epilepsy have primarily examined ictal hyperperfusion using CBF imaging and interictal hypometabolism using CMRGlu imaging, and in Parkinson's disease, where brain dysfunction is better understood at a neurochemical level, much of the functional imaging has involved receptor mapping of the dopaminergic system.

In cognitive and systems neuroscience, there has been great interest in using functional neuroimaging to map regional brain function in response to cognitive or sensorimotor tasks. In patients these approaches may also be used to map eloquent function as part of preoperative evaluation for neurosurgical procedures, and for studying reorganization of function following focal brain injury. Nearly all studies of task-specific activation using functional neuroimaging rely on the existence of a coupling between regional changes in brain metabolism and regional cerebral blood flow (CBF), herein referred to as activation-flow coupling (AFC). Changes in blood flow and metabolism occur with excitatory or inhibitory neurotransmission, both of which are energy consuming processes. Surprisingly little is known about the physiology underlying AFC, which was originally described in 1890 by Roy and Sherrington. Studies over the intervening century have yet

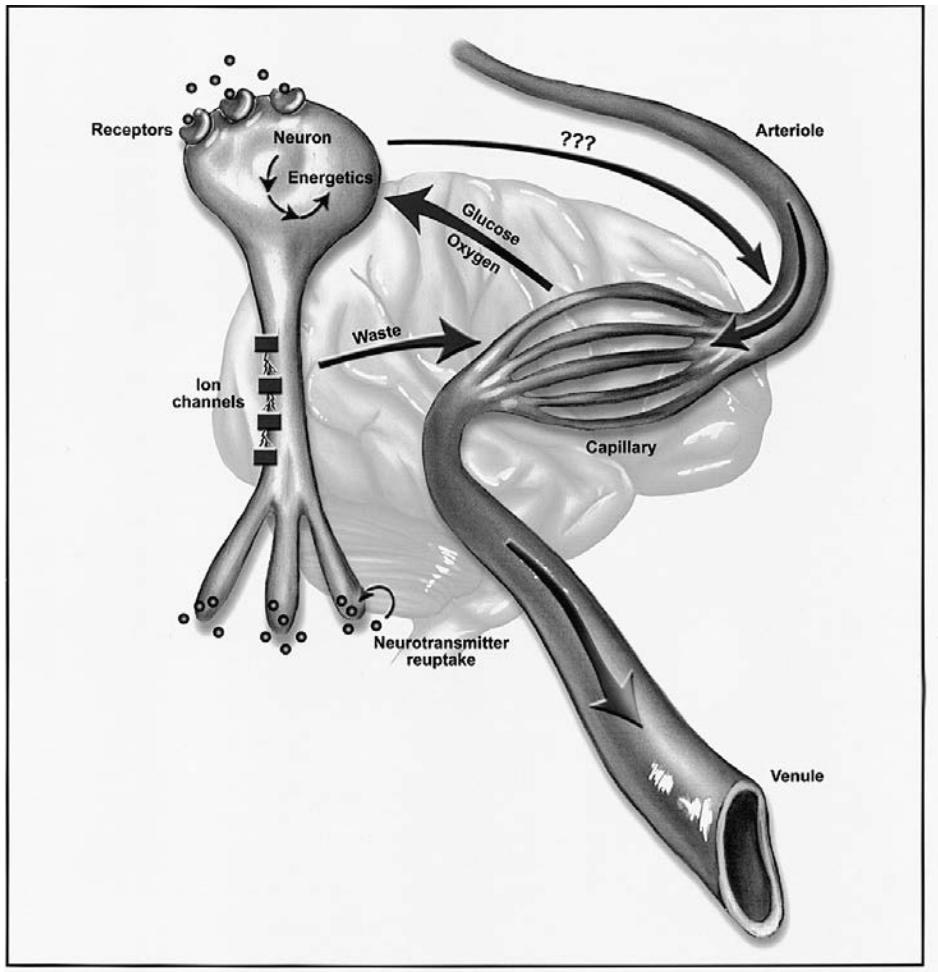

Fig. 10.1. Schematic diagram illustrating the physiological mechanisms which can be visualized by functional imaging. Brain function is represented by a neuron that receives synaptic input, conducts electrical signals by an energy dependent process, and has synaptic output with transmitter recycling. The adjacent microvasculature provides oxygen and glucose to support these functions through perfusion, which also affects local blood volume and blood oxygenation.

to fully characterize the mechanisms and mediators of AFC (Villringer & Dirnagl, 1995). The extent to which non-neuronal constituents of brain parenchyma contribute to the overall metabolic rate is also uncertain, and may be variable. Nonetheless, regional blood flow changes have typically colocalized with known functional specialization.

Functional imaging using radioactive tracers; PET and SPECT

The techniques of PET and SPECT enable the three-dimensional distribution of a radioactively labeled tracer to be measured in vivo. Radioisotopes used in PET imaging decay with the emission of positrons, which travel only a short distance in tissue before annihilating with an electron to form two colinear photons, each with 511 keV energy. In contrast, SPECT tracers emit just a single gamma ray, with energies dependent on the specific radioisotope used. The technology for detecting these gamma rays differs between the two systems, with PET generally having superior spatial resolution and system sensitivity, although SPECT is considerably less expensive, and much more widely available.

The spatial resolution of PET is limited by the range of positrons in tissue, and the slight acolinearity of the emitted gamma rays. Depending on the radioisotope, the absolute limit of resolution is approximately 1.5–2.5 mm, though generally this is not achieved in routine clinical practice. SPECT resolution is limited by the design of the

Table 10.1. Selected radiotracers for PET and SPECT imaging of the brain

Measurement	PET tracers	SPECT tracers
Cerebral blood flow	$H_2{}^{15}O$	[^{123}I]IMP, [^{99m}Tc]HMPAO, [^{99m}Tc]ECD
Cerebral blood volume	^{11}CO, $C^{15}O$	[^{99m}Tc]red blood cells
Oxygen metabolism	$^{15}O_2$	
Glucose metabolism	^{18}FDG	
Dopamine D_1 receptors	[^{11}C]SCH23390, [^{11}C]NNC756	[^{123}I]TISCH
Dopamine D_2 receptors	[^{11}C]raclopride, [^{11}C]NMSP	[^{123}I]IBZM, [^{123}I]IBF, [^{123}I]epidepride
Dopamine synthesis	[^{18}F]DOPA	
Dopamine transporters	[^{11}C]cocaine, [^{11}C]β-CIT, [^{11}C]FP-CIT, [^{11}C]CFT, [^{11}C]methylphenidate	[^{123}I]β-CIT, [^{123}I]FP-CIT, [^{123}I]IPT, [^{99m}Tc]TRODAT, [^{123}I]altropane
Serotonin 5-HT_{1A} receptors	[^{11}C]WAY100635, [^{18}F]MPPF	
Serotonin 5-HT_{2A} receptors	[^{11}C]MDL100907	[^{123}I]R-91150
Serotonin transporters	[^{11}C](+)McN5652	[^{123}I]β-CIT, [^{123}I]5-iodo-6-nitroquipazine, [^{123}I]IDAM, [^{123}I]ADAM
GABA receptors	[^{11}C]flumazenil	[^{123}I]iomazenil
NMDA receptors	[^{18}F]AFA	[^{123}I]MK801, [^{123}I]CNS1261
Nicotine receptors	[^{11}C]nicotine	[^{123}I]nicotine
Opioid receptors	[^{11}C]carfentanil, [^{11}C]diprenorphine	
Gene expression	[^{18}F]FIAU, [^{18}F]FGCV	[^{123}I]FIAU
Brain tumours (various types and modes of action)	^{18}FDG, [^{11}C]methionine, [^{11}C]thymidine	^{201}Tl, [^{123}I]MIBG, [^{111}In]octreotide

collimator, and the distance from the subject to the detector. Most clinical systems can attain a resolution of 6–7 mm, though better resolution is possible with more specialized collimators. The temporal resolution of both systems is poor, as it can take several minutes of scanning to acquire sufficient statistics to form an image. However, despite the poorer spatial and temporal resolution of PET and SPECT compared with other modalities, such as fMRI, their tremendous advantage is their exquisite sensitivity. PET and SPECT can measure picomolar (10^{-12} M) concentrations of tracer, many orders of magnitude less than can be detected with MRI. The quantity of radiotracer injected is tiny, and generally has no effect on the biological system under study.

Radiotracers for PET and SPECT

Many radioisotopes for PET imaging are found naturally in living organisms and are amenable to labeling biologically interesting molecules. These include carbon (^{11}C), nitrogen (^{13}N), oxygen (^{15}O), and fluorine (^{18}F). SPECT radioisotopes tend to be much larger, such as technetium (^{99m}Tc) and iodine (^{123}I), and are more difficult to incorporate into a radiotracer without disturbing the biochemical properties of the molecule. However, SPECT tracers generally have longer half-lives, and are therefore much more widely available than PET radioisotopes, which usually require an on-site cyclotron and production facility. Applications of these imaging technologies have gone hand-in-hand with developments in radiopharmaceutical chemistry. Both PET and SPECT are now capable of imaging biological systems with unprecedented accuracy and sensitivity, mainly due to the tremendous advances in the development of novel radiopharmaceuticals (Table 10.1).

Cerebral blood flow and metabolism

Originally, PET and SPECT were used to measure cerebral blood flow and metabolism. A number of tracers exist which can measure regional cerebral blood flow (rCBF), such as [^{123}I]IMP, [^{99m}Tc]HMPAO and [^{99m}Tc]ECD for SPECT, and $H_2{}^{15}O$ for PET. The SPECT tracers are examples of the 'trapping' mechanism for measuring cerebral function. For a molecule to enter the brain, it must be neutral

and lipophilic which enables it to pass by passive diffusion through the lipid bilayer in the blood–brain barrier (BBB). Once across the BBB, the molecule may become trapped if it interacts with an intracellular component that either reduces its lipophilicity or restricts further free diffusion of the tracer. Chemical instabilities in the ^{99m}Tc-complex in [^{99m}Tc]HMPAO result in the conversion to a less lipophilic species causing sustained retention in brain tissue. Hence, the concentration of tracers such as [^{99m}Tc]HMPAO in the brain are determined by the rate of tracer delivery by the blood supply, giving an indirect measure of rCBF at the time of injection of the tracer. Imaging of rCBF can be carried out at a later time, for example allowing rCBF during brief neurological events such as seizures to be determined without requiring immediate access to the scanner. Conversely, radioactive water, $H_2{}^{15}O$, used for PET measurements of rCBF is unchanged within the brain, freely diffusing across the BBB, and will concentrate in brain tissue at a rate proportional to rCBF. Unlike [^{99m}Tc]HMPAO, which only provides a single 'snapshot' of rCBF, the uptake of $H_2{}^{15}O$ changes over time as the demands for blood flow alter in the brain. This has led to its use as a sensitive and quantitative indicator of changes in rCBF in sensorimotor and cognitive tasks, though fMRI is now becoming more popular in this application.

Blood volume can be measured using a tracer that binds to red blood cells and remains within the vasculature of the brain. For PET, carbon monoxide can be labelled with either ^{11}C or ^{15}O and inhaled, where it will bind tightly to the hemoglobin in red blood cells. Alternatively, SPECT measurements of blood volume can be made using the subject's own red blood cells labelled with ^{99m}Tc. Both techniques give a quantitative measure of regional cerebral blood volume (rCBV). In a similar manner, equilibrium images of inhaled $^{15}O_2$ obtained in conjunction with these measures can yield the rate of cerebral oxygen metabolism ($CMRO_2$).

Another powerful indicator of cerebral function is the measurement of regional cerebral glucose metabolism. Glucose provides approximately 95–99% of the brain's energy requirement under normal conditions, and the rate at which glucose is utilized in different regions of the brain is an excellent indicator of local energy-requiring functions. Glucose is transported across the BBB where it is phosphorylated by the enzyme hexokinase to glucose-6–PO_4. The glucose analogue ^{18}F-labelled fluorodeoxyglucose (^{18}FDG) is a competitive substrate for this phosphorylation stage, where it, too, is converted to ^{18}FDG-6–PO_4. However, while glucose-6–PO_4 undergoes further metabolism, ^{18}FDG-6–PO_4 does not, and becomes trapped in brain tissue, as it cannot diffuse back across cell membranes. The metabolic trapping of ^{18}FDG can be used to derive the cerebral metabolic rate of glucose utilization (CMRGlu).

Measurements of cerebral blood flow and metabolism have been used widely to study a variety of disorders, ranging from cerebral infarct to drug addiction, and Alzheimer's disease (AD) to mood disorders. Large-scale changes in cerebral function can be detected with high sensitivity using blood flow tracers, and remains the gold standard in many diagnostic imaging applications, such as epilepsy (Spencer et al., 1995). However, structural and hemodynamic changes induced by many neurological and psychiatric disorders are generally small, and often only evident when the disease is into an advanced stage. In addition, the changes in cerebral activity measured using rCBF, rCBV, $CMRO_2$, CMRGlu, or any other index of cerebral blood flow or metabolism are highly non-specific. This has led to the further development of specialized radiotracers that enable PET and SPECT to image directly various neurotransmitter systems and the complex interactions between them.

Neuroligand binding studies

Neuroreceptors are proteins in the membrane of neurons, which are sensitive to neurotransmitters, chemicals that transmit signals from one nerve cell to another. Receptors play two key roles; they recognize only certain neurotransmitter(s), and they activate additional events based on that recognition. The interaction of the neurotransmitter with the specific receptor mimics the effects of nerve stimulation, and begins a sequence of events that either excite or inhibit further neuronal firing. The concentration of neurotransmitter within the synaptic cleft is controlled by other transmembrane transporter proteins, which reuptake the chemical back into the presynaptic nerve terminal.

To study receptor binding sites in vivo, several radiolabelled ligands have been developed which selectively bind to specific neuroreceptors or presynaptic reuptake sites (Table 10.1). The uptake and retention of a radioligand depends on a number of factors, such as its lipophilicity, the presence of non-specific binding, the affinity of the tracer for the receptor, and the concentration of available receptors. Most importantly, these radioligands are active competitors with other exogenous and endogenous chemicals for the binding site, a situation that has been used to great effect in many neurotransmitter studies. A compartmental kinetic model can describe neuroligand imaging. The free, unmetabolized tracer present in plasma crosses the BBB into cerebral tissue, where it can bind selectively

to the receptor under study. Simplifications of this kinetic model have been developed, most notably to eliminate the necessity of performing rapid arterial blood sampling (Lammertsma & Hume, 1996). Techniques also have been developed which use a continuous infusion of radiotracer to maintain a constant equilibrium state between specific binding and plasma activity (Laruelle et al., 1993).

Studies of neuroreceptor concentrations in disease initially focused on measuring differences between healthy control subjects and subjects with neurological and psychiatric disorders. In some cases the findings have been unequivocal, such as PET and SPECT measurements of dopaminergic neuronal degeneration in Parkinson's disease (PD) using radioligands which bind to the dopamine transporter (Brooks et al., 1990; Innis et al., 1993; Mozley et al., 2000). More recently, the availability of radioligands for imaging the serotonergic neurotransmitter system have given many insights into depression and other mood disorders (D'Haenen et al., 1992; Malison et al., 1998). However, many disorders, such as schizophrenia, have failed to exhibit the expected changes in receptor densities. This has led investigators away from studies of static receptor systems, in the belief that these disorders may be a result of neurotransmitter system dynamics, rather than simple alterations in receptor concentrations.

Drug challenge studies, using both exogenous and endogenous chemicals to stimulate the neurotransmission process, have yielded new information on several diseases. Many drugs occupy the same binding sites in the brain as the radioligand; reductions in specific binding of a tracer can be interpreted as an increase in the concentration of a competing drug. For example, the modes of action of antipsychotic drugs have been investigated in vivo by measuring the competition between the radioligand and the drug, which both bind to the same dopamine and serotonin receptors (Farde et al., 1992; Pilowsky et al., 1992).

While many interesting results have been obtained by introducing an exogenous drug that competes with the same binding sites as the radioligand, some of the most exciting recent developments have occurred using the endogenous neurotransmitter as the competing drug. If the levels of endogenous neurotransmitter can be manipulated, either chemically or using a cognitive or sensorimotor task, the degree of specific binding of the tracer will change to reflect the alterations in neurotransmitter. Other studies have used drugs to manipulate one neuroreceptor while studying the effects 'downstream' on another, revealing the modulatory effect neurotransmitters have on each other (Smith et al., 1997). Most recently the chemical manipulation of neurotransmitter behaviour was replaced by a cognitive task, where the release of endogenous dopamine as a result of playing a video game was measured using [^{11}C]raclopride and PET (Koepp et al., 1998). This potentially provides an opportunity to study cerebral activation at the neuronal level, where the involvement of each individual neurotransmitter system can be examined during a cognitive or sensorimotor task.

Other PET and SPECT studies

Recent developments in radiopharmaceutical chemistry have opened up entirely new applications for PET and SPECT imaging in the brain. For example, novel radiopharmaceuticals are being created which bind selectively to amyloid plaques in Alzheimer's disease, providing an early diagnostic tool for detecting amyloid deposition long before structural changes become apparent (Zhen et al., 1999). Imaging of gene expression is now possible, particularly in tumors, using reporter genes labelled by reporter probes (MacLaren et al., 1999). The ability to quantitatively and repeatedly measure the expression of particular genes in vivo will become a powerful tool in the study of genetic contributions to disease, and to monitor gene therapy.

Functional imaging using magnetic resonance

Magnetic resonance utilizes electromagnetic rather than ionizing radiation to probe structure and function. The vast majority of MRI utilizes the nuclear magnetic resonance signal of water protons that are present in high concentration in biological systems. Image contrast is derived from variations in the molecular environment of water in various structures and compartments. These contrast mechanisms are summarized in Table 10.2. FMRI simply refers to MRI scanning in which significant tissue contrast can be attributed to changes in blood flow and/or metabolism. For measurement of task activation, such changes are typically of the order of only a few per cent or less of the overall signal intensity. The primary contrast mechanisms used for detecting task activation with fMRI are blood oxygenation level dependent (BOLD) contrast and perfusion contrast obtained using arterial spin labelling (ASL). Because BOLD contrast is easier to obtain and generally provides higher signal-to-noise for task specific activation, it has been widely adopted as the method of choice for imaging regional brain activation using MRI. In contrast to PET methods for mapping task activation which have often relied on a multisubject design, BOLD fMRI provides sufficient sensitivity to reliably carry out studies in single subjects. To maximize temporal resolution and slice coverage

Table 10.2. Contrast mechanisms for functional MRI (fMRI)

MRI contrast	Imaging sequence	Physiological parameter
Dynamic susceptibility contrast (DCS)	T_2*-weighted during administration of MRI contrast agent, typically echoplanar or spiral.	Cerebral blood volume and mean transit time. CBF calculated through central volume principle
Arterial spin labeling	Preparatory radiofrequency labelling of arterial water. Any imaging sequence can be used, typically short TE echoplanar or spiral.	Cerebral perfusion in ml/g min or relative perfusion change
Blood oxygenation level dependent (BOLD)	T_2*-weighted, typically echoplanar or spiral.	Deoxyhemoglobin concentration (represents a complex interaction between CBF, CBV, and oxygen utilization)
Diffusion	T_2-weighted with and without diffusion sensitization gradients, typically echoplanar or spiral.	Apparent diffusion coefficient (ADC) reflects water mobility within voxel; ADC is reduced in cytotoxic injury and across myelinated fiber tracts

as well as to minimize image degradation by subject motion, most fMRI studies utilize ultrafast imaging methods such as echoplanar or spiral techniques in which each imaging slice is obtained in 100 ms or less using a single radiofrequency excitation (Vlaardingerbroek & den Boer, 1996).

For clinical applications, hemodynamic measurements can also be made by following the initial passage of an exogenously administered susceptibility contrast agent through the cerebral vasculature, termed dynamic susceptibility contrast (DSC) perfusion MRI. Since these agents remain intravascular, only mean transit time, time to peak, and blood volume can be precisely measured, while CBF must be estimated using the central volume principle (Sorensen et al., 1997). This approach was used to generate the first report of fMRI in humans during photic stimulation (Belliveau et al., 1991). However, since contrast administration is required for each measurement, its use for task activation studies in humans has waned.

The practical spatial resolution limits of fMRI are currently unknown. While MRI is capable of imaging structures in the micron range, signal-to-noise varies directly with voxel size and signal-averaging time for extremely small voxels would likely be prohibitive for most human applications. In addition, degradation by motion becomes a very significant problem with high-resolution imaging, particularly since even normal physiological motion such as that induced by arterial pulsatility can be of the order of millimeters. The spatial extent of AFC is also unknown, but current thinking is that flow effects are considerably less localized than metabolic effects. However, at least in some brain regions, the vascular supply is organized in a functionally significant manner. This has been demonstrated for rat whisker barrel cortex where the cortical region subserving each whisker appears to have a dedicated microvascular supply (Woolsey et al., 1996). Although these regions are less than 1 mm, it has been possible to visualize them using fMRI in the rat brain at high fields (Yang, Hyder & Shulman, 1996). It has also been possible to visualize similarly sized ocular dominance columns in calcarine cortex in cats (Kim et al., 1999) and in humans (Menon et al., 1997).

Blood oxygenation level dependent (BOLD) contrast

BOLD contrast reflects a complex interaction between blood flow, blood volume, and hemoglobin oxygenation (Ogawa et al., 1998). Functional contrast is obtained because the iron present in hemoglobin becomes paramagnetic only when it is deoxygenated, producing a local susceptibility increase manifested as a change in T2*, among other effects. This change in hemoglobin oxygenation is usually monitored using gradient echo echoplanar sequences which particularly emphasize T2* effects and allow multiple slices to be acquired at rapid intervals. With regional brain activation, a reduction in T2* is observed, reflecting a decrease in regional deoxyhemoglobin which has been attributed to increases in CBF which exceed increases in oxygen metabolism, though the universality and precise basis for this mismatch is uncertain.

A typical BOLD response consists of a 0.5–5% change in regional image intensity which develops over 3–8 s following task initiation. This peak latency of several seconds represents a major limiting factor in the temporal resolution of functional imaging methods that rely on AFC. There is growing evidence that prior to the increase in regional CBF,

there is a more localized decrease in hemoglobin oxygenation, presumably due to a more rapid increase in oxygen utilization than in blood flow (Malonek & Grinvald, 1996), however this subtle effect has been difficult to detect reliably. Sensitivity to T2* increases at higher magnetic field strengths, such that at 4.0 Tesla BOLD peak signal changes may approach 25% with sensorimotor tasks. This increased signal can be used to improve sensitivity or spatial resolution. Higher field strengths may also increase the sensitivity for detecting the initial decrease in BOLD signal. Task specific BOLD signal changes are not directly quantifiable in physiological units, but rather are expressed as a percentage signal change or as a statistical significance level based on a particular statistical model. Absolute or resting function cannot be easily assessed, and for clinical studies it may be difficult to know whether any observed abnormalities are due to baseline or task-specific effects.

Perfusion MRI

Classical perfusion can also be measured directly using endogenous contrast with ASL (Detre & Alsop, 1998). This class of techniques utilizes electromagnetically labelled arterial blood water as a diffusible tracer for blood flow measurements, in a manner analogous to that used for $^{15}0$ PET scanning. The 'electromagnetic' tracer has a decay rate of T1, which is sufficiently long to allow perfusion of the microvasculature and tissue to be detected. This form of image contrast can be sampled with any imaging sequence. ASL techniques are capable of quantifying cerebral blood flow in well-characterized physiological units of ml/100 g min, or may be used in a qualitative fashion similar to that used in BOLD fMRI. The development of multislice ASL (Alsop & Detre, 1998) has considerably enhanced its utility. The use of ASL methods for imaging task activation has been less widespread than BOLD methods because these techniques produce a lower signal change for activation and are somewhat more difficult to implement. However, potential advantages of ASL approaches include greater temporal stability due to absolute quantification of flow changes, direct comparison with PET rCBF studies, and the possibility of detecting activation in the presence of high static magnetic susceptibility.

Diffusion MRI

Diffusion weighted MRI (DWI) uses large magnetic field gradient pulses to spatially label tissue water, allowing its microscopic motion over tens of milliseconds to be measured (Le Bihan et al., 1986). The resulting apparent diffusion coefficient (ADC) reflects a weighted average of intracellular and extracellular water, and the shift from extracellular to intracellular water which occurs during early cytotoxic injury results in a large signal change using this contrast (Moseley et al., 1990). DWI and perfusion MRI are now in fairly routine use in hyperacute stroke evaluation (Baird & Warach, 1998; Neumann-Haefelin et al., 2000). Directional effects also occur in DWI due to anisotropy of microscopic diffusion of water in white matter tracts, an effect that has high sensitivity to changes in fibre tract myelination. By separately measuring diffusion effects using orthogonal gradients for diffusion sensitization, a diffusion tensor image can be generated which reflects fibre orientation (Pierpaoli et al., 1996) and may be used to examine connectivity between brain regions.

Mapping cognition with functional imaging

Perhaps the greatest promise for functional neuroimaging is to elucidate mechanisms of higher cognitive function. This pursuit has intensified with the advent of fMRI because it affords a sensitive and inexpensive means of detecting task-specific regional brain activation. Since hemodynamic changes occur on a drastically longer timescale and with considerably poorer spatial localization than neuronal firing, and since the mechanisms of coupling between neural activity and hemodynamic changes remain to be completely understood, cognitive mapping using functional imaging remains an indirect link to neural function. While considerable effort is now being given to determining the relationship between neural activity and hemodynamic effects as well as the spatial and temporal resolution limits of functional imaging, the strategies for making inferences about cognitive function based on imaging experiments are still being developed. At present, cognitive brain mapping experiments are most effective for determining the locations of task activation rather than their magnitude or relative contributions to overall task performance. Identification of the ventral 'what' and dorsal 'where' streams in visual function is an example of cognitive processing mechanisms that were elucidated at least partly through functional neuroimaging (Ungerleider & Haxby, 1994).

Paradigm design for cognitive brain mapping

Because PET studies of regional brain activation have poorer temporal resolution than fMRI, most PET activation studies have examined differences in regional brain

activation during blocks of repetitive stimuli of differing types. Subtraction of blocks of stimuli differing in a single cognitive process is then used to determine the localization of that process. For example, activation during reading of pseudofont words might be subtracted from reading true font words to determine brain region involved in written language processing. Based on this tradition, early fMRI studies also used blocked-trial designs with alternating epochs of task and control conditions, each consisting of multiple trials. This approach maximizes sensitivity, since large signal changes are sustained, and also minimizes the requirement of an accurate estimate of the hemodynamic response.

More recently, many investigators have explored techniques that allow fMRI responses to individual task stimuli to be segregated (Buckner et al., 1996). These approaches allow different classes of stimuli to be randomized, reducing habituation effects, and also facilitate retrospective analysis of fMRI data based on subject performance on individual trials (Brewer et al., 1988; Wagner et al., 1998). Thus, regional brain activation following only correctly or incorrectly performed trials can be compared across subjects or across control and patient groups, independent of overall performance on the task. However, the results of individual trial analysis may depend heavily on the assumed neural activity and AFC response.

A fundamentally different approach to functional brain imaging in clinical populations which circumvents the issue of task performance is to correlate specific neurocognitive deficits with alterations in resting brain function using quantitative functional imaging such as CBF measurements using ASL techniques (Alsop et al., 2000). Since only resting perfusion is measured, the interpretation of the imaging data is not confounded by task performance. This approach is also applicable to structural imaging data (Mummery et al., 2000).

Analysis of functional activation data

Task-specific functional activation is typically determined by statistical analyses of time series data with respect to the administered task. This can be accomplished using a simple correlation analysis, though multiple linear regression methods (Friston et al., 1994) including a variety of confounds now more common, and non-parametric approaches as well as task-independent approaches are being developed. Linearity between neural activity and AFC responses is often assumed in these analyses, though deviations from linearity clearly occur. For both resting and activation studies, time series data must be examined and corrected for motion effects. Task-correlated motion may be particularly difficult to distinguish from functional activation. A thresholded statistical map is ultimately superimposed upon high-resolution anatomical images or other representations of the brain. Thresholding for significance is complicated, and requires consideration of spatial and temporal autocorrelation in the data as well as false positive activation that may result from multiple comparisons, since three-dimensional images may contain thousands of pixels.

Comparison of functional localization across subjects presents yet additional challenges in the interpretation of clinical functional neuroimaging studies. Many such comparisons have been accomplished through the use of transformation into standard neuroanatomical spaces such as Talairach space (Talairach & Tournoux, 1988), though more complicated algorithms are available, including those which attempt to unfold cerebral gyri. These algorithms rely on characteristic signal intensities of gray matter, white matter, and cerebrospinal fluid that can be altered in the presence of lesions such as tumours, strokes, or focal atrophy. When lesions are large, they may distort the brain sufficiently to make automated or semiautomatic morphing into a standard space impossible.

Functional imaging in neurological diagnosis and management

Functional imaging techniques have been applied to nearly every category of central nervous system disorder, with variable results (Detre & Floyd, 2000). This section will focus on selected applications in which functional imaging has successfully contributed to neurological differential diagnosis or patient management.

Presurgical localization of function

Since fMRI provides sufficient sensitivity to map functional activation within a single subject, one of the earliest clinical applications of fMRI was the localization of motor cortices with respect to brain tumours requiring neurosurgical resection. In several studies, fMRI localization of finger tapping paradigms has been compared with cortical stimulation. Since cortical stimulation is essentially a 'lesion' study confined to the superficial cortex while BOLD fMRI measures endogenous function throughout the brain, these modalities may be expected to differ somewhat in functional localization. Nonetheless, an excellent correlation has been consistently found between regions of motor activation seen on BOLD-fMRI and intraoperative cortical stimulation (Yetkin et al., 1997).

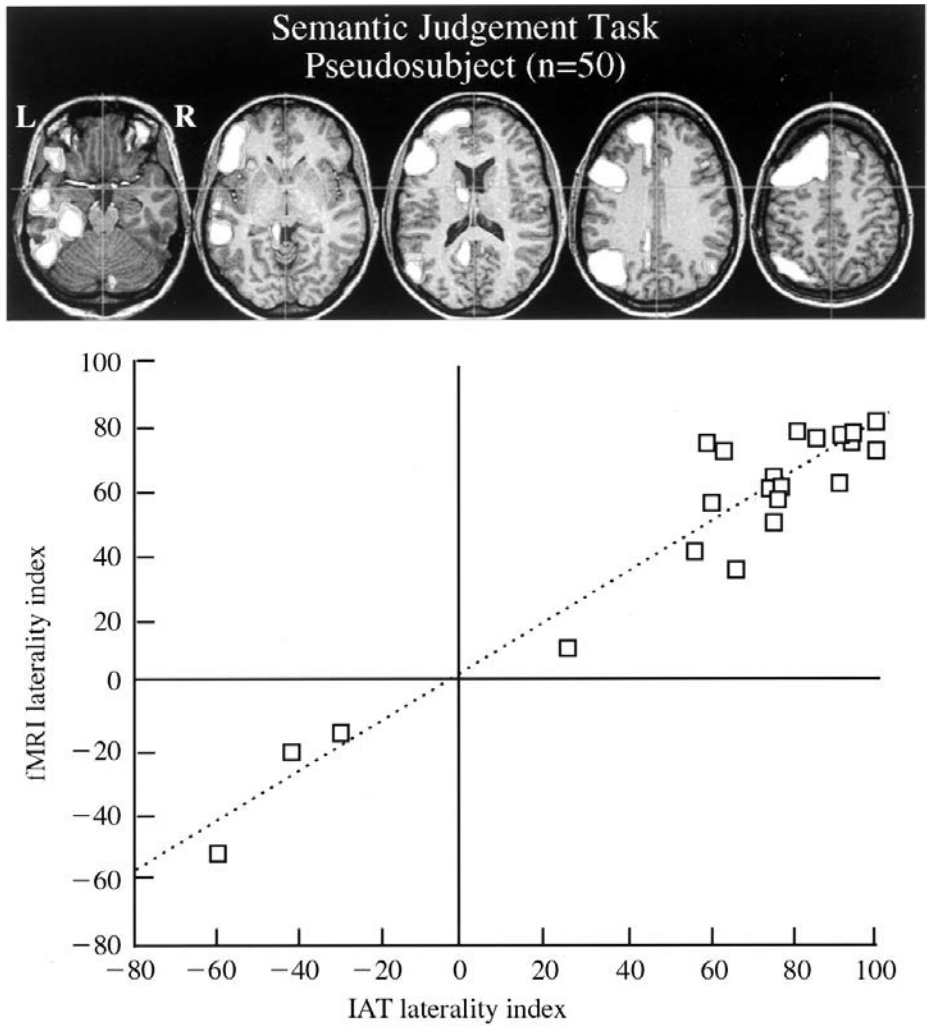

Fig. 10.2. FMRI lateralization of language and comparison with intracarotid amobarbital testing. These studies utilized a semantic judgement task with a tone sequence judgement task as a baseline. The top panel shows averaged fMRI task activation from 50 normal right-handed subjects, demonstrating left hemisphere lateralization of language-related activity. The scatter plot below shows the strong correlation ($r = 0.96$, $P < 0.0001$) between an IAT language laterality index and an analogous index based on fMRI in 22 epilepsy patients. (These data are presented courtesy of Dr Jeffrey Binder.)

FMRI has also been compared to intracarotid amobarbital testing (IAT) for presurgical lateralization of language and memory in several studies. While the IAT has been the gold standard for identifying lateralization of language and memory function preoperatively, it is invasive and carries significant risks. Further, fMRI offers the capability of spatially resolving functional activation within each hemisphere, potentially guiding tailored resections to spare eloquent cortex. Successful functional activation studies using motor and language tasks have been reported in partial complex epilepsy by several groups. Binder et al. (1996) reported a cross validation study comparing language dominance determined by both fMRI and IAT in 22 epilepsy patients. Examples of fMRI lateralization of language are illustrated in Fig. 10.2. A semantic decision task was used to activate a distributed network of brain regions involved in language specialization. Excellent agreement in language laterality was observed in this and other studies, though there has been some controversy concerning the optimum task for lateralizing language. A complex visual scene encoding task has been used to lateralize mesial temporal lobe memory dysfunction in patients with temporal lobe epilepsy, and showed a good correlation with memory lateralization by IAT in preliminary studies (Detre et al., 1998).

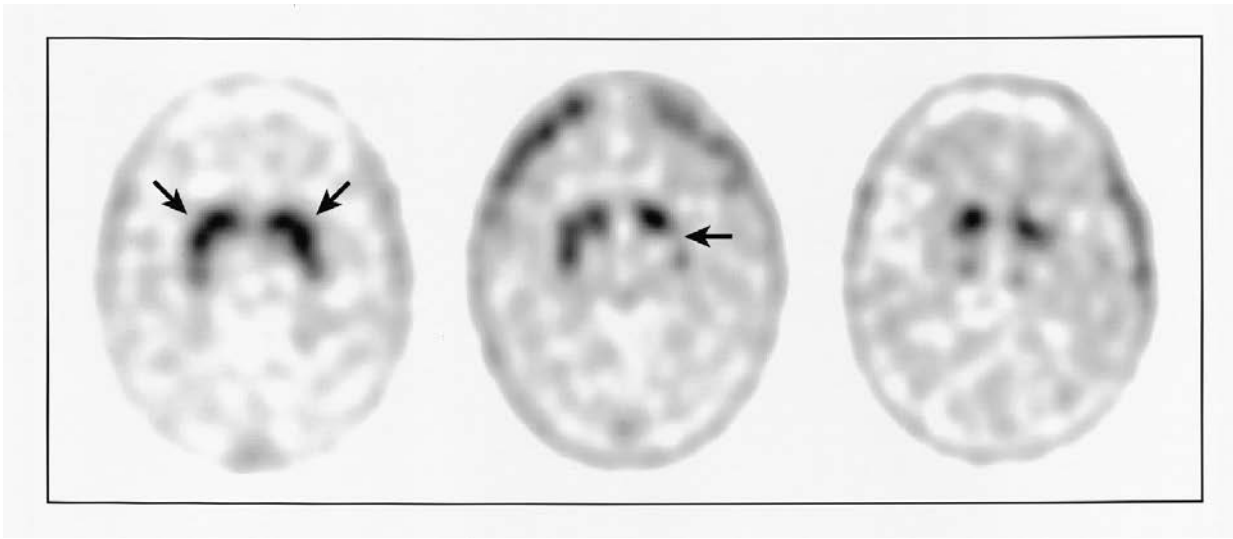

Fig. 10.3. SPECT images of [^{99m}Tc]TRODAT-1 binding to dopamine transporters in the striatum. The healthy subject (*left*) shows high uptake in the striatum (arrows), while patients with progressively more severe Parkinson's disease exhibit unilateral (arrow, *centre*) and bilateral (*right*) degeneration of dopaminergic neurons, and a reduction in tracer binding. (Images courtesy of Dr David Mozley, University of Pennsylvania.)

Functional imaging has also contributed to the localization of seizure foci. Interictal hypometabolism measured using FDG-PET is now widely accepted in clinical lateralization of temporal lobe epilepsy (Duncan, 1997). Ictal events can be localized using HMPAO-SPECT, as noted above, as well by fMRI with (Krakow et al., 1999) or without EEG triggering (Detre et al., 1995). Localized changes in tissue diffusion have also been observed in patients with focal status epilepticus (Lansberg et al., 1999).

Parkinsonian syndromes

PET and SPECT imaging of the dopaminergic system in the differential diagnosis of parkinsonian disorders may become the first routine clinical application of neuroligand imaging (Fig. 10.3). Studies of neuronal degeneration in the nigrostriatal pathway, using tracers that bind to dopamine transporters, have nearly 100% accuracy in diagnosing some forms of neurodegenerative disease (Brooks, 1997). The diagnosis at an early stage in the progression of PD, even before clinical symptoms have become apparent, is possible, although differentiating PD from other parkinsonian disorders, such as multiple system atrophy, progressive supranuclear palsy, or Huntington's disease, may require multiple imaging modalities or combinations of tracers.

Early diagnosis may become increasingly important once the genetic contribution to parkinsonian disorders is fully understood. PET and SPECT imaging are beginning to make important contributions to the understanding of the pathogenesis of PD, and may be able to elucidate the role of other neurotransmitter systems, such as NMDA and GABA, in the onset and progression of PD (Acton & Mozley, 2000). Longitudinal studies of patients undergoing treatment, whether by neuroprotective drugs or surgical intervention, will become increasingly important in the assessment of treatment efficacy, and also to determine the exact mode of action of each therapy.

Dementia

Post mortem studies have shown a high degree of misdiagnosis of dementia using clinical symptoms alone. This has led to a growing trend to use imaging techniques to provide a more accurate, unbiased diagnosis, and to assess treatment efficacy. PET and SPECT imaging in dementia generally measure reductions in cerebral blood flow or metabolism resulting from the disease, using tracers such as $H_2{}^{15}O$, [^{99m}Tc]HMPAO and ^{18}FDG (Frey et al., 1998). A pattern of hypoperfusion and hypometabolism in temporoparietal brain regions, with frontal changes occurring as the condition deteriorates, has been established in Alzheimer's disease (Fig. 10.4). Abnormalities on functional images may precede cognitive defects, raising the possibility of using PET and

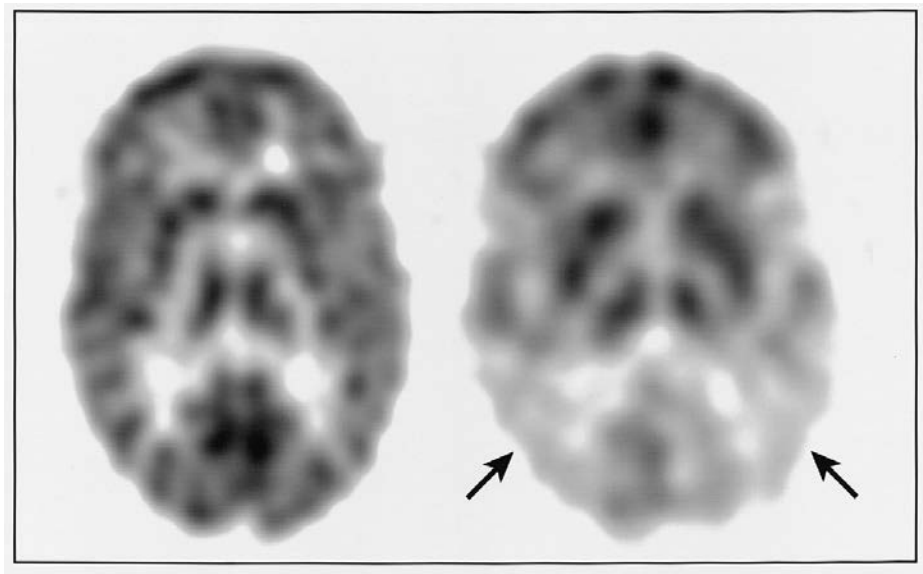

Fig. 10.4. Comparison of cerebral glucose metabolism, measured using ^{18}FDG and PET, in a normal healthy subject (*left*) and a patient with Alzheimer's disease (*right*). The pattern of hypometabolism reflects neuronal degeneration in the temporoparietal regions (arrows), which is consistently found in AD. (Images courtesy of Dr David Mozley, University of Pennsylvania.)

SPECT in the early, presymptomatic diagnosis of dementia (Rapoport, 1997). Some studies suggest that functional imaging with PET or SPECT is superior to structural imaging in the diagnosis of some dementias, particularly Alzheimer's disease.

Tumour imaging

Functional imaging plays an important role in brain tumour management due to the difficulty in differentiating post-therapy residual viable tumour tissue from local recurrence and necrosis using structural imaging. One of the most useful radiotracers for imaging tumours of almost any kind is ^{18}FDG, which takes advantage of the dramatic increase in glucose metabolism in tumour cells. PET imaging of the brain with ^{18}FDG is capable of the early detection of tumours, provides information on the staging and response to therapy, and is a good prognostic indicator. However, due to the high uptake of ^{18}FDG in normal brain tissue, the tumour-to-background ratios can be quite low. Alternatively, labelled amino acids, such as [^{11}C]methionine, or indicators of excessive DNA fabrication, such as [^{11}C]thymidine, provide high contrast images of many brain tumours, and can distinguish between viable tumour and radiation necrosis.

Radioactive thallium (^{201}Tl) has been used extensively for SPECT imaging of tumours. While the exact mechanism of thallium uptake by tumour cells is not clear, it provides very high contrast images of brain tumours. Thallium imaging provides good diagnosis and staging of malignant disease, clear delineation between viable tumour and cell necrosis, and is used to assess the response to chemotherapy and radiation treatment. Other SPECT tracers, such as MIBG, have been shown to be effective diagnostic tools for neuroblastomas and other neural crest tumours, and even can be administered in much larger radiation doses for radiotherapy. More recently, attention has focused on the overexpression of certain types of receptors by tumours. In particular, many tumours express somatostatin receptors, which has been used to great advantage in the development of radiolabelled somatostatin analogues, which bind selectively to these receptors and can be used to image many types of brain tumour.

Cerebrovascular disease

Functional imaging has been used extensively in cerebrovascular disease and acute stroke in an attempt to better characterize physiological changes accompanying brain ischemia, identify brain tissue at risk for infarction, and predict outcome. Studies of patients with stroke using ^{15}O PET measures of CBF, CBV, and oxygenation characterized the pathophysiology of cerebral ischemia, with initial autoregulation of CBF though vasodilatation, followed by hypoperfusion with increased oxygen extraction fraction (OEF) and finally decreased $CMRO_2$ and infarction (Heiss &

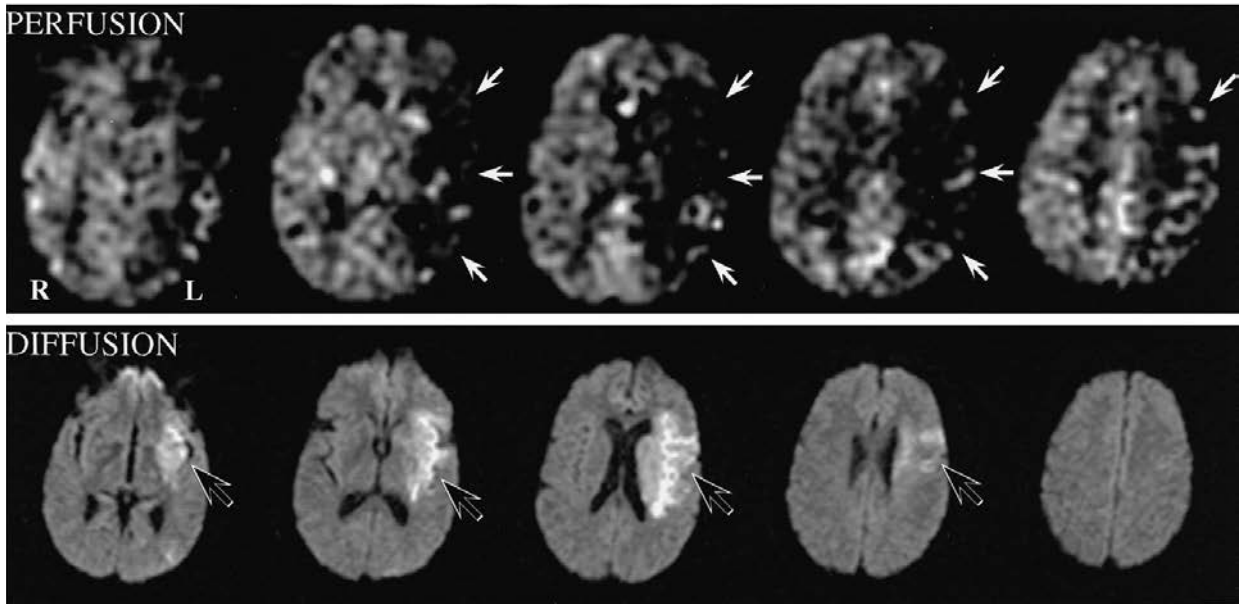

Fig. 10.5. Perfusion and diffusion MRI in a patient presenting with acute right hemiparesis and aphasia. Top panel: Perfusion MRI obtained using ASL demonstrates hypoperfusion throughout the left middle cerebral artery distribution (white arrows). Bottom panel: Diffusion MRI demonstrates a somewhat smaller region of cytotoxic injury (black arrows). Images are in radiological orientation (left is on the right).

Podreka, 1993). In chronic cerebrovascular disease, an increased OEF predicts an increased stroke risk (Grubb et al., 1998) and suggests a need for therapeutic intervention such as revascularization. Since PET scanning remains limited to only a few academic centres, over the past decade much interest has been focused on more widely available imaging modalities. A reduced CBF response to acetazolamide or carbon dioxide measured using computer-assisted tomographic (CAT) scanning with xenon or perfusion MRI has recently been used as an indication of hemodynamic compromise, and also indicates an increased stroke risk (Webster et al., 1995). While the relative contribution of primary hypoperfusion versus thromboembolism to stoke incidence remains controversial, it is hoped that these approaches can also be used to improve patient selection for interventions such as angioplasty or carotid endarterectomy.

The demonstration of effective thrombolytic therapy for hyperacute stroke has intensified the need for rapid assessment of regional brain physiology in stroke patients. This application of functional imaging would ideally be obtained in only a few minutes and would confirm the presence of ongoing ischemia, indicate the risk of hemorrhage following thrombolysis, and replace symptom duration as the determinant of reversible versus irreversible brain injury. There is also a rationale for using functional imaging to measure the effects of novel neuroprotective therapies in acute stroke, since clinical measures have thus far failed to detect any incremental benefits. MRI scanning with diffusion and perfusion contrast, along with magnetic resonance angiography, currently appears best suited for these purposes (Tong & Albers, 2000), though CT scanning with xenon perfusion and computed tomographic angiography also shows promise in this regard. An example of MRI scanning in a patient with acute stroke is illustrated in Fig. 10.5.

Recovery of function

Several groups have used functional neuroimaging to explore changes in functional brain organization in response to focal lesions such as stroke. Utilizing PET in humans after deep capsular infarcts, Weiller and Chollet (Chollet & Weiller, 1994) identified increased cerebral blood flow in bilateral premotor and supplementary motor areas, in unaffected primary motor cortex and along the rim of the cortical infarct, suggesting a hierarchical network of compensatory function. Some of this activation was ultimately attributed to mirror movements in the unaffected limb. FMRI studies in motor recovery have largely confirmed prior PET results with activation of a motor network in the unaffected hemisphere to a greater extent than found in

controls, increased degree of supplementary motor area activation, and perilesional activation. The location of ipsilateral motor cortex activation both in normals and following stroke appears to be ventrolateral to the region which is activated by contralateral movements (Cramer et al., 1999), suggesting that it may correspond to a separate motor homunculus. Although perilesional recovery of function has been confirmed by cortical and cellular electrophysiological methods in animals and using transcranial stimulation in humans, it remains difficult to conclusively prove that all of the perilesional effects observed with fMRI are functionally significant. Some apparent activation observed using blood flow as a surrogate marker for neural function might actually reflect vascular reorganization following ischemic brain injury.

In patients with stroke and aphasia, spontaneous redistribution of function to the right hemisphere has frequently been observed within days of the stroke. However, a prospective PET study of language activation in patients with acute left hemispheric stroke concluded that although right hemispheric activation clearly occurred, recovery of useful language only correlated with left hemispheric activation (Heiss et al., 1997). These results highlight the difficulties of interpreting regional activation in terms of being either necessary or sufficient for supporting a given cognitive or sensorimotor function.

Neuroimaging techniques have also been used to study the dynamic reorganization of function following amputation. In animal models, cortical sensory organization has been shown to occur within minutes. In human amputees, the somatotopic representation of the phantom limb may be activated by stimulation of other body regions such as the face. Since phantom limb effects probably occur independently of any alteration in cerebral vasculature, interpretation of fMRI findings in terms of neural reorganization is perhaps more convincing.

An emerging application of fMRI is in brain bionics. Implantable stimulators are now used in the management of a variety of neurological syndromes including Parkinson's disease, epilepsy, and chronic pain. It is possible to use fMRI to visualize the hemodynamic effects of neurostimulation (Rezai et al., 1999). FMRI can also be used to guide the placement of electrodes into brain regions under conscious control such as motor cortex. Such electrodes have been used to control computerized robotics in paralyzed patients (Kennedy & Bakay, 1998), and fMRI should also be of use in monitoring functional reorganization resulting from brain-electrode interactions.

In conclusion, functional imaging techniques provide numerous approaches to visualizing regional brain activity non-invasively, and are sensitive to a broad range of physiological and neurochemical processes. These techniques have numerous applications in basic and clinical neuroscience and should provide new insights into brain organization and function. Because the technology for functional imaging of the brain is now widely available, its impact on neurological diagnosis and management could be substantial.

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11

Windows on the working brain: magnetic resonance spectroscopy

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Nuclear magnetic resonance (NMR) spectroscopy is an observational technique based on detection of signals from magnetic atomic nuclei such as ^{1}H, ^{31}P, ^{13}C, ^{15}N, and ^{17}O. It is most familiar to physicians and the public as magnetic resonance imaging (MRI), which uses the strong signal from water protons to make the most highly detailed pictures of living tissue available from any non-invasive method. In consequence, MRI, including its special forms magnetic resonance angiography, diffusion-weighted imaging, and magnetization transfer imaging – quickly became a major tool for medical diagnosis and research on living creatures. Its applications to neurological disease are described in several other chapters of this book.

Magnetic resonance spectroscopy (MRS) is the designation used in the biomedical world for measurement of NMR signals from non-water protons and other magnetic nuclei. The usage is not accurate, MRI is the MRS of water, but it is convenient. MRS signals detectable in living brain are thousands of times weaker than the water proton signal; hence observing them requires extra time and special procedures. The reward for the effort is an abundance of chemically specific information which can be acquired as often as necessary, since the measurement process is non-invasive. In the living human brain, ^{1}H signals can be obtained from *N*-acetyl aspartate, creatine, choline moieties, glutamate, glutamine, lactate, and several other small molecules. Phosphocreatine, adenosine triphosphate, and inorganic phosphate can be measured directly by their ^{31}P signals, and intracellular pH calculated from its effect on these signals. Information from the ^{31}P spectrum allows calculation of the rate of the creatine kinase reaction. The spectra of ^{13}C, ^{15}N, ^{17}O, and other magnetic nuclei contain many more small signals from a variety of molecules which will become detectable as technology advances.

This unprecedented measurement capability provides an opportunity for characterization of human neurological diseases along several axes of chemical variation throughout their natural histories. The data are obtained without hazard to the patient, are free from artefacts of tissue preparation, and can be compared in as much detail as necessary to identically acquired information from normal subjects. As MRS matures technically over the first decades of the twenty-first century, it can be expected to take a place among the principal technologies contributing to illumination of disease processes and evaluation of new treatments.

For these reasons, MRS had become well established as an important research technology in neurology and neuroscience by 2001, but not yet as a diagnostic resource necessary for much of neurological practice, as MRI had been for some years. That is likely to change. The wealth of MRS data accumulated on diseases of the human brain since the mid-1980s indicates several possible avenues to routine diagnostic application. As this literature is far too extensive to review here, we emphasize three aspects of MRS which we believe will flourish during the years following publication of this volume, producing novel data of interest to most neurologists. These are: spectroscopic imaging (SI), a way of mapping anatomical distribution of specific compounds in the brain; measurement of γ-aminobutryic acid (GABA) in the ^{1}H spectrum; and labeling of brain metabolite pools with ^{13}C.

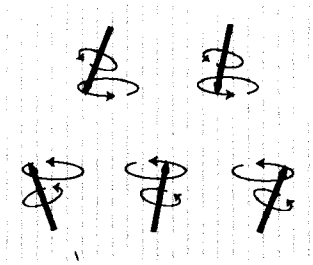
We first present a brief account of how NMR measurements are made, the signals available in the ^{1}H spectrum, localization methods, and some highlights of ^{1}H MRS findings in neurological disease.

The physical basis of NMR measurements

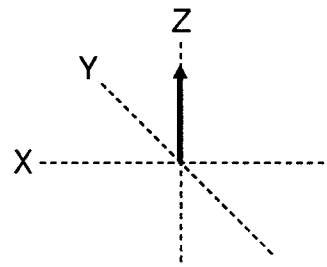
Figures 11.1 and 11.2 (see colour plate section) illustrate in cartoon form one common way of making basic NMR

1 Certain atomic nuclei are magnetic; ^{1}H, ^{31}P, ^{13}C, ^{15}N & ^{17}O are examples of biological interest. They behave like small compass needles which spin around their own long axis, even when bound to other atoms in molecular structures:

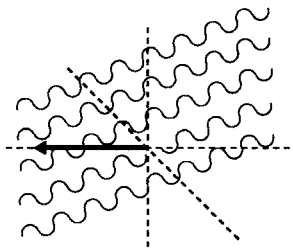
2 In the strong magnetic field of an NMR spectrometer, they line up along the flux lines in a Boltzmann distribution, a few more with the field than against it, and their spins cause them to precess around the flux lines:



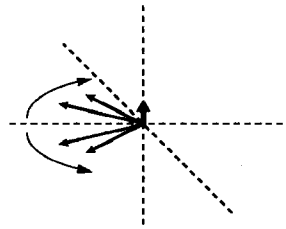
3 The net magnetization of such a spin population is a vector parallel to the flux lines, along the magnet's Z axis:



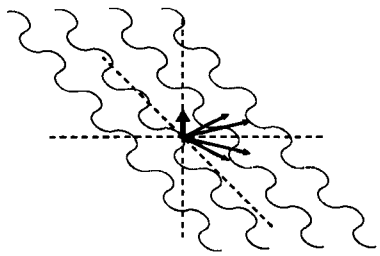
4 For measurements by the common spin echo method, an additional small magnetic field rotating near the precession frequency of the spins is applied briefly to tip the vector in the X–Y plane:



5 Slight differences in precession frequency due to magnetic field inhomogeneities cause spins to spread out in the X–Y plane (dephase), up spins one way, down spins the other (T2 relaxation), while some return to the Z axis (T1 relaxation):



6 Another kind of brief magnetic pulse flips spins still in the X–Y plane by 180 degrees:



7 Because spins still in the X–Y plane continue to precess in the same direction, their net magnetization refocuses as a vector along –X:

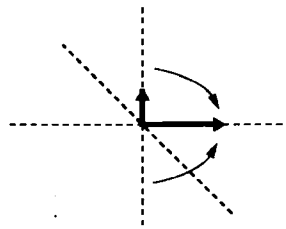


Fig. 11.1. NMR principles.

measurements, the spin echo technique, and the general procedure by which images are generated from NMR data. Many variations on these basic techniques exist, and new ones are constantly being developed.

Several aspects of NMR technology not evident in the cartoons are important for understanding both its power and its limitations:

MRS sensitivity is low

The Boltzmann distribution illustrated in panel 2 of Fig. 11.1 actually produces a difference between up and down spins not in the 2: 3 ratio shown, but only about 1 part in 10^6. The strength of NMR signals is proportional to the size of the difference, which is why they are weak. For this reason, MRS of the human brain cannot detect compounds below the millimolar range under most circumstances. Methods for temporarily increasing the polarization difference of spin populations are under development, but so far only for increasing the signal obtainable from inhalable gases used as MRI contrast agents.

MRS signals come from small, mobile chemical entities

Only molecules which tumble freely in solution or especially mobile parts of large fixed molecules yield signals large enough to detect in living tissue. Hence free glutamate and aspartate can be detected, but the same molecules are invisible when their movement is constrained by incorporation into proteins. Together with the inherent insensitivity mentioned above, this limitation precludes MRS measurement of many important brain substances, such as biogenic amines, acetylcholine, and most membrane structural elements.

MRS and MRI are sessile, motion-sensitive techniques

All measurements must be made in a large, heavy magnet which usually remains in a fixed location. Subjects must lie nearly motionless in the magnet bore while measurements are made, which can be an hour or more for MRS, due to the small size of the signals. These conditions circumscribe the range of physical activity that can be incorporated into study design essentially to small finger and toe movements.

MRS and MRI are safe

Because the Boltzmann difference between up and down spins is so small, only a small amount of energy is necessary to perturb the spin population for measurements. Neither that injected magnetic energy nor the static magnetic field used to align the spin population has any deleterious effect on living tissue. The major hazard to subjects is from movement of ferromagnetic objects within or near their bodies caused by the static field and is easily avoided by adherence to safety procedures.

Stronger magnetic fields give better measurements

The static magnetic field represented by vertical lines in panel 2 of Fig. 11.1 determines the strength of NMR signals and the degree to which signals from different chemical entities are resolved (separated) from each other. For most biomedical applications, the stronger the field, the higher the quality of the information that can be obtained. By 2001, the standard field for clinical MRI machines had reached 1.5 tesla, or about 30 000 times as strong as the terrestrial field which aligns a compass needle. Much stronger fields have been used for in vivo animal research for years with no indication that they damage tissue. Several dozen human research instruments with fields ranging from 2 to 8 tesla exist and have been shown to improve brain MRS signal quality. The outer limit of practical field strength is not yet known; it may be dictated more by instrument cost than by safety considerations.

The ^{1}H spectrum

Figure 11.3 is a ^{1}H spectrum acquired from a small volume of cat brain in a 2 tesla instrument. With special effort, spectra showing this degree of detail can be obtained from human brain at 1.5 tesla, but they are routine in the 2–7 tesla machines that were becoming available in research facilities by 2001. The figure therefore illustrates what can reasonably be expected from ^{1}H MRS over the decade or so following publication of this volume.

The spectroscopic signatures of several distinct molecules are evident in Fig. 11.3. The strongest determinant of signal intensity is the tissue concentration of the molecule that generates it, although the relaxation times T1 and T2 (see panel 5 of Fig. 11.1) of each signal also influence signal intensity and depend on conditions of signal acquisition. Apart from the water signal, which was selectively reduced by acquisition procedures, the strongest signal in the figure is from *N*-acetylaspartate (NAA). This amino acid of unknown function is present in neurons but not glia of normal mature brain at a concentration of 7–10 mmole/kg of tissue. The other labelled signals identify compounds that are consistently detectable in ^{1}H spectra of human

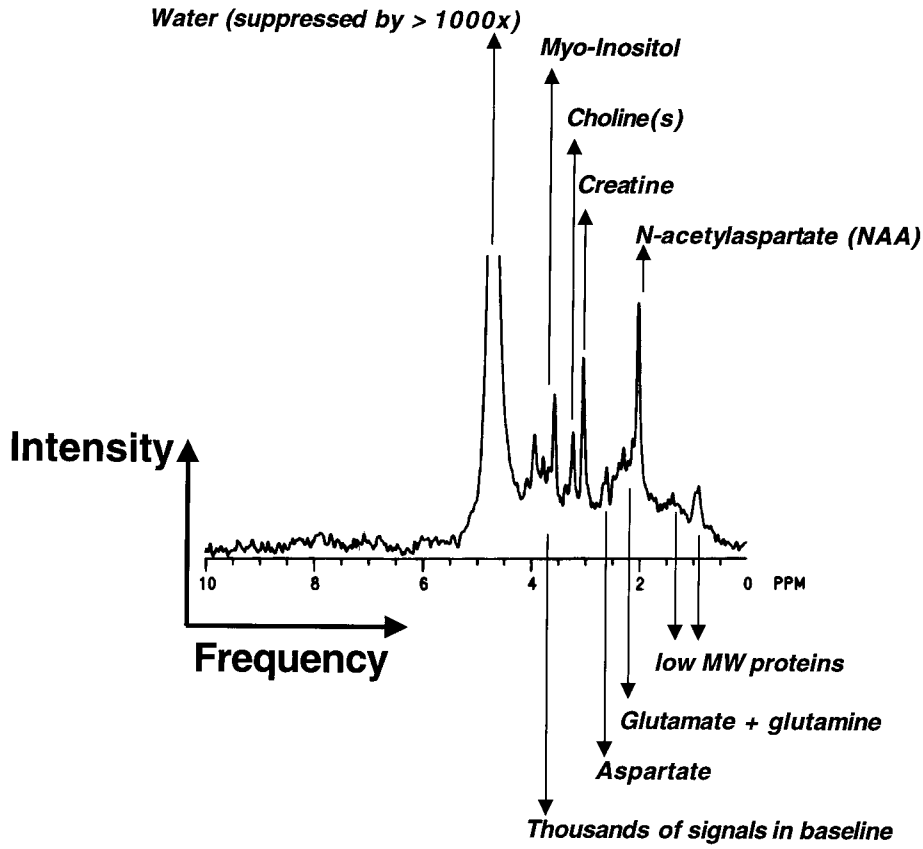


Fig. 11.3. Proton (^{1}H) spectrum of living cat brain obtained at 2 tesla. PPM: parts per million; standard units for expressing 'chemical shift', the displacement of resonant signals relative to that of a reference compound.

brain in standard 1.5 tesla clinical instruments equipped with MRS capability.

Spectral noise defines one ultimate limit on signal detection. This can be appreciated by comparing the NAA signal to the noise level that is most obvious in the leftmost portion of Fig. 11.3. Signals from a molecule with the same spectral properties but present at a concentration only 1/10th that of NAA would be barely discernible above noise, and signals only a little weaker would not be detectable at all. Metabolite detection threshold can be lowered by signal-to-noise ratio improvements achieved by time averaging or enlargement of the sampled volume. Averaging of repeated signal acquisitions tends to cancel the noise while accentuating signals that are the same every time. A bigger sampled volume increases the number of nuclei which contribute to the signal. Both procedures are quite useful in practice, but each brings its own new set of limitations: averaging degrades temporal resolution and increases the risk of movement artifact; larger volumes reduce anatomical resolution and may mix together signals that actually have different properties. The optimum balance among these factors must be matched specifically to each application.

Spectral crowding also complicates isolation of signals from individual molecular species. Many atomic nuclei transmit on very nearly the same frequency, and their signals overlap each other. The broad hump from about 0.5 to 5.5 ppm in Fig. 11.3 is the sum of thousands of small signals from a variety of molecules. Selective extraction of a single signal from many overlapping ones is sometimes possible by spectral editing procedures which exploit some property possessed only by the desired signal. The GABA detection scheme illustrated in Fig. 11.6 is an example of such a strategy, in that case based on selective magnetic perturbation of the C3 protons in a way that changes their influence on the C4 protons and distinguishes the signal of the latter from overlapping ones. Glutamate, lactate, and some other molecules can be detected selectively in similar fashion, but many more, including NAA, creatine, cholines, and myo-inositol among the large signal sources

in the ^{1}H spectrum, lack features of chemical structure which make editing of their signals possible. When signals of that kind change during brain activity or under the influence of disease, any combination of changes in the overlapping signals may be responsible; interpretation must therefore be guided by independent information about of how many overlapping signals are present and how the molecules generating them behave under the particular circumstances of the observation.

Signals from larger and less mobile molecules such as proteins, nucleic acid polymers and proteolipid aggregates are of special importance in this regard. Compounds with molecular weights greater than about 1000 daltons usually produce signals with very short T2 and very long T1. Because of short T2, their signals do not persist long enough to be measured accurately without a great deal of averaging of responses to repeated stimulations, and even when they are detectable, they are very broad, overlapping each other and the narrow signals from smaller, more mobile molecules. At the same time, their long T1s require long waiting times between successive stimulations. Both factors reduce the signal-to-noise ratios that can be achieved in a given time and thereby limit the ability of MRS to detect macromolecular signals selectively.

In one way, the low signal-to-noise ratio of macromolecular resonances is an advantage for measurement of the narrow signals in Fig. 11.3. If the intensity of myelin signals were proportional to myelin concentration, ^{1}H spectra from brain would be overwhelmed by them, and most of the observations described in this chapter would be extremely difficult or impossible. This does not happen because myelin protons have an extremely short T2 relaxation time.

But in another way, broad macromolecular signals complicate quantitative measurement of narrow ones, because they are a potentially variable baseline on which the latter are superimposed. Methods are under development for determining whether an apparent change in a narrow signal is actually due in whole, or in part, to changes in macromolecular signals underlying it.

Signal localization

Matching the spatial resolution of MRS to the anatomical heterogeneity of the brain well enough to permit reliable measurement of localized functional and disease effects on brain chemistry has absorbed the effort of many spectroscopists since human MRS research began. The problems are the same in principle as the ones encountered in the quest for ever greater anatomical resolution in MRI, which is below 1 mm; but because MRS signals are so much smaller than the water proton signal, resolution in the millimetre range is hard to achieve.

For most of its history, MRS was possible only on single volumes of brain. Recently, acquisition from multiple volumes simultaneously has become practical by techniques usually referred to as chemical shift imaging or spectroscopic imaging. The characteristics of the single volume approach make the advantages of the multiple volume approach clear.

Single volume MRS

Spectra can be acquired from single cubic or rectangular tissue volumes down to about 2 cubic centimetres, localized to a region of interest with the help of a guiding MRI. Appropriately equipped commercial MRI machines can acquire localized spectra from volumes of that size or larger in automated fashion, once the desired volume is selected.

Localized single volume MRS has distinct advantages and disadvantages. The principal advantage is that it provides a single spectrum from a tissue volume defined by MRI in a few minutes. The characteristics of the acquisition can be adjusted to permit a number of spectroscopic features to be accentuated. For example, it is usually possible to collect the spectroscopic information at relatively short echo time which provide the full array of detectable tissue signals without excessive loss associated with T2 relaxation. Alternatively, if less complex spectra are desired, the echo time may be lengthened to suppress signals with short T2s.

The principal disadvantages of localized single volume MRS are its inherent time inefficiency, poor conformance of acquisition volume to brain anatomy, and the difficulty of localizing signal to precisely the same volume in different subjects or in the same subject at different times. Acquisition of spectra from more than one brain location requires separate measurements, each taking several minutes. When several regions are to be compared, the limits of subject tolerance are quickly reached. Volumes of interest must be bounded by planes; practical methods for defining volumes with curved surfaces are not available. Therefore, fitting the acquisition volume to a region of interest is usually only approximate. Finally, the goal of detecting signal from a particular anatomical region in consistently reproducible fashion is an elusive one. Small variations in placement of the volume in different subjects or in the same subject from one examination to the next

can easily confound comparison of subjects and monitoring of changes over time in an individual.

Spectroscopic imaging (SI)

This method of localizing MRS signals works by acquiring spectra simultaneously from a grid of tissue regions within a brain volume. The techniques are similar to some of those used in conventional MRI. The entire volume of interest is excited by stimulating cues which induce the magnetic nuclei within it to broadcast their signals. Additional manipulations extract spatially localized information from the complicated signal by a series of measurements in which the cueing pulse sequence is altered slightly in a systematic manner. Analysis of how the total signal varies with alterations in the cueing process permits the signal contributions of each volume element in the grid to be determined.

SI has not yet come into routine use because of its technical complexity. However, it has been shown to be practical for research and diagnosis in several brain diseases, it is much more powerful than single volume methods in dealing with the heterogeneity of brain anatomy and pathology, and it offers significant gains in time efficiency. Accordingly, its clinical applications can be expected to increase rapidly.

MRS findings in neurological disease

Thousands of MRS studies covering all major categories of human brain disease were published in the first 15 years after the technique became available. More extensive consideration of this literature than can be given here is available in a recent book (Danielsen & Ross, 1999), where the reader can also find numerous examples of how an experienced research group has applied early MRS techniques to specific diagnostic problems in clinical neurology.

Most MRS studies of brain disease show some combination of three changes: loss of NAA signal, interpreted to signify loss of neurons; elevation of lactate, signifying lack of tissue oxygen or infiltration of high-lactate cells such as macrophages; and an elevated choline signal, thought to reflect acceleration of metabolic pathways involving components of biological membranes. As these changes appear to come about by different mechanisms in different diseases, they reflect general pathophysiological processes more often than disease-specific phenomena. In some instances, however, they have stimulated new thinking about particular diseases and shown promise for refinement of diagnosis and treatment evaluation. Space limits the examples we can offer to a few.

Stroke

Loss of NAA and elevation of lactate in acute stroke was predicted by decades of earlier work, and they were confirmed in human patients when ^{1}H MRS became available (Graham et al., 1992). However, persistence of lactate elevation for months after a stroke was not anticipated (Graham et al., 1993); the fact that it could be labelled with ^{13}C from infused glucose showed that it was metabolically active, not trapped in dead tissue (Rothman et al., 1991). Other MRS work suggested that persistently high lactate is in macrophages and other cells participating in the infarcted tissue's response to injury (Petroff et al., 1992).

An interesting body of data indicates that changes in ^{1}H spectra of hemispheres perfused by diseased carotids precedes clinical symptoms of cerebral ischemia (Klijn et al., 2000). If this finding is confirmed, MRS may one day help distinguish patients who need surgical intervention from those who can safely be treated by medical means.

Epilepsy

Decreased NAA in one or both temporal lobes compares well with lateralization of seizure foci and positron emission tomography in identifying the correct side for surgical treatment of intractable temporal lobe epilepsy (Cendes et al., 1997a). It may emerge as the single most useful laboratory technique for that purpose, due to its favourable combination of specificity with non-invasiveness.

Loss of NAA signal is apparently not always due to permanent loss of neurons. Normalization of temporal NAA during seizure-free periods in temporal lobe epileptics indicates that reversible neuronal dysfunction associated with the ictal state is a significant pathophysiological factor in this condition (Cendes et al., 1997b).

Multiple sclerosis

Decreased NAA is regularly observed in acute plaques, implying that more axonal damage occurs in such lesions than had been thought; as in the seizure-free temporal lobes mentioned above, NAA recovers partially in demyelinating lesions in a manner that correlates with clinical recovery, confirming the role of reversible axonal dysfunction in the disease (Matthews et al., 1991; Arnold et al., 1992; Davie et al., 1994). More recently, decreased NAA has been observed in white matter that is normal on MRI, and

in patients with chronic illness, this change correlates better with clinical disability than the MRI lesions (Fu et al., 1998).

Childhood ataxia with diffuse central nervous system hypomyelination (CACH)

This is a rare genetic disorder with variable clinical manifestations. A ^{1}H MRS study showed changes (low NAA, choline, and creatine in heterogeneous distribution) that were more consistent than the clinical data (Tedeschi et al., 1995). The result is an early example of what may become a prominent role for MRS in disease classification.

MRS observations have also been made repeatedly in Alzheimer's disease and other dementias, parkinsonism, motor neuron disease, HIV encephalopathy and metabolic disorders which affect the brain. New findings may bring it to the front line of diagnosis, treatment monitoring, or research in any of these areas as the technology matures.

Spectroscopic imaging of brain tumours

Intracranial neoplasia is a historically intractable clinical problem, which is much in need of new approaches. Accordingly, when magnetic resonance instrumentation capable of doing MRS on human brain became available in the mid-1980s, investigators almost immediately began using it to evaluate human intracranial neoplasms, and interest in the possibility that chemically specific data obtained non-invasively can facilitate brain tumour management has remained high ever since.

Single volume ^{31}P and, later, ^{1}H methods were the first available for this purpose, and in a short time they confirmed that a number of common biochemical characteristics of brain tumours could be detected in undisturbed lesions by MRS. However, these single volume measurements were subject to the same sampling problem that bedevils brain tumour biopsy data, the cellular heterogeneity of the lesions. MRI and X-ray computed tomography can document the vascular changes and edema associated with a particular brain tumour with a high degree of precision, but they cannot reliably identify the tumour's predominant cell type or detect anatomical variations in its chemistry.

One promising way to probe those areas is by positron and single photon emission tomography of radionuclide binding patterns specific for tumour type, once appropriate ligands are developed. Another is ^{1}H SI. Non-invasively obtained information about chemical variation within brain tumours has considerable potential for individual patient management and as a surrogate endpoint for evaluation of new treatments. Being free of hazard to the patient, the measurements can be repeated and correlated with MRI studies as often as necessary. With further technical development already under way, their anatomical resolution will be competitive with that of radionuclide methods.

The results of a ^{1}H SI study done on a patient with a tumour shortly afterward identified at surgery as a glioblastoma multiforme are shown in Fig. 11.4 (see colour plate section). The technique used long echo time (TE 272 ms) and multiple slices. Fig. 11.4(*a*) shows MRI scans of the three slices that were chosen for SI measurements. The white grids on the images in Fig. 11.4(*b*) show all the brain volume elements that generated an interpretable ^{1}H spectrum.

Figure 11.4(*c*) illustrates the characteristic chemical differences between the tumour (left spectrum and image) and adjacent normal tissue (right). In the tumour, choline-containing compounds (Cho) are greatly elevated, *N*-acetylaspartate (NAA) is undetectable, and a large lactate signal (Lac) is present. In the spectrum from normal tissue, these resonances appear as they would in a brain undisturbed by pathology. Of the prominent resonances, only the one from creatine (Cre) is the same in both spectra.

Figures 11.4(*d*) and 11.4(*e*) are the main point of this illustration. In the same way that the water proton signal was used to make the images in Fig. 11.4(*a*), the Cho and NAA signals were used to make (*d*) and (*e*). The metabolite images are much coarser, because the metabolite signals are so much weaker than that of water. Colour coding is commonly added to coarse images to emphasize variations, which are less obvious in grey-scale display of the same information. Elevated Cho in the tumour region and the void of NAA there are clearly evident in the images.

Single volume MRS cannot detect anatomical variations on the scale of Fig. 11.4(*d*) and 11.4(*e*). For chemical analysis of anatomically heterogeneous lesions in an anatomically heterogeneous organ, the future lies with SI.

Figure 11.5 (see colour plate section) shows ^{1}H SI results from another patient with a glioblastoma multiforme, also untreated at the time of study. The metabolite images demonstrate four distinct biochemical features of the lesion: Elevation of the choline signal in and near the tumour; relative diminution of the creatine and NAA signals; and elevation of lactate and lipid signals. The lactate signal appears in the same portion of the spectrum as signals generated by mobile lipid molecules and is therefore difficult to separate from them in the raw spectra, although spectral editing techniques mentioned elsewhere in this chapter can extract it cleanly when necessary.

Caveat spectator!

The metabolite images in Fig. 11.5 (see colour plate section) appear to be more finely resolved than the ones in Fig. 11.4 (see colour plate section). In fact, they were acquired in the same time with the same pulse sequences. Although the signal changes were actually somewhat larger in the Fig. 11.5 patient, most of the difference from Fig. 11.4 is due to postacquisition SI signal processing, for which no standards currently exist. Efforts to establish standards are under way. Meanwhile, SI interpretation for clinical purposes must be done with explicit awareness of how the data were processed.

The biochemical differences between tumours and normal brain illustrated in Figs. 11.4 and 11.5 (see colour plate section) are most pronounced in aggressive brain tumours, but they occur in various combinations in more slowly growing tumours of several histological types. By current biological interpretation, they reflect the reduced neuronal fraction of tumour cell mass (decreased NAA), anaerobic metabolism (elevated lactate), and acceleration of membrane metabolism (increased signals from cholines and small lipid molecules free to tumble in solution). To become useful in brain tumour management, the changes must be correlated quantitatively with tumour histology, treatment responsiveness, or both. These are active areas of current research.

Spectroscopic images are naturally registered with MRI scans and therefore offer an opportunity for chemical analysis of tumours and the tissue around them at the anatomical resolution of ^{1}H SI, currently about 0.2 cubic centimetres. As its anatomical and biochemical resolutions are improved yet further by intense technical development efforts under way in several countries, the rich store of chemically specific information from non-invasive SI can be expected to figure prominently in brain tumour research and therapy.

^{1}H MRS studies of GABA in the living human brain

GABA is the major inhibitory neurotransmitter in the cerebral cortex. It is synthesized from glutamate in specialized neurons, which release it from synaptic terminals that are intimately integrated into most cortical networks. Extensive studies in animals, isolated brain cells, and brain slices have shown that GABAergic function is altered in a variety of models of neurological and psychiatric disease (Roberts, 1986; Meldrum, 1989; Olsen & Avoli, 1997). Several antiepileptic and psychiatric drugs are targeted on GABAergic systems. Non-invasive measurements of GABA are therefore of interest to a wide range of neuroscientists, neurologists, and psychiatrists. Novel ^{1}H MRS techniques have made such measurements possible in recent years.

The most useful GABA resonance in the ^{1}H spectrum of living brain is overlapped by more intense resonances from glutathione and creatine (Behar & Boehm, 1994). Spectral editing techniques which permit separation of the GABA resonance from the others created a new opportunity for non-invasive study of GABA metabolism and GABAergic function in animals and humans (Rothman et al., 1984, 1993).

Figure 11.6 illustrates the current GABA editing technique. The remarkable signal-to-noise ratio of the GABA resonance in the difference spectrum allows measurement of rather small variations in GABA concentration caused by drugs and disease.

GABA studies in epileptics receiving vigabatrin

Impaired GABAergic function has been implicated in the etiology of epilepsy (Meldrum, 1989). Consistent with this proposal, ^{1}H MRS editing studies have found decreased brain GABA in adult (Petroff et al., 1996c, 2000) and pediatric (Novotny et al., 1999) epilepsy. Release of cytosolic GABA has been proposed as an important mechanisms for seizure suppression (Kocsis & Mattson, 1996; Richerson & Gaspary, 1997). The finding that low GABA concentration was strongly associated with poor seizure control in epileptics supports the idea that the relationship is causal rather than coincidental. An opportunity to test the idea by direct GABA measurements in the human brain was afforded by development of the ^{1}H MRS methods described above.

Vigabatrin is a drug which irreversibly inhibits the enzyme GABA transaminase (GABA-T), which catalyses breakdown of GABA in GABAergic neurons and in astrocytes, and thereby causes an elevation in GABA concentration. Animal studies indicate that vigabatrin reduces cortical excitability by this mechanism. Non-invasive measurement by ^{1}H MRS editing of GABA elevations caused by GABA-T inhibitors was first demonstrated in the rat brain (Behar & Boehm, 1994; Preece et al., 1994).

MRS editing studies of GABA have subsequently illuminated several aspects of vigabatrin action in the brains of epileptic patients. These include the following.

(i) The effectiveness of vigabatrin in controlling seizures depends upon elevating GABA concentration above the mean level found in non-epileptic subjects, and,

(ii) chronic dosing above 3 grams per day does not increase GABA concentration further (Petroff et al., 1996a; b, c).

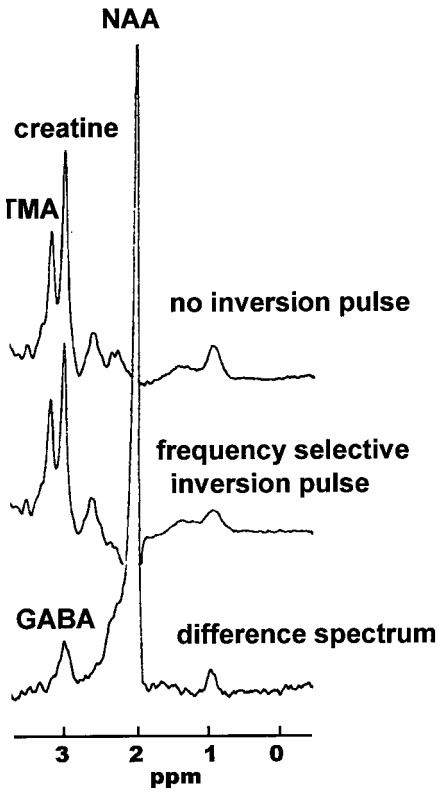


Fig. 11.6. GABA signal detection by spectral editing in human brain. The top spectrum is unmodified. During acquisition of the middle spectrum, the GABA C3 proton resonance near 1 ppm was selectively inverted by frequency-specific magnetic pulses. The C3 resonance itself is not visible due to a larger signal at the same chemical shift; the inversion pulse reduces the intensity of the larger signal in the middle spectrum compared to the top one. Magnetic interaction between the inverted C3 proton signal and the C4 proton resonance near 3 ppm alters the latter, transferring to it part of the effect of the inversion pulses at 1 ppm. When one spectrum is subtracted from the other, all of the metabolite signals drop out except the ones affected directly by the inversion pulses and the GABA C4 proton signal affected indirectly by them (difference spectrum). The GABA C4 proton signal is thereby isolated from larger coresonant signals, and its high signal-to-noise ratio allows accurate measurement of its intensity, which reflects GABA concentration. The residual water signal does not drop out because it is slightly affected by the inversion pulses and its high intensity magnifies the effect. TMA – tetramethylamines. (Unpublished data, similar to Rothman, 1993.)

(iii) GABA concentration reaches a maximum level within two hours of initial drug administration, and,
(iv) GABA concentration remains elevated over 48 hours after a single dose of vigabatrin (Petroff et al., 1999a, b).
(v) No down-regulation of GABA-A receptors occurs during chronic dosing with vigabatrin (Petroff & Rothman, 1998).

These data correspond well with other information about the clinical pharmacology of vigabatrin in epileptic patients. They imply strongly that the antiepileptic effect is due to elevation of brain GABA.

Data like these are available only from human brain MRS. They expose the human neuropharmacology of vigabatrin to a new standard of precise analysis, and they point the way to similar studies of other drugs which affect MRS-measurable resonances.

Some of these observations are of immediate practical significance. The finding that brain GABA concentration increases with vigabatrin dose up to, but not above, 3 grams per day suggests that, in general, better seizure control need not be sought above that dose. Figure 11.7 illustrates the phenomenon in quantitative form.

Such insights achieved by non-invasive observation of drug action directly in the brain can be expected to take clinical management of epilepsy to higher level of effectiveness, much as measurements of antiepileptic drug concentrations in the blood did by revealing individual differences in drug metabolism a generation ago. That earlier advance came about through better understanding of what happened to the drug outside the blood–brain barrier. Non-invasive MRS allows the analysis to be continued on the other side of that barrier, in the brain itself.

GABA studies of other antiepileptic drugs

MRS studies similar to the ones described above have found that several antiepileptic drugs with unknown mechanisms of action also cause rapid elevation of brain GABA concentration. These include gabapentin, topiramate, and lamotragine (Petroff et al., 1996b, c, 1999a, b, 2000; Hetherington et al., 1998; Kuzniecky et al., 1998). Their effects on GABA may be the mechanism of their antiepileptic action, as appears to be the case with vigabatrin. Data now available certainly motivate experiments to test that idea, but until a correlation between GABA elevation and seizure control is actually demonstrated, as was done for vigabatrin in the studies mentioned above, the idea is but an interesting possibility. Some antiepileptic drugs may elevate brain GABA and thereby prevent seizures. Others may elevate GABA but prevent seizures by a differ-

ent mechanism. Drugs which elevate GABA but do not prevent seizures may be found. The point here is that non-invasive MRS measurements of GABA in the human brain allow a more direct approach to such questions than is possible by any other means.

GABA studies of depression and other brain disorders

Reduced GABA concentration has been found in unipolar depression (Sanacora et al., 1999), alcohol withdrawal, and hepatic encephalopathy (Behar et al., 1999). Results from the depression study are shown in Fig. 11.8.

These disorders are associated with an alteration in inhibitory GABAergic function. The finding of low GABA associated with them is additional evidence that the brain metabolic GABA pool is closely related to GABAergic function.

Low cortical GABA in unipolar depression appears paradoxical since the condition is not associated with enhanced cortical excitability. A potential explanation is that the low GABA concentration is a compensation for the reduction in excitatory glutamatergic activity (Sanacora et al., 1999). Future studies using ^{13}C MRS to monitor the flow of ^{13}C through observable metabolic pools in the brain (see below) may be able to test this hypothesis.

Parsing the edited GABA resonance

Both GABA and the GABA derivative homocarnosine, a condensation product of GABA and histidine, contribute to this signal. Homocarnosine is a neuromodulator present in a specific subclass of GABAergic neurons in the primate brain. Short TE ^{1}H MRS with macromolecule suppression may be used to measure the homocarnosine histidine proton resonances in the downfield region of the short TE spectrum (Behar et al., 1994; Rothman et al., 1997). Combining the homocarnosine measurement and the total GABA editing measurements allows separate measurement of homocarnosine and GABA. By additional modification of editing selectivity the GABA derivative pyrrolidinone can also be measured in the edited spectrum (Hyder et al., 1999). Changes in concentrations of GABA, homocarnosine, and pyrrolidinone have been found to have different time courses in response to a first-time challenge with vigabatrin (Petroff et al., 1999a, b).

The homocarnosine resonance titrates with pH. Hence the cytosolic pH of the GABAergic neurons where it is principally localized can be measured in the ^{1}H spectrum (Rothman et al., 1997). Together with measurement by ^{31}P MRS of cytosolic pH in the large fraction of brain cells

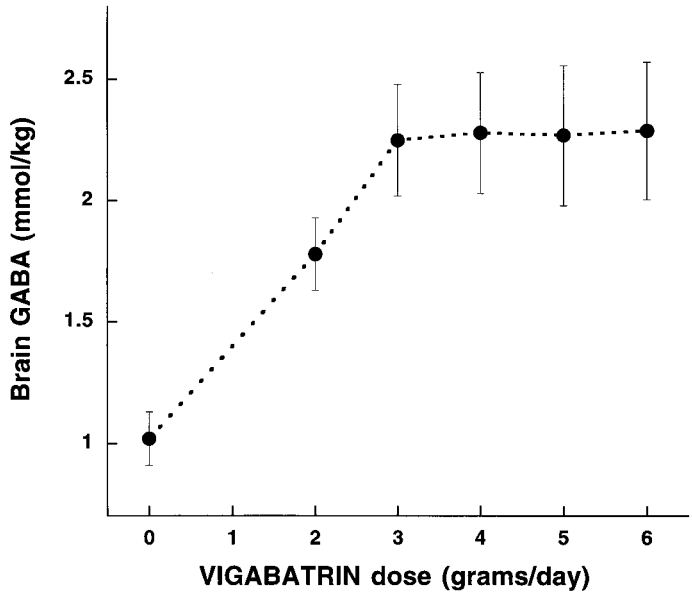


Fig. 11.7. Vigabatrin effect on occipital cortex GABA in a total of 26 patients with complex partial epilepsy. Doses above 3 grams/day caused no further GABA elevation, as the figure shows, and seizure control was not further improved either. Means ± standard deviation. (Redrawn with permission from Petroff et al., 1996a, 1999a.)

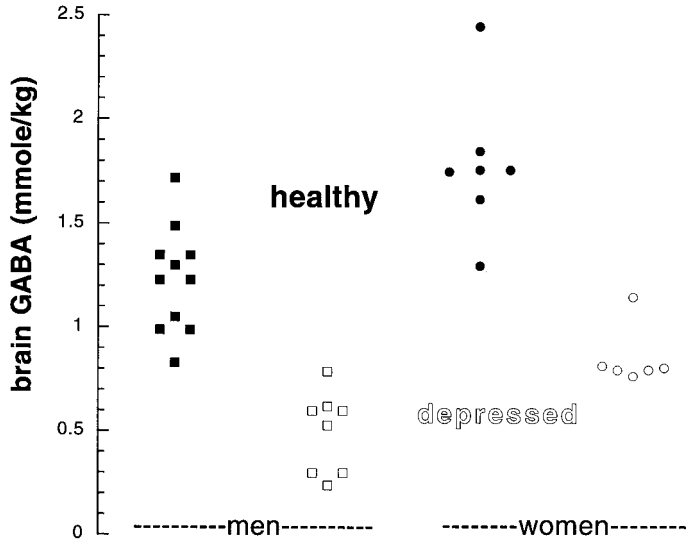


Fig. 11.8. Occipital cortex GABA in 18 normal (filled markers) and 14 medication-free depressed (open markers) men (squares) and women (circles). Analysis of covariance showed a highly significant 52% overall reduction of GABA in depressed patients. Significant age and sex interactions with GABA, but not diagnosis, were also present. (Redrawn with permission from Sanacora et al., 1999, Fig. 2. © American Medical Association.)

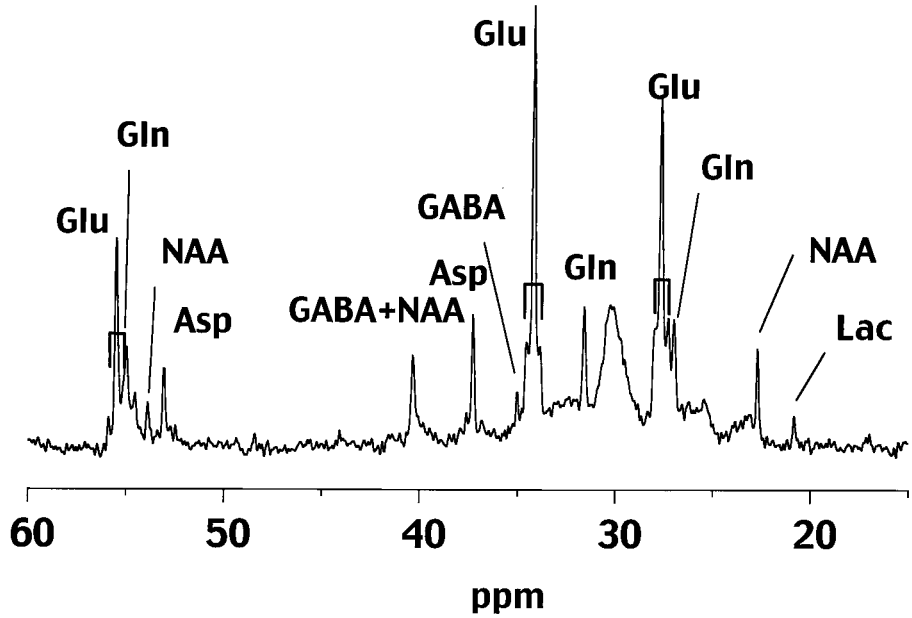


Fig. 11.9. ^{13}C spectrum from human occipital–parietal cortex acquired in a 4 tesla instrument after infusion of 1-^{13}C-glucose for 50 minutes. Only the resonances from NAA and the broad one at 30 ppm were present in the natural abundance spectrum prior to the infusion. The others reveal metabolic incorporation of ^{13}C into various positions of glutamate (Glu), glutamine (Gln), aspartate (Asp), and lactate (Lac), as well as GABA. Although the metabolite resonances are better resolved (separated) in ^{13}C than in ^{1}H spectra (see Figs 11.3 and 11.6), the long acquisition times required by the lower sensitivity of the ^{13}C nucleus make indirect detection of ^{13}C metabolites through the ^{1}H spectrum more useful for most metabolic studies, particularly if labelling time course is to be measured (see text and Fig. 11.10). (Reproduced with permission from Gruetter, 1998.)

which contain inorganic phosphate, this capability offers new opportunities for analysis of how pH is related to brain function and pathology (Prichard et al., 1998).

Metabolic rate studies by ^{13}C and ^{1}H-^{13}C MRS

The ^{13}C nucleus is a stable (non-radioactive) isotope of carbon which is 1.1% abundant in nature; the nearly 99% abundant ^{12}C nucleus is not magnetic. Thus, about 11 carbon atoms in every 1000 are potentially detectable directly by ^{13}C MRS. The isotopic fraction of ^{13}C in brain metabolic pools observable in vivo can be raised above 1.1% by infusion of ^{13}C enriched substrates, usually 1–^{13}C-glucose.

The presence of ^{13}C in brain metabolic pools can in some cases be measured with enhanced sensitivity by indirect detection of ^{13}C by ^{1}H MRS, which can report the presence of a ^{13}C atom covalently bonded to protons. Among the carbon atoms in important molecules that can be studied in this way are C1 of glucose, C3 of lactate, C4 of glutamate, and C2 of GABA. Measurements of ^{13}C flow through these positions yield estimates of glycolytic and oxidative fluxes which have been shown to agree with data from other techniques and to vary appropriately with changes in metabolic demand.

Building on methods developed in animal research, several groups have demonstrated the feasibility of using rates of ^{13}C incorporation into brain metabolic pools to measure metabolic flux, enzyme activity, and metabolic regulation in the living human brain (Rothman et al., 1992; Gruetter et al., 1994, 1998; Mason et al., 1995; Shen et al., 1999).

Figure 11.9 shows the ^{13}C-labelled resonances in a ^{13}C spectrum obtained from occipital/parietal region of the brain of a human subject after infusion of 1–^{13}C-glucose for 50 minutes. Only the NAA signals and the broad one at 30 ppm were present before the infusion.

As is evident from the figure, separation of resonances along the frequency axis is much greater in ^{13}C than in ^{1}H spectra. However, ^{13}C MRS is not the most effective way to do ^{13}C-labelling studies in vivo. The spectra take much longer to acquire, because ^{13}C gives a much weaker signal than ^{1}H, and they give information only about the fraction of a metabolite pool which contains ^{13}C. The combined ^{1}H/^{13}C method solves these problems.

Observation of the brain by ^{1}H techniques which reveal the presence of ^{13}C at certain positions of glutamate, glutamine, lactate, and other detectable metabolites (Rothman et al., 1992) opens a new era in the study of brain metabolism, both as it operates during normal brain function and as it is altered by disease.

Figure 11.10 shows the time course of ^{13}C labelling from 1–^{13}C-glucose of glutamate and glutamine in the human occipital region obtained with the $^{1}H/^{13}C$ method (Shen et al., 1999). The high sensitivity of ^{1}H MRS allowed a data point to be acquired every 5 minutes. Detection of the unlabelled portions of the metabolite pools allowed calculation of the time course of increase in their isotopic fractions (not shown). Data like these provide direct access to dynamic aspects of brain metabolism with time and space resolutions which surpass those available from any other non-invasive technology. Improvements in both kinds of resolution and detection of additional compounds are possible by use of higher magnetic fields and other technical advances which are known to be feasible. These facts ensure that MRS technology will figure prominently in metabolic research on the living human brain for years to come.

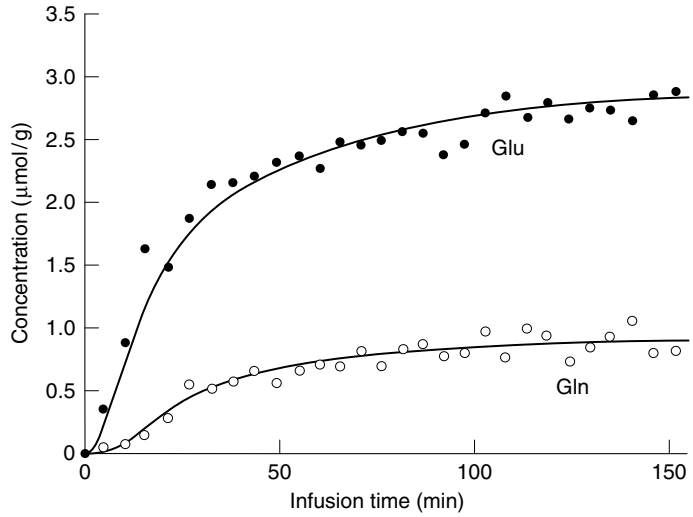


Fig. 11.10. Time course of incorporation of ^{13}C from infused 1-^{13}C-glucose into the C4 positions of glutamate (Glu) and glutamine (Gln) in human occipital cortex. Data were obtained by a combined $^{1}H/^{13}C$ method (see text) in a 2.1 tesla instrument. Curves were fitted by a model which allows rate calculations of glucose oxidation, the tricarboxylic acid cycle, and the glutamate/glutamine cycle. (Reproduced with permission from Shen, 1999 © 1999, National Academy of Sciences, USA.)

The future

Much of the achievement of brain MRS before 2001 was demonstration that it can observe, in the living organ, in an hour or less, phenomena that decades of invasive research had laboriously established to be true of brain function occurring normally and altered by disease. With confirmation of its capabilities now firmly in hand, MRS can be used with increasing confidence to acquire information about normal and pathological brain function that is beyond the reach of any other observational technology.

Books focused as this one is on mechanisms of neurological disease invite consideration of where precisely the boundary between normal and pathological brain function lies and how it may be defined. Most of the methods mentioned in this chapter can be used to improve that definition in novel ways.

An early example was demonstration of a lactate rise in human visual cortex during stimulation by flashing lights (Prichard et al., 1991; Sappey-Marinier et al., 1992). Previously, lactate elevations had been universally regarded as a sign of distress in brain tissue. This MRS-enabled finding provided new insight concerning how glycolytic and oxidative metabolism are integrated during normal brain activity, and it fuelled a controversy on the subject that can end nowhere but in improved understanding of how the brain works normally.

MRS methods have the potential to probe such matters much more deeply. The information gained is certain to anchor new data on brain disease mechanisms to a firm background of steadily improving insight into normal brain function.

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12

Windows on the working brain: evoked potentials, magnetencephalography and depth recording

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A number of techniques have been developed for the study of human brain functions in normal and disordered states. Each of them monitors function from a selective point of view. Whereas functional imaging techniques are based on neurovascular coupling (functional magnetic resonance imaging (fMRI), positron emission tomography (PET), near-infrared spectroscopy (NIRS) and optical imaging), electrophysiological methods directly reflect neuronal activity. Electroencephalography (EEG) and magnetencephalography (MEG) provide information about global as well as regional activity under stationary conditions or for evoked or event related responses. Subdural or epicortical recordings for the identification of epileptogenic foci and microelectrode recordings for functional target identification during stereotactic neurosurgery complement the spectrum of the clinical application of neurophysiological tools.

Taken together, the neurovascular and neurophysiological methods provide largely complementary information that allows better insights in normal and disturbed brain function. The superimposition of MEG data on MR images combines the high spatial and temporal resolution of the respective methods. EEG recordings can now be conducted inside the MR scanner allowing the recognition of epileptogenic foci during EEG-defined seizure episodes.

Towards an integrative MEG and EEG study of cognitive brain functions

EEG and MEG measures arise from the same cortical source, namely from ordered intracellular currents in the pyramidal cells (Okada, 1982). Since the pyramidal cells in a circumscribed area show basically the same orientation orthogonal to the surface, the superimposed neural currents may result in macroscopically measurable electromagnetic fields. The electric and magnetic fields have orthogonal orientation and bear formally equivalent information; however, it may well be that stimulus-triggered event related potentials (ERPs) or magnetic fields (MFs) reveal different aspects of the underlying neural sources depending, for example on the nature of the task and the anatomy of the cortical region of interest. For several reasons, source estimation based on MFs is often superior to ERP based fits. First, opposite to electrical currents MF remain almost unchanged when passing through anatomical structures between the cortex and the sensor sets. Hence, the MFs are less susceptible to inadequate head models, both regarding anatomical shape and tissue conductivities (CSF space, scull, scalp). Secondly, the superficially observed MF originate from the primary neuronal currents (i.e. currents inside the dendrites) whereas volume currents do not contribute for physical reasons. In contrast, ERPs reflect both primary and volume currents. As a consequence, in comparison to the MEG, the electrical signal shows spatial blurring that necessarily increases uncertainties during source localization. Thirdly, the magnetic field distribution outside the head arises mainly from source currents that flow tangentially to the head surface (Williamsen & Kaufman, 1987); radially oriented source components do not significantly contribute to the observed MEG for physical reasons. This contrasts with the ERP component distribution that reflects both tangential and radial current sources. In anatomical terms, measurable magnetic activity arises almost exclusively from the sulcal part of the cortical grey matter. Accordingly, the extracranial magnetic fields are linked to a selective part of the cortical sources and not obscured by overlying fields generated by radial sources.

The role of attention in visual perception

Higher visual functions involve a number of potentially overlapping radial and tangential electromagnetic sources in the visual cortex. For instance, visual attention can modulate the signal flow in adjacent early visual areas and is a

good example to illustrate the MEG/EEG comparison. Convergent input to subsequently higher cortical processing levels (V1 to V4, IT, MT) entails progressively enlarging receptive fields with a coarser representation of visual input at higher cortical levels. An increasing portion of stimuli competes inside receptive fields and, therefore, necessitates effective disambiguation mechanisms. There is evidence from brain imaging, human electrophysiology and single-cell recording that a competition bias on different cortical levels provides a solution for this coarse coding problem (Reynolds et al., 1999; Luck & Hillyard, 1994). For instance, recording ERPs triggered by a search array that contains a target feature or feature conjunction gives rise to a negative voltage of approximately 200–300 ms over posterior scalp electrodes contralateral to the field where the target occurs. This N2pc component (negativity in the N2 time range posterior contralateral) appears to be a common correlate of attentional selection across different feature types in visual search and is thought to represent a manifestation of cortical processes related to the suppression of interfering visual input from distractor items (Luck et al., 1997). So far, efforts to characterize the neural origin of the N2pc using ERP source analysis have not been successful.

In a recent study, the neural origin of this component was investigated by using a combined EEG and MEG analysis (Hopf et al., 2000). MEG data were recorded using a 148 whole-head magnetometer, and EEG data were simultaneously acquired from 32 electrode sites. As an experimental task, subjects had to identify a predefined target stimulus in the left or right visual field (LVF or RVF) among a number of randomly distributed distractor items. To derive the N2pc component, ERP-/MF-responses triggered by the RVF targets were subtracted from responses triggered by LVF targets. By this subtraction the electric and magnetic activity specifically related to the focusing of attention was obtained. Figure 12.1 (see colour plate section) illustrates the ERP scalp distribution (*a*) and magnetic field distribution (*b*) for two subsequent time windows that cover the early (180–200 ms) and late (220–240 ms) portion of the N2pc component. Shown are the average data over four independent experimental sessions of one subject. As can be seen, ERP voltage distributions in the early and late time window (Fig. 12.1(*a*)) are roughly identical showing the previously known bilateral occipital topography (Luck & Hillyard, 1994). Contrastingly, a comparison of magnetic field distributions in the early and late time range (Fig. 12.1(*b*)) reveals qualitatively different patterns. Between 180 and 200 ms the magnetic field configuration suggests a generating source in the parietal cortex as indicated by a parietal flux transition zone between the maximum magnetic outflux- and influx regions (arrow). The field configuration between 220 and 240 ms, however, shows two major transition zones over left and right inferior temporal sensors implying the presence of two independent posterior–temporal sources. A distributed source analysis using the minimum norm least square method in combination with a realistic volume conductor model derived from structural MR data indicates the presence of two qualitatively different source configurations for this late magnetic attention effect (Fig. 12.2(*b*), see colour plate section). In contrast, source density estimates of the ERP data revealed a similar pattern for the early and late attention effect with a broadly distributed scalp topography over the posterior cortex (Fig. 12.2(*a*), see colour plate section).

The source estimates for MF and ERP data differ in two major respects. First, there is no indication in the ERP data for a separation into early (parietal) and late (temporal) sources, and, secondly, source configurations between 220 and 240 ms are qualitatively different for both data sets. The first difference may be related to spatial blurring of ERPs leading to a confluence of scalp topographies of a weak early and stronger late field components. The second difference may result from inverse dipole modelling of the ERP data as illustrated in Fig. 12.3 (see colour plate section). In this case, ERP source modelling erroneously links two independent field components (Fig. 12.3(*a*) and (*c*), see colour plate section) to a common underlying source (Fig. 12.3, green dipole, see colour plate section) probably due to suboptimal field projections (Fig. 12.3(*b*) and (*d*)) of the underlying sources (Fig. 12.3, black dipoles, see colour plate section). Note, the problem of suboptimal field projections is not inherently linked to ERP data and may in other experiments also be relevant for MEG data. Taken together, the present example clearly demonstrates that the validity of inverse source modelling considerably benefits from a comparison of complementary electrophysiological measures like ERP and MEG. This is because EEG and MEG provide different electromagnetic views onto the same underlying current source. A combination of both datasets necessarily draws a more complete picture and clearly diminishes the risk of source mislocalization during inverse modelling.

The study of memory functions

The study of memory functions in humans is another example of how MF analysis can improve our analysis of higher brain functions. MEG sensors can detect hippocampal postsynaptic activity (Tesche et al., 1988; Wu & Okada, 1998; Okada et al., 1997). They selectively measure the tangential source components of the closed field and, therefore, are able to measure hippocampal pyramidal cell

activity. MEG sensors are now being used to record non-invasively stimulus-evoked neural population responses in human hippocampal structures (Tesche et al., 1996; Nishitani et al., 1999; Tesche & Karhu, 1999). These studies describe ongoing oscillatory 4–12 Hz activity (Tesche & Karhu, 1999) and P300-like activity in oddball tasks (Nishitani et al., 1999) generated by hippocampal structures of healthy humans.

Combined ERP and MF analysis can differentiate electrophysiological indices of episodic memory in humans. Cognitive models of recognition converge on the notion that normal recognition has two qualitatively different bases. Recollection-based recognition or 'remembering' is accompanied by contextual information about the episode in which an item was encountered, whereas familiarity-based recognition, or 'knowing' is devoid of such information (Tulving, 1985). Remembering and knowing, in turn, can be considered as characterizing episodic and semantic memory, respectively. There is experimental evidence from behavioural studies that recollection and familiarity-based judgements cannot be reduced to a quantitative difference, but, instead, reflect two qualitatively different aspects of recognition memory (Knowlton & Squire, 1995). This distinction is supported by ERP findings which have revealed qualitatively distinct electrical brain patterns associated with recollection and familiarity. Recollecting recognized words causes an increase in ERP positivity between 500 and 700 ms after the onset of word presentation, a shift sometimes referred to as the late positive component or LPC effect (Rugg et al., 1998). On the other hand, familiarity-based recognition causes an earlier shift in ERP positivity between 300 and 500 ms, referred to as the N400 effect (Duzel, 1997; Paller et al., 1995). These two ERP effects have a different scalp topography suggesting that they are generated by different neuronal populations.

It remains unclear from ERP studies, however, where the corresponding neural populations are located. Lesion studies in animals and humans raise the possibility that both recognition effects should receive contributions from different structures within the temporal lobes (Murray & Mishkin, 1998; Vargha-Khadem et al., 1997b). We used combined EEG and MF recordings to localize the generators of the N400 and LPC effects of recognition in 11 healthy young subjects. EEG and MF were recorded simultaneously for correctly recognized old (repeated) words (hits) and new words (correct rejections) in 11 subjects. Current sources were computed separately for hits and correct rejections for each single subject taking into account their individual brain anatomy. Figure 12.4 (upper part, see colour plate section) shows the current source results obtained for a single subject for correct rejections and hits in the N400 and LPC time window. It can be seen that in the N400 time window, correct rejections induce stronger current flows than hits in the anterior temporal lobe. In contrast, hits induce stronger current flows in the posterior inferior temporal lobe than correct rejections. To further quantify whether this relationship was significant across subjects, the current source maps were transformed into Talairach space. Scatter plots (lower part, Fig. 12.4) illustrate the current flow of each individual subject in the anterior inferior temporal cortex and for the LPC time window the same is illustrated for the posterior inferior temporal cortex. It can be seen that, in the anterior inferior temporal cortex, all but two subjects show higher currents for correct rejections than for hits. In contrast, in the posterior inferior temporal cortex all but two subjects show higher current flow for hits than for correct rejections. These findings suggest that the N400 old/new effect reflects mainly decremental current strengths during repetition while the LPC old/new effect reflects mainly incremental current strengths during repetition and these two types of processes are spatially dissociated in the left human inferior temporal cortex. So far, this conclusion was not possible on the basis of ERPs alone.

The investigation of sequential cerebral processing stages

A major potential of the MEG is to identify subsequent processing stages of the neural activations during well-defined behavioural states. The neurovascular imaging methods cannot only specify the multiple areas contributing to the functional network but by means of event related fMRI (efMRI) also separate subsequent activations if they are separated by long enough time spans. But efMRI cannot resolve fast sequential processing and the dynamic interactions of these structures. The advantage of the combination of the reasonably good spatial and excellent temporal resolution of the MEG can be illustrated by a study on single word reading in developmental stutterers (Salmelin et al., 2000). Stuttering represents a temporal disorder of still unknown pathophysiology and is therefore of considerable interest for such an inquiry. The task in this study was that normal subjects and stutterers read 7–8 letter words presented for 300 ms. After a blank interval of 500 ms a question mark appeared 2000 ms later prompting the subject to read the word aloud. Mouth movement and speech onset were used for motor related analyses. Figure 12.5 shows the source areas in fluent subjects and stutterers whereas the time histories of the neural activations as revealed by event related changes in the spectral power of distinct frequency bands are shown in Fig. 12.6. Although

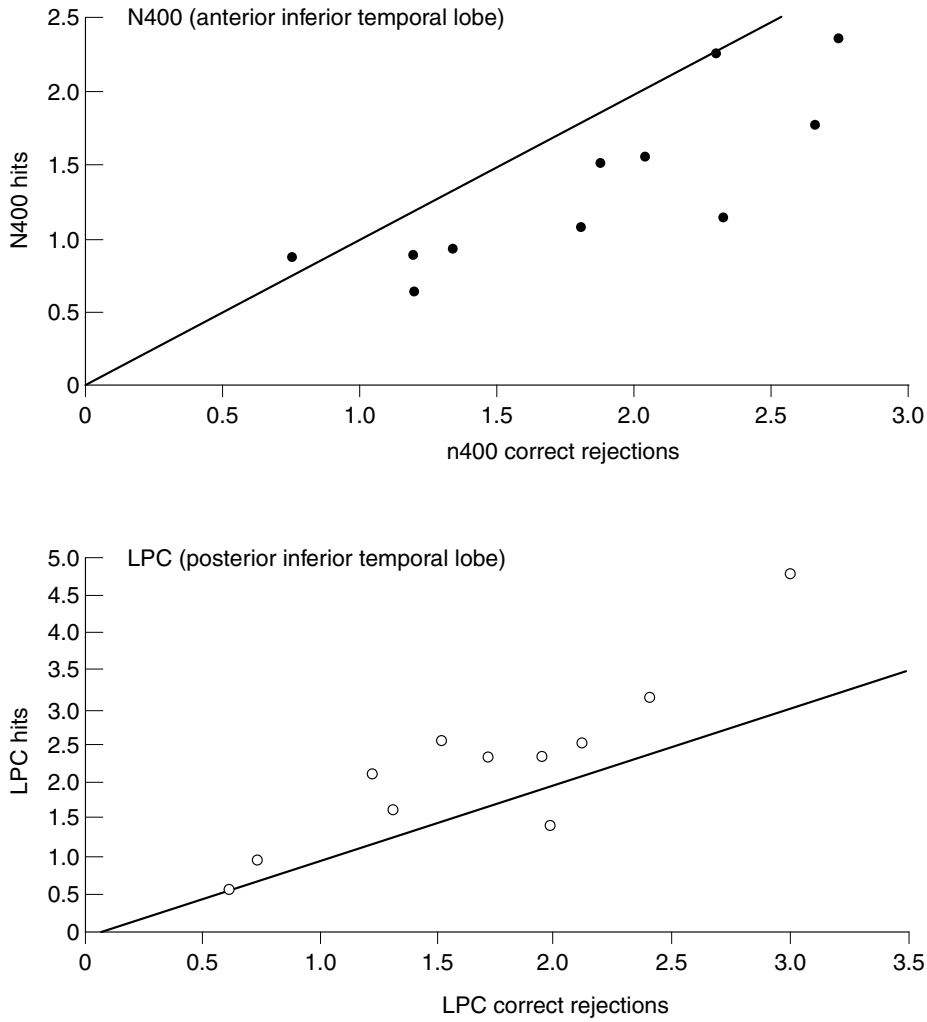

Fig. 12.4. *Lower part:* Scatter plots of the current source strengths for correctly rejected new words and hits measured in the N400 time window in the anterior inferior temporal lobe (upper diagram) and in the LPC time window in the posterior inferior temporal lobe (lower diagram). All but two subjects showed higher current flows for correctly rejected new words than hits in the anterior inferior temporal lobe in the N400 time window. In contrast, current flow was higher for hits in all but two subjects in the posterior inferior temporal lobe in the LPC time window.

the overt performance was essentially identical in the two groups, the stutterers were fluent in this task, cortical activation patterns showed clear differences for the evoked responses and the suppression of 20 Hz oscillation.

As shown in Fig. 12.6 cortical processing proceeded in the following stages:

(i) The overall temporal activation patterns showed occipital and parieto-occipital responses starting 100–150 ms after word onset (visual analysis, continuing until the appearance of the question mark) and in the left and right inferior occipito-temporal cortex (letterstring specific analysis).

(ii) Between 200 and 600 ms left more than right inferior frontal cortex responses probably reflect articulatory aspects of phonological processing, and in left middle superior temporal cortex semantic activation.

(iii) 200–800 ms following word onset, responses in the left and right posterior parietal cortices may reflect phonological aspects of linguistic processing or attentional factors of visual perception. In the third stage the left and right fronto-parietal cortices became involved and remained active throughout vocalization prompt and speech onset.

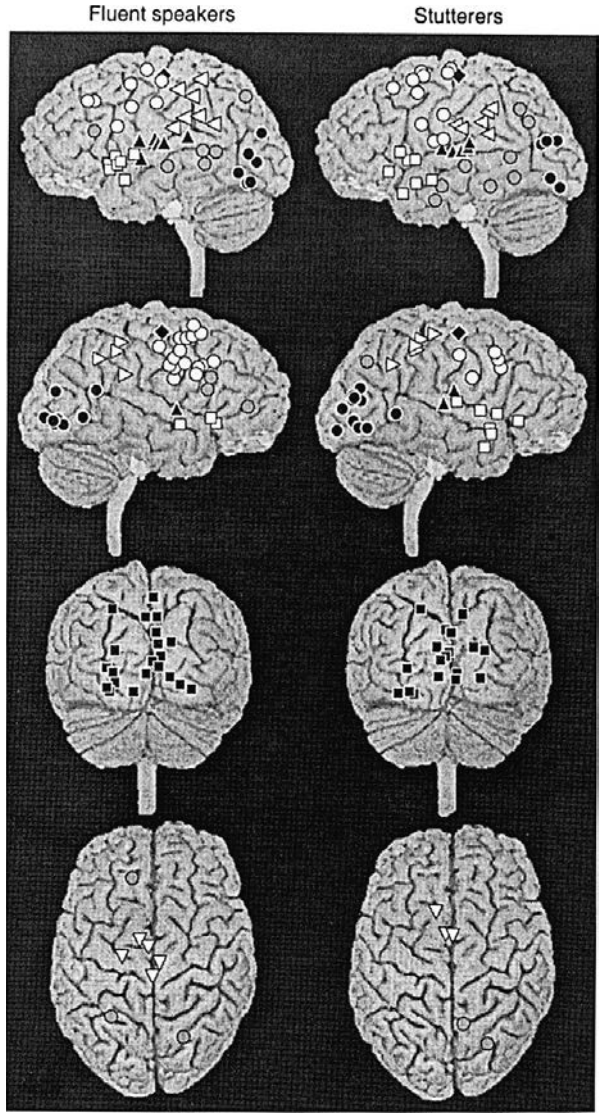

Fig. 12.5. Source areas in fluent subjects (left) and stutterers (right), when the MEG signals were averaged with respect to word onset. The different shapes and colours of the symbols (white and black circles, triangles, squares and arrows) depict the grouping of sources into distinct regions of interest. The grey circles denote sources which do not belong to any well-defined cluster. The black diamond indicates the location of the hand sensorimotor cortex. The size of the symbols equals the mean accuracy of localization (6 mm) (from Salmelin et al., 2000).

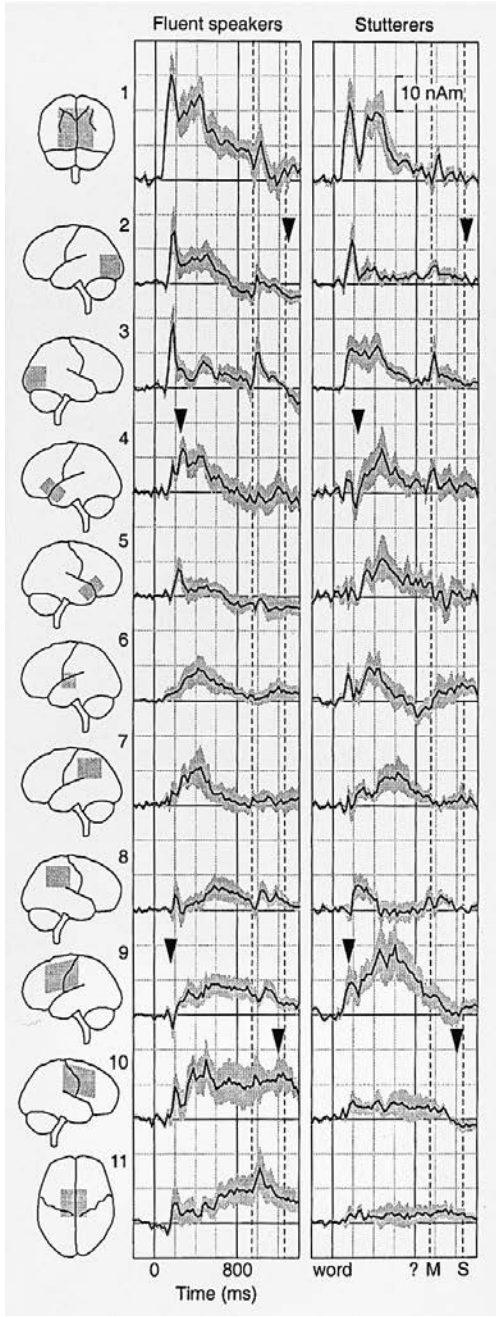

Fig. 12.6. Mean ± standard error of the mean (black curve and shading) source strengths as a function of time in fluent subjects (left) and stutterers (right). The word and question mark onsets are indicated with solid vertical lines and mouth movement (M) and speech (S) onsets with dashed lines. The black arrowheads denote the regions (ROI) and time windows of interest where the responses of stutterers and fluent speakers differed significantly from each other. The studied ROIs are illustrated on the schematic drawings of brains on the left. (From Salmelin et al., 2000.)

It follows that the normal subjects' activity proceeds from the left inferior frontal cortex (articulatory programming) to the lateral part of the left central sulcus and to the dorsolateral premotor cortex (motor preparation) within the first 400 ms after seeing the word. This sequence was reversed in the stutterers who showed an early left motor cortical activation followed by the inferior frontal signal. Stutterers thus appeared to initiate motor programmes before the preparation of the articulatory code. During speech production the right motor area was active in fluent subjects but was silent in stutterers. These findings disclose the nature of such a temporal disorder and demarcate the altered functional connectivity in the respective network, in this case between the left inferior frontal cortex and the right motor/premotor cortex, a circuitry supposed to be relevant for merging linguistic and affective prosody with articulation during fluent speech. This example is meant to illustrate the unique contribution of the MEG to our understanding of the pathophysiology of brain disorders that cannot be accomplished by any other method.

Parallel vs. sequential processing

The combination of relatively high spatial and superb temporal resolution opens new avenues for the study of brain physiology and pathophysiology. For somatosensation it was unclear how the processing of tactile and pain information proceeds in the postcentral primary somatosensory areas, each containing separate body representations for the different submodalities. The comparison of nociceptive as compared to tactile processing showed that the nociceptive sources in the postcentral gyrus were located 10 mm more medially than the early tactile responses arising from area 3b. Whereas tactile stimuli activate sequentially peaking sources in area 3b and 1, nociceptive stimuli activate area 1 indicating that this input does not share the complex hierarchical tactile processing chain (Ploner et al., 2000). MEG data further provided evidence for serial processing from SI to SII and from SI to posterior parietal cortex for tactile input. In contrast nociceptive afferents from the hand are projected to SI and SII in parallel (Ploner et al., 1999). Along these lines the channelling of information processing can be explored for other systems.

MEG in the evaluation of patients with epilepsy

Comparative recordings with MEG and invasive electrical recordings showed excellent agreement for the location of the interictal spike zones and of the spatial relationship of the irritative zone and the structural lesion (Baumgartner et al., 2000a). MEG is also helpful to guide the placement of subdural grid electrodes in patients with non-lesional neocortical epilepsies. For temporal lobe epilepsy (TLE) two types of MEG spike dipoles have been identified: an anterior vertical and an anterior horizontal dipole attributing spike activity to different temporal lobe compartments. This allows differentiation between patients with mesial and lateral temporal seizure onset (Baumgartner et al., 2000b). The disadvantage of the MEG, that it cannot be used for long-term recordings, may be counterbalanced by combined MEG/EEG recordings. The EEG can now even be recorded within the MRI scanner. This allows the use of functional MRI for the localization of EEG identified seizures in patients with focal or partial epilepsy.

The comparison between simultaneous MEG and invasive EEG recordings showed that epileptic foci in mesial temporal structures cannot be detected by MEG if they do not exceed an epileptogenic area of 6–8 cm^2. By contrast, lateral neocortical temporal lobe generators can better be detected. In a prospective study comparing several diagnostic methods (ictal and interictal scalp and intracranial EEG, MRI and MEG) in 58 patients with refractory partial epilepsy the main outcome measure was the efficacy of these methods to identify the resected epileptogenic zone (Simos et al., 2000). MEG (52%) was second only to ictal intracranial EEG in predicting the epileptogenic zone for the entire group of patients who had an excellent surgical outcome. For temporal lobe surgery this relation was MEG 57%, and ictal intracranial EEG 62%. For extratemporal resections ictal (81%) and interictal (75%) intracranial EEG were superior to MEG (44%) in predicting the surgery site in patients with excellent outcome. As compared with video-EEG, MEG was better than ictal (33%) or interictal (45%) scalp VEEG. In another series comprising 53 epilepsy surgery candidates MEG foci were identified in 47 patients in 46 of whom the lesions were resected (20 of the anterior temporal lobe and 26 of the extratemporal lobe cases) (Wheless et al., 1999). Results of this kind implicate that the MEG may obviate the need for invasive EEG in many cases. In cases selected for pediatric epilepsy surgery, the comparison with invasive intracranial EEG showed that both methods colocalized the epileptogenic focus (Minassian et al., 1999).

MEG for presurgical mapping

MEG can also be used for presurgical mapping in tumour cases in order to delineate eloquent areas (Ganslandt et al.,

1999). Comparative studies based on MEG/MRI comparisons indicate that both methods are suitable for mapping eloquent cortex in relation to tumour-invaded tissue. As a general result activations are almost exclusively seen outside the tumour invaded area (Wunderlich et al., 1998). Reliable mapping of the functionally active zone is particularly useful in the many cases with considerable displacement distorting the regional anatomy. Presurgical mapping is usually performed for the sensorimotor strip but also for the language areas. When comparing language lateralization by word-matching tasks or other language paradigms in the MEG the results are similar to those obtained to the Wada test (Simos et al., 2000).

The data on presurgical mapping are also of interest for the assessment of tumour induced plasticity following tumour resection. The rearrangement of the displaced activations can be monitored and the changes in functional maps related to functional recovery. Cortical plasticity may be associated with functional improvement but may also be maladaptive. An example for the latter case are the extensive changes in somatosensory cortical maps following amputation or somatosensory deafferentation. It has been shown (Flor et al., 1995) that the amount of cortical alteration and the magnitude of a phantom pain in amputees reveal a positive relationship ($r = 0.93$). But there was no correlation between non-painful phantom phenomena and the amount of cortical reorganization. This, and related data, indicate that phantom limb pain goes along with plastic changes in primary somatosensory cortex and its afferent stages.

Combination of electromagnetic and hemodynamic measures

The idea behind this approach is to relate the areas of functionally relevant brain activations, as identified by regional blood flow changes, to the time course of associated neural processes, as reflected by successive ERP or MF components. For a linear sequence of discrete cognitive events, for example, one would expect a corresponding sequence of electric or magnetic components mapped onto a distinct pattern of hemodynamic brain activations. However, our experiences suggest that these relationships are highly complex and usually do not allow for simple solutions. In this respect, an important question is whether and to what extent it is reasonable to assume that electromagnetic and hemodynamic parameters are related, given that ERP and MF components reflect postsynaptic activity and blood flow change might occur seconds after the electromagnetic events. Evidently, electrophysiological and hemodynamic indices of cortical activation do not necessarily match. For instance, cognitive ERP components in the later time range may reflect the integrated activity of multiple and broadly distributed sources and, therefore, are difficult to relate to few circumscribed hemodynamic sources as revealed by standard statistical mapping neuroimaging procedures. Therefore, some neural processes may be hidden in these results because the corresponding data just do not reach significance due to a poor signal-to-noise ratio or because of a too rigid significance thresholding. On the other hand, an activated area identified by hemodynamic measurements may generate electromagnetic signals that cannot be recorded at scalp locations because the fields cancel locally due to the cortical geometry. Together, the combined imaging approach does not aim for a complete integration of different physiological parameters; rather, the goal is to obtain complementary information about different aspects of the same neural process.

An important step towards a combined analysis of neural functions implies a physiologically, anatomically and mathematically profound approach to the so-called inverse problem. This term denotes the estimation of the intracranial sources of electromagnetic activity sampled at various scalp locations given the fact that a scalp recorded pattern of electromagnetic parameters does not have a unique intracranial solution. At present, most studies apply the so-called equivalent dipole model or the distributed cortical surface model. The dipole model simulates the neuroelectric activity as generated by a single point source with a certain location, an orientation and an amplitude, as can be assumed for a relatively small activated cortical region. The distributed source approach is suitable for the estimation of more widely spread activity sources. It assumes a multitude of dipoles distributed over the brain. For an improved solution, they may be constrained by restricting their location to the MR-based cortical surface and their orientation perpendicular to it; with the location and orientation of the dipoles fixed, only their strength needed to be solved. As a result, the solution resembles a distributed electrical solution of the cortical surface.

The source estimation provided by these different algorithms is only a first step in the combination of electromagnetic and hemodynamic parameters. Consider an experiment in which parallel recording of ERPs and fMRI in the same subject under the same experimental conditions has identified a number of electromagnetic sources and MR signal changes related to a particular performance. What kind of evidence substantiates the assumption that these different parameters reflect the same or different neural processes? There are different approaches to answer this question. One is called the ‘seeded forward

solution' (Heinze et al., 1994). This solution implies that the equivalent dipoles of electromagnetic activity are placed within the anatomical areas defined by MR signal change to test whether these dipoles could have generated the electrical patterns that were recorded from the scalp. If this is the case, the next step is to show that other possible locations of these dipoles provide a worse or at least not significantly better (in terms of goodness of fit) solution than the seeded dipole fit. Another approach is to test the covariation of MR and electrical signals when the task changes. The logic is that if both signals reflect the same cognitive event, one would expect a covariation over task manipulations. New developments in combined neuroimaging incorporate statistical approaches for estimating the most probable numbers, locations, orientations and strength of active cortical regions.

To illustrate such a comparative approach and the advantage of MEF measurements over EEG data a combined EEG, MEG and fMRI study assessing the neural indices of word fragment completion can be used. Seven subjects completed four-letter fragments to German words whose length varied between 7 and 9 letters and indicated the time point of completion with a right hand, index-finger button press. EEG and MF data were analysed response locked to the motor response that indicated completion. With both EEG and MF, response-locked waveforms deviated from zero starting at approximately 500 ms before the motor response. The current density solution of this 500 ms time window was derived using the MF data, and for comparison also using the EEG data alone. Both types of solutions were compared to the fMRI measurements (different subjects) obtained during the same task. In accord with the fMRI findings, the combined EEG and MF current density analyses revealed a left frontal and two bilateral temporal sources of activity (Fig. 12.7, see colour plate section). In contrast, current density performed with EEG data alone, misallocated the bilateral parietal sources to a single, widely distributed source located over the convexity of the parieto-central scalp. Both types of source analyses, however, correctly revealed activity in the left motor cortex starting from 20 ms prior to the motor response. These data provide fMRI supported evidence that source analysis based on EEG data alone can provide wrong solutions in the case of more complex, bilateral neural activity, and the MEG data can help to substantially improve the spatial resolution in these cases.

The study of cortical rhythms

EEG/MEG studies have provided evidence that the mixed frequency content of the human brain oscillations can be fractionated into several region specific intrinsic rhythms. The functional significance of these rhythms is still unclear, but there is increasing evidence that some of them respond to peripheral sensory or motor events. This can be shown by calculating the event related modulation in the spectral power of these cortical rhythms (Hari & Salmelin, 1997; Pfurtscheller & Aranibar, 1979).

Sources around the parieto-occipital sulcus generate the well known α-rhythm. They show dampening of the α-rhythm within 200 ms after the presentation of visual stimuli and also during visual imagery. The Rolandic Mu-rhythm consists of 10 and 20 Hz components with different source locations. The 10 Hz component is supposed to be somatosensory in origin, whereas the 20 Hz signal originates mainly from motor cortex (Hari & Salmelin, 1997) with clearly detectable somatotopy of the oscillatory sources. These components are suppressed by either somatosensory input or movement. The human auditory cortex shows spontaneous oscillations around 10 Hz (tau rhythm) that is transiently suppressed during auditory input (Lehtala et al., 1997). Oscillatory responses in the γ-band (25–50 Hz) also showed differences in relation to the perception of auditory stimuli.

The spatial analysis of these rhythms and their interdependence is of considerable significance for a better understanding of the pathophysiology of cortico-cortical and cortico-thalamic interaction, but also for cortico-muscular coupling. Llinas and coworkers (1999) have recently proposed that patients with neurogenic pain, Parkinson's disease or depression show increased low frequency theta rhythmicities associated with a pronounced increase in coherence between high and low frequency oscillations. This was supposed to indicate thalamo-cortical dysrhythmia as a common principle underlying the abnormal coherence in the theta range.

New approaches for the study of coherence

The understanding of the synchronization of neuronal firing within and across areas is pivotal for the understanding of brain function and dysfunction. Coherence between signals of sensors or electrodes covering different scalp areas is usually taken as a measure of functional coupling. This approach was hitherto limited by methodical constraints. A new method, dynamic imaging of coherent sources (DICS), has been introduced by Gross et al., (2001). Since MEG and EMG signals are non-stationary, this new tool has been implemented for the detection of phase synchronization in non-stationary noisy data (Tass et al., 1998). In contrast to classical coherence, this method

allows the separation of amplitude and phase information by means of the Hilbert transform. DICS allows different approaches to the study of coherence. One is to identify a cortical area showing the strongest coherence with a peripheral signal and to take this as a reference for calculating cortico-cortical coherences. Another strategy is to calculate coherences between all sensor pairs and then select the strongest coherence between non-adjacent sensors. Finally a *priori* information can be used to define a reference region based on knowledge of anatomical structures or pathways or results from other functional imaging studies.

The examination of cortico-muscular coherence during static isometric muscle contraction and simultaneous electromyographic and MEG recordings revealed significant coherence in the 15–33 Hz frequency range (Conway et al., 1995; Salenius et al., 1997). This corresponds to the 20–30 Hz coherence between local field potentials in primary motor cortex and rectified EMG from the contralateral hand and forearm muscles in monkey (Baker et al., 2000). The coupling of central oscillatory activity to peripheral muscle activity is apparent in the MEG signal averaged to the onset of motor unit potentials (Fig. 12.8(*a*)) and in the coherence (Fig. 12.8(*b*)) between rectified EMG signal and the neural activity of the contralateral primary motor cortex (Fig. 12.8(*c*)). The delays between the oscillatory motor cortical and EMG signals computed from their phase difference provide information about conduction times. Figure 12.9 shows the close agreement with the conduction times as determined by transcranial magnetic stimulation.

For the clinic this method opens new applications. One is the measurement of conduction times and conduction velocities in normal conditions and demyelinating disorders. Another possibility is the detection of abnormal synchronization. This is not only at issue for hypersynchronized states such as tremor, myoclonus or epilepsy but also for disclosing abnormal interareal coupling or changes due to afferent pathology. The latter has recently been demonstrated in cases with pseudo-chorea-athetosis, a condition characterized by continuous involuntary finger movements following partial or complete deafferentation. Whereas the coherence during isometric muscle contraction was normal, the involuntary finger movements during rest exhibited an abnormally strong 12 Hz coherence between motor cortex and EMG reflecting a disinhibition of rhythmic cortical output. This coherence was not seen during voluntary finger movements (Timmermann et al., 2001).

A major difference between MEG and fMRI lies in the detection of dynamic and static behavioural states. fMRI is well suited to detect dynamic changes of behaviour. When examining the relationship between the fMRI signal during a static finger flexion task and dynamic finger flexions no or inconsistent small fMRI responses were recorded during the static task (Thickbroom et al., 1999). In contrast, the MEG is well suited to continuously record cortico-muscular or cortico-cortical coherences during static muscle contractions or behavioural states (Gross et al., 2000).

Microelectrode recordings

Microelectrode recordings can specify pathophysiology at a finer grain than macropotentials. They can reveal changes characteristic for certain disorders such as altered neuronal discharge patterns and rates or abnormal synchronization as they occur in movement disorders. Although such recordings have been employed for the study of cortical functions, the major field for microelectrode studies in the human brain is functional target localization during stereotactic surgery for the treatment of Parkinson's disease (STN), tremor (thalamus) and dystonia (thalamus, GPi). One major issue is the determination of the borders of the target nuclei and of the somatotopy therein, thus improving the precision of electrode placement. Beside somatotopy the discharge behaviour, firing pattern and rate, are characteristic for different basal ganglia compartments along the trajectory to the target as illustrated in Fig. 12.10. The adequate interpretation of these discharge patterns rests on comparisons with data recorded from non-human primates because normal data cannot be obtained from human subjects.

Recordings in Parkinson's disease

Gold-standard for our understanding of the pathophysiology of Parkinson's disease is the comparison with its animal model, the MPTP monkey where recordings in the basal ganglia show typical changes in discharge rates and pattern. Intraoperative microelectrode recordings in Parkinsonian patients show similar abnormalities. Spontaneous discharge rates in the STN that normally lie around 40 Hz are increased in Parkinson's disease and decreased in Huntington's chorea (Fig. 12.11). The increased firing rates of the excitatory glutamatergic STN neurons elicit increased firing rates in the inhibitory GABAergic output neurons of the GPi resulting in strong inhibition of their thalamic or brainstem target neurons. This inhibition is thought to arrest the ongoing motor activity in the thalamo-cortical loops involved in the regulation of motor behaviour. In contrast, intraoperative micro-

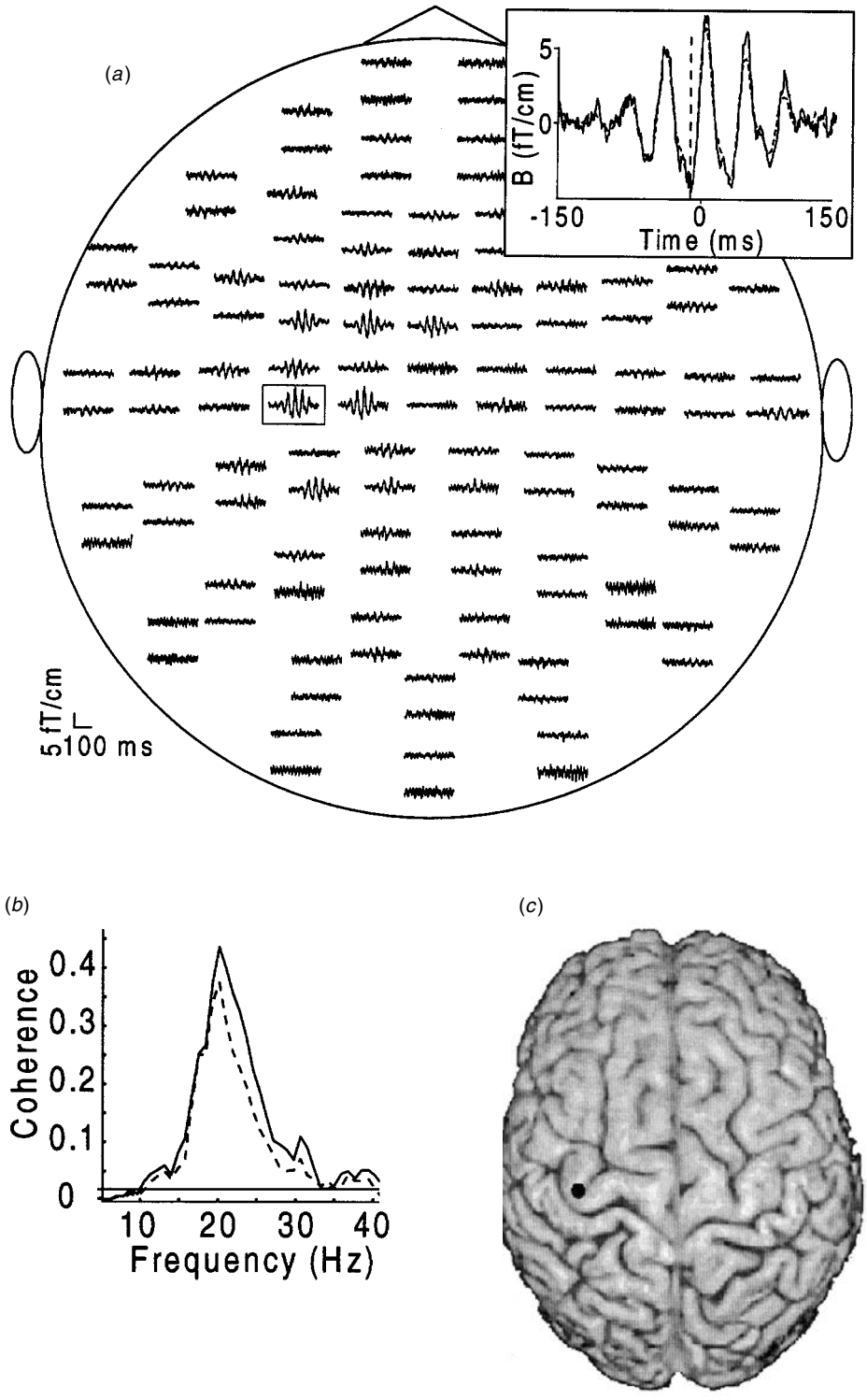

Fig. 12.8. (*a*) Unfiltered averaged MEG signals timelocked to onsets of the motor unit potentials (phase-triggered average). The dashed vertical line at –15 ms in the inset marks the minimum in the signal and the dashed trace shows the part of the signal that is accounted for by the dipole. (*b*) Coherence as function of frequency between EMG and M1 (solid line) and between EMG and the MEG signal with the highest coherence (dotted line). (*c*) The dipole superimposed on the subject's brain. (From Gross et al., 2000.)

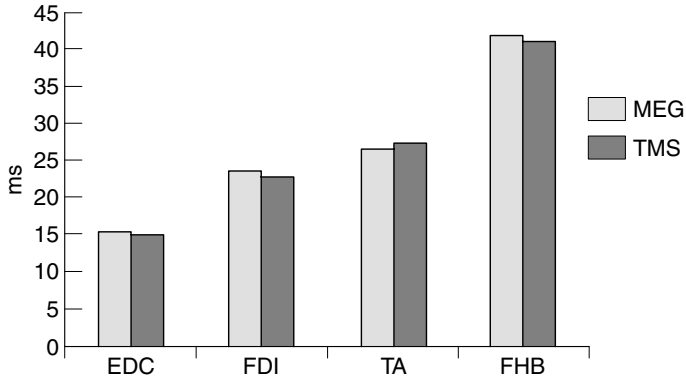

Fig. 12.9. Latencies calculated from cortico-muscular phase differences between MEG sources and EMG of the respective muscle (left column). The right column denotes the cortico-muscular conduction times determined by transcranial magnetic stimulation. (From Rothwell et al., 1991.)

electrode recordings from the GPi in dystonic patients revealed abnormally low spontaneous discharge rates of the pallidal neurons along with changes in the discharge characteristics from tonic to phasic discharge patterns (Lenz et al., 1999). The lower than normal firing rates in the GPi imply decreased inhibition of thalamic throughput to motor and premotor cortex.

The identification of the actual changes in firing rates and patterns along with the determination of increased synchronization between neurons, which is now possible with the use of multielectrodes, is of prime importance for disclosing the relevant aspects of the pathophysiology of the disease. They further provide the basis for a better understanding of the effects of deep brain stimulation (DBS) on these disordered neuronal states. DBS is assumed to act by desynchronizing and decreasing abnormal discharge rates thus counteracting the pathological discharge characteristics resulting from dopamine depletion.

What is presently unknown is the impact of DBS on neuronal discharge behaviour as it relates to the processing of motor but also limbic or complex loop information. Investigating the functional anatomy of these different basal ganglia loops in the monkey has shown that these segregated channels are funnelled through the basal ganglia via distinct microcircuitries. Accordingly, recordings in the human GPi or STN revealed that only a relatively small proportion of the neurons are motor related. Alterations in the discharge characteristics of the limbic and complex loop neurons will provide a more comprehensive picture of these complex relationships and hopefully allow a better understanding of the non-motor aspects of basal ganglia disorders.

Thalamic recordings

The thalamus is a major target for the treatment of tremor, but also for dystonia and pain (Hua et al., 2000). Thalamic recordings mainly in Vim show tremor related rhythmic burst activities possibly representing the neural drive for the motor network generating rhythmic motor output (Magnin et al., 2000). The thalamic oscillations are in part generated by the electrical properties of the neurons with the slow oscillatory tendency that is reinforced by the re-entry properties of the network connecting cortex and thalamus. Thalamic cells are barely activated by voluntary movements.

Recordings in the ventral caudal thalamus in dystonic patients showed large scale modifications of sensory maps with increased receptive fields of the somatosensory afferents showing extensive overlap and distortions of the somatotopic map (Hua et al., 2000). These changes are similar to those described in a monkey model where dystonia-like movements were induced by overuse of certain repetitive hand movements. Representations of the hand surface showed distinct remodelling in S1 with cutaneous receptive field extending across multiple digits and the whole hand, a somatotopic reorganization grossly different from the normal small distinct topographically ordered distribution (Byl et al., 1997). These alterations in thalamic somatotopic maps are particularly interesting with respect to receptive field enlargements in patients with amputations who show increases in the thalamic area from which stimulation evokes sensations in the stump area.

In conclusion, the microelectrode recordings are not only useful tools for improving the remaining inaccuracy of anatomical targeting but they provide new insights in the characteristic pathophysiological features. This information can solely be obtained by microphysiological exploration. For these reasons microphysiological recordings that are increasingly employed are relevant for new applications of DBS for the treatment of other disorders such as dystonia, bulimia and epilepsy.

Cortical recordings

Microelectrode recordings from the right and left superior, middle and inferior temporal gyri in conscious humans during open brain surgery for the treatment of epilepsy showed no significant differences between the right and left hemisphere with respect to neuronal responses to words and sentences (Creutzfeld et al., 1989a). All neurones in the superior temporal gyrus (STG) of both sides responded to various aspects of spoken language either by

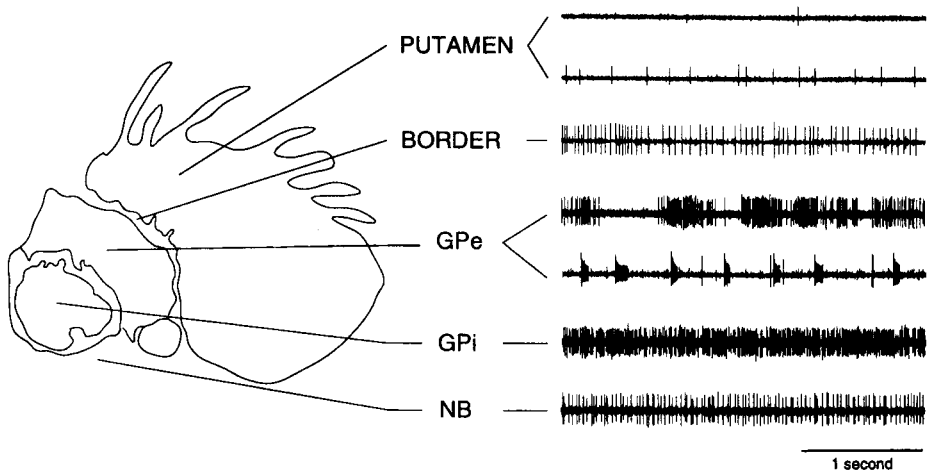

Fig. 12.10. Different patterns of neural activity encountered in the basal ganglia during a single penetration with the microelectrode. GPe: globus pallidus pars externa, GPi: globus pallidus pars interna, NB: nucleus basalis. (From Vitek et al., 1997.)

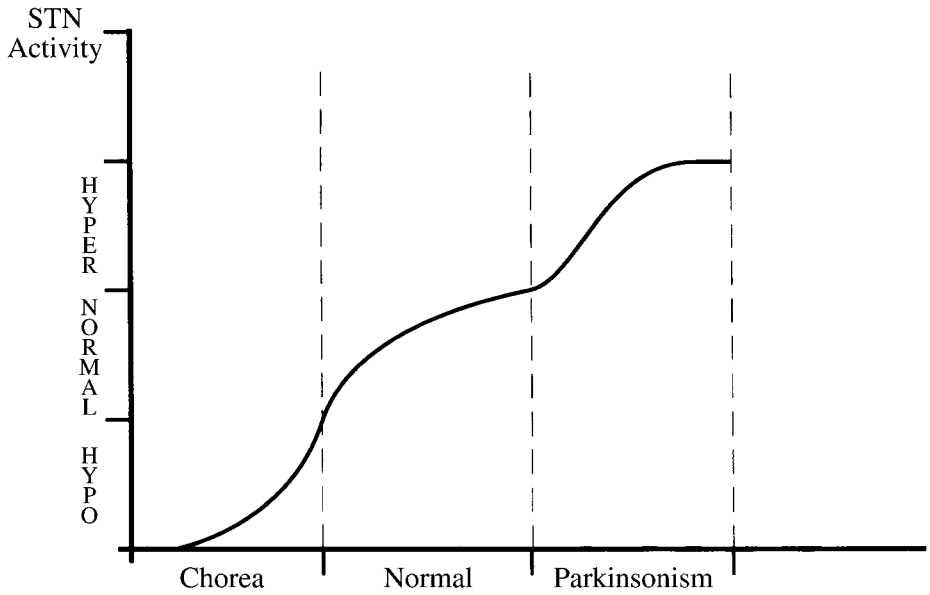

Fig. 12.11. Schematic explanation of how differences in the activity of the subthalamic nucleus (STN) modify the threshold for the appearance of chorea/ballism. In the parkinsonian state, STN activity is greatly augmented so that its lesion reduces basal ganglia output towards normal levels without necessarily reaching the threshold for dyskinesias. The normal state has a relatively wide range. Thus, a small focal lesion of the STN may not induce ballism. However, a large lesion will always be associated with ballism because it reduces the activity to well below the dyskinesia threshold. (From Guridi & Obeso, 1997.)

activation or inhibition without obvious changes in firing pattern or rate in response to non-linguistic acoustic input. Most neurones in the middle and inferior temporal gyri showed only minor modifications by listening to words or sentences.

Neuronal activity in response to the subject's own voice during overt naming or reading words or short sentences was also equally modified in the temporal lobes on both sides. Again, neurons in the STG responded clearly and in a characteristic manner (Creutzfeld et al., 1989b). These data demonstrate symmetrical language-related neuronal activity in both hemispheres of the adult brain. This opens

new perspectives for discussing concepts on asymmetries as known from clinical evidence and neuroimaging. The recordings are of particular interest with respect to the capacity of the minor hemisphere to take over language functions, as exemplified in children after left-sided hemispherectomies (Vargha-Khadem et al., 1997a).

In conclusion MEG and MEG/EEG combinations can identify event-related changes thus complementing fMRI and PET on a finer timescale. New developments overcame some previous limitations and now allow for reliable spatial localizations of multiple independent coherent sources. These maps can be compared with those established by fMRI and superimpose the fourth dimension of functional imaging, the high temporal resolution. For clinical neurology, MEG is a robust method for presurgical mapping, for the detection of epileptic foci and for the monitoring of postlesional plasticity. The examination of brain rhythms and coherences opens new inroads into the study of cortico-cortical and cortico-muscular coupling along with the determination of the respective conduction times. In contrast to the neurovascular methods they also provide information about this relationship in steady state conditions. Microelectrode recordings can assess regional pathophysiology in a unique way and help to understand how disturbed functions emerge and may be corrected.

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Part II

Disorders of higher functions

13

Congenital disorders of cerebral cortical development

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Developmental malformations of the cerebral cortex represent a heterogeneous group of disorders that are individually rare, but that collectively account for a large number of cases of epilepsy, mental retardation and other cognitive disorders. Though many of the disorders discussed in this chapter have been known for decades, our view of them has been revolutionized in recent years. Two recent major advances facilitated our understanding of these disorders. First is the use of non-invasive brain imaging techniques, particularly MRI, in clinical neurological practice (Osborn et al., 1988). This has enabled accurate diagnosis of disorders of cortical development, which had only been diagnosed by post mortem examinations in the past. Improved imaging techniques have also led to the recognition of new clinical entities and the recognition of mendelian inheritance of many cortical malformations. Second are the advances in molecular genetics, which have allowed identification of genes responsible for inherited diseases using methods of positional cloning (Walsh, 1999). Identification of genes responsible for cortical malformations has led to molecular diagnosis in many cases. Furthermore, genes identified as responsible for human disorders have provided us with important clues to understand the mechanisms of normal brain development.

With these advances in our knowledge, the traditional classification scheme of cortical malformations, which is solely based on morphological abnormalities, has been reassessed. Several attempts have recently been made to classify the disorders of cortical development, reflecting new insights into their pathogenesis. A classification based on the time that the derangement is presumed to have occurred has been proposed (van der Knaap & Valk, 1988). Another classification system devised by Barkovich et al., (1996) is based on a combination of embryology, genetics, imaging and pathology. Because our understanding of these disorders is still incomplete, any classification is somewhat provisional. In this chapter, the disorders are categorized according mainly to the disturbed developmental process. As our knowledge about their pathogenesis evolves, the classification systems will inevitably be modified and refined.

Normal development of the cerebral cortex

The neurons of the cerebral cortex are formed in the ventricular zone, which consists of a specialized proliferative region along the wall of the lateral ventricles. The postmitotic neurons then leave the ventricular zone and migrate over considerable distances to reach the cortex. The first postmitotic neurons to leave the ventricular zone form a pioneer layer called the primordial plexiform layer (Marín-Padilla, 1971). This layer is later split into an outer marginal zone and a deeper subplate layer by later arriving neurons, which form the cortical plate. The cortical plate subsequently increases its thickness as it is populated by arriving neurons. Neurons are added to the cortical plate in an 'inside-out' fashion so that newly arriving neurons always migrate past older cortical plate neurons until they arrest immediately underneath the marginal zone. Consequently, the deeper cortical layers contain neurons born earlier in gestation, while more superficial cortical layers contain neurons born later in gestation (Fig. 13.1). In the marginal zone, Cajal–Retzius cells secrete a large extracellular protein, Reelin, which appears to act as a 'stop signal' for migrating neurons (Dulabon et al., 2000). The long-range migration of cortical neurons is guided by long, radially aligned glial cells, termed radial glial cells (Rakic, 1971, 1972). These cells extend from the ventricular zone to the pial surface, and serve as a 'scaffold' for the migrating neurons (see Fig. 13.1, in colour plate section).

Recently, it became clear that a large fraction of cortical neurons, particularly inhibitory interneurons, actually

originate outside of the cortex itself (Anderson et al., 1997; Tamamaki et al., 1997; Lavdas et al., 1999). These neurons are generated in the ganglionic eminence, which gives rise to the basal ganglia, and then migrate into the developing cortex moving tangentially. This mode of migration is called 'tangential' migration in contrast to the classic 'radial' migration (Walsh & Cepko, 1992). Tangentially migrating neurons do not appear to be guided by radial glial fibres in their course from the ganglionic eminence to the cortex.

In human cortex, postmitotic neurons start to migrate out of the ventricular zone into the primordial plexiform layer between the sixth and seventh fetal week (Marín-Padilla, 1983). Initial formation of the cortical plate occurs from the seventh to tenth fetal week (Sidman & Rakic, 1973; Marín-Padilla, 1983). Migration of neurons into the cortical plate appears to peak between the eleventh and fifteenth week of gestation (Sidman & Rakic, 1973). A majority of neurons have entered the cortical plate by around the twenty-fourth week of gestation (Marín-Padilla, 1990), although it is not clear when migration is finally completed. Distal processes of the radial glia disappear between the fifth and seventh month of gestation (Marín-Padilla, 1970), suggesting that little or no glia-guided migration occurs after this stage. With this general background we will briefly review the major developmental disorders in the rough sequence in which they disrupt patterning, proliferation, specification, and later stages of cortical neuronal development.

Disorders of pattern formation in the forebrain

Holoprosencephaly

The left and right cerebral hemispheres derive from the prosencephalon, which represents the rostral end of the neural tube. Holoprosencephaly (HPE) is a malformation characterized by failure of the normal cleavage of the prosencephalon to form two cerebral hemispheres. HPE shows a wide spectrum of severity, and clinically is categorized into three subgroups, namely, alobar, semilobar and lobar types. Alobar HPE refers to cases with complete or almost complete lack of cleavage. A single ventricle in the midline is seen in these cases. In semilobar HPE, there is often cleavage in the posterior aspect of the hemispheres, but the anterior portion lacks a separation. Lobar HPE shows formation of an interhemispheric fissure in both posterior and anterior aspects, and only a mild degree of incomplete separation is seen. The prevalence of HPE has been estimated to be 5–12/100 000 live births (Croen et al., 1996; Rasmussen et al., 1996; Olsen et al., 1997), but this may underestimate the true incidence, as milder cases are increasingly recognized. Also, in one large series, HPE was found in 0.4 % of embryos (Matsunaga & Shiota, 1977).

The clinical manifestations of HPE cover a wide spectrum, reflecting the wide range of structural abnormalities. Microcephaly is the rule. Dysfunction of the hypothalamic–pituitary axis, including diabetes inspidus and growth hormone deficiency, can be seen. Children with alobar HPE have profound developmental delay, but even these children can often acquire new skills and interact with the environment, albeit slowly and in limited fashion (Barr & Cohen, 1999). Associated facial anomalies also vary widely. Alobar HPE can be accompanied by cyclopia, ethmocephaly (ocular hypotelorism with proboscis, which is a rudimentary nose-like structure), cebocephaly (ocular hypotelorism and a blind-ended, single-nostril nose) or a median cleft lip. In contrast, semilobar HPE or lobar HPE are often accompanied by milder facial phenotypes, including ocular hypotelorism, hypertelorism, a unilateral or bilateral cleft lip, or a single midline incisor (Cohen, 1989).

The etiology of HPE is complex, and both genetic and environmental factors seem to play a role. Approximately 20–40% of children with HPE have chromosome anomalies, with trisomy 13 being most common, followed by trisomy 18 (Kinsman et al., 2000). HPE can also be seen in association with various genetic syndromes, such as the Smith–Lemli–Opitz syndrome. These observations, as well as autosomal dominant inheritance in some families, strongly suggested genetic causes of HPE. A recent extensive search for causative genes has implicated at least 12 different loci in 11 chromosomes (Roessler & Muenke, 1998). So far, four genes have been identified as causative genes for HPE. The first one to be identified was the *Sonic Hedgehog* (*SHH*) gene on chromosome 7q36, which is homologous to the *Drosophila melanogaster* segment polarity gene *hedgehog* (Roessler et al., 1996). *SHH* is highly expressed in the ventral neural tube, and considered a critical molecule in dorsoventral patterning of the neural tube. *SIX3* (Wallis et al., 1999) and *ZIC2* (Brown et al., 1998), localized on chromosomes 2p21 and 13q32, respectively, are transcription factors that are implicated in forebrain development. More recently, a homeobox gene on chromosome 18p11.3, named *TGIF*, has been found to be mutated in HPE (Gripp et al., 2000). Cellular mechanisms by which mutations in these genes cause HPE are being studied intensely. Environmental factors also seem to be crucial in some cases, and maternal gestational diabetes has been associated with increased risk of HPE in the offspring (Martínez-Frías et al., 1998).

Disorders of cell fate, proliferation and specification

Microcephaly

Overview

Microcephaly is a condition in which the size of the cranial vault, measured by the occipito-frontal head circumference (OFC), is significantly smaller than the standard for the person's age and sex. OFC of less than 2 standard deviations below the mean is often used as a definition, although some researchers use other cut-off points such as 3 standard deviations. The etiology of microcephaly is extremely diverse, posing challenges to clinicians dealing with this condition, but can be broadly divided into environmental and genetic causes. Common environmental causes include congenital infection, intrauterine exposure to teratogenic agents, and hypoxic–ischemic injury. The clinical history usually provides important diagnostic clues in these cases. On the other hand, even the genetic causes of microcephaly are quite diverse (Table 13.1; Mochida & Walsh, 2001). For example, hereditary metabolic disorders, which cause neuronal degeneration, usually cause the postnatal onset of microcephaly (acquired microcephaly) and are not discussed here.

Genetic causes of microcephaly associated with microcephaly at birth (congenital microcephaly) frequently reflect developmental malformations of the cerebral cortex. For example, microcephaly is frequently seen in association with chromosomal abnormalities or other well-defined genetic syndromes (e.g. Smith–Lemli–Opitz syndrome). These disorders are not reviewed here. An overview of 'syndromal' microcephaly has also been provided by Opitz and Holt (1990). In these cases, the characteristic patterns of involvement of other organ systems and/or the presence of specific dysmorphic features often help make the diagnosis. Other well-characterized CNS disorders such as neuronal migration disorders (e.g. lissencephaly) can be associated with microcephaly without other organ involvement, and these conditions are described below. Finally, there are an increasing number of syndromes and genetic loci in which the central nervous system is typically the only affected organ system and in which the brain is characteristically quite small but the normal pattern is relatively well preserved ('isolated microcephaly'). The prototype of this group of disorders is microcephaly vera, which is discussed next. Other forms of isolated microcephaly are also briefly mentioned in the section.

Table 13.1. Genetic forms of microcephaly

I.	Isolated microcephaly
	A. Autosomal recessive microcephaly
	(i) Microcephaly vera
	(ii) Microcephaly with simplified gyral pattern
	B. Autosomal dominant microcephaly
	C. X-linked microcephaly
II.	Microcephaly associated with major brain malformations
	A. Holoprosencephaly
	B. Schizencephaly
	C. Lissencephaly
	D. Others
III.	Chromosomal disorders
	A. Down's syndrome and other trisomies
	B. Chromosome deletions/duplications
	C. Others
IV.	Microcephaly associated with genetic syndromes
	A. Smith–Lemli–Opitz syndrome
	B. Rubinstein–Taybi syndrome
	C. Angelman syndrome
	D. Rett syndrome
	E. Cornelia de Lange syndrome
	F. Others
V.	Microcephaly associated with hereditary metabolic disorders

Notes:
This table briefly summarizes genetic conditions associated with microcephaly. Only major disorders are listed in the categories II through IV, and the existence of additional syndromes that are not included is indicated by 'others'. The vast assortment of degenerative metabolic disorders associated with postnatal onset of microcephaly are described in other chapters and are not listed here.

Microcephaly vera

Introduction

This term, meaning 'true' microcephaly, was coined by Giacomini in 1885 to denote a condition in which no gross pathological abnormality other than smallness of the brain was observed (Friede, 1989a). When this term is used in a broader sense, it may include a wide variety of isolated microcephaly. Here we use a narrower definition, implying a subgroup of isolated microcephaly with certain clinical features described below.

Clinical features

Microcephaly vera is characterized by microcephaly at birth, relatively normal early motor milestones and mental retardation of variable severity. Usually, there are few

dysmorphic features, except narrow, sloping forehead and relative prominence of ears. Seizures are relatively uncommon. On imaging studies, there are little or no gross abnormalities of the brain architecture, except its smallness. Other subtypes of isolated microcephaly are often associated with different clinical manifestations (see below).

Pathology

Grossly, the gyral pattern is relatively well preserved despite the often striking smallness of the brain. Histopathological study of the brain may reveal no microscopic abnormality in cortical laminar formation (McCreary et al., 1996). In some cases, depletion of neurons in cortical layers II and III (i.e. later-born neurons), as well as early depletion of cells in the germinative zone near the ventricles have been observed (Evrard et al., 1989). This led to a hypothesis that premature exhaustion of neuronal progenitors in the ventricular zone might be responsible for microcephaly vera (Evrard et al., 1989).

Genetics

Microcephaly vera is often inherited as an autosomal recessive trait, and has recently become a subject of active linkage analysis. Microcephaly is frequently seen in geographical areas with high consanguinity rates, such as the Middle East (Farag et al., 1993). Recently, five genetic loci for autosomal recessive microcephaly have been mapped. These loci, termed *MCPH 1*, *2*, *3*, *4* and *5*, map to chromosomes 8p22-pter (Jackson et al., 1998), 19q13.1–13.2 (Roberts et al., 1999), 9q34 (Moynihan et al., 2000), 15q (Jamieson et al., 1999) and 1q25–32 (Jamieson et al., 2000; Pattison et al., 2000), respectively. The clinical presentation of the patients in pedigrees that map to these five distinct loci is similar enough to suggest that there will be significant genetic heterogeneity in autosomal recessive microcephaly.

Some cases of isolated microcephaly, however, are distinguished on the basis of imaging studies and clinical phenotypes. For example, there are patients who show an abnormally simplified gyral pattern, namely too few and often shallow sulci (Barkovich et al., 1998), and some of these cases are consistent with an autosomal recessive mode of inheritance(Peiffer et al., 1999; Sztriha et al., 1999). This group of patients tend to show more severe neurological signs and symptoms, such as spasticity, severe developmental delay and seizures. An autosomal dominant form of microcephaly has also been described, and is perhaps relatively common; however, this form is often associated with normal intelligence and may not come to clinicians' attention very often (Ramírez et al., 1983).

The assessment of recurrence risk of microcephaly is often challenging because of the heterogeneous nature of this condition. Unless the mode of inheritance is evident from family history and examination, accurate assessment may be difficult. In one population-based study in British Columbia, Canada, the recurrence risk of mental retardation in the siblings of microcephalic individuals was estimated to be 5.9%, one-third of whom also had microcephaly (Herbst & Baird, 1982). Another study estimated the recurrence risk of microcephaly in siblings of microcephalic individuals to be 19% (Tolmie et al., 1987), more suggestive of an autosomal recessive trait. This large difference may reflect differences in the percentage of autosomal recessive forms of microcephaly in each population studied.

Biological basis

Since no genes responsible for this condition have been found yet, the exact pathogenesis remains unclear. Although a decreased number of neurons in the cerebral cortex is considered to be primarily responsible for the smallness of the brain in microcephaly vera, there are many potential ways in which the number of cortical neurons can be subnormal. For example, decreased proliferation of neuronal progenitors, decreased production of mature neurons by each neuronal progenitor, or excessive cell death of neuronal progenitors or of mature neurons may all lead to an eventual decrease in the number of neurons. One or more of these mechanisms may be involved in the pathogenesis of microcephaly vera, but these mechanisms will not be clear until genes are identified.

Schizencephaly

Introduction

The term 'schizencephaly', originally coined by Yakovlev and Wadsworth in 1946, refers to a full-thickness cleft of the cerebral mantle (Yakovlev & Wadsworth, 1946a, b). The cleft extends from the pial surface to the lateral ventricle, and the walls of the cleft are usually lined by abnormal polymicrogyric cortex. Schizencephaly can be divided into two subtypes, namely, closed-lip type and open-lip type. When two walls, or lips, are in apposition, it is called closed-lip schizencephaly. On the other hand, in open-lip schizencephaly, the two walls are separated by a cerebrospinal fluid space (Fig. 13.2). Although the word schizencephaly has gained wide acceptance, the term 'porencephaly' is often favoured by pathologists in describing the same anatomical abnormality.

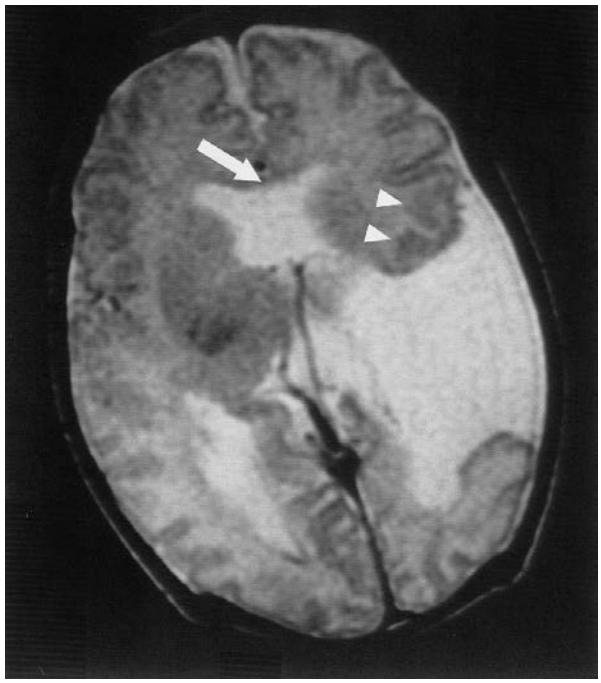

Fig. 13.2. Open-lip schizencephaly. Axial MRI shows a large schizencephalic cleft, which is lined by polymicrogyric cortex (arrowheads). Absence of the septum pellucidum is also noted (arrow).

Clinical features

The clinical presentation of patients with schizencephaly varies depending upon the type and extent of malformation, as well as the location of the cleft. The closed-lip type often presents with hemiparesis or seizures. The open-lip type can present with motor delay or seizures, but hydrocephalus may be the first presentation (Packard et al., 1997). In open-lip schizencephaly, sometimes large amounts of cerebral mantle, spanning more than one lobe, may be absent, and affected patients generally have poor neurodevelopmental outcome compared to the closed-lip variety. Seizures are commonly seen, and the seizure types can be either focal or generalized. Some cases may present with infantile spasms. Seizures can be refractory, but there are no good early predictors of seizures that are difficult to control.

Pathology

The walls, or lips, of the cleft are usually lined with polymicrogyric cortex (see Fig. 13.2). The areas of abnormal cortex may extend outside the cleft. Where the walls are in apposition, they form a so-called pia-ependymal seam. When followed from outer surface into the cleft, cells of the pia show transition to ependymal cells of the ventricular surface via this 'seam'. There are often other associated developmental abnormalities, such as absence of the septum pellucidum or focal cortical dysplasia.

Genetics

Schizencephaly is usually sporadic, but there have been case reports of recurrence in siblings, suggesting a possible genetic origin in at least some cases (Hosley et al., 1992; Hilburger et al., 1993; Haverkamp et al., 1995). In 1996, heterozygous mutations in a homeobox gene, *EMX2*, were reported in three patients with severe cases of schizencephaly (Brunelli et al., 1996). Subsequent reports described additional patients with mutations, including a family with two affected siblings (Faiella et al., 1997; Granata et al., 1997). These mutations were *de novo*, namely not present in the parents. At this point, it is not clear what proportion of patients with schizencephaly has mutations in *EMX2*. It is possible that there are other genes that can cause schizencephaly.

Biological basis

The role of *EMX2* in brain development is yet to be fully elucidated, but recent reports suggest it has a role in determining area identity in the neocortex. *EMX2* is expressed highly in caudal and medial areas of developing mouse neocortex, and in *EMX2* knockout mice, areas of neocortex with caudal and medial identity are found to be contracted (Bishop et al., 2000; Mallamaci et al., 2000). These mice, as well as heterozygous mutant mice, do not have a phenotype that resembles human schizencephaly.

There is also a strong argument for the presence of non-genetic causes of schizencephaly. Hypoxic–ischemic insult early in fetal life has been considered to be a strong possibility. Schizencephalic clefts are usually lined by polymicrogyric cortex, and this may argue for a common pathogenesis of schizencephaly and polymicrogyria. Since there is evidence suggesting hypoxic–ischemic injury as a cause of polymicrogyria in some cases (see below), it is conceivable that some cases of schizencephaly may be a result of a similar insult. This notion of shared pathogenesis between schizencephaly and polymicrogyria may further be supported by the observation that areas of cortical dysplasia in schizencephalic brains often appear to be polymicrogyria (Barkovich & Kjos, 1992c).

Focal cortical dysplasia

Introduction

Focal cortical dysplasia (FCD) refers to a localized area of disorganized cortex, which interrupts a morphologically

normal cortex. This concept was originally proposed by Taylor et al., (1971). They reported ten patients who underwent lobectomy for epilepsy and were found to have similar histopathologic features. Microscopic examination of the resected specimens showed 'localized disruption of the normal cortical lamination by an excess of large aberrant neurones scattered randomly through all but the first layer'. In most cases, 'grotesque cells, probably glial in origin, were also present in the depths of the affected cortex and in the subjacent white matter'. These bizarre cells are called 'balloon cells', and their origin is not clear.

Clinical features

Common clinical manifestations include seizures, focal neurological signs, and when the abnormality is extensive, developmental delay. FCD is a well-known cause of intractable epilepsy, and it is reported to be found in 15–40% of cases of extratemporal lobe resection (Wolf et al., 1993; Frater et al., 2000). MRI is useful in detecting FCD. Characteristic findings include blurring of the grey–white junction, widening of gyri, thickening of the cortical ribbon and increased T_2-weighted signal in subcortical white matter underlying the abnormal cortex (Yagishita et al., 1997; Chan et al., 1998; Lee et al., 1998). Detection of FCD by MRI frequently requires the use of specialized techniques and data reformatting (Barkovich et al., 1995; Grant et al., 1997). The term 'focal transmantle dysplasia' has recently been coined to describe a subtype of FCD, in which the area of dysplasia spans the entire thickness of the cerebral mantle (Barkovich et al., 1997).

Pathology

Histological changes in FCD include cortical laminar disorganization, neuronal cytomegaly (enlargement of the neuronal cell body), increased neurons in the molecular layer (layer I), heterotopic neurons in the white matter and balloon cell change (Mischel et al., 1995; Frater et al., 2000). Often two or more of these findings are seen in combination within a single lesion. The histological changes may be mild and, for example, limited to disorganization of cortical architecture, or marked with all of the features described in the original report by Taylor et al. The latter is sometimes called 'Taylor-type' FCD, and balloon cells are often considered its hallmark. These cells are typically located in the deep cortical layers or in the white matter underneath the abnormal cortex. They have a large cell body with glassy, eosinophilic cytoplasm and pleomorphic, eccentric nuclei. Immunohistochemical stains reveal variable staining with neuronal markers, glial markers or both (Vinters et al., 1992; Vital et al., 1994). In some cases, tumours, such as ganglioglioma or dysembryoplastic neuroepithelial tumour, may be found to coexist with an area of FCD (Prayson et al., 1993; Frater et al., 2000).

Genetics

FCD is usually encountered as a sporadic, non-inherited condition. Although one pedigree has been reported with apparently familial FCD, this is quite unusual (Muntaner et al., 1997).

Biological basis

The pathogenesis of FCD is not yet clear. However, it has been suggested that cell fate determination and differentiation are deranged in this condition. Balloon cells are known to express markers for neuronal and/or glial lineage, which may suggest failure of appropriate cell fate determination. Recently, altered staining patterns of proteins in the Wnt/Notch signalling pathway, which is important in neuronal cell fate determination and differentiation, was also reported, further suggesting abnormality in commitment of progenitor cells (Cotter et al., 1999).

The histopathological features of FCD show similarity to cortical tubers seen in tuberous sclerosis. Within the tubers, normal laminar structure is lost, and enlarged, dysmorphic neurons as well as 'giant cells' (or 'balloon cells') with abundant eosinophilic cytoplasm are seen. These giant cells variably express neuronal and glial markers (Hirose et al., 1995). These similarities have led to a debate whether FCD represents a 'forme fruste' of tuberous sclerosis, though this has not been settled yet (Andermann et al., 1987).

Disorders of neuronal migration

Classical lissencephaly

Overview

The term 'lissencephaly' derives from the Greek words '*lissos*', meaning 'smooth', and '*enkephalos*', meaning 'brain'. As the name implies, lissencephaly refers to a brain with a lack or severe paucity of normal gyri, and as a result, it appears smooth on the surface (Fig. 13.3). Related terms include 'agyria' and 'pachygyria'. Agyria refers to a complete lack of gyri, whereas pachygyria refers to a broadening of gyri. As many patients with lissencephaly have mixed agyric and pachygyric areas, some people prefer 'agyria/pachygyria'. Several clinical entities are associated with this type of malformation, including Miller–Dieker syndrome, isolated lissencephaly and double cortex/X-

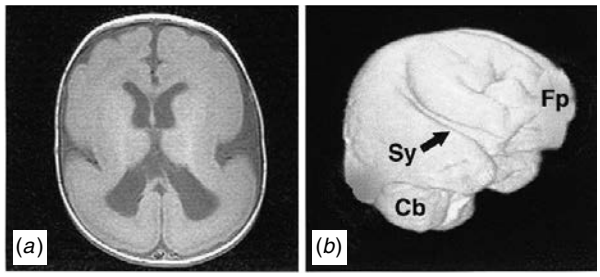

Fig. 13.3. Classical lissencephaly. Axial MRI image of classical lissencephaly (*a*) shows paucity of gyri and typical 'figure-eight' appearance. 3D-reconstruction of MRI images (*b*) illustrates lack of gyration, with posterior aspects of the brain being more severely affected, and a few rudimentary gyri remaining anteriorly. The sylvian fissure is exposed because of poor development of the operculum. Fp = frontal pole, Sy = sylvian fissure, Cb = cerebellum. (Courtesy of Dr P. Ellen Grant.)

linked lissencephaly syndrome. These disorders will be discussed below.

Miller–Dieker syndrome and isolated lissencephaly sequence

Introduction

The prototype of the disorders with classical lissencephaly is Miller–Dieker syndrome (MDS), which consists of classical lissencephaly and characteristic dysmorphic facial features. Even though the cases reported by Miller (1963) and Dieker et al., (1969) were familial, most cases of MDS are sporadic. Patients with classical lissencephaly, but without characteristic facial features of MDS, are classified as having isolated lissencephaly sequence (ILS) (Dobyns et al., 1984).

Clinical features

Essentially all children with classical lissencephaly have profound developmental delay. About half achieve essentially no developmental milestones, and the rest acquire some social and motor skills (Dobyns et al., 1993). The majority of the patients have seizures, which often start during the first 6 months of life (de Rijk-van Andel et al., 1990). Various seizure types are seen, but infantile spasms are common. Only a minority of patients are microcephalic at birth, but almost all fall within the microcephalic range during the first year of life due to a lack of normal brain growth (Dobyns et al., 1993). Patients with MDS have characteristic facial features, which include a prominent forehead, bitemporal narrowing, widely spaced eyes with upward slanting palpebral fissures, short nose with anteverted nares, thin vermilion border of the upper lip, and small chin (Jones et al., 1980; Dobyns et al., 1993). Some patients with MDS also have digital abnormalities (e.g. syndactyly), congenital heart disease and other visceral abnormalities (Jones et al., 1980; de Rijk-van Andel et al., 1990).

On imaging studies, the cerebral hemispheres have decreased convolutions. Often agyric areas coexist with pachygyric areas in a given patient. There is a lack of development of the frontal and parietal opercula, which leads to a characteristic 'figure-eight' shape of the brain on axial images. The lateral ventricles, particularly posterior aspects, are enlarged. Absence or hypoplasia of corpus callosum may be seen. Small midline calcifications in the region of the septum pellucidum may be present in patients with MDS (Dobyns et al., 1993).

Pathology

The cerebral cortex of classical lissencephaly is abnormally thick, and the ratio of grey to white matter is greatly increased. The cortex comprises four layers instead of the normal six layers (Crome, 1956). These four layers are (i) marginal layer, (ii) superficial cellular layer, (iii) sparsely cellular layer, and (iv) deep cellular layer. Whereas the cell-sparse subpial marginal layer corresponds to layer I of the normal cortex, the precise relationship of the three other lissencephalic layers to the five other normal cortical layers is not certain. In the brainstem, dysplastic inferior olivary nuclei with large heterotopias are characteristic (Kuchelmeister et al., 1993). On the other hand, the cerebellum in MDS is typically remarkably normal.

Genetics

Identification of patients with MDS and monosomy of chromosome 17p suggested that this locus might harbour a gene responsible for this condition (Dobyns et al., 1983). A decade later, the causative gene for MDS was found in this locus, and was named *LIS1* (Reiner et al., 1993). Subsequent analyses showed more than 90% of patients with MDS and approximately 40% of patients with ILS have deletions of the *LIS1* gene (Pilz et al., 1998). Point mutations of *LIS1* have also been identified among patients with ILS (Lo Nigro et al., 1997). As the deletions are generally larger in patients with MDS than those with ILS, it has been suggested that MDS may represent a contiguous gene syndrome, in which deletion of additional genes is responsible for the dysmorphic features of MDS (Dobyns et al., 1993).

Most of the mutations of *LIS1* that cause MDS and ILS seem to arise *de novo*. Therefore, if a deletion or a mutation of *LIS1* is found in a patient, the risk of recurrence in siblings is considered to be very low (Leventer et al., 2000). An

exception to this is when one of the parents harbours a balanced translocation involving the *LIS1* locus. In such a situation, the risk is considerably higher, with up to 33% of the offspring having an abnormal genotype (i.e. deletion or duplication of chromosome 17p) and/or phenotype (Pollin et al., 1999). Translocations involving chromosome 17p were later found in both families originally reported by Miller (1963) and Dieker et al., (1969), explaining recurrence in these families (Dobyns et al., 1984).

Biological basis

After identification as the causative gene for MDS, *LIS1* was found to encode a regulatory subunit of platelet activating factor acetylhydrolase, an enzyme which inactivates platelet activating factor (PAF) (Hattori et al., 1994). However, the role of PAF in neuronal migration has not been well established. It has been suggested that the LIS1 protein may regulate neuronal migration through pathways other than PAF. For example, LIS1 has been shown to associate with microtubules directly and to stabilize them (Sapir et al., 1997), and to interact with other protein components of the microtubule organizing center (Feng et al., 2000). As microtubules are important in cell motility, this function is probably pertinent to the control of neuronal migration.

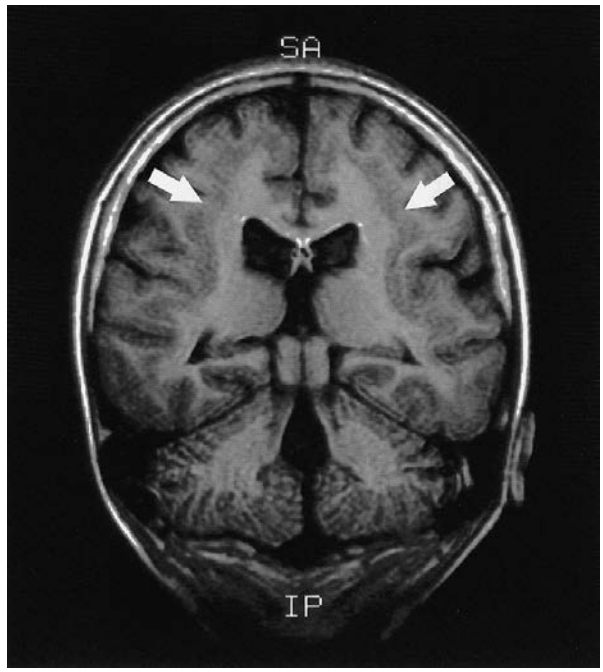

Fig. 13.4. Double cortex. Coronal MRI image shows a band of heterotopic grey matter (arrows) between the cortex and the lateral ventricles.

Double cortex/X-linked lissencephaly syndrome

Introduction

In this unusual condition, males and females are both clinically affected, but show very different disorders due to mutation in a common, X-linked gene. Males with mutation of the *doublecortin* (*DCX*) gene show classical lissencephaly that is generally similar to that seen in *LIS1* mutation. On the other hand, affected heterozygous females show a different malformation called 'double cortex' syndrome (DC; also known as 'subcortical band heterotopia' or 'laminar heterotopia'), where there is a band of heterotopic neurons in between the cortex and the lateral ventricles (Fig. 13.4). Even though DC has been known for many years from autopsy studies (Matell, 1893; Friede, 1989b), its recognition as an X-linked disorder, which causes lissencephaly in males, did not come until recently. In 1994, two families were reported, in which mothers with DC had sons with lissencephaly and daughters with DC (Pinard et al., 1994). This established the mode of inheritance, and also led to the recognition that there is a second genetic locus for classical lissencephaly.

Clinical features

The main clinical features of the affected females are epilepsy and mental retardation. Seizures often start during the first decade. Various seizure types have been documented, including generalized tonic–clonic, complex partial, myoclonic, atypical absence and atonic (Palmini et al., 1991; Barkovich et al., 1994; Gleeson et al., 2000a). Response to anticonvulsant therapy varies widely. Mental retardation is often mild to moderate. There is some suggestion that cognitive development may slow after the onset of seizures (Palmini et al., 1991). Imaging studies of the females usually show a symmetric, thick band of grey matter deep to the cortex (see Fig. 13.4; Barkovich et al., 1989). The overlying cortex often shows mild pachygyria (Barkovich et al., 1989; Palmini et al., 1991). On the other hand, the affected males show similar neurological manifestation as Miller–Dieker syndrome and isolated lissencephaly sequence, with profound developmental delay and epilepsy. Imaging findings of the males are also very similar to that of Miller–Dieker syndrome. However, the pattern of malformation is slightly different. In the X-linked lissencephaly (XLIS), anterior aspects of the brain tend to be more severely affected, in contrast to the lissencephaly due to *LIS1* mutations, where posterior aspects of the brain are almost always more severely affected (Pilz et al., 1998; Dobyns et al., 1999).

Pathology

Brains with DC show a symmetric band of grey matter between the cortex and the lateral ventricles. Microscopically, the overlying cortex shows a normal six-layered structure (Friede, 1989b). Heterotopic grey matter consists of coalescent clusters of unlaminated, well-differentiated neurons (Palmini et al., 1991). Males with XLIS show brain pathology similar to Miller–Dieker syndrome (Berg et al., 1998).

Genetics

Linkage analysis of familial cases and studies of a patient with lissencephaly and a translocation involving the X-chromosome localized the DC/XLIS locus in chromosome Xq22.3–q23 (des Portes et al., 1997; Ross et al., 1997). Subsequently, a novel gene in this region was cloned as the causative gene, and was named *doublecortin* (*DCX*) (des Portes et al., 1998; Gleeson et al., 1998). While most cases of DC or XLIS represent *de novo* mutations, families with multiple affected children can occur if the mother has subtle clinical signs or is a somatic mosaic for *DCX* mutation (Gleeson et al., 2000b). Mutation analysis of a large number of patients with DC revealed that there are patients who do not harbor a mutation in *DCX* gene (Gleeson et al., 2000a). This suggests that DC is a genetically heterogeneous disorder, and other genetic loci may be responsible for some cases of DC. Mutation analysis of patients with isolated lissencephaly sequence, who did not show deletion of *LIS1* locus detectable by fluorescence *in situ* hybridization, revealed mutations of *LIS1* gene in 40% of the cases and mutations of *DCX* gene in 20% (Pilz et al., 1998). Thus, these two genes are thought to be responsible for the majority of cases with isolated lissencephaly sequence.

Biological basis

Doublecortin is a protein that is specific to the developing nervous system, and that is widely expressed by migrating neurons (Francis et al., 1999; Gleeson et al., 1999). It has been shown to interact with microtubules, and to increase the stability of microtubules (Francis et al., 1999; Gleeson et al., 1999; Horesh et al., 1999), and the amino acid substitution mutations that cause DC/XLIS occur in the microtubule binding domain of the protein (Sapir et al., 2000; Taylor et al., 2000). It is interesting to note that two proteins that are associated with classical lissencephaly, LIS1 and Doublecortin, have been shown to interact with microtubules and possibly regulate them. This supports the hypothesis that regulation of microtubule dynamics is essential in neuronal migration, and that interruption of this process contributes to the pathogenesis of classical lissencephaly.

Lissencephaly with cerebellar hypoplasia

Lissencephaly with cerebellar hypoplasia is an autosomal recessive condition characterized by an abnormally thick and simplified gyral pattern of the cerebral cortex and hypoplasia of the cerebellum. Clinical features include hypotonia, severe developmental delay, seizures, and nystagmus (Hourihane et al., 1993; Al Shawan et al., 1996). Recently, mutations in the *RELN* gene were identified as a cause of this malformation (Hong et al., 2000). The protein product, Reelin, is a human homologue of a mouse protein, which was originally identified as the gene product that is mutated in the '*reeler*' mouse (D'Arcangelo et al., 1995). The anatomical abnormalities of the *reeler* mouse include disorganized lamination of the cerebral cortex, as well as severe hypoplasia of the cerebellum (de Rouvroit & Goffinet, 1998). Reelin is a protein secreted by Cajal–Retzius cells, which are early-born neurons that populate the embryonic marginal zone. Several molecules such as lipoprotein receptors (D'Arcangelo et al., 1999; Hiesberger et al., 1999; Trommsdorff et al., 1999), cadherin-related neuronal receptors (Senzaki et al., 1999) and $\alpha 3\beta 1$ integrin (Dulabon et al., 2000) have all been shown to act as potential receptors for Reelin. Although there is some evidence that Reelin functions in arresting migrating neurons at their proper cortical location (Dulabon et al., 2000), the precise molecular pathways through which Reelin regulates neuronal migration have not been completely elucidated.

Periventricular heterotopia

Introduction

Periventricular heterotopia (PH) is a malformation in which heterotopic nodules of grey matter are seen in the subependymal region (Fig. 13.5). Several familial cases of PH were recently reported, and this led to the recognition that this entity is genetic (DiMario et al., 1993; Kamuro & Tenokuchi, 1993; Huttenlocher et al., 1994). It was noted that typically only females were affected, and there was a high rate of miscarriages among affected females. These observations suggested that periventricular heterotopia was an X-linked disorder with prenatal lethality in affected males (Huttenlocher et al., 1994). It is now recognized that many of these cases reflect mutations of the X-linked gene, *FLN1*.

Clinical features

The most common presentation of PH in affected females is epilepsy. Common seizure types include generalized tonic–clonic and complex partial (Barkovich & Kjos, 1992a; Huttenlocher et al., 1994). Onset of the seizures is most

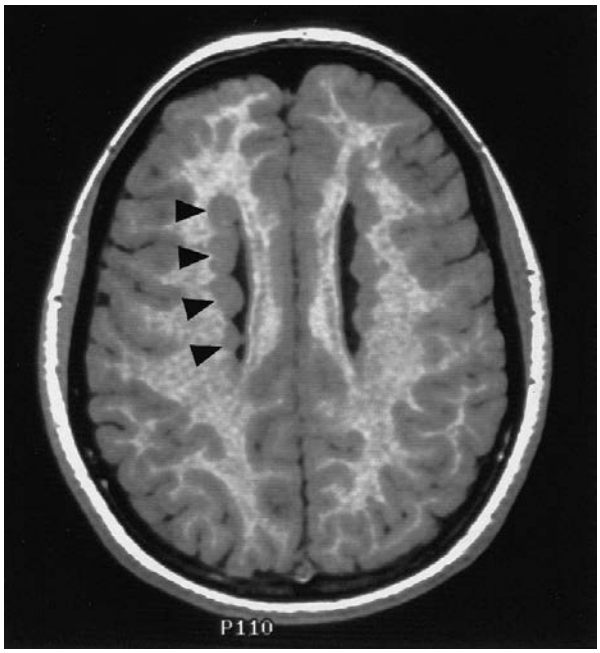

Fig. 13.5. Periventricular heterotopia. Axial MRI image shows nodular masses of grey matter (arrowheads) lining the wall of the lateral ventricles. Note that the nodules have the same signal characteristics as the normal grey matter.

commonly before the mid-20s, with an average of around 15 years (Ekşioğlu et al., 1996). Seizures may be infrequent and easily controlled, or intractable. Most individuals with PH have normal intelligence, and a minority have borderline mental retardation (Dobyns et al., 1996); 25% of affected patients may have no obvious neurological manifestations (Ekşioğlu et al., 1996). An increased incidence of patent ductus arteriosus and strokes at younger age has been reported (Fox et al., 1998).

MRI imaging characteristically shows nodular, subependymal masses, which are isointense with cortical grey matter in all imaging sequences (see Fig. 13.5; Barkovich & Kjos, 1992a). The heterotopic nodules are usually bilateral, though they may occur unilaterally. The overlying cortex is typically normal appearing. Enlargement of the cisterna magna, which may represent subtle cerebellar hypoplasia, is also common.

Pathology

The heterotopic grey matter lines the lateral ventricles as round nodules separated from each other by myelinated fibres. Microscopically, the nodules consist of highly differentiated neurons, which are haphazardly oriented (Ekşioğlu et al., 1996).

Genetics

PH may be familial or sporadic. Familial cases show X-linked dominant inheritance with presumed prenatal lethality in affected males. Most of the sporadic cases are also females, though sporadic male patients with a similar clinical presentation to females have been known (Huttenlocher et al., 1994; Dobyns et al., 1996).

Linkage analysis in familial cases identified the disease locus in chromosome Xq28 (Ekşioğlu et al., 1996). Subsequently, mutations in *FLN1* gene were identified as the cause of this disorder (Fox et al., 1998). Some of the sporadic cases have also been found to harbor mutations in *FLN1* (Fox et al., 1998).

Biological basis

The *FLN1* gene encodes Filamin 1, a large cytoplasmic actin-binding protein that is also known as actin binding protein 280 (ABP-280). It was originally identified as a high molecular weight protein isolated from macrophages that precipitated actin (Hartwig & Stossel, 1975). Subsequently, Filamin 1 was shown to be essential for migration in malignant melanoma cells (Cunningham et al., 1992) and macrophages (Stendahl et al., 1980) in vitro, but its role in neuronal migration was not suspected until it was identified as the causative gene in PH. *FLN1* gene is expressed by the cortical neurons during migration (Fox et al., 1998). It probably acts as a link between extracellular signals and the actin cytoskeleton, thereby controlling actin cross-linking, which is critical to the neuronal migration. Filamin 1 has been suggested to have roles in hemostasis and vascular remodelling, which may explain the high prevalence of strokes at young ages and patent ductus arteriosus in females, and the apparent prenatal lethality of affected males (Fox et al., 1998).

How the presence of heterotopic nodules leads to epilepsy is poorly understood. The heterotopic neurons were shown to form synapses, but the source of this innervation is unclear (Ekşioğlu et al., 1996). Knowledge of the functional connectivity of the heterotopic neurons will most likely help understand the pathogenesis of epilepsy in this disorder.

Disorders of the integrity of the pial surface

Cobblestone dysplasia

Introduction

Cobblestone dysplasia is characterized by disorganized cortical lamination and the proliferation of gliovascular

tissue, which contains ectopic neurons on the pial surface of the brain. This surface abnormality gives rise to a nodular appearance, therefore the term 'cobblestone dysplasia' is applied. It is also called 'type II lissencephaly' (in contrast to 'type I' or 'classical' lissencephaly) or 'cobblestone lissencephaly', because normal gyration is often absent and as a result, the brain appears smooth on its surface. However, cobblestone dysplasia often shows various abnormal gyral patterns, including agyria, pachygyria and polymicrogyria. Therefore, it is probably better to avoid applying the term lissencephaly in this condition, and the term cobblestone dysplasia has been developed to describe it more precisely.

Cobblestone dysplasia is seen in association with three human genetic disorders: Fukuyama-type congenital muscular dystrophy (FCMD), Walker–Warburg syndrome (WWS) and muscle–eye–brain disease (MEB). FCMD is primarily seen in Japan, and MEB is most commonly seen in Finland. WWS has been reported from various parts of the world.

Clinical features

Brain and muscle involvement is common to all three disorders, but the clinical features are more or less unique in each disorder. FCMD presents with early (before 8 or 9 months) hypotonia, generalized weakness (including facial muscles), mental retardation and occasional seizures, and the condition appears to be very slowly progressive (Fukuyama et al., 1981). WWS generally has a much more severe phenotype. Often, affected children present with severe hypotonia and lethargy during the neonatal period. Median survival for live-born infants in one study was 18 weeks, although some children survive beyond 5 years (Dobyns et al., 1989). Various forms of eye and retinal abnormalities are seen, including microphthalmia, coloboma, retinal dysplasia, retinal non-attachment/detachment (Pagon et al., 1983; Dobyns et al., 1989). Occipital encephalocele may be occasionally seen. The clinical features of MEB were reported by Santavuori et al., (1989). The patients often present during the neonatal period with hypotonia and weakness, and later develop spasticity and contracture to a various degrees. Mental retardation is severe. Eye abnormalities usually manifest as severe visual failure and myopia.

On imaging studies, cobblestone dysplasia usually appears as an agyric or pachygyric area. It should be noted, however, that even though the lesions may be described as agyria or pachygyria, these are entirely different from agyria and pachygyria seen in classical (type I) lissencephaly in histologic appearance. A thick outer layer of grey matter and a thinner, irregular inner layer may be distinguished (Barkovich, 1998). In FCMD, the frontal lobe typically shows polymicrogyria, and cobblestone dysplasia is limited to the temporo-occipital area (Barkovich, 1998; Aida, 1998). In WWS, abnormalities are more striking, coinciding with severe clinical manifestations. These include diffuse agyric or pachygyric cobblestone cortex, enlarged ventricles, hypoplasia of the pons and cerebellar vermis, and fusion of the superior and inferior colliculi (Barkovich, 1998; van der Knaap et al., 1997). Diffuse abnormality of the cerebral white matter signal is the rule in WWS, reflecting almost complete lack of myelination (van der Knaap et al., 1997; Barkovich, 1998). Imaging findings of MEB are similar to those of WWS, but usually less extensive, and the white matter abnormality is often patchy (van der Knaap et al., 1997; Valanne et al., 1994; Barkovich, 1998). Cerebellar polymicrogyria with or without small cysts may be seen in all three conditions.

Pathology

Pathological features of cobblestone dysplasia, that are common to all three disorders, include gliovascular proliferation near the surface and disorganized lamination with disoriented neurons (Takada et al., 1984; Williams et al., 1984; Dobyns et al., 1985; Haltia et al., 1997). The gliovascular tissue often obliterates the subarachnoid space, and may penetrate inward to separate the cortex into 'islands' of grey matter (Dobyns et al., 1985; Haltia et al., 1997). Although it is difficult to speculate about the pathogenesis of the cobblestone dysplasia from these findings, recent pathologic studies of fetal cases of FCMD (which presumably show the cobblestone dysplasia in evolution) have suggested that the basic defect may be abnormalities in the pial–glial barrier (the outermost surface of the brain composed of the pia, basement membrane and glial endfeet) (Takada et al., 1987; Nakano et al., 1996; Yamamoto et al., 1997). Overmigration of the neurons through 'breaches' in the pial–glial barrier into the subarachnoid space may be the fundamental pathogenetic mechanism for all three conditions. Muscle pathology in all three disorders is consistent with muscular dystrophy.

Genetics

FCMD, WWS and MEB are all inherited as autosomal recessive traits. FCMD was localized to chromosome 9q31 (Toda et al., 1993, 1994, 1996), and subsequently, the causative gene was cloned. This gene encodes futukin a novel secreted protein (Kobayashi et al., 1998). In 87% of the FCMD chromosomes, the mutation was the same insertion of retrotransposon sequence in the 3′ untranslated region, suggesting a Japanese founder mutation (Kobayashi et al., 1998). It has been suggested that this mutation only partly inhibits the function of the gene, whereas other reported mutations cause an even more

severe phenotype that can be prenatally lethal (Kondo-Iida et al., 1999). Thus, this single mutant allele is virtually solely responsible for the existence of FCMD. The biological function of fukutin in relation to the pial–glial barrier is not understood.

It has been debated whether these three conditions share the same genetic etiology, and this has been clarified recently. MEB has recently been shown to map to chromosome 1p32–p34 (Cormand et al., 1999), and hence is not allelic to FCMD. The locus for WWS has not been found, but a family with three siblings showing either FCMD or WWS phenotype has been reported (Toda et al., 1995). This might argue for genetic identity between these two disorders, though this still remains controversial.

Disorders of less certain pathogenetic mechanisms

Polymicrogyria

Introduction

Polymicrogyria refers to an area of the cortex with numerous small meandering gyri. It is heterogeneous both in clinical presentation and etiology. For example, as mentioned above, polymicrogyria can be seen in cobblestone dysplasia or schizencephaly. Traditionally, polymicrogyria has been regarded as a result of environmental insults, such as hypoxic–ischemic injury during fetal life or congenital infection, but recently genetic etiologies have been implicated in some cases.

Clinical features

The clinical presentation of polymicrogyria depends on the anatomical distribution and extent of the abnormality. Patients with bilateral, diffuse polymicrogyria often have severe developmental delay, seizures and hypotonia with subsequent development of spasticity (Barkovich & Kjos, 1992b). Patients with unilateral, focal polymicrogyria are more likely to present with less severe developmental delay, seizures and contralateral hemiplegia (Barkovich & Kjos, 1992b). On MRI imaging, polymicrogyric cortex appears as thickened cortex with shallow sulci, mimicking pachygyria. However, with high-resolution imaging, irregularity of the grey–white junction is usually apparent (Barkovich & Kuzniecky, 1996).

Pathology

Grossly, numerous small gyri are visible. However, because the molecular layers of the adjacent gyri often fuse, it may give an appearance of abnormally thick and broad gyri in low resolution MRI or even grossly (Friede, 1989b). There are two histological subtypes of polymicrogyria. One is called 'four-layered' type, and the other is called 'unlayered' type. Four-layered polymicrogyria consists of (i) molecular layer, (ii) outer cellular layer, (iii) cell-sparse layer, and (iv) inner cellular layer (Richman et al., 1974). Even though a four-layered lamination is also seen in classical lissencephaly, they are quite distinct entities. For example, the thickness of the cortex in polymicrogyria is much less than that of lissencephaly. In unlayered polymicrogyria, no cell-sparse layer is seen.

Genetics

Usually, polymicrogyria is encountered as a sporadic condition. However, genetic forms of polymicrogyria also appear to exist. For example, possible X-linked inheritance of a unique subtype of polymicrogyria called congenital bilateral perisylvian syndrome, in which polymicrogyria is seen in perisylvian region, has been documented in some cases (Guerreiro et al., 2000). Also, several reported patients with bilateral frontal or frontoparietal polymicrogyria were born to consanguineous parents, possibly suggesting autosomal recessive inheritance (Straussberg et al., 1996; Guerrini et al., 2000; Sztriha & Nork, 2000). Cases of polymicrogyria associated with chromosome 22q11 deletions have been reported as well (Cramer et al., 1996; Bingham et al., 1998).

Biological basis

There is convincing evidence that environmental insults such as hypoxic-ischemic injury to the developing cortex can lead to polymicrogyria. There are several cases with well-documented, dated prenatal insults leading to polymicrogyria. For example, a case of a child born with polymicrogyria after carbon monoxide poisoning of the mother during the 5th month of the pregnancy has been reported (Hallervorden, 1949). Richman et al., (1974) suggested that four-layered polymicrogyria resulted from post-mitotic laminar necrosis. They demonstrated by a detailed pathological analysis of a 27-week fetus with four-layered polymicrogyria that the cell-sparse layer corresponded to layer V of normal cortex, with normal topographical relationships retained in layers II, III, IV and VI. This finding was supported by a Golgi analysis of another case (Williams et al., 1976). On the other hand, animal models have produced four-layered polymicrogyria only when cortical injury was induced during the course of neuronal migration (Dvořák and Feit, 1977; Dvořák et al., 1978). Further studies are necessary to identify the relationship between the nature and the timing of injury and development of polymicrogyria.

Other types of intrauterine insults, in particular cytomegalovirus infection, have been associated with polymicrogyria. The pathogenetic mechanism of polymicrogyria in cases with cytomegalovirus infection is not clear.

Conclusions

With the combination of genetic and radiographic analysis, disorders of cerebral cortical development are increasingly coming into focus as a series of well-defined disorders. While their clinical features are often not distinctive, consisting of epilepsy and mental retardation, imaging studies are often distinctive, and give important keys to prognosis and recurrence risk. The near future promises clearer information and the broader application of DNA-based, as well as MRI-based, diagnosis.

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14

The aging brain: morphology, imaging and function

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Not too many years ago, the concept by both physicians and the general public was that your brain deteriorated as you got older. It was believed that, with aging, the brain shrank, there was significant drop out of nerve cells throughout the brain, and that once lost, those cells could not be replaced. In addition, at a subcellular level, data suggested that synaptic contacts markedly decreased. Moreover, it was thought that these changes began among individuals in young adulthood and progressed inexorably across the adult life span. As we will emphasize, among individuals who are optimally healthy these previously held concepts are wrong. The information that allows us to draw this conclusion is based on modern technologies for studying postmortem tissue, imaging the living brain, careful cognitive evaluations, and the innovative use of animal models.

Methodologic and technical issues

Focus on optimally healthy older individuals

One of the major changes to occur in the study of brain–behaviour relationships in aging is the focus on optimally healthy participants. This permits one to differentiate changes related to disease from those related to age. Among human subjects, this requires careful exclusion of subjects in the early stages of dementia. However, many medical diseases are common in older individuals (e.g. hypertension, respiratory or cardiac disease, vitamin deficiency), all of which may impair intellectual function. Ideally, if one wants to study healthy individuals, these disorders should be excluded as well. Subjects selected without evidence of clinical disease will differ greatly from a group of older persons that is chosen at random from a population, containing many individuals with serious medical illness. Some of these illnesses will include those with considerable impact on cognitive function, such as Alzheimer's disease (Odenheimer et al., 1994). Thus, optimally healthy individuals, although non-representative, can be of heuristic value, and may ultimately make it easier to identify interventions that can minimize age-related cognitive change.

Inter-individual differences and aging

In recent years, when researchers have focused their attention on animal models and human studies of aging, it has become clear that, even among optimally healthy subjects, there is considerable variability in both cognitive and physical abilities. Within a group of healthy older individuals, there are invariably individuals whose brain structure and function appears similar to that of persons many decades younger than themselves. Thus, the general statements about age-related changes in function apply to the changes for the average individual in the group, but cannot be said to apply to all individuals. For example, as shown in Fig. 14.1, the ability to recall information after reading a paragraph is better on average in younger subjects than in older ones; however, many older individuals perform just as well as their younger colleagues. The cause of this inter-individual difference is an area of intense interest, as it suggests that there may be ways of reducing change among a larger number of older persons.

Approaches to studying aging populations

In general, there are two approaches to the study of aging populations. The most commonly used, and certainly the easiest, is the cross-sectional approach. In this method, a group of younger people is compared to a group of older people at a particular point in time. The problem is that

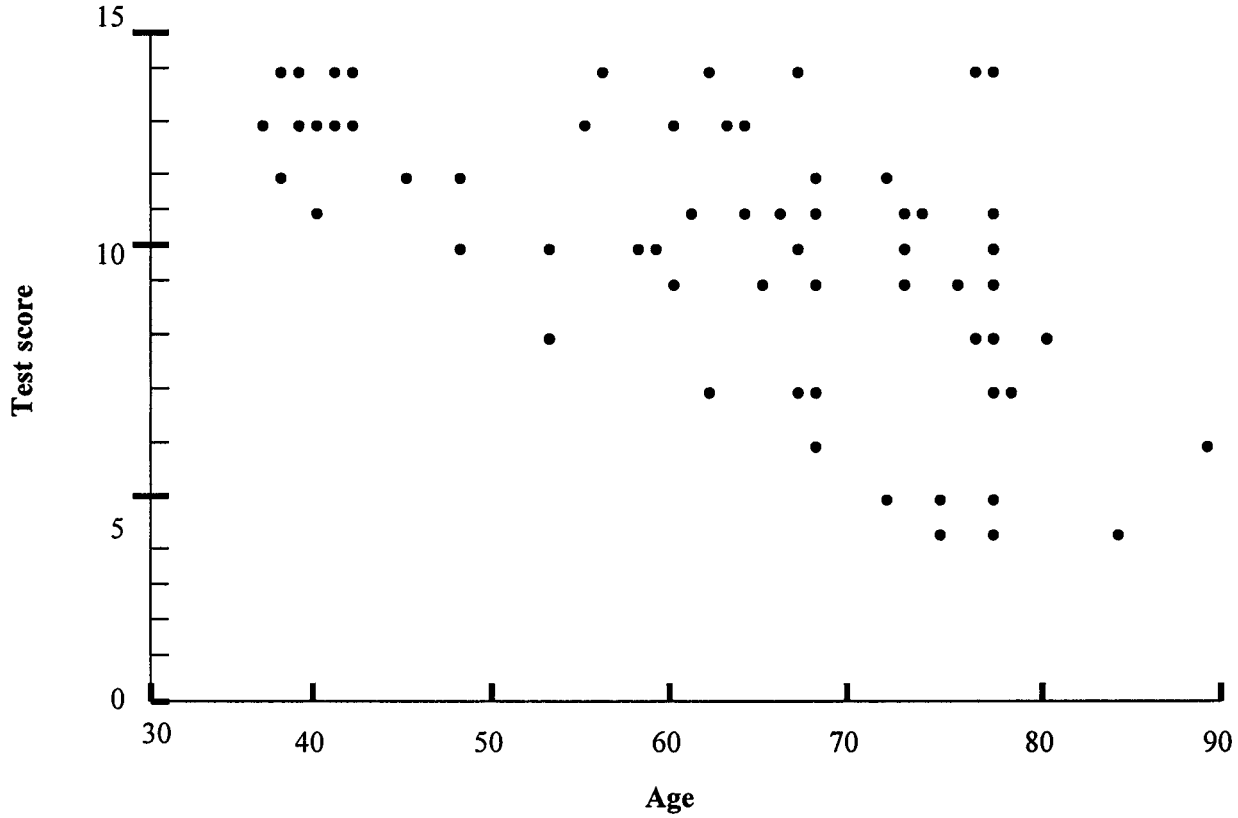

Fig. 14.1. Test scores by optimally healthy subjects 30–80 years of age on recall of a lengthy paragraph. Subjects were selected so that the level of education is not significantly different across the decades. Each dot represents the score of an individual subject.

humans born and raised at different time points have experienced different life events that can have long-term consequences on them. For example, individuals born in the 1920s to 1930s typically constitute the aging subjects in any current cross-sectional study of aging, and those born and raised in the 1970s to 1980s would constitute the sample of young adult subjects. During the 70+-year period from the 1920s, countless improvements in health care have taken place that have resulted in a dramatic change in the average human. For example, the improvements in prenatal care, postnatal care, nutrition and antibiotics have resulted in a population of young adults that not only are taller and heavier in body weight than their grandparents or great-grandparents but who also have bigger brains.

In addition, major worldwide events that have taken place at particular time points in history have had profound impacts on particular segments of a cohort. For example, large numbers of males were killed at relatively young ages by various wars. At the time of these wars, the screening process for determining who was potentially placed at greatest risk was not always socioeconomically or socioeducationally unbiased, suggesting that the remaining population of males, in particular, may have been biased by this selection process.

Longitudinal studies are designed to reduce these secular trends. While such studies must overcome the difficulties associated with the loss of subjects due to drop out, they nonetheless provide us with greater insights into the direct affects of age. Longitudinal studies have suggested that age-related declines occur slightly later in the life span than do cross-sectional ones. There is one area, as we will discuss, where longitudinal studies are essential, that is, the definition and establishment of predictive factors of change.

Postmortem examination of carefully screened subjects

Another change that has produced a dramatic revision of our concepts of brain aging derives from new techniques for the study of postmortem tissue. Postmortem examination of well-studied individuals represent the most long-standing method for establishing brain–behaviour relationships. The major technological advance pertains to

the development of non-biased stereological techniques, which permit investigators to accurately count neurons within a prescribed volume of tissue. It is this technological advance, combined with careful screening to assure that subjects with evidence of any relevant disease are excluded from examination, that has changed our concepts of the amount and nature of neuronal loss with advancing age, as described below.

Non-invasive imaging techniques

The advent of modern imaging techniques, beginning in about the mid-1970s, provided another major advance in the ability to study aging and structure–function relationships. For the first time it was possible to study the living brain. This was particularly advantageous for the study of aging, because it became possible to examine optimally healthy individuals and determine whether changes in the brain occurred in the absence of clinical disease and, if so, how this related to changes in cognition. These imaging techniques can loosely be divided into two basic types, structural scans and functional scans. The structural scans produce highly detailed images of the anatomical features of the brain. In fact, the images produced by the most advanced of these techniques look very similar in detail to that seen on postmortem examination of brain tissue. Examples of this type of structural scan include computerized tomography (CT) and magnetic resonance imaging (MRI). Functional scans, on the other hand, provide an indication of the activity of the brain, but do not tend to produce high anatomical detail. Examples of functional imaging scans include positron emission tomography (PET) and functional MRI (fMRI). When these functional methods are combined with structural scans, as is now commonly done, considerable localization of function is possible. Non-invasive imaging procedures have demonstrated that changes in the brain are, at least in part, responsible for age-related declines in cognition. However, a comprehensive explication of the reasons for these declines has not yet been provided by either the structural imaging procedures currently available, or by the initial functional methods that have been applied to this question, as will be discussed below.

Changes in brain structure and function with age

Neuronal studies

Neuronal number

Recent morphological data in humans (Haug, 1984; Leuba & Garey, 1989; Terry et al., 1987), indicate that, with advancing age, neuronal loss in the cortex is either not significant or not as extensive as reports prior to 1984 had suggested (Brody, 1955, 1970; Colon, 1972; Shefer, 1973; Henderson et al., 1980; Anderson et al., 1983). While large neurons appear to shrink, few are lost (Terry et al., 1987).

There are, in addition, comparable data in monkeys. Minimal neuronal cortical loss with age in monkeys has now been demonstrated in the striate cortex (Vincent et al., 1989), motor cortex (Tigges et al., 1992), frontal cortex (Peters et al., 1994), and the entorhinal cortex (Amaral, 1993). These general conclusions have been reached not only on the basis of a comparison of counts of neurons in young (5 to 6 years) and old (over 25 years of age) monkeys but also on the basis of an examination of the cortical tissue by electron microscopy (Peters et al., 1994). Beyond an accumulation of lipofuscin granules in the cell body of some neurons and some cellular debris in neuroglial cells, there is very little evidence of changes with age in the neurons of these cortical regions (Peters et al., 1991).

Given the intense interest in age-related changes in memory, it is important to emphasize that the weight of the evidence from postmortem studies supports the conclusion that the hippocampus also shows minimal structural change with advancing age. The postmortem data in humans and monkeys indicate that neuronal loss is surprisingly low in most subfields of the hippocampus. For example, the subiculum shows a significant age-related loss in humans, with a similar trend in monkeys, however, the CA1, CA2 and CA3 subfields of the hippocampus show no evidence of age-related neuronal loss (Amaral, 1993; Rosene, 1993; West et al., 1994; Gomez-Isla et al., 1996). Equivalent data have recently been reported in rodents, where it was shown that even in the subset of animals with declines on a memory task, there was no decrease in the number of neurons in the various hippocampal subfields (Rapp & Gallagher, 1996). (See Morrison & Hof, 1997, for a more detailed discussion of these issues.)

Neuronal loss and neurotransmitter changes

There is substantial neuronal loss in selected subcortical regions that is likely responsible for decreases in the production of neurotransmitters important for cognitive function, such as in the basal forebrain and the locus coeruleus (e.g. Chan-Palay & Asan, 1989; Rosene, 1993). For example, in humans and monkeys there is approximately a 50% neuronal loss with age in the basal forebrain and 35–40% loss in the locus coeruleus and dorsal raphe (Kemper, 1993). This compares with an approximate loss of 5% in the CA1 subfield of the hippocampus. The neuronal loss in these subcortical nuclei may be very important for memory function, as these brain regions influence the

production of several neurotransmitters important for memory (such as acetylcholine and serotonin). Though subcortical, these nuclei have extensive connections with the cortex, and thus are responsible for the level of many neurotransmitters within the cortex.

It should also be noted that there are alterations in at least one receptor type (i.e. NMDA receptors) within the hippocampus that play an important role in cognitive change, particularly in memory function (Gazzaley et al., 1996; Barnes et al., 1977).

Synaptic integrity

Even though there does not appear to be enough neuronal loss to account for age-related cognitive change, there could be changes in other aspects of neuronal function, specifically the number and/or function of synapses. Most of the studies that have explored this question with respect to aging pertain to learning and memory in rodents. Modern theories of memory mechanisms imply changing strengths of connections between neurons, based on activity-dependent synaptic plasticity in particular regions of the brain (Martin et al., 2000). It has been demonstrated that there are synaptic changes in the CA3 region of the hippocampus when one compares older rodents who are memory-impaired to younger rodents (Smith et al., 2000). Specifically, older rodents with spatial learning deficits display significant reductions in synaptophysin immunoreactivity in the CA3 region of the hippocampus, but not in other subfields. This region receives its input from layer II of the entorhinal cortex. Thus, it has been hypothesized that there are circuit-specific changes involving the entorhinal input to CA3 that influence the computational function of the hippocampus and are thereby related to age-related memory change (Smith et al., 2000). This hypothesis is consistent with electrophysiological alterations in aged rodents with learning deficits (Barnes et al., 1997; Tanila et al., 1977). Though comparable studies are not possible in humans, these results suggest that the variability seen in memory changes with advancing age among healthy individuals might be related to variations in synaptic integrity in specific brain circuits related to learning and memory.

Neuronal proliferation in the adult brain

One of the most strongly held dogmas of neurobiology was the concept that once nerve cells were formed they could only die. There was no such thing as endogenous neuronal replacement. There is increasing evidence that that concept is incorrect. The work of Altman over 30 years ago suggested that, in the rodent, neurogenesis could continue in selected regions of the brain into adulthood, particularly in the dentate region of the hippocampus, the olfactory system and cerebellum (Altman & Das, 1965). In recent years, this issue has been revisited in rodents and there is ample evidence, based on the DNA marker, bromodeoxyuridine, that neurogenesis occurs in the hippocampus and olfactory system. Similar findings have also been demonstrated in old world monkeys (Kornack & Rakic, 1999; Gould et al., 1999), and even in the human (Eriksson et al., 1998).

In the dentate gyrus of the macaque monkey, labelled cells are thought to proliferate in the border zone between the hilus and granular cell layer, and then to migrate and differentiate in the granule cell layer. The proliferation of new neurons decreases with age. In the rodent there appears to be a gradual increase in total numbers of neurons; in primates, such an accumulation is less certain. It has been suggested (Kornack & Rakic, 1999) that the number of neurons in the hippocampus is constant, but with a fixed replacement rate: neurogenesis balanced by the rate of apoptosis and cell removal. They even invoke the intriguing analogy of neurons being replaced 'like successive rows of shark teeth'.

The source of these new neurons may be pluripotential stem cells or neural progeniture cells. In the rodent it has been shown that physical activity stimulates this neurogenesis from stem cells (Kemperman et al., 2000). Investigators are exploring ways to cause these cells to produce new neurons. This is an active area of research in neuroregeneration.

White matter changes

In addition, age-related alterations in the white matter have recently been described in some detail (Peters et al., 1994; Peters, 1996; Neilson & Peters, 2000). At first glance, the data suggesting loss of white matter in the brain without a loss of grey matter can be difficult to understand. Conventional knowledge suggests that white matter consists of the axons of neurons and that if there is a loss of axons, there should be cell death and a loss of grey matter. However, the white matter of the brain is also composed of a number of glial elements, particularly oligodendrocytes. Evidence from the non-human primate suggests that the oligodendrocytes, that are responsible for forming the myelin sheath surrounding the axons, may be less efficient with age. For example, when the oligodendrocytes of old and young monkeys were compared (Peters, 1996) it was found that the myelin sheaths in the old monkeys were abnormal and appeared to be degenerating. However, when the number of axons in old and young monkeys was compared by the same investigators (Nielsen & Peters, 2000) relatively few degenerating axons were found in the

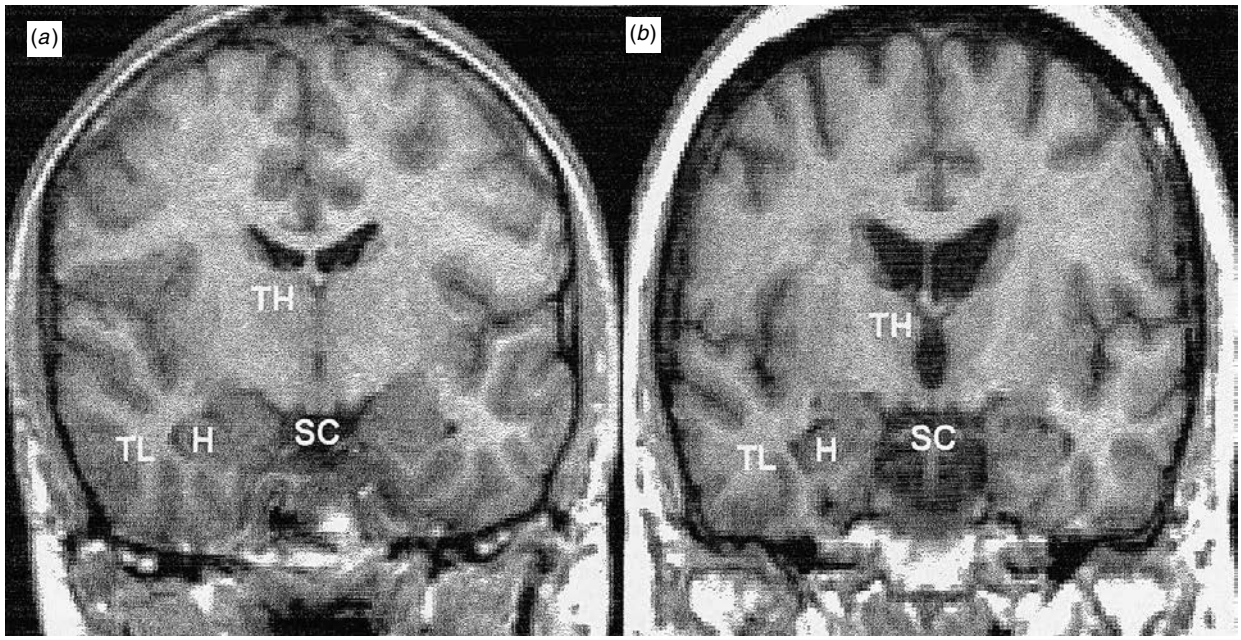

Fig. 14.2. An example of a structural MRI (*a*) in a healthy young and (*b*) healthy older individual. H = hippocampus, TH = thalamus, SC = suprasellar cistern

old monkeys. Taken together, these findings suggest changes in myelin, rather than axonal loss, are at least in part responsible for age-related changes in white matter observed with advancing age.

Imaging studies

Structural imaging

The first striking finding to emerge from computerized tomography (CT) studies of healthy adults across the age range was that there is clear evidence of decreases in the amount of brain tissue in older individuals compared with younger ones, i.e. atrophy. In general, CT studies have concluded that the average individual above 55 to 65 years of age demonstrates brain atrophy and increasing amounts of atrophy are seen as people get older. Thus, as people get older, the volume of CSF within the ventricles increases and the volume of brain tissue decreases (Roberts & Caird, 1976; Hughes & Gado, 1981; Barrow et al., 1976; Brinkman et al., 1981; de Leon et al., 1989; Gado et al., 1982, 1983; Huckman et al., 1975; Kaszniak et al., 1979; Stafford et al., 1988; Zatz et al., 1982).

CT studies conducted in the same individuals over time have demonstrated this phenomenon as well. Longitudinal evaluation over a 1-year period (Gado et al., 1983) and a 3-year period (e.g. de Leon et al., 1989) have demonstrated an approximate rate of atrophy of 2% per year among healthy older individuals over the age of 64. This rate of change is relatively low compared to the 9% rate of atrophy seen in the brains of patients with Alzheimer's disease (de Leon et al., 1989).

MRI studies of healthy adults across the age range have confirmed the findings described above for CT. That is, regardless of the sequence type, overall brain volume shows a decrease with age, while the amount of CSF increases, even if individuals are healthy (Christiansen et al., 1994; Coffey et al., 1992; Harris et al., 1994; Jernigan et al., 1990, 1991; Lim et al., 1992; Murphy et al., 1992; Matsumae et al., 1996; Pfefferbaum et al., 1994; Tanna et al., 1991).

Visual examination of an MRI image from a healthy young and older individual exemplifies some of the changes described above. Figure 14.2 shows an MRI image, taken at approximately the same anatomical level, in a healthy, young adult (see Fig. 14.2(*a*)) and a healthy, older adult (see Fig. 14.2(*b*)). As can be seen, the general shape and size of the bone around the brain is nearly equal in both subjects. However, the image on the right appears to have less tissue than the image on the left. The cavities within the brain that contain CSF are also larger in the older individual than in the young. The largest CSF spaces in the brain, the lateral and third ventricles, clearly appear

larger in the older person, but it is more difficult to determine visually whether the lower portion of the lateral ventricle (known as the 'inferior horn of the lateral ventricle') is enlarged. In addition, sulci on the cortical surface appear to be more spread apart in the older than in the younger subject. The space between the temporal lobes (i.e. the supracellar cistern, [SC]) also appears to be wider in the older person than the young.

However, the grey matter of the brain does not appear to be as changed as the CSF spaces. The ribbon of grey matter forming the outer surface of the cortex appears as thick in the older subject as it does in the young. The hippocampal formation (H) is of nearly equal size in the two subjects. The deep grey matter structures, such as the thalamus (TH), also appear to be of approximately equivalent size in the two individuals. Close inspection of the images suggests that the white matter of the brain may be changed in the older person. Overall, there appears to be less white matter in the older individual than in the young, however, this is difficult to assess convincingly with visual inspection.

Functional imaging

One of the most important innovations for the study of brain–behaviour relationships has been the development of functional imaging, using PET and fMRI. In PET scanning, a radioactive isotope is either injected or inhaled by the subject, and the scanning machine evaluates the differential decay of radioactivity in order to assess regional changes in blood flow in the brain. The blood flow is considered a surrogate for neuronal activity. Likewise, fMRI uses the magnetic qualities of water molecules to evaluate the differential distribution of oxygenated blood in the brain, and the ratio of oxygenated to deoxygenated blood is thought to be an indirect measure of neuronal activity.

To obtain information about how the brain performs cognitive tasks, these imaging techniques are combined with cognitive paradigms, which produce a range of brain activations. Through careful design of such paradigms, it becomes possible to obtain information about the brain regions that are involved in a specific cognitive activity. Perceptual and emotional experience can also be interrogated in a similar manner. When such functional imaging procedures are combined with structural imaging, one can obtain data with highly accurate anatomical detail.

Positron emission tomography

Most PET studies that have included older individuals have focused on the examination of memory changes with age. Due to the technological limitations of PET, these studies have generally focused on either the encoding or the retrieval phase of memory.

The most important general concept to emerge from such studies is that multiple brain regions are essential for encoding or retrieving new information. Moreover, some of the brain regions that appear to be integral to 'memory networks' have not been easy to evaluate by other imaging modalities. The most important in this regard is the frontal lobes, which are activated during both encoding and retrieval in normal young individuals (Kapur et al., 1994, 1996; Demb et al., 1995; Fletcher et al., 1995; Wagner et al., 1998a; Madden et al., 1999; Buckner et al., 1999).

The hippocampus, known to be essential for normal memory based primarily on lesion studies (Squire et al., 1988), is more difficult to activate than many other brain regions, for reasons that are not entirely clear. Nevertheless, many recent PET studies have shown that significant activations of the hippocampus may be demonstrated when an individual is attempting to learn or retrieve new information. The parahippocampal gyrus, a cortical region adjacent to the hippocampus, is also frequently activated in cognitive paradigms focused on explicit memory (Schacter & Wagner, 1999; Gabrielli et al., 1997; Brewer et al., 1998; Martin et al., 1997; Stern et al., 1996; Wagner et al., 1998a), as is the prefrontal cortex (e.g. Haxby et al., 1996; Wagner et al., 1998b).

The most consistent finding to emerge from PET studies of aging is that there are alterations in the activation of the frontal lobes during encoding and/or retrieval of new information, (e.g. Cabeza et al., 1997, 2000; Hazlett et al., 1998; Grady et al., 1999), although the specific nature of these age-related differences remains to be clarified. Some have found increased activity, while others have found decreases. However, the nature of the activation paradigms have differed considerably among these studies, no doubt contributing to the differential findings.

There has been even less agreement about age-related changes in the hippocampus. For example, a PET study in which young subjects demonstrated significant hippocampal and prefrontal activation during an encoding task failed to produce similar activations in the elderly (Grady et al., 1995). Conversely, a PET study that examined subjects during a recall task reported similar activations in the hippocampus and/or parahippocampal gyrus in both young and elderly subjects, but substantial differences between the age groups in other brain regions, particularly the frontal lobes (Schacter et al., 1996). Differences between the cognitive paradigms in the two studies, particularly in the degree to which the subjects learned the to-be-remembered material, are the most likely cause of these discrepancies.

Functional magnetic resonance imaging

Since fMRI does not involve exposure to radioactivity, and measurements are closer to real time, many investigators who previously employed PET are turning to fMRI. Though few such studies have been published, a number have been reported at meetings. They concur with the PET studies in finding altered prefrontal activity during encoding, mentioned above. Most of these fMRI studies have demonstrated decreased activation of the prefrontal lobe when older individuals are trying to learn new information (e.g. Sperling et al., 1999, Logan et al., 2002). It has been hypothesized that the differences in prefrontal activation between the young and the elderly subjects may reflect the fact that the two age groups use differing strategies to perform the task (e.g. Cabeza et al., 1997; Grady et al., 1999). This is consistent with numerous reports showing that elderly individuals are less likely to spontaneously use mnemonic strategies than the young, when trying to learn new information (for reviews see Craik, 1977; Arenberg & Robertson-Tchabo, 1977). An alternate possibility is that the same strategy is being applied in different ways by the two age groups.

Increased activation in the elderly compared with the young has also been demonstrated. For example, in tasks where the stimuli to-be-remembered are visual in nature, older individuals have shown greater activity than the young in the parietal cortex (one of the brain regions involved with spatial organization) (Bates et al., submitted; Sperling et al., 1999). This may also be a reflection of the differential deployment of cognitive strategies during the task, as mentioned above.

It should also be noted that some investigators have reported differences between the young and the elderly in hemodynamic response (D'Esposito et al., 1999; Ross et al., 1997; Taoka et al., 1998). While the nature of these changes is still controversial, ranging from the possibility of decreased hemodynamic response (and therefore signal change) in the elderly, to increased noise with no absolute reduction in the magnitude of signal change, it is clearly possible that these differences are, at least in part, responsible for some of the fMRI differences between healthy young and older individuals. It is, however, reasonable to hypothesize that, if such underlying hemodynamic changes exist, they might affect the ability to remember new information.

Domains of cognitive function

Although one could fractionate cognitive function into an almost unlimited number of components, most investigators in the field of neuropsychology view higher cortical function as composed of a relatively small number of major categories. For the purposes of this chapter, we will discuss changes in cognitive function with age within the following domains: (i) attention, (ii) memory, (iii) executive function, (iv) language, (v) visuospatial processing, and (vi) general intelligence.

Memory performance and aging

Workers in the field of memory have accepted the conclusion that memory is not a unitary phenomenon, and most models of memory function hypothesize that memory consists of a series of specific yet interactive stores (e.g. Waugh & Norman, 1965; Tulving, 1972). They include, at a minimum: sensory memory, primary memory, and secondary memory. In addition, a distinction has been made between information that is consciously learned (called explicit or declarative memory) and information that is acquired over time, unrelated to specific conscious effort of episodes (called implicit or procedural memory) (Reber & Squire, 1994).

Sensory memory

Sensory memory, also called registration, represents the earliest stage of information processing. It is modality specific (i.e. visual, auditory, tactile), highly unstable, and characterized by rapid decay.

Primary memory

The component of the memory system referred to as primary memory (or alternatively, immediate memory or short term memory) permits one to hold spans of auditory and/or visual information for relatively long periods of time by active rehearsal. The ability to concentrate on, rehearse, and recall a span of digits, words or visual features is perhaps the best example of this capacity. Any disruption to the rehearsal process results in the information being lost from immediate memory. Experiments by Petersen and Petersen (1959) have demonstrated that normal subjects forget a significant proportion of new information in less than 1 minute when distractions are present. The amount of information that immediate memory can store is limited to about five to seven items, as mentioned earlier. There is not complete consensus among neuropsychologists and memory researchers as to whether immediate memory should be considered a form of memory at all. Primary or immediate memory, as described here, may rely more on attentional skills. Thus, Spitz (1972), among others, has argued that digit span forward is actually a measure of attention rather than of memory.

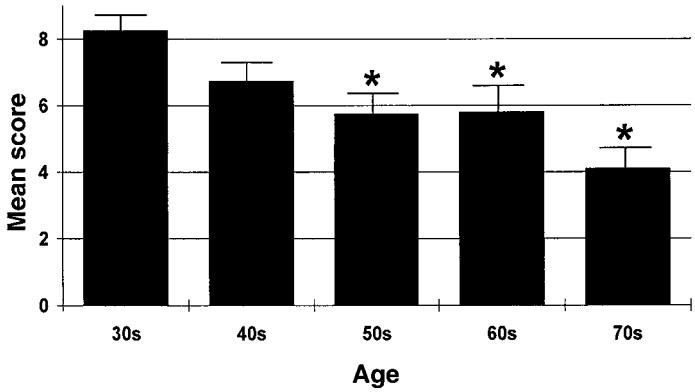

Fig. 14.3. Delayed recall performance of healthy subjects 30 to 80 years old. The subjects are asked to report what they remember of two lengthy paragraphs after a 15-minute delay.

Secondary memory

Secondary memory (also referred to as long-term memory) is involved when information must be retained over a long period of time. Thus, information from immediate memory must be assembled into multimodal units to be placed in storage. Storage of information by the memory system appears to take place differentially. As early as 1949, Hebb postulated that two processes were necessary for the brain to retain information. The first process, analogous to what we have termed primary memory, required the continual reverberation of a neural circuit. The second process, equivalent to secondary memory, required an actual structural change in the neural pattern of the central nervous system.

Sensory memory and age

There is considerable information to indicate that changes in explicit sensory memory are minimal with age. For example, the time necessary to identify a single letter does not change significantly between the late teens and early 70s. When seven-letter strings are used, the rate of letter identification increases with age by a factor of 1.3 (Cerella et al., 1982). These and other data indicate that there is a minimal decline in sensory memory with age (see Craik, 1977; for detailed review, see Poon, 1985).

Primary memory and age

Primary explicit memory also shows little decline with age. Most studies report no significant age differences in digit span forward (Drachman & Leavitt, 1972), no age differences in word span (Talland, 1967), and only moderate differences in letter span (Botwinick & Storandt, 1974). Older subjects show as much of a recency effect (i.e. retrieval of the last few items on a list in a word list learning task) as younger subjects (Raymond, 1971).

Secondary memory and age

However, there are substantial changes in explicit secondary memory, in contrast to the minimal age changes in sensory and primary memory (for a review, see Craik, 1977; Poon, 1985). The age at which changes in secondary memory occur depends upon the methods that are used to test the memory store. Difficult explicit memory tasks (e.g. delayed recall) demonstrate statistically significant differences by subjects in their 50s, in comparison to younger individuals (Albert et al., 1987a). Age decrements are greater on recall than recognition tasks. This is true whether words or pictures are used. Cueing during encoding or retrieval also alters the appearance of an age decline. Cueing at both encoding and retrieval produces the smallest age differences, whereas no cueing at either stage of the task maximizes age differences (Craik et al., 1987). However, even with cued recall and recognition, there are often declines. Rabinowitz (1986) reported a 33% age-related decrement in cued recall, and an 11% age-related decrement in recognition, when comparing young and old subjects (mean age 19 vs. 68).

Figure 14.3 shows the performance of subjects across the age range on delayed recall of two lengthy paragraphs. That is, each subject is read two lengthy paragraphs and, immediately after hearing each one, and then again after 20 min, the subject is asked to state what he/she can recall of the paragraphs.

A close examination of these data indicates that the older individuals are not more rapidly forgetting what they learned, but rather they are taking longer to learn the new information. For example, if one compares the difference between immediate and delayed recall over the lifespan, there are no statistically significant age differences (Petersen et al., 1992). Thus, if one allows older subjects to learn material well (i.e. to the point where few errors are made), they do not forget what they have learned more rapidly than the young (see Fig. 14.3). However, if older subjects are not given the ability to learn material to the same level of proficiency as younger individuals, after a delay, less information will be retained by the average older person.

However, there is considerable variability among older subjects on tasks of this sort. There are many healthy older subjects who have test scores that overlap those of subjects many years younger than themselves, e.g. about one-third of healthy 70-year-old humans have delayed recall scores that overlap those of 30-year-olds (equated for education).

Executive function

The complex set of abilities sometimes referred to as 'executive functions' include: concurrent manipulation of information (e.g. cognitive flexibility), concept formation and cue-directed behaviour. The wide variety of abilities that are sometimes included under the term 'executive function' is therefore striking.

Tests evaluating concept formation and set shifting uniformly show significant changes with age, primarily when subjects are in their late 60s or 70s. For example, the similarities subtest of the Wechsler Adult Intelligence Scale (WAIS), which asks subjects to identify how two objects (e.g. a table and a chair) are similar to each other, is the subtest on the Verbal scale of the WAIS that shows the greatest decline with age (Heaton et al., 1986). Education appears to be a modifier of this decline, in that subjects with lower amounts of education demonstrate declines at younger ages, however, all subjects in the oldest group (mean age 68 years), regardless of educational level, show significant declines in performance.

Series completion tests also show substantial age declines. These tests generally require the subject to examine a series of letters or numbers and determine the rule that governed the sequencing of the items in the series. Cross-sectional and longitudinal data demonstrate age-related declines on tasks of this sort (e.g. Lachman & Jelalian, 1984; Schaie, 1983).

Proverb interpretation tests, which require the subject to provide the general meaning of a proverb (e.g. 'barking dogs seldom bite'), also demonstrate age-related declines (Albert et al., 1990). This is true whether or not subjects are asked to provide the meaning of the proverb themselves or are given alternate choices among which to choose. Similarly, set shifting tasks, such as the visual–verbal test (in which subjects are asked to look at a series of cards and indicate how three of the four objects on each card are alike in one way, and then how three of the objects are alike in another way), also show substantial age-related declines. These changes appear to be related to the fact that older subjects have difficulty switching from one abstract answer to another (i.e. they tend to get the first item in the set correct but the second one wrong). Slowness in establishing mental set (i.e. getting the first item in the set wrong but the second one right) and failure to establish set (i.e. getting both items in the set wrong) did not increase differentially with age (Albert et al., 1990).

Visuospatial function

Visuospatial function is characterized by the ability to produce, and recognize figures and to form relationships among spatial locations. Specific visual functions include the ability to recognize familiar faces, the ability to copy or match objects or pictures, and the ability to translate spatial elements from one mode to another. Translation of mirror image spatial arrangements into self-oriented positions is an example of a task that requires intact and efficient visuospatial abilities.

Visuospatial ability therefore can be assessed by (i) constructional tasks, such as the assembly of blocks, sticks or puzzles; (ii) drawing tasks that involve copying; or (iii) matching tasks that require the subject to identify pictures with similar elements.

The most complex three-dimensional construction task in common use is the block design subtest of the WAIS. The subject is presented with a two-dimensional drawing in red and white of a target design, and a set of blocks (some sides of the blocks are all red, some are all white, and some are half red and half white). The subject is asked to arrange the blocks, which are, of course, three dimensional, so that they mimic the two-dimensional design. To receive credit, the subject must assemble the blocks correctly within a specified time limit. This task shows substantial declines with age (Doppelt & Wallace, 1955), perhaps because it is a timed task, and involves perception of three-dimensional space (see below) as well as a shifting and monitoring of behaviour.

Performance on figure drawing tasks is also affected by age. Older subjects are impaired, in comparison to the young, in depicting and perceiving three-dimensional drawings. Plude et al., (1986) asked a group of young and old adults (mean ages 21 and 67, respectively, and equated for static visual acuity) to draw a cube to command. The cubes were then rated by ten independent raters, with an interrater reliability of 0.98. The drawings of the young adults were rated as significantly better than those of the old. The older subjects were also less accurate than the young in judging the adequacy of drawings of cubes that were distorted to varying degrees. The elderly were less accurate than the young in discriminating between distorted and undistorted cubes. They were, however, equally able to copy a cube when landmarks were provided regarding the size of the lines. Comparable reports of the depiction and perception of two-dimensional drawings are not available.

Language

Linguistic ability is thought to encompass at least four domains: phonological, lexical, syntactic and semantic. It was previously assumed that linguistic ability is preserved into very old age, primarily because performance on the

vocabulary subtest of the WAIS, the best general estimate of verbal intelligence, is well maintained until individuals are in their 80s (Schaie, 1983). However, within the last decade, a number of studies have shown that some aspects of linguistic knowledge decline with age, although not until relatively late in the lifespan (i.e. >70).

Phonology

Phonologic knowledge refers to the use of the sounds of language and the rules for their combination. Phonologic capabilities are well preserved with age (Bayles & Kaszniak, 1987).

Lexicon

Psycholinguists distinguish between the lexical representation of a word, i.e. the name of an item, and its semantic representation, i.e. the meaning of a word (Clark & Clark, 1977). The lexicon of healthy older individuals appears to be intact, as are the semantic relationships of the lexicon.

Syntax

Syntactic knowledge refers to the ability to meaningfully combine words. A large number of studies have shown that age has little effect on syntax. Obler et al., (1985) found that syntactic forms that were difficult for older individuals were also difficult for younger ones.

Semantic knowledge

Older individuals appear to have difficulty with the semantic aspects of word retrieval. Several groups of investigators have reported that scores on a test of confrontation naming decrease with age (Borod et al., 1980; LaBarge et al., 1986; Albert et al., 1987b). However, declines in naming ability do not become statistically significant until subjects are in their 70s (Albert et al., 1987b). When subjects could not correctly name an item, the most common error they committed was semantic in nature, i.e. they produced semantically related associates, circumlocutions, and nominalizations. The nature of these semantic errors suggests that older individuals have a great deal of knowledge about the target word. For example, a semantically related associate ('dice' for 'dominoes') can only be produced if the subject apprehends the general category associated with the stimulus item.

Verbal fluency also assesses semantic ability. In a verbal fluency task a subject is asked to name as many examples of a category (e.g. animals or vegetables) as possible in specified period of time (e.g. 1 min) or as many words beginning with a particular letter (e.g. F) within a specified period of time. Several studies report a decline in verbal fluency with age (Obler et al., 1985; Albert et al., 1987b). These changes also occur relatively late in the life span (>70). Thus, semantic linguistic ability appears to change with advancing age, while other aspects of linguistic ability are relatively well preserved.

General intelligence

Although intelligence tests measure most of the abilities previously discussed, they do so in a complex way. Intelligence tests were designed to predict with a reasonable degree of certainty how a person would function in an academic environment, not to provide a complete assessment of cognitive function. Thus, intelligence tests do not assess all aspects of cognitive ability. For example, the Wechsler Adult Intelligence Scale does not include an evaluation of memory. In addition, IQ tests do not assess cognitive abilities in relative isolation from one another. Many of the tasks require a complex interaction of abilities and often depend upon speed for an adequate level of performance. Nevertheless, intelligence testing has been one of the most widely explored topics in the psychology of aging.

There is widespread agreement that there are changes in intelligence test performance with age. There has, however, been considerable debate about the point at which declines occur and the magnitude of the declines. The age at which declines are observed appears to depend upon the methodology employed. There is some consensus that relatively little decline in performance occurs prior to the time that people are in their 50s (Schaie & Labouvie-Vief, 1974). After this age, results differ depending upon whether cross-sectional or longitudinal testing designs were employed. The cross-sectional method shows declines of 1 SD or more beginning about age 60 (Doppelt & Wallace, 1955; Schaie, 1983), over the age of 70 scores drop sharply. The longitudinal method shows declines beginning in the late 60s. Both methods find substantial declines after individuals are in their mid-70s. Thus, the major difference between cross-sectional and longitudinal investigations is observed between subjects in their late 50s and early 60s. In this age range, the cross-sectional method shows greater age declines than the longitudinal method.

Summary

In summary, changes in cognitive function with age occur only in specific domains and in specific components of these domains, as indicated in Table 14.1.

Table 14.1. Cognitive changes with age

Domain	No change	Change	Age range
Memory			
sensory memory	*		
primary explicit memory	*		
secondary explicit memory		*	50s and over
Executive function		*	60s–70s
Visuospatial ability		*	60s and over
Language			
phonology	*		
lexicon	*		
syntax	*		
semantic knowledge		*	70s
General intelligence		*	60s–70s

Prediction of future cognitive status

Maintenance of cognitive function

As the aging population grows, there is increasing interest in maintaining cognitive function at its maximum. One of the major studies that sought to answer this question followed approximately 1000 participants who were 70 to 80 when the study began. These individuals had been selected because they fell within the top third of the population in terms of both physical and mental function (Berkman et al., 1993). Over time (i.e. 5–10 years), some of these individuals maintained their high level of cognitive performance and others declined. Thus, it was possible to determine what behaviours differentiated these two groups. Those who maintained cognitive function had higher levels of education, physical activity, lung function, and feelings of self-efficacy (Albert et al., 1995). It is hypothesized that each of these four variables directly influence the status of the brain and thereby, cumulatively, influence maintenance of cognition.

Prediction of decline in cognitive function

The concern of many older people, when they are unable to find their car keys or blank on attempting to recall a name, is that they have the first indication of a serious and progressive problem with memory. Thus, the ability to predict who has the expected cognitive changes with age, and who may go on to Alzheimer's disease or some other dementing process, it of utmost importance. Studies to answer this question have also employed a longitudinal approach, using data from baseline to predict subsequent outcomes. This baseline information has included cognitive performance, imaging and genetics (Albert et al., 2001a). Some of these studies compare those without significant memory complaints with those with mild memory complaints. Over time, some in each category may progress or 'convert' to the clinical symptoms of dementia. Predictions are based on comparing the baseline characteristics of the Converters with the non-Converters and with those who continue to have memory problems but do not have evidence of dementia. The cognitive measures that are predictive of conversion are tests of memory and executive function (Albert et al., 2001b). The imaging measures that are useful in this regard include volumetric measures of the entorhinal cortex, the anterior cingulate, and the hippocampus (Killiany et al., 2000), and perfusion measures of hippocampal-amygdaloid complex, the posterior cingulate and related structures (Johnson et al., 1998).

Another approach has been to compare individuals with a genetic risk for AD, based on their apolipoprotein E status (see Chapter 17), and to examine cognitive and imaging differences among them. These studies have not followed individuals to the point where a substantial number have converted to AD, however, they have demonstrated imaging differences, particularly using PET scanning, in posterior cingulate and superior parietal regions (Small et al., 1995; Reiman et al., 1996).

Based on these preliminary observations, it is likely that predictive paradigms for who will and who will not convert to dementia will be developed and validated. Such paradigms will be useful not only clinically, but in the design of intervention studies.

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15

Neurodegenerative diseases

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Twenty-five years ago, there was little understanding of the causes of neurodegeneration. In fact, the term degenerative disease was used as a wastebasket for illnesses of unknown etiology. But progress over the past quarter of a century in research focused on degenerative disorders of the central nervous system (CNS) has been impressive. It is now clear that neurodegenerative diseases are caused by the misprocessing of proteins. In each disease, one or more specific proteins have been identified that are misprocessed; this results in the accumulation of one or more particular proteins.

The proteins that accumulate in the CNS of patients with neurodegenerative diseases were initially identified by purifying these polypeptides from the brains of animals or humans with these diseases (Glenner & Wong, 1984; Masters et al., 1985; Prusiner et al., 1982). Subsequently, molecular genetics was used to identify the genes responsible for the familial forms of Alzheimer's and Parkinson's diseases as well as amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Similarly, molecular genetic investigations of Huntington's disease (HD) and the spinocerebellar ataxias have led to the identification of the genes responsible for the pathogenesis of these illnesses.

Of all the studies on neurodegenerative diseases, the discovery of prions has been most unexpected. The finding that a protein can act as an infectious pathogen and cause degeneration of the CNS was unprecedented (Prusiner, 1998b). The prion concept was so novel that achieving acceptance required a long and arduous battle (Prusiner, 1999). The prion concept not only explained how a disease can be both infectious and genetic, but it has also created new disease paradigms and revolutionized thinking in biology.

Although progress in the study of neurodegeneration has been impressive, there are still no curative treatments. Only for patients with Parkinson's disease is there a palliative drug with reasonable efficacy (Cotzias et al., 1967). L-dopa and related drugs do not stop the underlying degeneration, which often renders patients refractory to pharmacologic treatment in the later stages of Parkinson's disease (Marsden & Parkes, 1977). Stereotactic surgery has produced limited success in ameliorating the symptoms of Parkinson's disease when L-dopa becomes ineffective. Transplantation of cells secreting dopamine into the brains of patients with advanced Parkinson's disease is the subject of much research. It is noteworthy that many patients with Parkinson's disease develop dementia in the later stages of this disorder.

This chapter is not intended as an exhaustive review of neurodegenerative diseases and as such the bibliography is regrettably limited. Rather, it is an attempt to view the many common features of these degenerative illnesses from the perspective of the prion diseases (Prusiner, 1984). Progress in deciphering the etiologies of many neurodegenerative diseases has greatly strengthened the unifying concepts presented here. Based on the common features of these maladies, I suggest a new definition for the neurodegenerative diseases.

Aging and neurodegeneration

Age is the single most important risk factor for degenerative diseases of the CNS (Holman et al., 1996; Kawas & Katzman, 1999; Lilienfield, 1993). Many, but not all, cases of neurodegenerative diseases are sporadic in that no heritable, toxic, or infectious etiology can be discerned. These disorders are often characterized by a chronic, progressive deterioration of the CNS lasting from several months to more than a decade. Although the disease process is relentless, the immune system seems to remain quiescent.

Table 15.1. Epidemiology of neurodegenerative diseases[a]

Disease	Number of US patients	US prevalence per 100 000[b]
Prion diseases	400	0.1
Alzheimer's disease	4 000 000	1200
Parkinson's disease	1 000 000	300
FTD	40 000	14
Pick's disease	5000	2
PSP	15 000	5
ALS	20 000	7
Huntington's disease	30 000	10
Spinocerebellar ataxias	12 000	4

Notes:

[a] Abbreviations: FTD = frontotemporal dementia, PSP = progressive supranuclear palsy, ALS = amyotrophic lateral sclerosis.

[b] Population of United States is approximately 275 million in the year 2000.

Table 15.2. Sporadic, genetic and infectious etiologies of neurodegenerative diseases

	Etiologic frequency (%)		
Disease	Sporadic	Genetic	Infectious
Prion diseases	85	>10	<1
Alzheimer's disease	90	10	
Parkinson disease	95	<5	
FTD	90	10	
Pick's disease	95	<5	
PSP	95	<5	
ALS	90	10	
Huntington's disease		100	
Spinocerebellar ataxias		100	

Patients are afebrile and exhibit neither leukocytosis in blood nor pleocytosis in the cerebrospinal fluid (CSF).

While a complete compendium of neurodegenerative diseases is quite long, a brief list composed of the more common disorders and a few less common maladies, which have been particularly amenable to investigation, are discussed here (Table 15.1). Alzheimer's and Parkinson's diseases are the most common neurodegenerative diseases. Over four million people suffer from Alzheimer's disease (AD) in the United States and another million have Parkinson's disease (Kawas & Katzman, 1999; Lilienfield, 1993; Tanner & Goldman, 1996). Far less common are ALS, FTD, prion diseases, Huntington's disease and spinocerebellar ataxias. The vast majority of the first five neurodegenerative diseases are sporadic with 10% or less of cases being inherited (Table 15.2). In contrast, virtually all cases of Huntington's disease and the spinocerebellar ataxias are inherited disorders.

Because people are living longer, there is now considerable concern about the increasing numbers of individuals who are developing Alzheimer's and Parkinson's diseases. At age 60, the risk of developing AD is approximately 1 in 10 000 but by age 85 the risk is greater than 1 in 3 (Evans et al., 1989). Such statistics argue that, by the year 2025, more than 10 million people will suffer from AD in the United States and by the year 2050, the number of afflicted individuals will approach 20 million (Kawas & Katzman, 1999). Just as staggering as the number of people with AD is the cost of caring for these patients. It is estimated that AD currently costs the United States as much as $200 billion annually for the care of these people as well as in lost productivity of both the patients and caregivers.

Like Alzheimer's disease, age is the most important risk factor for Parkinson's disease. By age 85, nearly 50% of people exhibit at least one symptom or sign of Parkinsonism (Bennett et al., 1996).

Prions

Prions are infectious proteins. In mammals, prions reproduce by recruiting the normal, cellular isoform of the prion protein (PrP^{C}) and stimulating its conversion into the disease-causing isoform (PrP^{Sc}).

A major feature that distinguishes prions from viruses is the finding that both PrP isoforms are encoded by a chromosomal gene (Prusiner, 1998b). In humans, the PrP gene is designated *PRNP* and is located on the short arm of chromosome 20. Limited proteolysis of PrP^{Sc} produces a smaller, protease-resistant molecule of ~142 amino acids, designated PrP 27–30; under the same conditions, PrP^{C} is completely hydrolyzed (Fig. 15.1). In the presence of detergent, PrP 27–30 polymerizes into amyloid (McKinley et al., 1991). Prion amyloid formed by limited proteolysis and detergent extraction is indistinguishable from the filaments that aggregate to form PrP amyloid plaques in the CNS. Both the rods and the PrP amyloid filaments found in brain tissue exhibit similar ultrastructural morphology and green-gold birefringence after staining with Congo red dye.

PrP^{C} is rich in α-helix and has little β-sheet while PrP^{Sc} has less α-helix and a high β-sheet content. Comparisons

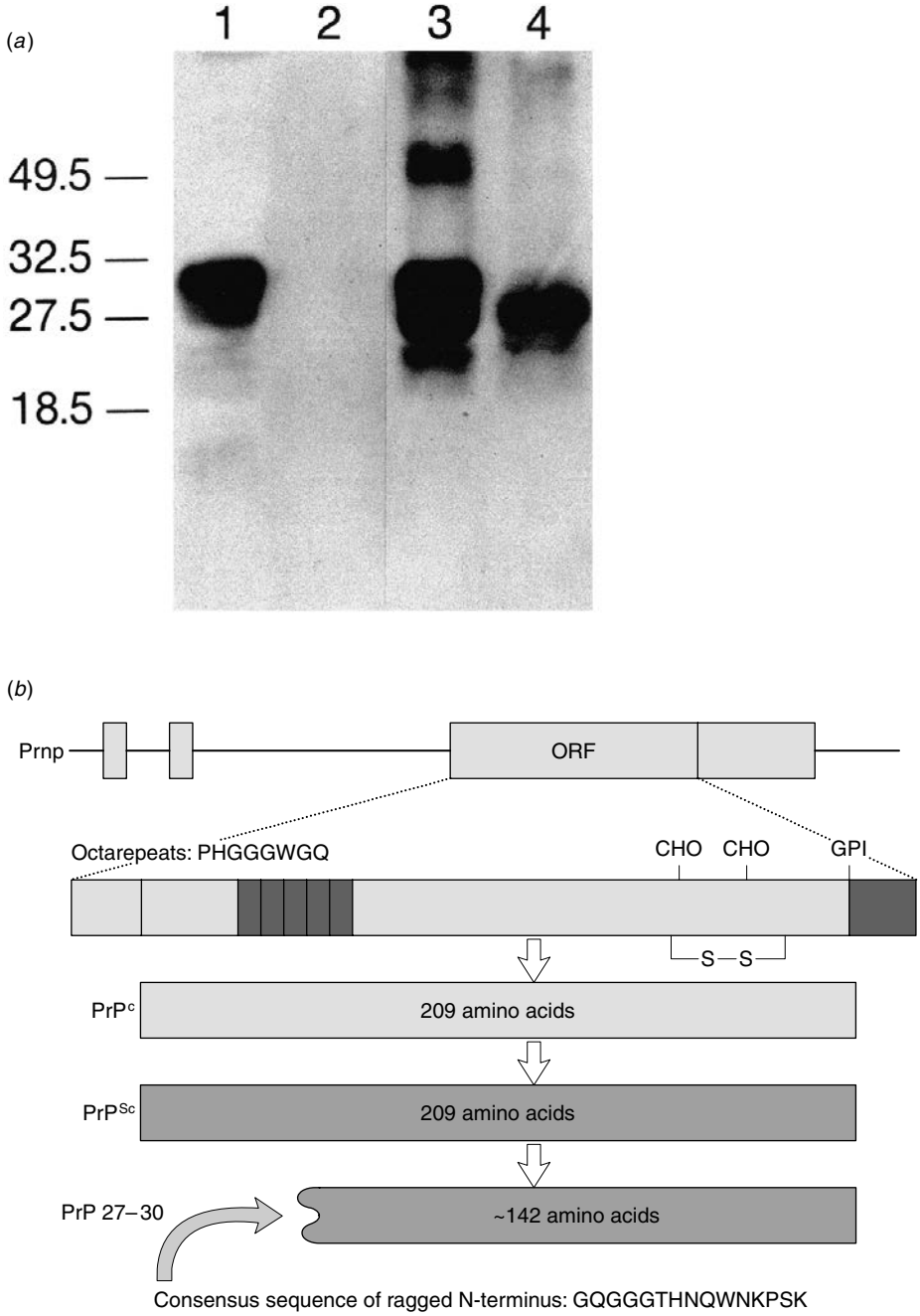


Fig. 15.1. Prion protein isoforms. (*a*) Western immunoblot of brain homogenates from uninfected (lanes 1 and 2) and prion-infected (lanes 3 and 4) Syrian hamsters (SHa). Samples in lanes 2 and 4 were digested with 50 μg/ml of proteinase K for 30 min at 37 °C. PrP^{C} in lanes 2 and 4 was completely hydrolyzed under these conditions whereas approximately 67 amino acids were digested from the NH_2-terminus of PrP^{Sc} to generate PrP 27–30. After polyacrylamide gel electrophoresis (PAGE) and electrotransfer, the blot was developed with anti-SHaPrP R073 polyclonal rabbit antiserum (Serban et al. 1990). Molecular size markers are in kilodaltons (kDa). (*b*) Bar diagram of SHaPrP gene which encodes a protein of 254 amino acids. After processing of the NH_2- and COOH- termini, both PrP^{C} and PrP^{Sc} consist of 209 residues. After limited proteolysis, the NH_2-terminus of PrP^{Sc} is truncated to form PrP 27–30 that is composed of approximately 142 amino acids, the N-terminal sequence of which was determined by Edman degradation.

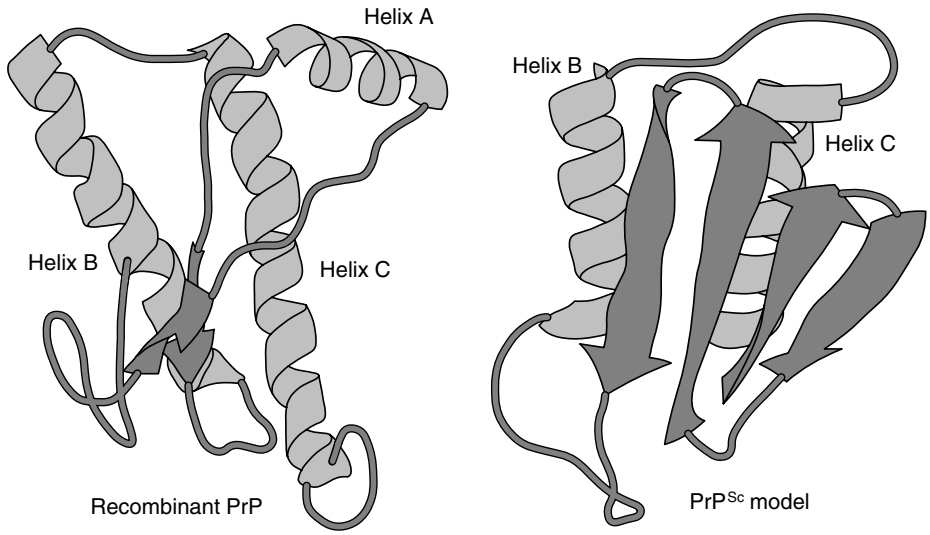


Fig. 15.2. Structures of prion protein isoforms. (*a*) NMR structure of Syrian hamster (SHa) recombinant (rec) PrP(90–231). Presumably, the structure of the α-helical form of recPrP(90–231) resembles that of PrP^{C}. recPrP(90–231) is viewed from the interface where PrP^{Sc} is thought to bind to PrP^{C}. α-helices A (residues 144–157), B (172–193), and C (200–227) residues 129–134 encompassing strand S1 and residues 159–165 in strand S2; the arrows span residues 129–131 and 161–163, as these show a closer resemblance to β-sheet. (*b*) Plausible model for the tertiary structure of human PrP^{Sc}. S1 β-strands are residues 108–113 and 116–122 in red; S2 β-strands are residues 128–135 and 138–144; α-helices B (residues 178–191) and C (residues 202–218). (Illustrations prepared by Fred E. Cohen.)

of secondary structures of PrP^{C} and PrP^{Sc} were performed on the proteins purified from Syrian hamster (SHa) brains (Pan et al., 1993). Based on these data, structural models for PrP^{C} and PrP^{Sc} were proposed (Huang et al., 1995). Subsequently, solution NMR structures of recombinant SHa and mouse PrPs produced in bacteria showed that it is likely that PrP^{C} has three α-helices and not four as predicted by molecular modelling (Fig. 15.2) (Liu et al., 1999; Riek et al., 1996). The computational model of PrP^{Sc} is supported by studies with recombinant antibody fragments, which have been used to map the surfaces of PrP^{C} and PrP^{Sc} (Peretz et al., 1997). This α- to-β transition in PrP structure is the fundamental event underlying prion diseases, which are disorders of protein conformation.

Much has been learned about the basic biology of prions using yeast in which two different proteins, unrelated to PrP, form prions (Sparrer et al., 2000; Wickner, 1994).

Four new concepts

Four new concepts have emerged from studies of prions. First, prions are the only known example of infectious pathogens that are devoid of nucleic acid. All other infectious agents possess genomes composed of either RNA or DNA that direct the synthesis of their progeny. Secondly, prion diseases may be manifest as infectious, genetic, and sporadic disorders. No other group of illnesses with a single etiology presents with such a wide spectrum of clinical manifestations. Thirdly, prion diseases result from the accumulation of PrP^{Sc}, the conformation of which differs substantially from that of its precursor PrP^{C}. Fourthly, PrP^{Sc} can exist in a variety of different conformations, each of which seems to indicate a specific disease phenotype. How a specific conformation of a PrP^{Sc} molecule is imparted to PrP^{C} during prion replication to produce nascent PrP^{Sc} with the same conformation is unknown. Additionally, it is unclear what factors determine where in the CNS a particular PrP^{Sc} molecule will be deposited, which results in neurologic dysfunction.

Common themes define neurodegeneration

With the recognition that a common feature of all well studied neurodegenerative diseases is the misprocessing of proteins, it is reasonable to propose a new definition of neurodegenerative disease based on this unifying etiologic characteristic. I suggest the following: 'neurodegenerative diseases are progressive nervous system disorders

of protein processing. Aberrant protein processing includes misfolding, altered post-translational modification, aberrant proteolytic cleavage, anomalous gene splicing, improper expression, and diminished clearance. The misprocessed proteins often accumulate because the cellular mechanisms for removing these proteins are ineffective. Neurodegenerative diseases typically present as sporadic and genetic maladies of delayed onset, but can also be infectious illnesses with prolonged incubation times. The particular protein that undergoes misprocessing determines the disease-specific phenotype, which results from the malfunction of distinct sets of neurons.'

In the past, degenerative diseases of the CNS have often been defined as idiopathic disorders accompanied by mental deterioration. Neuropathologically, they have been defined in terms of region-specific retrogressive changes in cells resulting in impaired function. Such pathologic changes have also been equated with the death of specific neuronal populations (Martin, 1999).

The broad spectrum of presenting clinical deficits in the prion diseases illustrates how ineffective a clinical classification scheme can be; these diseases can present with dementia, ataxia, insomnia, paraplegia, paresthesias and deviant behaviour (Will et al., 1999a). While none of the clinical presentations of prion diseases are diagnostic, patients who present with a rapidly progressive dementia accompanied by myoclonus often have Creutzfeldt–Jakob disease (CJD). The spectrum of neuropathologic changes in prion diseases ranges from none to widespread atrophy, from rare to frequent neuronal loss, from sparse to severe vacuolation or spongiform change, from mild to intense reactive astrocytic gliosis, and from none to abundant PrP amyloid plaques (DeArmond & Prusiner, 1997). None of these neuropathologic changes except the presence of PrP amyloid plaques is unequivocally diagnostic. Past attempts to classify and characterize other neurodegenerative diseases (Table 15.1) based on the clinical presentations or neuropathologic manifestations have been equally unsatisfying.

The discovery of amyloid in brain fractions enriched for prion infectivity was completely unexpected (Prusiner et al., 1983). The amyloid plaques in prion diseases and AD as well as large intracellular structures such as Lewy and Pick bodies were not considered to be of etiologic importance. Once anti-PrP 27–30 antibodies were raised, the amyloid plaques in prion diseases were found to stain readily (Bendheim et al., 1984; DeArmond et al., 1985).

It seems likely that the mechanisms, by which misprocessed proteins disrupt cellular functions such as signal transduction and gene transcription, are diverse. The secondary responses to misprocessed proteins may amplify the damage done by these macromolecules by activation of cytokine release, reactive gliosis, apoptosis, and oxidative injury (Cotman et al., 1999; Markesbery & Ehmann, 1999). In some neurodegenerative diseases, the misprocessed proteins might cause CNS dysfunction when they are monomers or oligomers while in other disorders, larger aggregates may prove to be the culprits (Chiti et al., 1999). In the case of PrP^{Sc}, the protein accumulates and fragments sometimes polymerize to form amyloid fibrils that are deposited in the extracellular space as plaques. With α-synuclein, tau and mutant huntingtin proteins, ubiquitinated deposits are found as Lewy bodies, Pick bodies and nuclear aggregates, respectively (Table 15.3). As discussed below, the aggregates may not cause cellular dysfunction but simply represent the attempt of cells to sequester these misprocessed proteins in a form that is less deleterious. Finding ubiquitinated deposits of α-synuclein, tau and mutant huntingtin argues that these proteins were destined for clearance but the process was incomplete. The covalent attachment of ubiquitin, which is a 76-residue polypeptide, to particular proteins targets them for degradation (Hershko & Ciechanover, 1998).

In sporadic cases, which account for more than 85% of all human prion disease (Table 15.2), the prion concept explains how wild-type (wt) PrP^{C} is progressively con-

Table 15.3. Protein deposition in neurodegenerative diseases

Disease	Protein	Aggregate
Prion diseases	PrP^{Sc}	PrP amyloid
Alzheimer's disease	Aβ tau	Aβ amyloid PHF in NFT[a]
Parkinson disease	α-synuclein	Lewy bodies
FTD	tau	straight filaments and PHF
Pick's disease	tau	Pick bodies
PSP	tau	straight filaments in NFT
ALS	neurofilament	neuronal aggregates
Huntington's disease	huntingtin	nuclear inclusions
Spinocerebellar ataxia 1	ataxin 1	nuclear inclusions
Spinocerebellar ataxia 2	ataxin 2	cytoplasmic inclusions
Machado–Joseph disease	ataxin 3	nuclear inclusions

[a] PHF, paired helical filaments; NFT, neurofibrillary tangles.

verted into PrP^{Sc}. Although the mechanism of prion replication is unclear, the stimulation of this process by PrP^{Sc} provides the driving force for the misfolding of PrP^{C} into PrP^{Sc}. No similar formulation exists to explain the progressive deterioration of the nervous system that follows the misprocessing of proteins in sporadic cases of AD, FTD, Parkinson's disease, and ALS. For example, factors driving the accumulation of the Aβ peptide in the CNS of people destined to develop sporadic AD are unknown except for the allelic variants of ApoE. Likewise, factors driving the accumulation of the α-synuclein to form Lewy bodies within the neurons of the substantia nigra of people destined to develop sporadic Parkinson's disease are unknown.

In the inherited neurodegenerative diseases, the same problem attends in the sense that these diseases are usually of late onset even though the mutations are present from conception. With few exceptions, the inherited neurodegenerative diseases are autosomal dominant disorders so the mutations are unlikely to produce disease through loss of function. Instead, such dominant mutations are likely to act as gain of dysfunction or as dominant negatives. Even though the mutant protein is expressed in the CNS early in life, no damage is detected clinically for decades in the inherited cases of AD, Parkinson's disease, FTD, ALS, and the prion diseases. Only in the triplet repeat diseases, such as HD, do children manifest neurologic disease when the repeat expansions become very large.

How the aging process features in these diseases is unclear. Is the misprocessing of a particular protein simply a stochastic process, which happens with a much higher probability when it is mutated? In such a model, prolonged periods of time are required for either the mutant or wt protein to be misprocessed into a disease-causing form. But perhaps, the milieu of the aging brain provides a more permissive environment for the misprocessing of proteins. The accumulation of proteins modified by oxidation has been suggested as a possible factor in virtually every degenerative disease (Markesbery & Ehmann, 1999). Clearance of misprocessed proteins may diminish with age and thus, may be responsible for their accumulation.

The neurodegenerative diseases elude detection by the immune and interferon defense systems: patients remain afebrile throughout the courses of their illness and show no leukocytosis in blood or pleocytosis in the CSF. Grossly, the brain can be atrophic with enlarged ventricles as in many cases of AD; alternatively, the basal ganglia may show selective atrophy as in HD. The degree of neuronal loss and the extent of reactive astrocytic gliosis can be quite variable for a particular disease. Although microglia often accumulate and cytokines are released late in the various neurodegenerative diseases, no inflammatory response characterized by accumulation of antigen–antibody complexes, lymphocytic infiltration or the perivascular accumulation of monocytes is generally seen.

Prion biology and diseases

Because prions and the mechanism of disease pathogenesis are without precedent, the classification of the prion diseases has been quite varied. For many years, the human prion diseases were classified as idiopathic degenerative disorders of the CNS based upon pathologic changes confined to the CNS. With the transmission of kuru and CJD to apes, investigators began to view these diseases as CNS infectious illnesses caused by 'slow viruses' (Gibbs et al., 1968).

The sporadic form of CJD is the most common prion disorder in humans and typically presents with dementia and myoclonus (Table 15.4). Sporadic CJD (sCJD) accounts for ~85% of all cases of human prion disease while inherited prion diseases account for 10–15% of all cases (Tables 15.2 and 15.4). Familial CJD (fCJD), Gerstmann–Sträussler–Scheinker disease (GSS), and fatal familial insomnia (FFI) are all dominantly inherited prion diseases caused by mutations in the PrP gene (Table 15.5) (Dlouhy et al., 1992; Gabizon et al., 1993; Hsiao et al., 1989a; Petersen et al., 1992; Poulter et al., 1992).

Even though the familial nature of a subset of CJD cases had been well described (Kirschbaum, 1968), the significance of this observation became more obscure with the transmission of CJD to animals (Gibbs et al., 1968). The conundrum that faced investigators reporting transmission of familial cases of CJD and GSS to apes and monkeys (Masters et al., 1981; Roos et al., 1973) is of considerable interest. They offered three hypotheses to explain fCJD and GSS. First the 'CJD virus' was transmitted to family members living in close proximity. Secondly, patients with fCJD or GSS carried a genetic predisposition to the ubiquitous CJD virus. Thirdly, the CJD virus was transmitted from parent to offspring either in utero or during birth as was later seen with HIV. All three of these explanations proved to be incorrect: the CJD virus does not exist and the familial prion diseases are caused by mutations in the PrP gene (Hsiao et al., 1989b).

The prion concept readily explains how a disease can be manifest as a heritable or sporadic disorder as well as an infectious illness. Moreover, the hallmark common to all of the prion diseases, whether sporadic, dominantly inherited, or acquired by infection, is that they involve the aberrant metabolism of the prion protein.

Table 15.4. The prion diseases

Disease	Host	Mechanism of pathogenesis
Kuru	Fore people	Infection through ritualistic cannibalism
iCJD*	Humans	Infection from prion-contaminated HGH, dura mater grafts, etc.
vCJD	Humans	Infection from bovine prions
fCJD	Humans	Germline mutations in PrP gene
GSS	Humans	Germline mutations in PrP gene
FFI	Humans	Germline mutation in PrP gene (D178N, M129)
sCJD	Humans	Somatic mutation or spontaneous conversion of PrP^{C} into PrP^{Sc}?
sFI	Humans	Somatic mutation or spontaneous conversion of PrP^{C} into PrP^{Sc}?
Scrapie	Sheep	Infection in genetically susceptible sheep
BSE	Cattle	Infection with prion-contaminated MBM
TME	Mink	Infection with prions from sheep or cattle
CWD	Mule deer, elk	Unknown
FSE	Cats	Infection with prion-contaminated beef
Exotic ungulate encephalopathy	Greater kudu, nyala, oryx	Infection with prion-contaminated MBM

Notes:
* Abbreviations: BSE, bovine spongiform encephalopathy; CJD, Creutzfeldt–Jakob disease; sCJD, sporadic CJD; fCJD, familial CJD; iCJD, iatrogenic CJD; vCJD, (new) variant CJD; CWD, chronic wasting disease; FFI, fatal familial insomnia; FSE, feline spongiform encephalopathy; sFI, sporadic fatal insomnia; GSS, Gerstmann–Sträussler–Scheinker disease; HGH, human growth hormone; MBM, meat and bone meal; TME, transmissible mink encephalopathy.

Table 15.5. Mutant genes in familial neurodegenerative diseases

Inherited disease	Gene	Mutation
Prion diseases	PrP	point mutations and octarepeat expansions
Alzheimer's disease	APP	point mutations
	PS1	point mutations
	PS2	point mutations
Parkinson's disease	α-synuclein	point mutations
	Parkin	point mutations
FTD	tau	point mutations deletions
Pick's disease	tau	point mutations
ALS	SOD1	point mutations
Huntington's disease	HD	polyglutamine expansions
Spinocerebellar ataxia 1	SCA1	polyglutamine expansions
Spinocerebellar ataxia 2	SCA2	polyglutamine expansions
Machado–Joseph disease	SCA3	polyglutamine expansions

In both the sporadic and inherited prion diseases, infectious prions are generated *de novo* within the host. In the sporadic prion diseases, wt PrP^{C} is converted into wt PrP^{Sc}, which is infectious. In the inherited prion diseases, mutant PrP^{C} is converted into mutant PrP^{Sc}, which in some cases appears to be able to stimulate the conversion of wt PrP^{C} into wt PrP^{Sc}. In these diseases, the process of prion formation begins endogenously. The accumulation of sufficient wt PrP^{Sc} to establish a slow infection and ultimately disease is a rare event and is presumably governed by both the frequency of PrP^{Sc} formation and the rate of PrP^{Sc} clearance. In contrast, the accumulation of sufficient mutant PrP^{Sc} to establish a slow infection and ultimately disease is a much more frequent event since all people carrying a PrP mutation will develop disease if they live long enough (Chapman et al., 1994; Spudich et al., 1995). Whether some pathologic PrP mutations act primarily by increasing the frequency of PrP^{Sc} formation and others by decreasing the rate of PrP^{Sc} clearance remains to be established.

Six diseases of animals are caused by prions (Table 15.4). Scrapie of sheep and goats is the prototypic prion disease. Mink encephalopathy, bovine spongiform encephalopathy (BSE), feline spongiform encephalopathy, and exotic ungulate encephalopathy are all thought to occur after the consumption of prion-infected foodstuffs.

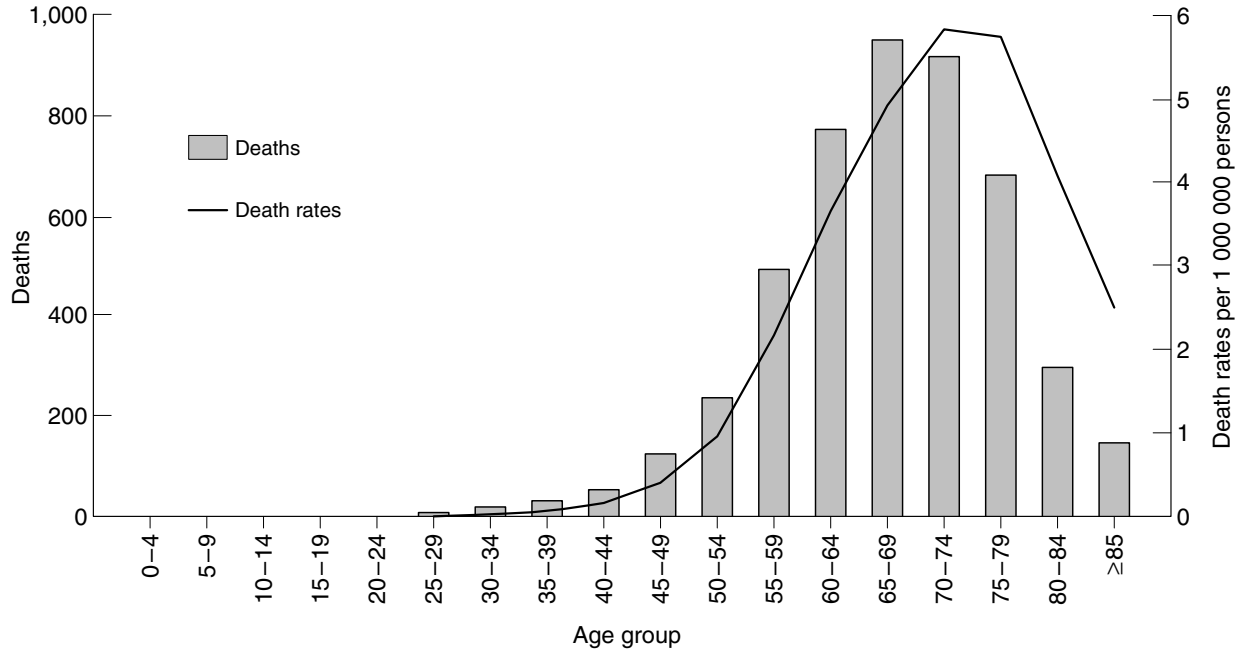


Fig. 15.3. Age-specific incidence of Creutzfeldt-Jakob disease in the United States. Total numbers of deaths for the period 1979 to 1998 are shown by the open bars and the death rates per million population are depicted by the solid line. (Graph prepared by Lawrence Schonberger.)

Epidemiology

Prions cause CJD in humans throughout the world. The incidence of sporadic CJD is approximately one case per million population (Masters et al., 1978), but is nearly five per million people between the ages of 60 to 74 (Fig. 15.3) (Holman et al., 1996). Patients as young as 17 years and as old as 83 have been recorded (Cathala & Baron, 1987; Masters et al., 1978). CJD is a relentlessly progressive malady that results in death usually within a year of onset. Each geographic cluster of prion disease was initially thought to be a manifestation of the communicability of the CJD virus (Kahana et al., 1974), but each was later shown to be due to a *PRNP* gene mutation, which results in a non-conservative substitution. Although infectious prion diseases account for less than 1% of all cases and infection does not seem to play an important role in the natural history of these illnesses, the transmissibility of prions is an important biologic feature. Attempts to identify common exposure to some etiologic agent have been unsuccessful for both the sporadic and familial cases (Cousens et al., 1990). Ingestion of scrapie-infected sheep or goat meat as a cause of CJD in humans has not been demonstrated by epidemiologic studies although speculation about this potential route of infection continues (Johnson & Gibbs, 1998). Studies with Syrian hamsters demonstrated that oral infection by prions can occur, but the process is quite inefficient compared to intracerebral inoculation (Prusiner et al., 1985).

Why the human prion diseases are so rare compared to the more common disorders of AD and Parkinson's disease is unknown. AD is about four times more common than Parkinson's disease and approximately 10 000 times more common than CJD (Table 15.1). Deciphering the mechanism of these remarkable differences in prevalence may help elucidate the factors underlying the etiologies and pathogenesis of these maladies.

Neuropathology

Frequently, the brains of patients with CJD show no recognizable abnormalities upon gross examination. In patients surviving several years, variable degrees of cerebral atrophy are likely to result in brain weights as low as 850 g.

The pathologic hallmarks of CJD at the light microscopic level are spongiform degeneration and astrogliosis (Fig. 15.4(*a*) and (*b*), see colour plate section) (DeArmond & Ironside, 1999). The lack of an inflammatory response in CJD and other prion diseases is an important pathologic feature of these degenerative disorders. Generally, the spongiform changes occur in the cerebral cortex,

putamen, caudate nucleus, thalamus, and molecular layer of the cerebellum. Spongiform degeneration is characterized by many 5–20 μm vacuoles in the neuropil between nerve cell bodies. Astrocytic gliosis is a constant but nonspecific feature of prion diseases (DeArmond & Prusiner, 1997). Widespread proliferation of fibrous astrocytes is found throughout the grey matter of brains infected with CJD prions. Astrocytic processes filled with glial filaments form extensive networks.

Amyloid plaques have been found in ~10% of CJD cases. Purified CJD prions from humans and animals exhibit the ultrastructural and histochemical characteristics of amyloid (Prusiner et al., 1983). In first passage to mice from some human Japanese CJD cases, amyloid plaques were found in the mouse brains (Tateishi et al., 1996). These plaques were stained with antisera raised against PrP.

The amyloid plaques of GSS are distinct from those seen in kuru, AD, or scrapie. GSS plaques consist of a central dense core of amyloid surrounded by smaller globules of amyloid (Fig. 15.4(*c*) and (*d*)). Ultrastructurally, they consist of a radiating fibrillar network of amyloid fibrils with scant or no neuritic degeneration. The plaques can be distributed throughout the brain but are most frequently found in the cerebellum. They are often located adjacent to blood vessels. Congophilic angiopathy has been noted in some cases of GSS. In addition to the multicentric plaques of GSS, unicentric kuru plaques may also be seen (Masters et al., 1981). In GSS caused by the F198S mutation, neurofibrillary tangles (NFT) composed of paired helical filaments (PHF) are frequently seen surrounding PrP amyloid plaques (Dlouhy et al., 1992; Gambetti et al., 1999).

In new variant CJD (vCJD), a characteristic feature is the presence of 'florid plaques'. These are composed of a central core of PrP amyloid surrounded by vacuoles in a pattern suggesting petals of a flower (Fig. 15.4(*e*) and (*f*)).

Species barrier

Studies on the role of the primary and tertiary structures of PrP in the transmission of prion disease have given new insights into the pathogenesis of these maladies. In general, transmission of prion disease from one species to another is inefficient, in that not all intracerebrally inoculated animals develop disease, and those that fall ill, do so only after long incubation times, which can approach the natural lifespan of the animal (Pattison, 1965). This 'species barrier' to transmission is correlated with the degree of homology between the amino acid sequence of PrP^{C} in the inoculated host and of PrP^{Sc} in the prion inoculum (Prusiner et al., 1990). Thus, the amino acid sequence of PrP encodes the species of the prion, and the prion derives its PrP^{Sc} sequence from the last mammal in which it was passaged (Scott et al., 1997). The importance of sequence homology between the host and donor PrP argues that PrP^{C} directly interacts with PrP^{Sc} in the prion conversion process; PrP^{Sc} seems to function as a template in determining the tertiary structure of nascent PrP^{Sc} molecules as they are formed from PrP^{C}.

Prion strains

The existence of prion strains raised the question of how heritable biological information can be enciphered in a molecule other than nucleic acid (Bruce & Dickinson, 1987; Dickinson et al., 1968; Ridley & Baker, 1996). Strains or varieties of prions have been defined by incubation times and the distribution of neuronal vacuolation (Dickinson et al., 1968). Subsequently, the patterns of PrP^{Sc} deposition were found to correlate with vacuolation profiles and these patterns were also used to characterize strains of prions (Bruce et al., 1989; DeArmond et al., 1987).

Mounting evidence supports the hypothesis that prion diversity is enciphered in the conformation of PrP^{Sc} (Prusiner, 1991); thus, prion strains seem to represent different conformers of PrP^{Sc} (Bessen & Marsh, 1994; Safar et al., 1998; Scott et al., 1997; Telling et al., 1996). Persuasive evidence that strain-specific information is enciphered in the tertiary and quaternary structure of PrP^{Sc} comes from transmission of two different inherited human prion diseases to mice expressing a chimeric human-mouse PrP transgene (Telling et al., 1996). In FFI, the protease-resistant fragment of PrP^{Sc} after deglycosylation has a molecular size of 19 kDa, whereas in fCJD with a substitution of a lysine (K) for glutamate (E) at residue 200 (E200K) and most sporadic prion diseases, it is 21 kDa (Table 15.6) (Parchi et al., 1996). This difference in molecular size was shown to be due to different sites of proteolytic cleavage at the NH_2-termini of the two human PrP^{Sc} molecules, reflecting different tertiary structures. These distinct conformations were not unexpected because the amino acid sequences of the PrPs differ.

Extracts from the brains of FFI patients transmitted disease into mice expressing a chimeric human-mouse PrP transgene about 200 days after inoculation and induced formation of the 19 kDa PrP^{Sc}, whereas fCJD(E200K) and sCJD extracts produced the 21 kDa PrP^{Sc} in mice expressing the same transgene (Telling et al., 1996). On second passage, transgenic (Tg) mice inoculated with FFI prions showed an incubation time of ~130 days and a 19 kDa PrP^{Sc}, whereas those inoculated with fCJD(E200K) prions exhibited an incubation time of ~170 days and a 21 kDa PrP^{Sc} (Prusiner, 1998b). The experimental data demonstrate that chimeric PrP^{Sc} can exist in two different conformations based on the sizes of the pro-

Table 15.6. Distinct prion strains generated in humans with inherited prion diseases and transmitted to transgenic mice[a]

Inoculum	Host Species	Host PrP Genotype	Incubation time [days ± SEM] (n/n_0)	PrP^{Sc}(kDa)
None	Human	FFI(D178N, M129)		19
FFI	Mouse	Tg(MHu2M)	206 ± 7(7/7)	19
FFI → Tg(MHu2M)	Mouse	Tg(MHu2M)	136 ± 1 (6/6)	19
None	Human	fCJD(E200K)		21
fCJD	Mouse	Tg(MHu2M)	170 ± 2 (10/10)	21
fCJD → Tg(MHu2M)	Mouse	Tg(MHu2M)	167 ± 3 (15/15)	21

Notes:

[a] Data from references (Prusiner, 1998a,b; Telling et al., 1996). Tg(MHu2M) mice express a chimeric human-mouse PrP gene. Clinicopathologic phenotype is determined by the conformation of PrP^{Sc} in accord with the results of the transmission of human prions from patients with FFI to Tg mice (Telling et al., 1996).

tease-resistant fragments; yet the amino acid sequence of PrP^{Sc} is invariant.

This analysis was extended when patients with sporadic fatal insomnia (sFI) were found. Although they did not carry a PrP gene mutation, the clinical and pathologic phenotype was indistinguishable from that of FFI patients. Furthermore, 19 kDa PrP^{Sc} was found in their brains and upon passage of these human prions to mice expressing a chimeric human-mouse PrP transgene, the 19 kDa PrP^{Sc} was also found (Mastrianni et al., 1999). These findings contend that the disease phenotype is dictated by the conformation of PrP^{Sc} and not by the amino acid sequence. The results also demand that PrP^{Sc} acts as a template for the conversion of PrP^{C} into nascent PrP^{Sc}.

Sporadic and genetic neurodegenerative diseases

Prion diseases

Initiation of sporadic disease may follow from a somatic mutation and thus, develop in a manner similar to that for germline mutations in inherited disease (Table 15.5). In this situation, the mutant PrP^{Sc} must be capable of recruiting wt PrP^{C}, a process known to be possible for some mutations (e.g. E200K, D178N) but less likely for others (e.g. P102L) (Telling et al., 1995). Alternatively, the activation barrier separating wt PrP^{C} from PrP^{Sc} could be crossed on rare occasions when viewed in the context of a large population (Fig. 15.3) (Cohen & Prusiner, 1998).

More than 20 different mutations in the human PrP gene resulting in non-conservative substitutions have been found to segregate with inherited human prion diseases, to date (Gambetti et al., 1999). Missense mutations and expansions in the octapeptide repeat region of the gene are responsible for familial forms of prion disease. Five different mutations of the PrP gene have been linked genetically to heritable prion disease (Dlouhy et al., 1992; Gabizon et al., 1993; Hsiao et al., 1989a; Petersen et al., 1992; Poulter et al., 1992).

Although phenotypes may vary dramatically within families, there is a tendency for certain phenotypes to associate with specific mutations (Gambetti et al., 1999). A clinical phenotype indistinguishable from typical CJD is usually seen with substitutions at codons 180, 183, 200, 208, 210, and 232. Substitutions at codons 117, 102, 105, 198, and 217 are associated with the clinicopathological variant of prion disease known as GSS disease. The normal human PrP sequence contains five repeats of an octapeptide sequence. Insertions of an additional 2 to 9 extra octapeptide repeats are associated with variable phenotypes ranging from a condition indistinguishable from CJD to a slowly progressive dementing illness of many years' duration. A mutation at codon 178, resulting in substitution of asparagine for aspartate, produces FFI if a methionine is encoded at the polymorphic 129 residue on the same allele (Goldfarb et al., 1992). Typical CJD is seen if a valine is encoded at position 129 of the mutant allele.

Particularly puzzling are the factors that determine the disease phenotype. As noted above, there is excellent evidence that the tertiary structure of PrP^{Sc} determines whether this disease-causing protein is deposited in subsets of thalamic neurons producing fatal insomnia or it is deposited more widely and resulting in a dementing illness labeled CJD. As more cases of inherited prion diseases have been studied, multiple exceptions have been recorded in which a mutation that produces GSS with ataxia also results in a dementing

illness and vice versa (Hsiao et al., 1990, Mastrianni et al., 1999). Within a single family carrying a PrP mutation, some patients develop peripheral neuropathologies while others do not. Elucidating all of the factors that govern the clinical and neuropathologic phenotypes will be challenging.

PrP gene polymorphisms and dominant negative inhibition

Polymorphisms influence the susceptibility to sporadic, inherited, and infectious forms of prion disease. The methionine/valine polymorphism at position 129 not only determines the clinical phenotype as noted above but it also modulates the age of onset of some inherited prion diseases (Gambetti et al., 1999; Palmer et al., 1991). The finding that homozygosity at codon 129 predisposes to sCJD supports a model of prion production that favours PrP interactions between homologous proteins, as appears to occur in Tg mice expressing SHaPrP inoculated with either hamster prions or mouse prions (Prusiner et al., 1990) as well as in Tg mice expressing a chimeric SHa/Mo PrP transgene inoculated with 'artificial' prions.

A lysine residue at 219 has been found in 12% in the Japanese population and this group seems to be resistant to prion disease (Shibuya et al., 1998). Substitution of the basic residue lysine at position 219 produced dominant negative inhibition of prion replication. In scrapie-infected neuroblastoma (ScN2a) cells and Tg mice, substitution of lysine at position 219 prevented PrP^{C} from being converted into PrP^{Sc} (Kaneko et al., 1997; Zulianello et al., 2000) (V. Perrier, K. Kaneko, S.J. DeArmond, F.E. Cohen and S.B. Prusiner, in preparation). Not only was PrP^{C}(219K) unable to support prion replication but it also prevented wt PrP^{C} from being converted into PrP^{Sc}. Dominant negative inhibition of prion replication has also been found in sheep with substitution of the basic residue arginine at position 171. The sheep with arginine are resistant to scrapie (Hunter et al., 1997; Westaway et al., 1994). Both the inability of PrP^{C}(171R) to support prion replication and exhibit dominant negative inhibition have been demonstrated in ScN2a cells and Tg mice.

Alzheimer's disease

In AD, Aβ amyloid plaques and NFT are found whether the disease is sporadic or inherited (Table 15.3). Like the familial prion diseases, the inheritance of familial AD is autosomal dominant. In contrast to the prion diseases in which only mutations in the PrP gene have been identified to cause familial prion disease, familial AD can be caused by a mutation in one of at least three different genes: amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2(PS2) (Table 15.5) (St. George-Hyslop, 1999). Cleavage of APP at residue 671 by β-secretase and at either residue 711 or 713 by γ-secretase produces Aβ(1-40) or Aβ(1-42), respectively. Aβ(1-40) is soluble and its levels do not correlate with AD whereas Aβ(1-42) readily forms fibrils and is thought to cause CNS dysfunction prior to being deposited in plaques (De Strooper and Annaert, 2000; Selkoe, 1999; Wilson et al., 1999). The cleavage of APP by γ-secretase within the plasma membrane is a highly regulated, complex process (Brown et al., 2000; De Strooper & Annaert, 2000). Cleavage at residue 687 by α-secretase prevents Aβ peptide formation. Six different mutations of the APP gene have been implicated in familial AD. More than 30 mutations of the PS1 gene and two of the PS2 gene in familial AD have been found (St. George-Hyslop, 1999). PS1 and PS2 are thought to form complexes with at least one other protein, nicastrin, and these complexes have γ-secretase activity (Yu et al., 2000). Mutations in PS1 have been shown to increase the amount of Aβ(1-42) peptide.

NFT in AD are composed of PHF that are composed of hyperphosphorylated tau (Goedert et al., 1988; Lee et al., 1991; Wolozin et al., 1986). The tau protein binds to microtubules and facilitates assembly of these polymers but hyperphosphorylated tau isolated from AD brains does not bind to microtubules. Six different isoforms of tau are produced by alternative splicing of a single copy gene expressed in brain. Although mutations of the tau gene cause neurodegeneration as described below, they do not cause AD.

The age of onset of both the sporadic and familial AD is modulated by the allelic variants of apolipoprotein E (ApoE) (Saunders et al., 1993). Three alternative allelic products of ApoE, denoted ε2, ε3 and ε4, differ at amino acid residues 112 and 158. Many people with two ε4 alleles can expect to develop AD at least a decade before those with two copies of ε2, whereas those with ε3 exhibit an intermediate age of onset (Farrer et al., 1997). How ApoE modulates the onset of AD is unknown but one hypothesis suggests that ApoE features in the clearance of the Aβ(1-42) peptide. A less compelling hypothesis argues that ApoE modulates the formation of NFTs that are composed of PHF (Roses, 1994).

Frontotemporal dementia

Mutations in the tau gene are responsible for inherited cases of FTD and Pick's disease (Clark et al., 1998; Hutton et al., 1998; Spillantini et al., 1998b). Like AD, about 90% of FTD cases are sporadic and approximately 10% are familial (Table 15.2). In familial FTD, straight filaments composed of hyperphosphorylated mutant tau have been found (Table 15.3) (Hong et al., 1998). In patients from

some families with FTD, NFT composed of PHF have been found; the formation of PHF seems to depend upon the specific tau mutation and the expression of specific isoforms that are determined by alternative splicing (Table 15.5) (Buée et al., 2000). In sporadic FTD, aggregates of tau are rarely found.

Approximately 15% of FTD cases coming to autopsy were found to have Pick bodies (Brun, 1993), which are the neuropathologic hallmark of Pick's disease. Pick bodies are intracellular collections of ubiquitinated tau fibrils (Kertesz & Munoz, 1998). Like FTD, most cases of Pick's disease are sporadic.

In some familial cases of FTD caused by tau mutations, Parkinson's disease and disinhibition have been found (Wilhelmsen et al., 1994). Additional disorders thought to be caused by the aberrant processing of tau include progressive supranuclear palsy (PSP), progressive subcortical gliosis, and corticobasal degeneration (Buée et al., 2000; Conrad et al., 1997; Goedert et al., 1999; Kertesz & Munoz, 1998).

Parkinson's disease

In Parkinson's disease, the same theme of protein deposits in the CNS of patients with sporadic and familial forms of the disease has been discovered. Although most patients with Parkinson's disease have a sporadic form of the disease (Nussbaum & Polymeropoulos, 1997; Tanner et al., 1999), mutations have been discovered in the α-synuclein gene of patients with familial Parkinson's disease (Polymeropoulos et al., 1997). When antibodies were raised to α-synuclein, they were found to stain intracellular aggregates of protein in the malfunctioning neurons of the substantia nigra called Lewy bodies (Spillantini et al., 1997). Lewy bodies are present in both the sporadic and familial forms of Parkinson's disease. While the inheritance of Parkinson's disease caused by mutations in the α-synuclein gene is autosomal dominant, a childhood form of Parkinson's disease caused by mutations in the ubiquitin-protein ligase gene (*parkin*) is a recessive disorder (Table 15.5) (Shimura et al., 2000). The recessive inheritance Parkinson's disease caused by mutations in the *parkin* gene is currently the only familial neurodegenerative disease that is not dominantly inherited. Whether people carrying mutations in the *parkin* gene develop Parkinson's disease due to decreased ubiquitination of α-synuclein is unknown, but the ubiquitin pathway is known to participate in the degradation of α-synuclein. There is considerable interest in the possible role of oxidative metabolism in the etiology of Parkinson's disease and selective nitration of α-synuclein in Lewy bodies has been found (Giasson et al., 2000).

The onset of Parkinson's disease in people age 70 or older is associated with a high incidence of dementia (Hughes et al., 2000). At autopsy, the brains of these people often display the neuropathologic hallmarks of both AD and Parkinson's disease. Ubiquitin and α-synuclein immunostaining to identify cortical Lewy bodies has helped resolve the conundrum of how a patient could have insufficient numbers of plaques and NFTs for diagnosis of AD but still be demented. It is estimated that α-synuclein deposition as Lewy bodies in cortical neurons may by itself or in combination with AD changes be the second most common form of neurodegeneration, accounting for 20 to 30% of dementia cases over the age of 60 (Hansen et al., 1990; Hashimoto & Masliah, 1999). A small group of younger people with Parkinson's disease become demented due to diffuse Lewy body disease, in which Lewy bodies are found throughout the cerebral cortex (Spillantini et al., 1998a).

For nearly two decades, some investigators have argued that Parkinson's disease is acquired by the accumulation of toxic molecules in neurons of the substantia nigra (Tanner et al., 1999). The dramatic ability of the synthetic heroin derivative MPTP to produce the symptoms and signs of Parkinson's disease in humans and apes provided seductive evidence in favour of the toxin hypothesis (Langston et al., 2000) as did the possibility that a molecule in cycad plants causes an ALS-Parkinson's disease complex in the indigenous people of Guam (Spencer et al., 1990). Studies of the etiology of Parkinson's disease have also been complicated by Parkinsonism (or the symptoms of Parkinson's disease) that is seen in a variety of neurologic disorders, including post-encephalitis lethargica following the influenza pandemic of 1916–1926 and post-hypoxic encephalopathy.

ALS

While most cases of ALS are sporadic, familial cases have been identified (Table 15.2) (Bobowick & Brody, 1973; Hudson, 1981; Swash, 2000). Approximately 20% of all familial ALS cases has been shown to be due to mutations in the cytoplasmic superoxide dismutase (SOD1) (Table 15.5) (Rosen et al., 1993). Deposits of SOD1 have been found in the CNS of some patients with sporadic and familial forms of ALS (Cleveland & Liu, 2000). Of note, some mutant SOD1 molecules exhibit increased SOD activity compared to wt SOD while others display activities that are similar or decreased compared to wt SOD (Wong et al., 1995). In some cases of ALS, abnormal collections of neurofilaments have been seen in degenerating motor neurons but no familial cases of ALS have been shown to be due to mutations in any of the neurofilament genes (Cleveland & Liu, 2000). In a few cases of sporadic ALS and one family with ALS, deletions in the tail domain of the large neurofilament subunit (NF-H) have been reported.

Huntington's disease and spinocerebellar ataxias

HD and the spinocerebellar ataxias (SCA) provide important contrasts and similarities to the foregoing neurodegenerative diseases. In contrast to AD, FTD, Parkinson's disease, ALS, and the prion diseases, in which most of the cases are sporadic, both HD and the SCAs are exclusively genetic diseases (Table 15.2) (Reed & Neel, 1959) caused by expanded polyglutamine repeats (Table 15.5) (Lin et al., 1999; Martin, 1999; Paulson, 1999). But like the inherited forms of AD, FTD, Parkinson's disease, ALS, and the prion diseases, most cases of HD and the SCAs present with neurologic deficits in adulthood despite the mutant gene products being expressed in the CNS from early in life. Childhood forms of HD and the SCAs are known to be due to enlarged expansions of the triplet repeats that cause these diseases (Lin et al., 1999; The Huntington's Disease Collaborative Research Group, 1993; Zoghbi & Orr, 2000).

In both HD and SCA, the mutant gene products appear to be deposited in the CNS of patients. These misprocessed mutant proteins seem to accumulate in malfunctioning neurons and to be responsible for the neurologic deficits that these patients exhibit. In HD, SCA1, and Machado-Joseph disease (SCA3) as well as in some cases of SCA2, nuclear inclusions of the mutant proteins, which are ubiquitinated, have been found (Koyano et al., 1999; Lin et al., 1999).

Additional disorders caused by the misprocessing of proteins with expanded polyglutamine repeats include spinobulbar muscular atrophy (SBMA) also called Kennedy's syndrome, in which the androgen receptor carries the expanded repeat (LaSpada et al., 1991), as well as dentatorubropallidoluysian atrophy (DRPLA), and the spinocerebellar ataxias 6 and 7 (Martin, 1999; Paulson, 1999).

The neurodegenerative diseases described here represent only a small fraction of the total number of neurologic maladies given this label. Undoubtedly, many of these disorders will require reclassification as the molecular basis of each is elucidated.

Infectious prion diseases

Although infectious prion diseases constitute less than 1% of all cases, the circumstances surrounding these infectious illnesses are often dramatic (Table 15.4) (Will et al., 1999a). The ritualistic cannibalism involved the transmission of kuru among the Fore people of New Guinea, the industrial cannibalism responsible for 'mad cow disease' in Europe, and the growing group of patients with vCJD contracted from prion-tainted beef products are all examples of infectious prion diseases that almost defy imagination.

Kuru

Kuru has disappeared, but the impact of this illness on medical science remains immense. Kuru was the first human prion disease to be transmitted to experimental animals (Gajdusek et al., 1966). Based on the similarities of the neuropathologic lesions of scrapie and kuru (Hadlow, 1959), transmission studies to apes were performed and similar investigations followed with CJD (Gibbs et al., 1968; Klatzo et al., 1959). The transmissibility of kuru suggested that the disease resulted from ritualistic cannibalism among the Fore people living in the highlands of New Guinea (Alpers, 1968). Presumably, kuru began with a person who had developed a sporadic case of prion disease; at death, the brain was removed and distributed to relatives in order to immortalize the spirit of the deceased.

Iatrogenic prion disease

Accidental transmission of CJD to humans appears to have occurred with corneal transplantation (Duffy et al., 1974) and contaminated EEG electrode implantation (Bernouilli et al., 1977). Corneas removed from donors who unknowingly had CJD have been transplanted to apparently healthy recipients who developed CJD after prolonged incubation periods. The same improperly decontaminated EEG electrodes that caused CJD in two young patients with intractable epilepsy were found to cause CJD in a chimpanzee 18 months after their experimental implantation (Gibbs et al., 1994).

Surgical procedures may have resulted in accidental inoculation of patients with prions during their operations (Collins et al., 1999; Gajdusek, 1977; Will & Matthews, 1982), presumably because some instrument or apparatus in the operating theatre became contaminated when a CJD patient underwent surgery. Although the epidemiology of these studies is highly suggestive, no proof for such episodes exists.

Dura mater grafts

More than 70 cases of CJD after implantation of dura mater grafts have been recorded (Centers for Disease Control, 1997). All of the grafts were thought to have been acquired from a single manufacturer whose preparative procedures were inadequate to inactivate human prions. One case of CJD occurred after repair of an eardrum perforation with a pericardium graft (Tange et al., 1989).

Human growth hormone therapy

The possibility of transmission of CJD from contaminated human growth hormone (HGH) preparations derived from human pituitaries has been raised by the occurrence of fatal cerebellar disorders with dementia in more than 100 patients ranging in age from 10 to 41 years (Fradkin et al., 1991; Will et al., 1999a). These patients received injections of HGH every 2 to 4 days for 4 to 12 years (PHS, 1997). Assuming these patients developed CJD from injections of prion-contaminated HGH preparations, the possible incubation periods range from 4 to 30 years. Even though several investigations argue for the efficacy of inactivating prions in HGH fractions prepared from human pituitaries using 6 M urea, it seems doubtful that such protocols will be used for purifying HGH because recombinant HGH is available. Four cases of CJD have occurred in women receiving human pituitary gonadotropin (Cochius et al., 1990).

New variant Creutzfeldt–Jakob disease

The restricted geographical occurrence and chronology of vCJD have raised the possibility that BSE prions have been transmitted to humans. Over 80 vCJD cases have been recorded, but the incidence has been too low to be useful in establishing the origin of vCJD (Balter, 2000; Will et al., 1999b). No set of dietary habits distinguishes vCJD patients from apparently healthy people. Moreover, there is no explanation for the predilection of vCJD for teenagers and young adults. It is noteworthy that epidemiological studies over the past three decades have failed to find evidence for transmission of sheep prions to humans (Cousens et al., 1990). Attempts to predict the future number of cases of vCJD, assuming exposure to bovine prions prior to the offal ban, have been questioned because so few cases of vCJD have occurred (Ghani et al., 2000). Are we at the beginning of a human prion disease epidemic in Great Britain like those seen for BSE and kuru, or will the number of vCJD (vCJD) cases remain small as seen with iatrogenic CJD (iCJD) caused by cadaveric HGH?

Although the mechanism of infection of vCJD has not been yet established, mounting evidence argues for transmission of bovine prions to humans. This conclusion is based on multiple lines of inquiry including: (i) the spatial-temporal clustering of vCJD (Will et al., 1996; Zeidler et al., 1997), (ii) the successful transmission of BSE to macaques with induction of PrP plaques similar to those seen in vCJD (Lasmézas et al., 1996), (iii) the similarity of the glycoform pattern of brain but not tonsil PrP^{Sc} in vCJD to that in cattle, mice, domestic cats, and macaques infected with BSE prions (Hill et al., 1997, 1999), and (iv) transmission studies in non-Tg mice suggesting that vCJD and BSE represent the same prion strain (Bruce et al., 1997). The prolonged incubation periods and inefficient transmission of prions that is seen after inoculation of foreign prions into non-Tg mice can readily confuse the interpretation of the findings (Lasmézas et al., 1997; Prusiner, 1998a).

The most compelling evidence that vCJD is caused by BSE prions has come from experiments using mice expressing the bovine (Bo) PrP transgene (Scott et al., 1999). The incubation times, neuropathologic profiles, and patterns of PrP^{Sc} deposition in Tg mice expressing the BoPrP gene are indistinguishable whether the inocula originated from the brains of cattle with BSE or humans with vCJD (Scott et al., 1999). Neither CJD nor fCJD(E200K) prions have transmitted disease to the Tg(BoPrP) mice. In contrast to CJD and CJD(E200K) prions, which transmit disease efficiently to mice expressing a chimeric human-mouse PrP transgene, vCJD prions do not. Interestingly, none of the Tg mice expressing the chimeric human-mouse PrP developed disease after more than 600 days when inoculated with BSE prions from cattle.

Since the Tg(BoPrP) mice are also excellent hosts for transmission of natural sheep scrapie, this raises the possibility that sheep carry several strains of prions, including the BSE strain (M. Scott and S.B. Prusiner, in preparation). But the BSE strain might replicate more slowly in sheep than many scrapie strains and thus, is present at low levels. If the scrapie strains were more heat labile than the BSE strain, then the rendering process used in the late 1970s and most of the next decade might have selected for the BSE strain. This BSE strain might have then been reselected multiple times as cattle were infected by ingesting prion-contaminated meat and bone meal (MBM). In this situation, the infected cattle were slaughtered and their offal rendered into more MBM, which was subsequently fed to more cattle.

The foregoing scenario suggests that the BSE strain may be widely distributed in sheep and these prions composed of sheep PrP^{Sc} are non-pathogenic for humans. Once the BSE prions are passaged through cattle, they acquire bovine PrP^{Sc} and become pathogenic for humans.

Diagnostic tests

The attempts to develop diagnostic tests for prion diseases are instructive with respect to the other neurodegenerative diseases. The need for accurate, sensitive diagnostic tests for neurodegenerative diseases, preferably blood- or urine-based, is extreme. Advances in imaging the CNS may also aid in the early diagnosis of neurodegeneration. When effective treatments for neurodegenerative diseases are

eventually developed as discussed later, early accurate detection of the disease will be critical in order to institute therapies before CNS function is substantially compromised. The difficulty in distinguishing between early AD and depression in older people would benefit from a diagnostic test since both disorders are so common.

With the exception of brain biopsy, there are no specific tests for CJD. If the constellation of pathologic changes frequently found in CJD is seen in a brain biopsy, then the diagnosis is reasonably secure (Fig. 15.4(*a*) and (*b*)). The rapid and reliable diagnosis of CJD postmortem can be accomplished by using antisera to PrP. Numerous Western blotting studies have consistently demonstrated PrP immunoreactive proteins that are proteinase K-resistant in the brains of patients with CJD. It is noteworthy that PrP^{Sc} is not uniformly distributed throughout the CNS so that the apparent absence of PrP^{Sc} in a limited sample, such as a biopsy, does not rule out prion disease (Serban et al., 1990; Taraboulos et al., 1992).

A highly sensitive and quantitative immunoassay was developed based upon epitopes that are exposed in PrP^{C} but buried in PrP^{Sc} (Fig. 15.5(*a*)). Unlike all other immunoassays for PrP^{Sc}, this conformation-dependent immunoassay (CDI) does not require limited proteolysis to hydrolyze PrP^{C} prior to measuring the protease-resistant core of PrP^{Sc} (PrP 27–30) (Safar et al., 1998). Using the CDI, a new form of PrP^{Sc} has been identified, which is protease-sensitive and is denoted $sPrP^{Sc}$. The levels of $sPrP^{Sc}$ are proportional to the length of the incubation time (Fig. 15.5(*b*)) and are often much higher than those of protease-resistant PrP^{Sc}. Why levels of $sPrP^{Sc}$ should be directly proportional to the length of the incubation time is unclear. Whether measurement of $sPrP^{Sc}$ will become the basis of diagnostic tests for prion diseases remains to be established.

If the patient has a family history suggestive of inherited CJD, sequencing the PrP gene may facilitate the diagnosis. Sometimes, the PrP sequence is helpful in even seemingly non-familial cases. Obviously, DNA sequencing is a crucial diagnostic tool in all of the inherited neurodegenerative diseases. In the sporadic form of AD, ApoE allelic typing is a necessary adjunct to any clinical study. Moreover, sporadic neurodegenerative diseases require that both alleles encoding the etiologic, misprocessed protein possess the wt sequence.

In the prion diseases, AD, FTD, and Parkinson's disease, the CT or MRI may be normal or show cortical atrophy. In the prion diseases, the MRI scan may show a subtle increase in intensity in the basal ganglia with T2 or diffusion-weighted imaging, but this finding is neither sensitive nor specific enough to make a diagnosis. In AD, widespread atrophy with enlarged ventricles is often seen, especially late in the disease, but this finding is not diagnostic. Many cognitively intact elderly people have similar radiographic findings (Gertz et al., 1988; Kitagaki et al., 1998). In FTD, atrophy is confined to the frontal and temporal lobes while in HD, profound atrophy of the basal ganglia is commonly seen. In all of the neurodegenerative diseases, the CSF is nearly always normal but may show a minimal protein elevation (Cathala & Baron, 1987). Although the protein 14-3-3 is elevated in the CSF of many CJD patients, similar elevations of 14-3-3 are found in patients with herpes simplex virus encephalitis, multi-infarct dementia, and stroke (Johnson & Gibbs, 1998; Zerr et al., 1998). In Alzheimer's disease, 14-3-3 is generally not elevated. In the serum of some patients with CJD, the S-100 protein is elevated, but like 14-3-3, this elevation is not specific (Zerr et al., 1998). Attempts to use Aβ(1–40) levels in blood and urine have been unrewarding (Ghiso et al., 1997) but use of fluorescence correlation spectroscopy with CSF may provide a reliable diagnostic test for AD (Pitschke et al., 1998).

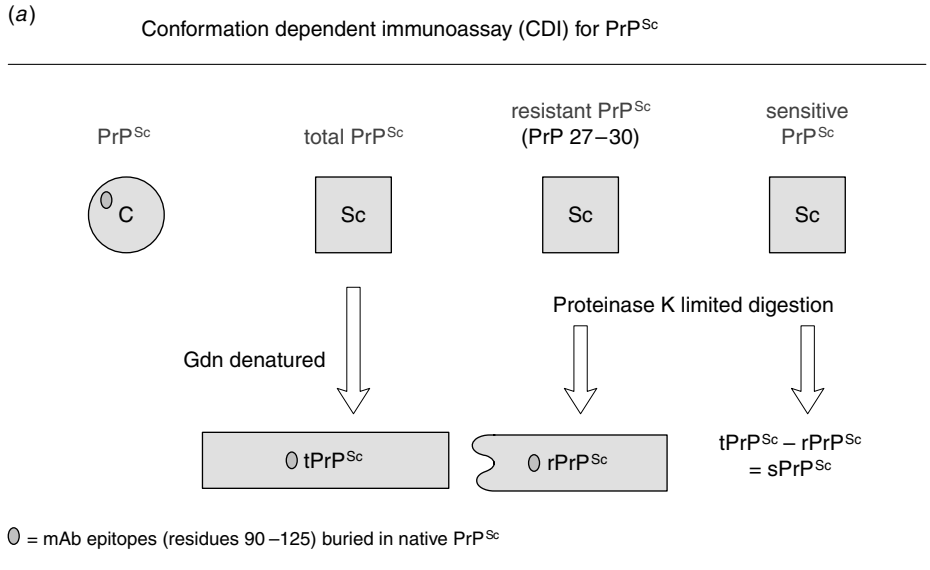
In contrast to AD, FTD, and Parkinson's disease, the electroencephalogram (EEG) is often useful in the diagnosis of CJD. During the early phase of CJD, the EEG is usually normal or shows only scattered theta activity. In most advanced cases, repetitive, high voltage, triphasic, and polyphasic sharp discharges are seen but, in many cases, their presence is transient. The presence of these stereotyped periodic bursts of $<$200 ms duration, occurring every 1 to 2 sec, makes the diagnosis of CJD very likely (Cathala & Baron, 1987; Johnson & Gibbs, 1998; Kirschbaum, 1968; Nevin et al., 1960). These discharges are frequently but not always symmetrical; there may be a one-sided predominance in amplitude. As CJD progresses, normal background rhythms become fragmentary and slower.

The possibility of Hashimoto's thyroiditis should always be considered in the differential diagnosis of CJD (Seipelt et al., 1999) since this autoimmune disease is treatable and CJD is not. That the clinical and neuropathologic findings can be so similar in Hashimoto's thyroiditis and CJD is striking; moreover, it raises the possibility that protein misprocessing may underlie both degenerative and autoimmune diseases.

Transgenic models of neurodegeneration

Prion diseases

The development of Tg mouse models that reproduce virtually every aspect of naturally occurring prion disease has created a firm foundation upon which to decipher



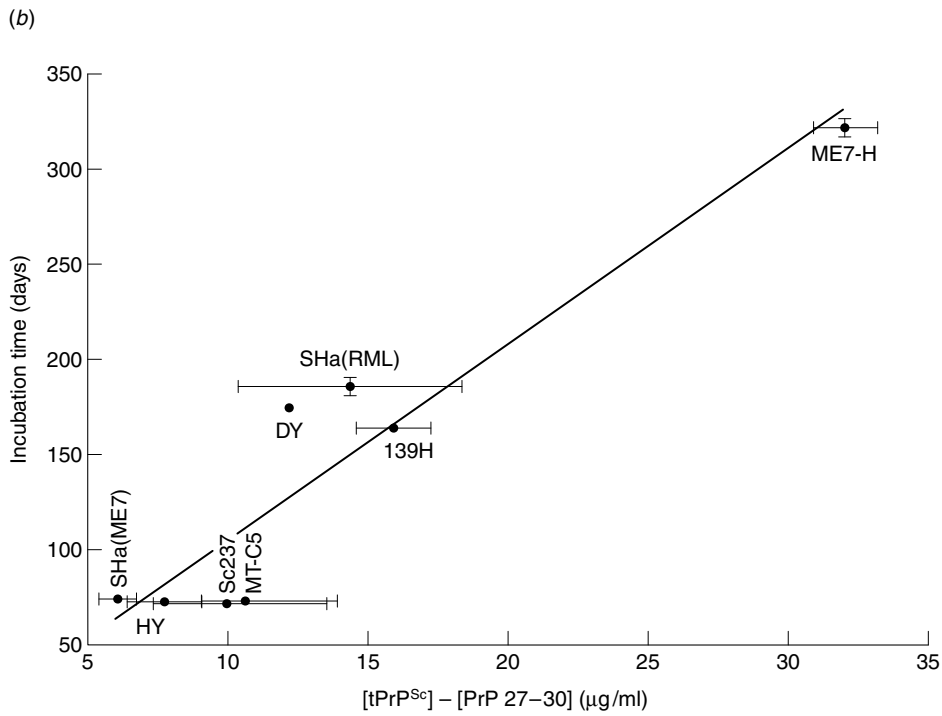


Fig. 15.5. Conformation-dependent immunoassay and prion strains. (*a*) The conformation dependent immunoassay (CDI) permits measurement of PrP^{Sc} without limited digestion by protease to eliminate PrP^{C}; instead, antibodies to epitopes that are exposed in PrP^{C} but buried in PrP^{Sc} are used to distinguish between the two isoforms. Using the CDI, it became possible to detect two different forms of PrP^{Sc}: one which is resistant to limited digestion by protease and the other which is readily digested. Using one fraction of a sample, total (t) PrP^{Sc} is measured while another aliquot is digested prior to determining the protease-resistant (r) PrP^{Sc} level. $rPrP^{Sc}$ is equivalent to PrP 27–30. By subtracting $rPrP^{Sc}$ from the $tPrP^{Sc}$, the amount of protease-sensitive (s) PrP^{Sc} can be determined. (*b*) When the levels of $sPrP^{Sc}$ in brain for eight different prion strains were plotted as a function of the incubation times in Syrian hamsters, a straight line was obtained with an r value of 0.94. (Data from Safar et al., 1998.)

the molecular pathogenesis of prion disease. Tg mice expressing mutant PrP develop CNS degeneration spontaneously and transmit disease to inoculated recipients (Hsiao et al., 1994). Tg mice expressing wt PrP from foreign hosts have been rendered susceptible to foreign prions with abrogation of species barriers (Prusiner et al., 1990), which manifest as a prolongation of the incubation time upon first passage in a foreign host (Pattison, 1965). As the level PrP transgene expression was increased, the incubation time decreased (Prusiner et al., 1990). The species barrier was reproduced in Tg mice expressing a mouse PrP molecule of 106 amino acids with two large deletions accounting for almost 50% of the residues. In these mice, a transmission barrier was observed after inoculation with prions from wt mice, but was abolished once miniprions composed of PrP^{Sc} with 106 residues were used as the inoculum (Supattapone et al., 1999a).

Tg mice expressing the P102L mutation causing GSS the mice developed signs of CNS dysfunction from 50 to 200 days of age (Hsiao et al., 1994). Although little protease-resistant PrP was found, widespread deposition of PrP amyloid and reactive astrocytic gliosis were observed. Extracts from the brains of these ill mice transmitted disease to Tg196 mice expressing the same mutant transgene at a low level that infrequently produces spontaneous disease. The Tg196 mice developed neurologic signs about 240 days after receiving the brain extract and the disease could be serially transmitted. A synthetic peptide of 55 residues carrying the P102L mutation produced disease in Tg196 mice about 360 days after inoculation and the illness could be serially transmitted (Kaneko et al., 2000). Only the mutant peptide in a β-sheet conformation induced by exposure to acetonitrile produced neurologic disease.

Some lines of PrP-deficient ($Prnp^{0/0}$) mice developed ataxia at about 18 months of age (Sakaguchi et al., 1996), while other lines did not (Büeler et al., 1992). Subsequent studies showed that those developing ataxia and Purkinje cell degeneration overexpress an adjacent gene designated Prnd, which encodes the protein doppel (Dpl) (Moore et al., 1999). PrP and Dpl represent an ancient gene duplication with considerable sequence divergence but structural conservation. In mice developing cerebellar degeneration, high levels of an intergenic mRNA were found where the two untranslated exons of the PrP gene were spliced to the Dpl exon containing the open reading frame (ORF) or protein coding region. High levels of Dpl protein expression were found to be toxic for Purkinje cells, but overexpression of PrP rescued the ataxic phenotype (Nishida et al., 1999).

Alzheimer's disease

Tg mice expressing mutant APP have been found to develop amyloid plaques filled with the Aβ peptide (Games et al., 1995; Hsiao et al., 1996). In some cases, these mice show behavioural abnormalities while in others, such changes have not been reported. The development of Aβ plaques was accelerated when extracts from the brains of patients with AD were injected into Tg mice expressing mutant APP (Kane et al., 2000). In earlier studies, AD brain fractions enriched for tau induced deposits of Aβ in the brains of rats (Shin et al., 1993). In uninjected bigenic mice, development of Aβ plaques was hastened by expression of mutant APP and PS1 transgenes (Borchelt et al., 1997). In other bigenic mice expressing human mutant APP and human ApoEε4 but not ε3, cognitive deficits were identified at 6 months of age even though no Aβ plaques could be found (Raber et al., 2000). These findings argue that the neuronal dysfunction in Alzheimer's disease may not be due to the Aβ plaques, but to events occurring prior to the sequestration of Aβ and other molecules into the plaques (Mucke et al., 2000). Such a scenario would be in accord with the findings for prion diseases in which PrP amyloid plaques are not obligatory for disease pathogenesis. In fruit flies, disruption of the APP-like gene or presenilin causes nervous system dysfunction, and overexpression of wt presenilin in flies causes cell death. In worms, suppression of nicastrin expression induces a phenotype similar to that seen with disruption of the presenilin-like genes (Yu et al., 2000).

Nicastrin and the presenilins are thought to form complexes that have γ-secretase activity, which may function in regulated intramembrane proteolysis (Rip) to produce the Aβ peptide from APP (De Strooper et al., 1999). Several other examples in intramembrane proteases acting in diverse metabolic processes have been discovered (Brown et al., 2000; De Strooper & Annaert, 2000).

Frontotemporal dementia

Expression of human tau with the P301L mutation in Tg mice produced neurofibrillary tangles and Pick bodies in neurons throughout the CNS (Lewis et al., 2000). By 10 months of age, ~90% of these Tg mice developed progressive neurologic dysfunction resulting in death within a month.

Parkinson's disease

The expression of either wt or mutant human α-synuclein in fruit flies produced adult onset loss of dopaminergic

neurons and locomotor dysfunction (Feany & Bender, 2000). Additionally, filamentous, intraneuronal inclusions of α-synuclein were found. In Tg mice expressing mutant and wt human α-synuclein, intraneuronal inclusions of human α-synuclein were found in the neocortex and hippocampus as well as substantia nigra where a significant loss of dopaminergic neurons was observed (Masliah et al., 2000; van der Putten et al., 2000).

ALS

In Tg mice expressing mutant SOD1, vacuolation, neuronal death, and reactive gliosis in the spinal cord have been found as well as cytoplasmic inclusions of SOD1 in motor neurons (Cleveland & Liu, 2000). Tg mice overexpressing the human large neurofilament subunit (NF-H) produced altered function in large myelinated motor neurons (Kriz et al., 2000). Of particular interest are bigenic mice in which wt NF-H and mutant SOD1(G37R) have been expressed. The overexpression of NF-H extended the lifespan of mice expressing mutant SOD1 by ~6 months (Couillard-Després et al., 1998). The results of these experiments suggest that much of the neurofilament protein was trapped in the cell bodies and thus, was prevented from being transported into the axons where altered neurofilaments would cause dysfunction. Less striking is the increase in survival by ~40 days in Tg mice expressing mutant SOD1(G37R) due to disruption of the neurofilament genes (Williamson et al., 1998).

Huntington's disease

Tg mice expressing the mutant huntingtin protein with 48 or 89 repeating Gln residues develop neurologic dysfunction and striated degeneration (Reddy et al., 1998). In attempts to reproduce all aspects of HD, a large number of Tg mice has been produced using different vectors and varying numbers of CAG repeats (Shelbourne et al., 1999). Notably, YAC clones of the huntingtin gene with 46 or 72 repeating Gln residues have been used to produce selective striatal degeneration (Hodgson et al., 1999). Using the tetracycline inducible transgene system, regulated expression of exon 1 of the huntingtin gene with 94 polyglutamine residues has been used to produce an HD model with reversible neurodegeneration (Yamamoto et al., 2000). Using exon 1 with 92 and 111 repeating Gln residues, gene targeting has been used to produce knockin mice that show accumulation of mutant huntingtin in the nuclei of spiny neurons of the striatum (Wheeler et al., 2000). In Drosophila, expression of the huntingtin protein carrying a polyglutamine repeat of 75 amino acids produced striking neuronal degeneration (Jackson et al., 1998).

Using cultured neurons from the striatum and hippocampus of the rat, expression of a fragment of the huntingtin protein with 68 repeating Gln residues produced nuclear inclusions of the mutant protein and apoptosis (Saudou et al., 1998). When the nuclear inclusions were diminished by inhibiting ubiquitination, apoptosis increased, arguing that aggregation of the mutant protein helps protect cells. Although some investigators argue that aggregation is an essential feature of the polyglutamine repeat diseases (Perutz, 1996), these results and those discussed below for Tg mice expressing mutant ataxin 1 argue that the misfolding of monomers or oligomers of proteins with Gln expansions is responsible for disease and that nuclear inclusions, which are often seen in humans and Tg models, may reflect sequestration of potentially pathogenic proteins.

Spinocerebellar ataxias

Expanded GIn repeats in ataxin 1 causing SCA1 have been expressed in Tg mice and shown to cause ataxia and Purkinje cell degeneration. Mutation of the nuclear localization signal in ataxin 1 with 82 repeating Gln residues prevented disease in Tg mice (Klement et al., 1998; Lin et al., 1999). In contrast, deletion of 122 amino acids comprising the self-aggregation domain in ataxin 1 with 77 repeating Gln residues did cause disease when expressed in Tg mice. These results argue that nuclear localization is required for disease pathogenesis but aggregation is not. In Tg mice, expression of ataxin 2 with an expanded glutamine repeat of 58 residues resulted in impaired motor skills and cytoplasmic but not nuclear aggregates of the protein in Purkinje cells (Huynh et al., 2000). Tg mice expressing ataxin 3 with an expanded glutamine repeat of 79 residues failed to develop neurologic dysfunction as well as degeneration of cerebellar dentate neurons and the basal ganglia that is seen in Machado–Joseph disease (MJD), also known as SCA3 (Ikeda et al., 1996). When the 79 Gln residues were expressed with adjacent 42 amino acids that are found immediately at the C-terminal of the repeat, they developed ataxia by four weeks of age and showed widespread degeneration of the cerebellum by eight weeks. In *Drosophila*, expression of the ataxin 3 carrying a polyglutamine repeat of 78 amino acids resulted in degeneration of the eye (Warrick et al., 1999).

The ability to reproduce virtually every aspect of the human prion diseases in Tg mice has proved to be a useful goal for studies of other neurodegenerative diseases. The progress in modelling other neurodegenerative disorders

in Tg mice, flies, and worms is impressive. When the CNS dysfunction accompanied by region-specific neuropathology mimicking the human disease is produced in organisms expressing mutant transgenes, it is reasonable to assume that significant progress in understanding the disease process is being made.

Oligomers vs. large aggregates

In a cell culture model of HD and Tg mice expressing mutant ataxin 1, formation of nuclear aggregates was separated from cell death as described above. The issue of whether large aggregates of misprocessed proteins or misfolded monomers (or oligomers) cause CNS degeneration has been addressed in several studies of prion diseases in humans as well as in Tg mice. In humans, the frequency of PrP amyloid plaques varies from 100% in GSS and vCJD to ~70% (Will et al., 1996) in kuru (Klatzo et al., 1959) and ~10% in CJD, arguing that these plaques are a non-obligatory feature of the disease (DeArmond & Prusiner, 1997). In Tg mice expressing both mouse and SHa PrP, those animals inoculated with hamster prions produced hamster prions and developed amyloid plaques composed of SHaPrP (Prusiner et al., 1990). In contrast, those Tg mice inoculated with mouse prions did not develop plaques even though they produced mouse prions and died of scrapie.

While intracellular collections of misprocessed proteins, such as Lewy bodies, nuclear inclusions and Pick bodies, may represent a mechanism whereby cells sequester proteins that cannot be readily degraded, PrP and Aβ amyloid plaques may play a similar role in the extracellular space of the CNS (Table 15.4).

Prevention and therapeutics

There is no known effective therapy for treating or preventing CJD or any of the other neurodegenerative diseases. Only in Parkinson's disease does an effective treatment exist that ameliorates the symptoms (Cotzias et al., 1967; Marsden & Parkes, 1977) but it does not halt the underlying degeneration. Because the prion diseases progress more rapidly than the other neurodegenerative disorders, fatalities from these maladies are more readily measured. There are no well-documented cases of patients with CJD showing recovery either spontaneously or after therapy, with one possible exception (Manuelidis et al., 1976), for which there is no confirmatory example. In the highlands of New Guinea, individuals who were thought to have recovered from kuru were eventually shown to have hysterical illnesses.

The difficulty of developing effective drugs for the prevention and treatment of the neurodegenerative diseases should not be underestimated. New principles of pharmacotherapeutics will undoubtedly emerge from development of drugs for treating neurodegeneration. The history of successful therapeutics for preventing or reversing protein misprocessing is extremely limited. As more is learned about the molecular pathogenesis of the neurodegenerative diseases, more opportunities for drug targets will emerge (Orr & Zoghbi, 2000). Directing these new drugs to specific regions of the CNS will also be challenging.

Preventing misprocessing

Structure-based drug design focused on dominant negative inhibition of prion formation has produced several lead compounds (Perrier et al., 2000). Prion replication depends on protein–protein interactions and a subset of these interactions gives rise to dominant negative phenotypes produced by single residue substitutions (Kaneko et al., 1997; Zulianello et al., 2000). The task of exchanging polypeptide scaffolds for small heterocyclic structures without loss of biological activity remains difficult. Whether this approach, designed to prevent the misfolding and aberrant processing of proteins, will provide general methods for developing novel therapeutics for Alzheimer's and Parkinson's diseases, as well as ALS and other neurodegenerative diseases, remains to be established.

The γ-secretase, which catalyses the hydrolytic cleavage of APP in the production of the Aβ peptide, continues to be a focus with respect to possible therapeutics for AD (Selkoe, 1999). Inhibitors of γ-secretase have been identified and are being evaluated for their efficacy in slowing the ravages of AD. Recent studies suggest that anti-inflammatory and cholesterol-reducing drugs can significantly reduce the risk of AD (Jick et al., 2000).

Enhanced clearance

Several compounds have been demonstrated to eliminate prions from prion-infected cultured cells. A class of compounds known as 'dendrimers' seems particularly efficacious in this regard (Supattapone et al., 1999b). Numerous drugs have been demonstrated to delay the onset of disease in animals inoculated with prions if the drugs are given around the time of the inoculation (Priola et al., 2000). The most common scenario in which one would want to treat humans is either patients showing signs of

disease or presymptomatic patients carrying mutations predisposing them to develop prion disease. No treatment has shown any efficacy in animal models of these two scenarios.

A novel approach to treating AD has been developed using Tg mice overexpressing a mutant APP gene. Immunization of these Tg mice with the Aβ peptide resulted in a profound decrease in the Aβ amyloid in the CNS, presumably by accelerating the clearance of Aβ peptides (Schenk et al., 1999). Whether this approach will prove fruitful in patients suffering from AD or applicable to other neurodegenerative disorders is unknown.

Replacement therapy

Because the neurodegeneration in Parkinson's disease is confined largely to the substantia nigra, especially early in the disease process, replacement therapy has proved to be useful; however, many patients eventually become refractory to L-dopa therapy (Marsden & Parkes, 1977).

Similar approaches to AD have been disappointing in large part because the disease process is so widespread. The widespread neuropathology in ALS, FTD, and prion diseases also makes replacement therapy an approach that is unlikely to be successful.

Speculation on the spectrum of degenerative diseases

Besides the neurodegenerative diseases that were discussed previously, it is tempting to speculate that protein misprocessing features in other common diseases of the CNS, such as schizophrenia, bipolar disorders, and autism. Most cases of schizophrenia, bipolar disorders, and autism are sporadic but a substantial minority appear to be familial. The lack of consistent neuropathologic changes in the brains of people with these diseases has impeded studies and complicated phenotypic analysis. Not unlike these diseases are alcoholism and other forms of addiction in which most cases are sporadic but a minority are familial. In one group of patients with inherited FTD, alcoholism and Parkinson's disease are prominent features; these people carry a mutation in the tau gene (Wilhelmsen et al., 1994).

Whether diseases, such as multiple sclerosis (MS), that are frequently classified as neurodegenerative diseases, are caused by protein misprocessing is unknown (Seboun et al., 1997). In MS, the immune system features prominently in the pathogenesis of the disease and thus, it is often argued that MS should be classified as a T-cell mediated autoimmune disorder. In some MS cases, antibody-mediated demyelination has been found (Genain et al., 1999) and in other cases, degeneration of oligodendrocytes has been observed with little or no evidence for immune-mediated damage (Lucchinetti et al., 2000).

Whether the misprocessing of proteins features in neurodegeneration that is independent of the inflammatory process in MS or it initiates an aberrant immune response is unknown. Like the neurodegenerative diseases discussed above, most cases of MS are sporadic while a minority are familial. The inheritance of MS is polygenic but to date, no single mutant gene causing MS has been identified (Haines et al., 1998). Molecular mimicry has been suggested as the mechanism that initiates the immune-mediated demyelination of the CNS in MS, in which an antigenic site on the protein of an infectious pathogen, such as a virus, provokes an immune response directed at an epitope of a myelin protein (Fujinami and Oldstone, 1985; Wucherpfenning and Strominger, 1995). The participation of an infectious pathogen in MS remains an attractive hypothesis that could explain the geographically isolated clusters as well as how the risk for MS is acquired during childhood.

Systemic diseases such as juvenile type I and adult onset type II diabetes mellitus are likely to be caused by protein misprocessing. Juvenile diabetes seems to be an autoimmune disease; despite control of the insulin deficiency, progressive degeneration of peripheral nerves, the retinas, and kidneys often proceeds (Taylor, 1995). In the β-islet cells of patients with type II diabetes, the protein amylin frequently accumulates as amyloid fibrils. Like the juvenile form of diabetes, control of the insulin deficiency does not prevent the development of polyneuropathy, retinopathy, and renal disease in adult onset diabetes. When reflecting on MS, perhaps illnesses like ulcerative colitis, Crohn's disease, rheumatoid arthritis and lupus ought to be considered as possible disorders of protein misprocessing in which misfolded proteins might evoke an autoimmune response. Like the neurodegenerative disorders (Table 15.2), a minority of cases of these autoimmune diseases are familial while the majority are sporadic.

The systemic amyloidoses share important features with the neurodegenerative diseases. In primary amyloidosis, immunoglobulin light chains form amyloid deposits that can cause cardiomyopathy, renal failure and polyneuropathy (Benson, 1995). In response to chronic inflammatory diseases, the serum amyloid A protein is cleaved to form the amyloid A protein, which is deposited as fibrils in the kidney, liver, and spleen. The most common systemic hereditary amyloidosis is caused by the deposition of mutant transthyretin. More than 40

mutations of transthyretin gene have been found to result in proteins causing familial amyloidotic polyneuropathy.

While speculation about the possible role of protein misprocessing in many diseases presents a series of attractive and, in some instances, provocative hypotheses, other mechanisms that compromise cell function need to be entertained. For example, apoptosis can be initiated by a variety of pathways, in which protein misprocessing is likely to play little or no role.

The future

As the lifespan of humans continues to increase through the efforts of modern medical science, an increasing burden of degenerative diseases is emerging. Developing effective means of preventing these disorders and treating them when they do occur are paramount to the personal, political, and economic future of our planet. The problems caused by AD and Parkinson's disease are already so large that if these maladies continue to increase in accord with the changing demographics of the world population, they will bankrupt both the developed and underdeveloped nations over the next 50 years. It is remarkable to think that by the year 2025, more than 65% of people over the age of 65 will be living in countries that are now designated as the developing nations (United Nations, 1999). Unless effective treatments and methods of prevention are developed, this immense group of people will be subject to the same risk for AD, Parkinson's disease, and other neurodegenerative disorders as people who are currently living in the most affluent of nations.

In summary, the discovery of prions and many other findings now permit a molecular definition and classification of the neurodegenerative diseases. Alzheimer's and Parkinson's diseases as well as ALS, FTD and the prion diseases are all disorders of protein processing as are Huntington's disease and the spinocerebellar ataxias. Until recently, clinical signs and neuropathologic lesions were the primary means of describing these disorders. While these characteristics remain useful in diagnosis, the etiologies can now be attributed to the misprocessing of particular proteins. In each of the neurodegenerative disorders, the particular protein that undergoes misprocessing determines the disease-specific phenotype, which results from the malfunction of distinct sets of neurons.

The remarkable progress in elucidating the etiologies of the major neurodegenerative diseases over the past two decades argues that the time has come to intensify the search for drug targets and develop compounds that interrupt the disease processes. In some of the neurodegenerative diseases, it may be most efficacious to design drugs that specifically block the misprocessing of a particular protein while in other cases, drugs that enhance the clearance of an aberrant protein or fragment may prove to be more useful. Regardless of the therapeutic approach, the need for accurate, early detection of neurodegeneration will be extremely important so that drugs can be given before significant damage to the CNS has occurred.

The task of developing useful diagnostic tests and effective therapeutics for neurodegenerative diseases should not be underestimated. Past experience with cardiovascular disease and cancer should be a forewarning of the difficult paths that lie ahead. Nevertheless, the remarkable progress in deciphering the etiologies of the neurodegenerative diseases and the urgency to prevent these age-dependent disorders should provide vigorous encouragement.

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16

Aging and dementia: principles, evaluation and diagnosis

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'Aging', or 'senescence' usually refers to the involutional changes that occur after an individual has reached full structural and functional maturity (Masoro, 1995). While it is clearly related to the passage of time, there is considerable variability among individuals in when the declines in function occur, the extent of the changes and the selective involvement of specific structures. The onset of impairment due to senescent changes, as well as the overall longevity of individuals, may vary by 50% or more. Senescent changes may involve the heart, joints, skin, brain or other organs in different individuals; and both the organ(s) involved and the degree of decline may be related to genetic and/or experiential factors. Adults between the ages of 65 and 85 years are classified as the 'young-old'; those over age 85 as the 'oldest-old' (Suzman et al., 1992). As the elderly are the fastest growing segment of the population, there is much interest in the causes of senescence, and potential medical means of preventing or delaying their effects, many of which constitute the 'degenerative diseases' of the elderly.

Because of the variability in senescent decline, the concept of 'normal' aging has been controversial, and the term has been used in at least three different ways:

- The optimal level of function seen in individuals of a given age;
- The level of function seen in individuals of a given age in the absence of disease; and
- The mean level of function of all individuals of a given age.

Each of these concepts of 'normal aging', used in the appropriate context, is of value in recognizing and defining the usual expectation, specific disorders, and maximum potential of individuals with advancing age (Rowe & Kahn, 1987). The genetic endowment, the accidents of chance, and the wear and tear of lifetime experience assure that no one definition is necessarily the correct one. Regardless, all three definitions endorse the fact that some decline in function occurs over time; and the relationship between gradual decrements in performance with age, and more rapid and significant impairment of function with disease, is a key issue in understanding the neurologic basis of dementia.

In this chapter we will review:

- anatomic, physiologic and pharmacologic changes that occur in the aging brain;
- cognitive changes with advancing age;
- the molecular basis for age-related changes (ARCs) that cause senescent decline;
- the relationship between aging and dementia;
- clinical manifestations of dementia; and
- a brief classification of dementing disorders.

Anatomical and physiological changes with aging

Gross changes in the aging brain

Autopsy studies have shown that brain weight declines increasingly after age 50, at a rate of about 2% per decade (Miller et al., 1980); by the age of 80 the brain weight is typically decreased by about 10% compared with young adults. CT and MRI studies on aging populations show a linear decrease in brain volume with increasing age (Murphy et al., 1992), and a proportionally more marked increase in ventricular and sulcal volume with age. There is more shrinkage of grey matter than white matter (Pfefferbaum et al., 1994), but gyral atrophy affects predominantly the association and limbic cortices, sparing the primary sensory and motor cortices. On MRI scans, atrophy is seen most prominently in the frontal lobes, less so in the temporal lobes and least in the parieto-occipital

lobes; frontal atrophy is more marked in males and parietal atrophy in females (Murphy et al., 1996). In the temporal lobes, medial temporal and hippocampal atrophy predominates, particularly on the left side. The rate of hippocampal atrophy over time correlates with the risk of developing dementia (Jack et al., 1998).

Age-related myelin loss in the brain involves predominantly the small myelinated fibers (Tang et al., 1997). On MRI imaging, white-matter hyperintensities increase exponentially in aging subjects, with only 4.4% of a large, community-dwelling elderly population being entirely free of these changes (Longstreth et al., 1996). The pathological basis and clinical significance of these MRI changes are uncertain; some are ischemic in nature, while periventricular 'caps' may be due to subependymal gliosis (Fazekas et al., 1993).

Microscopic pathology of the aging brain

Changes in the aging brain include neuronal loss, synaptic loss, gliosis and often the accumulation of neuritic plaques and neurofibrillary tangles. Neurons are primarily postmitotic cells and although some may be replaced by neural stem cells (Roy et al., 2000), the vast majority are believed to be irreplaceable. Different neuronal systems have differential vulnerability to aging; the neuronal systems most vulnerable to aging are located in the basal forebrain nuclei, hippocampus, entorhinal cortex, neocortex and brainstem monoaminergic systems. Neuronal loss appears to be regional and lamina specific rather than global, however, and modern stereologic counting techniques show less severe neuronal loss than was previously thought (Coleman & Flood, 1987). The regional pattern of neuronal loss appears to differ in normal aging and Alzheimer's disease: the number of neurons in the entorhinal cortex (layer II), hippocampal CA1 region and the locus ceruleus is not reduced in normal aging, while these regions lose up to 70% of their neurons in Alzheimer's disease (West et al., 1994; Gomez-Isla et al., 1996; Mouton et al., 1994). Similarly, losses of dendrites and synapses are not inevitable correlates of aging. Certain cortical areas show a decline in synaptic density (Lippa et al., 1992; Masliah et al., 1993) while in others there may even be an increase in the synaptic density with aging. While the increase in local synaptic density with aging may be an effort to compensate for regional neuronal loss (Arendt et al., 1995), it may reflect a decrease in neuropil volume. Loss of synapses correlates better with the severity of cognitive impairment in an aging brain than other changes, such as the accumulation of senile plaques and neurofibrillary tangles (NFTs), described below (Terry et al., 1991). Age-related changes also include granulovacuolar degeneration (1–5 μ intracytoplasmic, neuronal vacuoles with a 1 μ central, basophilic granule) and the appearance of Hirano bodies (eosinophilic, spindle-shaped, intracytoplasmic inclusions), both occurring predominantly in the hippocampus.

With aging, glial proliferation occurs (Hansen et al., 1987), and both neuritic plaques and neurofibrillary tangles are often found, sometimes in large numbers (Fukumoto et al., 1996; Wisniewski et al., 1979). Amyloid is the core constituent of the plaques, where it is surrounded by dystrophic neurites and glial proliferation. Amyloid may also be deposited in and around the walls of aging cerebral arterioles (amyloid angiopathy) or as diffuse plaques without a surrounding glial response. Neurofibrillary tangles (NFT) are intraneuronal silver-staining bodies, seen as paired helical filaments ultrastructurally, and consisting of hyperphosphorylated tau – a microtubule-associated protein, which may also be deposited as intracellular or as extracellular neuropil threads. While amyloid plaques and NFTs increase in frequency and number with normal aging, they are also considered the hallmark of Alzheimer's disease in demented patients (Ball & Murdoch, 1997), using semiquantitative counts of plaques or NFTs as well as their distribution (Khachaturian, 1985; Braak et al., 1993) to distinguish normal from disease. The quantitative histologic distinction between age-related and disease-related findings is still uncertain, especially in the oldest-old, however.

Age-related changes in neurophysiology

In older subjects, resting cerebral blood flow decreases frontally on MR angiography, PET and to a lesser degree SPECT studies (Buijs et al., 1998; Martin et al., 1991); while decreased parietal metabolism may be seen as a marker of early Alzheimer's dementia (Reiman et al., 1996). On EEG, 'healthy aging' by itself causes few EEG changes, such as diminished alpha reactivity and an increase in beta activity (Roubicek, 1977; Koyama et al., 1997). Other changes often seen with aging, such as a decrease in mean alpha frequency and focal temporal slowing, may be correlated with declines in performance on memory and cognitive tests (Drachman & Hughes, 1971).

Age-related changes in neurotransmitter function

Decline in neurotransmitter function is an important factor in the cerebral impairment of aging and dementia (Drachman, 1977; Strong, 1998). In Alzheimer's disease, loss of cholinergic projections from the nucleus basalis of Meynert to the hippocampus and cortex correlate with the

loss of memory (Bierer et al., 1995), and the visual hallucinations seen in Lewy body dementia are associated with decreased neocortical cholinergic activity (Perry et al., 1999). It is less certain that acetylcholine levels decline significantly in disease-free aging (Muller et al., 1991; Sarter & Bruno, 1998). A decline in nigral dopamine levels is also well documented in normal aging (Martin et al., 1989), and decreased serotonergic and peptidergic function have been invoked to explain mild age-related memory loss (Buccafusco & Terry, 2000). Response to neurotransmitters may be altered as well; even in the healthy, aging neurons become more susceptible than younger neurons to excessive extracellular glutamate or dopamine levels, and are more likely to suffer excitotoxic cell death (Beal, 1992).

Cognitive changes with aging

Some cognitive changes are nearly universal in the elderly, including a decline in memory storage (i.e. the ability to learn new information), and a decline in the speed of mental processing. Schofield found that 31% of healthy older adults reported memory complaints, such as difficulty remembering names and misplacing of commonly used objects such as keys (Schofield et al., 1997a). Conscious recall (declarative memory) is more often impaired than is motor memory for previously learned skills, such as playing the piano (procedural memory) (Fuld, 1980; Drachman, 1986). Recall of context-specific information (episodic memory) is more affected than the recall of general information (semantic memory); and retrieval is more impaired than recognition. Immediate memory span (what can be recalled after a single hearing) and long-term memory for events in the remote past are preserved. In patients who become demented, this pattern of memory impairment is exaggerated.

Cognitive tasks involving speed of processing begin to show impairment in the fourth decade, and as processing speed continues to slow (Salthouse, 1996), this affects many tests of cognitive function. Actual performance on global intelligence tests, such as the Wechsler Adult Intelligence Scale (WAIS), declines with age, although IQ scores are age corrected, thus numerically masking this decline. To achieve an IQ of 100 at age 75, for example, one need be correct on only half as many items as at age 21 (Wechsler, 1981). The greatest age-related decline in scores is noted in the timed 'performance' subtests (picture completion, digit symbol substitution, block design), with smaller, declines on the untimed 'verbal' subtests (vocabulary, digit span). The time required to perceive a stimulus increases, as measured by tests involving 'backward masking', i.e. the delivery of a second stimulus so close to the first, that the initial stimulus is not perceived (Kline & Szafran, 1975). The central processing time increases, as shown by a disproportionate increase in choice reaction time (Fozard et al., 1994), and documented by increased latency in the central component of event-related P300 evoked responses (Polich, 1996). Visuospatial construction ability decreases with age, but this does not typically affect daily function. 'Crystallized intelligence', accumulated knowledge as measured, e.g. in tests of vocabulary, tends to be retained, while 'fluid intelligence', the ability to manipulate new information to solve problems, declines with aging (Horn & Cattell, 1967). Cognitive decline with aging is more likely to be seen in elderly subjects with systemic disorders such as hypertension and diabetes mellitus, although the mechanism of causality is uncertain (Skoog, 1997; Skoog et al., 1996). The norms of cognitive function in the oldest-old, those above age 85, are inadequately defined, with only a few studies, such as the Mayo Clinic's Older Americans Normative Study, extended to include subjects in this age range (Ivnik et al., 1997; Lucas et al., 1998).

Other neurological changes with aging

A decrease in special senses is common. Visual acuity declines due to presbyopia and cataract formation (Kini et al., 1978); altered blue perception due to yellowing of the lens; decreased pupillary size and reactivity; and diminished upward gaze. Hearing, especially for high frequencies, decreases (presbyacusis) (Critchley, 1931; Kaye et al., 1994). Olfactory perception (Doty, 1991) and odour identification decrease (Larsson et al., 1999). Motor system changes include diminished muscle bulk and power (a consequence of decreased activity and atrophy of fast-twitch type II fibres) (Aniansson et al., 1986), mild increase in muscle tone (Kaye et al., 1994), slowing of movement (Waite et al., 1996) and an increased frequency of both essential and extrapyramidal tremors (Skre, 1972). Changes in gait include impairment of postural reflexes, a decrease in stride length, gait velocity and arm swing, and gait changes due to orthopedic problems (Murray et al., 1969; Larish et al., 1988) such as osteoarthritis and changes in the spine. The ankle jerks are often hypoactive (Prakash & Stern, 1973). The perception of vibratory and proprioceptive sensation is diminished in the lower limbs.

Molecular mechanisms for age-related changes (ARCs)

Senescence is the consequence of specific biological mechanisms that cause the progressive accumulation of

'age-related changes' (ARCs). Many of these ARCs originate at a molecular or cellular level; they result in clinically evident disorders when sufficient attrition in neural numbers or function occurs so that brain systems can no longer work effectively. ARCs result from both intrinsic events: those due to the inherent attrition of critical survival elements, and those designed to dispose of imperfect components, and from random, extrinsic adverse events. Genetic differences among individuals modify both the timing and the rate of progression of intrinsic events, and the susceptibility to, and effect of, extrinsic events. The precise point at which accumulating ARCs increase the vulnerability to neurodegenerative disorders, or may reach a threshold and become manifest as clinical 'disease', is as yet unclear.

Intrinsic ARCs

The nature of intrinsic ARCs is clearly exemplified by the finite survival of cells and their limited ability to divide in tissue culture, first demonstrated by Hayflick and Moorhead in the early 1960s (Hayflick & Moorhead, 1961). Until that time, it was widely believed that cells grown in culture were immortal. Rigorous studies by Hayflick and his colleagues showed that cells in culture could undergo only a limited number of divisions, then underwent growth arrest at the G_1-S boundary, became dormant and eventually died (Hayflick & Moorhead, 1961; Hayflick, 1965, 1980). Human fetal fibroblasts have the capacity to divide about 50 times, while adult cells can divide only about 20–30 times, the number of replications decreasing with advancing age. The capacity to divide resides in the cellular nucleus, rather than the cytoplasm. When nuclei taken from young cells were transplanted into the cell bodies of older cells, the number of subsequent divisions was increased, based on the age of the young donors; while nuclei from old cells transplanted into young cells bodies reduced the number of divisions and survival to that of the donors.

The nature of the mechanism enabling cells to 'keep count' of the number of divisions they have undergone is largely explained by *telomeric shortening*. The telomere, or chromosome tail, consists of hundreds of TTAGGG repeat sequences, found on each end of every chromosome. Each time a cell divides, its chromosomes lose part of their telomeric tails; when the tails become too short the cell can no longer divide. Most human cells undergo telomeric shortening with advancing age; although this does not apply to adult neurons which are postmitotic, it affects both glial cells and stem cells (Ostenfeld et al., 2000). The enzyme telomerase is present in normal cells but inactive; when activated, it allows cells to regenerate their telomeres. In germinal cells, cancer cells and 'immortalized cells' telomerase is active, and reactivation of telomerase may increase cell longevity (Greider 1990, 1998; Zhu et al., 2000).

Early concepts regarding the molecular mechanisms contributing to ARCs were the 'somatic mutation theory', proposed by the atomic physicist, Leo Szilard, and the 'error catastrophe theory' of Leslie Orgel. Szilard hypothesized that aging might be due to the accumulation of random mutations in DNA (Szilard, 1959); while Orgel suggested that errors occurring in key functional proteins, such as enzymes, might initiate a cascade of cumulative, increasingly destructive biochemical errors, resulting in senescence and death (Orgel, 1963). Neither of these theories has found direct experimental support, however (Norwood et al., 1990); chemically abnormal proteins are found only occasionally in cell cultures and rarely in vivo.

A novel process, thought to be restricted to aging cells and first described in neurons, is the incorrect conversion of genomic information from normal DNA into nonsense RNA transcripts with subsequent translation into mutant, non-functional proteins. This process has been called 'molecular misreading' and causes some errors unrelated to DNA damage (van Leeuwen et al., 2000).

Accumulation of catabolized structural protein products in increased amounts is found in normal aging and several dementias. The cerebral amyloid precursor protein (APP) normally undergoes enzymatic degradation to form β-amyloid 1–40 and 1–42 (Glenner & Wong, 1984) which accumulates in senile plaques with advancing age. In Alzheimer's disease the exaggerated deposition of β-amyloid 1–42 (Sisodia et al., 1990) results in the hallmark increase in cerebral plaque formation and may cause dementia (Jarrett et al., 1993). Tau, a microtubule associated protein (MAP) normally abundant in the axon stabilizes polymerized microtubules and plays a role in axonal transport. Excessive hyperphosphorylated tau is found in neurofibrillary tangles (Lee et al., 1991), which are found in aging, and are increased in Alzheimer's disease, frontotemporal dementia and other dementing disorders. Other protein products that accumulate in the brain and are associated with age-related degenerations include: α-synuclein (Parkinson's disease and Lewy body dementia) (Spillantini et al., 1998) and ubiquitin (Lewy bodies).

While genetic mutations producing chemical changes in key proteins are probably not an important aging mechanism, conformational changes in proteins may be (Danner & Holbrook, 1990; Johnson et al., 1996; Taubes, 1996; Gafni, 1997). These are post-translational structural changes due to initial misfolding of proteins, or alteration of their normal functional shapes due to cross-linking, covalent

bonding, phosphorylation, glycation or other changes (Gafni, 1997; Levine et al., 1996; Richardson & Holbrook, 1996). It is known, for example, that 0.1% of the body's proteins undergo dextrorotation each year, forming right-handed conformations that are non-functional. The chaperone systems, such as the heat-shock proteins (HSPs) of the HSP 70 group, normally both aid in the initial folding of proteins, and in the recognition and refolding, or removal, of conformationally abnormal proteins. The functional capacity of the chaperone systems declines with age, however, related in part to the energy requirements of the process, and the decline in available energy (see below).

Damage to DNA, proteins and membrane lipids may be a result of oxidative stress (Beal, 1995; Venarucci et al., 1999). As a byproduct of oxidative metabolism and normal energy production, oxygen alone or in combined forms (hydroxyl or peroxide radicals) may be produced with an extra unpaired electron. These volatile radicals rapidly oxidize adjacent molecules by donating their extra electrons. Mitochondrial DNA is particularly vulnerable to oxidative stress since it is close to the site of oxidative energy production via phosphorylation; and mitochondrial DNA lacks the repair capability of nuclear DNA. This initiates a cascade of destructive events: impaired mitochondrial function causes decreased energy production, with its consequences: calcium influx into cells, excitotoxic cellular damage, failure of chaperone repair mechanisms, and eventual cellular death (Harman, 1992; Nagley et al., 1992; Julius et al., 1994; Fletcher & Fletcher, 1994; Mattson, 1994). It is not clear whether oxygen free radicals play a major role in senescence, or whether they have an important etiological role in causing parkinsonism, Alzheimer's disease, amyotrophic lateral sclerosis or other degenerative neurologic disorders of aging (Beal, 1995; Mattson, 1994; Harman, 1996; Knight, 1995; Chiueh et al., 1994; Floyd, 1991; Wolozin et al., 1996).

In an experimental model, the brains of aged gerbils contained twice the amount of oxidized protein as those of young gerbils, and the levels of two enzymes helpful in disposing of oxidized products (neutral protease and glutamine synthetase) were reduced with age (Carney et al., 1991). Older gerbils made more errors than younger adult gerbils in running radial mazes, but this difference was abolished if *N*-tert-butyl-α-phenylnitrone (PBN), a powerful 'spin-trapping' agent that removes free radicals, was administered to both groups of animals (Carney et al., 1991). Accumulation of metals such as aluminium and ferrous iron may facilitate oxidative damage while Vitamins C and E, both antioxidants, are postulated to retard age-related changes. In the Honolulu–Asia aging study of 3385 men aged 71–93 years, use of vitamin C or E supplements was associated with better performance on tests of cognitive function (Masaki et al., 2000).

Caloric restriction (CR), limiting food intake of animals by 50–70%, consistently prolongs the lifespan of many experimental species by up to 40% and postpones most age-related pathology, possibly by reducing oxidative stress (Masoro, 2000; Eckles-Smith et al., 2000). A recent study with an experimental yeast model demonstrated a potential mechanism of this antiaging effect (Lin et al., 2000; Campisi, 2000). Caloric restriction in yeast prolonged survival, but only if genetic pathways for production of Sir2 protein were intact. Sir2p is a 'silencing protein' which maintains compactness of chromosomes by preventing recombination during cell cycling, and requires an energy-providing compound (NAD), which is decreased as a result of oxygen free radicals.

Thus, the cellular basis of aging appears to involve free oxygen radicals, chromosomal integrity, protein conformational accuracy and telomeric adequacy, in addition to as yet unknown changes that occur over time.

Apoptosis is an intrinsically (i.e. genetically) coded and regulated process that results in cell death by means of a predetermined degenerative pathway, in contrast to necrosis. Apoptotic cell death is characterized by a lack of inflammatory changes, the appearance of bullae in the apoptotic cells, and eventually segmentation of the nuclear DNA into small pieces to produce a 'laddered' appearance on electrophoretic gels. During normal cellular function there is an array of opposing factors that can promote or prevent cell survival or division. When the balance tilts sufficiently to invoke the cell death sequence, the apoptotic program begins. Ordinarily, oncogene proteins (e.g. Bcl-2, p35) promote survival and division, and antioncogene proteins (e.g. Rb, p53,) oppose cell division; cell cyclins vary in their roles (Monti et al., 1992). A vast array of opposing factors regulates the survival, growth and division of cells (Steller, 1995; Bump et al., 1995; Rubin et al., 1994). As cells age, these balanced regulatory controls are weakened, and the cells are more readily tipped towards excessive growth (malignancy) or death by apoptotic pathways. The final executioner for most neural apoptotic mechanisms appears to be caspase (Braun et al., 1999); caspase inhibitors may prevent neural degeneration in some age-related disorders such as Huntington's disease (Kim et al., 1999).

Lack of growth factors and generation of proinflammatory cytokines may also play a role in degeneration. Neural growth factors generate 'survival signals' for the neuron; for insulin-like growth factor this 'survival signal' is known to be phosphatidylinositol 3' kinase (PI3 kinase).

Cytokines, such as TNF-α and interleukin-1β, can induce cell-death because TNF receptor activation causes 'silencing of survival signals' (SOSS) (Venters et al., 2000), which may be an important mechanism of neuronal loss in ischemic brain injury and other conditions. Similarly, the interaction of nerve growth factor (NGF) with tyrosine kinase A (*trkA)*, a receptor for this growth factor, promotes survival, differentiation and growth of basal forebrain cholinergic neurons in mouse models; BDNF (brain derived neurotrophic factor) promotes survival and neuronal function in the substantia nigra (Hefti, 1986; Hyman et al., 1991).

Regulation of vascular function by vascular endothelial growth factor (VEGF) and nitric oxide may affect neuronal aging (Kalaria et al., 1998; Rivard et al., 1999; McCann, 1997). Recent reports suggest that dementia may be dramatically reduced in patients treated with HMGCoA reductase inhibitors (statins) for hyperlipidemia, probably independent of the lipid-lowering effects of these drugs, and due to their improvement of microvascular function by increasing endothelial nitric oxide synthetase (eNOS) and reducing endothelin-1, thereby increasing endothelial dilatation and cerebral blood flow (Jick et al., 2000; Wolozin et al., 2000).

The rate of brain aging is affected by the condition of the organ systems that nourish the brain. Systemic disorders can accelerate brain aging through a variety of mechanisms, some of these putative pathways including glycation or cross-linking of proteins (Masoro, 1991), lack of estrogen (Yaffe et al., 1998) and/or dihydroepiandrosterone (DHEA) (Huppert et al., 2000; Moffat et al., 2000), immune failure, or an exaggerated inflammatory response (Maes et al., 1999). Estrogen may improve cerebral circulation, allow brain cells to form and maintain synaptic connections, reduce amyloid deposition and increase brain levels of acetylcholine (McEwen, 1999).

The relationship between aging and dementia

Aging, with the progressive accumulation of ARCs, is the most important risk factor for the development of dementia (Drachman, 1994; Bierer et al., 1995). The annual incidence of dementia rises exponentially with age from less than 1% at age 60 to more than 12% above age 85 (Jorm et al., 1987); the prevalence at 85 is 30-fold greater than at 65. The adverse effects of any brain insult, such as a subarachnoid hemorrhage or a brain tumour, are also greater in older adults (Lanzino et al., 1996; Recht et al., 1989). Women are more likely to develop dementia than men, in part because they live longer. For a 65-year-old woman, the remaining lifetime risk for dementia is approximately 17%, nearly twice the risk of a man the same age (9%); higher than her risk for breast cancer, and equivalent to her lifetime risk of sustaining a hip fracture (Seshadri et al., 1997). Elderly subjects demonstrate a spectrum of cognitive decline, ranging from the normal changes in memory, response speed and channel capacity described earlier, through 'mild cognitive impairment' (MCI) of uncertain clinical significance, to progressive clinical dementia. The extent to which these degrees of impairment represent a spectrum of change, or a series of distinctive disorders, is as yet not entirely clear.

Mild cognitive impairment

Several terms have been used to describe mild decline in cognition in the elderly. In 1962, Kral termed stable minor memory impairment with preserved insight 'benign, senescent forgetfulness' (Kral, 1962). In 1986, Crook and colleagues (Crook et al., 1986) defined age-associated memory impairment (AAMI) as subjective memory loss in the elderly with performance more than 1 S.D. below mean values for young adults on formal memory tests. Aging-associated cognitive decline (AACD) was defined using age-adjusted norms, rather than normal values for young adults, and involved cognitive domains besides memory (Levy, 1994); it is used as a functional category in the DSM-IV classification.

Some investigators take the position that all cognitive decline with age is a consequence of disease, either systemic or involving the brain, and that the standard of 'normal' is optimal cognitive function. Neuropathological changes and measurable neuropsychological declines invariably occur to some extent with aging; yet in some individuals, these changes may represent the beginning of a progressive dementia (Elias et al., 2000). The early stage of cognitive impairment, with impaired memory or cognitive functioning for age, but preserved ability to function in daily life, has been called mild cognitive impairment (MCI) (Zaudig, 1992; Petersen et al., 1999), a diagnosis restricted to older adults when no systemic, psychiatric or neurological disease explaining the memory impairment can be identified. MCI, defined in this way, may represent a preclinical stage of Alzheimer's disease, and a predisposition to clinical dementia following unrelated neurological insults, such as a stroke. A 10–15% annual rate of progression to clinical dementia has been documented in some studies (Petersen et al., 1997). At autopsy the brains in subjects with MCI appear to have significantly more Alzheimer-type changes than those of cognitively intact age-matched subjects (Haroutunian et al., 1999; Price &

Morris, 1999). There is considerable interest in the development of drugs for this group that would delay dementia; but it is not clear what proportion of subjects with MCI would eventually develop dementia, or how to distinguish those who will show progressive deterioration. Accepting MCI as a clearly identifiable diagnostic entity has legal, ethical and financial implications and currently is of use primarily in a research setting.

Dementia

Dementia is defined as a clinical syndrome characterized by the acquired loss of cognitive abilities severe enough to interfere with work or usual social activities, including family obligations. The definition of dementia requires a decline from a prior level of cognitive function and persistence of the condition, the duration being defined in months and years rather than days or weeks. Usually, though not always, the condition is progressive. It requires a diffuse disturbance affecting multiple domains of intellectual function. The DSM-IV criteria require involvement of short-term and long-term memory and at least one of the following spheres of mental activity: language, praxis, executive function (abstract thought, judgment and problem solving) and cortical perception (gnosis) (American Psychiatric Association, 1994). Finally, the diagnosis presupposes an alert patient, without clouding of consciousness (thus excluding the acute confusional states or delirium).

Epidemiology of dementia

Estimates of the prevalence of dementia vary greatly depending on the criteria used to define dementia and the life expectancy of the population. In developed countries, fewer than 1% of the population aged 65 or younger are demented; the prevalence increases exponentially, doubling approximately every 5 years (Molsa et al., 1982; Rocca et al., 1986). Over the age of 85, between 25% and 50% of all subjects are at least mildly demented (Evans et al., 1989), and 20% are completely incapacitated (Wernicke et al., 1994). The incidence of dementia probably increases indefinitely with age; but because of shorter survival in patients over age 90 the prevalence tends to level off at about 45–50% (Ebly et al., 1994; Drachman, 1994). In population-based studies more than 50% of all dementia is due to Alzheimer's disease; a further 15% to vascular dementia; and another 15% to a combination of the two ('mixed dementia') (Schoenberg et al., 1987). Other causes of progressive degenerative dementia of the aged are listed in Table 16.1.

Genetic basis of aging and dementia

Most late-onset dementia is sporadic, with a few identified polymorphisms that modify the risk of dementia, most notably the Apolipoprotein E $\varepsilon 4$ allele (Pericak-Vance et al., 1991; Seshadri et al., 1995). The APOE $\varepsilon 4$ allele increases the risk of late-onset Alzheimer's disease two- or threefold when present, and halves the risk if absent. Some dementias have an autosomal dominant inheritance, including Huntington's disease; early-onset AD with mutations on chromosome 14 (S182/ PS1) (Sherrington et al., 1995), chromosome 21 (trisomy and APP mutations) (St George-Hyslop et al., 1987), or chromosome 1 (STM2/ PS2) (Rogaev et al., 1995); and frontotemporal dementia with chromosome 17 mutations (tau) (Hutton et al., 1998).

Survival to old-age is not entirely a chance event; the gene pool in very-old subjects differs from that in young adults, (e.g. there is a lower incidence of the APOE $\varepsilon 4$ allele) (Yashin et al., 1999; Sobel et al., 1995). Among the oldest-old survivors there may be different etiologies of dementia, and pathological series suggest that 'dementia of unknown etiology' increases to nearly 50% in nonagenarians (Crystal et al., 2000), although clinical Alzheimer's disease remains a major cause of dementia.

Environmental risk factors for dementia

Head injury and minimal education are reported to increase the risk of dementia (Stern et al., 1994; Schofield et al., 1997b). The effect of education may be due to socioeconomic disadvantages, a cohort effect (Cobb et al., 1995), an artefact of culturally biased testing, or to an actual beneficial effect of education on brain development. A cerebrovascular accident increases the risk of dementia fivefold in the first year following stroke and doubles the control risk thereafter (Tatemichi et al., 1990). Risk factors for vascular disease have been recognized as risk factors for dementia: e.g., hypertension and diabetes (Breteler et al., 1998; Swan et al., 1998). Physical activity may improve cognitive function and reduce the risk of dementia (Kramer et al., 1999).

Approach to the diagnosis and differential diagnosis of dementia

Screening for dementia and scales used in the assessment of dementia

Simple cognitive screening tests are useful to evaluate cognitive function and establish a performance baseline in

Table 16.1. Disorders that may produce adult-onset dementia

1. Static dementia due to a known cause of brain injury
a. Traumatic brain injury
b. Post anoxic syndrome
c. Single stroke
d. Post infectious sequelae (after recovery from meningitis, encephalitis, ADEM)
e. Dementia pugilistica

2. Symptomatic dementias (some potentially reversible)
a. Endocrine disturbances: hypothyroidism, hyperthyroidism, hyperparathyroidism, Cushing's syndrome, insulinoma
b. Nutritional deficiencies: Wernicke–Korsakoff syndrome, Vitamin B12 or folate deficiency
c. Malignancy (primary or secondary brain tumour, para-neoplastic syndromes, radiation dementia)
d. Chronic subdural hematoma
e. Normal pressure hydrocephalus
f. Multiple sclerosis, adult-onset leukoencephalopathies
g. Systemic lupus erythematosis, cerebral vasculitides
h. AIDS-associated dementias
i. Creutzfeldt–Jakob disease, fatal familial insomnia and other prion diseases
k. Other CNS infections (tuberculous and fungal meningitis, neurosyphilis, neurocysticercosis)
l. Alcoholic dementia, drug or toxin-induced dementias
m. Metabolic encephalopathy: hepatic failure, renal insufficiency, dialysis dementia, hypoxia
n. Inherited metabolic causes of dementia: Wilson's disease, cerebrotendinous xanthomatosis, Kuf's disease, mitochondrial disorders: MELAS, MERRF, lysosomal storage disorders, adult polyglucosan body disease

3. Vascular dementia

4. Alzheimer's disease

5. Non- Alzheimer degenerative dementias with extrapyramidal features
a. Dementia with Lewy bodies
b. Progressive supranuclear palsy
c. Huntington's disease
d. Multisystem atrophy

6. Non-Alzheimer degenerative dementias with focal lobar involvement
a. Frontotemporal dementias (including Pick's disease)
b. Corticobasal ganglionic degeneration

Source: Modified from Rossor (1992).

those over 75. Such screening tests include the Folstein Mini-Mental Status Examination (MMSE) (Folstein et al., 1975), the self-administered Cognitive Assessment Screening Test (CAST) (Drachman & Swearer, 1996; Drachman et al., 1996), and Clock-drawing. More extensive psychometric tests are useful in research settings, or when screening tests signal the need for more detailed clinical evaluation.

Standardized cognitive and functional batteries are used to measure the severity of cognitive impairment (e.g. the Blessed Dementia Rating Scale (Blessed et al., 1968) and Mattis Dementia Rating Scale (DRS) (Mattis, 1988)), and assess both cognitive function and the patient's ability to perform adequately in activities of daily living. The Clinical Dementia Rating Scale (CDR) (Berg, 1988) is a functional rating scale that derives scores from a clinical interview with the patient and caregiver regarding performance in six functional domains (memory, orientation, judgement, home and hobbies, community affairs and personal care). The Index of Activities of Daily Living (IADL) (Lawton & Brody, 1969) and the Physical Self-Maintenance Scale (PSMS) (Lawton & Brady, 1969; Lawton et al., 1982) are used to document impairment in daily activities. These scales document both the diagnosis of dementia and progression of deterioration. There are also well-validated scales to address behavioural changes in dementia, such as the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994), the BEHAVE-AD (Reisberg et al., 1987) and the caregiver obstreperous behaviour rating assessment (COBRA) (Swearer & Drachman, 1996), and to assess depression in

the setting of dementia (Cornell Scale for depression in dementia (Alexopoulos et al., 1988); Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1967)). The Hachinski Ischemic Score (HIS) (Hachinski et al., 1975), is used to evaluate the probability of vascular dementia.

Clinical evaluation of a patient with suspected dementia

Individuals may be evaluated for dementia because of self-expressed concerns, referral by a family member or by a physician. The history, obtained from a reliable family member, should include the duration of symptoms, the nature of initial complaints, the rate and pattern of deterioration, and specific areas of cognitive and behavioural impairment including memory, orientation, judgement and problem solving, affect and behaviour. The subject's financial, work, driving, shopping, homemaking and recreational abilities and interests should be documented, as well as the ability to handle personal ADLs (dressing, grooming, bathing, toileting and feeding) compared to prior performance. The instrumental ADLs (cooking, laundry, using a telephone, etc.) are typically impaired before basic ADLs.

Entirely normal performance on office screening tests makes significant dementia less likely; but at times, despite even a detailed clinical and neuropsychological evaluation, the diagnosis may remain uncertain. In these subjects, repeat testing after 6 months or a year can often clarify the diagnosis.

Differential diagnosis of dementia

Once the presence of dementia has been established, the specific underlying dementing disorder is based on the clinical picture: the subject's age, family history, initial symptoms, rate and pattern of progression, findings on systemic and neurological examination, cognitive deficits and behavioural patterns, laboratory evaluation and imaging studies.

The various etiologies of dementia are listed in Table 16.1. Evaluating patients and distinguishing among these numerous causes is facilitated by using a stepwise approach (Drachman et al., 1994). Static dementias, those due to a single event such as a head injury or encephalitis, without progressive deterioration, can be distinguished by the history from progressive dementias. Progressive dementias may be divided into symptomatic dementias, due to an identifiable, and often reversible, cause; and the degenerative dementias. Table 16.2 lists a battery of investigations that permit the identification of most symptomatic dementias. A detailed discussion of the differential diagnosis of dementia is found in Chapter *xxx*.

Table 16.2. Investigations in patients with dementia

Laboratory:	CBC and differential BUN/Creatinine Electrolytes (sodium, potassium, calcium) Liver function tests Thyroid function tests Serum B12
Imaging:	MRI scan
When indicated:	EEG (CJD, metabolic encephalopathy, recurrent CPS) CSF examination Screening for malignancy Carotid and cardiac evaluation HIV serology; serological tests for syphilis, Lyme disease Urine for drug studies, heavy metals Brain biopsy

The degenerative dementias are divided into three groups: (i) Alzheimer's disease and its variants; (ii) the extrapyramidal dementias such as Lewy body dementia; and (iii) focal cortical dementias. Consensus clinical criteria have been published for several etiologies of progressive dementia. Widely accepted clinical criteria exist for the diagnosis of Alzheimer's dementia (McKhann et al., 1984); and more recently criteria have been proposed for dementia with Lewy bodies (McKeith et al., 1996), progressive supranuclear palsy (Litvan et al., 1996), frontotemporal dementia (Neary et al., 1998), and corticobasal ganglionic degeneration (Grimes et al., 1999). Definite diagnosis of dementia type is often possible only by using clinicopathological correlation of clinical and postmortem findings. Some subjects with clinical dementia do not fit pathological diagnostic criteria for any of the classical degenerative dementias, and a number of new disease entities have been proposed, including: argyrophilic grain disease (Braak & Braak, 1998); dementia lacking distinctive histology (Knopman et al., 1990); and hippocampal sclerosis (Dickson et al., 1994; Corey-Bloom et al., 1997). The clinical categorization of some patients with degenerative dementia may be difficult, because of an atypical presentation or unusual overlap of symptoms.

The entity of vascular dementia (VaD) has remained difficult to define. In the first half of the twentieth century, 'cerebral arteriosclerosis' was considered the commonest cause of dementia in the elderly (Mayer-Gross et al., 1960). In 1970, Tomlinson and colleagues showed that, in patients

with 'senile dementia' the most frequently found pathologic changes were those of Alzheimer's disease (Tomlinson et al., 1970). Hachinski coined the term 'multi-infarct dementia', and defined criteria for this entity (Hachinski et al., 1974); it was generally accepted that brain tissue loss due to cerebral infarction was the cause of VaD. More recently, the criteria for the diagnosis of VaD have been debated (Drachman, 1993; Roman et al., 1993); and it has become evident that vascular compromise may play a major role in much dementia of the elderly, including Alzheimer's disease (Jick et al., 2000).

In conclusion, chronological aging, with its associated senescent age-related changes (ARCs) is the single most important risk factor for the development of sporadic dementias. The cumulative effect of a number of known and as yet unknown ARCs produce molecular, cellular, anatomical, physiological and pharmacological changes that render the aging brain vulnerable to neuronal and functional loss, and to degenerative disorders that produce more rapidly progressive cognitive impairment. Although mild declines in cognitive function are inevitable with aging, the factors that transform the vulnerable, aging brain into one with a progressive dementing disorder are not as yet well understood. Genetic, environmental, vascular and experiential factors undoubtedly interact with the normal ARCs to lead to progressive degenerative dementias. Prevention and treatment of Alzheimer's disease, vascular dementia, fronto-temporal dementia, Lewy body dementia and others will depend both on elucidating the specific mechanisms of each of these diseases, and on developing strategies to forestall the ARCs that make the aging brain so vulnerable to these disorders.

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17

Alzheimer's disease

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Alzheimer's disease (AD) is an age-related, neurodegenerative disorder that represents the most common cause of dementia and is one of the leading causes of medical morbidity and mortality in the developed world. The implications of increasing longevity and shifting population demographics have led to the recognition of AD as a public health problem of major proportions. The percentage of the US population over age 65 will more than double over the next 30 to 40 years. According to these projections, as many as 10 million persons will be afflicted with dementia, the majority of whom will suffer from AD, with associated annual health care costs of over $100 billion (Cummings, 1995). On a personal level, the insidious but relentless decline in the affected individual's cognitive and functional abilities imposes a particularly heavy burden on patient, caregivers and family members alike. These considerations have greatly increased public awareness of AD during the past 20 years, and have stimulated the increasingly rapid pace of scientific progress directed toward the development of effective, disease-modifying treatments.

Historical perspective

In 1907, Alois Alzheimer published the initial report of the clinical and pathologic features of the disease that was soon named after him by Emil Kraepelin (Alzheimer, 1907; Kraepelin, 1910; Maurer et al., 1997). This report summarized a lecture he had given the prior year on the case of 'Auguste D', a 51-year-old woman admitted in 1901 to the Hospital for the Mentally Ill and Epileptics in Frankfurt, Germany. Alzheimer described a syndrome of 'rapidly increasing memory impairments', aphasia, disorientation, paranoia, and auditory hallucinations. His detailed histopathological analysis upon her death in 1906, which was aided by the new staining techniques introduced by his colleague Franz Nissl, revealed 'numerous small miliary foci . . . caused by the deposition of a peculiar substance in the cortex'. These 'foci' or neuritic plaques, as they came to be called, were accompanied by extensive loss of cortical neurons and striking neurofibrillary changes: 'In the center of an otherwise normal cell there stand out one or several fibrils due to their characteristic thickness and peculiar impregnability.' Alzheimer provided a more thorough description of this original case, along with an account of a second case ('Johann F'.) from his Munich clinic, in a subsequent publication that included numerous illustrations of the characteristic neuritic plaques and neurofibrillary tangles (Alzheimer, 1911).

Alzheimer's description of the key pathologic features, along with contemporaneous reports of similar findings by Fischer (1907), Bonfiglio (1908) and Perusini (1909), promoted the acceptance of 'Alzheimer's disease' as a distinct and important disease entity. Despite the relatively young age of Alzheimer's original two patients, it gradually became apparent that the clinical and pathologic features of presenile and senile cases were essentially indistinguishable. For example, Perusini stated in 1909: 'The pathological process recalls the main features of senile dementia; however, the alterations in the cases described are more far-reaching, although some of them represent presenile diseases.' (cf. Maurer et al., 1997). In the eighth edition of his influential textbook *Psychiatrie*, published in 1910, Kraepelin was the first to attribute the definitive description of the disease to Alzheimer, who was then his colleague in Munich: 'The clinical interpretation of this Alzheimer's disease [*Alzheimersche Krankheit*] is still unclear. Although the anatomical findings suggest that we are dealing with a particularly serious form of senile dementia, the fact is that this disease sometimes starts as early as in the late forties.' The following year, Alzheimer himself accordingly entered the postmortem diagnosis of Johann F. in the Munich clinic records as '*Alzheimersche Krankheit*' (Graeber et al., 1997). From this modest initial

description of two case reports, AD has come to be recognized as the most important cause of intellectual deterioration in adult life, and the underlying neuropathological abnormalities described by Alzheimer represent the most common disease process leading to progressive cerebral atrophy, neuronal death and dementia.

Epidemiology and risk factors

Age is the single greatest risk factor for AD. Estimates of the prevalence of dementia among individuals older than age 65 in population-based studies from the US, Europe, and Asia have ranged from approximately 2% to 10% (Rocca et al., 1986; Schoenberg et al., 1987; Evans et al., 1989; Zhang et al., 1990), with the variability probably attributable to differences in study design and diagnostic criteria. AD is uncommon before the age of 60 years, but increases exponentially thereafter, with incidence and prevalence estimates doubling every 5 years after age 65 (Ott et al., 1995; Jorm et al., 1987; Ritchie et al., 1992; Hebert et al., 1995). The proportion of individuals affected by dementia thus increases from 1% in the age group 65–69 years to greater than 40% among nonagenarians, with AD accounting for the majority of cases regardless of age, sex or ethnic group. Incidence estimates increase from 0.6% among those 65–69 years old to 8.4% among persons over age 85. Inasmuch as prevalence estimates remain well short of 100%, even among the oldest old, dementia is not an inevitable consequence of the aging process, at least not within the current limits of human lifespan.

The next most significant risk factor for AD is a positive family history of the disease. Familial aggregation of AD has been recognized for many years; 20–40% of AD patients have an affected first-degree relative, and increases in the cumulative incidence of dementia among first-degree relatives of AD patients ranging from two- to sixfold have been reported in various studies (Heston et al., 1981; Heyman et al., 1983; Breitner & Folstein, 1984; Nee et al., 1987; Breitner et al., 1988; Farrer et al., 1989; Mayeux et al., 1991; Silverman et al., 1994). In a small number of families, perhaps 150–200 worldwide, there is a clear, autosomal-dominant mode of disease transmission, with early onset between 30 and 60 years of age. In the majority of these early-onset familial AD pedigrees, the disease is caused by point mutations in one of three chromosomal loci: the amyloid precursor protein (APP) gene on chromosome 21; the presenilin-1 (PS1) gene on chromosome 14; and the presenilin-2 (PS2) gene on chromosome 1 (see below). In contrast to these early-onset pedigrees, 90% of AD cases exhibit onset after age 65 and occur in a sporadic fashion without any clear familial pattern of transmission.

More than 25 genetic risk factors have been associated with late-onset AD, including polymorphisms in the genes encoding apolipoprotein E (ApoE), α2-microglobulin, cystatin C, LDL receptor-related protein (LRP), and interleukin-1 (for review see Price et al., 1998; St.George-Hyslop, 1999). Of these, the best-characterized susceptibility locus for sporadic AD is the gene on chromosome 19 encoding ApoE, a lipid transport protein (for review see Roses, 1996). The *APOE* gene was initially identified as a susceptibility locus for late-onset familial AD by positional cloning strategies, but was subsequently shown to represent a major risk factor for sporadic AD as well (Corder et al., 1993; Poirier et al., 1993; Rebeck et al., 1993; Saunders et al., 1993; Strittmatter et al., 1993). Polymorphisms in the *APOE* gene define three distinct alleles, designated ε2, ε3, and ε4, which influence the relative risk and age of onset for the development of AD. Inheritance of the ε4 allele confers an increased risk and earlier age of onset for both familial and sporadic AD, while the ε2 allele appears to be protective in both respects.

Additional minor risk factors for AD identified in some but not all studies include prior head trauma (Heyman et al., 1984; Mortimer et al., 1985) and low educational level (Katzman, 1993; Stern et al., 1994; Ott et al., 1995). The roles of these potential risk factors have been disputed due to their confounding effects on cognitive performance. There is some evidence for a higher prevalence of AD among women, independent of longer life expectancy (Kay, 1986; Katzman et al., 1989). Various environmental exposures have been proposed as predisposing factors for AD, particularly aluminium and other heavy metals (Basun et al., 1991; Perl & Good, 1987), but the weight of evidence has fallen against a causative role for such exposures. Retrospective analyses have identified several factors that may exert a protective effect against the development of AD, most notably the use of non-steroidal anti-inflammatory drugs (NSAIDS) (Breitner, 1996), estrogen replacement therapy (Paganini-Hill & Henderson, 1996), the use of HMG-CoA reductase inhibitors (Jick et al., 2000; Wolozin et al., 2000) and wine consumption (Orgogozo et al., 1997).

Clinical features and course

AD is characterized clinically by prominent impairments in cognition, often accompanied by neuropsychiatric behavioural disturbances, in the face of an otherwise bland elementary neurologic examination. Clinical criteria for the diagnosis of AD (DSM-IV, ICD-10, and NINCDS–ADRDA) all share common features: onset between ages 40

and 90; progressive dementia, as defined by prominent memory loss plus impairment in at least one other cognitive domain (such as language or praxis) sufficiently severe to impair social and/or occupational function; no disturbance of consciousness; and absence of other brain and systemic diseases that can cause dementia (McKhann et al., 1984). The NINCDS–ADRDA criteria further subdivide the diagnosis into definite (autopsy-proven), probable (meets all clinical criteria) and possible (some atypical features). The accuracy of these criteria relative to the neuropathological diagnosis of AD has been validated in clinicopathologic studies (Joachim et al., 1988; Tierney et al., 1988). Staging schemes for AD generally incorporate ratings of the severity of impairments in both cognitive and functional abilities; the systems in widest use are the Global Deterioration Scale (GDS) and the Clinical Dementia Rating scale (CDR) (Reisberg et al., 1988; Hughes et al., 1982). The CDR, for example, defines the severity of dementia as questionable (CDR 0.5), mild (CDR 1.0), moderate (CDR 2.0) or severe (CDR 3.0) based upon the scores in subcategories for memory, orientation, judgment, problem solving, community affairs, home and hobbies, and personal care.

AD typically begins with the gradual onset of forgetfulness (amnesia). Impairment of explicit memory for recent events is the most prominent early deficit. The observation that patients have difficulty learning or retaining new information reflects the early involvement of medial temporal lobe structures, including the entorhinal cortex and hippocampal formation, in the disease process. Forgetfulness for recent events or conversations, misplacement of objects, and repetitive questions are gradually noticed by family members or friends, even though patients themselves may be unaware of the problem (anosognosia). Word-finding difficulty (anomia) is the next most common manifestation. This feature generally emerges after the onset of amnesia, and reflects dysfunction of the temporal and frontal neocortices. An important practical index of the significance of reported cognitive disturbances is the extent to which they interfere with everyday functional abilities in the home or workplace. Difficulty with organizational tasks that were previously easily accomplished, such as management of the household finances or occupational duties, may become evident during the early stages of the illness and prompt neurologic evaluation. A change in personality is common: some patients become anxious or irritable, while others become quiet, withdrawn, and lose interest in their surroundings. These behavioural changes may resemble depression, but most often stem from apathy related to frontal lobe dysfunction. In spite of these limitations, social graces and other automatic behaviours are generally well preserved in the early stages of AD.

As the disease progresses, the impairments in memory and language become more profound, and the patient is no longer able to work. Visuospatial difficulties and trouble with dressing or the use of utensils (apraxia) become evident to varying degrees. The patient may become lost when out of the house, and assistance with the activities of daily living becomes necessary. Eventually, daily supervision may be required to prevent wandering or protect the patient from harm. Neuropsychiatric manifestations become more frequent and may include disinhibition, agitation, disruption of the sleep–wake cycle, hallucinations and frank delusions. These features probably arise as a primary consequence of the neurodegenerative process, and are thus 'organic' in nature. In the latter stages of the disease, speech disintegrates and functional abilities are progressively lost. Ultimately the patient is left in a mute, rigid, bedridden state requiring complete care; death usually results from a superimposed infection or medical illness. The average duration of AD is approximately 8 years from onset to death (Barclay et al., 1985), with a range of 1 to 25 years. There is considerable variation in the rate of progression; the clinical course is often marked by long periods of apparent stability, while in other cases patients can experience a rapid, relentless decline.

The elementary neurologic examination is generally unremarkable in the early stages of AD. The presence of primitive reflexes, such as snout, palmomental, grasping or suck responses, is frequently noted as the disease progresses to involve the frontal lobes. Olfactory deficits have been reported in a small number of patients (Serby et al., 1985). Focal neurologic signs are not observed unless the disease has been complicated by a discrete parenchymal lesion, such as a stroke, tumour or hemorrhage. Late in the course, patients may develop parkinsonian extrapyramidal signs of bradykinesia and rigidity, but rarely tremor. Some exhibit myoclonus, and a small fraction develop generalized seizures. The presence of prominent parkinsonism early in the course of dementia should prompt consideration of the alternative diagnosis of diffuse Lewy body disease (DLBD), while prominent early myoclonus should suggest the possibility of metabolic encephalopathy or Creutzfeld–Jakob disease.

Neuropathologic features

The gross appearance of the brain in AD is marked by diffuse cerebral atrophy, gyral atrophy with thinning of the cortical grey matter ribbon and secondary ventricular

enlargement. These features are not specific for AD, however, since considerable age-associated atrophy can be seen in the absence of dementia or AD pathology. The cerebral atrophy in AD reflects the underlying neuronal degeneration and is most prominent in the temporal lobes, hippocampi and association areas of the frontal and parietal lobes. Primary motor and sensory cortices are relatively spared, as are subcortical structures, with the notable exception of the amygdala, basal forebrain nuclei and locus ceruleus.

The microscopic hallmarks of AD are the presence of numerous extracellular neuritic or senile amyloid plaques (SPs), intraneuronal neurofibrillary tangles (NFTs), neuropil threads and cerebral vascular amyloid deposits. These changes are accompanied by selective neuronal and synaptic loss in the cerebral cortex and certain subcortical regions. Microscopically, neuronal loss is evident in the subiculum and CA1 fields of the hippocampus, the neocortex of the frontal and temporal lobes, the cholinergic nucleus basalis of Meynert, septal nuclei, amygdala, noradrenergic locus ceruleus, serotonergic dorsal raphé nucleus, and dorsal tegmental nucleus. In some regions, such as the entorhinal cortex and superior temporal sulcus, 50% of the neurons are lost (Gomez-Isla et al., 1996). Synaptic loss, revealed by electron microscopy and immunostaining with markers for synaptic terminals, has been described in many of these regions, particularly in the hippocampus and neocortex (Masliah et al., 1989; Hamos et al., 1989; Scheff et al., 1990). Although the SPs and NFTs are the most readily detected pathologic features, neuronal loss and decreased synaptic contacts are the proximate causes of the clinical manifestations of dementia in AD.

The mature SP has a dense central core of amyloid surrounded by dystrophic neuronal processes ('neurites') interspersed with the processes of activated microglia and reactive astrocytes, indicating an inflammatory response and neuronal injury associated with the amyloid deposition (Fig. 17.1(*a*) and (*b*)). Ultrastructurally, the plaque core consists of ordered arrays of amyloid fibrils, and the binding of Congo red dye to the core indicates that these fibrils possess a β-pleated sheet structure (this feature is the basis of the descriptive term amyloid, as in the case of other diseases characterized by extracellular, Congo red-positive deposits). In the brains of normal elderly individuals, diffuse deposits of amyloid lacking neuritic features are a common finding. These diffuse, non-neuritic plaques stain weakly with Congo red and ultrastructurally exhibit little fibrillary character. The principal molecular constituents of both neuritic and non-neuritic plaques are 40 to 42 amino acid β-amyloid (Aβ) peptides derived from proteolytic processing of the large amyloid precursor protein, a finding which led to the identification of mutations in APP as the first known genetic cause of AD (see *Etiology*, below). Biochemical analyses have revealed that the diffuse plaques are primarily composed of the slightly longer and more hydrophobic 42-amino acid form of Aβ, whereas neuritic plaques contain both Aβ42 and the more soluble, abundant Aβ40 peptide (Iwatsubo et al., 1994). Amyloid

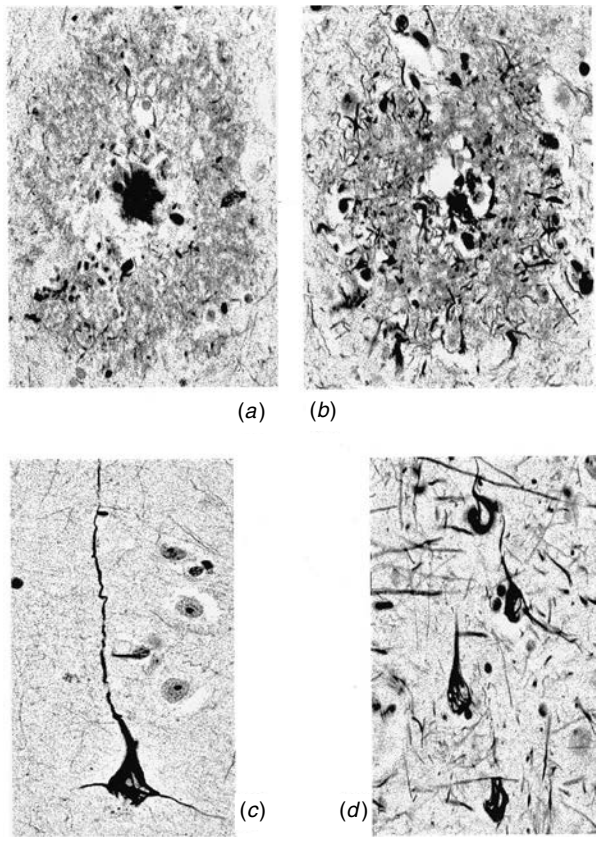

Fig. 17.1. Microphotographs of neuritic plaques (*a*), (*b*) and neurofibrillary tangles (*c*), (*d*) in the brain of a 65-year-old woman with end-stage Alzheimer's disease. (*a*) Neuritic plaque involving the amygdala. The discrete, centrally located amyloid core is surrounded by a clear halo, with argyrophilic dystrophic neurites scattered at the periphery of the plaque (Bielschowsky stain, original maginification 500×). (*b*) Neuritic plaque involving the neocortex (third layer of Brodmann area 9). The centrally located amyloid core is fragmented and dystrophic neurites are abundant (Bielschowsky, 500×). (*c*) Argyrophilic neurofibrillary tangles involving the uncus. Note the presence of three apparently normal neurons alongside the tangle (Bielschowsky, 500×). (*d*) Four argyrophilic neurofibrillary tangles involving the third cortical layer of the superior parietal lobule (Brodmann area 40; Bielschowsky, 500×). (Photomicrographs courtesy of Dr Jean-Paul Vonsattel, Massachusetts General Hospital.)

deposition in the form of diffuse plaques can thus clearly precede the onset of the clinical manifestations of AD, particularly in the case of Down's syndrome (Rumble et al., 1989), suggesting that diffuse plaques may represent a substrate for the formation of neuritic plaques. The deposition of Aβ42 may therefore be an initiating event that in some circumstances leads to the further deposition of Aβ40 and neuritic plaque formation. Aβ oligomers also form within neurons, and may contribute directly to cell dysfunction and death (Walsh et al., 2000).

NFTs are composed primarily of hyperphosphorylated, ubiquitinated forms of the microtubule-associated axonal protein tau (Fig. 17.1(*c*) and (*d*)). These cytoplasmic deposits also have an ultrastructural fibrillary appearance, consisting of dense bundles of long, twisted filaments. Such paired helical filaments are also found in the dystrophic neurites of neuritic plaques. Like amyloid deposits, NFTs are not specific to AD, as they can occur in much smaller numbers with normal aging. Moreover, NFTs with slight variations in ultrastructural and biochemical features characterize a number of neurodegenerative diseases, including Pick's disease, progressive supranuclear palsy, and corticobasal degeneration. This observation has prompted the conceptualization of these diseases as 'tauopathies', postulating a central role for NFTs in their pathogenesis (Goedert, 1998; Lee & Trojanowski, 1999).

SPs and NFTs exhibit distinct topographic distributions within the AD brain (Arnold et al., 1991). NFTs initially and preferentially affect the structures of the medial temporal lobe, including the amygdala, hippocampal formation, and parahippocampal regions, whereas amyloid plaques are more uniformly distributed throughout the neocortex of the frontal, temporal and parietal lobes. In late-stage AD, NFTs are plentiful in temporal, parietal and frontal neocortices. Given this hierarchical distribution, NFTs are a better pathological correlate of the pattern of neuronal loss and the severity of dementia than are amyloid plaques, and a pathological staging system has been proposed based on NFTs alone (Braak & Braak, 1991; NIA/Reagan criteria, 1997). In contrast to the NFT criteria, CERAD criteria for the neuropathological diagnosis for AD depend on an assessment of the frequency of amyloid plaques in three specific neocortical regions, the superior temporal gyrus, the prefrontal cortex, and the inferior parietal lobule, with an emphasis placed on the presence of neuritic plaques. In conjunction with the clinical findings, the 'plaque scores' for these areas define AD as possible, probable, or definite. The correspondence between the NIA/Reagan and CERAD criteria is high (Newell et al., 1999).

Multiple neurochemical abnormalities have been identified in the AD brain, reflecting the depletion of specific neuronal subpopulations (Francis et al., 1985; Mann & Yates, 1986; Bowen et al., 1994). Decreases in indices of the neurotransmitter acetylcholine in hippocampus and neocortex reflect atrophy and loss of cholinergic neurons in the ventral forebrain (Whitehouse, 1998). Similarly, neuronal loss in the noradrenergic locus ceruleus and the serotonergic dorsal raphé nuclei correlates with deficiencies in the corresponding neurotransmitters, and the depletion of excitatory pyramidal neurons in association neocortex contributes to a reduction in cortical glutamate levels. The deficiencies in multiple neurotransmitter systems suggest that pharmacologic therapies based on transmitter replacement will be of limited benefit, and that effective treatment will require prevention of the underlying neuronal loss.

Etiology

Molecular genetics and the amyloid hypothesis

Genetic studies based on large, multigenerational families with early-onset AD have identified causative mutations in three genes that can cause autosomal-dominant AD: the genes encoding APP, PS1 and PS2 (for review see Selkoe, 1996; Wasco & Tanzi, 1997; St. George Hyslop, 2000). The observation that pathogenic mutation in all three of these genes increases the production of β-amyloid underlies the amyloid hypothesis of AD, which postulates that amyloid deposition in the brain initiates a cascade of events that eventually leads to neuronal dysfunction and death. Additional chromosomal loci responsible for familial AD also apparently exist, since FAD pedigrees without mutations in these genes have been reported.

The *APP* gene encodes a type I integral membrane glycoprotein whose normal function remains unclear. Proteolytic processing of APP around its C-terminal transmembrane domain gives rise to a complex array of secreted and membrane-associated fragments (Fig. 17.2). APP cleavage by α-secretase splits the β-amyloid region and generates a long, soluble N-terminal fragment that possesses neurotrophic properties. Aβ peptides, which have neurotoxic properties (Yankner et al., 1989), are produced by the sequential action of two other proteases: β-secretase, which cleaves the juxtamembranous extracellular region of APP to yield the N-terminal end of Aβ, and γ-secretase, which cleaves the transmembrane portion of APP at two distinct positions to yield secreted Aβ peptides of either 40 or 42 amino acids (for review, see Vassar & Citron, 2000).

Although the cleavage of APP within the Aβ region by α-secretase predominates, Aβ peptides are produced at low

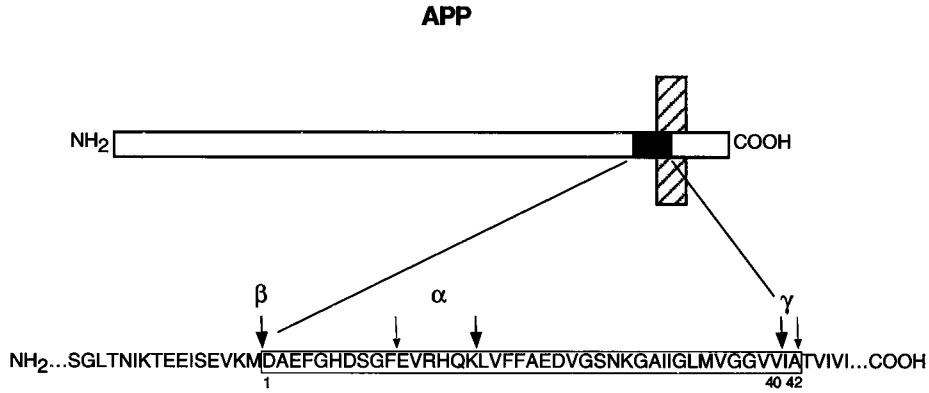

Fig. 17.2. Schematic diagram of proteolytic processing of the amyloid precursor protein (APP). The hatched box represents the plasma membrane, and the solid area of APP represents the β-amyloid region, whose amino-acid sequence is expanded below. The cleavage sites of the α-, β- and γ-secretases are indicated by the corresponding arrows. The boxed area of the β-amyloid region corresponds to the 40–42 residue Aβ peptides produced by the sequential action of β- and γ-secretase. Note that α-secretase cleaves within the β-amyloid region, thereby precluding the generation of Aβ species. The alternative intramembranous cleavage sites for γ-secretase produce either Aβ40 or Aβ42.

levels during normal cellular metabolism, and increased Aβ production (or an increased ratio of the levels of Aβ42 to Aβ40) has been consistently associated with the genetic lesions in familial AD (for summary, see Selkoe, 1997, 1999). All known FAD-linked mutations in APP occur at or near the sites of β- and γ-secretase cleavage that release the Aβ fragment, increasing the generation of Aβ42, and elevation of the Aβ42: Aβ40 ratio can be detected presymptomatically in carriers of an FAD mutation. Similarly, patients with Down's syndrome show increased levels of Aβ production, and the invariant association of the classic neuropathology of AD with adult cases of Down's syndrome is likely explained by the presence of an additional copy of the APP gene.

In addition to overproduction of Aβ, it is possible that alterations in degradation or clearance mechanisms may contribute to amyloid deposition in AD. Endogenous pathways for the degradation of Aβ and its clearance from brain tissue, which may antagonize cerebral amyloid deposition, have been identified. Several metalloendopeptidases have been implicated in the proteolytic degradation of Aβ, including insulin-degrading enzyme (IDE) (Vekrellis et al., 2000; Qiu et al., 1998) and neprilysin (NEP) (Iwata et al., 2000). NEP, which was shown to degrade Aβ42 in vivo, is a zinc–metalloprotease that inactivates several biologically active brain peptides, including enkaphalins, tachykinins, bradykinin and endothelins. Interaction of Aβ with ApoE and α-macroglobulin may provide another major clearance route. Both of these molecules are internalized by low-density lipoprotein receptor related protein, which is hypothesized to regulate the complex metabolic cascades that balance Aβ synthesis and clearance (Hyman et al., 1984).

Reproduction of the genetic alterations associated with familial AD in animal models has provided important experimental support for the 'amyloid hypothesis.' Overexpression of APP-bearing FAD-linked mutations in transgenic mice is sufficient to cause persistently elevated levels of soluble Aβ and an age-dependent accumulation of amyloid plaques in the cerebral cortex that closely resemble those in the brains of AD patients (Games et al., 1995; Hsiao et al., 1996). In contrast, mice in which both copies of the *APP* gene have been inactivated (*APP* 'knockout' mice) exhibit only slight phenotypic abnormalities, and do not develop AD-like neuropathological changes (Zheng et al., 1995). Consistent with the autosomal-dominant inheritance pattern of FAD, the results from mouse model systems suggest that APP mutations do not result in a loss of protein function, but rather promote the abnormal accumulation of cerebral amyloid through a gain-of-function mechanism.

While APP mutations have been found in fewer than 2–3% of reported AD pedigrees, mutations in the *PS1* gene on chromosome 14 account for the majority of early-onset, familial AD. The *PS1* gene was initially identified by positional cloning based on genetic linkage to a region of the long arm of chromosome 14 (Sherrington et al., 1995), and more than 50 pathogenic mutations in the *PS1* coding region have subsequently been identified (Wasco & Tanzi, 1997; Fraser et al., 2000). Mutations in the highly related *PS2* gene on chromosome 1, which was originally identified on the basis of homology with *PS1*, have been linked

to familial AD in a small number of pedigrees (Rogaev et al., 1995; Levy-Lahad et al., 1995a, b). (An annotated compendium of the mutations in APP, PS1 and PS2 linked to FAD is available at http: //www.alzforum.org.)

The presenilins are integral membrane proteins that are involved in the proteolytic processing of both APP and Notch (for review see Selkoe, 1998; Haass & De Strooper, 1999). Studies in cell culture and transgenic mice have demonstrated that pathogenic mutations in PS1 and PS2 enhance Aβ production (particularly the production of the more amyloidogenic species, Aβ42). Conversely, Aβ levels are considerably reduced in cultured neurons derived from *PS1* knockout mice, with the reduction primarily attributable to decreased γ-secretase activity (De Strooper et al., 1998). As in the case of APP, mutations in the presenilins thus appear to contribute to the pathogenesis of AD through a gain-of-function mechanism. Analysis of *PS1* knockout mice and studies of PS1-deficient cultured cells have further shown that PS1 regulates the activity of the Notch transmembrane receptor protein, a key regulator of cellular differentiation during development (Shen et al., 1997; De Strooper et al., 1999; Song et al., 1999; Handler et al., 2000).

Presenilin mutations produce effects on APP processing in the brains of affected individuals that are consistent with their apparent role in γ-secretase cleavage: levels of Aβ are elevated in patients bearing PS1 or PS2 mutations, even at presymptomatic stages; the density of plaques containing Aβ42 is increased in the brains of such patients; expression of mutant presenilin genes in cultured cells causes increased Aβ (Aβ42) production; overexpression of mutant PS1 in transgenic mice results in increased brain levels of Aβ42, and causes accelerated formation of amyloid plaques in the presence of a mutant APP transgene. On the basis of these observations and additional structure-function studies, it has been proposed that presenilins may themselves possess γ-secretase activity (Wolfe et al., 1999). At the very least, PS1 is a component of a multiprotein complex necessary for γ-secretase activity (Yu et al., 2000).

Beyond amyloid: tau pathology and neurodegeneration

The amyloid hypothesis may paint an incomplete picture of the pathogenesis of AD, as major unanswered questions remain concerning the connection between Aβ deposition and the other neuropathological features of AD. With respect to neuronal loss, it has been proposed that Aβ may exert a direct neurotoxic effect, or that it may injure neurons indirectly through the activation of an inflammatory response mediated by microglia and astrocytes (Yankner, 1996). The inflammatory response is associated with the formation of dystrophic neuronal processes in the neuritic plaques, and may contribute to derangement of neuronal metabolism, alterations in the cytoskeleton and the formation of neurofibrillary tangles. One limitation of the amyloid hypothesis, however, has been the failure to observe neurofibrillary changes as a result of experimental manipulations that increase Aβ production or deposition in any of the systems studied. In addition, significant neuronal loss has not been observed in the transgenic mouse models of AD, despite massive amyloid deposition in older animals (Irizarry et al., 1997). These considerations lead to the interpretation that amyloid accumulation, while likely a critical step in the pathogenesis of AD, is not sufficient to produce the full neuropathological picture of AD (Fig. 17.3).

The significance of neurofibrillary changes in the mechanistic process leading to neuronal loss has been emphasized by the discovery that mutations in the tau protein are sufficient to cause neurodegeneration and dementia in the absence of Aβ deposition. A variety of mutations occurring in and around the microtubule-binding repeats of the tau protein have been identified in autosomal-dominant pedigrees with frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17; for review see Goedert, 1998; Lee & Trojanowski, 1999). The neuropathology of some FTDP-17 cases resembles that of Pick's disease, with prominent circumscribed atrophy and neuronal loss in the frontal and temporal lobes, accompanied by intraneuronal filamentous deposits of hyperphosphorylated tau. Additional subcortical changes and intraglial tau deposits are sometimes seen, but significant amyloid pathology is absent. These findings provided strong evidence linking tau dysfunction and deposition to the pathogenesis of the large group of neurodegenerative diseases ('tauopathies') characterized by neurofibrillary lesions independent of Aβ accumulation. Exonic tau mutations associated with FTDP-17 have been shown to decrease the binding of tau to microtubules, impairing its ability to promote microtubule assembly (Hong et al., 1998). Hyperphosphorylation of tau also inhibits its binding to microtubules, though the relationship between hyperphosphorylation and tau deposition is unclear (Goedert, 1998). These observations suggest that biochemical alterations in tau structure and function may contribute to neuronal dysfunction through destabilization of the neuronal cytoskeleton and disruption of axonal transport. In addition, an increase in cytoplasmic levels of tau that is not bound to microtubules may promote its aggregation, possibly conferring an additional 'toxic' gain of function. In support of this notion, overproduction of wild-type tau or tau bearing an FTDP-17-linked mutation (P301L) in the brains of transgenic mice resulted in an age-

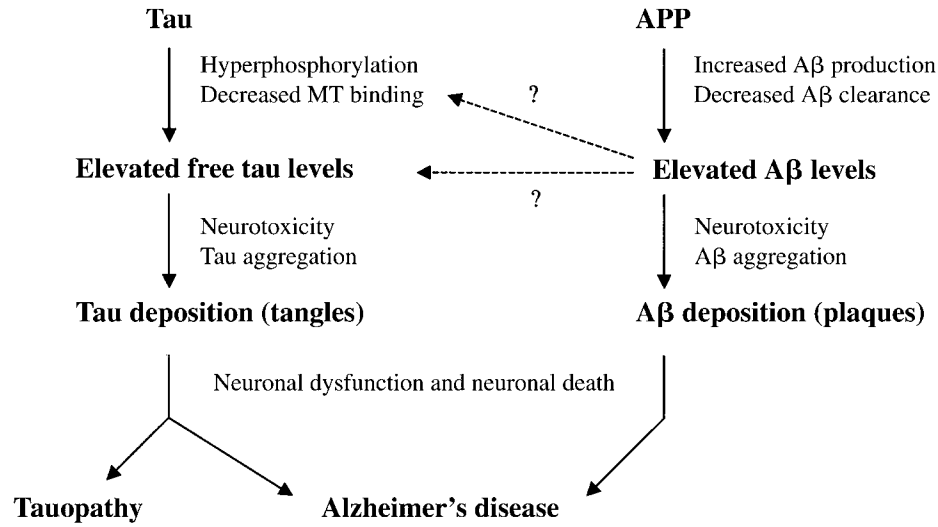

Fig. 17.3. A model for the pathogenesis of Alzheimer's disease (AD). The central roles of tau and the amyloid precursor protein (APP) in the molecular and cellular events leading to neurodegeneration are highlighted. Tau hyperphosphorylation and decreased microtubule binding may promote tau aggregation by elevating the levels of free unbound tau, possibly resulting in neurotoxicity as a result of cytoskeletal dysfunction. Elevated levels of β-amyloid (Aβ) peptides, particularly the more amyloidogenic species Aβ42, may result from either increased β- and/or γ-secretase cleavage of APP or decreased Aβ degradation and clearance. Increased soluble Aβ and Aβ aggregation, either intracellularly or in the form of amyloid plaques, are thought to promote neurotoxicity and neurodegeneration. Tau pathology and neuronal death in the absence of Aβ pathology characterize the 'tauopathies', whereas the neuronal death in AD is associated with the presence of both NFTs and amyloid deposition. Although the connections between tau and amyloid pathology (indicated by dashed lines) in AD remain unclear, a sustained increase in the levels of Aβ may be the initiating event that activates multiple cellular pathways leading to neuronal dysfunction and death, including tau aggregation and NFT formation.

and dose-dependent accumulation of filamentous deposits containing phosphorylated tau (Ishihara et al., 1999; Lewis et al., 2000). In two recent reports, overexpression of a mutant human APP transgene or intracerebral injection of $A\beta_{42}$ fibrils enhanced the formation of tau deposits in the brains of mutant tau transgenic mice (Lewis et al., 2001; Götz et al., 2001), providing experimental evidence that Aβ can influence the development of tau neurofibrillary pathology (see Fig. 17.3).

Despite advances in understanding the molecular basis of AD, the events that ultimately precipitate neuronal death remain uncertain. Programmed cell death, or apoptosis, is a potential mechanism for the neuronal loss in a variety of neurodegenerative diseases (Rinkenberger & Korsmeyer, 1997; Nijhawan et al., 2000). Apoptosis is a cellular suicide pathway, largely operative during embryogenesis and in the immune system, that induces characteristic molecular and cellular alterations leading rapidly and irreversibly to cell death, such as activation of specific death proteases, endonucleolytic degradation of DNA and dissolution of cellular membranes. It has not been convincingly shown, however, that the neuronal loss in AD and other neurodegenerative diseases occurs via an apoptotic mechanism. In addition, studies in a variety of cell culture systems have produced conflicting results on the effects of the presenilins on sensitivity to apoptosis, suggesting both pro- and anti-apoptotic functions. Lack of PS1 function in the embryonic brain of *PS1* knockout mice, however, does not lead to increased neuronal cell death (Handler et al., 2000). Other avenues of investigation into the mechanisms of neuronal death in neurodegenerative disease have implicated free radical injury and mitochondrial dysfunction, which can produce neuronal death through both apoptosis and necrosis (Beal, 2000). Such pathways may represent primary causes of neurodegeneration, or alternatively, they may be activated as downstream events subsequent to some other initiating event, such as amyloid deposition.

Diagnostic evaluation

There are more than 50 medical, psychiatric, and neurological diseases considered in the differential diagnosis of dementia (Mayeux et al., 1993). Alzheimer's disease is by far the most common cause of dementia; DSM-IV and ICD-10 criteria follow closely on the NINDS-ADRDA guidelines first published in 1984 (McKhann et al., 1984).

Because of these common international standards, diagnostic procedures for AD are remarkably uniform throughout the world. In a survey of 26 centres specialized for AD care in the U.S., Europe, and Japan, six items out of a menu of 17 were specified as essential steps in the diagnosis of AD (Growdon, 2001). These procedures were: history of illness, physical examination, laboratory blood tests, a mental status test, psychometric testing, and a CT or MR brain scan. There was a high (>50%) frequency of use and importance ascribed to results obtained from these six measures, regardless of the geographic region. All other procedures, including many proposed as biomarkers of AD, were much less frequently used. Thus, there is worldwide consensus regarding the core features of the diagnostic evaluation for AD-type dementia.

The history is always obtained from an informant who knows the patient well, e.g. spouse or adult child. While interviewing the family members, it is always necessary to conduct the diagnostic assessment with the differential diagnosis of dementia in mind, so that history can be obtained to support or exclude diagnostic possibilities. The physical examination, including a compulsory neurological evaluation and a psychiatric examination as indicated, seeks to identify signs that might point to causes of dementia that might be confused with AD, such as Huntington's disease or Parkinson's disease. Laboratory blood tests are conducted to exclude underlying medical or metabolic derangements that can produce dementia. For example, it is necessary to exclude liver or kidney failure, or thyroid abnormality as a contributing cause of dementia. Mental status testing is recommended to document the presence of dementia and to estimate its severity. The three most common tests employed: the Information, Memory and Concentration subscale of the Blessed Dementia Score (Blessed et al., 1968), the Mini-Mental State Examination (Folstein et al., 1975), and the Alzheimer's Disease Assessment Scale (Rosen et al., 1984), are comparable rating scales. These tests require five to ten minutes to administer, and have a high intertest correlation (Solomon et al., 1999).

Psychometric tests explore aspects of cognition that are affected in AD in greater detail than mental status testing. Results of psychometric tests give confidence to the diagnosis of dementia by showing that AD patients have impairments in multiple cognitive domains. Cognitive tests range from such standard neuropsychiatric measures as the Wechsler Adult Intelligence Scale and the Wechsler Memory Scale to sets of tests that have been developed specifically for AD patients, such as the CERAD set of tests (Welsh et al., 1992) and the set of tests administered in the Massachusetts Alzheimer's Disease Research Center (Locascio et al., 1995). These latter specialized tests assess memory, language capacity, visual-spatial function, abstract reasoning, and frontal lobe function. Regardless of the set of cognitive tests, the findings are similar: in AD, there is an early and pronounced deficit in explicit memory, as tested by delayed recall. In addition, there are variable impairments in the other cognitive domains that decline over time. The decline in explicit memory is rapid and curvilinear; the decline in other functions, such as verbal fluency and naming objects, tends to be more linear and steady (Fig. 17.4). The results of cognitive tests provide an index of brain function and reflect the underlying pathology in AD. The pathologic bases of impaired delayed recall are atrophy of cholinergic ventral forebrain neurons (Whitehouse, 1998) and deafferentation of the hippocampus (Hyman et al., 1984), both of which occur early in the course of AD. Worsening language and visual-spatial abilities likely reflect progressive loss of neocortical neurons and their connections.

Neuroimaging is the sixth standard procedure. Standard CT or MRI scans are performed to search for brain lesions that could account for dementia or contribute to it; examples include hydrocephalus, stroke, and brain tumour. Conventional interpretations of these morphologic brain images do not add to the positive diagnosis of AD, but serve to exclude these and other conditions that can masquerade as AD. To extract more diagnostic information from the images, quantitative methods are being developed to measure brain regions vulnerable to AD pathology, such as the medial temporal lobe. There is ample experimental data now that atrophy of the medial temporal lobe, and hippocampal structures in particular, is greater in AD than in age-matched non-demented control subjects (de Leon et al., 1993; Jack et al., 1997). With sophisticated MR quantification, even greater precision is possible: in one study (Killiany et al., 2000), baseline MRI measures of atrophy in the entorhinal cortex, superior temporal sulcus and anterior cingulate were characteristic of AD, and identified with 95% sensitivity and 90% specificity non-demented individuals with mild memory difficulty who converted to Alzheimer's disease after three years. These findings are internally consistent with what is known about the pathophysiology of memory loss in AD: the deficit in explicit memory is usually the first sign of AD dementia (Locascio et al., 1995); explicit memory depends heavily upon the entorhinal–hippocampal–medial temporal lobe region (Corkin et al., 1997); and there is massive loss of neurons in the entorhinal cortex in AD (Gomez-Isla et al., 1996).

As dementia worsens, deficits in cognitive domains other than memory emerge or worsen, even if they had been normal at initial examination. The neuropathological substrate for further cognitive decline is decreased

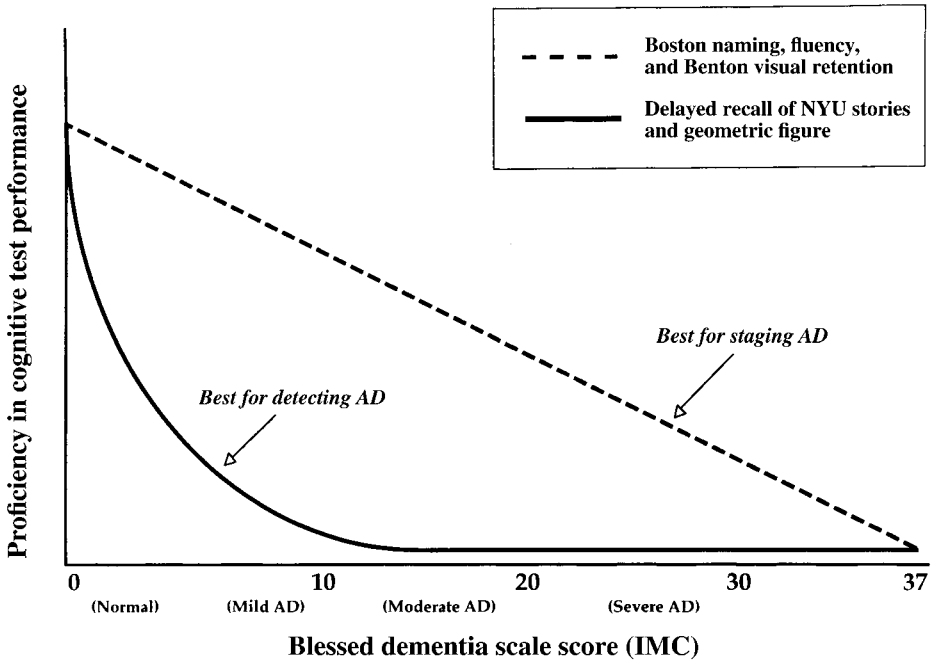

Fig. 17.4. Relation between specific cognitive test scores and a continuous index of dementia severity in AD patients: the information, memory and concentration (IMC) score of the Blessed Dementia Scale. Performance on tests of explicit memory, such as delayed recall of stories and geometric figures, falls precipitously early in the course of AD, and is therefore helpful in detecting the presence of dementia. Since performance on other measures, such as language tests, declines in a steady linear fashion over time, the Boston Naming and verbal fluency tasks are best for staging the severity of dementia and tracking its course. (Reproduced by permission from Locascio et al. 1995).

number of cortical synaptic contacts and neuronal loss (Gomez-Isla et al., 1997). Based upon serial MRI examinations, total brain volume in AD was found to decrease by about 2–3% per year compared to less than 1% per year in normal control subjects (Fox et al., 1999). Physiological brain imaging with positron emission tomography (PET) or single photon computed tomography (SPECT) brain scans has made it possible to detect neuronal dysfunction in life, even when the brain structure is normal on conventional CT or MR scan. Bilateral posterior parietal/temporal hypometabolism and hypoperfusion are characteristic of AD and found in 80–85% of cases (Kennedy, 1998). This pattern of deficit matches the distribution of pathological lesions in AD, which affects the multimodal association neocortices in temporal and parietal lobes out of proportion to the somatosensory and occipital regions (Arnold et al., 1991).

In centres that specialize in the diagnosis and care of patients with dementia and Alzheimer's disease, these six diagnostic procedures lead to a clinical diagnosis of AD that is confirmed pathologically in about 90% of cases. Diagnostic accuracy may be lower in practices outside of specialized academic centres, and regardless of site, these conventional diagnostic procedures are labour-intensive, time-consuming, and expensive. Thus, there is a need for a biomarker or set of biomarkers that would quickly and accurately diagnose AD and circumvent the current practice of expensive and time-consuming testing. The search for biomarkers builds upon advances in understanding the biology of AD, and ranges from uncovering genetic risk factors to documenting the pathology of AD and describing the resultant molecular and biochemical changes that result from the AD process. These advances have sparked the hope of detecting some of these characteristic changes, especially those noted in brain tissue, during life (NIA/Reagan workshop 1998).

Although there are scores of biological correlates of Alzheimer's disease, no biological marker has yet gained full acceptance in practice as the sole test needed to diagnose AD. Several biomarkers, however, show promise, usually as a confirmatory aid in the conventional diagnostic assessment of a patient with dementia. Detecting a mutation in the *APP*, *PS1* or *PS2* gene carries high specificity for the diagnosis of AD, but such screening cannot be recommended as a routine measure because of extremely low sensitivity (infrequent number of affected individuals) in the total AD population. Thus, searching for a mutation should generally be limited to instances of familial AD

cases under the age of 50 years. Detecting the $\varepsilon 4$ allele of *APOE* can add a small increment of confidence to the AD diagnosis when used in conjunction with conventional diagnostic workup, but by itself has low diagnostic sensitivity and specificity.

Given the central position of cerebral amyloid deposition as the potential toxic event initiating a cascade of neurodegeneration, many molecular biomarkers centre on amyloid fragments in blood and CSF. Characteristic findings are increased levels of Aβ42 in plasma of patients with familial AD due to mutations in the *APP, PS1* and *PS2* genes (Scheuner et al., 1996); increased Aβ42 levels in some non-familial cases (Mayeux et al., 1999); and reduced APP isoform ratio in platelets of AD patients compared to control subjects (Baskin et al., 2000). CSF levels of Aβ42 are reduced in AD whereas CSF levels of the hyperphosphorylated tau protein are increased (Motter et al., 1995; Hulstaert et al., 1999). These tests have not achieved widespread diagnostic use either because they lack sufficient diagnostic sensitivity and specificity, or because they are available only in an experimental setting. Neuroimaging procedures appear most promising in the diagnosis of AD, especially quantitative measures of medial temporal lobe structures and whole brain volume. Because conventional brain scans are part of the standard diagnostic evaluation, quantitative measures can be readily adapted to the image data that are collected. In contrast to MRI, the use of PET scans will likely be limited to confirmatory or experimental studies performed in academic centres because of limited availability and expense.

Therapy

Currently available therapies for AD are symptomatic in nature, and ameliorate the cognitive or neuropsychiatric impairments without altering the course of the disease. Drugs that inhibit acetylcholinesterase are the current mainstays of treatment for the cognitive abnormalities of AD. Their use is based on the cholinergic hypothesis of memory dysfunction, which links pathological, biochemical and pharmacological evidence for a deficit in cholinergic neurotransmission with impaired memory (Bartus et al., 1982). The initial drug of this class, tacrine (Cognex®), improved memory in some patients but is now rarely prescribed due to its associated hepatotoxicity and the availability of safe alternative agents. Aricept® (donepezil), the cholinesterase inhibitor presently in widest use, produces modest improvement in memory performance when given as a single daily dose of 5 or 10 mg (Rogers & Friedhoff, 1996; Greenberg et al., 2000). Rivastigmine (Exelon®) is available in twice-daily dosing and has similar efficacy to donepezil (Corey-Bloom et al., 1998).

Apathy, depression, agitation, delusions and hallucinations are common neuropsychiatric alterations in AD. The selective serotonin reuptake inhibitors (SSRIs) are the drugs of choice to treat depression in the context of AD due to their favourable side effect profile, and particularly the absence of significant anticholinergic effects. Low doses of sedative or anxiolytic drugs may be used to treat agitation, but should be monitored closely to avoid possible side effects such as increased confusion or even a paradoxical increase in agitation. Paranoia, hallucinations and agitation generally respond to antipsychotic therapy, and the newer atypical neuroleptics (e.g. risperidone, olanzepine) are preferred because of their low risk of causing extrapyramidal side effects.

Agents that simply replace, or bypass, a neurotransmitter deficit will produce at most only short-term symptomatic benefit. The next generation of therapies for AD will attempt to correct the underlying pathogenic processes that lead to dementia. The first step in this effort was to administer high doses (2000 I.U./day) of the anti-oxidant vitamin E, which reportedly slowed the rate of deterioration in AD patients (Sano et al., 1997). Attempts to develop more effective disease-modifying therapies for AD have focused on antiamyloidogenic approaches that either block Aβ production or reduce its deposition in brain. The clinical implementation of such strategies will thus represent a formal test of the amyloid hypothesis of AD. Promising lines of development include small molecules that inhibit β- and γ-secretase, which should decrease Aβ production (Vassar & Citron, 2000). Another proposed approach is immunization against Aβ peptide, which is postulated to increase immune-mediated clearance of soluble Aβ (Schenk et al., 1999). Such strategies to decrease brain levels of soluble Aβ may also promote the dissolution of insoluble Aβ deposits by shifting the equilibrium in favour of solubility.

Future approaches to AD therapy may exploit other aspects of our understanding of the pathogenesis of AD. For example, stimulation of endogenous pathways for the degradation and clearance of Aβ may offer an alternative approach to antiamyloidogenic therapy. Inhibition of tau aggregation and NFT formation, possibly through modulation of tau phosphorylation, may help to promote neuronal survival in AD and other tauopathies. Strategies that block the pathways leading to neuronal death, whether apoptotic or otherwise, may provide benefit in neurodegenerative disorders of diverse etiologies. Finally, therapies relying on implantation of neural stem cells (Erickson et al., 1996) or stimulation of endogenous adult neurogenesis

(Björklund & Lindvall, 2000) may help to combat neuronal loss and restore or preserve cognitive function in AD.

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18

Dementia with Lewy bodies

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History

The concept of the clinical syndrome of 'dementia with Lewy bodies' arose within the context of correlations with the pathological descriptions of Lewy body inclusions. These inclusions were first described by F. H. Lewy in 1912 in the dorsal motor nucleus of the vagus and substantia innominata (Lewy, 1912), and Lewy bodies in the substantia nigra were postulated to be specific for Parkinson's disease by Tretiakoff in 1919 (Tretiakoff, 1919). Cortical Lewy bodies were initially described in association with postencephalitic parkinsonism (Lipkin, 1959), in elderly with incidental nigral Lewy bodies (Forno, 1969), in severe dementia (Okazaki et al., 1961), and in institutionalized psychiatric patients (Woodward, 1962). From a clinicopathologic study of 20 cases in 1980, K. Kosaka proposed that the neuroanatomical spectrum of Lewy bodies ranged from isolated substantia nigra inclusions to widespread cortical inclusions; he coined the term 'diffuse Lewy body disease' to describe a clinical syndrome of parkinsonism, dementia, and/or psychosis associated pathologically with Lewy bodies in cortical and limbic regions in addition to subcortical nuclei (Kosaka et al., 1980). In more recent nomenclature, the clinicopathological syndrome has been termed 'Dementia with Lewy bodies' (DLB).

Epidemiology

DLB has been recognized as the second most common form of degenerative dementia, after Alzheimer's disease, occurring in 15–36% of pathological series of dementia (Hansen et al., 1990; Holmes et al., 1999; Perry et al., 1990), with an estimated prevalence of 10–25% in hospital and community elderly with dementia (Ballard et al., 1995; Shergill et al., 1994). Furthermore, cortical Lewy bodies are found in more than 25% of AD cases (Bergeron & Pollanen, 1989; Ditter & Mirra, 1987; Forno & Langston, 1993). In a review of autopsy-confirmed cases of DLB and AD, the frequency of males was greater in DLB (M:F 1.7 in DLB vs. 0.53 in AD), the average age of onset was similar (70 years old in DLB, 71 years old in AD), with a trend toward more rapidly progressive illness in DLB (duration 6.25 of years in DLB vs. 7.3 of years in AD) (McKeith & O'Brien, 1999).

Clinical features

The clinical features of DLB have been incorporated into consensus criteria for the clinical diagnosis of DLB (Table 18.1) (McKeith et al., 1996). The criteria list dementia in association with fluctuating mental status, visual hallucinations, and parkinsonism as required or core features of DLB; supportive features are repeated falls, syncope, transient loss of consciousness, sensitivity to extrapyramidal side effects of neuroleptics, delusions and other hallucinations. Additional proposed supportive features include depression and REM sleep behavioural disorder (McKeith et al., 1999). Several studies have addressed the accuracy of the clinical criteria for DLB. The specificity (proportion of non-DLB cases correctly identified) of the clinical criteria for probable DLB compared to neuropathological diagnosis ranges from 0.84–1.00 in prospective and retrospective studies (Holmes et al., 1999; Litvan et al., 1998; Luis et al., 1999; McKeith et al., 2000a; Mega et al., 1996; Verghese et al., 1999). The sensitivity of the clinical criteria for probable DLB has been more variable, as high as 0.83–0.89 in prospective studies (McKeith et al., 2000a; McShane et al., 1998), and ranging from 0.40–0.65 in retrospective studies (Litvan et al., 1998; Luis et al., 1999; Mega et al., 1996; Verghese et al., 1999).

Dementia (slowly progressive global cognitive impairment) is a mandatory feature of DLB, and is the presenting

Table 18.1. Clinical and pathological features in dementia with Lewy bodies

Clinical features	Pathological features
1. Central feature: Progressive dementia	1. Essential for diagnosis: Lewy bodies
2. Probable (2/3)[a] or possible (1/3) if:	2. Associated but not essential
– fluctuating cognition and alertness	Lewy-related neurites
– recurrent visual hallucinations	Amyloid plaques (all types)
– spontaneous parkinsonism	Neurofibrillary tangles
3. Supportive features: repeated falls, syncopes, neuroleptic hypersensitivity, delusions, hallucinations in other modalities, REM – sleep, behaviour disorder, depression	Neuronal loss / synapse loss
	Spongiform change (temporal)
	Neurotransmitter abnormalities

Notes:
[a] Two of the three features are required for a diagnosis of probable DLB, one for possible DLB.
Source: From McKeith et al. (1996).

feature in about 82% (range 40–100%) (McKeith & O'Brien, 1999). Psychometric features of the cognitive dysfunction in DLB such as amnesia, dyscalculia, and aphasia, overlap those of AD, not surprising given the frequently coexisting pathology. However, several studies suggest that, compared to AD patients of comparable global severity of dementia, patients with DLB perform less poorly on tests of verbal memory, and worse in tests of attention, visuospatial and visuoconstructive function, and fluency (Galasko et al., 1996; Gnanalingham et al., 1997; Hansen et al., 1990; Mori et al., 2000; Shimomura et al., 1998; Walker et al., 1997). Early in the illness, memory deficits may be minimal, or consist of selective deficits of memory retrieval, with recall significantly improved by prompting. This may be distinct from the deficits in memory acquisition and consolidation characteristic of AD (Ballard et al., 1999a; Walker et al., 1997). Frontal lobe dysfunction and visuospatial impairment may be more prominent early on in DLB. Language dysfunction of dysnomia progressing to dysphasia tends to parallel the clinical course of AD, although speech block has been described early in the illness. The rate of cognitive decline is faster in DLB compared to AD (Ballard et al., 1996; Olichney et al., 1998), and DLB has been associated with shorter survival, 7.7 ± 3.0 years after onset of cognitive symptoms versus 9.3 ± 3.5 years in AD (Olichney et al., 1998), although in a prospective study, no differences were found between age of onset, age of death, or survival between AD and DLB (Walker et al., 2000a, b).

A particular feature of the mental status in DLB is fluctuations, including periods of confusion, inattention, somnolence, or worsening cognitive impairment alternating with more lucid periods. These periods of variation may last from minutes to days (McKeith et al., 1996), and are unrelated to exogenous factors such as anxiety or unfamiliar surroundings; they are distinct from 'sundowning' episodes of evening confusion common in Alzheimer's disease. The prevalence of fluctuation in cognition in autopsy-proven DLB has ranged from 40–86% (Hohl et al., 2000; McKeith et al., 1992b; Verghese et al., 1999), and can be noted early in the course of the illness (McKeith & O'Brien, 1999). Episodes of syncope or transient loss of consciousness may be more extreme forms of the fluctuations. In the elderly, these symptoms must be differentiated from delirium from infection or toxic–metabolic encephalopathy, transient ischemic attacks, focal seizures, orthostasis, and cardiac disease.

Spontaneous, complex visual hallucinations occur in 40–75% of DLB patients, typically early in the illness and unrelated to medications (Galasko et al., 1996; Klatka et al., 1996; McKeith & O'Brien, 1999; Mega et al., 1996; Weiner et al., 1996). Delusional misidentification is also common early in DLB (Ballard et al., 1999b). Auditory hallucinations are less common, noted in an average of 19% of patients at presentation or during the entire course of illness (McKeith & O'Brien, 1999).

Parkinsonism is common as an early or initial feature of DLB, occurring at presentation in 43% (range 10–78%), and during the entire course in 77% (range 50–100%) (McKeith & O'Brien, 1999). The parkinsonism is usually symmetric, consisting of parkinsonian gait with reduced arm swing and *en bloc* turning, bradykinesia, rigidity, and hypomimia. Parkinsonian resting tremor is less common. Parkinsonism may contribute to falls, which occur in 28% of DLB patients at presentation, and 37% of DLB patients during the entire course of illness (McKeith & O'Brien, 1999). Patients with DLB also are sensitive to the extrapyramidal side effects of neuroleptic medications, including

severe rigidity and obtundation at low doses of neuroleptics that persist after drug withdrawal. Neuroleptic sensitivity is noted in an average of 61% of DLB patients relative to 15% of AD patients (McKeith & O'Brien, 1999).

Depressive features are nearly twice as common in DLB relative to AD, noted in an average of 29% of DLB patients at presentation, and 38% during the course of illness (McKeith & O'Brien, 1999).

Atypical Lewy body syndromes include primary autonomic failure, associated with Lewy bodies in the sympathetic neurons of the spinal cord, and Lewy body dysphagia, associated with Lewy bodies in the dorsal vagal nuclei.

The differential diagnosis of DLB involves other parkinsonian and/or dementia syndromes in addition to Parkinson's disease and Alzheimer's disease, such as multiple system atrophy, progressive supranuclear palsy, cortical basal degeneration, Pick's disease and frontal lobe dementias, Creutzfeld–Jakob disease, normal pressure hydrocephalus, multi-infarct dementia and Binswanger's disease, and Hallervorden–Spatz disease.

Imaging and laboratory investigations

There has been considerable interest in the use of CT and MRI imaging studies to differentiate the dementias. A CT measure of minimum temporal lobe width was significantly reduced in dementia (10.4–10.9 mm) relative to depression (13.7 mm), but could not distinguish DLB from AD or vascular dementia (VD) (O'Brien et al., 2000). MRI imaging in DLB is non-specific. While both AD and DLB brain show generalized atrophy relative to non-demented brains (Hashimoto et al., 1998), medial temporal atrophy tends to be intermediate between non-demented cases and AD (Barber et al., 1999b; Harvey et al., 1999; Hashimoto et al., 1998). White matter hyperintensities on MRI, which occur with increased aging, are more extensive in dementia than controls, although they do not differentiate AD from DLB (Barber et al., 1999a).

Metabolic studies of DLB using SPECT and PET suggest a more global pattern of hypermetabolism compared to the typical temporal–parietal hypometabolism of AD. This may be reflected in reduced frontal (Defebvre et al., 1999) or occipital perfusion (Donnemiller et al., 1997; Ishii et al., 1999) by SPECT in DLB relative to AD, and reduced occipital glucose metabolism by PET in DLB relative to AD (Higuchi et al., 2000; Ishii et al., 1998). Dopamine transporter function as assessed by CIT SPECT may also be more impaired in DLB than AD (Donnemiller et al., 1997). PET measures of occipital glucose utilization in particular could differentiate DLB from AD with relatively high sensitivity (86–92%) and specificity (91–92%) in a small clinical studies (Higuchi et al., 2000; Ishii et al., 1998). Nonetheless, conventional SPECT scan is limited in its diagnostic utility in distinguishing AD from DLB given the heterogeneity of perfusion patterns, semiquantitive nature, and low sensitivity and specificity (Pasquier et al., 1997; Talbot et al., 1998).

Electrophysiologic studies with EEG in DLB show slowing with loss of alpha activity as the dominant rhythm and temporal slow wave transients. EEG slowing is common in DLB, characterized by loss of alpha activity as the dominant rhythm, and may be correlated to MMSE (Barber et al., 2000; Briel et al., 1999). Temporal lobe slow wave transients have also been described, correlated to reported episodes of loss of consciousness in DLB (Briel et al., 1999). Fluctuating cognition may correlate with fluctuation in mean EEG frequency over 1.5 minutes by EEG brain mapping (Walker et al., 2000a, b). While slowing of alpha rhythm and temporal slow wave transients are common in DLB, they are not specific, and may be seen in AD (Briel et al., 1999).

The usefulness of CSF biochemical markers in DLB is unclear, as most studies have looked at small clinical samples. Some studies show elevated CSF tau in DLB similar to AD (Arai et al., 1997; Higuchi et al., 2000), while others demonstrate normal CSF tau and low Aß42 (Kanemaru et al., 2000).

Genetics

Genetic factors in the etiology of DLB are suggested by pedigrees of familial DLB (Hardy et al., 1998; Ohara et al., 1999) or PD in which members have developed dementia. Furthermore, some studies find an increased risk of dementia in first-degree relatives of PD patients (Van Duijn et al., 1991), and of PD in first-degree relatives of AD patients (Amaducci et al., 1986; Hofman et al., 1989), although other studies have disputed these findings (Mickel et al., 1997). Genetic studies in DLB have assessed genetic risk factors and causative genes that are important in PD and AD.

AD related polymorphisms that have been evaluated in DLB include apolipoprotein E (*APOE*), butyrylcholinesterase, α1-antichymotrypsin (*AACT*), presenilin-1 (*PS1*), and α2-macroglobulin (*A2M*). The *APOE* ϵ4 allele is a risk factor for late-onset sporadic and familial AD (Rebeck et al., 1993; Saunders et al., 1993). The *APOE* ϵ4 allele is over-represented in DLB cases to a lesser degree than in AD (Benjamin et al., 1994a; Lamb et al., 1998; Morris et al.,

1996). Under-representation of the *APOE* ϵ2 allele, which may be protective for AD (Benjamin et al., 1994b; Corder et al., 1994; West et al., 1994), has not been found in DLB (Lamb et al., 1998; Morris et al., 1996).

The butyrylcholinesterase K allele is not over-represented in DLB; however, an increased number of homozygotes for the K allele was found in a small number of DLB cases (Singleton et al., 1998). No association with DLB was found with the *PS1* allele 1 intronic polymorphism (Singleton et al., 1997), the *AACT* A allele (Lamb et al., 1998), the *A2M*Val1000Ile polymorphism, or the *A2M* pentanucleotide deletion, although a trend toward increased homozygotes for the pentanucleotide deletion polymorphism was noted in DLB and AD (Singleton et al., 1999).

PD related genes evaluated in DLB include α-synuclein and the cytochrome P450 CYP2D6 (*CYP2D6*). α-Synuclein mutations have been identified in five pedigrees of autosomal dominant familial Parkinson's disease, but have not been found in sporadic PD or DLB (Higuchi et al., 1998). While allele 4 of the *CYP2D6* gene has been associated with PD, it is not associated with AD or DLB (Atkinson et al., 1999). Finally, a pentanucleotide repeat polymorphism in the promoter region of nitrogen oxide synthase 2A gene (*NOS2A*) has been linked to DLB but not AD in a single report (Xu et al., 2000).

Clinical management

Management of DLB targets motor, cognitive and behavioural symptoms. General principles of dementia management should be employed, including regular assessment of functional capabilities, family education, social service support, environmental modification, optimization of medications, and aggressive recognition and treatment of delirium. In addition, specific medication therapy may be required for treatment of motor, cognitive and behavioral symptoms. Trials of L-dopa or dopaminergic agonists may ameliorate motor symptoms of parkinsonism; however, patients with DLB are less likely to respond than PD patients, and are more sensitive to side effects of hallucinations, delusions, and agitation.

Similar to patients with AD, cholinergic agents can improve memory and behaviour in DLB. A double-blind, placebo- controlled study of the cholinesterase inhibitor rivastigmine (Exelon) 3–12 mg/d in DLB demonstrated greater improvement relative to placebo in the Neuropsychiatric Inventory (McKeith et al., 2000b).

Behavioural symptoms may require drug therapy if they are unresponsive to environmental modification and are disturbing to the patient and caregiver. Agitation may respond to non-neuroleptic medications such as anxiolytics (benzodiazepines, buspar), antidepressants (trazadone) or anticonvulsants (gabapentin, valproate). Hallucinations and delusions may require carefully monitored treatment with atypical neuroleptics. High potency neuroleptics such as haloperidol should be avoided, as patients with DLB are particularly susceptible to severe extrapyramidal side effects (McKeith et al., 1992a). Low doses of atypical neuroleptics such as risperidone, olanzepine, seroquel, and clozaril are preferable; however, even these may potentiate extrapyramidal symptoms in DLB.

Table 18.2

Pathological features in DLB

1. Essential for diagnosis: Lewy bodies in cortical areas
2. Associated but not essential:
Lewy-related neurites
Amyloid plaques (all types)
Neurofibrillary tangles
Neuronal loss/synapse loss
Spongiform change (temporal)
Neurotransmitter abnormalities

Pathological features in DLB

The hallmark and the essential pathological requirement for the diagnosis of DLB is the presence of Lewy bodies. Other pathological features are frequently associated with the Lewy bodies (Table 18.2).

Lewy bodies

Lewy bodies (LB) are eosinophilic intracytoplasmic inclusions with hematoxilin and eosin stain, that can be recognized with more sensitivity with ubiquitin immunostaining (Kuzuhara et al., 1988; Lennox et al., 1989b) and with great specificity with α-synuclein antibodies (Irizarry et al., 1998; Spillantini et al., 1997). The presence of this presynaptic protein seems to be so specific for the LB that α-synuclein intraneuronal immunoreactivity is considered now parallel to Lewy-related pathology. However, more than 20 different antigens have been detected in the LB (Gómez-Tortosa et al., 1998; Pollanen et al., 1993). The appearance of the LB varies slightly depending on their location in brainstem or in cortical regions (Fig. 18.1). Classic LB, as seen in brainstem, are compact,

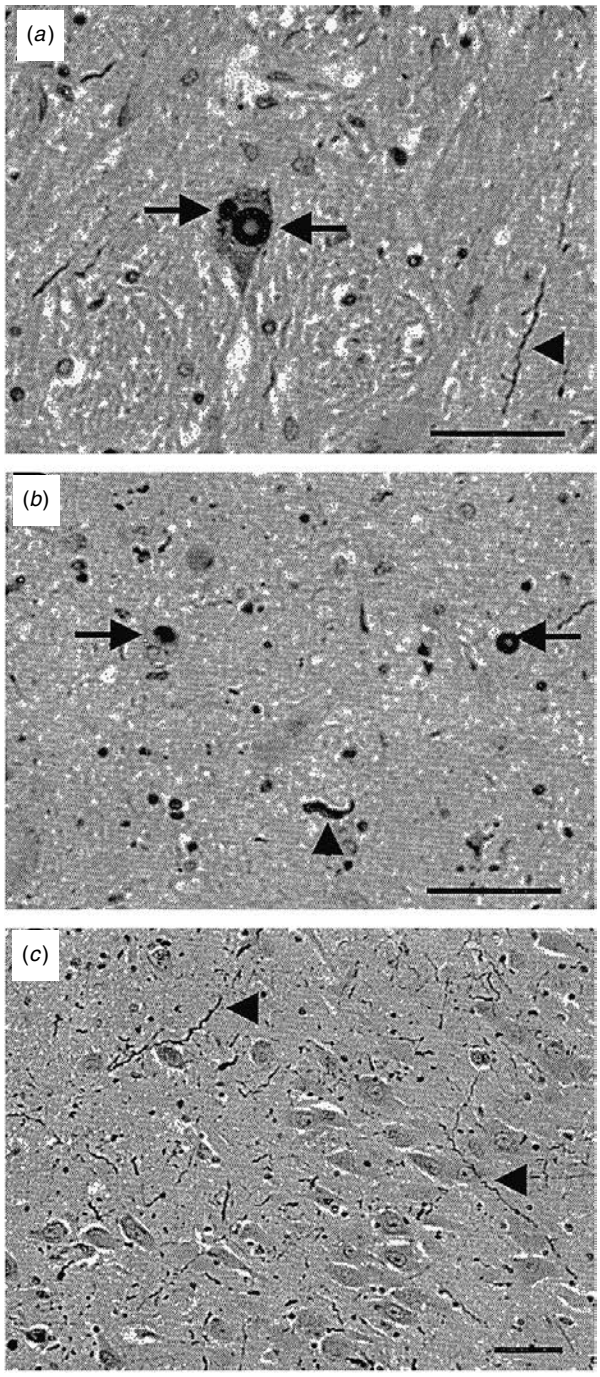

Fig. 18.1. Lewy bodies (arrows) and Lewy neurites (arrowheads) in substantia nigra (*a*), entorhinal cortex (*b*), and hippocampal CA2/3 subfields (*c*) in DLB by α-synuclein immunostaining (hematoxylin and eosin counterstain.) Scale bars = 50 μm.

with a well defined halo. When double immunostained for α-synuclein and ubiquitin, the first shows a tendency to be distributed in an outer rim, while ubiquitin is present more towards the core. In substantia nigra, α-synuclein immunoreactivity also shows a wide spectrum of intracytoplasmic inclusions with variable ubiquitin costaining that may represent progressive stages of aggregation and LB formation (Gómez-Tortosa et al., 2000). Cortical LB are less well defined, lack the halo (Lowe, 1994), and the pattern of double immunostaining is more homogenous.

The distribution of the LB in cases with DLB shows a very consistent hierarchical vulnerability to LB formation across brain regions. Substantia nigra and other brainstem nuclei are affected with the highest density of LB, followed by paralimbic regions (basal forebrain nuclei, entorhinal, cingulate and insular cortices) and neocortical regions having the lowest density (Gómez-Tortosa et al., 1999; Rezaie et al., 1996) (Fig. 18.2, see colour plate section). Depending on the more or less widespread distribution of the LB, the spectrum of Lewy body disorders is classified into three types (McKeith et al., 1996). LB restricted to brainstem and basal forebrain nuclei define the brainstem type which is basically the pathology of idiopathic PD. In the transitional type, LB are found in limbic and paralimbic regions, but not in neocortex. When LB are also present in neocortex, it is the neocortical type. The density of LB in substantia nigra does not necessarily correlate with the density of LB in paralimbic and neocortical areas (Gómez-Tortosa et al., 1999) which suggests that DLB does not simply reflect severe or long-lasting PD. In cortical regions, LB frequently occur in the deep cortical layers V and VI as if only certain subpopulations of neurons are vulnerable to develop the inclusions.

Lewy neurites

Lewy neurites in the CA2–3 regions of the hippocampus are a pathological feature frequently associated with the presence of LB (Dickson et al., 1991). They show the same immunohistochemical profile as the LB, in terms of containing α-synuclein, ubiquitin and neurofilaments (Dickson et al., 1994; Irizarry et al., 1998). Lewy neurites are found in about two-thirds to three-quarters of the cases with Lewy bodies and their presence is very specific for Lewy body diseases, because they do not appear in other neurodegenerative diseases with nigral degeneration but without LB (Kim et al., 1995). Thus, CA2–3 neuritic degeneration seems a manifestation of the same process that leads to LB formation. Double immunostaining against α-synuclein and either SMI-32 (non-phosphorylated neurofilament present in

dendrites) or SMI-312 (axonal phosphorylated neurofilament) suggests that Lewy neurites are mostly axonal fibres. Because the cell bodies in the hippocampus generally lack α-synuclein inclusions, these neurites are likely to derive from axonal afferents to CA2–3. The absence of tyrosine hydroxylase immunoreactivity suggests that CA2–3 neuritic processes do not derive from brainstem dopaminergic afferents to the hippocampus (Dickson et al., 1994). Thus, the origin of these neurites may be entorhinal cortex or septal nuclei, regions projecting to the CA2–3 fields of the hippocampus and usually affected by α -synuclein inclusions. Recent studies show that hippocampal pathology in PD and DLB is more extensive than recognized with α -synuclein immunostaining, as revealed by abnormal neurites immunostained with antibodies against β- and γ-synucleins in the dentate gyrus and mossy fibres that synapse on hilar neurons (Galvin et al., 1999).

In DLB, scattered neurites are also found in other regions, especially in the nigra, basal forebrain nuclei, amygdala, entorhinal and cingulate cortices (Braak et al., 1999; Gómez-Tortosa et al., 2000; Pellise et al., 1996).

Alzheimer changes

Concomitant Alzheimer changes, that is amyloid plaques and neurofibrillary tangles (NFT), are very common in DLB, but the frequency of this association varies depending on the criteria used to define neuropathological AD. About 30% of cases fulfilling neuropathological criteria for definitive or probable AD have some cortical LB and constitute what is called the Lewy body variant of AD. Thirty-two to 89% (depending on the criteria used) of the DLB cases have concomitant Alzheimer-type changes (Hansen, 1996). In general, the Alzheimer changes found in DLB are characterized by the predominance of senile plaques, mostly of diffuse type rather than neuritic, with more Aβ 42 than Aβ 40, and fewer NFT, especially in the neocortex (Hansen, 1996; Hansen et al., 1993; Heyman et al., 1999; Mann et al., 1998; Samuel et al., 1997b). A simplified but useful schema would be to consider AD with LB or the Lewy body variant of AD those cases having enough neocortical tangles to meet a Braak stage V or VI, while cases with only entorhinal and paralimbic tangles (Braak I to IV) would be considered as DLB (Gearing et al., 1999; Hansen, 1996).

In DLB, Alzheimer and LB pathology seem to be independent of each other, both in terms of distribution and quantity. The distribution of LBs does not coincide with that of neurofibrillary tangles, which are most abundant in the hippocampus and layers III and V of association cortex. There is no correlation between LB density and the degree of neurofibrillary tangle involvement or the amount of cortical senile plaques, which suggests an independence in the formation or in the dynamic turnover of these pathological structures (Gómez-Isla et al., 1999).

Neuronal loss

Neuronal loss in DLB is significant in brainstem and nucleus basalis of Meynert associated with Lewy-pathology (Lippa et al., 1999), but it seems that cortical neuronal loss is just modest, which is consistent with the lack of gross atrophy of DLB brains (Hashimoto et al., 1998; Lippa et al., 1998). Several studies have examined neuronal loss in different cortical regions. In the temporal cortex, DLB brains showed a 10 to 20% (non-significant) neuronal loss in comparison with controls, while DLB cases with concomitant AD changes had pronounced neuronal loss (around 40 to 50%), comparable to that of pure AD cases (Gómez-Isla et al., 1999; Lippa et al., 1994; Wakabayashi et al., 1995). The study of specific neuronal subpopulations characterized by the expression of neurofilaments (pyramidal neurons) and several calcium binding proteins (gabaergic interneurons) in the superior temporal sulcus cortex, also shows no differences in neuronal densities between DLB cases and controls (Gómez-Tortosa et al., 2001).

In entorhinal cortex, neuronal loss has been examined in specific layers and it is not significant in comparison with controls unless Alzheimer changes are present. Lippa et al. (1997) did not find neuronal loss in layer II, origin of the perforant pathway and a group of neurons affected very early by neuronal loss in AD (Gómez-Isla et al., 1996b). Nor is there neuronal loss in pure DLB cases in layers V/VI, where the LB are mainly found, compared to controls. The number of LB does not correlate with neuronal loss, suggesting that they are not directly implicated in widespread neuronal death in pure DLB. Other studies have not found neuronal or synapse loss in frontal cortex (Hansen et al., 1998; Lippa et al., 1994; Samuel et al., 1997a) or hippocampus (Ince et al., 1991; Lippa et al., 1994) of DLB compared with control brains. Thus, in contrast with AD, widespread cortical neuronal loss is not a major feature in the pathology of DLB. However, there is still the possibility of a selective or restricted neuronal loss, not yet recognized.

Other neuropathological features in DLB

Circumscribed spongiform change occurs in some DLB cases in layers II–III of the perirhinal cortex and in the

accessory basal amygdaloid nucleus (Iseki et al., 1997). This pathological feature is usually associated with a more aggressive disease with rapid onset of symptoms and a rapid course with a total duration of illness of less than three years (Hansen et al., 1989).

Finally, because of the involvement of basal forebrain and brainstem nuclei there are widespread neurotransmitter deficits in cortical regions. Monoamines and, especially, acetylcholine are severely depleted in the cortex of DLB brains in comparison with controls and AD (Langlais et al., 1993; Samuel et al., 1997a; Tiraboshi et al., 2000). Marked losses in midfrontal choline acetyltransferase (ChAT) activity occurs in DLB independently of coexistent AD changes (Tiraboshi et al., 2000). Reduced cortical ChAT correlates with neuronal loss and LB densities in the nucleus basalis of Meynert (Lippa et al., 1999).

Clinico-pathological correlations

It is not clear yet to what extent each of the above neuropathological features contributes to the clinical phenotype in DLB. It is also not known whether cortical LB are directly responsible for neuronal injury and, therefore, for the clinical syndrome; or whether the α-synuclein deposits within the Lewy neurites interfere with normal neurotransmission. Pathological changes coexisting with the Lewy pathology, such as Alzheimer-type changes, may also contribute to the clinical phenotype.

Lewy-related pathology

The contribution of the LB to the clinical phenotype has been studied with different approaches. The first has been to examine whether PD cases with dementia consistently have cortical LB that may account for the cognitive decline. What seems clear from clinicopathologic studies of PD patients is that there is not a clear threshold for cortical LB density that distinguishes between demented and nondemented PD. Among the 30 to 40% of idiopathic PD patients who develop dementia not all have cortical LB. In one study, cortical LB were considered to be the likely cause of dementia in only 10% of the demented cases (Hughes et al., 1993). AD changes seem to be the major determinant of the cognitive decline in PD patients (de Vos et al., 1995; Hughes et al., 1993).

The second is to correlate LB densities with the severity of the disease as assessed by a cognitive or functional score close to the time of death. The results with this approach are not uniform. Some studies have found a significant correlation between dementia severity and cortical LB counts (Lennox et al., 1989a; Mattila et al., 1998; Samuel et al., 1997a; Samuel et al., 1996), while others have failed to find any correlation (Churchyard & Lees, 1997; Gómez-Isla et al., 1999; Perry et al., 1990, 1996). There are several differences among these studies in terms of the clinical data used to represent severity of the disease, the degree of concomitant AD in the DLB cases, and the methodology used to quantitate LB, that may account for the different results. In several studies finding a significant correlation between cortical LB and severity of the disease, the significance seems to rely mainly upon the most severely demented cases having the highest LB densities (Lennox et al., 1989a; Mattila et al., 1998). Thus, there is the possibility that LB may be just a marker or be in parallel with a more widespread pathology underlying the disease and not necessarily be the cause of the cognitive decline.

The third approach is to correlate the density of LB in certain brain regions with specific clinical phenotypes. A plausible hypothesis would be that the presence in DLB cases of motor symptoms (such as parkinsonism or recurrent falls) would be associated with higher LB densities in substantia nigra and that the presence of psychiatric symptoms, such as delusions or hallucinations, would be related with a higher density of LB in paralimbic or neocortical regions, in comparison with cases who did not present these symptoms. However, no significant differences have been found in LB densities in substantia nigra, paralimbic regions and neocortex comparing patients with or without specific symptoms (Gómez-Tortosa et al., 1999). It is surprising that DLB patients with or without clinical parkinsonism had similar LB densities in nigra. There was a slight tendency for cases with hallucinations and delusions to have a higher density of LB in paralimbic regions versus those without these symptoms, but the differences were not statistically significant. One group has found an association between the presence of cortical Lewy body pathology and persistent hallucinations (McShane et al., 1995, 1996) but other studies have failed to demonstrate any correlation (Perry et al., 1990). Therefore, the distribution and number of cortical LB do not seem to be clearly associated with the clinical symptoms. In most clinico-pathological studies the density of cortical LB also does not correlate with the duration of the disease (Gómez-Isla et al., 1999; Gómez-Tortosa et al., 1999; Mattila et al., 1998).

The contribution of the Lewy neurites to the cognitive impairment is not understood yet, but they may well play a prominent role. Churchyard & Lees (1997) found a positive correlation between the density of hippocampal CA2–3 neurites and cognitive impairment (MMSE) in Parkinson's disease patients, even when in this same study

there was no correlation with the density of LB. The CA2–3 regions of the hippocampus receive major inputs from the dentate gyrus, entorhinal cortex, septal nuclei, amygdala and hypothalamus, and then project to the CA1 field, which in turn projects to the subiculum. These connections are crucial for memory and cognition, suggesting that the neuritic inclusions may disrupt hippocampal function by interfering with inputs to the CA1 field and contribute to the cognitive deficits in DLB. Furthermore, more extensive hippocampal neuritic abnormalities can be revealed with β- and γ-synuclein immunostaining in the dentate gyrus and mossy fibres that synapse on hilar neurons (Galvin et al., 1999). These abnormal processes are likely to impair synaptic transmission in the perforant pathway, which is a critical network for memory and cognition, known to be severely affected in AD. Therefore, the same hippocampal circuitry may be involved in Alzheimer and DLB diseases. As widespread α-synuclein-positive neuritic processes are revealed in DLB brains, there is a growing impression that abnormal neurites, not only in hippocampus but also in other cortical regions, may impair neuronal connectivity and play a significant role in the progression of the cognitive deficits in DLB.

Neuronal loss/Alzheimer changes

Alzheimer-type pathology likely has an additive or synergistic effect in producing the clinical phenotype of DLB, but cannot be the sole cause. First, there is a well documented number of DLB cases that represent pure LB pathology (Armstrong et al., 1997; Perry et al., 1996). Secondly, Alzheimer changes do not correlate with the severity of cognitive impairment in DLB (Gómez-Isla et al., 1999; Samuel et al., 1996). This is not surprising considering that there are few neurofibrillary tangles, which are most strongly correlated with neuronal loss and cognitive impairment in AD (Gómez-Isla et al., 1996a, 1997), and that amyloid plaques are mostly of the diffuse type, which are not associated with cognitive impairment and are present in cognitively preserved elderly (Crystal et al., 1993; Dickson et al., 1992). Furthermore, DLB cases are equally demented as AD cases with many fewer neurofibrillary tangles and senile plaques, which suggests that other pathological features besides the Alzheimer changes are contributing to the clinical phenotype. On the other hand, DLB cases are less demented than cases with the Lewy body variant of AD for equal LB densities and ChAT loss, which suggests that when present, AD changes have an additive effect in the clinical phenotype (Samuel et al., 1997a).

Neurochemical deficits

There is severe ACh depletion in DLB cases all through cortical regions (temporal, parietal, midfrontal, septal). This ACh depletion correlates with dementia severity, and its role in the cognitive phenotype is supported by the good response some DLB cases have to treatment with cholinesterase inhibitors. The most robust neurobiological correlate of the dementia so far identified appears to be extensive cholinergic deficits in the neocortex (Perry et al., 1997).

Finally, impairment of the mesocortical and mesoneocortical dopaminergic projections may be also implicated in cognitive dysfunction. The lesion of these connections in animals produces behavioural changes and it has been suggested that in humans such lesions may be responsible for the cognitive manifestations in PD, and for some neuropsychiatric disorders such as schizophrenia or Tourette's syndrome.

Underlying biochemical abnormalities reflected in Lewy bodies: the role of alpha-synuclein

An abundant component of Lewy bodies in dementia with Lewy bodies and related disorders is the presynaptic protein, α-synuclein (Irizarry et al., 1998; Spillantini et al., 1997). α-Synuclein is a highly conserved 140 amino acid phosphoprotein of unknown function that was originally isolated from *Torpedo californica* (Maroteaux et al., 1988). The name synuclein was coined on the basis of both synaptic and nuclear localization in *Torpedo*, however, nuclear localization has not been consistently observed in subsequent studies (George et al., 1995; Iwai et al., 1995; Jakes et al., 1994; Maroteaux et al., 1988). Although the normal function of α-synuclein is unknown, studies of song-learning in the zebra-finch have implicated a role for the protein in neuronal plasticity. In juvenile birds just learning their song, α-synuclein is especially abundant in the glutamatergic presynaptic terminals of the key regulatory projection essential for song memorization (George et al., 1995).

The structure of α-synuclein may provide clues to its possible function. The amino-terminal region contains 7 degenerate 11 amino acid imperfect repeat sequences predicted to form 5 amphipathic alpha helices. α-Synuclein is predicted to have a random coil conformation in solution (Weinreb et al., 1996), however, when studied in the presence of synthetic membranes, lipid binding is accompanied by an increase in alpha helicity (Davidson et al., 1998),

suggesting that, in an isolated system, α-synuclein may be membrane associated.

Studies into the genetic basis of familial Parkinson's disease have led to the identification of two missense mutations in the gene encoding α-synuclein (Ala53Thr and Ala30Pro) in some families with early onset familial Parkinson's disease (Krüger et al., 1998; Polymeropoulos et al., 1997). It is unclear how the mutations effect the normal function of α-synuclein but it has been hypothesized that the normal localization of the protein is disrupted, causing α-synuclein to accumulate in the cell bodies of degenerating neurons as a component of Lewy bodies.

Research aimed at understanding the role of α-synuclein in normal and parkinsonian cell function have led to the identification of several potential interacting species. α-Synuclein was found to bind synthetic vesicles containing acidic phospholipids in vitro (Davidson et al., 1998), and investigators have reported interactions of α-synuclein with the structural protein tubulin (Alim et al., 2002), tau (Jensen et al., 1999), microtubule-associated protein 1B (MAP-1B) (Jensen et al., 2000), and with a previously unknown protein called 'synphilin-1' (Engelender et al., 1999). Subsequently, MAP-1B (Jensen et al., 2000) and synphilin-1(Wakabayashi et al., 2000) have been identified as components of Lewy bodies suggesting that interactions of α-synuclein with these proteins may be a critical component of Lewy body formation.

Studies into the effects of the Parkinson's disease associated mutations have revealed that the Ala30Pro mutation abolishes the binding of α-synuclein to brain vesicles in vitro (Jensen et al., 1998) suggesting that this may lead to the accumulation of the protein and, as a result, its assembly into Lewy bodies. By contrast, neither the Ala30Pro nor Ala53Thr mutation was found to have an effect on the association of α-synuclein with cellular membranes (McLean et al., 2000). Further examination of the normal function of α-synuclein and the effect of the mutations on subcellular localization will provide insight into the mechanisms that lead to the accumulation of the protein in certain neurodegenerative disorders.

α-Synuclein protein has a demonstrated propensity to aggregate in vitro (Conway et al., 1998; Giasson et al., 1999) with the Ala53Thr mutant seemingly forming fibrils faster than both wild-type and Ala30Pro α-synuclein (Conway et al., 1998). Subsequent studies have suggested that both Parkinson's disease associated mutations (Ala53Thr and Ala30Pro) accelerate the rate of α-synuclein aggregation (Nahri et al., 1999). More recently, it has been suggested that a nonfibrillar oligomer species precedes the formation of fibrils of α-synuclein and that acceleration of oligomerization, rather than acceleration of fibrillization, is a shared property of both mutant proteins (Conway et al., 2000a). Interestingly, the fibrils generated in vitro from both wild-type and mutant α-synuclein have been found to possess features that are characteristic of amyloid fibrils (Conway et al., 2000b; Serpell et al., 2000).

A common mechanism whereby manipulations of the C-terminus lead to aggregation and inclusion body formation is suggested by recent studies where C-terminally truncated forms of α-synuclein more readily formed fibrils in vitro (Crowther et al., 1998). Furthermore, although Lewy bodies contain predominantly full-length α-synuclein, Baba et al. (1998) reported the presence of truncated α-synuclein in purified Lewy bodies which suggests that a truncation event occurs. In addition, α-synuclein aggregation in vitro was recently demonstrated to be a nucleation-dependent event (Wood et al., 1999) which raises the possibility that a C-terminally modified form of the protein acts as a seed for fibril formation. SH-SY5Y cells overexpressing C-terminally truncated α-synuclein, particularly the 1–120 residue protein, have been shown to be more susceptible to oxidative stress following exposure to hydrogen peroxide or to the dopaminergic neurotoxin MPP+ (Kanda et al., 2000).

Chemical manipulations have also been determined to promote α-synuclein aggregation in vitro. Coincubation of recombinant α-synuclein with cytochrome *c*/hydrogen peroxide or hemin/hydrogen peroxide induced α-synuclein aggregation that could be blocked by anti-oxidant agents such as *N*-acetyl-L-cysteine (Hashimoto et al., 1999a). Likewise, human α-synuclein was found to aggregate in the presence of ferric ion and this was inhibited by the iron chelator, deferoxamine (Hashimoto et al., 1999b). Consistent with the in vitro study by Hashimoto et al. (1999b), Osterova-Golts and colleagues demonstrated aggregation of α-synuclein in neuroblastoma cells in culture following exposure to iron or iron plus either hydrogen peroxide or dopamine, which generate free radicals (Osterova-Golts et al., 2000). Moreover, they observed that the Ala53Thr α-synuclein mutation had an increased tendency to aggregate, consistent with observations in vitro (Conway et al., 1998, 2000a; Giasson et al., 1999).

It is unclear at this time if the aggregation of α-synuclein into Lewy bodies is neurotoxic, which would suggest that Lewy bodies are analogous to amyloid plaques in Alzheimer's disease, which have been proposed to be toxic. Alternatively, Lewy bodies could be a result of neuronal damage, but are in themselves, not toxic. Finally, it has been proposed that Lewy bodies may be an inert end point in a process that, early on, produces a neurotoxic species, and that Lewy body formation may actually protect against

cell death by sequestering the toxic species (Conway et al., 2000a).

It has yet to be determined what role, if any, α-synuclein plays in neurotoxicity however, several studies have examined the effect of α-synuclein overexpression on cell death. Overexpression of human mutant α-synuclein (Ala53Thr) selectively induced apoptotic programmed cell death of primary dopamine neurons as well as mesencephalon-derived N27 cells (Zhou et al., 2000), with the mutant protein also potentiating the neurotoxicity of 6-hydroxydopamine (6–OHDA). Likewise, human dopaminergic neuroblastoma SH-SY5Y cells overexpressing Ala 53 Thr α-synuclein were significantly more vulnerable to oxidative stress following exposure to hydrogen peroxide or to the dopaminergic neurotoxin MPP^+ (Kanda et al., 2000). Similarly, aggregates of NAC and α-synuclein proteins induced apoptotic cell death in SH-SY5Y cells (El-Agnaf et al., 1998) and preaggregated NAC was toxic to rat primary mesencephalic neurons and to a PC12 cell line differentiated with nerve growth factor (Forloni et al., 2000).

Transgenic models

Animal models aimed at addressing the fundamental aspects of α-synucleinopathy have yielded some clues as to the normal function of α-synuclein and the effect of overexpression of the Parkinson's disease associated mutations. Mice lacking α-synuclein (α-syn$^{-/-}$) do not display any gross pathological abnormalities and possess a normal complement of dopaminergic cell bodies, fibres and synapses (Abeliovich et al., 2000). However, the α-syn$^{-/-}$ mice exhibit altered stimulus-dependent dopamine release, which suggest that α-synuclein is an activity-dependent negative regulator of dopamine neurotransmission. Neuronal expression of human α-synuclein and the Ala30Pro mutant in mice results in a progressive, abnormal accumulation of α-synuclein in neuronal cell bodies and neurites in several regions of the brain (Kahle et al., 2000; Masliah et al., 2000). Behavioural deficits are observed only in mice expressing the highest levels of wild-type α-synuclein (Masliah et al., 2000) and correspond to increased amounts of α-synuclein immunoreactive neuronal inclusions. Such an observation suggests that a critical threshold of α-synuclein accumulation is required before dopaminergic and behavioural deficits become apparent.

Analogous phenotypes have also been observed in a *Drosophila* model of Parkinson's disease where expression of wild-type and mutant forms of α-synuclein in *Drosophila melanogaster* produce adult-onset loss of dopaminergic neurons, filamentous intraneuronal inclusions containing α-synuclein, and locomotor dysfunction (Feany & Bender, 2000). These recent mouse and drosophila models of Parkinson's disease support a central role for the process of α-synuclein aggregation in the pathogenesis of α-synucleinopathies.

In conclusion, Lewy body dementia has emerged as a major clinical and pathological entity contributing to dementia. Although substantial data have been presented regarding the clinical and pathological features of this illness, and the identity of some of the proteins involved in the neuronal inclusions has been uncovered, major questions remain unanswered. The vast majority of instances of Lewy body dementia show at least some pathological overlap with Alzheimer's disease-related changes. This concordance far exceeds that which might be expected by chance alone; it suggests strongly that the disease processes are interrelated. This impression is reinforced by the observation that certain cases of early onset autosomal-dominant familial Alzheimer's disease show, in addition to marked Alzheimer changes, Lewy bodies in the cortex (Lantos et al., 1994; Lippa et al., 1995). It is uncertain whether this represents a common genetic predisposition to neurodegenerative diseases, common environmental influences that predispose to both diseases, or a more fundamental intertwining of these pathophysiological processes.

Although most cases of Lewy body dementia overlap with Alzheimer-type pathology, some cases exist where the Lewy bodies in widespread cortical regions are the sole neuropathological alterations. Clinically, these cases are essentially indistinguishable from those that overlap with Alzheimer's disease. Nonetheless, there is minimal or no neuronal loss, and the absolute number of Lewy bodies seems small in comparison to the devastating nature of the severe dementia syndrome. Thus, a major unanswered question remains 'what effect does the presence of Lewy bodies have on the cortex to impair neural systems so profoundly?'

Perhaps better understanding of the protein constituents that precipitate in Lewy body formation would be revealing. α-Synuclein appears to be the major protein constituent, and the presence of the mutations in α-synuclein that lead to autosomal dominantly inherited Parkinson's disease encourages the belief that α-synuclein dysfunction lies at the heart of the illness. Unfortunately, the neuronal functional role of α-synuclein remains unknown. α-Synuclein knockout mice have only a subtle phenotype and minimal electrophysiological dysfunction, suggesting that the impact of α-synuclein alterations in Lewy body diseases is not a simple loss of function (Abeliovich et al., 2000).

It has been suggested that protein misfolding, and thereby potential gain of function, lies at the heart of synuclein aggregation into Lewy bodies and, perhaps more generally, is a cause of synaptic dysfunction in Lewy body dementias. This is an appealing idea from the perspective of other neurodegenerative diseases in that similar mechanisms have been evoked in prion diseases, triplet repeat disorders, and Alzheimer's disease. Nonetheless, direct experimental evidence to support this idea remains elusive.

Thus, while the clinical, neuropathological, genetic, and even biochemical characterization of dementia with Lewy bodies is well underway, definitive understanding of the pathophysiology and therapy await answers to some of these remaining questions. The recent development of a transgenic mouse model of dopaminergic loss and inclusion body formation after overexpression of α-synuclein (Masliah et al., 2000) and the Drosophila model also based on genetic manipulation of α-synuclein (Feany & Bender, 2000), provide important tools for future studies.

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Frontotemporal dementia

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Historically, classification schemas for degenerative dementias were framed around the clinical and pathological phenomenology of the illness. With improved understanding of the molecular basis for many degenerative conditions, traditional taxonomies are being replaced by molecule-based schemas. Nowhere has this transition been more evident than with frontotemporal dementia (FTD) where, until recently, FTD (or Pick's disease) was used to define a group of patients with selective degeneration of frontotemporal cortex in whom Alzheimer's disease (AD) pathology was absent. With the discovery of tau exon mutations (Poorkaj et al., 1998; Spillantini & Goedert, 1998; Clark et al., 1998) and intron mutations (Hutton et al., 1998) in familial cases with selective frontotemporal degeneration, a clinical/pathological syndrome suddenly had a well-defined molecular and genetic basis. This work clarified the importance of tau protein in the pathogenesis of both sporadic and familial FTD and many hoped that this would lead to a molecule-based diagnostic schema for FTD. However, not all cases with tau pathology have selective frontotemporal anatomic involvement and there are many patients with selective frontotemporal degeneration in whom tau pathology is absent (Kertesz et al., 2000). This has left the field somewhat in limbo with many patients falling in between clinical, pathological or molecule-based diagnostic criteria. Thus, although new insights about abnormalities in tau metabolism are an important piece of the FTD story, it is clear that other factors contribute to producing the clinical syndrome that is recognizable as FTD.

Despite still unresolved issues related to nomenclature, FTD represents an important disorder with distinctive epidemiology, genetics, neuropathology, clinical features and treatment. Importantly, it is possible to diagnose most FTD patients during life (Lopez et al., 1999) and to differentiate them from patients with AD. Because FTD has a distinctive pattern or brain degeneration, it offers many clues to the function of the frontal and anterior cortical regions.

Terminology and epidemiology

In recent years FTD has been recognized as a common cause for degenerative dementia. However, in many clinical settings FTD is rarely, if ever, diagnosed. One problem limiting its recognition is that many patients present with psychiatric symptoms (Gustafson, 1993; Lesser et al., 1989) and do not develop a dementia until much later in the course of their illness. Persistent variability in the diagnostic accuracy and diagnostic suspicion from site to site has compounded the confusion related to the epidemiological features of FTD. Indeed, defining the disease has proven difficult from its very beginnings. The term Pick's disease was coined not by Pick, but by two of his students, Onari and Spatz (Berrios, 1996). Although for many decades Pick's disease has been considered as a frontal lobe degeneration associated with neuronal inclusions, Arnold Pick had more interest in focal temporal than focal frontal atrophy. Similarly, the Pick body that carries Pick's name was first described by Alzheimer, and Pick never focused upon the microscopic features of FTD (Berrios, 1996). For many years after Pick's original discoveries, investigators took a restrictive view of the frontotemporal dementias, limiting the diagnosis to cases that demonstrated the classic neuropathological findings of Pick's disease, frontal atrophy with Pick bodies and Pick cells (silver-staining neuronal inclusions). Basing a diagnosis of a degenerative disorder upon the presence or absence of a sometimes-elusive silver-staining inclusion has always been problematic. Many FTD patients have inclusions that do not stain with silver, while other FTD cases lack any cellular inclusions (Nasreddine et al., 1999).

Beginning in the 1980s, investigators began to take a more inclusive view of FTD. Brun and Gustafson from Lund, Sweden and Neary and Snowden from Manchester, England, began considering all cases of non-AD, presenile dementia with frontal lobe atrophy under the category of frontal dementia (Brun, 1987; Neary et al., 1987). Although most investigators continued to separate patients with classical Pick bodies from those without these inclusions, some suggested an even more unified approach classifying all such cases under the category of Pick-Complex disorder (Kertesz et al., 1999). The term FTD was coined in 1994 by the Lund–Manchester groups in an attempt to establish reliable diagnostic criteria for a clinically heterogeneous group of disorders that still shared many pathological features (Brun et al., 1994). Recent advances in molecular genetics have supported the validity of this more inclusive perspective. In 1998 these criteria were modified further and the new diagnostic criteria for FTD divided frontotemporal dementias into three subgroups; primary progressive aphasia, semantic dementia and frontotemporal dementia.

The most frequently cited prevalence figures for FTD come from Europe. Based on clinical, pathologic, and imaging studies, these groups estimate that 12–16% of presenile dementias suffer from frontal lobe atrophy without AD pathology (Neary et al., 1988; Brun, 1987). Fewer than 20% of these cases show the classic pathologic findings of Pick's disease. FTD's true prevalence remains unknown but the disease is relatively common. If AD has a prevalence of four million (Evans et al., 1989) and is somewhere between 10 to 20 times more common than FTD, this would still leave FTD with a prevalence of somewhere between 200 000 and 400 000 cases.

Genetics

Roughly 40% of FTD cases are familial with up to 80% of these familial cases inherited in an autosomal dominant pattern (Gustafson, 1987; Chow et al., 1999). Wilhelmsen and colleagues made a major stride toward defining the genetic basis for this condition in 1994 with linkage of a familial FTD syndrome to chromosome 17 (Wilhelmsen et al., 1994). In 1998 came the discovery of at least ten new exonic or intronic mutations in at least 20 different families with FTD (Poorkaj et al., 1998; Spillantini & Goedert, 1998; Clark et al., 1998; Hutton et al., 1998). These families were extraordinarily diverse both in their clinical and pathological features, despite the fact that they carried nearly identical genetic mutations. In some families clinical features were dominated by frontal lobe degeneration (Lynch et al., 1994), while in others the presentation was shaped by loss of function in the amygdala and anterior temporal lobe (Bird et al., 1999). More recently, cases suggestive of corticobasal ganglionic degeneration (Bugiani et al., 1999) or progressive supranuclear palsy (Reed et al., 1998) have been noted, broadening the phenotype of familial-FTD. Remarkably in one family, a tau mutation led to frontotemporal degeneration in a father with a clinical presentation of corticobasal ganglionic degeneration in the son (Bugiani et al., 1999). Based upon clinical features alone, it is difficult to differentiate a sporadic from a genetic case of FTD.

The neuropathological cases with familial FTD linked to tau mutations show neuronal inclusions that stain positively for tau suggesting abnormal cellular processing of tau (Reed et al., 1998). In some families tau-staining neuronal inclusions alone are prominent, while in others, glial inclusions are also present. Even though neuronal inclusions are evident in most of the families, classical silver-staining Pick bodies are uncommon (Nasreddine et al., 1999). Neurofibrillary tangles are present in some cases, but absent in most. The majority of cases of FTD linked to chromosome 17 have demonstrated a mutation in tau (Heutink, 2000), although four kindreds with linkage to chromosome 17 have yet to yield specific mutations in the tau gene. Recently, Lee and colleagues found that in one of these families an absence of brain tau was a characteristic feature: so-called 'no tau tauopathy'. (Zhukareva et al., 2001). In total, these cases suggest that overexpression or underexpression of tau, or expression of mutated tau represent a major risk factor for FTD. Some even suggested that FTD should be considered a tauopathy.

However, the initial excitement for tau has been tempered. Not all familial cases of FTD are caused by tau gene mutations. At least three families have been identified which do not show linkage to the tau region of chromosome 17 (Gasser et al., 1996) and almost no sporadic cases have demonstrated tau mutations (Rizzu et al., 1999). Estimates of familial FTD cases with a known mutation in tau range from less than 10% up to 40% (Houlden et al., 1999; Rizzu et al., 1999). Similarly, other chromosomal locations have been found in familial FTD including chromosome three (Brown et al., 1995). Additionally, the mixture of FTD and amyotrophic lateral sclerosis has been linked to chromosomes 9 (Hosler et al., 2000) and 15 (K.C. Wilhelmsen et al., personal communication).

Pathology and pathogenesis

The more inclusive view of FTD includes patients with classical Pick's disease as well as those with the other non-

AD dementias with frontal or temporal lobe atrophy. The unifying feature across all these cases is the presence of focal atrophy in the frontal lobes, the temporal lobes, or both. The gross pattern of atrophy in FTD can have a unilateral predominance or it can be symmetrical and bilateral. In the temporal lobes the more anterior regions typically show greater pathology than the posterior regions. The amygdala, for example, shows more involvement than does the hippocampus (Brun, 1999), and the posterior parietal and temporal-occipital regions are relatively preserved. Subcortical structures such as the substantia nigra, putamen, and globus pallidus may show marked involvement by microscopy. Those cases with a motor neuron component also show pathological changes in the anterior horn cells.

The microscopic changes in the affected regions include neuronal loss, synaptic loss, gliosis, and spongiosis often most prominent in the first three cortical layers (Brun, 1993). Some cases of FTD demonstrate swollen neurons with inclusion bodies. Only a minority of the cases with cellular inclusions will exhibit the classic silver staining that is typical of a Pick body. However, in many cases 'Pick-like' inclusions in both neurons and glia that are not silver staining are identified (Nasreddine et al., 1999). Recent work has shown that the silver-staining is due to deposition of three repeat tau rather than the four repeat isoform found in the other inclusions (Delacourte, 1999). Tau immunoreactivity is the most common finding in familial and sporadic FTD. Furthermore, the presence of tau-positive inclusions in progressive supranuclear palsy (PSP) and corticobasal ganglionic degeneration (CBD) has even prompted some to view PSP, CBD, and FTD as clinical variants of a 'tauopathy' (van Slegtenhorst et al., 2000).

Tau is a microtubule-associated protein that binds, stabilizes and promotes the assembly of microtubules (Hong et al., 1998). Depending on how the tau gene is transcribed, the microtubule-binding region of the protein can have either 3 or 4 tandem repeats of a 31–32 amino acid sequence yielding 3Rtau or 4Rtau (Spillantini & Goedert, 2000). Mutations in the tau gene can cause either altered binding properties of tau or changes in the ratio of 3R to 4Rtau. With exon mutations, altered binding properties cause a relative loss of function by destabilizing microtubules and disrupting axonal transport (Hong et al., 1998). Alternatively, altered binding properties may result in a toxic gain of function by providing an excess of free, cytoplasmic tau available to form insoluble protein aggregates. A number of tau gene mutations increase the amount of 4Rtau presumably resulting in a toxic gain of function caused by insoluble protein aggregates (Hong et al., 1998). Tau aggregates typically contain the 4R isoform, although the aggregates found in Pick bodies contain the 3R isoform (Delacourte, 1999). The significance of different filament morphologies within tau aggregates (paired helical filaments, straight filaments) and their differential prevalence in AD vs. FTD remains to be elucidated (Spillantini & Goedert, 2000). Transgenic mice with tau abnormalities have recently been developed and offer promise for better understanding the pathogenesis of FTD.

Mice expressing the P301L human mutations and mice overexpressing human tau develop behavioural and motor changes, remarkably similar to those seen in the human forms of this condition (Lewis et al., 2000; Ishihara et al., 1999). These changes develop within 6 months allowing researchers the opportunity of studying interventions related to abnormal tau processing that might accelerate or slow this process. However, there are many cases of FTD where abnormal tau is not visualized in the brain and tau does not unify all of FTD. Munoz (2000) has emphasized that there are tau-negative and ubiquitin positive inclusions in many of the cases of FTD associated with motor neuron disease and none of the families with both prominent FTD and motor neuron disease have shown tau mutations.

A few studies on the neurochemistry of FTD suggest a specific neurochemical profile. In particular, there are severe losses of brain serotonin, of both pre- and post-synaptic receptors (Sparks et al., 1991). In contrast, FTD is one of the few conditions where cholinergic cell concentration in the nucleus basalis of Meynert is normal (Sparks, et al., 1991). The changes with dopamine are more variable. These neuropathological findings suggest that the AD treatments based upon a cholinergic deficit are unlikely to work with FTD. The clinical symptoms of irritability, depression, compulsions and hyperorality may be explained by the loss of brain serotonin seen with FTD (Miller et al., 1995).

Diagnosis

The mean age of onset for FTD is the sixth decade, although formal diagnosis is often delayed for many years due to the insidious course and early predominance of behavioural symptoms. The clinical presentation of FTD can vary depending on where the disorder begins in the brain. The illness starts in the anterior frontal or temporal lobes (Miller et al., 1993; Hodges et al., 1992; Neary et al., 1987). Lifespan following a diagnosis of FTD can vary considerably with an 8–9 years on average (Rossor, 1999).

A consensus group delineated three main cognitive subtypes of FTD (Neary et al., 1998). The first, referred to as

FTD, is characterized mainly by behavioural changes and develops in the patient with degeneration in the frontal lobes bilaterally or unilaterally in the right frontal lobe. Patients with this subtype will demonstrate loss of normal social interactions and may become withdrawn or disinihibited. Other features include lack of insight or empathy for others, blunted affect, decreased grooming, hyperorality, perseverative behaviours and social inappropriateness (Rosen et al., 2000).

The second subtype is referred to as progressive nonfluent aphasia. These patients display expressive language dysfunction with effortful speech, word-finding difficulty, grammatical errors and relatively preserved comprehension. Behaviour and social conduct are often remarkably spared until late in the illness in patients with progressive non-fluent aphasia. Complicating this diagnosis is that some patients with selective left parietal degeneration present with non-fluent aphasia and many of these individuals suffer from AD, not FTD (Galton et al., 2000).

The last subtype outlined by the consensus group is semantic dementia (Snowden et al., 1989). Here, the bulk of the pathology occurs in the left anterior temporal lobe, but most cases also show involvement of the right anterior temporal lobe. These patients progressively lose their semantic knowledge of the world (facts, words, objects, etc.). The content of speech eventually deteriorates with loss of language specificity. Hawks become 'birds', then 'animals' and then 'things' (Graham et al., 1999). Naming and comprehension are impaired due to loss of word knowledge. Many of the semantic dementia cases have right as well as left temporal degeneration. This group shows loss of insight, disinhibition, disregard of interpersonal space, and antisocial behaviour (Miller et al., 1993). Those with the right temporal variant exhibit loss of empathy, irritability, fixed and rigid thinking, poor grooming, and decreased facial expression (Edwards-Lee et al., 1997). These clinical distinctions are most apparent earlier in the course and many ultimately progress to more global impairment in frontal and temporal lobe functions.

The current terminology for FTD is complex, even for the experienced neurologist. In particular, it excessively relies upon language based clinical syndromes such as semantic dementia. However, most FTD patients can be reliably diagnosed during life (McKhann et al., 2001). In one study, hyperorality, loss of personal conduct, disabling compulsions, progressive loss of speech and sparing of drawing separated 30 FTD patients from 30 with AD (Miller et al., 1997). In a recent study of autopsy-proven FTD cases we found that loss of social conduct, relative absence of amnesia and hyperorality separated the vast majority of FTD patients from those with AD.

In addition to the various cortical symptoms, some FTD patients will develop Parkinsonian features or symptoms of motor neuron disease. The Parkinsonian features overlap with progressive supranuclear palsy with falls, axial rigidity and ophthalmoplegia more common than tremor. Knopman and colleagues (Knopman et al., 1990; Munoz, 2000) suggest that nearly 80% of FTD patients demonstrate midbrain degeneration. In our cohort, nearly 15% of FTD patients developed symptoms of motor neuron disease during life.

Given the pronounced variation in initial presentation and the common early prominence of behavioural symptoms, misdiagnosis is a common problem for patients and their families. Clinical criteria alone can be useful in distinguishing FTD from AD. Increasingly, however, neuroimaging is being relied upon to increase both the sensitivity and specificity of the diagnosis. The addition of SPECT to clinical criteria has been shown to improve diagnostic accuracy to as high as 90% (Read et al., 1995). FTD patients tend to show bifrontal and bitemporal hypoperfusion vs. the typical temporal parietal defects seen in AD (Miller et al., 1991). Specific patterns of tissue loss which relate to the clinical presentation can often be appreciated with MRI scanning as well (see Fig. 19.1, in colour plate section). Additionally, FTD patients show global atrophy of the corpus callosum (Kaufer et al., 1997), while AD patients show selective atrophy of the third and fourth segments of the callosum. Structural MRI has also shown promise as a test to help distinguish FTD from AD and other dementias (Miller & Gearhart, 1999).

Treatment

There are few diseases in all of medicine that cause greater difficulties for a family than does FTD. Poor judgement in the work place, financial arena or home environment can lead to loss of income, financial devastation or legal difficulties. Because loss of insight is such a prominent feature of FTD it is often difficult to reason with the FTD patient. When family members are probed, they often describe puzzling social withdrawal and loss of concern in the patient that profoundly disrupts the family unit. This, in turn, can diminish the empathy for these patients that they truly deserve. Because apathy intervenes in nearly all cases, the later stages of FTD can be easier to manage than the initial stages (Levy et al., 1996).

Treatment of FTD is limited to the behavioural disorders and there are no known preventive therapies or therapies that improve cognition. No placebo-controlled studies of FTD have been performed, although open-label studies

suggest that selective serotonin reuptake inhibitors may be beneficial in management of the disinhibition, depressive symptoms, carbohydrate craving, and/or compulsions frequently encountered in FTD (Swartz et al., 1997). Support for such an approach can be found in molecular studies showing low serotonin receptor binding in FTD (Sparks et al., 1991). Some behavioural symptoms may require more aggressive pharmacotherapy, including the use of antipsychotics, in which case, as with AD, the newer, atypical agents are favoured in order to minimize Parkinsonian side effects. Anticholinesterase medications do not appear to improve cognitive status and can worsen irritability (Perry, 2001).

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20

Consciousness and its disorders

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Background and working definition of consciousness

It is generally acknowledged that understanding the neurobiological mechanisms responsible for consciousness is one of the most difficult tasks in the agenda of neuroscience. At first glance, however, the notion of consciousness appears uncontroversial, and it has even been claimed that since everyone is conscious and the notion of consciousness obvious, there is hardly any need to define the phenomenon. Clinicians, neurologists and others tend to believe that determining whether consciousness is present or not is a simple matter. The view presented in this chapter, however, is less optimistic. Although experts and non-experts can come to an agreement on what constitutes the essence of consciousness, the full scope of the phenomena described under that term requires careful consideration and a provisional definition that can guide clinical evaluations and research. Both fundamental scientists and neurologists need a working concept of consciousness, and nothing prevents us from possibly modifying that concept in the future according to new evidence. Moreover, given the particular nature of consciousness, there are no standard neuropsychological tools to assess its impairments, and there may never be. Also, because the study of those phenomena is of recent vintage, we do not have yet available diagnostic imaging procedures for the evaluation of such impairments. For these reasons, the assessment of patients with impairments of consciousness relies primarily on systematic and comprehensive clinical observations, complemented by a good history and by fine structural neuroimaging and electrophysiologic studies.

Whether one consults a good dictionary, a neurology textbook, or a psychology textbook, the current definitions of consciousness one is likely to encounter are fairly similar: the definitions state that consciousness is the ability to be aware of self and surroundings. These are hardly ideal definitions, considering that consciousness is being defined in terms of awareness and that awareness and consciousness are usually regarded as synonyms. In spite of their awkwardness, however, these definitions capture something that we can agree on: 'consciousness is the ability to know of our own existence and of the existence of objects and events, inside and outside our organism'. Our proposed working definition of consciousness is in line with this idea and states that consciousness is 'a momentary creation of mental knowledge which describes a relation between the organism, on the one hand, and an object or event, on the other'; the definition also indicates that 'the presence of consciousness, as a mental phenomenon, is accompanied by certain observable behaviours'. To be conscious, at a given moment, is to have a sense of our own organism in the act of knowing an object (or event). Consciousness is not just about the object being known; it is always about the owner of the organism in the process of knowing. Individuals whom we describe as conscious are generating, continuously, 'moments of consciousness' which conjoin organism and object. They are generating in a seamless manner multiple and consecutive periods of mental knowledge along with the external behaviours that accompany such knowledge. (For more on the cognitive and neuroscientific background for this definition see Damasio, 1998, 2000. For other views on the phenomena of consciousness from philosophical, cognitive and neurobiological perspectives see Baars, 1988; Crick, 1994; Dennett, 1991; Edelman, 1989; Metzinger, 1995, 2000; Searle, 1992.)

A practical consequence of this definition is that consciousness must be considered from two standpoints: the external (or behavioural), and the internal (cognitive or mental). Taking the external standpoint, the human organism can be said to be conscious when it exhibits sustained

attention towards objects and events in its environment and when it gives evidence of sustained purposeful behaviour relative to those objects and events. The temporal scale for the qualification of 'sustained' is in the order of minutes, not seconds (a practical yardstick is 10 minutes). From the internal standpoint, a human organism can be said to be conscious if its mental state represents objects and events in relation to itself, in other words, if the representation of objects and events is accompanied by a sense that the organism is in the act of perceiving, that the perception is owned by the organism and established in its perspective.

The fundamental components of consciousness: mind and self

From the internal standpoint, we regard consciousness as a combination of two related processes. The first is the process of generating inside the human organism the mental patterns we call images, relative to an object or event. (By object we mean entities as diverse as a person, a place, a melody, state of localized pain, or a state of feeling; by image we mean a mental pattern in any of the sensory modalities, e.g. a sound image, a tactile image, the image of a state of pain or well being that is conveyed by visceral senses; images convey the physical characteristics of an object or the reaction of like or dislike one may have for an object or the plans one may formulate for it, or the relationships of the object to other objects.) The images that constitute the fabric of the mind are integrated spatially and temporally, across sensory modalities. For example, when we watch a person talking, we generate visual images of the person and also auditory images of her speech, yet those two streams of images are synchronized and spatially coherent, as we can verify by noting that the lip movements are in sync with the speech sounds, and the sound waves come from the appropriate region in space.

This first process of consciousness, then, consists of generating neural patterns in neural circuits and turning those neural patterns into the mental patterns we call images. When we commonly use the term consciousness, however, and certainly when we talk about consciousness according to the working definition provided earlier, we are referring to more than this first process of 'mind', to more than the process of generating spatially and temporally integrated mental images. We are also referring to a second process, that of engendering a sense of 'self in the act of knowing', a process that is parallel to, and combined with that of, engendering mental patterns for an object. This process allows the images of an object and of the complex matrix of relations, reactions, and plans related to it, to be sensed as the unmistakable mental property of an automatic owner who becomes an observer, a knower and a potential actor. This process allows us to know that we own our minds, and that the contents in our minds are shaped in a particular perspective, that of the individual inside of whom the mind is formed. This second process of consciousness allows us to construct not just the mental patterns of objects and events, the temporally and spatially unified images of persons, places, melodies, and of their relationships, but also the mental patterns which convey, automatically and naturally, the sense of a self in the act of knowing. The process of mind and the process of self are so intimately related that the latter is nested within the former. In effect, the second process is that of generating the appearance of an owner and observer for the mind, within that same mind (Damasio, 2000).

Kinds of consciousness

Consciousness can be separated into simple and complex kinds, and the evidence from neurological patients makes the separation transparent. The simplest kind, which we call core consciousness, provides the organism with a sense of self about one moment, now, and about one place, here. The scope of core consciousness is the here and now. Core consciousness does not illuminate the future, and the only past it vaguely lets us glimpse is that which occurred in the instant just before. The complex kind of consciousness, which we call extended consciousness and of which there are many levels, provides the organism with an elaborate sense of self, and places that self in individual historical time, in a perspective of both the lived past and the anticipated future. Core consciousness is a simple, biological phenomenon; it has one single level of organization; it is stable across the lifetime of the organism; and it is not dependent on conventional memory, working memory, reasoning, or language. Extended consciousness is a complex biological phenomenon; it has several levels of organization; and it evolves across the lifetime of the organism.

Extended consciousness is built on the foundation of core consciousness. Neurological impairments reveal that impairment of extended consciousness allows core consciousness to remain intact. This is exemplified by patients with profound disturbances of autobiographical memory caused by global amnesia. By contrast, impairments of core consciousness entail the collapse of extended consciousness, as happens in akinetic mutisms, absence seizures and epileptic automatisms, persistent vegetative state, coma, deep sleep (dreamless), and deep anesthesia. When core consciousness fails, in keeping with its foundational nature, extended consciousness fails as well.

To the two kinds of consciousness, correspond two kinds of self. The sense of self which emerges in core consciousness is the core self, a transient entity, ceaselessly recreated for each and every object with which the brain interacts. Our traditional notion of self, however, is linked to the idea of personhood and identity, and corresponds to a non-transient collection of unique facts and ways of being which characterize a person, the autobiographical self. The autobiographical self depends on systematized memories of situations in which core consciousness was involved in the knowing of the most invariant characteristics of an organism's biography (Damasio, 2000).

Other components of consciousness

In addition to separating the processes of mind and self within the larger process of consciousness, and in addition to distinguishing kinds of consciousness related to their complexity, it is important to tease apart subcomponents that contribute to consciousness but are not the same as consciousness. This componential analysis is vital both for research and for clinical assessment, and is usually neglected to the peril of proper research and diagnosis. For example, it is possible to separate consciousness in general from functions such as wakefulness, low-level attention, working memory, high-level (focused) attention, conventional memory, language, and reasoning.

Core consciousness is not the same as wakefulness or low-level attention, although it requires both to operate normally. Patients with absence seizures or automatisms or akinetic mutism are technically awake but not conscious. On the other hand, patients who lose wakefulness can no longer be conscious, the only exception to this rule being dream sleep.

Core consciousness is also not the same as holding an image over time, a process known as working memory (see Baddeley, 1992; Smith et al., 1996). The sense of self and of knowing is so brief and so abundantly produced, that there is no need to hold it over time in order for it to be effective. However, working memory is vital for the process of extended consciousness.

Core consciousness does not depend on making a stable memory of an image or recalling it, i.e. it does not depend on the processes of conventional learning and memory. Core consciousness is not based on language either. No less importantly, core consciousness is not the same as manipulating an image intelligently in processes such as planning, problem solving, and creativity. Patients with profound defects of reasoning and planning may exhibit normal core consciousness although the higher levels of extended consciousness may be compromised. In brief, wakefulness, image making, attention, working memory, conventional memory, language, intelligence, can be separated by appropriate analysis and investigated separately in spite of the fact that they operate in concert to permit consciousness or assist with functions that require consciousness, such as reasoning.

The relation between emotion and core consciousness, on the other hand, is quite different. Emotion and core consciousness are associated. Patients whose core consciousness is impaired do not reveal emotion by facial expression, body expression, or vocalization. The entire range of emotion, from background emotions to secondary emotions, is usually missing in these patients. By contrast, patients with preserved core consciousness but impaired extended consciousness have normal background and primary emotions. This association suggests that some of the neural devices on which both emotion and core consciousness depend are located within the same region.

Consciousness as a central resource

Disturbances of core consciousness affect the whole of mental activity and the full range of sensory modalities. Patients with disturbed core consciousness, from those with coma and persistent vegetative state to those with epileptic automatisms, akinetic mutisms, and absence seizures, have no island of preserved consciousness and the impairment covers mental images originating from all sensory modalities. Core consciousness serves the entire compass of mental images, i.e. of thoughts that can be made conscious. It is a central resource.

By contrast, the impairment of image making within one sensory modality, for example, visual or auditory, compromises only the conscious appreciation of one aspect of an object, e.g. the visual or the auditory, but does not even compromise consciousness of the same object through a different sensory channel, e.g. olfactory or tactile. Naturally, because consciousness operates on images, an impairment of all image-making capability abolishes consciousness altogether. The sensory processing for a sensory modality may be lost in its entirety as in cortical blindness, or one aspect of the modality may be lost, as in achromatopsia, or a substantial part of a process may be disrupted, as in prosopagnosia (Damasio et al., 1990). Those patients have a disturbance of the processing of the object to be known, but they have normal core consciousness for all the images formed in other sensory modalities, and they even have normal core consciousness for the specific stimuli that they fail to process normally. Patients who cannot recognize a previously familiar

face have normal core consciousness for the stimulus that confronts them, and are fully aware that they do not recognize a face that others expect them to. Those patients have normal core consciousness, and a normal extended consciousness outside of the island of defective knowledge. Their circumscribed defect underscores the fact that core consciousness and its resulting sense of self is a central resource.

The fact that core consciousness is separable from other cognitive processes does not mean that consciousness does not have an influence on them. On the contrary, core consciousness assists with the focusing and enhancement of attention and working memory; favours the establishment of memories; is indispensable for the normal operations of language; enlarges the scope of intelligent manipulations of images, e.g. planning, problem solving and creativity.

The clinical evaluation of consciousness

One of the notable areas of recent progress in neurology and neuroscience came from the development of standardized neuropsychological testing instruments which allow both clinicians and researchers to measure a large range of cognitive performances, from those related to reasoning, attention, and perceptual abilities, to those related to learning and memory, language, and personality. As noted, however, no comparable tests are available or are likely to become available to assess most impairments of consciousness. More often than not, consciousness is either normal (in which case a large range of other neuropsychological functions can be evaluated and found intact or disturbed), or so impaired that assessment of any neuropsychological functions is only possible indirectly by means of careful clinical observations.

Because the study of human consciousness requires both internal and external views, the investigation of consciousness is partially indirect. Behavioural acts are expressions of the mental process, but they are not the same thing as the mental process that precedes or accompanies them. The same is true of any kind of encephalogram, electrical or magnetic, and of functional imaging scans. All of these methods of analysis capture only correlates of the mental process.; they are not the same as the mental process. The fact that mental processes are only accessible to the organism who owns them, however, does not preclude their characterization through appropriate cognitive approaches, and the connection between the result of those characterizations and the correlates obtained through external approaches.

Table 20.1. The key areas of behavioural observation in the assessment of consciousness

State of wakefulness
Presence of background emotions
Presence of basic and sustained attention
Presence of purposeful behaviour

As noted, although consciousness occurs in the interior of an organism it is associated with a number of external manifestations. Those manifestations do not translate the internal process in the same direct way that a spoken sentence translates a thought, but there they are available to observation as correlates and signs of the presence of consciousness. Based on what we know about private human minds and on what we know and can observe of human behaviour, it is possible to establish a three-way correspondence among: (*a*) certain external manifestations, e.g. wakefulness, background emotions, attention, specific behaviours; (*b*) the corresponding internal manifestations of the human being having those behaviours as reported by that human being; and (*c*) the internal manifestations that we, as observers, can verify in ourselves when we are in circumstances equivalent to those of the observed individual. This three-way correspondence permits us to make reasonable inferences about human internal mental states based on external behaviours.

In brief, the contemporary approach to studying the biological basis of the private human mind involves two steps. The first step consists of observing and measuring the actions of an experimental subject; or collecting and measuring the reports of internal experience offered by a subject or both. The second step consists of relating the collected evidence to the measured manifestation of one of the neurobiological phenomena we are beginning to understand, at the level of molecules, neurons, neural circuits, or systems of circuits.

The evaluation of the state of consciousness in a neurological or psychiatric patient should concentrate on analysing their wakefulness, background emotions, attention, and purposeful behaviour. Let us consider these varied processes individually (Table 20.1).

Wakefulness

Wakefulness is easy to establish on the basis of a few objective signs. The eyes of the subject should be open; the muscular tone should be compatible with movements against gravity; and the electroencephalogram should reveal the

characteristic awake EEG pattern. Normal consciousness requires wakefulness, but the presence of wakefulness does not guarantee normal consciousness. As noted below, patients with impaired consciousness in conditions such as persistent vegetative state, epileptic automatisms, and akinetic mutisms, are technically awake. Wakefulness is disrupted in coma, general anesthesia, and during episodes of fainting.

Background emotion

The term emotion usually conjures up the primary emotions, e.g. fear, anger, sadness, happiness, disgust, or the secondary emotions, e.g. embarrassment, guilt, pride, but the field of emotion also includes background emotions, those that occur in continual form when the organism is not engaged in either primary or secondary emotions. Background emotions are experienced in configurations of body movement, in the face, the trunk and the limbs, and suggest to the observer states such as fatigue or energy; discouragement or enthusiasm; malaise or well-being; anxiety or relaxation. The continuity of background emotions is an important fact to consider in our observation of normal human behaviour. When we observe someone with intact consciousness, well before any words are spoken, we find ourselves presuming the subject's state of mind. Correct or not, the presumptions are largely based on the emotional signals available in the subject's behaviour. Importantly, normal consciousness is accompanied by background emotions, and the absence of background emotions usually betrays impairments of consciousness.

Attention

Besides exhibiting wakefulness and background emotions, conscious subjects also exhibit attention. They orient themselves toward objects and concentrate on them as needed. Eyes, head, neck, torso, and arms move about in a coordinated pattern which establishes an unequivocal relationship between subject and certain stimuli in their surround. The mere presence of attention toward an external object usually signifies the presence of consciousness, but there are exceptions. Patients in states of so-called akinetic mutism, whose consciousness is impaired, can pay transient attention to a salient object or event, for example, a phone ringing, a tray with food, an observer calling their name. Attention only guarantees the presence of consciousness when it can be sustained, over a substantial period of time, focused on the objects or events that must be considered for behaviour to be appropriate in a given context. This period of time is measured in many minutes and hours rather than seconds. As noted, a sample of 10 minutes is usually sufficient. Another important qualification is needed. Lack of attention toward an external object may indicate that attention is being directed toward an internally represented mental object and does not necessarily indicate impaired consciousness. This is the basis for absentmindedness. Sustained failure of attention as happens in drowsiness, confusional states, or stupor, is associated with the dissolution of consciousness. Attention is entirely disrupted in coma, general anesthesia, and episodes of fainting.

Conscious subjects are attentive to certain objects and concentrate on them, something that matches our own introspection when we think about our own mental events in comparable situations. Attention and consciousness are thus related, the former being necessary for the latter, but neither attention nor consciousness are monoliths. They occur in levels and grades, and they influence each other as they become more complex. Low-level attention is needed to engage the processes that generate core consciousness, but the process of core consciousness drives higher-level attention toward a focus.

Purposeful behaviour

The presence of adequate and purposeful behaviour is easy to establish in patients who can converse with the observer. When there are impairments of communication, however, the observation requires more detail. Conscious subjects behave purposefully toward the stimuli on which they concentrate, which means that their behaviour is part of an immediately recognizable plan that could only have been formulated by an organism cognizant of its immediate past, present, and anticipated future conditions. The sustained purposefulness and adequateness of behaviour requires the presence of consciousness even if consciousness does not guarantee purposeful and adequate behaviour. By sustained, we mean, once again, minutes to hours. A sample of 10 minutes, complete with evidence from the patient's history may be sufficient.

Sustained and adequate behaviour is accompanied by a flow of emotional states as part of their unfolding. The background emotions discussed above continuously underscore the subject's actions. Telltale signals include the overall body posture and the range of motion of the limbs relative to the trunk; the spatial profile of limb movements, which can be smooth or jerky; the speed of motions; the congruence of movements occurring in different body tiers such as face, hands, and legs; and last, and perhaps most important, the animation of the face. Even when the observed subject speaks, emotional aspects of the communication are separate from the content of the words and

sentences spoken. Moreover, specific emotions often succeed stimuli or actions that seemingly motivate them in the subject, as judged from the perspective of the observer. In effect, normal human behaviour exhibits a continuity of emotions induced by a continuity of thoughts.

The impairment of consciousness is not compatible with the maintenance of purposeful behaviour.

Confusing terms

On occasion, terms such as alertness and arousal are incorrectly used as synonyms of wakefulness, attention, and even of consciousness. The term alertness should be used to signify that the subject is both awake and disposed to perceive and act. The proper meaning of alert is somewhere between 'awake' and 'attentive'. The term arousal denotes the presence of signs of autonomic nervous system activation such as changes in skin colour (rubor or pallor), behaviour of skin hair (piloerection), diameter of the pupils, sweating, sexual erection and so on, which correspond to the lay term of excitement. Subjects can be awake, alert, and fully conscious without being aroused, in this sense, and subjects can be aroused, in this sense, during sleep and even coma, obviously when they are not awake, attentive or conscious.

Disorders of consciousness

A clinical classification of the disorders of consciousness

Consciousness is disrupted in a number of neurologic conditions and the profile of impairment varies with the neural systems that are rendered dysfunctional. For practical purposes, we classify the disorders of consciousness according to those profiles. In the largest group of these disorders both core consciousness and extended consciousness are impaired. The impairment or intactness of the other components of consciousness that we discussed earlier permit a further subclassification. In another group of disorders extended consciousness is impaired but not core consciousness.

An overview of the classification we have adopted is as follows.

Disruption of consciousness accompanied by disruption of wakefulness

The examples are coma, the transient loss of consciousness caused by head injury or fainting, and general (deep) anesthesia. The cases of coma caused by structural lesions reveal that the primary site of dysfunction is in structures of the upper brain stem, hypothalamus, and thalamus (Plum & Posner, 1980), although dysfunction in brainstem entails dysfunction elsewhere in the brain, namely in the cerebral cortex. In a recent study of 50 patients with brainstem stroke, we found that all 12 patients whose coma was caused by a structural lesion, had lesions in the upper brainstem tegmentum, involving either pons or midbrain or both (Parvizi et al., 2000). It is now apparent that, at least in some forms of general anesthesia, for example, propofol anesthesia, the anesthetics act in these same regions (Fiset et al., 1999).

In situations of coma caused by metabolic imbalance, drug overdose, and circulatory collapse, brain dysfunction is far more pervasive and compromises both cortical and subcortical territories (Plum & Posner, 1980).

Disruption of consciousness with preserved wakefulness but defective minimal attention/behaviour

Absence seizures and persistent vegetative state are the prime examples. Absence seizures are related to dysfunction in regions such as the thalamus and the anterior cingulate cortex and have a distinctive electroencephalographic pattern.

Persistent vegetative state can be distinguished from coma in that vegetative patients have cycles of sleep and wakefulness as shown by the opening and closing of their eyes and, sometimes, also by their EEG patterns. Vegetative states are typically caused by dysfunction in the same set of structures of the upper brainstem, hypothalamus, and thalamus that are compromised in coma, and often vegetative states become a stage in the recovery of comatose patients. But vegetative states can also be caused by extensive cortical damage affecting both hemispheres as, for example, in carbon monoxide poisoning (see Plum & Posner, 1980).

Disruption of consciousness with preserved wakefulness and preserved minimal attention/behaviour

The prime examples are akinetic mutisms and epileptic automatisms. Akinetic mutisms are caused by dysfunction in the cingulate cortex, in the basal forebrain, in the thalamus, and in the medial, parietal cortex surrounding the posterior cingulate cortex (see section below and Damasio, 2000, Chapter 8).

Selective disruption of extended consciousness with preserved core consciousness

The prime examples occur with disorders of autobiographical memory, as seen in permanent and transient global amnesia (see below and Damasio, 2000).

Further assessment of patients with impairments of consciousness

The several varieties of impaired consciousness, coma, persistent vegetative state, deep anesthesia, afford little opportunity for behavioural analyses because nearly all behavioural manifestations of consciousness are abolished, and all or nearly all the internal manifestations are presumed abolished as well. The notion that consciousness is suspended, in such situations, is an intuition based on solid reflections on our own condition and on equally solid observations of the behaviour of others. The notion is also supported by the rare but valuable reports of persons who return to consciousness after being in coma, and by reports of being placed under anesthesia and returning to consciousness. Patients can recall the loss of consciousness on the way to coma, much as we can recall the induction of general anesthesia, and both patients and non-patients can recall the return to knowingness. However, nothing at all is recalled of the intervening period, which can span weeks or months in the case of coma or vegetative state. It is reasonable to assume, given all the evidence, that little or nothing was going on in the mind in such circumstances.

Three groups of patients, however, afford some opportunity for behavioural analyses. One group is made up of patients with a complicated phenomenon known as epileptic automatism. The other group brings together patients who, as a result of a variety of neurologic diseases, develop a condition known by the blanket term akinetic mutism. In both groups, core consciousness and extended consciousness are profoundly affected, and yet not all of the manifestations of consciousness are abolished, thus allowing for the analysis of a residual performance. A third group is made up of patients with global amnesia in whom extended consciousness is compromised but core consciousness is intact.

Epileptic automatisms

Epileptic automatisms can appear as part of seizures or immediately following seizures (Penfield & Jasper, 1954; Penry et al., 1975). The most revealing, in relation to the phenomena of consciousness are associated with absence seizures, although automatisms are also seen in association with so-called temporal-lobe seizures. Absence seizures are one of the main varieties of epilepsy, in which consciousness is momentarily suspended along with emotion, attention, and purposeful behaviour. The disturbance is accompanied by a characteristic pattern in the EEG. Absence seizures are of great value to the student of consciousness, and the typical variety of absence seizure is one of the most pure examples of loss of consciousness, the term absence being shorthand for 'absence of consciousness'. The absence automatism that follows an especially long absence seizure is perhaps the purest example of all.

Patients so affected interrupt their behaviours abruptly (e.g. stop in the middle of a sentence) and freeze whatever movement was being performed, and stare blankly, the eyes focused on nothing, the face devoid of any expression, a meaningless mask. The patients remain awake, the eyes remain open and the muscular tone is preserved. The patients do not fall, or have convulsions, or drop whatever they are holding. This state of suspended animation may last for as little as 3 seconds, and for as long as tens of seconds. The longer it lasts, the more likely it is that absence proper will be followed by absence automatism, which can take a few seconds or many. As the automatism starts, the events are not unlike the unfreezing of film images when you release a freeze-frame control. As the patients unfreeze they look about, vacantly, their faces remaining a blank, with no recognizable emotional expression. They may smack their lips, fumble with clothes, get up and move without colliding with objects, and execute correctly a number of isolated actions that will never form a coherent pattern. One of several scenarios might unfold. In the most likely scenario, the patient might stop and stand somewhere in the hallway, appearing confused; or he might sit on a bench, if there were one. But the patient might possibly enter another room or continue walking. In the most extreme variety of such episodes, in what is known as an 'epileptic fugue', the patient might even get out of the building and walk about in a street. To a good observer he would have looked strange and confused, but he might get by without any harm coming to him. Along the trajectory of any of these scenarios, most frequently within seconds, more rarely within a few minutes, when the automatism episodes come to an end, the patients look bewildered. Consciousness returns as suddenly as it disappeared. The patients have no recollection whatsoever of the intervening time. They do not know what their organisms were doing during the episode. They remember what went on before the seizure and can retrieve those contents from memory, an indication that their learning mechanisms were intact prior to the seizure. They immediately learn what goes on after the seizure ends, a sign that the seizure did not produce a permanent impairment of learning. But the events that occur during the period of seizure are not committed to memory (or are not retrievable if they have been).

When the patients are interrupted at any point during the episode, they look bewildered or indifferent. They do

Table 20.2. The main sites of structural brain damage associated with impaired consciousness

Brainstem tegmentum (pons and midbrain)
The hypothalamus
The thalamus
The cingulate cortex
The mesial parietal cortices (especially in precuneus)
The *right* somatosensory cortex complex (insula, SII, and SI)

not know who they or the observers are, spontaneously or upon specific questioning. The contents that make up a conscious mind are missing, and accordingly there are neither verbal reports nor intelligent actions. The patients remain awake and attentive enough to process the object that comes next into their perception, but that may be all that is going on in their minds. There is no evidence of plan, of forethought, of sense of individual wishing, wanting, considering, believing. There is no sense of self.

During such states, the presence of an object promotes the next action and that action may be adequate within the microcontext of the moment, e.g. opening a door. But that action, and other actions, will not be adequate in the broader context of circumstances in which the patient is operating. As one watches actions unfold, one realizes that they are devoid of ultimate purpose and are inappropriate for an individual in that situation (Table 20.2).

Akinetic mutisms

Another important source of information regarding impaired consciousness comes from the study of patients with akinetic mutism, a term suggestive of what goes on externally, but fails to account for the inside view. From all the available evidence, consciousness is severely diminished or even suspended altogether.

Akinetic mutism is often produced by bilateral cerebrovascular lesions in the mesial regions of the frontal lobe. The cingulate cortex, along with nearby regions is almost invariable damaged. Patients become suddenly motionless and speechless, and remain so for weeks or months. They lie in bed with eyes open but with a blank facial expression. When they catch an object in motion, they may track it for a few instants, eyes and head moving along for a moment, but the non-focused staring is rapidly resumed. The term neutral conveys the equanimity of these patients' facial expressions, but their bodies are no more animated than their faces. They may make a normal movement with arm and hand, but in general their limbs are in repose. Body and face never express any emotion, background, primary, or secondary, in response to the many stimuli that would normally evoke such emotions.

When asked about their situation, the patients are invariably silent, although, after much insistence they may say their names. They have nothing to say about the events leading to their admission, their past or present. They do not react to the presence of relatives or friends. As they emerge from this state and gradually begin to answer some questions, the patients have no recall of any particular experience during their long period of silence; they do not report having fear or anxiety or wishing to communicate. Unlike the patients with locked-in syndrome, akinetic mutes seem not to have had any sense of self and surroundings, any sense of knowing, for most of their akinetic mute period.

In some patients with advanced stages of Alzheimer's disease consciousness is also impaired, and in a manner similar to the one just described for akinetic mutism. Early in the disease, memory loss dominates the clinical presentation and consciousness is intact, but as the ravages of Alzheimer's deepen, one often finds a progressive degradation of consciousness. Unfortunately, textbooks and lay descriptions of Alzheimer's emphasize the loss of memory and the early preservation of consciousness and often fail to mention this important aspect of the disease. The decline first affects extended consciousness by narrowing its scope progressively to the point at which virtually all semblance of autobiographical self disappears. Eventually, it is the turn of core consciousness to be diminished to a degree in which even the simple sense of self is no longer present. Wakefulness is maintained and patients respond to people and objects in elementary fashion, but in a matter of a few seconds, the continuity of the patient's attention is disrupted, and the lack of overall purpose becomes evident. It is interesting to note that several brain regions whose integrity is necessary for normal consciousness are severely damaged in Alzheimer's disease. This is true of nuclei in the brainstem tegmentum, as has been shown recently by Parvizi et al. (2000), who demonstrated a selective involvement in some brainstem nuclei by both neurofibrillary tangles and amyloid plaques. This is also true of the posterior cingulate cortex and surrounding mesial parietal regions (Van Hoesen & Damasio, 1987).

Global amnesia

Loss of core consciousness entails the compromise of extended consciousness, but the converse is not true. Patients in whom extended consciousness is compromised retain core consciousness. The most notable exam-

ples of isolated impairments of extended consciousness occur acutely in transient global amnesia (TGA). Beginning acutely and lasting for a period of a few hours, an otherwise normal individual is suddenly deprived of the access to records that have been recently added to the autobiographical memory. The objects and events processed in the instants, minutes and hours before the onset of TGA, are no longer available to the mind. On occasion, nothing that has happened in the days prior to the beginning of TGA is available at all (Damasio, et al., 1983).

Because our memory constantly includes records of the events that we anticipate, it follows that patients struck by TGA do not have available any record of the intended plans for the minutes, hours, or days that lie ahead. Patients with TGA are thus deprived of both personal historical provenance and personal future, but retain core consciousness for the events and objects in the here and now. When patients fail to recognize a particular situation, there is core consciousness for the fact that some aspect of knowledge is no longer present. In spite of adequate consciousness for the current objects and actions the situation fails to make sense to the patient because, without an updated autobiography, the here and now is not meaningful. The predicament of TGA patients reveals the significant limitations of core consciousness. Without a way of explaining where current objects come from along with the motive for the current actions, the here-and-now is an indecipherable puzzle. This is the reason why TGA patients constantly repeat the same anxious questions: Where am I? What am I doing here? How did I come here? What am I supposed to be doing? The patients tend not to ask who they are because they often retain a basic sense of their persons, although even that sense is almost always impoverished. In conclusion, while patients with epileptic automatisms are good examples of the suspension of core consciousness and of everything that depends on it (core self, autobiographical self, extended consciousness), patients with TGA are a good example of suspended extended consciousness and autobiographical self, with the preservation of core consciousness and core self.

The loss of extended consciousness is seen in other conditions. One is the stable global amnesia caused by bilateral temporal lobe damage in patients with herpes simplex encephalitis (Tranel et al., 2000). Another condition is posttraumatic amnesia, one of the frequent consequences of acute head injuries. In such cases, the drama of TGA is frequently played in a matter of minutes. While the amnesia lasts, the patient is confined to core consciousness. Finally, extended consciousness is also impaired in Alzheimer's disease. When the loss of memory for past events is marked enough to compromise autobiographical records, the autobiographical self is gradually reduced and extended consciousness collapses. Only later in the progression of the disease does core consciousness collapse as well.

Ancillary tests

It has long been known that there is an electroencephalographic pattern characteristic of the awake state. Moreover the electroencephalogram can identify patterns characteristic of different types of seizure, of coma, and of persistent vegetative state. The electroencephalogram is thus an important complement to clinical observation in the assessment of consciousness (see Chapter 00).

By far the most important ancillary information for a clinician who is evaluating a patient with impaired consciousness comes from structural imaging, namely from magnetic resonance (MR). Leaving aside the situations of coma due to drug overdose and metabolic imbalance, most significant impairments of consciousness are associated with structural damage in a number of critical territories: (i) the brainstem tegmentum, especially at pontine and midbrain levels; (ii) the diencephalon, i.e. the hypothalamus and thalamus; (iii) the cingulate cortex, in its entirety, and the mesial parietal territories which surround the posterior section of this region, namely in the precuneus; (iv) the right hemisphere complex of somatosensory cortices formed by the insula, and the secondary (SII) and primary somatosensory cortices (SI).

The results of functional imaging tests are somewhat less helpful in clinical management, although they can provide important information especially for research. Cerebral blood flow is generally depressed in the most severe disorders of consciousness, namely, coma and persistent vegetative state, even when the cause is structural and confined to the brainstem (Laureys et al., 1999a, b), although on occasion islands of nearly intact blood flow may be seen (Plum et al., 1998). Notably, conditions such as locked-in syndrome do not reveal significant depressions of cerebral blood flow. Of interest, patients in persistent vegetative state who were studied with functional imaging, revealed activation of inferotemporal areas that are normally engaged by processing faces, when faces were flashed in their retinas (Meno et al., 1998). This result supports the notion that preserving the neural basis for image processing by no means guarantees that the processed images become conscious.

Reflection on the neuropathological correlates of the most frequent impairments of consciousness reveals one important fact. Most of the sites of brain damage associated with a significant disruption of consciousness share

one important trait: they are located near the brain's midline, and the left and right sides of these structures are like mirror-images of each other across the midline. At the level of the brainstem and diencephalon, the damaged sites are close to the system of canals and ventricles that defines the midline of the central nervous system. At cortical level, they are located in the mesial surface. These structures are evolutionarily old, they are present in numerous non-human species, and they mature early in individual human development.

The neurobiological basis of consciousness

We defined consciousness in terms of two participants, the organism and the object, and in terms of the relationships those participants hold. In this perspective, consciousness becomes the problem of constructing knowledge about two facts: the fact that the organism is involved in relating to some object, and that the object in the relation is causing a change in the organism. In its normal and optimal operation, consciousness is the process of achieving a particular mental pattern which brings together, in about the same instant, the pattern for the object, the pattern for the organism, and the pattern for the relationship between the two. The emergence of each of these patterns and their conjoining depends on the contributions of individual brain sites working in close cooperation. Elucidating the neurobiology of consciousness consists of identifying those individual contributions, namely discovering how the brain can construct neural patterns that map each of the two participants and the relationships they hold, and how the brain can conjoin the patterns.

Consciousness begins to occur when the brain generates an imaged, non-verbal account of how the organism's representation is affected by the organism's processing of an object, and when this process enhances the image of the causative object, thus placing it saliently in a spatial and temporal context. There are two component mechanisms: the generation of an imaged non-verbal account of the organism–object relationship; and the enhancement of the images of the object.

The imaged account is based on second-order neural patterns generated from structures capable of receiving signals from maps which represent both the organism and the object. The imaged account describes the relationship between the reactive changes in the internal milieu, the viscera, the musculoskeletal frame, and the object that causes those changes. The assembly of the second-order neural pattern describing the object–organism relationship subsequently modulates the neural patterns which describe the object and leads to the enhancement of the image of the object. The feeling of self knowing an object, emerges from the contents of the imaged account, and from the enhancement of the object.

The neural pattern which underlies core consciousness for an object, the sense of self in the act of knowing a particular thing, is a large-scale neural pattern involving activity in two interrelated sets of structures: the set whose cross-regional activity generates an integrated view of the organism (the proto-self) and second-order maps; and the set whose cross-regional activity generates the representation of the object. The latter set has a dual role: it is both the initiator of the changes in the former set and the recipient of its modulating influences.

The neuroanatomical structures required to accomplish these component mechanisms encompass, respectively, (i) the structures needed to map the structure and state of the organism; (ii) those needed to process the object; and (iii) those needed to generate the imaged account of the relationship and produce its consequences. Let us consider each of these anatomical requirements.

Much is known about how the organism is represented in the brain, although the idea that such representations could be linked to the notion of self has received little attention. The brain represents, within itself, varied aspects of the structure and current state of the organism in a large number of neural maps from the level of the brainstem and hypothalamus to that of the somatosensory cortices (insula, SII, SI). The state of the internal milieu, the viscera, the vestibular apparatus, and the musculoskeletal system are thus continuously represented (Damasio, 2000; Parvizi & Damasio, 2001).

There have been considerable efforts to understand the neural basis of object representation. Extensive studies of perception, learning and memory, and language, have given us a workable idea of how the brain processes an object, in sensory and motor terms, and an idea of how knowledge about an object can be stored in memory, categorized in conceptual or linguistic terms, and retrieved in recall or recognition modes. In the relationship process we have proposed for consciousness, the object is exhibited as neural patterns in the sensory cortices appropriate for its nature. For example, in the case of the visual aspects of an object, the appropriate neural patterns are constructed in a variety of regions of the early visual cortices, while memory records pertaining to the past perception of such objects are held in highest-order association cortices located in temporal, parietal, and frontal regions. These cortices are interconnected with the early visual cortices (Damasio & Damasio, 1994). In brief, early sensory cortices, and higher-order cortices are involved (*a*) in signalling the objects and

the events which come to be known because of core consciousness; (*b*) in holding records pertaining to their experience; and (*c*) in manipulating those records in reasoning and creative thinking. Thus, the early sensory structures are also involved in the process of making consciousness, but in a different manner from the structures involved in representing the organism. The participation of early sensory structures; includes: (*a*) initiating the process of generating consciousness by influencing the organism-representing structures (*b*) signalling to second-order structures, and (*c*) being the recipients of the modulatory influences consequent to the second-order neural patterns. It is because of the latter influence that the enhancement of the neural patterns which support the object does occur, and that varied components of the object being known in consciousness can become integrated.

The neuroanatomy underlying the imaged account of the relationship depends on several structures, the most important of which are the cingulate cortices and the medial parietal cortices which surround their posterior sector. Finally, the subsequent image enhancement is achieved via modulation from basal forebrain/brainstem acetylcholine and monoamine nuclei, as well as thalamocortical modulation.

In brief, core consciousness depends most critically on the activity of a restricted number of phylogenetically old brain structures, beginning in the brainstem and ending with the somatosensory and cingulate cortices. The interaction among the structures in this set: (*a*) supports the creation of an integrated map of the organism state (the proto-self); (*b*) engenders the second-order neural pattern which describes the relationship between the integrated organism representation (proto-self) and the object representation; and (*c*) modulates the activity of object-processing regions which are not part of the set.

The specificity with which these neural structures are enumerated should not be taken to mean that any one of them alone can be the basis for consciousness. None of the functions outlined above is executed at the level of a single structure, but emerges, rather, as a result of cross-regional integrations of neural activity.

There is a remarkable overlap of biological functions within the structures which support the integrated mapping of the organism state (the proto-self) and the second-order mappings. For example, the brainstem nuclei and the cingulate cortices are involved in most of the following functions: (*a*) regulating homeostasis and signalling body structure and state, including the processing of signals related to pain, pleasure, and drives; (*b*) participating in the processes of emotion and feeling; (*c*) participating in processes of attention; (*d*) participating in the processes of wakefulness and sleep; (*e*) participating in the learning process.

The meaning of these functional overlaps may be gleaned by focusing on the brainstem, where distinct 'families' of nuclei are closely contiguous, and in spite of their anatomical distinctiveness, the varied families of nuclei are highly interrelated by anatomical connections. It would be functionally convenient to have structures governing attention and emotion in the vicinity of each other. Moreover, it makes good functional sense that such structures should be in the vicinity of those which regulate and signal body states since the causes and consequences of emotion and attention are related to the fundamental process of managing life within the organism, and it is not possible to manage life and maintain homeostatic balance without data on the current state of the organism's body-proper. Finally, if we regard consciousness as another contributor to the regulation of homeostasis, it also makes functional sense to place the critical neural machinery of consciousness within and in the vicinity of the neural machinery involved in basic homeostasis, that is, the machinery of emotion, attention and regulation of body state.

This perspective does not deny that some brainstem structures are involved in wakefulness and attention, and that they modulate the activity of cerebral cortex via the intralaminar thalamic nuclei, via the non-thalamic cortical projections of monamines, and via the thalamic projections of acetylcholine nuclei. The point is that nearby brainstem structures, and perhaps even some of the very same structures, have other activities, namely, managing body states and representing current body states. Those activities are not incidental to the brainstem's well established activation role: they may be the reason why such an activation role has been maintained evolutionarily and why it is primarily operated from the brainstem.

The roles that have been traditionally assigned to the brainstem's 'ascending reticular activating system', and to its extension in the thalamus, as presented in the classical work of Moruzzi and Magoun (1949), Penfield and Jasper (1954), and in the modern work of Llinas and Paré (1991), Llinas and Ribary (1993), Hobson (1994), Steriade (1988, 1993a, b, 1995), Munk et al. (1996), and Singer (1998) is compatible with this interpretation. The activity of the 'ascending reticular activating system' contributes to creating the selective, integrated and unified contents of the conscious mind, although such a contribution is not sufficient to explain consciousness comprehensively.

Although even the simplest form of consciousness requires ensemble activity that involves varied regions of the brain, consciousness depends most critically on regions that are evolutionarily older rather than recent,

and are located in the depth of the brain rather than on its surface. These basic mechanisms are anchored on ancient neural structures, intimately interwoven with homeostasis, rather than on the modern structures of the neocortex, those on which fine movement, perception, language and high-reason are based.

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21

Mechanisms of memory and amnestic syndromes

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Memory comprises the recording, retention and retrieval of knowledge. All that we know, except for what is genetically predetermined, is acquired through experience. Such knowledge includes the events we remember, the facts we know, and the skills we master. Memory is not a unitary faculty, but rather an ensemble of multiple forms of learning that differ in their uses, their operating characteristics, and the neural networks that mediate their processing (Gabrieli, 1998). A memory system may be defined as a particular neural network that mediates a specific form of mnemonic processing. Neurological and psychiatric diseases result in characteristic mnemonic deficits that reflect which memory systems are injured by a particular disease.

Levels of analysis: cells and systems

Learning and memory reflect experience-induced plasticity in the brain. An experience leaves a memory trace composed of an enduring alteration in the cellular organization of the brain called an engram. Experience-induced plasticity can be examined at many levels of analysis, including molecular events at the cellular and synaptic level, reorganization of local neuronal circuits, and large-scale alterations in the functional neural architecture of memory systems.

Cellular mechanisms of memory

Little is known about neural plasticity in the human brain, but findings from in vitro and invertebrate models offer suggestions about the cellular bases of human memory. Studies of the marine snail *Aplysia* have revealed links between learning and alterations in neurotransmitter release. *Aplysia* have a gill withdrawal reflex that is triggered when the gill is touched by a rod. Repeated stimulation leads to habituation such that the gills are no longer withdrawn in response to the rod. Short-term habituation has been linked to decreased presynaptic transmitter release. Repeated stimulation with a highly noxious stimulus, such as an electric shock, can lead to sensitization, an intensification of the withdrawal response. Short-term sensitization involves increased neurotransmitter release from a facilitating interneuron (Kandel & Schwartz, 1982). Modulation of neurotransmitter release may underlie short-term changes in functional connectivity between neurons.

Long-term memory processes, in contrast, require messenger RNA and protein synthesis (Davis & Squire, 1984) to establish structural changes in synaptic connectivity as a record of experience. Long-term habituation may involve pruning of presynaptic terminals, whereas long-term sensitization may involve proliferation of presynaptic terminals (Bailey & Chen, 1983; Fig. 21.1). The best-studied candidate for a cellular basis of mammalian learning is long-term potentiation (LTP), usually examined in in vitro slice preparations from mammalian brains (Fig. 21.2). A neuron becomes potentiated (i.e. exhibits enhanced response to a given input) when bombarded with brief but rapid series of stimulations. LTP develops rapidly and can last for long periods, and is specific to the activated synapses. LTP has associative properties because it is driven by cooperativity, the simultaneous stimulation of different synapses. LTP has been studied most extensively in hippocampal synapses, in which NMDA glutamate receptors are essential for the establishment, but not the maintenance, of LTP. LTP has also been induced in the amygdala, cerebellum, and cerebral cortex, but differences in LTP properties across brain regions suggest that they are mediated by multiple cellular mechanisms. Mechanisms for long-term depression of synaptic efficacy have also been found in the hippocampus (Malenka, 1994) and cerebral cortex.

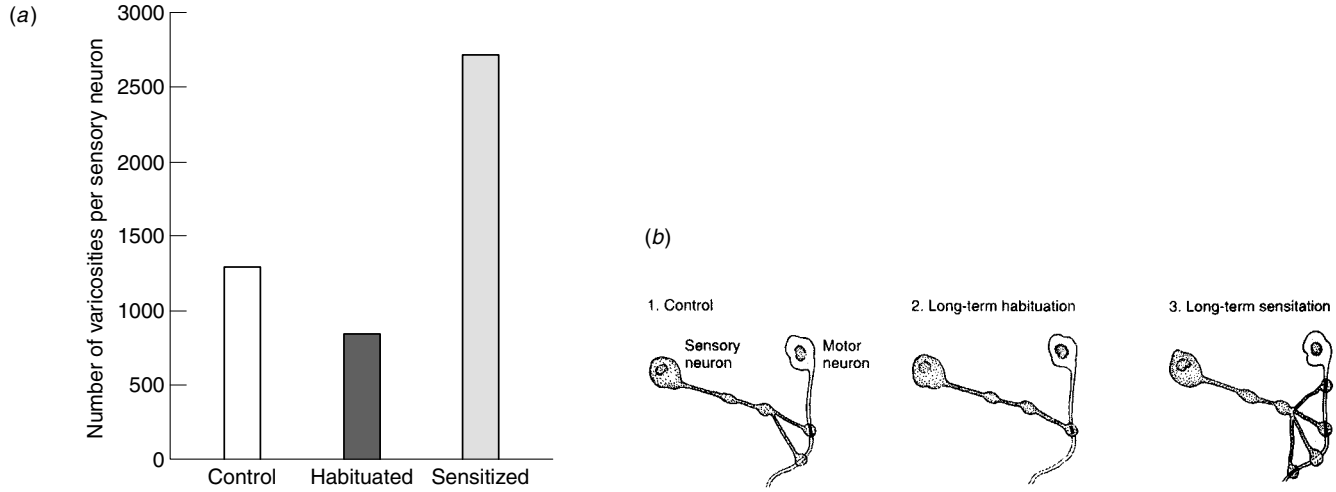
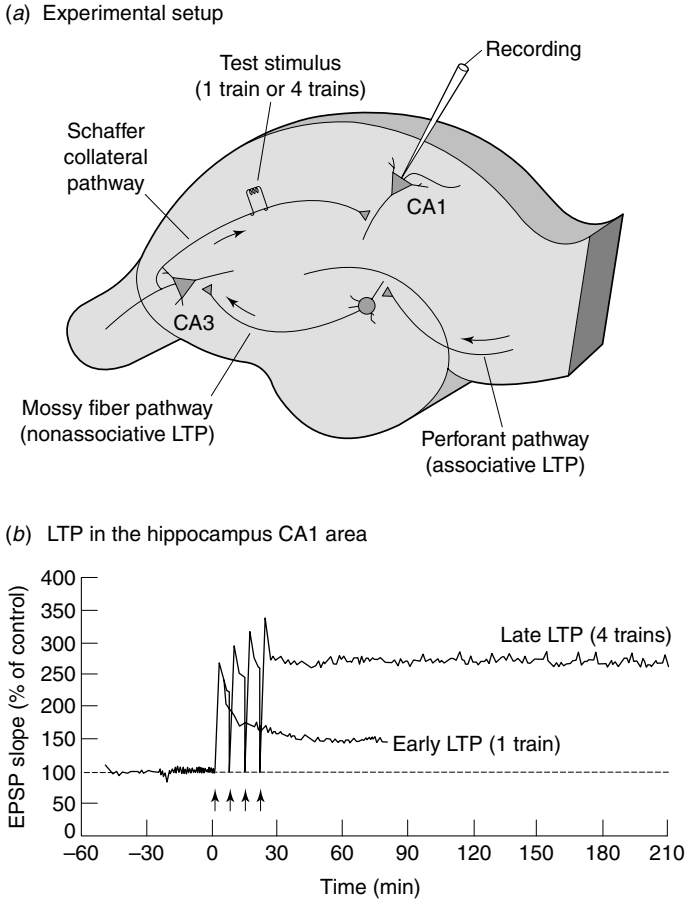


Fig. 21.1. Long-term habituation and sensitization in *Aplysia* involve structural changes in the presynaptic terminals of sensory neurons. (*a*) Number of presynaptic terminals in habituated and sensitized animals relative to control animals. (*b*) Long-term habituation leads to a loss of synapses, whereas long-term sensitization leads to an increase in synapses. (Adapted from Kandel et al., 1991.)



Large-scale memory systems

In humans, the functional neural architecture of memory is best understood in terms of mnemonic functions associated with particular anatomic structures. Studies of patients with brain lesions have provided the foundations of our knowledge about the biological organization of human memory. Lesions have produced dramatic and often unexpected mnemonic deficits that provide clues about the brain regions that are necessary for particular memory processes. The behaviour of memory-impaired patients with brain lesions, however, does not definitively point to the process subserved by the injured tissue. Rather, the behaviour reflects what uninjured brain regions can accomplish after the lesion. Further, naturally occurring lesions often impair multiple brain systems, either by direct insult to a large brain area or through disconnection of interactive brain regions. It is, therefore, difficult to associate particular brain structures with specific memory processes.

Fig. 21.2. LTP in the hippocampus. (*a*) Experimental setup for studying LTP in the CA1 region of the hippocampus. The Schaffer collateral pathway is stimulated electrically and the response of the population of pyramidal neurons is recorded. (*b*) Early and late LTP in a cell in the CA1 region of the hippocampus. Shown is a plot of the slope (rate of rise) of the excitatory postsynaptic potentials in the cell as a function of time. A test stimulus was given every 60 s to the Schaffer collaterals. To elicit early LTP, a single train of stimuli is given for 1 s at 100 Hz. To elicit the late phase of LTP, four trains are given separated by 10 min. The resulting early LTP lasts 2–3 hours, whereas the late LTP lasts 24 or more hours. (Adapted from Kandel et al., 2000.)

Functional neuroimaging studies using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) now permit the visualization of memory processes in the healthy brain. Functional neuroimaging studies allow for the design of psychological experiments targeted at specific memory processes. They are limited, however, by several factors. PET and fMRI derive their signals not from direct measures of neural activity, but rather from local changes in blood flow or metabolism related to neural activity. These indirect measures of neural activity limit the temporal and spatial fidelity of activations. Additionally, there is a great deal of psychological interpretation involved in understanding the meaning of an activation, i.e. in specifying the mental process signified by an activation. The combination of lesion and neuroimaging studies may overcome the limitations of each source of evidence and provide powerful, mutual constraints on ideas about memory systems.

Types of memory

Distinctions between different kinds of memory are useful from both clinical and neuroscience perspectives. A fundamental distinction is that of declarative versus nondeclarative forms of memory (Cohen & Squire, 1980). Declarative memory refers to the everyday sense of memory, and is responsible for the learning and remembrance of new events, facts and materials. It encompasses both episodic memories (remembrance of personal experiences that occurred at a particular time and place) and semantic memories (knowledge of generic information, such as the meaning of a word) (Tulving, 1983). It is the form of memory that people use to recollect facts and events consciously and intentionally, and is therefore also referred to as explicit memory (Graf & Schacter, 1985). In the clinic or experimental laboratory, declarative memory is usually tested directly by asking a person to recall or recognize information that was presented recently.

Non-declarative memory refers to the many forms of memory that do not depend on the psychological processes or brain regions essential for declarative memory. Non-declarative memories are not retrieved intentionally or explicitly, but rather incidentally or implicitly through behaviour. These forms of memory are established during an experience, and guide future behaviour in a way that is unrelated to any conscious awareness of that experience. Non-declarative forms of memory are tested implicitly or indirectly by measuring the influence of a specific prior experience upon subsequent performance, but without making any direct reference to that prior experience. Such experience-induced alterations in behaviour must reflect the consequence of memories established during the initial experience. Three main classes of non-declarative memory (skill learning, conditioning, and repetition priming) are discussed below.

Temporal properties distinguish one form of memory from another. Immediate memory refers to the recall of information without delay, either immediately after presentation or after uninterrupted rehearsal. Immediate memory is characterized by sharply limited capacities for how much and how long information can be remembered. For example, people can remember no more than about seven random digits, and only as long as they rehearse those digits. Immediate memory often has perception-like characteristics. For example, errors in immediate memory for words are more likely to reflect word sounds than word meanings (e.g. a person might recall 'pound' when they actually heard 'sound').

Working memory is a multi-component psychological system that mediates the temporary processing and storage of internal representations that guide and control action. Information can be held in working memory beyond the span of immediate memory, but only insofar as is useful for solving a problem at hand. Working memory is conceptualized to include immediate memory capacities and the executive or control processes that guide the goal-driven selection of relevant information to be held in immediate memory stores (Baddeley, 1986).

Long-term memory refers to large and permanent stores of episodic and semantic memories. Long-term memories are not, however, passively stored records of experience. Rather, they are constantly used to interpret new experiences. Our knowledge of words and concepts, for example, is used to interpret the meaning of sentences that we hear or see, and past experiences that resemble a current event are used to interpret that event. Long-term memory is often organized by meaning (semantics) or gist rather than by the perceptual characteristics of an experience. For example, people remember the content or gist of a sentence they have read far better than the specific order of words or the font in which the sentence was seen. Similarly, people remember a set of related words (e.g. birds) better than a set of unrelated words.

The rapid application of prior knowledge to interpret the meaning of a novel experience is a powerful mechanism for comprehension, but it can also generate inaccurate memories. Ongoing use of a long-term memory can alter the original memory (retroactive interference); indeed it is thought that forgetting is due much more to subsequent interference (multiple, related experiences are inadvertently blended) than to simple disuse of a memory.

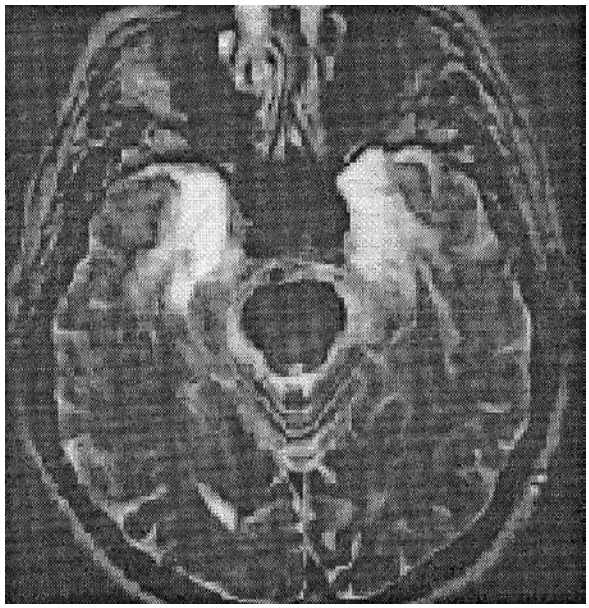


Fig. 21.3. T_2-weighted MRI image showing an axial slice through the temporal lobes of patient E.P. Damage to the bilateral medial temporal lobe extends caudally from the temporal pole and includes the hippocampal region, the entorhinal cortex, the perirhinal cortex, the parahippocampal cortex and the amygdaloid complex. The lesion also extends laterally to include the anterior portion of the fusiform gyrus. (Adapted from Teng & Squire, 1999.)

Remembering the gist of an experience is an efficient way to learn without recording minor details, but it is also prone to errors. For example, one can falsely remember that the name of a particular bird was included in a list of birds when it was not actually presented, simply because one has considered the gist of the set to be about birds.

Long-term memory involves three successive temporal phases. Encoding refers to processes that originally register an experience, including attentional, perceptual, and semantic processes. Storage (or consolidation) refers to the enduring maintenance of that memory. Retrieval refers to recovery of the memory at a later time. Accurate retrieval of a memory requires all three phases to be executed successfully. Long-term memories include those established many years or decades ago, sometimes referred to as remote memories.

The relation between short-term and long-term memory is susceptible to misunderstanding, in part due to various meanings of the term short-term memory. Sometimes short-term memory is used to refer to attention. An individual who cannot repeat back even a single digit or word is better described as having a deficit in attention than a deficit in any sort of memory. A second use of short-term memory is to refer to a memory mechanism that supports remembrance of a memory after a delay of seconds or minutes without rehearsal. There is, however, no evidence of any anatomical system that has a temporal span intermediate to those of immediate and long-term memory. Rather, there is constant and rapid loss of long-term memory for most events and facts. Therefore, memory for an episode after a brief delay of seconds or minutes will be superior to memory for that episode after a longer delay, just as memory for most episodes that occurred last week is superior to episodes that occurred last year. These differences, however, all reflect the temporal dynamics of long-term memory, and not the existence of a memory store that is intermediate between immediate and long-term memory. It is common to refer to an inability to acquire new long-term memories as a deficit in short-term memory. In this case, failure to learn new information is being contrasted with the preservation of remote memories, but the deficit is really one of failing to establish new long-term memories.

Amnesia and the declarative memory system

Amnesia is a selective disorder of declarative memory. It is defined by a behavioural syndrome rather than by etiology or lesion location. A pure amnesia refers to a relatively circumscribed disorder of declarative memory that cannot be accounted for by non-mnemonic deficits such as attention, perception, language, or motivation, because those abilities are all intact. In amnesia, immediate memory and cognitive abilities are intact. Anterograde amnesia refers to the inability to acquire new declarative memories. Retrograde amnesia refers to the loss of memories acquired prior to the onset of amnesia. Retrograde amnesia is described as flat when it extends back uniformly through an individual's life. More often however, retrograde amnesia is temporally graded, being most severe for, or limited to, a period of time immediately preceding the onset of the amnesia, and less severe or absent for more remote periods. Depending on the size and location of lesions, amnesias can vary considerably in extent and severity of anterograde and retrograde memory loss. Typically, the severity of the anterograde amnesia and the temporal extent of the retrograde amnesia are correlated, such that patients with a complete inability to form new memories have retrograde amnesia extending for long periods, up to decades (Rempel-Clower et al., 1996).

Amnesia results from injury to medial temporal lobe (Scoville & Milner, 1957; Fig. 21.3), diencephalic (von

Cramon et al., 1985; Dusoir et al., 1990), or basal forebrain (Damasio et al., 1985) regions. Bilateral lesions in any of these regions lead to global amnesia, a pervasive declarative memory failure that encompasses both verbal and non-verbal information. Patients with severe global amnesia fail all tests of declarative memory in all modalities, regardless of the difficulty of the test. They do not remember the most famous of public events or the most salient of personal events, such as the deaths of loved ones. Because the patient retains all other mental abilities, severe amnesia can appear to be a relatively minor problem. It is, however, remarkably debilitating because patients cannot take care of themselves, hold jobs, or develop human relations. When asked their age, the current year, or their home address, such patients respond with answers that are many years out of date. They cannot remember goals or intentions for more than a few moments, unless explicitly reminded with instructions. Milder cases of amnesia allow for some learning of especially salient or often repeated information, but even these patients have great trouble at home or at work. Unilateral left- or right-sided lesions typically result in material-specific memory dysfunctions for verbal or non-verbal information, respectively (Milner, 1974). This asymmetry can be more complex, however, in patients with longstanding unilateral injury when there is opportunity for reorganization, as can occur in epilepsy.

The medial temporal lobe region (Fig. 21.4) is comprised of a number of interconnected but anatomically distinct structures: the amygdala, the hippocampal formation, which includes cornu ammonis (CA) fields, dentate gyrus, subiculum, and fornix, the entorhinal cortex; the perirhinal cortex; and the parahippocampal cortex. Research with animals and humans indicates that each of these structures makes a unique contribution to declarative memory, and that they act in complex concert to establish new memories. It is now thought that the amygdala is not critical for most aspects of declarative memory. Rather, this region plays a specific role in the emotional modulation of memories, as reviewed below.

Higher-level olfactory, frontal, parietal, and temporal cortices provide widespread, convergent inputs to the medial temporal lobe region (Fig. 21.5). Two-thirds of these inputs traverse the perirhinal and parahippocampal cortices that surround the hippocampal formation. These regions send major input to the entorhinal cortex, which, in turn, provides major input to the hippocampal formation. The fornix is a major fibre bundle that connects the hippocampal formation to the septum and other subcortical structures.

Damage to medial temporal lobe structures is the most common etiology for pure amnesia or declarative memory disorders that are part of a more widespread dementia. This region is highly susceptible to a variety of insults, including epilepsy, anoxia, and herpes simplex encephalitis. Postmortem and in vivo imaging studies indicate that the entorhinal cortex and hippocampus are the first structures typically affected by Alzheimer's disease, in which a declarative memory disorder is the most common and severe initial behavioural deficit (Hyman et al., 1984; de Leon et al., 1993).

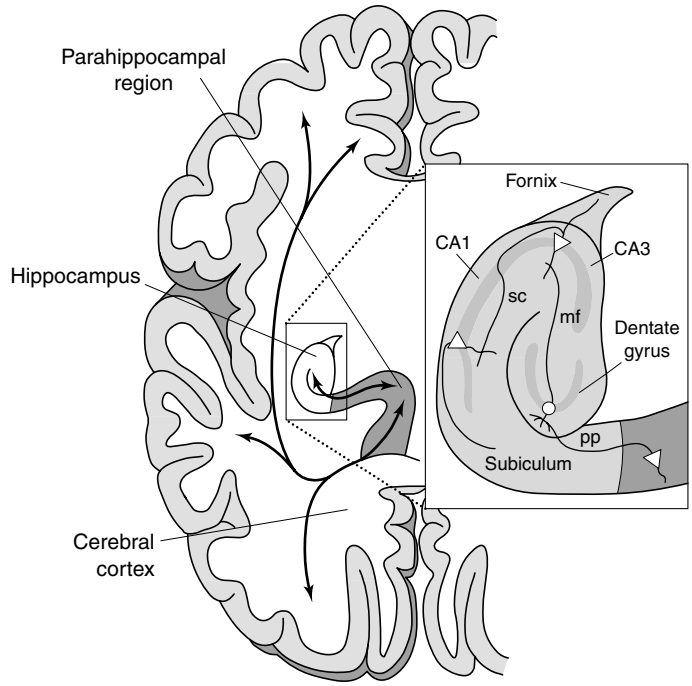


Fig. 21.4. Major pathways of the hippocampus. Left: A horizontal section through the human brain showing major pathways by which the hippocampus is connected with cortical areas. Inset: Diagram of major intra-hippocampal connections. (Adapted from Eichenbaum & Cohen, 2001.)

For many years, it was thought that the hippocampus *per se* was the critical structure among these for declarative memory. Focal damage restricted to the CA1 component of the hippocampus is indeed sufficient to yield a clinically substantial declarative memory deficit (Zola-Morgan et al., 1986). Animal research has shown, however, that perirhinal or other lesions can have at least as great a consequence on memory performance as hippocampal lesions (Murray & Mishkin, 1986; Zola-Morgan et al., 1989). In humans, more widespread damage to entorhinal, perirhinal, and parahippocampal cortices results in an increasingly devastating memory deficit (Rempel-Clower et al., 1996; Corkin et

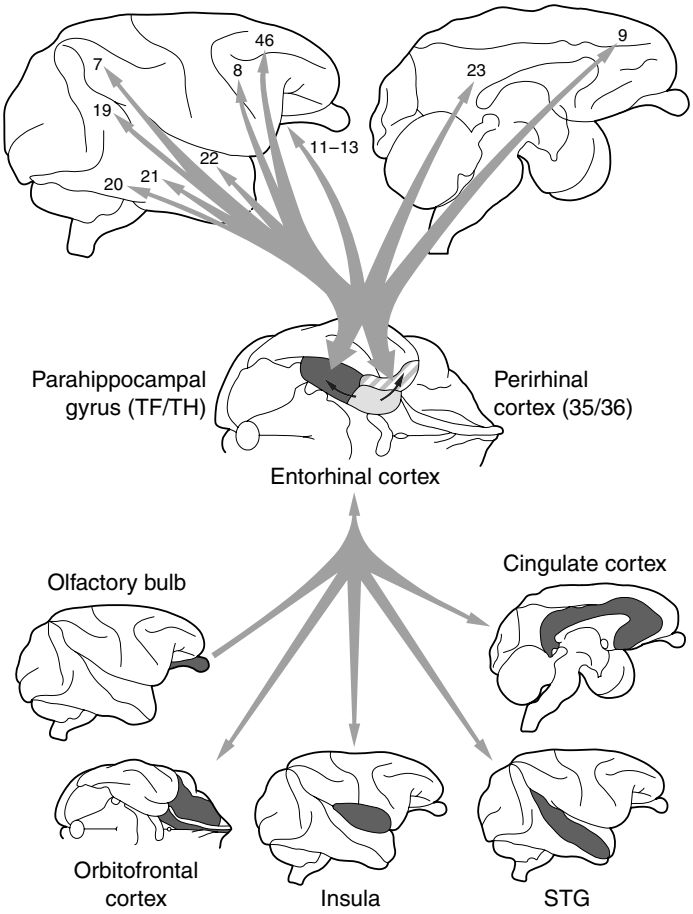


Fig. 21.5. Major cortical areas that compose the afferent sources and efferent targets of information to and from the parahippocampal region in monkeys. (Adapted from Eichenbaum & Cohen, 2001.)

al., 1997). In addition, damage to the fornix can produce global amnesia (Gaffan & Gaffan, 1991). The specific mnemonic roles of particular medial temporal lobe structures have not yet been well characterized in humans, because it is rare for an injury to damage one of these structures without injuring neighbouring structures.

Diencephalic regions linked to declarative memory include the dorsomedial and anterior nuclei of the thalamus, the mammillary bodies, the mammillothalamic fibre tract connecting the medial hippocampal complex to the anterior thalamic nuclei, and the ventroamygdalofugal fibre tract connecting the amygdala to the dorsomedial nuclei (Victor et al., 1971; Fig. 21.6). Damage to these regions is sufficient to produce severe memory impairments even when medial–temporal regions remain anatomically intact (Press et al., 1989). The precise roles of these structures are not well specified, in part because damage tends to co-occur in multiple structures. For example, the mammillary bodies and dorsomedial nuclei are both greatly affected in alcoholic Korsakoff's amnesia, the most common etiology of diencephalic amnesia. Acute thalamic lesions producing amnesia often injure both the dorsomedial nucleus of the thalamus and the surrounding mammillothalamic and ventroamygdalofugal tracts. The preponderance of evidence favours a critical role in declarative memory for the dorsomedial nucleus, perhaps in combination with the surrounding fibres of the mammillothalamic tract (von Cramon et al., 1985). The consequence of a lesion limited to the mammillary bodies is less certain. Lesions there sometimes appear to account for declarative memory deficits in patients (Dusoir et al., 1990), but do not yield the long-lasting memory impairments seen in monkeys after medial-temporal or dorsomedial thalamic lesions (Zola-Morgan & Squire, 1985). Declarative memory failure after diencephalic lesions appears quite similar to that seen after medial–temporal lesions, although additional non-mnemonic deficits may result from diencephalic lesions.

The basal forebrain is composed of midline structures including the septal nuclei, diagonal band of Broca, and substantia innominata. These regions provide the largest input of acetylcholine, the neurotransmitter most directly implicated as critical for declarative memory, to the hippocampus and many neocortical areas. The basal forebrain also supplies other neurotransmitters to the cerebral cortex that contribute to the modulation of memory, including dopamine, norepinephrine, and serotonin. An extensive lesion to the basal forebrain yields a severe declarative memory impairment (Damasio et al., 1985). Partial damage to this and adjacent ventromedial frontal cortex often occurs after ruptures of anterior communicating artery aneurysms, which often lead to mild but persistent anterograde amnesia.

Amygdala and the emotional modulation of memory

Lesion and functional neuroimaging findings have illuminated the importance of the amygdala in emotional aspects of human (Phelps & Anderson, 1997). Medial temporal lobe lesions are rarely restricted to the amygdala, but valuable information can be gained from a rare congenital dermatological disorder, Urbach–Weithe syndrome. This disorder leads to mineralization of the amygdala that spares the hippocampal formation (Fig. 21.7). It is also possible to study patients who have undergone amygdala resection for treatment of pharmacologically intractable

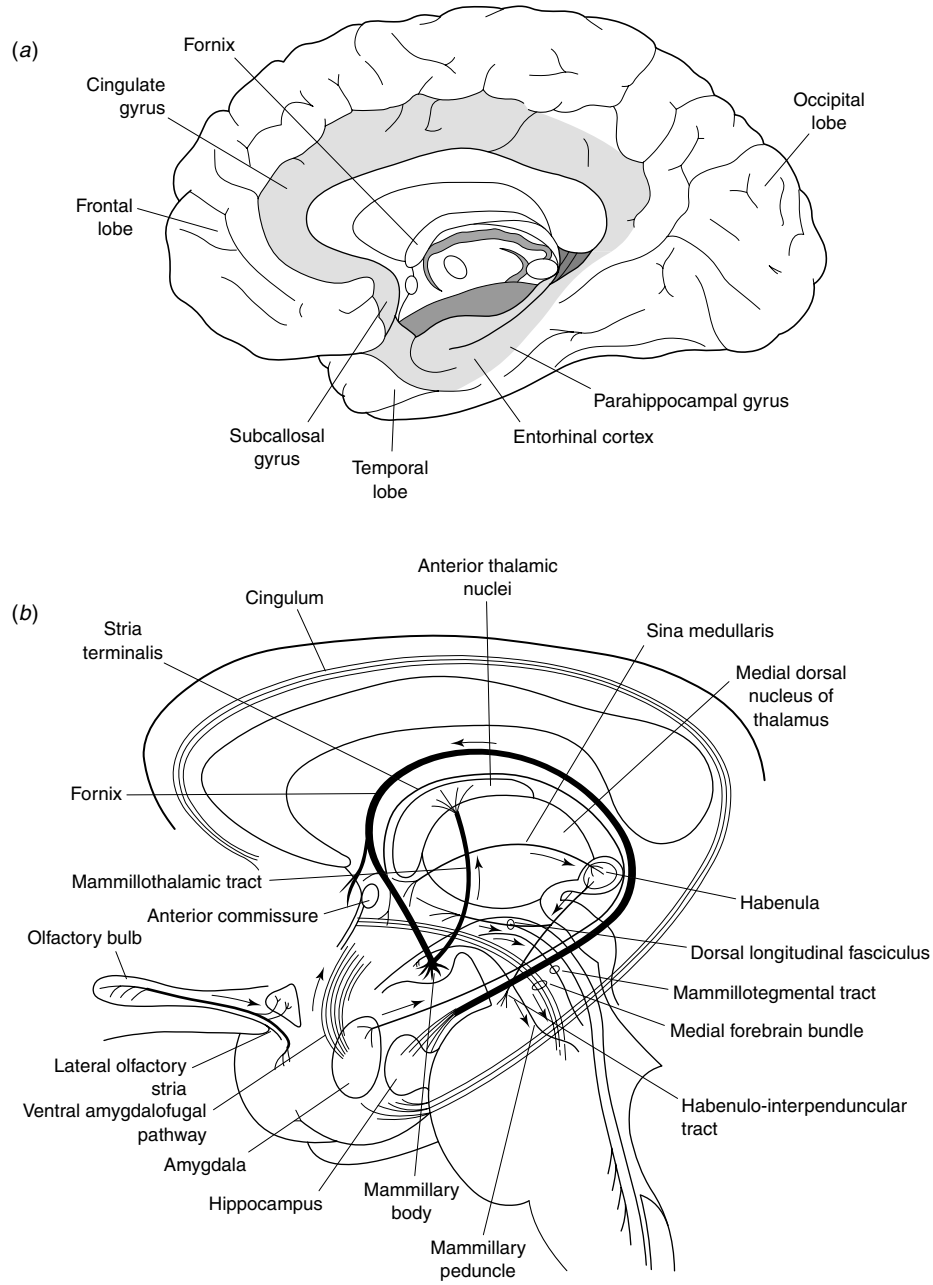


Fig. 21.6. The limbic system, consisting of the limbic lobe and deep-lying structures. (*a*) Medial view of the brain showing the limbic lobe (stippled area). (*b*) Interconnections of the deep-lying limbic structures. The predominant direction of flow of neural activity in each tract is indicated by an arrow, but the designated tracts are typically bidirectional. (Adapted from Kandel et al., 1991.)

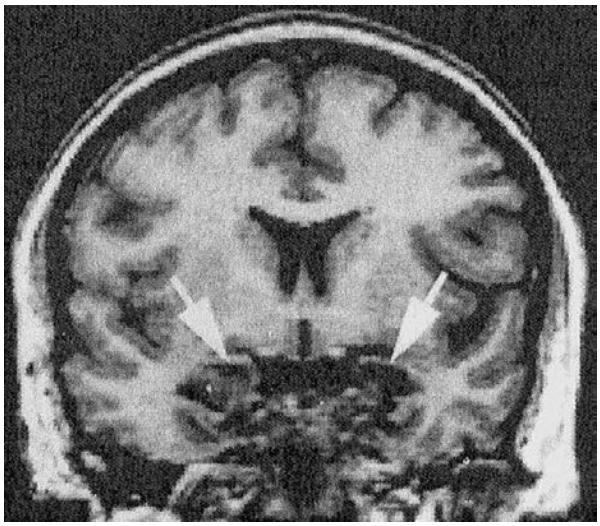


Fig. 21.7. T_1-weighted MRI image showing a coronal slice through the brain of a patient with Urbach–Wiethe disease. Arrows indicate loci where the amygdala would normally be found. (Adapted from Adolphs et al., 1995.)

epilepsy, but the resection usually involves additional medial–temporal structures.

There is convergent evidence of a specific role for the amygdala in emotional declarative memory. Healthy people show superior memory for emotionally disturbing relative to emotionally neutral stimuli. An Urbach–Weithe patient showed normal memory for neutral slides, but failed to show the normal additional memory for the emotionally salient slides (Cahill et al., 1995). In a PET study, amygdala activation correlated with individual differences in subsequent recall for emotional, but not for neutral, film clips (Cahill et al., 1996). In an event-related fMRI study, amygdala activation correlated with how emotionally intense people rated individually presented scenes (Canli et al., 2000). For scenes rated most emotionally intense, the magnitude of amygdala activation predicted later recognition memory. Most studies have examined participation of the amygdala in memory for negative events, but amygdala activation also predicts memory for positive emotional events (Hamann et al., 1999). Patients with amygdala lesions, however, typically report normal emotional evaluation of situations or stimuli, so the amygdala does not appear critical for generating emotions. Rather, the amygdala enables emotional arousal to strengthen memory encoding.

The amygdala participates not only in explicit memory for aversive stimuli, but also in implicit memory for aversive stimuli (reviewed later). Patients with amygdala lesions exhibit emotion-selective deficits in the identification of fearful or angry facial expressions (Adolphs et al., 1994) or prosody (Scott et al., 1997). Amygdala activations occur in PET and fMRI studies during the perception of fearful facial expressions or scenes (Morris et al., 1996). Thus, the amygdala appears to have a widespread role in processing negatively salient stimuli. This subcortical structure, however, is composed of multiple nuclei with distinct connectivity, and is adjacent to another brain region important for emotion, the substantia innominata. Thus, it is unclear whether some of these emotional and memory processes are mediated by the same or different specific pathways in that region. It is clear, however, that injury restricted to this region affects emotional memory without resulting in a global amnesia.

Neocortical basis of declarative memory

Declarative memory likely depends on interactions between the domain-independent regions described above, where injury results in broad memory failure, and domain-specific neocortical regions. Long-term episodic and semantic memories are thought to be stored in the neocortex, with different regions representing different types of knowledge. Thus, knowledge about the visual appearance of a tool may be stored near visual cortex, separate from knowledge about its use, which may be stored in areas such as premotor cortex (Martin et al., 1995). There is evidence that semantic memories for the names of people, tools, and animals are represented in distinct, adjacent left temporal lobe regions (Damasio et al., 1996). Damage to a cortical area can result in both the loss of previously acquired memories stored in that area and an inability to acquire new memories involving that kind of knowledge. A patient with a specific anomia for names of people, for example, would be unable to learn a new person's name but able to learn new names for animals or tools.

Personal knowledge also appears to be organized topographically in the neocortex. Some patients with mild anterograde amnesia exhibit a remarkable loss of personal memories concerning major life events or family members (Kapur et al., 1992). These patients typically have sustained damage to lateral temporal cortex, most often in the right hemisphere, which may store long-term autobiographical memory representations. They do not exhibit the temporally graded retrograde amnesia characteristic of patients with medial temporal lobe lesions.

Memory for an event or fact is conceptualized as being widely distributed in the neocortex, with specific perceptual, conceptual, and emotional features of an event represented in specialized cortical regions. It is hypothesized

that medial temporal lobe structures bind or relate the multiple features that define memory for an event across physically disparate neocortical regions.

Over time, the features somehow become consolidated in the neocortex and no longer require the medial temporal lobe for binding. It is thought that temporally limited retrograde amnesia reflects the sparing of remote, well-consolidated memories and the disruption of ongoing consolidation for more recent memories.

Immediate memory

Immediate memory, such as the recall of a series of digits that one has just heard or spatial locations that one has just seen, depends on cortical areas specialized for both modality (visual or auditory) and material (verbal or non-verbal). Patients with lesions of the left inferior parietal cortex may be able to repeat only two digits or words immediately after hearing them, in contrast to the normal span of seven items (Warrington et al., 1971). More posterior and inferior lesions at the occipital-temporal boundary can result in reduced visual–verbal immediate memory spans (Kinsbourne & Warrington, 1962). Reduced immediate memory for spatial locations and other visual–spatial displays can result from right occipital–parietal lesions (Warrington & James, 1967). Immediate memory, therefore, does not depend upon a common set of brain structures. Rather, there are distinct cortical regions, specialized both by modality and material, that briefly store information just heard or seen.

The consequences of a greatly reduced immediate memory span are remarkably few. Patients with very limited auditory–verbal immediate memory have trouble comprehending grammatically complex sentences and learning new foreign words, two situations in which a person may have to review carefully the sounds just heard because their meanings were not instantly grasped. Such patients, however, have normal or near-normal long-term memory for auditory–verbal information. This finding counters the expectation that information must pass through short-term memory in order to reach long-term memory. Instead, information from the environment enters immediate-memory and long-term memory stores in parallel rather than serially.

Working memory and strategic declarative memory

The frontal lobes appear to play a critical role in working memory (maintaining and manipulating information in a goal-directed manner for a brief period) and in strategic declarative memory. Frontal regions are thought to select goal-relevant information from immediate and long-term memory stores in posterior cortices (Fig. 21.8). Evidence that working memory depends critically on frontal cortices comes from many sources, including human and animal lesion studies (Goldman-Rakic, 1987; Owen et al., 1996), single-cell recording studies (Funahashi et al., 1989), and neuroimaging studies (e.g. Cohen et al., 1994; Jonides et al., 1993). Functional neuroimaging studies indicate that executive processes (working memory resources beyond immediate spans) in humans may be especially linked to dorsolateral prefrontal cortex (e.g. D'Esposito et al., 1995; Petrides et al., 1993). Patients with frontal-lobe lesions are impaired on tasks that demand substantial working memory resources, such as reasoning (Milner, 1963; Shallice, 1982). These patients do not, however, exhibit the pervasive or severe declarative memory deficit seen in amnesia.

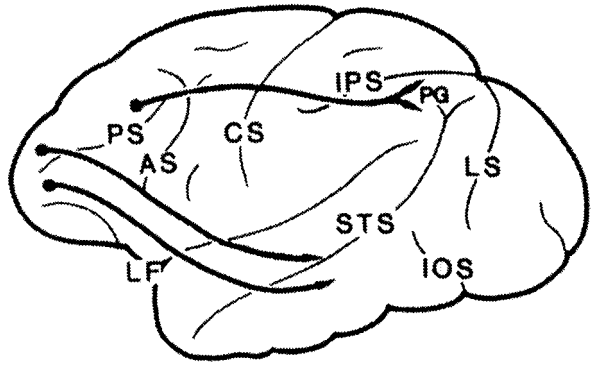


Fig. 21.8. Schematic of long-range projections between prefrontal and posterior association areas in the monkey. (Adapted from Pandya & Yeterian, 1985.)

Patients with dorsolateral prefrontal lesions are impaired on declarative memory tasks that have great strategic demands, i.e. memory tasks that demand substantial planning, organization, evaluation, or manipulation of information for accurate performance. Some declarative memory tasks have relatively minimal strategic demands. Recognition tests, in which studied items are re-presented along with novel distracter items, typically require little strategy, as responses can be guided relatively easily and quickly on the basis of stimulus familiarity. Free recall tests, on the other hand, require people to devise their own strategy for recollecting prior experiences without experimenter-supplied assistance.

Lesions to dorsolateral and anterior prefrontal regions lead to specific impairments on tests of source memory

(Janowsky et al., 1989), list discrimination (Butters et al., 1994); frequency of occurrence (Angeles-Jurado et al., 1997; Smith & Milner, 1988); recency (Milner et al., 1991), temporal ordering (Shimamura et al., 1990), and free recall (Wheeler et al., 1995). What is common across these tasks is that a person has to make a difficult memory judgment that requires the active planning and organization of a retrieval strategy. These strategic memory deficits occur even when performance on corresponding recognition tests is normal. Specific impairments in strategic declarative memory may be contrasted with those seen in amnesia. In most cases, amnesic patients perform poorly on both strategic and nonstrategic memory tests. The strategic memory deficit in amnesic patients, however, is the consequence of their global declarative memory deficit.

The working memory and reasoning deficits that result from frontal lesions may be related to the specific failure in strategic memory performance. Difficult memory tasks require that reasoning capacities be brought to bear on, or work with, memory retrieval. Thus, the strategic memory failure may be the consequence of diminished reasoning and working memory resources being applied to otherwise intact declarative memory processes.

Selective deficits of strategic declarative memory have been found also in degenerative or developmental diseases of the basal ganglia, such as Parkinson's disease (PD), Huntington's disease (HD), and Gilles de la Tourette's syndrome (Gabrieli, 1996). Striatal diseases also impair reasoning (Lees & Smith, 1983) and working memory (Gabrieli et al., 1996b), and these deficits are correlated with the strategic memory deficits.

Thus, strategic declarative memory appears to depend on the integrity of corticostriatal circuits (Alexander et al., 1986) that mediate working memory and reasoning. Furthermore, animal (Brozoski et al., 1979; Sawaguchi & Goldman-Rakic, 1991) and human (Luciana et al., 1992; Müller et al., 1998) drug studies indicate that the neurotransmitter dopamine plays a critical role in working memory. PD patients have severely reduced dopamine functioning, and dopamine treatment can enhance their working memory performance (Cooper et al., 1992).

Non-declarative memory systems

Despite their global anterograde amnesia, even the most severely amnesic patients have demonstrated entirely normal learning on a number of skill learning, repetition priming and conditioning tasks. These findings provide compelling evidence for the independence of multiple memory systems in the human brain. Preservation of these forms of memory in amnesia demonstrates that they do not depend upon the medial temporal lobe or other structures essential for declarative memory. Some of the neural systems underlying non-declarative memory have been identified in neuropyschological and neuroimaging studies. Non-declarative forms of memory do not depend on any common brain regions in the way that all forms of declarative memory depend on medial temporal lobe or diencephalic regions. Rather, each kind of non-declarative memory appears to involve experience-induced plasticity in the neural systems engaged by a particular task (e.g. motor areas for motor tasks, perceptual areas for perceptual tasks).

Skill learning

Skill learning (sometimes referred to as procedural memory) is expressed as the enhancement of accuracy or speed in performing a task across multiple training sessions. Amnesic patients have shown entirely normal and long-lasting skill learning on motor tasks (e.g. mirror tracing and rotary pursuit) (Milner, 1962; Corkin, 1968; Gabrieli et al., 1993), perceptual tasks (e.g. reading mirror-reversed text) (Cohen & Squire, 1980), and cognitive tasks (e.g. probabilistic classification) (Knowlton et al., 1994). Amnesic patients learn how to perform these tasks skillfully without knowing that they have had prior practice. Patients with basal ganglia diseases, especially HD, have shown impaired skill learning on many of these motor (Gabrieli et al., 1997b; Heindel et al., 1989), perceptual (Martone et al., 1984), and cognitive (Knowlton et al., 1996a, b) tasks. Thus, the basal ganglia appear to play an essential and widespread role in human skill learning that extends to cognitive skills.

Functional neuroimaging studies have revealed a dynamic plasticity of brain activations associated with skill learning. Learning a new skill is associated with expansion and reduction of initial activations and shifts in brain areas activated during initial, unskilled performance vs. later, skilled performance. For example, some motor skill learning tasks involve an expansion of activation in primary motor cortex and the basal ganglia (Grafton et al., 1992; Karni et al., 1995; Doyon et al., 1996; Hazeltine et al., 1997). For the perceptual skill of mirror reading, activation has been shown to increase in left inferior occipito-temporal cortex and decrease in bilateral parietal cortex as people improved their reading skill (Poldrack et al., 1998). These shifts in activity may represent a shift from reliance upon visuospatial decoding of mirror-reversed words in unskilled performance to more direct reading in skilled performance. These alterations in activation must reflect

alterations in neural connectivity that mediate skilled performance.

Conditioning

The neural circuitry underlying classical and other forms of conditioning has been studied extensively in animals. There appears to be a remarkable conservation of memory mechanisms for conditioning across mammalian species, which provides an opportunity to integrate invasive animal and noninvasive human research about memory systems.

The memory system underlying classical delay eyeblink conditioning has been delineated with great precision in the rabbit, and may be the most precisely understood mammalian memory system (Thompson, 1990; Fig. 21.9). In the typical delay paradigm, a 250–500 ms tone (conditioned stimulus or CS) is repeatedly followed by an air-puff (unconditioned stimulus or US) delivered to the eye that elicits a blink reflex, the unconditioned response (UR). The tone and air-puff coterminate. With repeated CS–US pairings, subjects learn to associate the tone with the air-puff, and initiate an eyeblink (conditioned response or CR) to the CS before the onset of the US. The convergence of CS and US projections in eyeblink conditioning occurs in the cerebellum ipsilateral to the eye receiving the air-puff. Lesions of the cerebellar dentate–interpositus nuclei prevent acquisition or abolish retention of the conditioned association, but lesions of the hippocampus do not affect delay conditioning (Schmaltz & Theios, 1972). In humans, delay eyeblink conditioning is intact in amnesic patients with bilateral medial–temporal (Gabrieli et al., 1995b) or bilateral thalamic lesions (Daum & Ackermann, 1994), but abolished in patients with cerebellar lesions (Daum et al., 1993).

More complex forms of conditioning, however, are impaired after medial–temporal lobe lesions in humans and rabbits. In animals, medial–temporal lesions impair trace eyeblink conditioning, which differs from delay conditioning in that there is a short time period, a second or less, between the offset of the CS and the onset of the US (Solomon et al., 1986). Amnesic patients with medial–temporal lesions who are unimpaired on delay conditioning show impaired trace conditioning with CS–US trace intervals as short as 500 ms (McGlinchey-Berroth et al., 1997). In animals, medial–temporal lesions also impair discrimination reversal, in which the two CS stimuli are switched in terms of their association with the US (Berger & Orr, 1983). Amnesic patients with medial–temporal lesions also have impaired conditioning for discrimination reversal (Daum et al., 1989). These findings suggest that the same medial–temporal lobe structures that are essential for declarative memory also mediate processes required for more complex forms of conditioning in humans and other mammals.

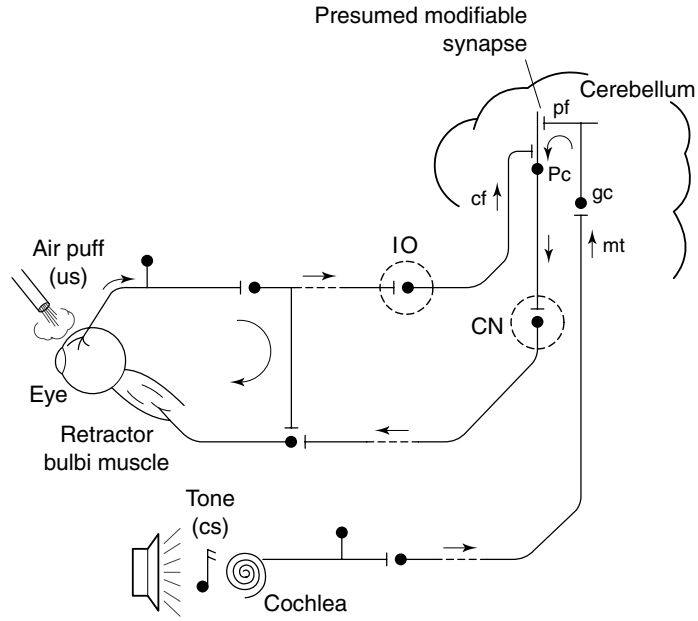


Fig. 21.9. Proposed minimal circuitry for eyeblink conditioning in the rabbit. An airpuff to the eye (us) is signalled to cerebellar Purkinje cells (PC) via the climbing fibres (cf), which originate in the inferior olive (IO). The tone (CS) is also signalled to the Purkinje cells through mossy fibres (mf), the cerebellar granule cells (gc), and the parallel fibres (pf). Modification at the putative plastic synapse (pf to Purkinje cell) would depend on properly timed activity in cf and pf. The Purkinje cells project to the cerebellar dentate–interpositus nuclei and then onto the motor neurons mediating the eyeblink response. (Adapted from Squire, 1987.)

The critical role of the amygdala in fear conditioning to aversive stimuli such as electric shocks has been well established in rats (Hitchcock & Davis, 1986). Amygdala damage also impairs fear conditioning in humans. In two studies, participants were exposed to pairings of initially neutral conditioned visual stimuli (CS) preceding aversive unconditioned auditory stimuli (US), white-noise or boat-horn bursts, which elicited an unconditioned response measured as a change in skin conductance response. Over multiple trials, normal participants showed fear conditioning, as evidenced by conditioned skin conductance responses to the CS. An Urbach–Weithe patient (Bechara et al., 1995) and patients with amygdala resections (LaBar et al., 1995) showed little or no fear conditioning. The fear-conditioning deficit was dissociated from declarative

memory because the patients had excellent declarative memory for the experimental experience, including the stimuli. In contrast, amnesic patients without amygdala damage demonstrated intact fear conditioning but impaired declarative memory for the experimental experience (Bechara et al., 1995).

Repetition priming

Repetition priming refers to facilitated processing of a stimulus, such as a word or picture, due to prior exposure to that or a related stimulus. In a typical experiment, participants process a set of stimuli in a study phase. In a subsequent test phase, participants perform a task with 'old' stimuli identical or related to the study-phase stimuli, and with 'new' stimuli that are unrelated to the study-phase and provide a baseline measure of performance. The difference in performance with old and new stimuli, the consequence of memories established during study, constitutes the measure of repetition priming (hereafter referred to as priming). For example, seeing the word STORK or a picture of a stork in a study phase makes people in a test phase more likely to identify that word or picture correctly when it is presented very briefly (e.g. less than one-twentieth of a second) or in a partial, fragmented form. People are also faster to read that word aloud and to name that picture aloud, and more likely to say 'STORK' when asked to complete three letters (STO _ _) with the first word that comes to mind, or to add letters so as to make a fragment (S _ _ R _) into a real word, or to say the first word that goes with BABY, or to provide examples of birds. Some of these examples of priming are primarily perceptual in nature and are linked to stimulus form (e.g. identifying a rapidly presented word); others are primarily conceptual in nature and are linked to stimulus meaning (e.g. listing examples of birds) (Roediger & McDermott, 1993).

Amnesic patients exhibit normal priming on many perceptual and conceptual tasks, despite little or no declarative memory for the stimuli they are identifying or producing with measurable benefits from prior processing (Warrington & Weiskrantz, 1970; Graf et al., 1984, 1985; Shimamura & Squire, 1984; Cermak et al., 1985; Cave & Squire 1992; Vaidya et al., 1995; Verfaellie et al., 1996). Amnesic patients can also show normal priming for novel materials (Gabrieli et al., 1990) and novel associations between materials (Moscovitch et al., 1986; Musen & Squire, 1993; Gabrieli et al., 1997a). Therefore, priming does not depend on medial–temporal lobe or other structures important for declarative memory. HD patients show intact priming (Heindel et al., 1989), so priming is also not dependent upon basal ganglia structures critical for skill learning.

Several lines of evidence indicate that priming is mediated by neocortical areas, with perceptual priming being mediated by modality-specific cortical areas and conceptual priming by amodal language areas. One source of evidence is the performance of AD patients, who exhibit severely reduced conceptual priming (Monti et al., 1996) but intact perceptual priming on visual tasks (Fleischman et al., 1995; Keane et al., 1991, 1995a). This pattern of impaired conceptual and intact perceptual priming may be interpreted in terms of the characteristic neocortical neuropathology in AD. In vivo metabolic imaging studies (e.g. (Frackowiak et al., 1981)) and postmortem studies of late-stage AD patients (Brun & Englund, 1981) find substantial damage to association neocortices in the frontal, parietal, and temporal lobes but relatively little compromise of primary visual, somatosensory, auditory, and motor cortices, the basal ganglia, or the cerebellum. The sparing of modality-specific cortices and the compromise of association cortices may account, respectively, for intact perceptual and impaired conceptual priming observed in AD. More direct evidence that modality-specific neocortex mediates modality-specific perceptual priming comes from patients with right occipital lesions. These patients have exhibited an absence of priming on visual tasks despite intact declarative memory and intact conceptual priming (Fleischman et al., 1995; Gabrieli et al., 1995a, b; Keane et al., 1995a).

Neuroimaging studies also indicate that separate cortical areas mediate perceptual and conceptual priming. Priming on visual tasks is associated with reduced activity in bilateral occipito-temporal regions (Squire et al., 1992; Schacter et al., 1996). Priming on conceptual tasks is associated with reduced activity in left frontal neocortex in healthy subjects (Raichle et al., 1994; Demb et al., 1995; Blaxton et al., 1996; Gabrieli et al., 1996a) and amnesic patients (Gabrieli et al., 1998).

Thus, lesion and imaging studies provide convergent evidence that different forms of priming reflect process-specific plasticity in separate neocortical regions. Visual priming is associated with changes in occipital cortex, whereas conceptual priming is associated with changes in language-related areas in left frontal cortex. Repetition priming in a given domain appears to reflect experience-induced changes in the same neural networks that subserved initial processing in that domain (Gabrieli et al., 1996a; Raichle et al., 1994). These changes facilitate or bias the subsequent reprocessing of the stimuli. The enhanced efficiency of reprocessing may diminish computational demands and thus lead to reduced activations relative to baseline conditions.

In conclusion, the global amnesia resulting from bilateral medial, diencepahlic, or basal forebrain lesions constitutes

the most striking and debilitating memory disorder. Clinical and experimental studies have shown, however, that the brain is composed of multiple memory systems that include the cerebral cortex, amygdala, basal ganglia, and cerebellum. Indeed, all brain regions appear to be involved in one sort or another of memory. Further, it is likely that many effective forms of human learning involve collaborative interactions among multiple memory systems. Memory systems may be seen as highly specialized instruments of memory that normally act in seamless concert to allow lessons from the past to guide actions in the future.

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22

Acquired disorders of language

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In 1915, the British neurologist Henry Head commented on recent developments in clinical aphasiology and concluded that: 'It is generally conceded that the views on aphasia and analogous disturbances of speech found in the textbooks of today are of little help in understanding an actual case of disease' (Head, 1915). This may still be true to a certain extent, although perhaps for different reasons from those that Head had in mind. Most textbooks typically describe classical aphasia syndromes that are based on chronic, stable patients; thus by definition different from the patient with acute symptoms that the neurologist typically encounters. It has been estimated that only 20–30% of all patients with aphasia will fit neatly into one of the classical aphasia syndromes (Albert et al., 1991). Nonetheless, the clinical use of the classical syndrome classification as a basis for diagnosis has continued more or less unchanged.

The convenience of this approach in clinical settings notwithstanding, increasing dissatisfaction with the classical taxonomy of aphasia has been expressed by researchers in the field of aphasia, in particular psycholinguistics and cognitive psychologists (Schwartz, 1984). The principal concern is that the classical model does not necessarily generate any meaningful generalizations about the nature of brain-language relationships. Some have argued that the classical aphasia syndromes do not meet standard criteria for a syndrome, in that none of the syndromes can be characterized in terms of invariant features that are shared by all patients given a certain classification and are absent in patients with a different classification (Caramazza, 1984). Classical taxonomy can thus best be characterized as polytypic, implying that any given feature or impairment, for example phonological paraphasias, can be part of more than one syndrome (Schwartz, 1984).

Despite the controversy over classical aphasia taxonomy in research settings and the limited number of aphasic patients it accounts for, the clinical utility of classic aphasia syndromes has rarely been questioned. It appears to have been assumed that the syndromes are associated with a certain degree of anatomical predictability, which may allow the clinician to infer lesion location, etiology, and prognosis (Albert et al., 1991). Recent studies have questioned the validity of these assumptions, however. In particular, the expectation that aphasia syndromes have localizing value does not appear to have stood the test of time (Willmes & Poeck, 1993; Basso et al., 1985; Vignolo et al., 1986). The evidence that classic aphasia syndromes carry prognostic implications is also not compelling. The Boston Diagnostic Aphasia Examination (BDAE) diagnostic classifications are somewhat predictive of outcome for syndromes characterized by mild impairment, such as anomic and conduction aphasia, and for those characterized by severe syndromes, such as global aphasia. This is consistent with the findings from several studies showing that one of the best prognostic indicators for recovery from aphasia is initial degree of severity (Pedersen et al., 1995). Syndromes that are characterized by a greater range in severity, such as Broca's and Wernicke's aphasia, are not predictive of outcomes (Kertesz & McCabe, 1977).

Thus, classic subtyping of aphasia does not appear to offer any particular benefits for either research or clinical purposes. In the absence of a better system for characterizing clinical aphasia subtypes, it is nonetheless likely to persist. One commonly used alternative to the classic aphasia taxonomy is to dichotomize patients on the basis of speech fluency. Fluency can be rated on the basis of conversational speech. The BDAE criteria for fluency are based on the 'longest occasional uninterrupted string of words' that the patient is able to produce. The speech of non-fluent patients may range from complete mutism to slow, halting, and effortful production of individual

words. Mutism is a rare finding in aphasia and most often occurs as a transient initial sign. Non-fluent speech is often associated with articulatory problems or dysarthria, but some non-fluent aphasics have normal articulation. A subset of non-fluent patients have a tendency to omit grammatical words from their speech, resulting in telegraphic or agrammatic speech output. The speech of patients with fluent aphasia resembles normal speech in terms of rate of word production and phrase length. Non-fluent aphasia may be somewhat more common in younger patients, whereas fluent aphasia tends to predominate in patients 70 years or older (Ferro & Madureira, 1997). Speech fluency provides an approximate guide to lesion location in that non-fluent aphasia is most commonly associated with lesions that include anterior regions of the perisylvian language areas, whereas fluent aphasia is frequently associated with posterior lesions. This classification by itself does not necessarily carry much prognostic implication, although patients who remain non-fluent at 1 month after stroke are not likely to show substantial future improvement in fluency (Knopman et al., 1983).

Overall, there is no single language symptom that can adequately capture the nature of observed language disorders or provide adequate anatomic specificity to allow for an anatomic classification of aphasic disorders. Nor at this point, does any one language symptom provide a clear theoretical framework to account for what a particular brain region 'subserves' (e.g. there is no brain region that specifically performs a function like 'comprehension'). Thus, clinicians have been faced with performing a systematic evaluation of aphasia by characterizing a group of standard language components (e.g. speech, comprehension, naming, and repetition), assessing the pattern of impaired performance on these components, and inferring anatomic localization resulting in these deficits from these patterns.

Signs and symptoms of aphasia

Most cases of aphasia are secondary to stroke, and the abrupt onset of change in language-related functions may be the most reliable indicator that the symptoms stem from an aphasia. Very few aphasic symptoms are by themselves unique or diagnostic of aphasia. Dysnomia, paraphasias, and dysgraphias may occur in neurologically intact individuals. Therefore, it may be difficult to diagnose cases of aphasia due to causes other than stroke, such as primary progressive aphasia, during the early stages of the disease.

Dysnomia

Of the variety of symptoms associated with aphasia, none is more ubiquitous than dysnomia. A disorder of word finding or retrieval is present in all types of aphasia. In most cases, word finding difficulties are readily apparent in the patient's attempts at spontaneous speech. In milder cases, formal testing with confrontation naming may be required to document the dysnomia. Whereas non-fluent patients struggle to find individual words, the fluent patient often will substitute non-specific grammatical function words for content words. Poor recovery of naming has been associated with lesions involving either the posterior superior temporal lobe or the insula/putamen (Knopman et al., 1984). Unlike patients with Alzheimer's disease, whose naming failure may be principally on the basis of an impairment at the level of semantics, the dysnomia of patients with aphasia typically is on the basis of an impairment at the level of phonological activation. In some patients, the dysnomia may be restricted to certain semantic categories, such as colours, fruits and vegetables or tools (Warrington & Shallice, 1984; Hart et al., 1985). Although cases of category-specific naming deficits are relatively rare, detailed study of these cases may eventually provide critical information about the organization of the normal lexicon and its neural substrates (Caramazza & Shelton, 1998). Dysnomia in the absence of significant impairment in other aspects of speech and language does not appear to carry any specific localizing value.

Paraphasias

These refer to unintended substitutions at the level of individual sounds or words and are common in all types of aphasia. The principal subtypes of verbal substitutions are phonemic, semantic, and neologistic. Phonemic paraphasias refer to substitutions of one *sound* (or phoneme) for another, such as saying 'tork' instead of 'fork'. Phonemic paraphasias are common to most subtypes of aphasia, but are particularly abundant in aphasia secondary to incomplete lesions of the posterior language areas, such as conduction aphasia. Semantic paraphasias, or substitution of another word for an intended one, generally occur with significant involvement of the posterior superior temporal lobe (Wernicke's area). Neologisms are substitutions that are so far removed from the intended word that the target can no longer be recognized as an English word. Neologistic substitutions are most often seen with severe aphasias involving lesions of Wernicke's area and posterior extensions. Although both the frequency and type of paraphasic errors are relevant,

phonemic paraphasias are typically associated with milder forms of aphasia, while neologisms are associated with more severe forms.

Perseverations

Verbal perseverations, the unintended repetition of a preceding response, are common during the early stages of any acute aphasia syndrome, but occur in non-aphasic brain injured patients as well. Subtypes of verbal perseveration have been described (continuous, recurrent, stuck-in-set), but it is not clear whether these carry any prognostic information. The lesion correlates of perseverations are varied, but a recent study reported an association between head of caudate lesions and perseveration in patients with acute aphasia (Kreisler et al., 2000).

Echolalia

This refers to unsolicited, compulsive repetition (echoing) of verbal stimuli. Patients with echolalia do not echo everything they hear, but only utterances directed towards them. It is typically associated with poor comprehension. Despite this, aphasic patients with echolalia often demonstrate a completion-response (Stengel et al., 1947). If given a simple, but incomplete sentence, the patient will frequently complete the sentence spontaneously. Because of the implied intact repetition, echolalia does not usually occur with perisylvian lesions but is most common in so-called transcortical aphasias (Kornyey, 1975). Echolalia is also frequent in certain non-aphasic conditions, such as degenerative disorders and autism (Rapin & Dunn, 1997).

Stereotypical utterances

The speech of patients with severe non-fluent or global aphasia may sometimes be limited to one or two utterances, repeated in succession. These utterances may be real words or meaningless nonsense syllables. Repetitive stereotypical utterances, first described by Hughlings-Jackson (1880), represent a symptom that typically occurs only in patients with global aphasia (Brunner et al., 1982). The speech of Broca's initial patient Leborgne, who was only capable of uttering the word *Tan*, is one of the first known cases of stereotypical utterances. Curiously, it also suggests that Broca's first patient may, in fact, have had a global rather than what we today think of as Broca's aphasia (Selnes & Hillis, 2000). Stereotypical utterances, which may be one of the few pathognomonic signs of aphasia, invariably carry a poor prognosis.

Aprosody

Prosody, sometimes referred to as melodic line, refers to features such as stress, rhythm and intonational contours that convey both linguistic and non-linguistic information. Impairments of speech prosody are seen most often with non-fluent aphasia. In rare cases, the prosodic and articulatory changes are so prominent that the impression is given that the patient is speaking with a foreign accent. This condition was first described by the Norwegian neurologist Monrad-Krohn (1947), who reported the case of a woman with a war-related shrapnel injury to her left frontal lobe. When she recovered her speech, the rhythm and sentence melody were altered, and she was thought to be speaking with a German accent (Ryalls & Reinvang, 1985). Although an infrequent manifestation of aphasia, the foreign accent syndrome may occur during the recovery from severe non-fluency to a more fluent output. Foreign accent syndrome in the absence of aphasia has also been reported (Takayama et al., 1993). The role of the right hemisphere in prosody still remains controversial (Ryalls, 1986).

Palilalia

This is an acquired speech impairment characterized by recurrent repetition of a word or part of a word. With each recurrence, the rate tends to increase and the loudness decreases until the palilalia fades away. This symptom is relatively rare in aphasias with primarily cortical involvement, but can occur with subcortical involvement. Thus, palilalia with thalamic infarctions has been reported (Abe et al. 1993) and it frequently occurs in patients with Parkinson's disease.

Bedside language examination

At a minimum, the bedside language examination should include the basic elements listed in Table 22.1. Information about the quality of speech fluency and the ability to comprehend conversational speech can be obtained from the clinical interview. For patients with non-fluent aphasia, the use of automatic sequences, such as asking the patient to count from 1–10, reciting the letters of the alphabet, days of the week, and months of the year, can be helpful in eliciting enough speech to allow assessment of articulation and fluency. The critical elements in assessing spontaneous speech include: articulation, fluency, melodic line (prosody), grammatical form (syntax), paraphasic errors, and word-finding. In patients with no verbal output,

Table 22.1. Elements of the bedside language exam

Spontaneous speech
automatic sequences
Auditory comprehension
single word
sentences (commands)
Naming
objects, body parts, colours
Repetition
Writing
spontaneous
dictation
copying
Reading
aloud
comprehension

assessment of writing can help differentiate between aphasia versus aphonia. Auditory comprehension for individual words can be tested by asking the patient to point to body parts, everyday objects, or items in the room. Single word comprehension may be the best index of initial aphasia severity, and thus carries potential prognostic implications (Selnes et al., 1984). Sentence comprehension can be assessed by asking the patient to perform single or multistep commands. The ability to comprehend more complex syntactical relationships can be probed by the use of so-called syntactically reversible sentences. For example, in response to a sentence such as 'the lion was killed by the tiger, ' some patients have difficulty answering the question: 'which animal died?' Regardless of the severity of the aphasia, most patients will be able to demonstrate comprehension of commands that involve the body axis, such as: 'look up, look down, stand up, lean forward.' (Albert et al., 1991).

Naming can be assessed by asking the patient to name objects, body parts, or colors. For more detailed assessment, quantitative tests such as the Boston Naming Test are recommended (Kaplan et al., 1983). Repetition can be screened with sentences such as 'no ifs ands or buts'. Patients who are able to repeat this sentence generally have intact repetition. If the patient does not repeat this sentence correctly, however, additional testing of repetition with single words and simpler sentences should be performed. Writing can be assessed by asking the patient to write a sentence spontaneously. Patients unable to write a sentence should be asked to attempt to copy single words or sentences. In patients with severe motor deficits or apraxic agraphia, testing oral spelling can be useful. Reading aloud of single words, sentences, and paragraphs should be assessed. Most patients with problems in reading comprehension also have problems when reading aloud, but the converse is not true. A selective deficit of reading words that do not conform to standard sound-to-print rules, such as 'lieutenant, beautiful, steak', is sometimes observed.

Traditional anatomy of aphasia

For decades, our understanding of the anatomy of the left hemisphere language system was constrained by a bias in patient investigation: only patients with 'classic' symptoms of aphasia were investigated. Patients with left hemisphere lesions but no aphasia were rarely subjected to systematic study. Consequently, this resulted in a somewhat biased and restricted view. Advances in neuroimaging technologies over the past several decades have resulted in several modifications of the Wernicke–Lichtheim standard model of the left hemisphere language system. Although contemporary textbooks still feature the standard model of Wernicke's and Broca's areas interconnected by the arcuate fasciculus, evidence from several different lines of inquiry is now accumulating that this model is an oversimplification. There have been three major trends. First, it is now appreciated that lesions restricted to the traditional language areas of Broca and Wernicke are neither necessary nor sufficient to produce the classical syndromes. Secondly, it is now commonly accepted that multiple left hemisphere regions other than Broca's and Wernicke's areas appear to participate in language functions. Thirdly, there is significant variability in the lesion correlates of the so-called traditional syndromes (Basso et al., 1985; Vignolo et al., 1986).

Broca's area (Brodmann's area 44/45)

The first major revision to standard teaching about the role of Broca's area in language came with the studies of J.P. Mohr, who showed that a lesion restricted to Broca's area does not produce the clinical syndrome of Broca's aphasia (Mohr et al., 1999). According to Mohr, the lesion responsible for the clinical picture of Broca's aphasia is a large infarct in the sylvian area, which includes the operculum, the insula, and surrounding deep white matter. Others have shown that although the anterior insula is consistently involved, Broca's area proper need not be part of the lesion (Knopman et al., 1983; Blunk et al., 1981). Thus, a lesion of Broca's area is neither sufficient nor necessary for producing the syndrome of persistent non-fluent aphasia

of Broca. More detailed analysis suggests that despite considerable variability, components of the syndrome of Broca's aphasia, such as impaired articulation, delayed initiation of speech, and aprosody can be related to regional involvement of the frontal operculum (Alexander et al., 1992). Although there have been some contemporary studies of the anatomy of this area, more detailed studies of the cytoarchitecture, individual variability, and connectivity of this area are just beginning to emerge (Amunts et al., 1999; Petrides & Pandya, 1988).

Wernicke's area

The anatomical boundaries of the part of the posterior superior temporal lobe that constitutes Wernicke's region have never been specified, because there are no specific cytoarchitectonic or other criteria for supporting such a definition (Bogen & Bogen, 1976). A lesion of the posterior superior temporal lobe is almost always associated with fluent, paraphasic speech and poor comprehension. It has also been demonstrated that the degree of destruction of the posterior superior temporal lobe is correlated with outcome. Partial lesions are associated with favorable outcomes, whereas lesions that include more than 50% of the region are associated with poor outcomes (Selnes et al., 1984). If the lesion is limited to the posterior superior temporal lobe, prognosis for improvement to anomic aphasia is good, but if the lesion includes anterior extensions, prognosis for recovery is poor (Naeser et al., 1987).

Planum temporale

The planum temporale is a triangular structure located on the superior plane of the temporal lobe within the sylvian fissure. The normal anatomy of this region is quite variable, but cytoarchitectonically it consists of auditory association cortex. It has attracted considerable research attention after the discovery by Geschwind and Levitsky (1968) that this particular region of the brain tends to be larger on the left. Although the distribution of the anatomical asymmetry (left larger in 64% of brains) did not exactly fit with estimates of left hemisphere dominance, the assumption was made that the asymmetry somehow reflected the important role of the posterior superior temporal lobe in language. However, a specific role of this area in language, if any, has not yet been demonstrated (Binder et al., 1996).

Insula

The role of the insula in speech and language has been controversial since the time of Pierre Marie. The anterior insula is almost always implicated in patients with persistent non-fluent aphasia. A recent study reported that patients with so-called apraxia of speech all had lesions that involved the anterior insula, while none of the patients without apraxia of speech had a lesion that included this area (Dronkers, 1996). There is also evidence to suggest that some of the connections from the posterior superior temporal lobe to anterior speech areas actually pass through the extreme capsule (Petrides & Pandya, 1988). Lesions of the insula therefore frequently produce impaired repetition (Damasio & Damasio, 1980).

Angular/supramarginal gyri

The angular and supramarginal gyri are part of the inferior parietal lobe, and are strategically located for polymodal association of vision, touch and hearing. These areas may play an important role during language development, because basic linguistic functions, such as object naming, depend on establishing an association between auditory and other sensory modalities. Although there is some evidence that lesions restricted to the angular gyrus may produce an agraphia, the role of the angular gyrus in reading is less clear. Although traditionally implicated in the syndrome of alexia with agraphia, the lesions responsible for this syndrome typically include other structures as well (Sakurai et al., 2000). The so-called Gerstmann syndrome has also been shown to be associated with larger lesions that include the angular gyrus but not restricted to this area (Benton, 1992). With disconnection of visual input to the angular gyrus, alexia without agraphia occurs. Comprehension of written words is impaired, but writing is generally intact. Spelling, and comprehension of spelled words, is generally intact.

Arcuate fasciculus

The long white matter tract known as the arcuate fasciculus has traditionally been conceptualized as the direct pathway between the posterior and anterior language areas. Lesions of the arcuate fasciculus have been thought to be responsible for the repetition deficit observed in patients with conduction aphasia. The presumptive role of the arcuate fasciculus in repetition disorders has been surprisingly resistant to more recent findings suggesting that a lesion of the arcuate fasciculus is neither necessary nor sufficient for the production of the syndrome of conduction aphasia (Selnes et al, 1985; Damasio & Damasio, 1980; Brown, 1975; Shuren et al., 1995; Anderson et al., 1999). Recent anatomical studies also suggest that it is only the

most posterior areas of the superior temporal lobe that project to anterior speech areas via the arcuate fasciculus. The anterior two thirds of the posterior superior temporal lobe appear to be connected through white matter tracts that pass through the extreme capsule (Petrides & Pandya, 1988). Thus, there is neither compelling behavioural nor anatomical evidence for a specific role of the arcuate fasciculus in repetition.

Basal temporal language area

Functional localization of language-relevant cortex by using electrical stimulation has become routine in patients who are candidates for epilepsy surgery (Lesser et al., 1986, 1987; Schaffler et al., 1993). This methodology has revealed evidence of interference with language functions in areas outside the classical language areas. Electrical stimulation of the dominant basal temporal area has been shown to produce problems in both comprehension and production in some patients (Luders et al., 1986, 1991). Surgical resection of this area does not produce any lasting language deficits in most patients, but some patients have persistent dysnomia (Krauss et al., 1996). Thus far, the specific role this region subsumes in language functions is unclear.

Supplementary motor area

The anterior part of area 6 on the medial surface of the cerebral hemisphere, the supplementary motor area, has been implicated in speech functions since the work of Penfield and Roberts (1959), but its specific functions are still poorly understood. Stimulation of the supplementary motor area most commonly results in speech arrest (Fried et al., 1991). Surgical lesions of the dominant supplementary motor area may produce moderate to severe initial deficits, but significant lasting speech changes are uncommon (Rostomily et al., 1991).

The basic Wernicke–Geschwind model of the anatomy of language has thus undergone considerable evolution over the past several decades. The following quote from Mesulam is representative of this more contemporary view: 'There are no "centres" dedicated to comprehension, articulation, or grammar but a distributed network in which nodal foci of relative specialization work in concert.' (Mesulam, 1990). The extent to which this updated model will prevail remains to be seen, but as noted by Damasio: 'The time for modernizing the classic view is now, and the past decade has brought forth a number of new findings likely to make the modernization stick.' (Damasio, 1997).

Integrated cognitive neuroscience approach to the neural basis of language

Rapid developments in cognitive neuroscience in the past two decades have allowed us to develop a cognitive neuroscience model that describes how the brain encodes language operations and explains aphasic behaviour. The advantages of these types of models are that they (*a*) can account for the observed aphasic language disorders, (*b*) provide more theoretically and clinically relevant language components that correlate with specific brain regions, and (*c*) take advantage of the multitude of activation studies conducted in control subjects to understand how the normal brain performs language functions. This point raises the important issue that an integrated account of language and aphasia is required to reconcile the findings of activation and lesion studies in describing how the brain performs language operations.

The basic language operations assessed above in the classical approach are still correlated with their associated anatomic regions including this within their framework. The cognitive neuroscience approach supplements the classical approach by assessing the networks of brain regions associated with the linguistic components of semantic, orthographic, and phonological lexicons and syntax. These components are most useful for developing both theoretical and practical explanations for normal and aphasic language function. It is believed that these networks consist of various combinations of circumscribed brain regions subserving processing or access to representation of language units (e.g. words, letters, sounds, among others), some of which may be encoded in spatially distributed representations (Hinton, 1981).

Although the tests for assessing each of these components and their access can be similar to those outlined above, the results are interpreted and framed in terms of linguistic and cognitive components. The following outlines a framework for an integrated cognitive neuroscience approach to language representation in the brain and its application to explaining aphasic behaviour. As further studies are completed, clarification and expansion of the framework will provide a more detailed account of the networks involved.

Semantic lexicon (stores in the brain encoding the linguistic meaning of words)

This component is usually assessed by how a patient performs on comprehension questions (e.g. 'Do birds have wings?'), comprehension of single words, confrontation naming, and the output of spontaneous speech (e.g. error

patterns, word-finding difficulties). The pattern of performance across these types of tasks indicates deficits in the lexical semantic system, for example, if the patient has empty speech with word-finding difficulties and impaired comprehension.

Studies of clinical patients and activation studies have both demonstrated behavioural and anatomical aspects of the organization of the semantic lexicon and possible associated processing regions (see Hart et al., 2001). Evidence from focal brain lesions and from degenerative brain conditions has shown that aspects of the lexical semantic system may be organized by semantic category (see Caramazza & Shelton, 1998), because categories can be differentially affected by these neural injuries. Nielsen (1946) was the first to describe a double dissociation between the ability to name living things and non-living things (with opposite patterns of preservation or impairment across different patients). Since then, there have been many individual and group reports of such dissociations for a variety of categories including living things, animals, plants, food, fruits and vegetables, body parts, countries, emotional facial expressions, small manipulable objects, shapes, colours, letters, numbers, action names, verbs, case marking prepositions and tense, girls' and boys' names, family and friends, famous people, proper names, cities, rivers, countries, mountains (Semenza & Zettin 1988, 1989; Goodglass et al., 1966, 1986; Funnell & Sheridan, 1992; Hillis & Caramazza, 1991; Farah et al., 1991, 1996; Silveri et al., 1991; Damasio et al., 1990; Farah & Wallace, 1992; Farah, 1989; Temple, 1986; Warrington & Shallice, 1984; Rapcsak et al., 1989, 1993; McCarthy & Warrington, 1988; Hart et al., 1985; Berndt, 1988; Humphreys & Riddoch, 1987; Damasio, 1990; Silveri & Gainotti, 1988; Warrington & McCarthy, 1983, 1987; Hart & Gordon, 1992; Sartori et al., 1993; Robinson et al., 1996; Gainotti et al., 1995; Mauri et al., 1994; Tippett et al., 1996; Sartori & Job, 1988; Sacchett & Humphreys, 1992; Damasio et al., 1996; Cappa et al., 1998; Garrard et al., 1998; Ferreira et al., 1997; see Grossman et al., 1998 for similar issues in degenerative conditions). In addition, functional imaging studies of the picture naming task have suggested that aspects of this categorical organization may be localized to specific brain regions (e.g. animals selectively activated the left medial occipital lobe and tools selectively activated the left middle temporal gyrus and the left premotor region (Martin et al., 1996) or animals were associated with activation of the left 3rd (inferior) and fourth temporal gyri, whereas naming of tools was associated with activation of the left middle and inferior temporal gyri (Damasio et al., 1996). These distinctions have not yet been fully reconciled (see Spitzer et al., 1995; Moore & Price, 1999a).

In addition, there are distinct brain regions associated with aspects of semantic processing, including the left dorsal lateral prefrontal cortex (DLPFC) with selection between multiple semantic stimuli (Thompson-Schill et al., 1997; Posner et al., 1988; Demb et al., 1995; Kapur et al., 1994; Demonet et al., 1992; Ricci et al., 1999), left inferior parietal-posterior superior temporal region (Hart & Gordon, 1990; Vandenberghe et al., 1996) and the left fusiform gyri (Hart et al., 1998; Nobre et al., 1994; Abdullaev & Posner, 1988) with categorization, synonymity and property judgment as well as other semantic processing, and bilateral inferior (ventral) temporo-occipital regions.

As investigative techniques provide greater resolution, and further regions involved in the lexical semantic network are identified with their associated function, the anatomic substrates of the lexical semantic system will be further defined, resulting in descriptions of pure and mixed deficits associated with lexical semantics. In addition, further specification of lexical semantic components will aid in describing the selective language impairments seen in semantic aphasia and semantic dementia (Hodges et al., 1992).

Orthographic lexicons (stores in the brain encoding written version of words)

The most efficacious method of assessing these components is by having the patient write, read, and perform a lexical decision task (e.g. deciding if a letter string is a word or a non-word, 'trest' vs. 'treat'). These tasks readily assess the integrity of the orthographic lexical elements as well as access to them.

Localization of the input and output orthographic lexicons has been a controversial issue in functional imaging studies. Whereas some investigators suspect that the word representations or stores themselves are encoded in a spatially distributed fashion (Hart et al., 2000), others have suggested a more focal circumscribed localization (Petersen et al., 1988). These focal localizations isolated with functional imaging studies, however, have not always been substantiated by similar localizations in numerous lesion studies. Until more definitive studies are performed, at a minimum these activation studies identify regions associated with access to orthographic lexicons. These regions include the superior and middle temporal gyri and inferior parietal lobule (Hart et al., 2000; Moore & Price, 1999b; Simos et al., 2000) for the input lexicon; middle part of the left superior and middle temporal gyri for the input and posterior part of the left middle temporal gyrus for the output orthographic lexicon (Howard et al., 1992); the lateral occipital extrastriate area for the input orthographic

lexicon (Petersen et al., 1988); and the left frontal lobe for orthographic to phonological transformation (Fiez et al., 1999).

Extensive lesion studies of patients with alexia have delineated several plausible pathways involved in the three proposed routes to reading (direct access to an orthographic lexicon, orthographic-to-phonologic conversion, and direct access to semantics) and provide converging evidence that the above localizations may be important in accessing the input orthographic lexicon (see Coslett, 2000; Coltheart et al., 1980; Patterson et al., 1985). There is less evidence for anatomic localization of an independent output orthographic lexicon, although aspects of that lexicon have been behaviourally described (Hillis et al., 1999).

Phonological lexicons (stores encoding the sounds of words)

Speech discrimination tasks, repetition, and analysis of spontaneous speech are useful indices of the integrity of the phonological lexicons and their access. Phonemic paraphasic errors have been considered a hallmark feature of damage to the brain's internal storage system for the sounds of words for speech production, but it is also clear that inability to discriminate speech sounds can reflect impairment of an input phonological lexicon. This was demonstrated in the description of patient J.S., whose pure word deafness clinically was shown to stem from a disruption involving the input phonological lexical system (Caramazza et al., 1983).

It is clear that different neural mechanisms support input and output phonology, as well as different routes into these proposed lexical systems (e.g. access to input phonology from reading differs from access from speech perception) (Bub & Kertesz, 1982). As in the orthographic lexicons, it is not yet clear that anatomic localization defines the lexicons themselves or access to them. The localization of regions associated with access to input phonology from speech has been dissociated by focal, circumscribed temporary, reversible lesions produced by cortical electrical interference in left lateral superior temporal gyrus during speech discrimination tasks (Boatman et al. 1995, 1997). These regions bordered the primary auditory cortex, but were distinctly dissociated from it.

The network supporting the output phonologic lexicon has been shown through functional imaging studies to extend from the mouth representation in the primary motor cortex, the supplementary motor area, the inferior lateral premotor cortex (Broca's area), the anterior insula, and the cerebellum (Fox et al., 2000). In addition, the left posterior superior temporal gyrus has been shown to participate in phonemic aspects of speech production, as well as its previously described role in speech perception (Hickok et al., 2000). Distinguishing between the specific cognitive components that each region encodes, if they do function independently, is left to future studies.

Syntax (system of grammar)

Syntactical structures can be examined in both production and comprehension. Typical assessment of syntactic production extends from evaluating spontaneous speech for grammatical complexity (Kaplan et al., 1983), repetition of syntactically complex sentences or sentences with numerous function words (e.g. no ifs, ands, or buts), and reading of concrete and abstract words. Syntactic comprehension is routinely assessed at a basic level in a picture-sentence matching task using semantically reversible passive sentences ('Point to the correct picture describing this sentence, "The car was hit by the truck."')

Anatomical localization of syntactic processes have been variable (see Caplan, 1999). For example, in two patients aphasic syntactic and morphological aspects of grammar were localized to the left frontal lobe and the postcentral perisylvian cortex, respectively (Nadeau, 1988). In an activation study of syntactic processing, however, there was selective involvement of a deep component of Broca's area, a right inferior frontal region, and the left caudate nucleus and insula were activated (Moro et al., 2001). Alternatively, by studying sentences of increasing syntactic complexity, increased blood flow was found in Broca's area during syntactic judgment tasks (Caplan et al., 2000). Part of the variability in localizing syntactic processing may be attributable to different stimuli, testing paradigms, and investigative techniques, although some investigators have suggested that the variability is due to the lack of focal, circumscribed localization to syntactic processes.

Overall, the cognitive neuroscience approach is evolving as both functional imaging studies of normal and aphasic subjects are conducted. The success of this model will likely depend on several factors, not the least of which is to formally reconcile the disparities between activation and lesion studies to best determine the cognitive operation an anatomic region subserves. Another major factor will be the ability to combine experimental paradigms with the evolving investigative techniques to explore, in both spatial and temporal domains, the networks involved in the processing of these various linguistic components. As these techniques evolve, the cognitive neuroscience framework will also need to incorporate in the model the neural mechanisms (for example, electrophysiological

coherence, neurotransmitter mediation) that subserves the cognitive operations involved in language. And finally, it will be essential to integrate in this model not only the connections between the linguistic components within language (e.g. the interface between orthography and phonology, and others) but also with other cognitive components outside the language system proper but necessary to its successful operation. For example, while not included directly in the above neural circuits, it has become increasing clear through a variety of functional imaging studies (D'Esposito et al., 1999) that the dorsal lateral prefrontal cortex (DLPFC) is involved in aspects of working memory. As this region and its connections to other linguistic components are explored, it will be useful to integrate working memory and its substrates into the network model of language proposed here.

Aphasia in degenerative conditions

It is well recognized that changes in speech and language may occur during the later stages of most forms of dementing illness. If symptoms of aphasia occur as the presenting symptoms, alternate etiologies should be considered. In 1982, Mesulam described six patients with a history of slowly progressive speech and language symptoms in the absence of any signs of dementia (Mesulam, 1982). Although previous cases of slowly progressive aphasia had been described (Poeck & Luzatti, 1988), Mesulam's publication resulted in widespread recognition of the entity now commonly referred to as primary progressive aphasia (Mesulam, 1982). The epidemiology and risk factors for primary progressive aphasia are not known, in part because the disease is rare. In 1997, Westbury and Bub reviewed the findings from 112 cases published since 1982 (Westbury & Bub, 1997). Most patients with this condition will eventually develop a more generalized dementia syndrome. In rare cases, the patient may remain cognitively intact (except for language) for a number of years, but in most instances, some degree of cognitive impairment can be detected on standardized neuropsychological testing after 2–3 years of progression. Therefore, it has been suggested that a period of 2 years of language-related decline in a patient otherwise free of symptoms of dementia is sufficient for making the diagnosis (Weintraub et al., 1990). The average age of onset of symptoms in progressive aphasia is approximately 59 years, somewhat earlier than for typical Alzheimer's disease. Most patients present with a non-fluent aphasia, making it relatively easy to differentiate from early Alzheimer's disease (Caselli, 1995). The most common initial symptom is word-finding difficulty, but some patients also report early problems with comprehension of spoken language. Phonemic paraphasias and speech hesitancy may also occur relatively early. In rare cases, the patient may present with an otherwise isolated dysarthria (Selnes et al., 1996; Broussolle et al., 1996; Cohen et al., 1993). The degree of agraphia often mirrors the degree of speech impairment. Reading and repetition tend to be relatively preserved, during later stages of the disease. With progression of the disease, all language modalities become impaired, and vocalization may be reduced to single word utterances or complete muteness. MRI findings are not very specific, but often demonstrate bilateral atrophy in the perisylvian regions. Of the cases of primary progressive aphasia with autopsy information, some have shown changes consistent with Alzheimer's disease (Benson & Zaias, 1991), but the most common findings involve gliosis and neuronal loss of superficial cortical layers.

Other degenerative conditions that are sometimes accompanied by prominent speech and language changes include Pick's disease (Holland et al., 1985) and corticobasal degeneration (Sakurai et al., 1996). Detailed neuropsychological testing can be helpful for early differentiation of these syndromes from primary progressive aphasia.

Aphasia recovery and treatment

Recovery from aphasia has traditionally been thought to depend on a complex interaction of lesion size and location with patient characteristics such as age, gender and handedness. Nevertheless, large scale prospective studies of aphasia recovery have not confirmed a significant predictive relationship between demographic variables and degree of recovery. Although methods for assessing initial severity have varied across studies, there is considerable agreement that the most important factor predicting recovery from aphasia after stroke is initial degree of severity of language symptoms (Pedersen et al., 1995). Few systematic studies have compared recovery from aphasia after etiologies other than stroke, but some have found that post-traumatic aphasia has a better prognosis than aphasia due to cerebral infarction (Kertesz & McCabe, 1977).

Although it is well known that small lesions cause milder and shorter lasting impairments, only a handful of studies have examined the effect of lesion volume on aphasia recovery. Selnes and colleagues found that single word comprehension at 6 months after stroke was significantly related to lesion volume (Selnes et al., 1984). One subsequent study has also confirmed the importance of overall

lesion volume for degree of recovery (Goldenberg & Spatt, 1994). Furthermore, Naeser and her colleagues demonstrated that region-specific volume is also of importance, in that the degree of destruction within Wernicke's area itself was significantly related to levels of auditory comprehension. Patients with less than 50% destruction of Wernicke's area had good recovery of auditory comprehension at 6 months, whereas patients with destruction of more than half of Wernicke's region had limited recovery even at one year after onset. As with lesions of Broca's area, extension of the lesion beyond Wernicke's area was also associated with poor outcomes (Naeser et al., 1987).

The time course of recovery after aphasia may also depend on the initial level of severity. Patients with mild initial symptoms of aphasia often recover within a few weeks after the onset. With symptoms of moderate initial level, spontaneous recovery may last several months before a stable level of functioning is achieved (Pedersen et al., 1995). Patients with severe Global or Wernicke's aphasia may show some spontaneous recovery during the first 18 months after stroke, but the majority of the improvement takes place during the first 6 months (Nicholas et al., 1993).

There have been a number of studies attempting to quantify the degree of improvement, over and beyond spontaneous recovery, offered by speech therapy. In a recent meta-analysis of the findings from 21 studies, treatment by a speech-language pathologist was found to result in better outcomes (Robey, 1994). Treatment initiated during the acute stages of recovery was found to be significantly more effective than treatment initiated at later stages. In addition to behavioural treatments, pharmacotherapy for the treatment of symptoms of aphasia has also begun to be explored. Some studies have suggested a benefit of catecholaminergic drugs when used as an adjunct to behavioural therapy. At this time, further studies with appropriate controls are needed to assess which patients might potentially benefit from pharmacotherapy (Small, 1994).

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23

Neglect

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A patient with the neglect syndrome fails to report, respond or orient to, novel or meaningful stimuli presented to the side opposite a brain lesion (Heilman, 1979). If this failure can be attributed to either sensory or motor defects, the patient is not considered to have neglect.

The two basic mechanisms that are thought to be responsible for the failure to report, respond, or orient are defects in the systems that mediate sensory attention or motor intention. Whereas attentional defects may be associated with unawareness, intentional disorders may cause a failure to respond despite stimulus awareness. Attention and intention defects may occur in two domains: spatial and personal. Patients with neglect can also have spatial memory defects. This defect can be for new information or old memories (representational defects). This chapter describes tests that may be used to assess patients and behaviourally define these disorders. This chapter also discusses the pathophysiology underlying these disorders and their treatment.

Behavioural testing for the components of neglect

Tests for inattention and extinction

The attentional aspects of the neglect syndrome are detected by observing abnormal responses to sensory stimuli. Stimuli should be given in at least three modalities, somatesthetic, visual, and auditory, but other stimuli, such as gustatory and olfactory, may be used. Examiners often request immediate responses, however, delaying the response and using distractor techniques may help amplify the symptoms.

When testing with somatesthetic stimuli, one may control the intensity of a tactile stimulus by using Von Frei's hairs. However, fingers or cotton applicators are more convenient. Other cutaneous stimuli, such as pins, may be used. For bedside auditory testing, we use sounds made by either rubbing the fingers together or snapping them. When possible, perimetric and tangent screen studies should be used for testing visual fields. However, for bedside testing the confrontational method may be used; the examiner's finger movement can be used as the stimulus. A modified Poppelreuter diagram or written sentences may also be used.

These somatesthetic, auditory and visual stimuli should be presented to the abnormal (contralateral) side and to the normal side of the body in random order. If the patient responds normally to unilateral stimulation, simultaneous bilateral stimulation may be used. Unilateral stimuli should be randomly interspersed with simultaneous bilateral stimuli. Bender (1952) noted that normal subjects may show extinction to simultaneous stimulation when the stimuli are delivered to two different (asymmetric) parts of the body (simultaneous bilateral heterologous stimulation). For example, if the right side of the face and the left hand are stimulated simultaneously, normal subjects sometimes report only the stimulus on the face. Normal subjects do not extinguish symmetric stimuli (simultaneous bilateral homologous stimulation). Simultaneous bilateral heterologous stimulation can sometimes be used to test for milder defects in patients with extinction. For example, when the right side of the face and the left hand are stimulated, patients with left-sided neglect might not report the stimulus on the left hand, but when the left side of the face and right hand are stimulated, they might report both stimuli.

The most frequent response by patients is verbal (i.e. right, left or both). In addition, the patient may be instructed (verbally or non-verbally by gesture) to move the extremity or extremities the examiner has touched.

Patients may be considered to have hemi-inattention when they fail to orient, report, or respond to contralateral stimuli and when it can be demonstrated that the lesion does not interrupt afferent projectors and does not destroy primary sensory cortex or sensory thalamic nuclei. However, unless the site of the lesion is known, it may be difficult to distinguish between hemianesthesia or hemianopsia and severe somatesthetic and visual hemiattention. Occasionally, visual inattention may be distinguished from hemianopsia by changing the hemispace of presentation. Kooistra and Hellman (1989) reported a patient who could not detect single stimuli presented in the left visual field when the eyes were directed straight ahead, but could detect stimuli in the same retinotopic position when the eyes were directed toward right hemispace so that the left visual half-field was in the right hemispace.

Patients with hemianesthesia from unilateral cortical lesions probably suffer from inattention rather than from deafferentation. Elementary somatic sensation such as touch can be subserved by the thalamus. Lesions of the ventral posterolateral and ventral posteromedial thalamic nuclei result in hemianesthesia, but lesions in somatosensory cortex should not. Some patients with cortical lesions who appear to have tactile anesthesia can detect contralesional stimuli when cold water is injected into the contralesional ear. This increases orientation toward the side of the cold ear via vestibular mechanisms, suggesting that the hemianesthesia in fact results from sensory neglect (Vallar et al., 1995). One can also use psychophysiological procedures, such as early evoked potentials and skin conductance responses, to discriminate between inattention and deafferentation.

Although hemianesthesia and hemianopsia are fairly common manifestations of central nervous system lesions, unilateral hearing loss is almost always due to a disturbance in the peripheral hearing mechanisms or in the auditory nerve. Because the auditory pathways that ascend from the brainstem to the cortex are bilateral, each ear projects to both hemispheres. Thus, a unilateral central nervous system lesion will not produce unilateral hearing loss. Consequently, patients without peripheral hearing loss who fail to orient to, or report, unilateral auditory stimulation usually have hemi-inattention. Furthermore, because sound presented on one side of the body projects to both ears, patients with unilateral hearing loss caused by a peripheral lesion usually respond to unilateral auditory stimulation unless the stimulus is extremely close to the ear. Therefore, patients who neglect unilateral auditory stimuli most often have unilateral inattention.

Patients with unilateral neglect are most inattentive to stimuli contralateral to the lesion, but they are often also inattentive to ipsilateral stimuli, although ipsilateral inattention is not so severe.

Tests for personal neglect

Whereas the failure to detect tactile stimuli described in the preceding section may be a sign of personal neglect, patients with flagrant personal inattention may deny that their own limbs belong to them. This deficit is also called asomatognosia. The examiner can demonstrate personal neglect by asking patients to show a limb or by showing them their own limb and asking them to whom the limb belongs. Patients with personal neglect may also fail to groom or dress half of their body. Although anosognosia of a left hemiplegia and allesthesia (misplacing contralesional stimuli to the ipsilesional part of the body) are often associated with personal neglect, these three signs are often dissociable.

Coslett (1998) showed right hemisphere damaged patients diagrams of the palmar or dorsal aspect of the right or left hand and asked them to tell if the picture showed a right or left hand. To perform this task, one has to image one's own right or left hand in either the prone or supine position. Coslett's patients were impaired when shown diagrams of the left hand but not the right hand, suggesting a defect in the left side of a personal representation.

Tests for spatial neglect

Patients fail to act on contralesional stimuli presented in space. They may fail to act on stimuli presented to the left of their body (viewer centred hemispatial neglect), or they may fail to act on the left side of the environment or they may fail to act on the left side of the stimulus (allocentric spatial neglect). The three most frequently used methods for testing spatial neglect are the line bisection, the cancellation tasks and drawing. In the cancellation test, small lines are randomly drawn on a sheet of paper and the patient is asked to cross out all the lines. This can be made more difficult by using a task in which patients must either discriminate or focus their attention (Rapcsak et al., 1989). In the line bisection task an 8- to 10-inch line is presented to the patient, who is asked to bisect the line (find the middle of the line). This task can be made more difficult by using longer lines (Butter et al., 1988a) or by placing lines to the left of the midsagittal plane (Heilman & Valenstein, 1979).

When using very short lines patients with contralesional neglect may place their bisection mark on the side of the line that is contralateral to their hemispheric lesion. This

has been termed the cross-over effect (Halligan & Marshall, 1991).

Lastly, one can test for spatial neglect by having a subject copy drawings. Because neglect is often associated with right hemisphere lesions, patients may have constructional apraxia. Therefore, simple drawings (flower, clock) should be used.

Although spatial neglect is most often described in the horizontal plane (left spatial neglect), vertical neglect (Rapcsak et al., 1988) and radial neglect (Shelton et al., 1990) have also been reported. Vertical neglect and radial neglect can be assessed by orienting the line to be bisected in a radial or vertical direction.

Bisiach and Luzzatti (1978) asked patients to describe a familiar scene. Patients with left-sided neglect failed to recall the left side of the scene. Unfortunately, there is no simple bedside test for examining spatial representations. However, one can ask patients to describe the layout of their house, describe the sites on a famous street in their hometown going in a specific direction, or name the cities in the state in which they live. Failure to describe more items on one side than the other may suggest spatial representational neglect. Asking a patient to spell words from memory may also elicit spatial representational neglect but is an insensitive test. Finally, one could ask a patient who can copy drawings to make the same drawings from memory.

There are patients with hemispheric dysfunction who will bisect long lines toward contralesional rather than ipsilesional hemispace (Kwon & Heilman, 1991; Na et al., 1998a). This is called ipsilateral neglect.

Tests for motor-intention deficits: akinesia and motor neglect

Akinesia is the inability to initiate a movement that cannot be attributed to a defect in the motor unit or corticospinal neurons. Milder forms of akinesia may be expressed as a delay in initiating a movement (hypokinesia) or decreased amplitude of movement (hypometria). Akinesia may affect one or more body parts (legs, limbs, eyes, head) and may be spatial or directional. It may be seen only with spontaneously evoked activities (endo-evoked akinesia) or only in response to stimuli (exo-evoked akinesia) or may be mixed. When akinesia is mixed, involves a limb, and is not spatially or directionally specific, it may be difficult to dissociate from a motor defect caused by corticospinal tract damage, and one may have to rely on imaging studies or caloric stimulation.

When examining a patient for akinesia, one must make multiple observations, including watching spontaneous activity to see if the patient moves their eyes, head, and limbs in all directions. After an acute insult to the right hemisphere, it is not unusual for the head and eyes to be deviated to the right and not to move toward the left either spontaneously or in response to stimuli and instructions. However, even in the absence of this florid manifestation, contralesional directional akinesia may be detected using a modification of the crossed response task (Watson et al., 1978). The examiner holds one hand in the patient's right visual half-field and the other in the left visual half-field. In the first series of trials, the index finger of the examiner's right or left hand is moved and the patient is instructed to look at the moving finger. A patient who fails to look at the contralesional stimulus may have hemianopsia, visual inattention, or directional akinesia. These can be dissociated by instructing the patient to look to the side opposite that stimulated, so that when the examiner's right index finger is moved, the patient looks toward the left hand and vice versa. Failure to look at the contralesional hand indicates directional akinesia, and failure to look at the ipsilesional finger suggests inattention or hemianopsia (Butter et al., 1998b). In less severe cases of directional akinesia, patients may move in a contralesional direction by making multiple hypometric saccades (Heilman et al., 1980).

A condition similar to eye deviation may be detected in the arm by asking blindfolded patients with neglect to point to their midsagittal plane (Heilman et al., 1983a). Patients may point toward the ipsilateral hemispace. To detect directional akinesia of the limbs, a blindfolded patient may be placed before a table that has pennies randomly distributed over the top and be asked to pick up all the pennies. Patients with directional akinesia may fail to explore left hemispace. Patients may also have a directional hypokinesia of the limbs, so that movements toward the left are initiated more slowly than movements toward the right (Heilman et al., 1985). Patients may demonstrate hemispatial akinesia of the limbs such that when the limb is in contralateral hemispace it does not move or it moves less than when it is in ipsilateral hemispace (Meador et al., 1986).

Testing for anosognosia

Explicit verbal denial or unawareness of illness is termed anosognosia. Patients with neglect often deny a left hemiplegia, and they may also be unaware of a left hemianopsia. Verbally acknowledging a problem but failing to be concerned is called anosodiaphoria. Anosognosia and anosodiaphoria are best tested by asking patients why they came to the hospital. If they fail to describe their problems,

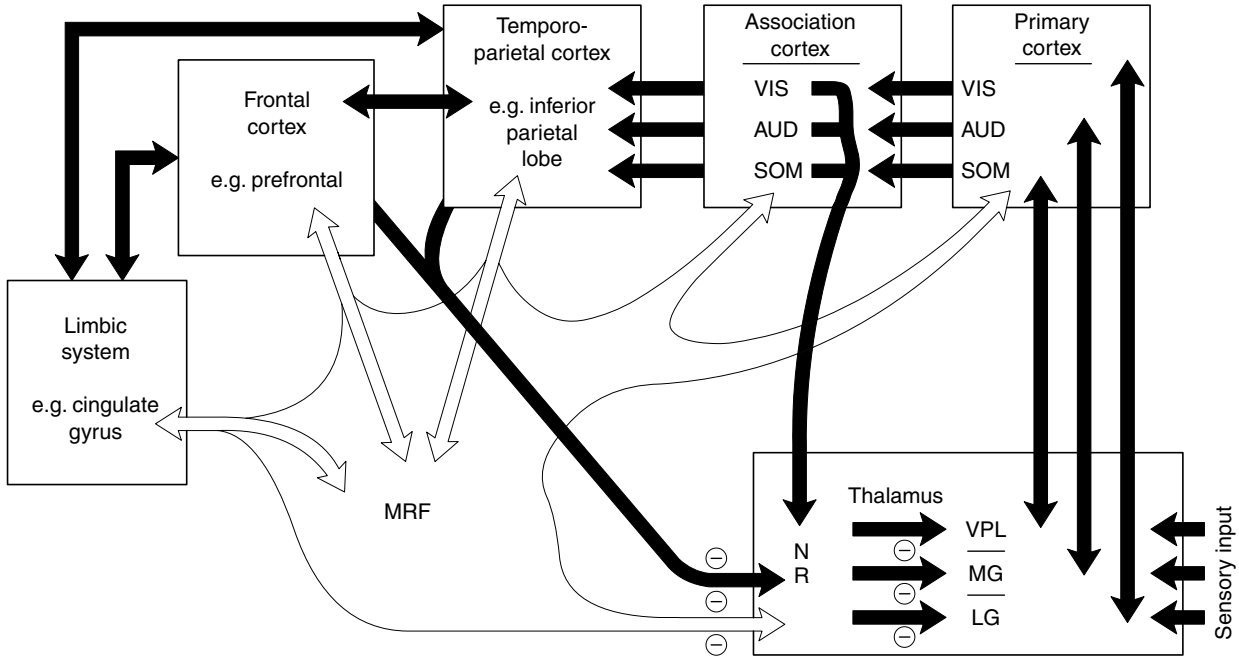

Fig. 23.1. Schematic representation of systems important in attention and arousal (see text for details). NR = nucleus reticularis thalami; MRF = mesencephalic reticular formation; VPL = ventralis posterolateris; MG = medial geniculate; LG = lateral geniculate; VIS = visual; AUD = auditory; SOM = somatosensory.

more specific questions may be asked. If patients have hemispatial inattention, the hemiparetic limbs should be brought into ipsilesional hemispace and the patients should be asked to move the limb and then asked again if they are impaired.

Testing for allesthesia and allokinesia

When stimulated on the side contralateral to a lesion, patients with allesthesia misplace the location of the stimulus to the normal side. Patients with allokinesia respond with the wrong limb or move in the wrong direction. Allesthesia and allokinesia should be distinguished from right–left confusion. Patients with right–left confusion do not make systematic directional errors, whereas patients with allesthesia misattribute left side stimuli to the right, but not vice versa.

Pathophysiology of the components of neglect

Pathophysiology of inattention

Unilateral inattention can be induced in humans by lesions in a variety of loci. Contralateral inattention may be induced by lesions in the temporal–parietal–occipital junction or inferior parietal lobe (Critchley, 1966; Heilman et al., 1983b). In humans, inferior parietal lobe lesions are probably most commonly associated with inattention, but lesions of the dorsolateral frontal lobe may also be associated with inattention (Damasio et al., 1980; Heilman & Valenstein, 1972). In humans and monkeys, lesions in the cingulate gyrus (Heilman & Valenstein, 1972; Watson et al., 1973) and subcortical lesions in such areas as the thalamus and mesencephalic reticular formation (Watson & Heilman, 1979; Watson et al., 1974) may also induce inattention.

Cerebral infarction is the most common cause of cortical lesions associated with neglect. Intracerebral hemorrhage is the cause of most subcortical lesions associated with inattention; however, other disease processes, including tumours, may induce inattention.

Inattention is probably caused by dysfunction in a cortical–limbic–reticular formation network (Heilman & Valenstein, 1972; Watson et al., 1974, 1981) (Fig. 23.1). A discussion of possible mechanisms requires some consideration of the phenomena of arousal, a physiologic state that prepares the organism for sensory and motor processing.

Stimulation of the mesencephalic reticular formation is associated with arousal and also with desynchronization of

the electroencephalogram, a physiologic measure of arousal (Moruzzi & Magoun, 1949). Unilateral stimulation induces greater desynchronization of the electroencephalogram in the ipsilateral than in the contralateral hemisphere (Moruzzi & Magoun, 1949). Bilateral mesencephalic reticular formation lesions result in coma. Unilateral lesions result in contralateral inattention, which is probably due to unilateral hemispheric hypoarousal (Reeves & Hagamen, 1971; Watson et al., 1974). The mesencephalic reticular activating system probably projects to the cortex in a diffuse polysynaptic fashion (Schiebel & Schiebel, 1967). This projection may occur through the thalamus (Steriade & Glenn, 1982) or basal forebrain.

There is another way in which the mesencephalic reticular activating system can affect cortical processing of sensory stimuli. Sensory information that reaches the cortex is relayed through specific thalamic nuclei. The nucleus reticularis thalami, a thin reticular nucleus enveloping the thalamus, projects to the thalamic relay nuclei and appears to inhibit thalamic relay to the cortex (Schiebel & Schiebel, 1966). The mesencephalic reticular formation projects to the nucleus reticularis. Rapid stimulation of the mesencephalic reticular formation (or behavioural arousal) inhibits the nucleus reticularis and is thereby associated with enhanced thalamic sensory transmission to the cerebral cortex (Singer, 1977). Unilateral lesions of the mesencephalic reticular formation may induce neglect because in the absence of mesencephalic reticular formation-mediated arousal, the cortex is not prepared for processing sensory stimuli and the thalamic sensory relay nuclei are being inhibited by the nucleus reticularis thalami.

Modality-specific association areas may detect stimulus novelty (Sokolov, 1963). When a stimulus is neither novel nor significant, corticofugal projections to the nucleus reticularis thalami may allow habituation to occur by selectively influencing thalamic relay. When a stimulus is novel or significant, the corticofugal projections may inhibit the nucleus reticularis thalami and allow the thalamus to relay additional sensory input.

Unimodal association areas converge on polymodal association areas (see Fig. 23.1) in the prefrontal cortex and in the posterior superior portion of the temporal lobe and inferior parietal lobe (Pandya & Kuypers, 1969). Polymodal convergence areas may subserve cross-modal associations and polymodal sensory synthesis. Polymodal sensory synthesis may also be important in the detection of stimulus novelty (modelling) and significance. In contrast to the unimodal association cortex that projects to specific parts of the nucleus reticularis thalami and thereby gates sensory input in one modality, these multimodal convergence areas may have a more general inhibitory action on the nucleus reticularis thalami and provide further arousal after cortical analysis. These convergence areas also may project directly to the mesencephalic reticular formation, which may either induce a general state of arousal because of diffuse multisynaptic connections to the cortex or increase thalamic transmission through connections with the nucleus reticularis thalami, or both. Evidence that polymodal areas of the cortex, such as the prefrontal and inferior parietal lobe, are important in arousal comes from neurophysiological studies showing that stimulation of these cortical sites induces a generalized arousal response (Segundo et al., 1955). When similar sites are ablated, there is electroencephalographic evidence of ipsilateral hypoarousal (Watson et al., 1977).

Although the sensory association cortex may mediate determination of stimulus novelty, stimulus significance is determined in part by the needs of the organism (motivational state). Limbic system input into the brain regions important for determining stimulus significance may provide information about biologic needs. The frontal lobes may provide input about needs related to goals that are neither dependent directly on the stimulus nor motivated by an immediate biologic need, because the frontal lobes have a critical role in goal-mediated behaviour and in developing sets.

The inferior parietal lobe has prominent limbic (cingulate) and frontal connections (Baleydier & Mauguiere, 1980; Pandya & Kuypers, 1969; Vogt et al., 1979) that may provide an anatomic substrate through which motivational states (for example, biologic needs, sets, and long-term goals) may influence stimulus processing (Heilman, 1979; Heilman & Valenstein, 1972; Watson et al., 1981).

Investigators have been able to study the physiologic function of specific areas of the nervous system by recording from single neurons in awake animals. In this experimental situation, the firing characteristics of individual neurons can be measured in relation to specific sensory stimulation or motor behaviour. Investigators have thus defined the properties of neurons in the inferior parietal lobule (area 7) of the monkey (Lynch, 1980; Mountcastle et al., 1975). Unlike the activity of single cells in primary sensory cortex, the activity of many neurons in the inferior parietal lobule correlates best with stimuli or responses of importance to the animal, and similar stimuli or responses that are unimportant are associated with either no change or a lesser change in neuronal activity. These cells appear to be critical in directing attention.

The attentional model we have discussed is summarized in Fig. 23.1. Unilateral inattention follows lesions of the unilateral mesencephalic reticular activation system

because loss of inhibition of the ipsilateral nucleus reticularis by the mesencephalic reticular activating system decreases thalamic transmission of sensory input to the cortex or because the mesencephalic reticular formation does not prepare the cortex for sensory processing, or both. Unilateral lesions of the primary or association cortices cause contralateral unimodal sensory loss or inability to synthesize contralateral unimodal sensory input. Corticothalamic collaterals from the association cortex to the nucleus reticularis may serve unimodal habituation and attention. Unilateral lesions of multimodal sensory convergence areas that project into mesencephalic reticular activating system and nucleus reticularis induce contralateral inattention because the subject cannot be aroused to, or process, multimodal contralateral stimuli. A lesion of the inferior parietal lobule, because of its reciprocal connections with polymodal areas and the limbic system, may impair the subject's ability to determine the significance of a stimulus.

Pathophysiology of extinction

Although patients may initially have hemi-inattention, most improve. Whereas at first they fail to detect stimuli presented to the side opposite the lesion, they eventually become able to report these stimuli. When given bilateral simultaneous stimulation, however, they often fail to report the stimulus presented to the side contralateral to the lesion (Anton, 1899; Bender, 1952; Loeb, 1885; Poppelreuter, 1917).

Extinction can be seen in normal subjects as well as in patients with central nervous system lesions (Benton & Levin, 1972; Kimura, 1967). The lesions causing extinction are often in the same areas as lesions that cause inattention. However, certain forms of extinction may also occur after lesions of the corpus callosum (Milner et al., 1968; Sparks & Geschwind, 1968), and left-sided extinction has even been reported after left hemisphere lesions (Schwartz et al., 1979).

The mechanisms underlying extinction in normal subjects and in patients with callosal lesions, sensory defects, or hemispheric lesions may differ and, in general, are poorly understood. Several investigators have suggested that extinction and perhaps obscuration in normal subjects and patients with sensory loss result from suppression or reciprocal inhibition. In the case of cerebral damage, the normal hemisphere inhibits the damaged hemisphere more than the damaged hemisphere inhibits the normal hemisphere. Consequently, stimuli contralateral to the damaged hemisphere are not perceived when the normal side is stimulated. The physiologic mechanisms that induce this reciprocal inhibition are unknown. However, as discussed earlier, the thalamic reticular nucleus can selectively inhibit various thalamic sensory nuclei. Each association cortex may not only project to the ipsilateral thalamic reticular nucleus but also influence the contralateral thalamic reticular nucleus. Unlike the ipsilateral connections, which are inhibitory, the contralateral projections may be facilitatory. Therefore, even under normal conditions, a stimulus on one side should induce an increase of threshold for stimuli on the other side. With a lesion of association cortex there should be less ipsilateral inhibition of nucleus reticularis thalami, which in turn should inhibit the thalamic sensory nuclei, thus making the thalamus less sensitive to contralateral stimuli. If the opposite side were simultaneously stimulated, activated attentional cells should further increase contralateral nucleus reticularis thalami activity, further inhibiting the thalamic sensory nuclei and thereby inducing extinction. The pathway by which one association cortex may influence the contralateral nucleus reticularis thalami is unknown.

Birch et al. (1967) proposed and provided support for the hypothesis that the damaged hemisphere processes information more slowly than does the intact hemisphere. Because of this inertia, the damaged side is more subject to interference from the normal side. When stimuli must be processed by a lateralized system, callosal lesions may induce extinction because the information cannot reach the processor or is delayed.

Another explanation for extinction, the limited attention theory, proposes that under normal circumstances bilateral simultaneous stimuli are processed simultaneously, each hemisphere processing the contralateral stimulus. However, a damaged hemisphere may be unable to attend to contralateral stimuli, making the organism inattentive to those stimuli. As the organism recovers, it can attend to contralateral stimuli. This improvement may be mediated by the normal (ipsilateral) hemisphere. The normal hemisphere, however, may have a limited attentional capacity. Therefore, with bilateral simultaneous stimulation the normal hemisphere's attentional mechanism, occupied with the contralateral stimulus, may be unable to attend to the ipsilateral stimulus (Heilman, 1979).

These theories may not be mutually exclusive. Because extinction can be caused by lesions in a variety of anatomically and functionally different areas, the reciprocal inhibition, limited attention, and interference theories may each be correct, but for different lesions.

Pathophysiology of akinesia and motor neglect

Attention and intention (preparation to make a movement) are closely linked, and lesions in many of the areas

that induce inattention and extinction may also induce akinesia. For example, unilateral sensory neglect (inattention) has been reported to follow unilateral dorsolateral frontal lesions in monkeys (Bianchi, 1895; Kennard & Ectors, 1938; Welch & Stuteville, 1958) and humans (Heilman & Valenstein, 1972). In most testing paradigms the animal is required to respond to a stimulus contralateral to the lesion either by orienting to the stimulus or by moving the limbs on the side of the stimulus. These animals with frontal lobe lesions were not weak, so it was assumed that they had sensory neglect when they failed to make the appropriate response. Although this neglect was usually assumed to result from inattention to the sensory stimuli, we suggested that it could equally well be caused by unilateral akinesia (Watson et al., 1978). Therefore, we trained monkeys to use the left hand to respond to a tactile stimulus on the right leg and the right hand to respond to a tactile stimulus on the left. After a unilateral frontal arcuate lesion, the monkeys appeared to have contralateral neglect, but when stimulated on their neglected side, they responded normally with the limb on the side of the lesion. When stimulated on the side ipsilateral to the lesion, however, they often failed to respond (with the limb on the neglected side) or responded by moving the limb ipsilateral to the lesion. These results cannot be explained by sensory or perceptual hypotheses and are thought to reflect a defect in intention to make a correct response.

In considering the possible role of the dorsolateral frontal lobes in attention and intention related to multimodal sensory and limbic inputs, it is important to examine their connections. The dorsolateral frontal lobe has reciprocal connections with unimodal and polymodal posterior sensory association cortex (Chavis & Pandya, 1976) and is an area of sensory convergence (Bignall & Imbert, 1969). The dorsolateral frontal lobe has reciprocal connections with medial (non-specific) thalamic nuclei. Projections to the mesencephalic reticular formation (Kuypers & Lawrence, 1967) and non-reciprocal projections to caudate also exist. Also, the dorsolateral frontal lobe receives input from the limbic system, primarily from the anterior cingulate gyrus (Baleydier & Mauguiere, 1980).

Its connections with neocortical sensory association and sensory convergence areas may provide the frontal lobe with information about external stimuli that may call the organism to action. The limbic connections (anterior cingulate gyrus) may provide the frontal lobe with motivational information. Connections with the mesencephalic reticular formation may be important in arousal.

Because the dorsolateral frontal lobe has sensory association cortex, limbic and reticular formation connections, it seems to be ideal for mediating a response to a stimulus to which the subject is attending. Physiologic studies support this hypothesis (Goldberg & Bushnell, 1981).

Motor neglect or akinesia may also accompany lesions of the non-specific intralaminar thalamic nuclei (Watson et al., 1978), which project to both the frontal lobe and the neostriatum. Akinesia may result from basal ganglia and ventral thalamic lesions (ventralis lateralis and ventralis anterior) (Velasco & Velasco, 1979). The basal ganglia project to the ventral thalamus, and this motor portion of the thalamus is also gated by nucleus reticularis thalami. The nucleus reticularis thalami may be inhibited by the mesencephalic reticular formation during an arousal or orienting response and be inhibited by the frontal lobes during a motor set.

Akinetic mute states are often induced by bilateral lesions of the frontal lobes, cingulate gyri, and medial thalamus. These lesions are usually caused by vascular disease (Segarra & Angelo, 1970). A cingulate gyrus lesion may be induced by an infarct in the distribution of the anterior cerebral artery, secondary to thrombosis, embolism, or aneurysm-induced spasm. Akinetic mutism of thalamic origin is most often the result of occlusion of the posterior thalamic–subthalamic paramedian arteries (Segarra & Angelo, 1970).

Degenerative diseases that affect the basal ganglia, limbic system and frontal lobes may also induce akinesia. These include Parkinson's disease, progressive supranuclear palsy, striatonigral degeneration, olivopontocerebellar degeneration and related diseases. Late in the course of several degenerative dementias, including Pick's disease and Alzheimer's disease, akinesia may be a prominent sign.

Lesions that disrupt the connections of the frontal lobes, limbic system, basal ganglia and thalamus may also be associated with akinesia. Hydrocephalus, tumours (such as butterfly gliomas), lacunae and Binswanger's disease are common causes of such lesions.

Pathophysiology of spatial neglect

Lesions associated with contralesional hemispatial neglect are similar to those associated with inattention and extinction. Although hemianopsia may enhance the symptoms of hemispatial neglect, hemianopsia alone cannot account for the deficit because some patients with hemispatial neglect do not have hemianopsia (McFie et al., 1950) and some patients with hemianopsia do not have spatial neglect.

The abnormal performance of patients in contralesional hemispace suggests that brain mechanisms related to the opposite hemispace have been disturbed. It also suggests that each hemisphere is responsible not only for receiving stimuli from the contralateral visual field and for controlling

the contralateral limbs but also for attention and intention in and toward contralateral hemispace, independent of which visual field the stimulus enters or which hand is used (Bowers & Heilman, 1980; Heilman, 1979). The postulate that each hemisphere attends to and intends in and toward contralateral hemispace has been supported by studies of normal subjects (Bowers et al., 1981).

Hemispace can be defined according to the visual half-field (eye position), head position, or trunk position. With the eyes and head facing directly ahead, the hemispaces defined by the eyes, head, and body are congruent. But if the eyes are directed to the far right, for example, the left visual field falls in the right hemispace, as defined by the head and body midline. Similarly, if the head and eyes are turned far to the right, the left head and eye hemispaces can both be in the right hemispace of the body. There is evidence that head and body hemispaces are important in determining the symptoms of hemispatial neglect (Bowers & Heilman, 1980; Heilman & Valenstein, 1979). For example, when patients with left hemispatial neglect are asked to bisect a line, their performance is poorer in left body hemispace than in right hemispace even when a strategy is used to ensure that the line is seen in the normal right hemifield (Heilman & Valenstein, 1979). Similarly, independent of visual field and body hemispace, lines are more poorly bisected in left head hemispace than in right head hemispace (Coslett et al., 1985).

Several neuropsychological mechanisms could account for the hemispatial defect associated with neglect. Patients with hemispatial neglect may have a hemispatial sensory-attentional deficit. Although the line is seen in the normal visual field, it is not attended and thus is not fully processed; the percept is therefore not consolidated and the stimulus does not affect the patient's behaviour. Alternatively, the percept can be weakened and appear of less magnitude. The attentional defect may also be associated with a hemispatial memory defect (Heilman et al., 1974).

Patients with neglect may have an attentional bias such that their attention is drawn to the side of space ipsilateral to their lesion (Kinsbourne, 1970) and they are unable to draw their attention away from the ipsilateral part of space. Partial support for the attentional bias hypothesis comes from the observation that, in a cancellation task, erasing lines is associated with better performance than cancelling lines. When lines are erased, they no longer draw attention (Mark et al., 1988).

Hemispatial neglect may be associated with a directional and hemispatial akinesia of the eyes and the arm. The former together with inattention would prevent patients from fully exploring the left side of space, and the latter would prevent patients with neglect from acting with their arms in the left side of space. As previously discussed, patients with neglect may have a directional akinesia of their eyes that is independent of their inattention (Butter et al., 1988b). In regard to the arm, Coslett et al. (1990) prevented patients from looking directly at their hand when performing a line bisection task; instead, a video camera projected the hand and the line to a video monitor. Using this technique, the hemispace where the action took place could be dissociated from the hemispace where visual feedback took place. Some patients did better when the monitor was in ipsilateral hemispace than in contralateral hemispace. Others were not affected by the position of the monitors but did better when the action took place in ipsilateral hemispace than they did when the action took place in contralateral hemispace. Coslett et al. (1990) suggested that patients with intentional neglect had more involvement of the frontal lobes than those with attentional spatial neglect who had involvement of the parietal lobes.

That spatial neglect can be associated with a motor-intentional bias or a sensory attentional bias is also supported by the work of Bisiach et al. (1990). They used a loop of string stretched around two pulleys. An arrow was attached to the top segment of string. Subjects with neglect and control subjects were asked to place the arrow midway between the two pulleys. In the congruent condition, the subject held the arrow on the upper string and in the non-congruent condition, the subject moved the arrow by lateral displacement of the lower string, which moved the arrow in the opposite direction. If neglect was caused by a directional hypokinesia, the error in the congruent and noncongruent conditions should be in opposite directions but if it was caused by an attentional bias it will remain in the same direction. Six of 13 subjects showed a significant reduction of neglect in the noncongruent condition, suggesting that they had a significant motor-intentional bias and these patients had predominately frontal lesions. The other subject showed an attentional bias. Na and coworkers (1998b) also attempted to dissociate attentional and intentional aspects of neglect by having subjects view their performance of a line bisection task on a video monitor on which the task was displayed either normally (direct condition) or right-left reversed (indirect condition). Subjects could not view the work space directly, but only on the monitor. This technique allows the investigator to investigate the relative contribution of attentional and intentional biases in the same subject. Using this apparatus Na et al. (1998a, b) found that most patients with spatial neglect have both intentional and attentional biases, but in patients with frontal lesions the intentional bias dominated, whereas in patients with temporal–parietal lesions

the attentional bias predominated. The finding of mixed attentional and intentional bias is consistent with the idea that the networks subserving attention and intention influence one another. Anatomically, the parietal and frontal lobes are involved in both networks.

Pathophysiology of ipsilateral neglect

Butter et al. (1988a, b), studied the eye movements of a patient with left-sided neglect from a right dorsolateral frontal lesion by asking the patient to move his eyes in the direction opposite a lateralized stimulus. When presented with a left-sided stimulus, instead of looking rightward the patient first looked leftward. This has been termed a visual grasp. The patient with ipsilateral neglect reported by Kwon and Heilman (1991) also had a visual grasp from a frontal lesion. Kim et al. (1999) studied a series of patients with ipsilateral neglect and demonstrated that most had frontal lesions. Patients with frontal lesions have manual grasp, sucking, and rooting reflexes. They also may have mitgehen and facilitory paratonia, all approach behaviours. Denny-Brown and Chambers (1958) proposed that the parietal lobes mediate approach behaviours and the frontal lobes mediate avoidance behaviours. Therefore, injury to the frontal lobes disinhibits the parietal lobes and induces aberrant approach. Kwon and Heilman suggested that the left-sided visual grasp and ipsilateral neglect may both be manifestations of inappropriate approach behaviours. Robertson et al. (1994) replicated Kwon and Heilman's observations, but suggested that ipsilateral neglect was related to a learned compensatory strategy. Some of the patients with ipsilateral neglect, however, reported by Kim et al. (1999), demonstrated this phenomenon almost immediately after their stroke suggesting that ipsilateral neglect could not be attributed entirely to a compensatory strategy. Na et al. (1998a) also demonstrated that ipsilateral neglect, like contralateral neglect, can be induced by both a contralesional attentional bias and a contralesional intentional bias.

Pathophysiology of representational defects

Denny-Brown and Banker (1954) described a patient who could not describe from memory the details of the side of a room opposite her cerebral lesion. Bisiach and Luzzatti (1978) asked two patients with right hemisphere damage to describe from memory a familiar scene in Milan from two different perspectives, one facing the cathedral and the other facing away. In both orientations, left-sided details were omitted. On the basis of these findings, the investigators postulated that the mental representation of the environment is structured topographically and is mapped across the brain so that it is split between the two hemispheres (like the projection of a real scene). With hemispheric damage there is a representational disorder for the contralateral half of this image. Brain (1941) proposed that the parietal lobes contain personal (body) and spatial schemata (representations). The two patients of Bisiach and Luzzatti (1978) and the one described by Meador and colleagues (1987) with hemispatial representational disorder all had right temporo-parietal damage.

There are at least three explanations for the failure of Bisiach and Luzzatti's patients to envision one half of the mental image: (i) the representation may have been destroyed, as suggested by Bisiach and Luzzatti; (ii) the representation may have been intact but could not be activated, so an image could not be formed; and (iii) the image was formed, but it could not be fully explored or attended to (e.g. hemispatial inattention to an internal representation). If a representation is destroyed, attentional manipulation should not affect retrieval, but if patients with neglect have an activational or attentional deficit, attentional manipulation may affect retrieval. Meador et al. (1986) not only replicated Bisiach and Luzzatti's observations but also provided evidence that behavioural manipulations could affect performance. When normal subjects are asked to recall an object in space, they move their eyes to the position the object occupied in space (Kahneman, 1973). Moving one's eyes to a specific spatial location may aid recall. Having patients move their eyes toward neglected hemispace may aid recall because the eye movement induces hemispheric activation or helps direct attention. Meador et al. (1986) asked a patient with left hemispatial neglect and defective left hemispatial recall to move his eyes to either right or left hemispace while recalling a scene. The patient's recall of details on the left side was better when he was looking towards the left than towards the right. This finding provides evidence that hemispatial representational deficit may be induced by an activation or an exploratory-attentional deficit.

Pathophysiology of denial of hemiplegia (anosognosia)

Denial or unawareness of hemiplegia is most often seen with right hemisphere lesions. The lesion usually includes both the frontal and parietal regions. There have been many explanations of this dramatic behavioural aberration. Weinstein and Kahn (1955) studied the premorbid personalities of patients with anosognosia and found that, before their strokes, they used denial mechanisms more frequently than did controls. However, Weinstein and Kahn's study cannot explain why denial of hemiplegia is

more frequently associated with right hemisphere dysfunction (Gilmore et al., 1992). Denial of hemiplegia is often associated with neglect, and perhaps patients do not recognize that they are hemiplegic because they have personal neglect. However, Bisiach et al. (1986) demonstrated that personal neglect was not always associated with denial of hemiplegia. The disconnection hypothesis has also been used to explain denial of hemiplegia, postulating that the damaged right hemisphere is disconnected from other areas of the brain, including speech–language areas (Geschwind, 1965). It is well established that the left hemisphere speech areas in the absence of input often confabulate a response (Gazzaniga, 1970). Neither the disconnection hypothesis nor the neglect hypothesis can explain why patients still deny hemiplegia when the paretic hand is brought into right hemispace or into the right visual field, where it gains direct access to the left hemisphere (Adair et al., 1995).

Many theories of anosognosia are related to defective feedback. Even though these feedback theories may help explain failure to recognize a hemianopsia, they cannot explain denial of hemiplegia when the arm is brought into a normal visual field and gains access to the normal hemisphere. We propose a 'feed-forward' or 'intentional' theory of denial of hemiplegia, in which the previously discussed intentional system may be responsible not only for activating the motor systems but also for feeding information about motor expectations to comparator systems. When a patient without anosognosia attempts to move a paretic limb, the comparator notes a mismatch between expectations and performance. However, when the intentional system is impaired (independently or along with the motor systems), not only is there inability to activate the motor neurons but also expectations are not fed to the comparator. When the patient fails to move there is no mismatch and, therefore, no awareness of a deficit. Perhaps this is why patients who have denial of left hemiplegia, when asked why they are not moving their arm, call it 'lazy' (Weinstein & Kahn, 1955). As discussed, intentional defects such as akinesia are more commonly associated with right then left hemisphere lesions. If denial of hemiplegia is related to intentional defects, it is not surprising that denial of hemiplegia is also more common with right hemisphere lesions.

Hemispheric asymmetries and the neglect syndrome

Many early investigators noted that inattention is more often associated with right than with left hemisphere lesions (Brain, 1941; Critchley, 1966; McFie et al., 1950). To account for hemispheric asymmetry of attention in humans, it has been postulated that temporo-parietal regions of the human brain have attentional or comparator neurons, but that the neuronal networks in the right hemisphere are more likely to have bilateral receptive fields than those in the left hemisphere. Thus, the networks in the left hemisphere would be activated predominantly by novel or significant stimuli on the right, but the networks in the right hemisphere would be activated by novel or significant stimuli on either or both sides (Heilman & Van Den Abell, 1980). If this were the case, right hemisphere lesions would cause inattention more often than left hemisphere lesions. When the left hemisphere is damaged, the right can attend to ipsilateral stimuli, but the left hemisphere cannot attend to ipsilateral stimuli after right-sided damage. Support for this hypothesis has been provided by electrophysiologic (Heilman & Van Den Abell, 1980) and imaging (Prohovnik et al., 1981; Rosen et al., 1981) studies. Extinction has also been shown to be more frequent with right than left hemisphere dysfunction (Meador et al., 1988) and may also be related to the hemispheric asymmetries in attentional capacity.

Some patients with right hemisphere lesions are also inattentive to right-sided stimuli (Albert, 1973). Although damage to attentional or comparator networks in the right hemisphere may induce an ipsilateral defect, the cortical lesions may also induce an arousal defect. Using a galvanic skin response and electroencephalographic power spectrum recording, it has been shown that right hemisphere lesions reduce arousal to stimuli presented to the hand ipsilateral to the lesion (Heilman et al., 1978) as well as to the opposite hand.

Patients with right hemisphere lesions also have contralateral limb akinesia more often than do patients with left hemisphere lesions (Coslett & Heilman, 1989). Hypokinesia, however, is not always limited to the contralateral extremities. Howe and Boller (1975) found that patients with right hemisphere lesions had slower reaction times than did patients with left hemisphere lesions. In their patients, the right hemisphere lesions associated with this slowing were not larger than those on the left. Although the right parietal lobe lesions appeared to induce the most profound slowing, these investigators did not mention whether the patients with ipsilateral slowing had unilateral neglect. In monkeys, no hemispheric asymmetries in production of the neglect syndrome have been noted. However, monkeys with lesions inducing neglect had slower ipsilateral reaction times than did monkeys with equal-sized lesions that did not induce neglect (Valenstein et al., 1987).

Lansing and colleagues (1959) have shown that warning stimuli may prepare an organism for action and thereby reduce reaction times. Pribram and McGuinness (1975) used the term activation to define the physiologic readiness to respond to environmental stimuli. Because patients with right hemisphere lesions have reduced behavioural evidence of activation (Howe & Boller, 1975), it has been postulated that in humans the right hemisphere dominates in mediating the activation process (Heilman & Van Den Abell, 1979). That is, the left hemisphere prepares the right extremities for action, and the right prepares both. Therefore, with left-sided lesions, left-sided limb akinesia is minimal, but with right-sided lesions there is severe left limb akinesia. In addition, because the right hemisphere is more involved than the left hemisphere in activating the right extremities, there is more ipsilateral hypokinesia with right hemisphere lesions, than with left hemisphere lesions.

That the right hemisphere dominates mediation of activation or intention (physiologic readiness to respond) has been demonstrated in normal subjects. They show more activation (measured behaviourally by the reaction time) with warning stimuli delivered to the right hemisphere than to the left hemisphere. That is, warning stimuli projected to the right hemisphere reduced reaction times of the right hand more than stimuli projected to the left hemisphere reduced left-hand reaction times; warning stimuli projected to the right hemisphere reduced reaction times of the right hand even more than did warning stimuli projected to the left hemisphere. These results support the hypothesis that the right hemisphere dominates activation or intention (Heilman & Van Den Abell, 1979).

Physical therapists and occupational therapists have noted that it is more difficult to rehabilitate patients with right hemisphere damage than those with left hemisphere damage. Right hemisphere-damaged patients have a greater mortality (related to pulmonary emboli and pneumonia) immediately after stroke. Both the difficulties in rehabilitation and the greater mortality after stroke may be related to the akinesia induced by right hemisphere lesions.

Lesions in the right hemisphere more often induce hemispatial neglect than do those in the left hemisphere. The neglect induced by right hemisphere lesions is also more severe (Albert, 1973; Costa et al., 1969; Gainotti et al., 1972). Verbal stimuli might activate the left hemisphere and thereby further enhance attentional–intentional hemispatial asymmetry (Heilman & Watson, 1978). However, when paradigms that do not use verbal stimuli or verbal instructions are tested, right hemisphere lesions induce more severe hemispatial neglect than do those on the left (Albert, 1973). The mechanism of this asymmetry may be similar to mechanisms already discussed. The left hemisphere may be able to attend and intend only in and toward the right hemispatial field. Therefore, with left hemisphere lesions the right hemisphere will attend and intend in and toward ipsilateral (right) hemispace. However, with right hemisphere lesions, the left hemisphere attends and intends in and toward the right hemispace and the left hemispace is neglected.

Recovery of function and treatment

Recovery

Hier et al. (1983) demonstrated that neglect spontaneously improves in many patients. The mechanism underlying recovery is not completely understood. One hypothesis is that the undamaged hemisphere is involved in recovery.

Crowne et al. (1981) showed that neglect resulting from frontal ablations was worse when the corpus callosum was simultaneously transected than when the callosum was intact, and Watson et al. (1984) demonstrated that monkeys that had a frontal arcuate gyrus ablation several months after a corpus callosum section had worse neglect than did animals with an intact callosum. Although callosal section worsened the severity of neglect, it did not influence the rate of recovery, suggesting that recovery is an intrahemispheric process.

Hughlings Jackson (Taylor, 1932) postulated that certain functions could be mediated at several levels of the nervous system. Lesions of higher areas (e.g. cortex) would release phylogenetically more primitive areas that might take over the function of the lesioned cortical areas. The superior colliculus receives not only optic but also somatesthetic projections (Sprague & Meikle, 1965). Sprague and Meikle thought that the colliculus is more than a reflex centre controlling eye movements: it is a sensory integrative centre. Tectoreticular fibres project to the mesencephalic reticular formation, and ipsilateral fibres are more abundant than contralateral fibres (Truex & Carpenter, 1964). Stimulation of the colliculus (like stimulation of the arcuate gyrus of the frontal lobe) induces an arousal response (Jefferson, 1958). Unilateral lesions of the superior colliculus induce a multimodal unilateral neglect syndrome, and combined cortical–collicular lesions induce a more profound disturbance, regardless of the order of removal (Sprague & Meikle, 1965). On the basis of these observations, we suspect that much of the recovery seen after cortical lesions may be mediated by the colliculus.

Subcortical lesions of ascending dopamine projections in rats induce permanent neglect (Marshall, 1982). The severity

and persistence of neglect induced by 6-hydroxydopamine injections into the ventral tegmental area of rats correlate with the amount of striatal dopamine depletion: those with more than 95% loss of striatal dopamine have a permanent deficit. The extent of recovery of these animals is also directly related to the quantity of neostriatal dopamine present when the animal is killed. Non-recovered rats show pronounced contralateral turning after injections of apomorphine, a dopamine receptor stimulant. Recovered rats given methyl-*p*-tyrosine, a catecholamine synthesis inhibitor, or spiroperidol, a dopamine receptor blocking agent, had their deficits reappear. These results suggest that restoration of dopaminergic activity in dopamine-depleted rats is sufficient to reinstate orientation (Marshall, 1979). Further investigation of these findings indicates that proliferation of dopamine receptors may contribute to pharmacologic supersensitivity and recovery of function (Neve et al., 1982). Implanting dopaminergic neurons from the ventral tegmental area of fetal rats adjacent to the striatum ipsilateral to the lesion induces recovery in rats with unilateral neglect resulting from a 6-hydroxydopamine lesion in the ascending dopamine tracts (Dunnett et al., 1981). This recovery is related to growth of dopamine-containing neurons into the partially denervated striatum.

Incorporation of ^{14}C-labelled 2-deoxy-D-glucose (2-DG) permits a measure of metabolic activity. In rats with 6-hydroxydopamine lesions of the ventral tegmental area that had shown no recovery from neglect, the uptake of labelled 2-DG into the neostriatum, nucleus accumbens septi, olfactory tubercle, and central amygdaloid nucleus was significantly less on the denervated side than on the normal side. Rats that recovered by 6 weeks showed equivalent 2-DG uptake in the neostriatum and central amygdaloid nucleus on the two sides. Recovery is therefore associated with normalization of neostriatal metabolic activity (Kozlowski & Marshall, 1981).

Similar results have been obtained for monkeys recovering from frontal arcuate gyrus-induced neglect (Deuel et al., 1979). Animals with neglect showed depression of ^{14}C-labelled 2-DG in ipsilateral subcortical structures, including the thalamus and basal ganglia. Recovery from neglect occurred concomitantly with reappearance of symmetric metabolic activity.

Treatment

Since neglect and related disorders are behavioural manifestations of underlying cerebral disease, evaluation and treatment of the underlying disease are of primary importance.

There are several behavioural and pharmacologic interventions that can be done to manage and treat some of the symptoms of the neglect syndrome. After he had a large right hemisphere stroke, President Wilson's wife would place him in a room so his left side was against the wall. This placement insured that he would be able to interact with visiting dignitaries. To optimize interactions, we also suggested that patients be positioned such that their 'good' side faces the area where interpersonal actions are most likely to take place. However, Kunkel et al. (1999) treated patients who had a hemiparesis and did not use their weak arm by binding their non-paretic arm and forcing them to use this hemiparetic arm. They found that this procedure induced recovery. It is possible that some of their patients' motor deficit was related to limb akinesia associated with motor neglect, rather than to weakness associated with corticospinal damage. In the last decade, studies have demonstrated that experience can change neuronal networks. It is possible, therefore, that stimulation of the contralesional side may induce functional reorganization and thereby reduce the severity of neglect. Some evidence for this postulate come from treating patients with hemispatial neglect by making them wear special glasses. Patients with neglect often fail to move their eyes to the contralesional (e.g. left) side and miss stimuli on that side because they fail to explore. Both lenses on these glasses are opaque on one side. The opaque half of the lens is ipsilateral to the hemispheric lesion. Thus for patients to see anything they must learn to move their eyes to contralesional hemispace (Arai et al., 1997). In contrast to these stimulation paradigms, studies of rats suggest that acute sensory depravation, such being kept in absolute darkness, may induce recovery from neglect (Corwin & Vargo, 1993). Unlike people, however, rats are nocturnal, and studies in humans have to be performed to help learn if stimulation is beneficial or harmful in the recovery from neglect.

Although we do not know if patients with neglect should be stimulated or sensorily deprived, we do know that we should not allow them to perform activities that may cause injuries to themselves or others. So long as a patient has the neglect syndrome, s/he should not be allowed to drive, or to work with anything that if neglected could cause injury to her himself or to others.

Many patients with neglect have anosognosia which makes rehabilitation difficult. For example, after a right hemisphere stroke Justice Douglas repeatedly checked himself out of hospitals being unaware that he was terribly disabled. In most patients, however, anosognosia is transient. In addition, because patients with neglect remain inattentive to their left side and in general are poorly motivated, training is laborious and in many cases unrewarding. Diller and Weinberg (1977) were able to train patients with neglect to look to their neglected side before they

acted; however, it was not clear that these top-down attentional–exploratory treatments generalized to other situations.

In contrast to this top-down treatment Butter et al. (1990) used a bottom-up attentional treatment. Structures such as the superior colliculus may play an important role in recovery from neglect. Dynamic stimuli readily summon attention in normal subjects and are potent activators of the visual colliculi. Butter et al. used dynamic stimuli and demonstrated that, when these stimuli were presented on the contralesional (left) side, the severity of neglect was reduced. Neglect patients with hemianopsia also improved, providing evidence that these dynamic stimuli influence the colliculi. Robertson and North (1993) demonstrated that having patients move their contralesional hand in contralesional hemispace can reduce the severity of hemispatial neglect and these investigators have used a hand movement strategy to manage neglect.

Asymmetrically activating the vestibular system in normal subjects may induce a spatial bias similar to that observed in neglect (Shuren et al., 1998). Rubens (1985) induced asymmetrical vestibular activation in patients with left-sided neglect by injecting cold water into the left ear and noting that unilateral spatial neglect abated. Valler et al. (1995) reported that vestibular stimulation could help sensory inattention, and Rode et al. (1992) found that vestibular stimulation even helped motor neglect. Inducing optokinetic nystagmus, by having patients look at series of stimuli moving in a contralesional direction (Pizzamigialo et al., 1990), and using vibration to stimulate muscle afferents from the neck (Karnath et al., 1995) also reduce neglect. Unfortunately, all these procedures produce only temporary relief, but it is unknown if repeated trials may confer a lasting benefit.

Coslett et al. (1990) demonstrated that patients with the attentional form of hemispatial neglect improved when visual feedback was presented to the ipsilesional side. Rossi et al. (1990) used 15-diopter Fresnel prisms to shift images from the neglected side toward the normal side. After using the prisms for four weeks, the treated group performed better than the control group in tasks such as line bisection or cancellation. However, activities of daily living did not improve. Rossetti et al. (1998) had subjects with neglect adapt to prisms by having them repeatedly point straight ahead while wearing the prisms. After this treatment, on tests of neglect, these treated patients showed a reduction of their ipsilesional bias. Although the effects of this treatment lasted for two hours after the prisms had been removed, it is uncertain how long this effect lasts. It is also unknown if this treatment generalizes to instrumental activities of daily living.

Neglect associated with cortical lesions may be reduced by destroying the ipsilateral colliculus or the intercollicular commisure (Sprague & Meikle, 1965). These findings suggest that the normal colliculus may inhibit the damaged colliculus. Because each colliculus gets greater input from the retina of the contralateral eye than it does from the ipsilateral eye, Posner and Rafal (1987) suggest that patching the ipsilesional eye may reduce neglect because it would deprive the superior colliculus ipsilateral to the intact hemisphere of retinal input and this reduced input may reduce collicular activation. Although some have found this ipsilesional patching procedure useful in reducing the signs of neglect (Butter & Kirsh, 1992) others have found that ipsilateral patching can make neglect more severe (Barrett et al., 1999). Therefore, when patching to treat neglect each eye should be tested before deciding which eye should be patched.

In regard to pharmacological treatment, we discussed the role of dopamine in neglect and recovery. Neglect in rats with unilateral frontal (Corwin et al., 1986) and parietal lesions (Burcham et al., 1997) were treated with apomorphine, a dopamine agonist. Dopamine agonist therapy significantly reduced neglect in these animals. Spiroperidol, a dopamine receptor blocking agent, blocked the therapeutic effect of apomorphine. Fleet et al. (1987) treated two neglect patients with bromocriptine, a dopamine agonist. Both showed dramatic improvements. Subsequently, other investigators have also shown that dopamine agonist therapy may be helpful in the treatment of neglect (Hurford et al., 1998; Geminiani et al., 1998). In addition Geminiani et al. found that dopaminergic agonist treatment helped both the sensory attentional and motor intentional forms of spatial neglect. In contrast, Barrett et al. (1999) and Grujic et al. (1998) found that in some patients dopamine agonist therapy increased rather than decreased the severity of neglect. Barrett et al.'s patient had striatal injury and it was suggested that the paradoxical effect seen in their patient may be related to involvement of the basal ganglia. In patients with striatal injury, dopamine agonists may be unable to activate the striatum on the injured side but instead activate the striatum on the uninjured side and thereby increase the ipsilesional orientation bias. Thus, if a patient has striatal injury, one should probably not use dopamine agonists. In addition, all patients should be repeatedly tested for neglect while these medications are being given. If there is an improvement over baseline, treatment should probably be periodically withdrawn so that one can be certain that the improvement was induced by treatment rather than spontaneous recovery.

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24

Brain death

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'Brain death' is the colloquial term for the determination of human death by showing the irreversible cessation of the clinical functions of the brain. It is an unfortunate term because it erroneously implies that there are two types of death: ordinary death and brain death. It also misleadingly implies that only the brain and not the human being is dead. In fact, the term properly refers to a method by which physicians may determine the unitary phenomenon of human death in the relatively rare situation in which ventilation (and hence circulation) are mechanically supported. Because the term 'brain death' is ingrained in common usage, it is essential that we understand and use it correctly. There is evidence that the term and concept of brain death are widely misunderstood by the public and by physicians (Youngner et al., 1989).

Several other terms have been used synonymously or in related contexts. The term 'cerebral death' should be abandoned because it adds nothing and promotes confusion. Some have used it to refer generally to brain death and others specifically to the higher brain formulation of death (discussed below) in which some scholars advocate the unaccepted idea that loss of functions of the cerebrum alone should be sufficient grounds for death. Translations of the term 'brain death' into other languages add to the confusion because it is *morte cerébrale* in French, *muerte cerebrale* in Spanish, and *morte cerebrale* in Italian.

Within the concept of brain death, scholars have argued about how much and what part of the brain must cease to function for a patient to be dead, and have coined the terms 'whole brain death', 'brainstem death', and 'neocortical death' discussed later (Bernat, 1992). These terms may be useful as theories of brain death but should not be used synonymously with the overall concept. The term 'irreversible coma', cited in the title of the Harvard Ad Hoc Committee Report (Ad Hoc Committee 1968), also adds confusion by suggesting that the brain dead patient is simply in a coma; it should be omitted in this context. The clearest statement a physician can make about a patient declared brain dead is 'the patient was declared dead using brain death tests'. This statement clarifies that death is a unitary phenomenon and brain death tests are merely one way to determine death.

History

The concept that the human being is dead when the brain is destroyed or irreversibly ceases functioning is not new but has become prominent in the past 50 years as the development of the mechanical ventilator has permitted such cases to be commonplace. In the ancient Hebrew tradition, the absence of *ruach* or breath was regarded as the primary sign of death, not the absence of heartbeat. Maimonides, the distinguished twelfth-century physician, philosopher, and rabbi, stated that the decapitated human was immediately dead and that the twitches of the limb muscles often present transiently following decapitation were not signs of life because they lacked central direction (Pernick, 1988). Throughout the eighteenth and nineteenth centuries, much fear was expressed over the incorrect medical diagnosis of death and premature burial. Several of the stories of Edgar Allen Poe are noteworthy in that regard.

In the late 1950s, French neurologists first described patients with what later would be called brain death. Several patients had suffered profound and diffuse brain injuries such that they had lost all clinical brain functions. The newly invented mechanical ventilator permitted their ventilation to be supported (which otherwise would have ceased) and hence their heartbeat and circulation could be maintained, at least temporarily. The neurological examination of these patients revealed a complete absence of all

clinical brain functions. Their coma was so profound that the neurologists coined the term *coma dépassé* to emphasize that they were in a state beyond coma (Mollaret & Goulon, 1959).

Throughout the next decade, several case reports of similar patients were published. In 1968, a committee of Harvard Medical School faculty published a seminal report that for the first time asserted that these patients were dead and provided tests to demonstrate it (Ad Hoc Committee 1968). They used the term 'brain death' which greatly influenced its subsequent popularity. They did not offer a rigorous philosophical defense of why such patients were dead but instead offered pragmatic reasons for the change, especially the growing need for organ donors and the futility of continued treatment (Giacomini, 1967).

Since 1980, the concept of brain death has been endorsed by American (President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioural Research, 1981), Canadian (Law Reform Commission of Canada, 1979), and British (Conference of Medical Royal Colleges and their Faculties in the United Kingdom, 1976) commissions charged with studying death, as well as numerous others from around the world. Brain death has become codified into law throughout the western and developed world. Medical societies from around the world have formulated and validated batteries of tests to determine brain death and all are remarkably similar (Quality Standards Subcommittee of the American Academy of Neurology, 1995; Canadian Neurocritical Care Group, 1999; Haupt & Rudolf, 1999). The public has accepted brain death as a standard of human death, and has widely supported the current program of multiorgan procurement for transplantation from brain dead donors.

The relatively little controversy that remains is centreed in universities where some scholars continue to argue that brain death is not truly human death but rather is a misunderstanding of the biology of death (Shewmon, 1998a, b), an inconsistent formulation of death (Halevy & Brody, 1993), a legal fiction to permit organ procurement (Taylor, 1997), or an anachronism to permit unilateral termination of life support (Truog, 1997). There is also opposition from some religious authorities who maintain that brain death is not compatible with their religious teachings (discussed below). However, at a recent meeting convened by the National Academy of Sciences Institute of Medicine to study the philosophical, medical, legal, and public policy issues of brain death, there was no support for changing current public laws permitting brain death determination based on the whole-brain criterion (Burt, 1999).

Biophilosophical basis

The concept of brain death became accepted by physicians and codified into law before it was conceptually grounded in rigorous philosophical analysis. Beginning in 1978 with the writings of Julius Korein (1978) and continuing with the papers of my colleagues, Bernard Gert and Charles Culver, and me (Bernat et al., 1981, 1982), brain death was provided a biophilosophical foundation as the most accurate biological representation of human death in our contemporary technological age. While it is beyond the scope of this chapter to provide the complete biophilosophical discussion, interested readers can consult my recently published comprehensive analysis (Bernat, 1998; Bernat, in press) that I briefly review here.

An analysis of death must begin by accepting certain preconditions and assumptions about death. First, death is primarily a biological concept so any definition of it must be compatible with biological reality. Secondly, a concept of death of the human should be consistent with death of other higher animal species. Thirdly, the concept of death should be applied to organisms and not components of organisms. Fourthly, all organisms must be either alive or dead; none can be in neither or in both states. Fifthly, death is an event, not a process, because the transition from alive to dead is necessarily instantaneous, but the timing of the event may not be able to be measured precisely and then only in retrospect. Finally, death is irreversible so no one can return from the dead.

The analysis of death must proceed in three sequential steps. First, one must conduct the philosophical task of defining death by making explicit our consensual concept of death. Secondly, one must conduct the medical and philosophical task of identifying a criterion of death to provide a general, measurable standard showing that the definition has been satisfied. Finally, physicians should construct and validate a set of tests to show that the criterion has been satisfied.

My colleagues and I believe that death is best defined as the irreversible cessation of the critical functions of the organism as a whole. Thus, death refers to the dissolution of the unity of the organism after which all that remains is a group of individual and independent subsystems that may continue functioning because of physiological support. The best criterion of death is the permanent cessation of the clinical functions of the brain because it is these functions that are responsible for the critical functioning of the organism as a whole. The clinical functions encompass those of the entire brain, thus this position has been dubbed 'whole brain death'. The tests for death are divided into two groups. In the most common situation in

which there is no mechanical ventilation provided or planned, the prolonged absence of respiration and circulation serves as a valid test of death because it quickly and inevitably produces destruction of the brain. In the rare situation of mechanically maintained ventilation (and hence preserved circulation) the batteries of brain death tests discussed below must be employed.

Some scholars reject outright the concept of brain death. Using philosophical analysis, Alan Shewmon holds that the brain does not provide sufficient integrating functions of the organism as a whole (Shewmon, 1999). Baruch Brody and Robert Truog believe that there is a mismatch between the definition and the criterion of death (Brody, 1999; Truog, 1997). Robert Taylor (1997) holds that brain death is a legal fiction and that the only true death is circulatory failure. Linda Emanuel (1995) holds that there can be no unitary criterion of death because death is an ineluctable process (Emanuel, 1995). I have addressed these criticisms elsewhere (Bernat, 1998).

Other scholars accept brain death on a conceptual basis but disagree on the criterion of death, that is, on precisely how much brain must be destroyed for death to occur. Robert Veatch (1993) advocates for the 'higher brain formulation' which requires only that the neocortex be destroyed ('neocortical death'), a concept that would declare dead patients in persistent vegetative states or with anencephaly (Veatch, 1993). Christopher Pallis holds the concept of 'brainstem death' in which the capacity for consciousness and respiration in the brain stem are the essentials of life (Pallis, 1997). Interestingly, there are only very minor differences in practice between this concept and the 'whole brain death' concept that prevails throughout the majority of the world outside the United Kingdom. I have analysed and critiqued these positions elsewhere (Bernat, 1992). Suffice it to say that despite over a quarter century of these scholars arguing to abandon or change 'whole brain death', its acceptance remains strong in the developed world and is becoming even more widespread in the developing world.

Pathophysiology

The primary pathologic events producing brain death in adults are traumatic brain injury, intracranial hemorrhage, cerebral infarction, brain tumours, and hypoxic–ischemic encephalopathy suffered during cardiopulmonary arrest. In cardiopulmonary arrest, there is evidence that ischemia is a more important cause of neuronal death than hypoxia (Simon, 1999; Miyamoto & Auer, 2000). In children, the most common primary pathologic events are traumatic brain injury, bacterial meningitis, asphyxia, and drowning (Staworn et al., 1994).

The widespread neuropathologic consequences of these primary illnesses and injuries are responsible for the global neuronal destruction that ensues. Following the direct cellular injury from the primary event, a series of widespread destructive changes are initiated including hypoxia, cerebral acidosis, endothelial swelling, intracranial hypertension, cessation of intracranial blood flow, and transtentorial herniation (Black, 1978). In most cases, as a result of diffuse cerebral edema, intracranial pressure rises until it exceeds mean arterial blood pressure. Intracranial pressure may transiently exceed even systolic blood pressure. In either event, intracranial hypertension produces a cessation of intracranial blood flow. This intracranial circulatory arrest produces global neuronal necrosis at sites distant to the primary pathology. The well-known syndromes of transtentorial herniation inevitably occur, permitting relatively easy clinical confirmation of the irreversibility of the global neuronal destruction by showing signs confirming the complete loss of brain stem clinical functions (Plum & Posner, 1980). Later, intracranial pressure falls and there is reperfusion of the necrotic tissue (Schroder, 1983).

Neuropathologic examination reveals widespread neuronal necrosis that is proportional to the time of continued perfusion following the event of brain death. It takes at least 12 hours for the first neuropathologic signs to be present (Black, 1978). In the early studies of Earl Walker and colleagues, the pathologic *sine qua non* was the 'respirator brain', a state of global liquifactive necrosis of all intracranial contents (Walker et al., 1975). The 'respirator brain' findings are the result of a completely infarcted brain in which liquefactive necrosis has been permitted to evolve by continued warm perfusion. If systemic circulation ceases earlier, these changes do not occur.

Clinical studies of patients admitted with diffuse brain injury who progressed to brain death have been reported in two series of patients admitted with Glascow Coma Scale scores of 3. The mean progression to brain death was 18 hours in one study (Matuschak, 1993) and 22 hours in another (Cabrer et al., 1992). Prior to brain death, the patients were markedly unstable with profound hypotension, spontaneous cardiac arrest, hypokalemia, temperature dysregulation, diabetes insipidus and coagulopathy (Matuschak, 1993).

The physiologic changes resulting from brain death in patients undergoing organ procurement have been summarized by Power and Van Heerden (1995). The two principal mechanisms are diffuse vascular regulation injury and diffuse metabolic cellular injury. The first phase of the

diffuse vascular regulation injury is a massive sympathetic outflow ('autonomic storm') resulting from the Cushing reflex. Organs can be damaged from direct neural stimulation or by catecholamine effect. In the secondary phase, there is a marked drop in sympathetic outflow producing inotropic and chronotropic cardiac effects leading to cardiac failure. In other organs, the loss of sympathetic tone produces generalized vasodilatation and impaired autoregulation (Power & Van Heerden, 1995). Some investigators believe that the sympathetic withdrawal is more important than the autonomic storm in the production of organ damage (Herijigers & Flaming, 1998).

Hemodynamic changes during incipient brain death include cardiac arrhythmia, hypertension, tachycardia, increased contractility and cardiac output, elevations in pulmonary and systemic vascular pressure, and elevation in pulmonary capillary 'wedge' pressure (Powner & Darby, 1999). After the event of brain death, hemodynamic changes include profound hypotension, vasodilatation and decreased cardiac contractility (Powner & Darby, 1999). Some hemodynamic responses may persist after brain death, including transient elevations in blood pressure and heart rate observed during organ procurement (Wetzel et al., 1985), but cold pressor tests usually detect no changes (Goldstein et al., 1993). In a recent series of brain dead organ donors treated to maintain hemodynamic stability, whereas 78% were hemodynamically stable on admission, only 30% remained stable by the time of procurement (Lagiewska et al., 1996).

Pituitary and hypothalamic function have been studied extensively in brain dead patients. Anterior pituitary releasing tests show severe hypothalamic failure whereas posterior pituitary secretion measurements suggest only partial hypothalamic failure of antidiuretic hormone secretion (Arita et al., 1993). It long has been observed that most brain dead patients develop diabetes insipidus, but some do not (Outwater & Rockoff, 1984; Fiser et al., 1987). These finding suggest that there may be a separate circulation for antidiuretic hormone secretion or that only a tiny residual function is sufficient to prevent diabetes insipidus.

Animal experimental models of brain death have been created to study its pathophysiology and its effects on other organs. Experimental models in the baboon and other species have been devised using an epidural balloon catheter that can be inflated to gradually or suddenly raise intracranial pressure (Novitsky et al., 1989; Shivalkar et al., 1993; Chen et al., 1996). The cardiac, pulmonary, renal and endocrine abnormalities have been summarized and analysed, and used as a basis to plan supportive therapy for brain dead organ donors prior to procurement to maximize success (Power & Van Heerden, 1995). For example, there is evidence that judicious administration of vasopressin and epinephrine (Yoshioka et al., 1986) and thyroid hormone (Randell & Hockerstedt, 1992) improves brain dead donor prolonged physiologic maintenance.

'Prolonged somatic survival'

In the early writings on brain death, it was asserted that, irrespective of treatment, no patients correctly declared brain dead could maintain heartbeat or circulation longer than two weeks because of refractory hypotension and cardiac failure (President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioural Research, 1981). Beginning in the early 1980s, reports began being published of cases of 'prolonged somatic survival': patients whose heartbeat and circulation were supported for months following a diagnosis of brain death as the result of aggressive medical treatment (Parisi et al., 1982). Many of the cases were reported as technologic *tours de force*, documenting the immense ICU effort made to physiologically maintain the patients using advanced ventilation techniques, vasopressors, hormones, temperature control, antibiotics, anticoagulants, and other advanced-technology intensive care therapies (Catanzarite et al., 1997).

Alan Shewmon recently reported a remarkable series of such cases he has termed 'chronic brain death' (Shewmon, 1998a, b). He described 56 cases of brain dead patients with circulatory persistence for greater than one week that were culled from his experience, that of colleagues, and a review of over 12 000 published articles describing cases or series of brain dead patients. Half the group retained circulatory function at 2 months following brain death declaration. He concluded that the medical instability of the brain dead patient is temporary and, if aggressively supported, some patients can enter a period of relative quiescence in which their circulation can be maintained for prolonged periods.

The Shewmon series is a mix of well-documented cases in which the patients clearly were brain dead and less well-documented cases in which the patients were presumed to be brain dead. Although all of them apparently received the clinical diagnosis of brain death, the documentation for many of them remains questionable or absent. Although Shewmon correctly points out that they are no less well documented than many other cases encountered in clinical neurology, there is a well-known but unfortunately great variation in the practice of brain death determination on adults and children (Earnest et al., 1986; Mejia & Pollack, 1995), and as a result, there are undoubtedly

false-positive diagnostic errors. The standard for making a serious claim such as Shewmon has made, that the presence of these cases invalidates the concept of brain death, requires documentation that the patients were clearly and convincingly brain dead. This standard is higher than that achieved in the presentation of many of his cases (Wijdicks & Bernat, 1999). In any event, the persistence of circulation in even those unequivocally documented cases remains a relatively rare occurrence.

Epidemiology

There are relatively little data on the incidence and prevalence of brain death. A large study from the United Kingdom found that approximately 10% of all patients dying in hospital ICUs were declared brain dead (Gore et al., 1992). A similar study in Spain found that 14% of patients dying in ICUs were brain dead (Navarro, 1996). In two reported large series of children in the United States, brain death accounted for 0.9% of pediatric ICU admissions (Staworn et al., 1994) and 37% of all pediatric ICU deaths (Mejia & Pollack, 1995).

Diagnosis

The determination of brain death has been a critical question since 1968 when the Harvard committee published the first battery of tests (Ad Hoc Committee, 1968). Throughout the next 15 years, several other medical centres and organizations proposed similar test batteries, which were reviewed in 1984 by Julius Korein (1984). The current definitive tests are those proposed by the President's Commission medical consultants in 1981 (Medical Consultants to the President's Commission, 1981) and by the American Academy of Neurology in 1995 (Quality Standards Subcommittee of the American Academy of Neurology, 1995), generated by the evidence-based review by Eelco Wijdicks (1995).

The diagnosis of brain death should be considered in the ventilated patient with profound, irreversible brain damage, apnea, unresponsiveness, and cranial nerve areflexia. A diagnosis of brain death requires that: (i) a structural lesion is present that can account for the clinical findings; (ii) no evidence of clinical brain functions can be found on repeated neurological examinations, by demonstrating utter unresponsiveness, apnea in the presence of hypercapnia and cranial nerve areflexia; and (iii) all potentially reversible metabolic and toxic factors have been excluded. If these conditions cannot be met, the diagnosis of brain death should be withheld until a confirmatory laboratory test can prove the irreversible absence of all clinical brain functions by showing an absence of intracranial circulation. The diagnosis should be made by an experienced physician, usually a neurologist, neurosurgeon, or intensivist. A diagnostic algorithm for the less experienced physician has been published (Kaufman & Lynn, 1986).

The first condition requires the presence of a structural lesion sufficient to account for the clinical findings. This condition usually is easy to fulfil in cases of massive head trauma, intracranial hemorrhage, stroke, and meningitis complicated by intracranial hypertension. Diffuse hypoxic–ischemic neuronal injury during cardiopulmonary arrest or asphyxia may be less obvious, and therefore, generally requires a longer period of observation.

Unresponsiveness

The coma of the brain dead patient is the deepest coma possible. Patients lie absolutely motionless when the ventilator is stopped. They make no response to any sensory stimuli including bright lights, loud noises, and noxious stimuli. They do not posture or make any other response to stimulation. Deep tendon reflexes usually are absent but may be retained. Because tendon reflexes are integrated at a spinal level, their presence or absence is not necessarily indicative of brain functioning.

A group of spontaneous movements rarely have been observed in brain dead patients. In the best-described movement, called the 'Lazarus' sign, the patient may slowly elevate both arms and adduct them across the chest (Ropper, 1984). Because this movement has been seen most often during apnea testing in the brain-destroyed patient with an intact spinal cord, it has been hypothesized to result from ischemia to cervical spinal cord motor neurons (Turmel et al., 1991). A series of other odd movements occasionally may be encountered, including automatic stepping (Hanna & Frank, 1995), decerebrate-like posturing (Marti-Fabregas et al., 2000), and finger jerks (Saposnik et al., 2000).

Apnea

Testing for apnea must be done while maximally stimulating the brainstem respiratory centres through hypercapnia while protecting against hypoxia. Although there are accepted standards for conducting apnea tests, they are often not followed in practice (Earnest et al., 1986; Mejia & Pollack, 1995). The impulse to breathe is generated in medullary respiratory centres stimulated by chemoreceptors sensitive to rises in pCO_2 (Bruce & Cherniak, 1987).

Intubated, brain-damaged patients in ICUs often are maintained with low pCO_2, however, so merely disconnecting them from the ventilator for a few minutes to see if they breathe is an inadequate test for apnea. To prove true apnea, the pCO_2 must be permitted to rise to a level high enough to maximally stimulate the medullary breathing centres. The optimal target pCO_2 is unknown, but most authorities state it is 60 torr (Schafer & Caronna, 1978; Ropper et al., 1981; Marks & Zisfein, 1990). In patients with chronic CO_2 retention from chronic obstructive lung disease, the target pCO_2 is higher (Prechter et al., 1990) and such patients often breathe primarily by their hypoxemic drive.

The technique of apneic oxygenation assures the preservation of the O_2 level while allowing the pCO_2 to climb to high levels (Ivanov & Nunn, 1969; Marks & Zisfein, 1990). The pCO_2 is permitted to normalize to the 40 torr range by adjusting the ventilator rate and volume. The inspired air is made 100% O_2 and the pO_2 is permitted to rise. In the absence of pulmonary edema or other pulmonary disorders blocking gas exchange, the PO_2 usually rises to the 350–400 torr range. At this point, the ventilator is stopped and 100% O_2 is permitted to passively exchange by introducing a catheter down the endotracheal tube and infusing the O_2 at 8 l/minute, or using blow-by. Because the pCO_2 climbs at a mean rate of 3–4 torr/minute of apnea, depending on the rate of CO_2 production (Schafer & Caronna, 1978; Ropper et al., 1981), the duration of apnea necessary to permit the pCO_2 to climb to 60 torr may be calculated. For true apnea to be present, there should be no respiratory effort, sighing, or hiccuping. The major complications of the apnea test are hypotension, acidosis, and hypoxemia, but usually it can be conducted safely (Belsh et al., 1986; Ebata et al., 1991; Jeret & Benjamin, 1994). An alternative apnea test shortening the duration of disconnection from the ventilator may be conducted by increasing the pCO_2 in the inspired air (Lang, 1995).

Cranial nerve areflexia

The brain dead patient must have unreactivity of all cranial nerve reflexes including those of the pupil to light, the cornea to touch, the vestibulo-ocular, gag, and cough reflexes. Pupils in brain dead patients usually are midposition and irregular in shape, reflecting simultaneous denervation of sympathetic and parasympathetic supply. They should be tested with a bright point light source. Pupillary reactivity may be absent from pre-existing disorders such as diabetes. Pupillary reflexes are usually unaffected by atropine given intravenously during resuscitation (Goetting & Conteras, 1991). Pupillary light reflexes similarly are unaffected by neuromuscular blockade in therapeutic dosages such as that given during general anesthesia (Gray et al., 1997).

The vestibulo-ocular reflex should be tested with the technique of maximal cold caloric stimulation. After inspecting the external auditory canals to exclude canal impaction with wax and punctured tympanic membrane, the canals are irrigated sequentially with 50 ml ice water with the head elevated 30 degrees and an assistant holding the eyelids open (Hicks & Torda, 1979). There should be neither reflex eye movement, grimace, limb movement, nor any response from the patient. Patients who have previously received large doses of vestibulotoxic drugs, such as aminoglycoside antibiotics, may have permanently lost vestibulo-ocular reflexes.

Corneal reflexes should be tested with a cotton-tipped applicator and should be completely absent. The gag and cough reflexes can be tested by observing the nurses cannulating the endotracheal tube with deep tracheal suctioning of the patient. There should be no coughing or 'bucking' movements of the chest.

Death declaration

The presence of unresponsiveness, apnea, and cranial nerve areflexia shows the absence of clinical brain functions. To prove that the absence is irreversible, a structural lesion accounting for the findings should be identifiable by CT scan, and potentially reversible metabolic and toxic factors must be excluded. In the case of asphyxia or hypoxic–ischemic encephalopathy from cardiopulmonary arrest, the test battery should be repeated after an interval of time and show the same results. The interval between tests varies as a function of the age of the patient and whether a laboratory confirmatory test has been done. In the latter circumstance, an interval of 4 hours is sufficient. As noted below, in children it is desirable to wait at least 24 hours between tests.

It is essential to exclude potentially reversible metabolic and toxic factors such as depressant drug toxicity, neuromuscular blockade, and severe hypothermia ($T<32.2$ °C). For example, barbiturate intoxication and profound hypothermia can mimic the clinical features of brain death yet be completely reversible. Neuromuscular blockade can produce nearly all the signs, except for the pupillary reflex absence. If there is a question of reversibility, it is best to treat the patient, allow time to elapse, and order toxicologic studies. Confirmatory tests are essential for a diagnosis of brain death in the presence of significant toxic and metabolic effects.

The patient ordinarily is declared dead upon completion of the second set of tests. This practice is consistent with

declaring death using cardiopulmonary tests. If the patient is an organ donor, following the second apnea test, the ventilator is reattached and the newly declared dead patient is taken to the organ procurement suite with respiratory support and intact circulation. If the patient is not an organ donor, the patient is not reattached to the ventilator following the second apnea test.

If the above tests are performed and interpreted correctly, there is no differential diagnosis; the patient is dead. Avoidance of the pitfalls noted above is critical to eliminate false-positive determinations (Posner, 1978).

Infants and children

The application of brain death tests to infants and children remains controversial, because of the greater tendency for young people to recover from illnesses and injuries. The Task Force for the determination of Brain Death in Children published guidelines in 1987 that have been generally though not universally accepted (Task Force for the Determination of Brain Death in Children, 1987). The guidelines prohibit brain death determination on premature infants or on infants under the age of one week. Infants between age one week and two months require two examinations separated by a 48-hour interval and a confirmatory test. Infants aged two to 12 months require two examinations separated by a 24-hour interval and a confirmatory test. Children over the age of 12 months are treated as adults. The experience of declaring brain death in children and infants reported from pediatric ICUs is similar to that in adults (Staworn et al., 1994; Parker et al., 1995). The specific considerations of neonatal brain death declaration have been reported (Kohrman, 1993; Ashwal, 1997).

Confirmatory tests

Brain death is a clinical diagnosis but the determination may be validated by several laboratory procedures called confirmatory tests. Confirmatory tests are useful in several situations. First, in some cases the clinical tests cannot be performed. Many patients with massive head trauma also have suffered facial trauma to the extent that it is impossible to assess pupillary reflexes, corneal reflexes and vestibulo-ocular reflexes. In many patients with severe pulmonary disease it is unsafe to perform an apnea test because of simultaneously producing severe hypoxemia. Secondly, the tests may be necessary to conform to regulations for the determination of brain death imposed by some authorities. This situation is true in some hospitals, several countries, and when declaring brain death on infants in the United States. Thirdly, the tests are useful in expediting organ donation by reducing the mandated interval between examinations. Finally, they may be useful in potentially medicolegal situations in which it may be desirable to have objective test data to supplement the physician's examination.

Laboratory tests to confirm brain death are of two types: those showing an absence of electrical activity from the brain, and those showing a cessation of intracranial blood flow. In general, the blood flow tests are more useful but the decision of which to order should be based upon their availability and on the experience and confidence of the clinician in their interpretation. Wijdicks has provided an evidence-based critique of the available studies as of 1995 (Wijdicks, 1995).

Electrical potentials

If electrical tests are chosen, it is desirable to choose both EEG and evoked potentials. The EEG assesses cerebral electrical activity and the brainstem auditory and somatosensory-evoked potentials assess brainstem electrical activity. While electrical activity also may be suppressed by metabolic and toxic disorders, the evoked potentials are less likely to be affected. Technical standards for the performance and interpretation of the EEG in brain death have been published by the American EEG Society (American Electroencephalographic Society, 1994). The EEG should show 'electrocerebral silence' with no recordable potentials greater than 2 μV at a gain of 2 μV/mm, using appropriate filters, and allowing at least a 30-minute recording. All experienced electroencephalographers are aware of the troublesome artefacts that occur at such a high gain (Hughes, 1978). The sensitivity of this study is limited. Grigg and colleagues found that 20% of brain dead patients continued to have rudimentary but measurable EEG activity for a week (Grigg et al., 1987). The specificity of EEG is also limited because electrocerebral silence has been reported in non-brain-dead patients after a variety of drug intoxications (Powner, 1976) and in the severest forms of persistent vegetative state (Brierley et al., 1971; Boutros & Henry, 1982).

Several studies have shown the absence of brainstem auditory-evoked potentials in brain death (Starr 1976; Goldie et al., 1981; Garcia-Larrea et al., 1987; Firsching, 1989; Machado et al., 1991; Hantson et al., 1997; Ruiz-Lopez et al., 1999). For example, Goldie and colleagues showed that all potentials except the cochlear microphonic potential (a peripheral potential) were absent in brain death. All potentials were easily recordable in patients in a persistent vegetative state (Goldie et al., 1981). The small series of published cases permits no clear esti-

mate of the positive and negative predictive value of these tests. Because they are not susceptible to metabolic and toxic suppression, they are useful in declaring brain death in patients with depressant drug intoxication (Hantson et al., 1997).

Short-latency somatosensory evoked responses in brain dead patients have been found to be absent beyond Erb's point in several studies (Anziska & Cracco, 1980; Goldie et al., 1981; Belsh & Chokroverty, 1987; Stohr et al., 1987; Chancellor et al., 1988; Wagner, 1996; Hantson et al., 1997; Ruiz-Lopez et al., 1999; Sonoo et al., 1999). For example, Wagner found that the median nerve-stimulated P14 evoked potential recorded at Fz-Pgz was absent in 100% of 108 brain dead patients but preserved in 100% of the 108 comatose but living patients. Chiappa has reviewed and critiqued the evoked potential studies up to 1997 (Chiappa, 1997).

Blood flow

The demonstration of cessation of intracranial blood flow is a sufficient confirmatory test for brain death because it proves there can be no surviving clinical functions of the brain. At some point in nearly all brain dead patients, intracranial pressure rises to exceed mean arterial blood pressure, at which time there can be no intracranial blood flow. Historically, contrast angiography was the first test used to demonstrate absent intracranial flow of the contrast medium as the internal carotid and vertebral arteries penetrate the dura (Bradac & Simon, 1974). Contrast angiography to confirm brain death is rarely performed in the United States now because it is cumbersome and other technologies can confirm brain death as accurately and more easily.

Intravenous radionuclide angiography is used widely for this purpose. Several studies have employed serum albumin-tagged technetium 99m injected intravenously with static and dynamic images of the brain recorded by a portable gamma camera. In brain death there is no observable intracranial blood flow, but blood is seen to flow into the face and scalp through the patent external carotid arterial system (Korein et al., 1977; Goodman et al., 1985; Flowers & Patel, 1997). There is an excellent correlation with conventional contrast angiography (Korein et al., 1977). One limitation is that slight flow through the posterior circulation may be difficult to detect.

More recently, single photon emission computed tomography (SPECT) scintigraphy using technetium-99m hexamethylpropyleneamineoxime (HMPAO) has been studied in several reports (Reid et al., 1989; Wilson et al., 1993; Yoshikai et al., 1997). The isotope is injected intravenously and a portable gamma camera records images. The images must be recorded immediately after the isotope is injected. The 'hollow skull' sign is seen in brain death revealing the absence of intracranial blood flow (Yoshikai et al., 1997).

Transcranial Doppler (TCD) ultrasound has been studied widely. Skull insonation and recording of the pulses of the intracranial arteries provides a highly specific recording of arterial blood flow in the brain. Several abnormal patterns have been described in brain death, depending upon the ratio of systemic blood pressure to intracranial pressure (Ropper et al., 1987; Powers et al., 1989; Petty et al., 1990; Ducrocq et al., 1998; Razumovsky et al., 1999). When intracranial pressure exceeds systolic blood pressure, no systolic pulses can be recorded. In the more usual circumstance, in which intracranial pressure exceeds mean arterial blood pressure but is lower than systolic blood pressure, the pattern of 'reverberating flow' is seen. It is called reverberating (or oscillating) because there is a forward progression of blood flow during systole but an equal reversal of blood flow to the original starting point during diastole. Multiple vessel insonations must be recorded to confirm the cessation of intracranial blood flow and the results are operator dependent. The American Academy of Neurology Therapeutics and Technology Assessment Subcommittee has published a statement supporting the use of TCD ultrasound in this circumstance (American Academy of Neurology Therapeutics and Technology Assessment Subcommittee, 1990). The reported sensitivity is 91.3% and the specificity is 100% (Petty et al., 1990).

Other techniques used to assess intracranial blood flow in brain death include xenon-enhanced CT scanning (Darby et al., 1987; Ashwal et al., 1989) and diffusion-weighted magnetic resonance imaging (Lovblad & Bassetti, 2000). The former requires specially equipped CT units not generally available. The latter has been reported in only a single case but is worthy of further study because of the wide availability and ease of this technology.

Ethical issues

The introduction of the concept of brain death has raised a series of challenging ethical issues that result from the unique circumstance of our technologic capacity to physiologically maintain certain bodily systems despite death of the human organism. Like many contemporary ethical issues, the question can be framed 'should we perform an intervention simply because we have the technologic capacity to do it'. I have considered these issues in further depth elsewhere (Bernat, 2002) and briefly review them here.

Brain death during pregnancy

Several reports have been published over the past two decades of pregnant women rendered brain dead by head trauma or intracranial hemorrhage in whom the decision to continue physiologic support was made, permitting the Ceasarian delivery of healthy infants (Dillon et al., 1982; Field et al., 1988; Bernstein et al., 1989; Nuutinen et al., 1989; Antonini et al., 1992; Catanzarite et al., 1997). Success in these cases required heroic efforts in the ICU to treat and compensate for myriad metabolic disturbances including respiratory failure, cardiac failure, hypothermia, diabetes insipidus, disseminated intravascular coagulation, infection, and hypopituitarism, as well as management of the pregnancy and nutritional support. Aside from the technical issues, the essential question is whether the good of salvaging a human life justifies subjecting the dead patient to the indignity of prolonged physiologic support, the family to the enormous emotional distress of suspending closure of a loved one's life, and society to the expense of such treatment (Kantor & Hoskins, 1993).

The first question is who should make such a decision. It is most reasonable that in the setting of a stable conjugal relationship in which the father intends to raise the child, the father should decide. In other situations in which grandparents or other family members may be raising the child, the decision should be made jointly among those with the greatest interest in the welfare of the dead mother and the fetus. Hospital ethics committees can assist families and physicians in the decision making in such difficult cases (Spike, 1999).

The ethical duty to try to rescue the fetus in this circumstance has been the subject of several analyses (Loewy 1987; Field et al., 1988; Kantor & Hoskins, 1993; Spike, 1999). In obstetrical practice, there is an ethical duty to insure the welfare of both the pregnant woman and the fetus (Mattingly, 1992). When the two goals come into conflict, ordinarily the welfare of the fetus is sacrificed for the welfare of the mother. But when there is no hope to save the mother, the primary goal is to rescue the fetus. Loewy has argued that the ethical duty to rescue the fetus in these cases increases with increasing fetal maturity because of the growing probability of therapeutic success and the diminishing harms to the mother resulting from the reduction of time for physiologic maintenance (Loewy, 1987).

Religious acceptance and rejection

Organized religions have not remained silent on the brain death issue. In the early writing on brain death, Frank Veith and colleagues asserted that brain death was consistent with the teachings of Roman Catholicism, Protestantism, and Judaism (Veith et al., 1977). This assertion remains mostly true. For the religious groups comprising Protestantism, including the most fundamentalist sects, this acceptance is universal (Campbell, 1999). For Roman Catholics, the acceptance is also strong. In an August 2000 address, Pope John Paul II asserted that the Roman Catholic Church formally regarded brain death as human death. Further, three Vatican Pontifical Councils and Academies assigned to study this topic over the past two decades have opined that brain death is consistent with Catholic teachings (White et al., 1992; Pontifical Council for Pastoral Assistance, 1994; Pontifical Academy of Life, Vatican City, Msgr. Elio Sgreccia, personal communication). In the United States, the National Catholic Bioethics Center (formerly known as the Pope John Center) has published opinions strongly supportive of the concept of brain death (Furton, 1999). Brain death determination and multiorgan procurement for transplantation are permitted at Roman Catholic hospitals throughout the world.

In Judaism, the acceptance of brain death is less uniform and it remains a point of heated rabbinic debate (Rosner, 1999). In general, Reform Judaism and most of Conservative Judaism accept the concept of brain death. But many Orthodox rabbis reject the concept insisting that ancient Jewish law dictates that the human being is not dead until breathing and circulation stop irreversibly, as required by the Talmud (Bleich, 1979; Soloveichik, 1979). But other Orthodox rabbis hold that brain death is consistent with ancient Jewish law because it is the functional equivalent of decapitation (Tendler, 1978; Rosner & Tendler, 1989). As a practical matter, brain death determination is accepted by a large majority of Jews in the United States and only the strictest Orthodox sects, such as Chasidim, reject it.

Islam has embraced the concept of brain death by a ruling of the Council of Islamic Jurisprudence Academy, and now permits multiorgan procurement for transplantation. In Saudi Arabia, for example, the Ullamah Council has authorized physicians to permit brain death determination (Yaqub & Al-Deeb, 1996). The recommended brain death tests are identical to those used elsewhere in the world (Abomelha & Al Kawi, 1992). The Sixth International Conference of Islamic Jurists addressed the various issues of determining brain death and facilitating organ procurement (Albar, 1991).

The acceptance by other religions in the world is varied. Hinduism, as expressed by the official practice in India, permits brain death (Jain & Maheshawari, 1995). In Japan, a cultural battle has been raging during the last quarter-

century over the acceptance of brain death advocated by western influences pitted against traditional Shinto, Confucian, and Buddhist religious and cultural practices (Kimura, 1991; Lock, 1995). The western influences appear to be winning because in 1997, Japanese law for the first time explicitly permitted brain death determination and organ transplantation (Akabayashi, 1997).

Research and teaching on brain-dead subjects

Brain-dead patients have been used as subjects for research and teaching purposes. As research subjects, brain-dead patients are ideal for experiments requiring normal organ system physiology in those organ subsystems remaining intact, particularly for dangerous experiments that could not be performed safely on living subjects. The ethical question is whether it is justified to continue physiologic support of dead subjects, with its attendant harms to the patient and family, solely for the purpose of experimentation (Martyn, 1986). Some have argued that it is acceptable because the dead may not have interests (Nelkin & Andrews, 1998).

Thoughtful investigators have proposed guidelines for using the brain dead as research subjects. Coller and associates stated that the research team should not participate in the brain death determination, the research protocol should be approved by the institutional review board, and the research protocol should not bar the possibility of organ procurement (Coller et al., 1988). La Puma added several conditions. The dignity of the human body should be preserved. The experiment should be brief. The consent of an authorized proxy decision maker should be obtained. The importance of the experiment should be great. And any resultant clinical charges should be borne by the investigators (La Puma, 1988).

Similarly, newly dead patients, including brain dead patients, have been used as subjects on whom physicians in-training may practice endotracheal intubation and other resuscitation techniques (Iserson & Culver, 1986). A few scholars have argued that the benefit to society of training young physicians in lifesaving procedures that cannot be learned effectively by any other means eliminates the duty to obtain consent from the patient's next-of-kin for this activity (Orlowski et al., 1988). Others have insisted that consent is necessary and should be requested, despite the awkwardness of such a request (Burns et al., 1994).

Organ procurement

The principal utility of brain death determination is to permit multiorgan procurement for transplantation. Except for the relatively new and not widespread practice of 'non-heart-beating organ donation' (Youngner & Arnold, 1993), and the evolving practice of 'partial donation' of liver and lungs from living donors (Singer et al., 1989), the brain-dead patient comprises the only acceptable donor for unpaired vital organs. There are ethical duties and legal requirements (in the United States) for physicians to identify potential organ donors from among brain-dead patients, and to ask families if they are willing to consent for their dead loved one to be an organ donor, the so-called 'required request' laws (Tolle et al., 1987; Darby et al., 1989). The ethical duty to encourage organ procurement stems from the lives potentially saved of the organ recipients.

Currently, and for the foreseeable future, the number of dying patients in need of vital organ transplants far outpaces the number of organ donors (Evans et al., 1992). Several strategies have been implemented to increase donation. The required request laws have not had the hoped-for effect of increasing organ donation rates (Caplan & Welvang, 1989). Organ procurement rates have been shown to increase with more expeditious brain death determination using confirmatory tests (Jenkins et al., 1998), and when the request for organ donation is made by trained organ procurement personnel (Gortmaker et al., 1998). Traumatic brain-injured patients deemed unsalvageable in emergency rooms should be admitted and declared brain dead to permit organ procurement, rather than be extubated (Riad & Nicholls, 1995). The criteria for the identification and management of the ideal multiorgan donor have been reviewed (Darby et al., 1989; Soifer & Gelb, 1989).

When brain-dead patients had completed organ donor cards, their families should be strongly encouraged to consent to donation to permit the autonomy of the patient to be respected, even after death. There must be a strict separation of the process of brain death determination and the request for organ donation. No member of the organ donor team should participate in the death determination. There is evidence that 'uncoupling the brain death determination from the organ procurement process in the family's mind improves the donation consent rate' (Hauptman & O'Connor, 1997). Families should understand that the benefit of organ donation is not restricted to the organ recipients. There is evidence that family members granting consent for donation experience transcendent meaning that renders the otherwise meaningless tragedy of illness or injury into a profound personal good (Douglass & Daly, 1995).

Legal issues

Laws in the United States, Canada, Mexico, Australia, and in nearly all European and in many South American, Asian, and African countries permit physicians to declare brain death as a test of death. Nearly all use the 'whole-brain' criterion, except for the United Kingdom that uses a brainstem criterion. As noted previously, the brainstem tests are essentially identical to the whole-brain tests, except the brain stem tests cannot use confirmatory tests showing EEG electrocerebral silence (Pallis, 1983) or intracranial blood flow studies showing an absence of intracranial circulation (Kosteljanetz et al., 1988) because these findings are not necessary for 'brainstem' death declaration.

In the United States, since Kansas enacted the first brain death statute in 1970, all states have enacted similar statutes or have issued administrative regulations permitting brain death declaration (Beresford, 1999). Most states employ the Uniform Determination of Death Act, sponsored in 1981 by the President's Commission, that provides:

> An individual who has sustained either (i) irreversible cessation of circulatory and respiratory functions, or (ii) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. A determination of death must be made in accordance with accepted medical standards (President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioural Research, 1981).

There are similar statutes or regulations in other countries permitting brain death declaration.

In the United States, the question of accommodating religious disagreement with brain death has been drafted into law in two states: New Jersey and New York. New Jersey amended its death statute (New Jersey Declaration of Death Act, 1991) whereas New York issued administrative regulations through the State Department of Health (NY Comp Codes, Rules and Regs, 1992). The New Jersey statute prohibits physicians from using brain death tests when they 'violate the personal religious beliefs of the individual' (Olick, 1991) whereas the New York regulations require physicians to 'mandate notification of an individual's next of kin' and allow for a 'reasonable accommodation to an individual's religious or moral objections to the use of neurologic criteria to diagnose death' (Beresford, 1999). An important future public policy question for our society is the amount of latitude our public laws should permit in the determination of death (Veatch, 1999).

A clinical problem, encountered more commonly than a religious objection, is the family that for emotional reasons, cannot bear to see the ventilator discontinued on their loved one, despite the determination of brain death. Although there are legal precedents in the United States authorizing physicians to discontinue ventilators is such cases over the objection of the family (*In re Bowman* 1980; *Matter of Haymer* 1983), compassionate physicians try to help the family accept the inevitable futility of further treatment attempts (Cranford, 1999). Many physicians will continue the ventilator temporarily pending acceptance of the family, but the length and extent of such futile treatment to accommodate family wishes remains debatable (Hardwig, 1991; Miedema, 1991).

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25

Disorders of mood

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Depression refers in the medical setting to clinically significant but transient emotional states which are called adjustment disorders and also to a clinical syndrome called major depression which occurs in unipolar depressive disorder and bipolar disorders. Confusion of adjustment disorders with depressive syndromes plagues both medical care and reasoning about mechanisms. Once identified, mood disorders (unipolar and bipolar disorders) are treated quite successfully with any of several medications and/or psychotherapy. The pathophysiology of mood disorders remains obscure, but clues are emerging as to the neuroanatomic components, molecular systems and genes involved in the vulnerability to mood disorder. The cumulative effect of these developments on a number of scientific fronts will be to unravel the complex knot of etiologic factors, leading to the refinement of current empirical treatment and the development of rational treatment. When we can identify the mechanisms of mood disorder, we will also gain an improved perspective from which to understand the role of environmental factors in the development of depressive and manic disorders.

In the official diagnostic nomenclature of American psychiatry a transition from the term 'affective disorders' to 'mood disorders' was made in 1987, though the diagnostic criteria for major depression and mania did not change appreciably. We use the term mood to denote a persistent emotional state, and affect or affective to refer to a constellation of phenomena generally associated with and including mood. We will use the term depression, hereafter, only to denote the syndrome of depressive illness.

Epidemiology

Mood disorders are among the most common illnesses in the community and in the medical clinic. Depression, in a variety of community samples worldwide, affects as many as one in six individuals in the course of a lifetime (Doris et al., 1999). Mania occurs in 1–2% of the population. Ten to twenty per cent of patients screened in a primary care clinic have a major depressive disorder (Zung et al., 1993); depression was found in over one-quarter of patients in a neurology practice (Carson et al., 2000). Mania is less often a presenting problem for non-psychiatric physicians, but can occur as an iatrogenic complication from the use of antidepressants (Benazzi, 1997), corticosteroids (Sharfstein et al., 1982), or psychostimulants (Masand et al., 1995). Moreover, a number of medical conditions are associated with the syndromes of mania and depression, as will be described below.

Mood disorders are extremely painful for families as well as patients, and are costly to society. Suicide is the cause of death in at least 5% of individuals with a mood disorder, as found in community samples (Inskip et al., 1998), and the rate of suicide among patients requiring hospitalization is three- to fourfold greater than that. Psychological autopsy studies reveal consistently that at least two-thirds of completed suicides had strong evidence for a mood disorder prior to death, even though many were never diagnosed or treated for it (Barraclough et al., 1974). Depression carries high direct costs from absenteeism and occupational disability (Druss et al., 2000; Greenberg et al., 1993) and medical expenditure (Simon et al., 1995), as well as high indirect costs via other highly destructive behaviours like those related to substance abuse.

Clinical facts

Central features

The depressive syndrome consists of a persistent and pervasive disturbance of affective state. The mood itself,

however, is described as sad or depressed in only 50% of patients with major depression. The mood may be constantly dysphoric, or cycling through different dysphoric states, ranging from despair to apathy, anxiety, numbness, or irritability. The mood in the manic syndrome may be pleasantly euphoric, though often the accompanying excitement gives way to anxiety or irritability. A depressive or manic syndrome, as opposed to a normal lowering or elevation of mood, is concomitant with changes in self-attitude, vitality and neurovegetative functioning. The change in self-attitude manifests itself in depression with pathological guilt, self-loathing, feelings of worthlessness and failure. In mania, patients express expansive confidence and grandiosity, and with mixed or irritable manic states, there is often a combative self-righteousness. Vitality, or the physical sense of energy, capability, and stamina tend to be diminished in the depressed patient and elevated in the manic. Neurovegetative appetites for sex, sleep, food and stimulation are almost universally disturbed in some way in patients with mood disorder.

Mood disorder generally causes functional impairment, but impairment is neither necessary nor sufficient to differentiate mood disorder from normal emotional variation. Perturbations of energy and cognition tend to interfere with the conduct of work. Depressed patients tend to take longer to perform tasks, or think their way through problems. Manic patients can be so restless or distracted that they fail to complete tasks properly. However, the degree to which impairment is noticeable depends heavily on contextual factors, such as the difficulty of the work being performed, the stability of the patient's basic temperament (e.g. stoic vs. neurotic), and the depth of social resources on which the patient may draw. From similar reasoning, it is easy to see that many patients can exhibit severe functional decompensation in the absence of ongoing symptoms of mood disorder, if their discouragement leads to markedly altered behaviour.

Depressive and manic syndromes can be suspected based on chronic behavioural changes. However, behavioural changes alone do not make the diagnosis. The clinician must elicit the symptoms as described above to make the diagnosis. Depression, for example, should be suspected in patients exhibiting suicidal or self-mutilatory behaviour and in patients who withdraw socially and uncharacteristically fail to follow through with family and occupational obligations. Mania should be suspected when patients spend lavishly, engage in uncharacteristic sexual promiscuity, or exhibit other disinhibited behaviour. Because these behaviours may all arise under a variety of circumstances, it is important not only to elicit a history of any accompanying symptoms but also to know how the patient behaves at other times. In many cases, the diagnosis cannot be made without information from the patient's family about changes from prior behaviour.

A patient's resistance to or ignorance of the concept of mood disorder often obstructs diagnosis and treatment. Patients often do not recognize mood disorder as the primary source of their suffering. Mood disorder from the patient's perspective can be so insidious and pervasive that patients see their symptoms (however exaggerated compared to the normal range of human response) as an understandable reaction to adverse life events or to their own insufficient (or inflated) value as persons. Patients with depression may come to feel they deserve their despair; the belief that others would be better off without them all too often leads to suicide attempts. Manic patients, on the other hand, can evince an impenetrable arrogance, which thwarts efforts at management.

Classification

Patients with episodes of mania or hypomania are designated bipolar (synonymous with manic depressive illness) regardless of whether they have had documented depressive episodes. Patients with depressive episodes but no mania are called unipolar in the scholarly literature, and are given the diagnosis major depressive disorder in the official nomenclature of the American Psychiatric Association, the *Diagnostic and Statistical Manual (DSM)* (American Psychiatric Association, 1994). In many cases it is not easy to differentiate mild bipolar from unipolar depressive disorders, as patients and their families may not have recognized the milder manifestations of hypomania.

While most patients with bipolar or unipolar disorders have an episodic course, with substantial periods of remission, variations in the course of illness are accounted for in the classification scheme. Dysthymia refers to a mild-to-moderate depressive disorder, lasting years. Patients with four or more episodes of mania or depression per year are described as having 'rapid cycling'. Such patients can experience an episode once per season or can even cycle on a daily basis. Patients with the distinctive symptoms of mania and depression simultaneously are in what are called 'mixed states', first described by Kraepelin at the turn of the twentieth century (Kraepelin, 1921). Patients in mixed states often experience low and very irritable moods, but are physically and mentally hyperactive to the point of restlessness and distraction. Patients in these states are prone to violent and self-injurious rages.

The official operational definitions used in DSM diagnostic categories and based on clinical criteria sets ensure reliability, but not a valid nosology of mood disorders.

There is strong evidence for the validity of four or five of the subtypes listed in the manual. There may be meaningful biological distinctions between melancholic depression (blunted affect, insomnia, loss of appetite) and atypical depression (reactive mood, hypersomnia, hyperphagia) (Asnis et al., 1995) and between mood disorders with and without psychotic symptoms (Coryell, 1996). Other means of subtyping patients based on family history, comorbidity, and symptom severity remain a focus of research. Panic disorder, an anxiety disorder characterized by paroxysmal acute, severe anxiety, a feeling of impending death, derealization, and physical symptoms such as palpitations, shortness of breath, chest tightness and dizziness, occurs in 20% or more of individuals with bipolar and unipolar depressive disorders. Panic disorder comorbidity with bipolar disorder clusters in a subset of families containing multiple bipolar relatives and may be a marker of genetic heterogeneity in bipolar disorder (MacKinnon et al., 1998).

Somatic diseases and mood disorder

Patients with an unrecognized mood disorder often present with non-psychiatric complaints. Suspicion of an underlying mood disorder should be raised when patients present with uncontrollable pain, fatigue, requests for sleeping pills, and when there is uncharacteristic or unusually severe non-compliance with treatment or failure to rehabilitate after a medical illness. In the elderly, depression may manifest as an abrupt cognitive decline, though the diagnosis should be made only after delirium and dementia have been ruled out.

Depression is one of the most common comorbidities of medical illness (Coulehan et al., 1990). The interrelationship of depression and medical disorders underscores the significance of the task of identifying and treating depression. Depression is a major risk factor for the development of and morbidity from cardiovascular disease (Musselman et al., 1998). Mood disorders complicate the treatment and course of many neurological disorders, including seizure disorders (Wiegartz et al., 1999), cerebrovascular disease (Morris et al., 1993), Parkinson's Disease (Cummings & Masterman, 1999; Starkstein et al., 1990), Huntington's Disease (Peyser & Folstein, 1990), and multiple sclerosis (Patten & Metz, 1997). Mood disorders occur commonly with cancer (Spiegel, 1996) and AIDS, which produces both depressive and manic syndromes (Treisman et al., 1998). In some medical disorders with obscure pathology, like fibromyalgia (Ackenheil, 1998) and chronic fatigue syndrome (Lane et al., 1991) depression commonly coexists with the somatic symptoms and exacerbates the pain and fatigue.

In medically comorbid depression, however, the task of differentiating discouragement, which is also a common complication of illness, from depression is critical. The undertreatment of depression or overmedication of discouragement can have severe medical consequences in medically ill patients (Cassem, 1995). Medical illness often raises the risk for suicide in either case (Harris & Barraclough, 1994). Medically ill patients with depression have higher mortality rates (Covinsky et al., 1999; Herrmann et al., 1998). On the other hand, caution in prescribing is dictated by the significant risks of adverse side effects from medications (e.g. cardiac conduction delays with tricyclic antidepressants, delirium with any psychotropic medications), or unforeseen pharmacologic interactions (e.g. fluoxetine's inhibition of a cytochrome P-450 enzyme, lithium toxicity from concomitant use with thiazide diuretics or ibuprofen).

Therapeutic issues

Prior to the development of effective biological treatment for mood disorders, treatment focused on the containment of dangerous behaviour: suicide in melancholics, and violent agitation in manics, through institutionalization, sedation, and 'rest' (Goodwin & Jamison, 1990). In the middle third of the twentieth century, patients with milder forms of mood disorder often pursued psychoanalytically informed psychotherapy which, because it took place over a longer period than the expected natural duration of an episode of illness, was seen as probably effective in many cases. In the latter half of the twentieth century, an increasing array of effective pharmacologic and other biological treatments have supplanted the psychoanalytic and supplemented the pragmatic approach with empiric remedies and prophylaxis. The empiric means used to treat and forestall illness promise to inform our understanding of mechanisms of illness.

The first issue often confronting the physician treating depression is that patients can at the same time have major depression and be discouraged about having depression. Discouragement is an understandable emotional response to a state in which a mental disorder has caused one's enjoyment of life to be lost, one's bodily functions (sleep, appetite, libido) to be awry, and one's energy and cognitive fluency to be sapped. Biological treatments for depression all take weeks to months to have a full therapeutic effect, but patients tend to begin to feel better quickly when they are provided with hope for recovery. The amelioration of discouragement accounts for the rapid partial response seen both in placebo and treatment groups in many studies of antidepressant efficacy; however, after a week

the continued progress towards recovery tends to occur only in the treatment groups.

All biological treatments in use for the treatment of mood disorders were discovered either serendipitously or from analogy with treatments discovered serendipitously. The older antidepressant classes, tricyclics (TCA) and monoamine oxidase inhibitors (MAOI) were observed incidentally to relieve depression in patients treated for psychosis and tuberculosis, respectively (Pletscher, 1991; Potter et al., 1991). Lithium, though it was known to be a component of mineral waters and even soft drinks early in the twentieth century, was found to be an effective antimanic agent only after its sedative properties were observed, incidentally, in guinea pigs being studied for the toxic effects of uric acid. Electroconvulsive therapy (ECT) arose from the observation (false, as it turns out) that epileptics are somehow protected from depression. Carbamazepine was observed, again incidentally, to improve mood symptoms in patients treated for epilepsy, and was applied to the treatment of bipolar disorder based on speculation about shared pathophysiologic mechanisms (Post et al., 1982).

Investigation of putative mechanisms of action of these treatments has led to newer generations of treatment either in use or under investigation for use against mood disorders. Serotonin selective reuptake inhibitors (SSRI) arose from insights derived from research on the binding properties of TCAs that showed, for example, high affinity of TCAs for serotonin receptors (Paul et al., 1981). Valproic acid was applied to mania because of its overlapping specificity with benzodiazepines for GABA receptors (Emrich et al., 1980). While the mechanism of action of ECT remains obscure, the concept of ECT has led to investigation into transcranial magnetic stimulation (TCMS) as a means to deliver a highly focused magnetic field across the skull without inducing the significant cognitive side effects often seen with ECT (George et al., 1995b).

Efficacy of many antidepressant and antimanic treatments has been established; however, efficacy of treatment with the aim of preventing relapse has been established only for the use of lithium in bipolar disorder. Antidepressant agents, when given in an adequate dose over 6 to 8 weeks tend to bring recovery in two-thirds to three-quarters of patients, across different antidepressant types (Nelson, 1999). ECT is more effective still in treating acute depression and mania (Mukherjee et al., 1994). Efficacy in alleviating mania has been established for lithium, several anticonvulsants, and an atypical neuroleptic (olanzapine). Long-term efficacy of antidepressant maintenance for recurrent depression is not well established, as effective dosages of medications tend not to be maintained in the long run (Mueller et al., 1999). In bipolar disorder long-term efficacy is established for lithium (Davis et al., 1999), while the evidence is less strong or nonexistent for other agents currently in wide use (Bowden et al., 2000). Aside from medication, the advice offered by Kraepelin remains salient today:

> That a very even tenor of life in *protected circumstances*, especially also with *avoidance of alcohol*, may have a certain prophylactic effect with individuals who are liable to attacks, may be regarded as probable considering the frequently indubitable influence of external injuries [Kraepelin, p. 202, emphasis his].

Patients with mood disorder are well advised to avoid alcohol and drugs and to sleep, work and exercise regularly.

Pathophysiology and etiology

Development of rational treatments to enhance the specificity of action in order to target patient subgroups, minimize side effects, and possibly accelerate treatment response, hinges on the elucidation of pathophysiologic mechanisms. Explorations of the biology of human emotional distress, pharmacologic mechanisms of action of antidepressant and antimanic agents, and variation in brain structure and function have opened windows to these mechanisms. Pathophysiologic investigation informs and is informed by the discovery of genetic markers linked to mood disorder vulnerability.

Depression and the stress response

Many patients and their physicians accept at face value the intuition that stress causes depression. A biochemical correlate of this intuition is the hypothesis that depression arises from an abnormality in the stress response mechanism, i.e. the hypothalamic–pituitary–adrenal (HPA) axis. There is some support for a relationship of HPA axis dysfunction and mood disorder, however the nature of the relationship remains uncertain. Depressive and manic syndromes occur with considerable frequency in Cushing's syndrome and with the use of corticosteroids. Patients with depression sometimes abnormally manifest nonsuppression of morning cortisol levels after an evening dose of dexamethasone (Carroll et al., 1968), however, without sufficient predictive power to aid in diagnosis (Arana et al., 1985). Consistent evidence of elevated cortisol levels in depressed patients has been difficult to establish (Posener et al., 2000; Steckler et al., 1999). Nevertheless, evidence continues to accumulate regarding the association of stress and HPA axis perturbations with

altered emotional state. Corticotropin releasing factor (CRF) and its receptors have been implicated in the modulation of the stress response; mice bred to be lacking a CRF receptor show abnormally low anxiety in response to stress (Timpl et al., 1998), and human subjects with depression, panic disorder, or alcoholism all show a blunted corticotropin (ACTH) response to CRF (Holsboer et al., 1987). However, it is less clear that HPA axis dysfunction can be seen as a cause, rather than a cofactor or a result of mood disorder. Abnormal regulation of cortisol is seen with a variety of conditions that produce chronic stress, including non-depressed individuals who had experienced significant childhood trauma (Heim et al., 2000). Implication of chronic elevated stress and glucocorticoid levels as a cause of atrophy of hippocampal neurons (Magarinos et al., 1997; Sapolsky, 1996), which would predict diminished hippocampal volume in depressed patients, has found only mixed empirical support (Brown et al., 1999; Vakili et al., 2000).

Monoaminergic hypotheses

The noradrenergic hypothesis, derived in part from the emergence of depressive symptomatology in hypertensive patients taking reserpine, explains the mechanism of action of TCA medications and continues to gain empirical support (Lambert et al., 2000), but serotonergic dysfunction has been implicated more consistently as a possible pathophysiologic factor in depression. One line of empirical support for the serotonergic hypothesis is evidence of diminished serotonin function in the brains of depressed suicidal patients. The levels of serotonin metabolites have been found persistently to be decreased in the cerebrospinal fluid of patients with depression and suicidal intent (Traskman et al., 1981) and evidence for diminished functioning in the brain can be inferred from an increase in the number of serotonin receptors in the brains of suicide victims (Arango et al., 1990). The degree of serotonin deficiency correlates with the violence of the suicidal intention (Mann & Malone, 1997). Diminished levels of serotonin metabolites also have been discovered in the cerebrospinal fluid of violent and impulsive subjects in general (Stanley et al., 2000), so altered serotonin function is not necessarily specific to depression. The serotonin hypothesis is supported by the observation that correction of an apparent deficiency in serotonin neurotransmission correlates with alleviation of depressive symptoms. When depressed patients treated to at least partial remission with SSRI agents, which selectively block serotonin reuptake, are depleted of tryptophan, an amino acid precursor for serotonin, symptoms of depression return (Delgado et al., 1990); however, recurrence of depressive symptoms under tryptophan depletion is not observed in patients in full remission (Moore et al., 2000). Continued elucidation of the mechanisms of regulation of serotonin activity at the synapse may lead to improvement in the focus of pharmacotherapy (Blier & de Montigny, 1994).

Mood instability and the mechanisms of action of lithium

Lithium exerts a variety of effects on neurons. One or some combination of these effects might be the key to the therapeutic mechanism of action of lithium, thus to the pathophysiologic mechanisms of mood disorder (Manji et al., 2000b). A general hypothesis is that lithium's modulating effects on signal transduction and thus gene expression may be salient for understanding affective psychopathology (Lachman & Papolos, 1995; Manji et al., 1995). Chronic lithium administration interferes with receptor-G protein coupling (Wang & Friedman, 1999), reduces levels of inositol triphosphate precursors (Huang et al., 2000), and inhibits phosphorylation of cyclic AMP (Wang et al., 1999) in rat brains. There is not, as yet, evidence of dysfunction in any of these pathways to explain why lithium's modulating effect is required in bipolar patients. There is evidence, however, to suggest that chronic administration of lithium and valproate may protect neurons by stimulating expression of a cytoprotective protein bcl-2 (Manji et al., 2000a). Whether mood instability is the result of a primary pathological process in structures related to affective modulation, or the effect on brain of manic hyperarousal is focal neurotoxicity, demonstration of the salutary effect of chronic lithium on brain corresponds nicely with the long-term efficacy of lithium in bipolar disorder.

Anatomy of mania and depression

A key challenge for neuroanatomic hypotheses of mood disorder is to explain both the state of illness and the episodic course of affective disorder. Epilepsies notwithstanding, the complete resolution of symptoms between mood disorder episodes appears inconsistent with an illness model involving a static brain lesion. Studies of depressive illness following stroke suggest that lesion location, the time since the stroke, and the extent of functional impairment independently predict depressive illness. Functional neuroimaging of actively depressed and remitted patients and of healthy subjects under emotional activation paradigms point to the limbic–cortical systems as important structures in the genesis and resolution of depressive states. Integration of structural and functional anatomy

with hormonal, neurotransmitter and gene transcription hypotheses remains to be done.

Postmortem brain studies of patients with mood disorder, including suicide victims, have revealed no consistent histopathological differences in the brains of affected individuals, or gross evidence for pathology related to mood disorder (Goodwin & Jamison, 1990). Association of post-stroke lesions and depressive symptomatology became feasible with the advent of clinical neuroimaging. Depression in the immediate poststroke period has been associated with left anterior stroke location (Astrom et al., 1993; Robinson & Szetela, 1981). These depressions were comparable phenomenologically to idiopathic major depressions. They also responded similarly to treatment with a tricyclic antidepressant (Lipsey et al., 1984). Depression following months or years behind a stroke tends to correlate more with the degree of residual functional impairment than with specific location of injury; however there is some association of delayed post-stroke depressive states and right occipital location (Robinson, 2000; Shimoda & Robinson, 1999).

Expanding on these lesion studies, volumetric and functional analysis of depressed patients without brain injury tends to implicate frontal and limbic structures in affective pathophysiology. One illustrative volumetric analysis revealed diminished frontal lobe volume relative to controls (Coffey et al., 1993); however, no particular portion of the frontal lobe was consistently affected, and other studies investigating structural changes with mood disorder have been inconsistent (Steffens & Krishnan, 1998). PET scanning of patients with depression has confirmed diminished metabolic activity in the left prefrontal cortex (Martinot et al., 1990), which correlates specifically with degree of mood disturbance and psychomotor retardation (Bench et al., 1993). Emotional activation paradigms involving the elicitation of sad emotions typically implicate frontal cortex as well as limbic structures, however laterality varies across studies (Beauregard et al., 1998; George et al., 1995a). Evidence for limbic–frontal reciprocity has emerged from PET studies of both depressed patients before and after successful pharmacologic treatment and healthy subjects induced to experience sad emotions, suggesting that mood regulation is a function of the relationship of cortical and limbic structures rather than the function of a single structure (Mayberg et al., 1999). Thus, a left frontal lobe diminished structurally and functionally by ischemic injury or other pathogenic processes may contribute to core symptoms of low mood and psychomotor disturbance, but may not be a necessary factor in pathophysiology.

Structures associated with the limbic system have a role to play in mood regulation, and probably do so as well in the pathophysiology of affective disorders. The amygdala, in particular, has been established through animal studies to be a centre for integration of the fear response (LeDoux, 2000) and has been found in one report to be activated (on the left side) with induction of sad mood in normal humans (Schneider et al., 1997). A contribution of the amygdala to affective psychopathology might explain mania seen in patients with temporal lobe epilepsy (Lyketsos et al., 1993) and could provide some anatomic support for the kindling model in idiopathic affective disorders (Post et al., 1982). The amygdala has extensive connections with prefrontal cortex (PFC), in particular with the subgenual prefrontal cortex, a structure implicated in the neuroanatomy of depression that also has connections with the lateral hypothalamus, nucleus accumbens, locus ceruleus, substantia nigra, and other deep brain and brainstem nuclei (Drevets, 1999). Functional and structural lesions in the subgenual PFC have been associated with mood disorder; patients with depression show diminished size and local cerebral blood flow in this region (Drevets et al., 1997); histopathological analysis finds a diminution principally in glia cells (Ongur et al., 1998). Lesions in this area do not duplicate a classic depressive syndrome; however, the amotivational syndrome arising from subgenual PFC certainly resembles a core feature of depressive states.

Linkages of brain dysfunction to depressive and manic psychopathology in the context of dementia and delirious states are not easily interpreted. Delirious states can present with depressive affect, withdrawal, and nihilistic or even suicidal statements; alternatively, delirious patients may appear as agitated, combative, or with manic features (e.g. denial of impairment from an obvious illness). Such symptomatology emerges routinely in the hospital setting in the context of delirium, whether due to systemic illness or intoxication. While the pathophysiology of manic or depressive-like symptoms in these contexts may in time prove informative to the understanding of idiopathic mood disorder, one must be alert to dissimilarities (not highlighted in many reports) between these known pathologic states and bipolar or depressive disorders. For example, late onset mood disorders have been associated with diffuse periventricular white matter ischemia, but also are independently correlated with generalized cognitive deficits (Steffens & Krishnan, 1998). Diffuse white matter hyperintensities have often been reported in bipolar disorder (Altshuler et al., 1995; Dupont et al., 1990) and in vascular and demyelinating disorders without affective syndromes. However, they have not been observed in first-episode manic patients (Strakowski et al., 1993), suggesting that diffuse white matter lesions are

likely a contributing but not a primary causative factor in some cases of bipolar disorder.

Genetic risk

Familial risk for mood disorders is well established from family, twin, and adoption studies. Specific genetic risk factors for bipolar and unipolar disorders have not yet been discovered; however, it is possible from the evidence available to predict a complex genetic contribution to etiology. Genetic analysis promises to play a critical role in validating pathophysiologic mechanisms suggested by research in neuroanatomy and neuroendocrinology, and in suggesting further research into molecular mechanisms of illness.

Elevated familial risk for mood disorder is well established from family, twin and adoption studies (Bertelsen et al., 1977; MacKinnon et al., 1997; Mendlewicz & Rainer, 1977). Siblings of patients with bipolar disorder have about a fivefold elevated risk for bipolar disorder, and siblings of patients with unipolar disorder have about a twofold elevated risk (Tsuang & Faraone, 1990). Family study evidence also supports the conclusion that mood disorders do not elevate familial risk for schizophrenia, and vice versa (Gershon et al., 1982), so that these disorders may be seen as separate phenotypes, with probable separate pathophysiology. Analyses of patterns of inheritance of mood disorders have not consistently supported a dominant vs. recessive vs. X-linked mode of inheritance. Numerous explorations of the genome in families ascertained for bipolar disorder linkage study (genomic studies of unipolar disorder are, as of this writing, few in number) have yielded inconsistent support for linkage at a variety of genetic loci (Berrettini, 2000). While any one of these loci may or may not contain a gene coding for a protein involved in a mechanism salient to mood disorder, the fact that no one genetic locus is found to be linked to bipolar disorder in even a large minority of families suggests that bipolar disorder (and most likely unipolar disorder as well) is complex genetically as it is clinically.

The pattern of findings and non-findings in studies of genetic risk factors for mood disorder is consistent with a model in which vulnerability to mood disorder derives from the interaction of several proteins, neither of which is necessary or sufficient to produce symptoms individually. In other words, individual No. 1 may have an elevated risk for developing a first episode of mania or depression because of inheriting genetic variants A, B, and C, while individual No. 2 may have a similar risk because of C, D, and E, while No. 3's risk derives from F, G, and H. It can be seen that risk factors like C may be present in most, but not all individuals, while other risk factors may overlap not at all across individuals. Each genetic factor may elevate the risk by a factor of 2 or less, making detection even more difficult since a large proportion of individuals with a possible genetic risk factor will show no evidence of the phenotype. Multigenic etiology also may account for intrafamilial heterogeneity, a phenomenon that would severely limit the power to detect genetic risk using the methodologies available.

Progress in understanding the pathophysiology and etiology of mood disorders, therefore, is likely to hinge on cross-fertilization of scientific exploration across disciplines. This occurs already, in the form of candidate gene approaches in which known genetic loci coding for proteins involved in the function of neurotransmitter systems are tested for the association of polymorphisms (preferably with functional significance) with the phenotype under investigation. As the genome becomes completely mapped, and functions are assigned to the tens of thousands of genes as yet undiscovered as of this writing, it will be possible to evaluate using genetic analysis additional hypotheses to account for signal transduction defects, focal cytotoxicity in brain regions subserving affective modulation, impaired neuroendocrine regulation, and so on.

Conclusions and predictions

One of the most challenging and labour-intensive puzzles to be resolved in coming years is to differentiate mood disorders into clinically and pathophysiologically meaningful phenotypic subtypes. One can begin with the insight that unipolar depression responds differently than bipolar depression to antidepressants, sometimes. Increasingly, it will be possible to test hypotheses of clinical heterogeneity genetically, by linkage studies that show a common genetic variation in the affected individuals in some families, but not in others. Association of particular disease-related alleles with disease across families may yield additional pathophysiological insight, as molecular variations are related to physiologic dysfunction. While a presentation of current knowledge underscores the enormity of the gaps in our understanding of mood disorders, over the past generation the evidence has strengthened that mood disorders involve specific sorts of dysfunction in the brain and neuroendocrine systems. The means may now exist to begin to untangle the complexity of mental illness.

The intersecting study of neuroendocrine dysfunction, neuroanatomical pathology, cellular signal transduction and the genome will merge in time to provide the basis for

a full description of the biological vulnerability to mood disorder. As soon as a single gene can be definitively linked to mood disorder, it will be possible to begin to dissect the genetic and biochemical complexities, and to investigate the brain functions underlying mood disorders. Once the biological mechanisms are understood, the environmental risk factors for depression will stand in stark relief, and may be approached with full knowledge of the potentials and limitations of interpersonal, behavioural, or social intervention in alleviating or preventing mood disorder. In time, cross-disciplinary correlations of genomic markers and specific biochemical or neuroanatomic markers of vulnerability traits and disease states will aid in the development of comprehensive theories of mood and mood disorder and the development of rational therapeutics.

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26

Schizophrenia

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Although not the commonest psychiatric disorder, schizophrenia is at the heart of psychiatry. It is also the disorder which has caused most controversy in terms of its nature, its treatment, even its very existence. One particular debate has concerned its organic basis and, indirectly, the extent to which it is a disorder of brain or of mind. As such, schizophrenia, like epilepsy, has exemplified both the bridge and the gulf between neurology and psychiatry. When Kraepelin described the syndrome at the end of the nineteenth century, he persuaded his young colleague Alzheimer to investigate its neuropathology. However, no substantive progress was made and by the middle of the twentieth century the pendulum had swung almost entirely to psychological and sociological views of schizophrenia. The pendulum has swung back over the past 25 years, with convincing evidence of differences in the structure and function of the brain of patients with schizophrenia finally emerging.

Clinical features and epidemiology

Schizophrenia remains a clinical diagnosis, based upon the presence of certain types of delusions and hallucinations (sometimes grouped together as 'first rank symptoms') and thought disorder (Andreasen, 1995). These 'positive' symptoms are often complemented by the 'negative' symptoms of avolition, alogia and affective flattening. The criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition) (DSM-IV; American Psychiatric Association, 1994) are used for most research studies (Table 26.1); the World Health Organization ICD-10 criteria are similar but require only a 1-month duration. Depending on the balance of symptoms, different subsyndromes are classically recognized: paranoid, hebephrenic (disorganized), catatonic, undifferentiated and simple subtypes. A final clinical domain, neglected until recently, is that there are neuropsychological deficits, with impaired performance across a wide range of memory and language tasks apparent in first episode patients (Bilder et al., 2000) as well as in most long-standing cases (Palmer et al., 1997). Interest in this aspect of schizophrenia has increased with recognition that the cognitive impairments may be a major contributor to poor outcome (Green, 1996).

Schizophrenia can begin at any time from early childhood onwards, with a peak age of onset in the third decade, occurring a few years earlier in men than women. The course and outcome are remarkably variable and unpredictable, but the prognosis is better than sometimes believed. Only a minority have a chronic, deteriorating course, though many others have recurrent or enduring functional deficits, including persistent negative symptoms and the cognitive deficits mentioned. There is a significant excess mortality from suicide and natural causes (Brown, 1997).

The diagnosis of schizophrenia is reliable, but as with any other syndromal diagnosis there are problems establishing its validity, deciding where its boundaries should be drawn, and debate as to whether it is a categorical or dimensional construct. In clinical practice, there are three main differential diagnostic issues. The first is to exclude a neurological or medical disorder producing a schizophrenia-like syndrome; there are many examples, including temporal lobe epilepsy, metachromatic leukodystrophy, Wilson's disease, Huntington's chorea, thyroid disease, and cerebral vasculitis (Lishman, 1998). The second is to identify a drug-induced psychosis; NMDA glutamate receptor antagonists such as phencyclidine (PCP) produce the most schizophrenia-like picture, although psychosis is also associated with amphetamine, cocaine, hallucinogen, and alcohol abuse. In one large study, an organic cause was identifiable in ~6% of people presenting with schizophrenia (Johnstone et al., 1987). Having excluded an organic

Table 26.1. Abbreviated DSM-IV diagnostic criteria for schizophrenia

A. Characteristic symptoms. Two or more of the following, each present for a significant part of a 1-month period:
1) Delusions
2) Hallucinations
3) Disorganized speech (e.g. derailment)
4) Disorganized or catatonic behaviour
5) Negative symptoms (i.e. affective flattening, alogia, avolition)

NB: Only one symptom needed if delusions are bizarre, or if the hallucinations consist of a voice keeping up a running commentary on the person's actions or thoughts, or two or more voices conversing with each other.

B. Functioning. Significant decline in one or more functional areas (work, relationships, self-care)

C. Duration. Continuous signs of disturbance for at least 6 months. (This may include prodromal or residual phases.)

D. Exclusion criteria.
1) Mood disorders or schizoaffective disorder
2) The disturbance is not due to the direct physiological effects of a substance
3) The disturbance is not due to a general medical condition
4) Autism or other pervasive developmental disorder

disorder, schizophrenia must be distinguished from other psychiatric disorders, especially bipolar disorder (manic depression), delusional disorder, schizoaffective disorder and certain personality disorders.

The lifetime risk of schizophrenia is about 0.8%, and is broadly similar across all cultures and countries (Cannon & Jones, 1996). There is an increased risk amongst relatives (e.g. 10% in the child of a schizophrenic parent, and about 40% in a monozygotic cotwin). Twin (Cardno & Gottesman, 2000) and adoption (Ingraham & Kety, 2000) studies show that the familial clustering is largely (if not entirely) due to shared genes not shared environment. Heritability is estimated at 60–90%, with most evidence implicating multiple genes and non-Mendelian inheritance. Several suggestive but small-effect loci have been identified, notably on chromosomes 1p, 5q, 6p, 8p, 13q and 18p (Owen et al., 2000); there is also an association with microdeletions of 22q11 (Bassett & Chow, 1999). Epigenetic factors may also be important (Petronis et al., 1999). There are few established environmental risk factors (McDonald & Murray, 2000), although prenatal events, especially birth complications, confer a small excess risk (Geddes et al., 1999).

Neuropathology

Structural imaging

Key findings

There have now been a large number of CT and MRI studies of the brain in schizophrenia. The cardinal findings are summarised in Table 26.2 (see also Hopkins & Lewis, 2000). There is enlargement of the cerebral ventricles, accompanied by a loss of cortical volume (Ward et al., 1996; Lawrie & Abukmeil, 1998; Wright et al., 2000). Greater reductions occur in temporal lobe, especially medial structures (hippocampus, parahippocampal gyrus and amygdala; Nelson et al., 1998). Cerebral asymmetries may be reduced (Petty, 1999). Subcortical structures have not been well characterized, though there is good evidence for basal ganglia enlargement, especially of the globus pallidus; unlike all the other volume changes, this is due to antipsychotic medication (Harrison, 1999b;

Table 26.2. Macroscopic brain changes in schizophrenia

Established by systematic reviews[1]
- Enlargement of lateral and third ventricles (+25–40%)
- Smaller brain volume (−3%)
- Smaller cortical volume (−4%)
- Smaller cortical grey matter volume (−6%)
- Relatively smaller medial temporal lobe volume (−5%)
- Relatively smaller thalamic volume (−4%)
- Larger basal ganglia (esp. globus pallidus)[2]

Other replicated (though still controversial) findings
- Greater cortical involvement of heteromodal association areas (esp. superior temporal gyrus)
- Decrease (or loss) of cerebral asymmetries

Notes:
[1] Summarized from Ward et al., 1996; Lawrie & Abukmeil, 1998; Nelson et al., 1998; Wright et al., 2000.
[2] Due to antipsychotic medication.

Wright et al., 2000). There is some evidence for smaller thalamic size.

Characteristics of the findings

Monozygotic twins discordant for schizophrenia have provided valuable information. In virtually all pairs, the affected twin has the larger ventricles and smaller cortical and hippocampal size (Suddath et al., 1990). The discordant monozygotic twin study design allows two conclusions to be drawn. First, that structural abnormalities are a consistent finding in schizophrenia, their identification being aided by controlling for other genetic and environmental influences on neuroanatomy. Secondly, that the alterations are associated with expression of the schizophrenia phenotype rather than merely with the underlying shared genotype. Family studies support this interpretation, in that schizophrenics have bigger ventricles and smaller brains than their unaffected relatives. However, relatives who are obligate carriers (i.e. unaffected by schizophrenia but who seem to be transmitting the gene(s)) have larger ventricles than other relatives; moreover, both groups of relatives have larger ventricles and smaller brain structures than control subjects from families without schizophrenia (Harrison, 1999d). These data indicate that a proportion of the structural pathology of schizophrenia may be a marker of genetic liability to the disorder.

Ventricle–brain ratio (VBR) in schizophrenia follows a unimodal distribution, indicating that ventricular enlargement is not restricted to a subgroup but is present to a degree in all cases (Daniel et al., 1991). Conversely, it is important to emphasize that despite the mean group differences there is a significant overlap between subjects with schizophrenia and controls for every structural parameter. Furthermore, none of the established changes are known to be diagnostically specific. Hence the importance of the imaging data is in demonstrating the existence and location of brain pathology in schizophrenia, rather than for clinical purposes.

The structural abnormalities are present in first episode cases, excluding the possibility that they are a consequence of the illness or its treatment. Furthermore, cross-sectional studies show no correlation with duration of illness, suggesting that the alterations are largely static after onset. However, as longitudinal data emerge, the picture is becoming more complicated. First, there is increasing evidence that medial temporal lobe volumes selectively decrease in size during the prodrome and first episode of psychosis. Secondly, some longitudinal studies, spanning up to 10 years, find continuing divergence from controls (DeLisi, 1997) Overall the timing, progression and possible heterogeneity of brain changes in schizophrenia remain controversial, and are important as they bears upon the hypothesised nature of the disease process (see below).

There are few established correlations between brain structure and the symptoms or course of schizophrenia. For example, the expectation that enlarged ventricles might be a correlate of poor outcome has not been consistently demonstrated.

Microscopic and molecular neuropathology

Spurred on by the in vivo imaging evidence that there is a pathology of schizophrenia to be found, contemporary histological studies have addressed two main areas. First, to clarify the frequency and nature of neurodegenerative abnormalities in schizophrenia. Secondly, to investigate the cellular organization (cytoarchitecture) of the cerebral cortex and limbic system.

Gliosis

The issue of gliosis (reactive astrocytosis) has been extensively investigated since a report that gliosis was common in schizophrenia, especially in the diencephalon around the third ventricle (Stevens, 1982) . As gliosis is a sign of past inflammation, this implicated etiopathogenic scenarios for schizophrenia involving infective, ischemic, autoimmune, or neurodegenerative processes. However, over a dozen subsequent investigations have not found gliosis, and the consensus is now that gliosis is not a feature of schizophrenia (Roberts & Harrison, 2000). The issue has considerable implications. The gliotic response is said not to begin until the end of the second trimester in utero, and hence an absence of gliosis is taken as *prima facie* evidence of a disease process occurring before this time. Unfortunately, both the absence of gliosis, and its interpretation, are less clear than often assumed. Firstly, detecting gliosis is surprisingly difficult, and it can be argued that the data do not wholly rule out its occurrence. Secondly, despite the widely cited time point at which the glial response is said to begin, the matter has not been well investigated and it is prudent not to use this to time the pathology of schizophrenia with spurious accuracy. Furthermore, it is a moot point whether the subtle kinds of morphometric disturbance described in schizophrenia, whenever and however they occurred, would be sufficient to trigger detectable gliosis.

Alzheimer's disease in schizophrenia

It is sometimes claimed that Alzheimer's disease is commoner than expected in schizophrenia (perhaps on the assumption that it explains the high prevalence of cognitive impairment in elderly patients). However, a meta-

analysis shows that this is false (Baldessarini et al., 1997), a conclusion which even applies in elderly schizophrenics with severe dementia, who show no evidence of any other neurodegenerative disorder either (Arnold et al., 1998). As such, the cognitive impairment of schizophrenia is unexplained. It may be a more severe manifestation of whatever substrate underlies schizophrenia, or it may be that the brain in schizophrenia is more vulnerable to cognitive impairment in response to a normal age-related amount of neurodegeneration.

Neural cytoarchitecture in schizophrenia

If neurodegenerative abnormalities are uncommon in, or epiphenomenal to, schizophrenia, it begs the question as to what *is* the pathology and how the macroscopic findings are explained microscopically. The answer has been sought in the cytoarchitecture of the cerebral cortex, with measurements of parameters such as the size, location, distribution and packing density of neurons and their synaptic connections (Table 26.3).

Three cytoarchitectural alterations have generated particular interest: abnormal neuronal organization (dysplasia) in the entorhinal cortex, disarray of hippocampal neurons, and an altered distribution of neurons in the subcortical white matter. These findings are important because they support the hypothesis of an early neurodevelopmental anomaly underlying schizophrenia. However, none have been unequivocally and independently replicated, and for each there is at least one non-replication (for references see Harrison, 1999a).

A less well-known yet seemingly more robust cytoarchitectural feature of schizophrenia is that many neurons are smaller (i.e. have a reduced cell body area or volume). This has been shown in three studies of pyramidal neurons in the hippocampus, and has also been reported in dorsolateral prefrontal cortex and for cerebellar Purkinje cells. Some studies find that neurons are also more closely packed. Outside the cerebral cortex, extensive cytoarchitectural data are limited to the thalamus, for which there are reports of a loss of neurons from the dorsomedial and anterior nuclei, though the matter remains controversial.

In summary, a range of differences in neuronal structure and organization have been reported to occur in schizophrenia (Table 26.3). The abnormalities sometimes taken to be characteristic of the disorder, V12 disarray, displacement and paucity of hippocampal and cortical neurons, are features which in fact have not been well demonstrated. This undermines attempts to date the pathology of schizophrenia to the second trimester in utero based on their presence (see below).

Table 26.3. Histological findings in schizophrenia

	Weight of evidence
Lack of neurodegenerative lesions (e.g. Alzheimer changes)	+++++
Lack of gliosis	++++
Smaller cortical and hippocampal pyramidal neurons	+++
Decreased cortical and hippocampal synaptic markers	+++
Decreased dendritic spine density	+++
Loss of neurons from dorsal thalamus	++
Abnormalities of white matter neurons	+
Entorhinal cortex dysplasia	+
Disarray of hippocampal neuron orientation	(±)
Loss of hippocampal or cortical neurons	0

Notes:
0: no good evidence. ±: equivocal data. + to +++++: increasing amount of supportive data.
Source: For detailed review and citations, see Harrison (1999a).

Studies of synapses and dendrites

Synapses and dendrites represent a potential site for pathology undetectable using standard approaches. Because they are hard to visualise directly, proteins localised to these parts of the neuron are used as markers for them (Honer et al., 2000).

Markers of presynaptic terminals are generally reduced in the hippocampus in schizophrenia. The magnitude of the loss varies according to the individual synaptic proteins (and hippocampal subfields) studied, implying that the synaptic pathology is not uniform. There is some evidence for preferential decrements in excitatory connections, in keeping with the indications of glutamatergic involvement mentioned above. Presynaptic markers are also reduced in prefrontal cortex, though in this region a subset of inhibitory neurons and terminals appears most affected (Lewis, 1997). Complementing these changes, a decreased density of dendritic spines has been seen in three studies (Glantz & Lewis, 2000). Although unproven, the usual and simplest interpretation is that these changes reflect fewer (or otherwise aberrant) synaptic contacts being formed and received.

Integrating the neuronal and synaptic findings

There is an encouraging convergence between neuronal and synaptic findings in schizophrenia. In particular, the decreases in presynaptic and dendritic markers are in keeping with the smaller neuronal cell bodies, since the size of the latter is proportional to the dendritic and axonal

Table 26.4. Major transmitter systems implicated in schizophrenia

Transmitter	Main supporting evidence
Dopamine (DA)	DA-releasing agents produce psychosis All antipsychotic drugs are DA (D_2 receptor) antagonists Postmortem: Increased levels of D_2 receptors and loss of cortical DA innervation In vivo: Increased basal and amphetamine-stimulated striatal DA levels
Glutamate	NMDA receptor antagonists produce a schizophrenia-like psychosis Postmortem: altered presynaptic glutamate, NMDA and non-NMDA receptors Partial NMDA receptor agonists (e.g. cycloserine) have some therapeutic benefit Roles of NMDA receptors in development and neurotoxicity
5-HT (Serotonin)	5-HT_2 agonists (e.g. LSD) are psychotomimetic Postmortem: Altered cortical 5-HT_{1A} and 5-HT_{2A} receptors 5-HT_2 receptor polymorphisms associated with schizophrenia and clozapine response Atypical antipsychotics have high affinity for several 5-HT receptors Developmental and trophic roles of 5-HT
GABA	Postmortem: loss of cortical GABAergic cells, receptors, and synaptic markers

spread of the neuron. It is also consistent with the findings of increased neuronal density, in that dendrites and synapses are the major component of the neuropil and, if this is reduced, neurons will pack more closely together (Selemon & Goldman-Rakic, 1999). Moreover, it also corresponds with the results of proton magnetic resonance studies which have shown reductions of the neuronal marker *N*-acetyl-aspartate (NAA), as one would predict if the neurons are on average smaller and have less extensive projections (Bertolino et al., 1998).

Postmortem studies are limited to chronic schizophrenia, so it is impossible to prove that cytoarchitectural abnormalities are not the result of the illness or its treatment. However, several lines of evidence suggest that this is not the case. First, as the structural brain abnormalities and lower NAA signals occur in unmedicated and first-episode schizophrenia, it is reasonable to assume that the cytoarchitectural differences are also present then. Secondly, no correlations with duration of disease or medication exposure have been seen in postmortem studies. Thirdly, although antipsychotic treatment does have morphological consquences, the effects are largely restricted to the basal ganglia (Harrison, 1999b).

Where and what is the pathology?

Most of the positive findings reported in schizophrenia are in the hippocampal formation, dorsolateral prefrontal cortex and cingulate gyrus. However, this may be merely a sign that these areas have been the most intensively studied. Few studies have included a comparison region (e.g. striate cortex) and those which have do not provide a clear picture as to the uniformity vs. selectivity of cerebral involvement in schizophrenia. Neither are any of the individual histological abnormalities specific or pathological in the sense that a neurofibrillary tangle or Lewy body is. Rather, at present the favoured interpretation of the structural pathology as a whole is that it is a quantitative deviation of normal neuronal parameters, probably arising during development and putatively affecting functional connectivity between various brain regions. These hypotheses are elaborated below. However, it is important to remain critical of the empirical data, which could equally lead to the conclusion that, though brain structure is clearly altered in schizophrenia, its location, nature, origins, and consequences remain unknown.

Pathophysiology

Neurochemistry and neuropharmacology

A wide range of neurochemical parameters have been investigated in schizophrenia, both postmortem (Reynolds, 1995) and in vivo (Bigliani & Pilowsky, 1999; Soares & Inins, 1999), and a diverse collection of abnormalities reported. These especially affect monoamine and amino-acid neurotransmitter systems (Table 26.4).

Dopamine

The dopamine hypothesis of schizophrenia has been preeminent for over 30 years (Bennett, 1998). It proposes that the symptoms of schizophrenia result from dopaminergic overactivity, whether due to excess dopamine, or to an elevated sensitivity to it, e.g. because of increased numbers of

dopamine receptors. The hypothesis originated with the discovery that effective antipsychotics were dopamine (D_2) receptor antagonists, and that dopamine-releasing agents such as amphetamine produce a paranoid psychosis. It received support from various postmortem findings of increased dopamine content and higher densities of D_2 receptors in schizophrenia. However, despite its longevity it has proven difficult to refine or refute the hypothesis, for two reasons. First, because antipsychotics have marked effects on the dopamine system, confounding all studies of medicated subjects, hence making postmortem studies problematic. Secondly, molecular biology has revealed a large and complex dopamine receptor family, increasing the potential sites and mechanisms of dysfunction.

Much attention has focused on D_2 receptors. Overall, the studies show an increased density in schizophrenia, but it has been difficult to distinguish what proportion of this is not attributable to antipsychotic medication (Zakzanis & Hansen, 1998). Most PET studies of unmedicated patients have not shown a change in D_2 receptors. However, recent evidence suggests that there may in fact be a genuine increase of D_2 receptors in schizophrenia, the uncertainty being due to methodological issues and perhaps an altered receptor conformation (Seeman & Kapur, 2000). Altered expression of D_1 and D_3 receptors has also been reported but this is either unconfirmed or contradicted by other studies. Particular controversy has surrounded the D_4 receptor, following a report that it was up-regulated several fold in schizophrenia; it has also been a candidate receptor to explain the unique therapeutic profile of the atypical antipsychotic drug clozapine. However the result appears to have been due to a 'D_4-like site' not the true D_4 receptor, and the status of the latter in schizophrenia is unknown (see Harrison, 1999c).

In contrast to the equivocal evidence about dopamine receptors, strong evidence for a functional abnormality of dopamine neurons in schizophrenia is emerging. Several PET and SPET studies have shown elevated striatal dopamine release in response to amphetamine, implying a dysregulation and hyper-responsiveness of dopamine neurons (Laruelle & Abi-Dargham, 1999). Importantly, the dopamine release abnormality is present in untreated patients, and is only present during an acute episode, suggesting that a hyperdopaminergic state may underlie the florid, positive symptoms – dopamine as the 'wind for the psychotic fire' (Laruelle & Abi-Dargham, 1999). Dopamine synthesis may also be increased (Lindström et al., 1999). Finally, a new study shows that dopamine levels and D_2 receptor occupancy are elevated in schizophrenia (Abi-Dargham et al., 2000), providing the best evidence yet for an underlying hyperdopaminergia in the disorder (Harrison, 2000). The position of dopaminergic abnormalities in the pathogenesis of schizophrenia is unknown, though one model envisages them as a consequence of a developmental pathophysiology affecting corticostriatal connections (Grace, 2000).

5-HT (Serotonin)

Suggestions of 5-HT involvement in schizophrenia arose because the hallucinogen lysergic acid diethylamide (LSD) is a 5-HT agonist. Recently, interest has focussed on the 5-HT_{2A} receptor (Harrison, 1999c). A high affinity for the receptor may explain the therapeutic advantages of atypical antipsychotics, and variants in the gene are a minor risk factor for schizophrenia and for non-response to the antipsychotic drug clozapine. Many studies have found lowered 5-HT_{2A} receptor expression in frontal cortex in schizophrenia, and there is a blunted neuroendocrine response to 5-HT_2 agonists. Elevated cortical 5-HT_{1A} receptors are also a replicated finding. Hypotheses to explain the role of 5-HT in schizophrenia include the trophic functions of the 5-HT system in neurodevelopment, interactions between 5-HT and dopamine neurons, and impaired 5-HT_{2A} receptor-mediated activation of prefrontal cortex (Kapur & Remington, 1996).

Glutamate

The observation that phencyclidine and other non-competitive antagonists of the NMDA subtype of glutamate receptor produce a psychosis resembling schizophrenia has driven hypotheses of glutamatergic dysfunction in the disorder. There is now some evidence in schizophrenia itself to support this proposal. For example, in medial temporal lobe, glutamatergic markers are decreased, with reduced expression of non-NMDA glutamate receptors (Meador-Woodruff & Healy, 2000). However, a different pattern is seen in other brain regions and affecting other glutamate receptor subtypes, precluding any simple conclusion. Mechanisms proposed to explain glutamatergic involvement in schizophrenia centre on its interactions with dopamine, and subtle forms of glutamate-mediated neurotoxicity (Tamminga, 1998).

Cerebral metabolic activity

Cerebral metabolism in schizophrenia has been extensively investigated using PET to measure regional cerebral blood flow (rCBF) and glucose utilization. SPET and fMRI have been applied as well (Du & McGuire, 1999).

Hypofrontality has been the most widely reported abnormality. Initially it was thought to be a reliable feature of schizophrenia, present in the resting state. However, whilst hypofrontality does occur in unmedicated subjects, it is not invariable, being seen most clearly when subjects are performing tasks which require activation of the

frontal lobes (Andreasen et al., 1997; Spence et al., 1998). The interpretation of hypofrontality is still debated, notably the causality of its relationship to the undoubted impairment of schizophrenics on prefrontal working memory tasks (Weinberger & Berman, 1996).

The most comprehensive analysis correlating regional cerebral activity with clinical features is by Liddle and colleagues, who showed that the three subsyndromes of chronic schizophrenia which they had previously identified have characteristic patterns of rCBF (Liddle, 1996). For example, subjects with psychomotor poverty (a concept allied to negative symptoms) are hypofrontal whereas those with prominent positive symptoms have increased rCBF in the temporal lobe, especially in the hippocampus. Other studies show that the latter region does not activate normally during cognitive tasks, and that superior temporal gyrus activity has a relationship with auditory hallucinations.

Neurophysiology

Two aspects of sensorimotor functioning in schizophrenia are relevant to its neurobiology. First, sensory evoked potentials are altered. In particular, the P300 component is reduced and delayed in response to auditory stimuli, indicative of impaired sensory processing and further implicating the temporal lobes (Ford, 1999). The P300 alterations are also a trait marker of genetic vulnerability to schizophrenia (Blackwood, 2000). Secondly, there is a high rate of eye movement abnormalities in schizophrenia (Hutton & Kennard, 1998), especially affecting smooth pursuit tracking, suggesting impairment in the pathways subserving oculomotor control.

Together, the neurochemical, functional imaging and neurophysiological data illustrate the range and complexity of cerebral dysfunction which occurs in schizophrenia. Like the structural findings, they point to widespread abnormalities which cannot be reduced to a single locus or transmitter system. These uncertainties lead on to consideration of the two main pathogenic neurobiological theories of schizophrenia: as a disorder of neurodevelopment, and as a disorder of neural connectivity.

Pathogenic theories

Schizophrenia as a neurodevelopmental disorder

The neurodevelopmental model of schizophrenia in essence states that the disorder is due to abnormalities during maturation of the brain. It has become the prevailing pathogenic hypothesis (see Weinberger, 1995; Harrison, 1997; Waddington et al., 1999). A range of evidence is adduced in support of it (Table 26.5).

Table 26.5. Evidence for a neurodevelopmental origin of schizophrenia

- Structural brain changes present at or before onset of symptoms, and largely static thereafter
- No gliosis or other pathological signs of progressive or degenerative disease process
- Environmental risk factors are mostly pre- and perinatal
- Neurological, social and intellectual abnormalities seen in preschizophrenic children
- Increased prevalence of minor physical anomalies and abnormal fingerprint patterns, suggestive of intrauterine growth disturbance
- Increased prevalence of septum cavum pellucidum

A 'strong' version of the theory is that the pathology of schizophrenia originates in the second trimester in utero. An earlier timing is excluded since overt brain abnormalities would be seen if neurogenesis were affected, whilst the lack of gliosis is taken to mean that the changes must have occurred prior to the third trimester. However, this form of the neurodevelopmental model is weak on two neuropathological grounds. First, because of the limitations of the absence-of-gliosis argument mentioned earlier. Secondly, the types of cytoarchitectural disturbance adduced in favour (neuronal disarray and malpositioning) are those suggestive of aberrant neuronal migration, a process which occurs at the appropriate gestational period. Yet, as mentioned (Table 26.3), these cytoarchitectural abnormalities have not been unequivocally shown to be present in schizophrenia. By comparison, the seemingly more robust cytoarchitectural findings (e.g. alterations in neuronal size, synapses and dendrites) could originate much later, such parameters being modifiable throughout life.

Other forms of the neurodevelopmental theory advocate a much wider and later time frame and include many maturational processes (e.g. cell adhesion, apoptosis, myelination and synaptic pruning), or suggest that it applies only to a subgroup of cases, or that neurotoxic processes are involved as well (DeLisi, 1997; Lieberman, 1999). Overall, a parsimonious view is that the data are indicative merely of an essentially developmental, as opposed to degenerative, disease process, rather than as pointing to a particular mechanism or timing. A simplified illustration of the neurodevelopmental model is shown in Figure 26.1.

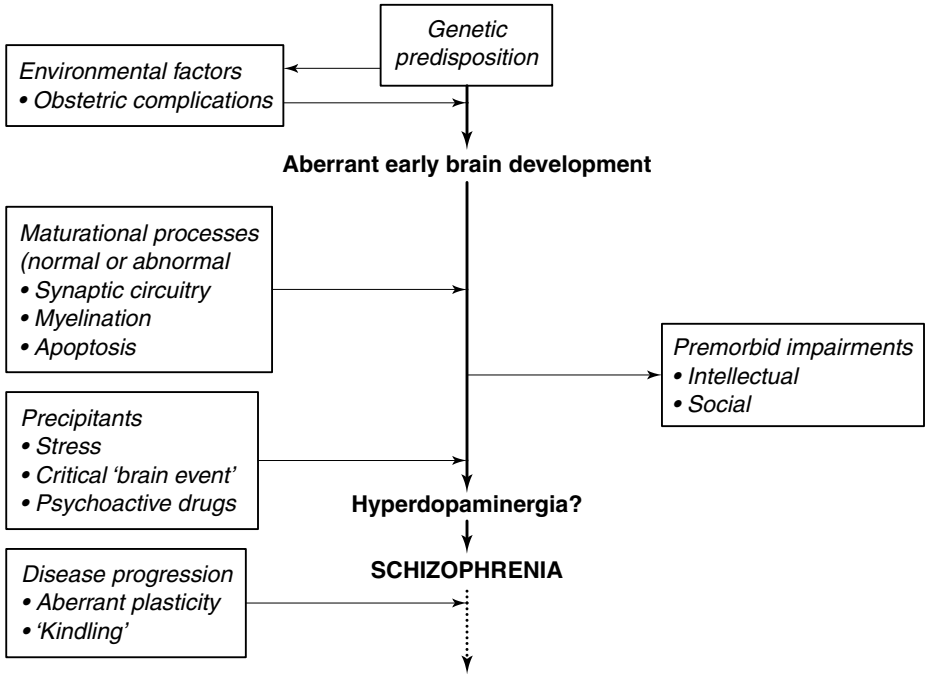

Fig. 26.1. Schematic representation of the neurodevelopmental model of schizoprenia.

Schizophrenia as a disorder of neural connectivity

Bleuler, who coined the term schizophrenia 90 years ago, proposed that the key symptoms are those of 'psychic splitting'. This view now has its counterpart in theories of aberrant functional connectivity between brain regions as the putative mechanism of psychosis (McGuire & Frith, 1996). One model advocates involvement of a circuit between frontal cortex, thalamus, striatum and cerebellum (Andreasen, 1999); another implicates fronto-temporal cortical connections. The conceptual and empirical basis for these proposals originated mainly in the functional imaging studies which show different patterns of activation and deactivation in schizophrenics. The cytoarchitectural features of schizophrenia described above may represent the neuroanatomical basis of this aberrant functional connectivity (Harrison, 1999a).

Treatment

The mainstay of schizophrenia treatment continues to be antipsychotic medication, which is effective in treating acute episodes in 60–70% of patients, and which markedly reduced relapse rates during maintenance therapy (Kane, 1999). However, the drugs cause many and severe side effects, and they have at most minimal efficacy against negative symptoms, depressive symptoms or cognitive deficits. The only drug which is unequivocally more effective than other antipsychotics is clozapine (Wahlbeck et al., 1999), and it is also free of extrapyramidal side effects. Unfortunately, its use is restricted because of the risk of agranulocytosis and the consequent need for regular blood tests.

Clozapine is the prototypical 'atypical' antipsychotic. The term was originally applied to drugs which in rodents were predictive of antipsychotic efficacy but which did not produce catalepsy; it is now often used just to refer to all recently introduced antipsychotics. The main controversy in schizophrenia therapy is whether these new drugs are, like clozapine, more effective and/or cause fewer side effects than conventional antipsychotics. A recent systematic review concluded that atypical antipsychotics as a group (other than clozapine) do cause less extrapyramidal side-effects, but their overall efficacy and tolerability is not clearly superior (Geddes et al., 2000). However, the trials have not adequately examined other outcomes, such as cognitive functioning, suicide rates, quality of life, and rates of tardive dyskinesia; it may well be in these domains that the atypical antipsychotics have their main advantages (e.g. Purdon et al., 2000).

Psychosocial treatments are an integral aspect of management (McGrath & Emmerson, 1999). Family interventions, cognitive therapy aimed at residual psychotic symptoms, and psychological therapy to increase medication compliance have all been shown to be effective (Huxley et al., 2000). In many countries, most patients are looked after by multidisciplinary mental health teams, which in addition to psychiatrists, psychologists and psychiatric nurses include social workers, occupational therapists and others. This range of skills and input is necessary given the range of difficulties and needs which many patients with schizophrenia have.

As yet, there have been few clear therapeutic improvements arising from the various advances in understanding schizophrenia, and the complexity of the disorder makes incremental progress more likely than fundamental advances in the near future. However, there are noteworthy efforts under way, such as trials to enhance glutamatergic functioning (Goff et al., 1999), early intervention to improve outcome (Birchwood et al., 1997) and even discussions about prevention (Tsuang et al., 2000).

In conclusion, considerable progress has been made in revealing the relationship between schizophrenia and the brain. Twenty-five years ago, even the existence of this relationship was doubted (Weinberger, 1995). Nevertheless, there has been no critical breakthrough in terms of identifying a specific biochemical or pathological marker for the disorder, nor a causative gene, and hence the understanding remains in many ways rudimentary. Equally, treatment continues to rely on dopamine-blocking antipsychotic drugs and complementary psychosocial interventions. Currently attention is focused on providing stronger evidence as to the origins and precise details of the molecular neurobiology which underlies this complex and heterogeneous syndrome.

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Obsessive–compulsive disorder

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Introduction

Obsessive–compulsive behaviour has long been described; religious scrupulosity is documented in medieval texts (Adams, 1973), repetitive hand washing as symbolic of guilt has been depicted by playwrights (Shakespeare: Macbeth) and 'obsessive–compulsive neurosis' generated by unconscious conflict was a cornerstone of psychodynamic theory (Freud, 1973). More recently, however, a new paradigm has emerged; obsessive–compulsive behaviour is now viewed as symptomatic of a highly prevalent medical disorder, characterized by specific psychobiological dysfunctions. Indeed, obsessive–compulsive disorder (OCD) is arguably one of the most incisive exemplars of a neuropsychiatric disorder, insofar as clear models now exist of how its characteristic psychopathology is mediated by specific neuroanatomical circuits and neurochemical systems. This chapter aims to provide a comprehensive review of the current state of knowledge on OCD, including epidemiology, clinical features, neurobiology and management.

Epidemiology

Prevalence

Until the 1980s OCD was viewed as a rare disorder, which only affected 0.005% of the population. These figures were based on a study by Rudin, which looked at the prevalence of OCD in a psychiatric in-patient population (Rudin, 1953). The Epidemiological Catchment Area (ECA) study of 1980–1984 radically changed views of the prevalence of OCD (Karno et al., 1988). Undertaken in five US communities, this study found lifetime prevalence rates for OCD to be 1.9–3.3%, making it the fourth most common psychiatric disorder, with a prevalence that was 25–60 times higher than previously believed. These figures were subsequently confirmed in similar studies in Canada (Kolada et al., 1994), Taiwan (Hwuh & Chang, 1989), and several other countries (Weismann et al., 1994), demonstrating that OCD is a disorder with a similar prevalence across nationalities.

The ECA figures, however, have been challenged. The ECA and cross-national study used the Diagnostic Interview Schedule (DIS); a structured interview designed for trained lay interviewers, to arrive at diagnoses. Several later studies have questioned the validity of DIS diagnoses. Nelson and Rice (1997) examined the 1-year temporal stability of the DIS and found it to be low, with only 19.2% of those who were originally diagnosed with OCD having this diagnosis confirmed on follow-up interview. Two follow-up studies of the ECA, using semistructured interviews conducted by psychiatrists (Antony et al., 1985; Helzer et al., 1985), supported these findings. However, these studies have been criticized in view of their small sample size and failure to use objective instruments to ascertain the diagnosis of OCD. More carefully designed studies, using standard rating scales followed by clinician rated diagnostic interviews have confirmed the ECA findings (Rasmussen & Eisen, 1998).

If OCD is so prevalent, why then has its prevalence been underestimated for so many years? In part this is perhaps due to reluctance on the part of sufferers to seek help, whether because of shame about symptoms or because of a lack of awareness of effective treatments. For example, survey of OCD patients found that the mean age of onset was 14.5 years and that professional help was only sought some 10 years later (Hollander et al., 1997a, b). The development of patient advocacy groups in the area of anxiety

disorders and OCD, will hopefully contribute to increased awareness and earlier treatment.

Also important, however, is the problem of clinical misdiagnosis: in this study, the correct diagnosis was made only 6 years after professional help was sought (Hollander et al., 1997a, b). Patients with OCD may present to a range of different clinicians (e.g. to dermatologists for chapped hands following excessive washing, to primary medical practitioners for somatic obsessions, to internists for repeated concerns about AIDS, or to dentists for gum lesions from excessive tooth-brushing), and the diagnosis may be missed in these settings (Hollingsworth et al., 1980; Rapoport, 1989).

Demographic variables

Gender

In epidemiological samples of adults OCD appears to have equal prevalence between males and females (Karno et al., 1988; Valleni Basile et al., 1996; Zohar, 1999). Male gender may be associated with earlier age of onset, comorbid tics, and increased likelihood of perinatal trauma (Bogetto et al., 1999; Lensi et al., 1996).

Race

The ECA study found significantly fewer blacks presenting with OCD (Karno et al., 1988). However, this feature was observed in nine other mental disorders, and is probably a reflection of sociocultural issues, rather than representing a genetic difference in propensity to OCD. Similarly, although studies in Africa (Carothers, 1953; German, 1972) have found the prevalence of OCD to be lower than that described for the US, significant methodological problems exist with many of these studies (failure to use structured clinical interviews, lack of standardized diagnostic criteria). The Cross-National Epidemiological study (Weismann et al., 1994) found prevalence in Korea and Japan to be similar to the US, as did studies of OCD in India (Khanna et al., 1986) and Puerto Rico (Canino et al., 1987)

Socioeconomic status

In the ECA study (Karno et al., 1988) patients with OCD were more likely to be of lower socioeconomic status, and unemployed. However, in two epidemiological studies of children and adolescents, patients presenting with OCD were more likely to be of higher socioeconomic class (Thomsen, 1994; Valleni Basile et al., 1996). It is plausible that the lower socioeconomic status of adults with OCD reflects the impact their disease has on their ability to function in society.

Marital status

OCD sufferers are more likely to be single or divorced than the general population, a likely reflection of the degree of impairment associated with the disorder. Small clinical studies have suggested that the degree of impairment in sexual and marital functioning in OCD is not appreciably different from major depression (Staebler et al., 1993; Coryell, 1981) and panic disorder (Staebler et al., 1993).

Religion and culture

While the prevalence of OCD across different cultures appears to be similar, culture and religion may influence the content of obsessions and compulsions. Several studies in strictly religious communities (primarily Orthodox Jewish and Muslim), have found an increased prevalence of religious obsessions and scrupulosity (Greenberg & Witzum, 1994). Raphael et al. (1996) found more religious affiliation among patients with OCD than other psychiatric patients, but this was not specific to a single religion, and there is little evidence to suggest that increased religiousness is a predisposing factor to develop OCD (Greenberg & Witzum, 1994).

Quality of life and OCD

The enormous negative impact of OCD on patient's lives is reflected in the World Bank and WHO Global Burden of Disease study (Murray & Lopez, 1996), which found OCD to be among the ten most disabling conditions worldwide. The costs of OCD are enormous, reduced or lost productivity from OCD in the US alone has been estimated at $5.9 billion dollars a year (Dupont et al., 1995). Misdiagnosis may cost several billions of dollars a year in the USA (Hollander et al., 1997b).

Quality of life is a concept that is becoming increasingly important in health care and encompasses dimensions such as physical and social role functioning, interpersonal relationships, perceived health and mental well being. Studies of OCD show that it has significant impact on quality of life. Koran et al. (1996b) in a study of medication free patients, for example, found instrumental role performance (i.e. work, homemaking or student role functioning) and social functioning to be worse than that of the general population and of patients with type II diabetes.

These findings underscore the need for effective treatment of OCD. Both retrospective (Stein et al., 1996; Hollander et al., 1997b) and prospective (Bystritsky et al., 1999; Emmelkamp et al., 2000) studies have fortunately indicated that current treatments result in significant improvement in the quality of life in OCD patients.

Clinical features and diagnosis

Age of onset

The ECA study found a mean age of onset of OCD between 21 and 25 years, a figure that has been confirmed by several later studies (Kolada et al., 1994; Rasmussen & Eisen, 1998). However, a significant proportion of patients has onset of symptoms several years prior to the development of the full disorder. The Zurich cohort study (Degonda et al., 1993) reported that 70% of patients developed symptoms before the age of 20 and this has been confirmed in other studies. As noted earlier, there may be significant gender differences in the onset of OCD. Several studies have found males to have an earlier age of onset (17–19 years) than females (19–22 years) (Rasmussen & Eisen, 1990; Degonda et al., 1993).

Natural history and course of disease

OCD has typically been viewed as a chronic progressive unremitting disease. However, the picture may be more complex. Skoog and Skoog (1999) followed 144 patients over 40 years, with average length of follow-up from onset of 47 years. Eighty-three per cent of patients improved, with complete recovery in 20% and subclinical symptoms in 28%. Early age of onset, the presence of both obsessions and compulsions, magical obsessions and compulsive rituals, low baseline functioning and initial chronic course were associated with a worse course. What makes this study particularly interesting is that only 17 patients received medication and in 14 this was instituted after more than 30 years of OCD.

Studies in adolescents also suggest that OCD may improve over time. Flament et al. (1988) in a study of high school students, found that, of 12 students with OCD at baseline, only 5 still had clinical symptoms at 2 year follow-up; and Valleni Basile (Valleni Basile et al., 1996) found that in adolescents with OCD, the most common transition was from the more severe to the less severe category of OCD. While these studies paint a less gloomy picture of the course of OCD it must be emphasized that a significant proportion of patients continue to have disease after many years.

Symptomatology

The hallmark of OCD is the presence of obsessions and compulsion. While the spectrum of obsessions and compulsions is vast, the majority can be grouped into one of the following clusters (Rasmussen & Tsuang, 1986; Rettew et al., 1992).

Contamination fears

These are the most common of obsessions, and are often coupled with avoidance, checking and handwashing. Patients experience intense anxiety about being contaminated, often going to great lengths to avoid the feared object(s). It is interesting to note that, while the symptom structure has remained relatively constant, the actual feared object has changed over time, from the plague to syphilis and now AIDS (Rachman & Hodgson, 1980).

Checking

These patients experience intense worry that something terrible will happen because they failed to check something completely. Often they acknowledge that their fears are absurd, but experience intense anxiety if they do not perform their checking. They often experience a sense of 'incompleteness' (Janet, 1904) until their specified ritual is performed a certain number of times, when the anxiety stops. These patients show the experience of pathological doubt in its purest form. Leckman et al. (1997) found that checking was highly correlated with sexual, religious and somatic obsessions and that the strongest correlations were between aggressive impulses and checking rituals.

Sexual and aggressive obsessions

Some patients suffer from recurrent, unacceptable sexual thoughts or actions, which as Janet (1904) noted, are often the ones calculated to cause the most horror to the patient. For example, a deeply religious woman will have recurrent sexual thoughts of Jesus, or a mother will experience impulses to harm her children. Patients may experience severe guilt and anxiety, often coupled with the need for continual forgiveness or reassurance.

Symmetry and precision

Patients with obsessions about symmetry and precision may line objects up, straighten things, or perform ordering rituals. This may be accompanied by magical thinking; such patients worry that, unless things are ordered or symmetrical, a potential disaster may occur. Symmetry and ordering obsessions have been found to be associated with chronic tic disorders (Leckman et al., 1997).

Obsessional slowness may also occur as a result of symmetry and ordering concerns. Alternatively, however, obsessional slowness may reflect avoidance (for example, patients with contamination concerns may move slowly to avoid exposure to dirt). Patients with obsessional slowness tend to have more neurological soft signs (Hymas et al., 1991), and may represent a subgroup of patients with more severe illness (Veale, 1993).

Somatic obsessions

Somatic obsessions (for example, that a particular part of the body is misshapen or dysfunctional) occur in many disorders and differential diagnosis includes hypochondriasis, body dysmorphic disorder (BDD), and major depression with somatic features. Patients with OCD, however, tend to have multiple obsessions and compulsions.

Hoarding

Hoarding is defined as the acquisition of, and failure to discard possessions that are useless or have limited value (Frost & Gross, 1993). It may occur in response to several different kinds of obsessions e.g. fear of throwing something out by mistake, fear of misfortune occurring. It is a common symptom of OCD, present in up to 18% of patients (Rasmussen & Tsuang, 1986). It has been suggested that hoarding is associated with less insight (Greenberg, 1987; Frost & Gross, 1993), is found more frequently in patients with comorbid tic disorders, and is a predictor of worse response to SRIs (Black et al., 1998; Mataix-Cols et al., 1999).

OCD subtyping

Although advances in OCD demonstrate that it is a specific neuropsychiatric entity, the available data also indicate a degree of heterogeneity. Research interest has recently been directed at finding homogenous OCD subgroups with prognostic and therapeutic implications. Subtyping OCD by means of symptomatology (as above) provides a preliminary approach, to be supplemented by more sophisticated factor analytic techniques.

One of the first factor analyses (Hodgson & Rachman, 1977) used the Maudsley Obsessive Compulsive Inventory and yielded four factors 'checking', 'cleaning', 'slowness' and 'doubting'. However, the Maudsley is biased towards checking and cleaning items. Furthermore, over time patients' symptoms have been shown to evolve from one of these symptom clusters to another.

Rasmussen and Eisen (1991) have proposed three core subtypes of OCD: abnormal risk assessment, pathological doubt, and incompleteness. They argued that these subtypes cut across symptom clusters. In their work, symptoms involving incompleteness were more often associated with tics and compulsive personality features, whereas those without incompleteness were more likely to be associated with high levels of anxiety and comorbid anxiety disorders.

Baer (1994) in factor analysis of the Y-BOCS have provided data partially consistent with this hypothesis. Three factors best summarized the major symptoms: symmetry/hoarding, contamination/checking, and 'pure' obsessions, such as sexual, aggressive and religious obsessions. They noted similarities between symmetry/hoarding and incompleteness, a feature frequently found in Tourette's Syndrome. Symmetry/hoarding was significantly correlated with comorbid Tourette's Syndrome. Several later studies largely confirmed these findings but found symmetry and hoarding to be two different factors (Leckman et al., 1997).

Neuroimaging studies suggest that these factors may have different neuroanatomical correlations. Rauch and colleagues (Rauch et al., 1998a) found that pure obsessions correlated with bilateral striatal activity, symmetry and ordering negatively correlated with right caudate activity, and washing and cleaning symptoms correlated with orbitofrontal and anterior cingulate cortical activity.

These factors also appear to have clinical implications, for example cleaning/checking may respond best to behavioural treatment (Ball et al., 1996), while as we noted earlier, hoarding is associated with comorbid tic disorders and more likely to require the addition of neuroleptic medication (McDougle et al., 1993, 1994).

The relationship between OCD and tic disorders may provide particular insight into the subtyping of OCD. OCD is common in tic disorders and vice versa. Similarly, family studies have found higher rates of OCD in Tourette's syndrome probands, and higher rates of TS in OCD probands, suggesting a genetic link between the two disorders (Pauls et al., 1995).

Patients with and without tics may have phenotypic differences. For example, OCD patients with tics have male predominance, earlier age at onset, and higher frequency of tic-like compulsions such as the need to touch, tap, or rub items, blinking and staring rituals, as well as symmetry obsessions and feelings of incompleteness. Patients with tics are also more likely to experience sensory phenomena, such as bodily sensations, mental urges and a sense of inner tension (Miguel et al., 2000).

OCD patients with tics differ from those without tics in their response to treatment as well. A retrospective case controlled analysis found fluvoxamine to be less effective in patients with tics (McDougle et al., 1993). Furthermore, in one study patients with tics were more likely to respond to typical neuroleptic augmentation (McDougle et al., 1994). Such data suggests that patients with OCD and tics may represent a neurobiologically distinct subgroup. However, contrary to expectations, a recent controlled trial of risperidone (McDougle et al., 2000) found no significant difference in response between patients with and without tics.

Other aspects of the neurobiology of OCD may provide

an alternative basis for subtyping. Increased neurological soft signs have been found in OCD patients as compared to normal controls (Hollander et al., 1990), and in some but not all studies, this has been a predictor of poorer response to pharmacotherapy (Hollander et al., 1992; Thienemann & Koran, 1995). Similarly, the group of OCD patients with symptom onset in the context of streptococcal throat infection (see below) may represent a distinct subgroup. Thus, several possible ways of integrating data on symptoms, neurobiology and treatment into meaningful subgroups of OCD have been proposed, but further work is required to consolidate these approaches.

Diagnosis

DSM-IV (American Psychiatric Association, 1994) has provided diagnostic criteria for OCD. Like earlier versions, DSM-IV requires patients to experience either obsessions or compulsions which cause marked distress and significantly interfere with the person's social and/or occupational functioning. However, DSM-IV differs from earlier versions in two important ways: The need for insight and the presence of mental rituals.

The DSM-IV field trial (Foa et al., 1995) found that the large majority of patients were uncertain about whether or not their symptoms were unreasonable, and as result the need for insight was de-emphasized and a subcategory 'with poor insight' was added. Furthermore, the majority of patients were found to have mental rituals, and the definition of compulsions was changed to indicate that these are not necessarily physical actions.

Differential diagnosis

Other psychiatric disorders can present with phenomena similar to OCD. Patients with OCD spectrum disorders often experience recurrent, intrusive thoughts or behaviours but these are limited to a specific context (e.g. preoccupation with appearance in body dysmorphic disorder, hair pulling in trichotillomania, or excessive fears of having an illness as in hypochondriasis.) Similar distinctions occur with other anxiety disorders: social or specific phobia is characterized by preoccupations that are limited to a particular feared object or situation, while generalized anxiety disorder is characterized by excessive worry which involves real life situations.

Patients with dementia may display excessive list making, hoarding, counting and other behaviours that resemble compulsive rituals but are compensatory mechanisms. Patients with major depression may show somatic or paranoid ruminations, and patients with schizophrenia can display contamination concerns and hoarding behaviours. These patients however, typically have other symptoms as well, and the form of their symptoms may differ from the classical pattern of ego-dystonicity that characterizes OCD.

Tics and stereotyped movements must be distinguished from compulsions. The key differences are that they are not performed in response to an obsession and the patient does not attach meaning to these movements. However, it is important to bear in mind that the diagnosis of OCD and a tic disorder often coexist.

OCD must also be distinguished from obsessive compulsive personality disorder (OCPD). Unless they have a coexisting diagnosis of OCD, patients with OCPD do not have obsessions or compulsions, but rather their personality is characterized by a pervasive pattern of preoccupation with orderliness, perfectionism and control.

Superstitions and rituals are commonly encountered among a wide variety of people, but a diagnosis of OCD should only be considered if these behaviours are ego-dystonic, and cause significant distress or functional impairment.

Neurological disorders involving lesions of the frontal lobe, basal ganglia (particularly the caudate nucleus) or both, should be excluded. In a review of the relationship between frontal lobe degeneration and repetitive behaviours Ames et al. (1994) found 78% of patients showed some type of repetitive or compulsive behaviour. Similarly, many patients with lesions of the striatum develop behaviours that are consistent with a diagnosis of OCD. Case reports attest to a wide variety of etiologies for such lesion ranging from neurodegenerative disorders such as Huntington's disease, to infarction, to toxins like carbon monoxide or manganese (Cummings & Cunningham, 1992). There are also a few reports of temporal lobe lesions leading to OCD (Jenike & Brotman 1984; Zungu-Dirwayi et al., 1999).

Comorbid conditions

Comorbid conditions are frequent in OCD, with studies reporting that at least 50% of patients have a comorbid Axis I disorder and at least 40% of patients also meet criteria for personality disorder(s) (Piggot et al., 1994).

Axis I disorders

Major depressive disorder is the most common comorbid disorder in OCD, with at least 30% of patients meeting the criteria for a concurrent major depressive episode and lifetime prevalence as high as 70% (Piggot et al., 1994). Depression usually occurs secondary to OCD, with most patients reporting an onset of depressive symptoms after the onset of OCD. However, others report a separate course for their depressive symptoms vs. those of OCD, suggesting

that in a subgroup of patients the disorders are unrelated or at least separate.

The relationship between OCD and mania has been less well studied, but recent evidence suggests that a significant number of patients have both disorders. Chen and Dilsaver (1995) found that 21% of subjects with bipolar disorder in the ECA survey had comorbid OCD while Kruger et al. (1995) found an incidence of 35%. Perugi et al. (1999) found that 16% of patients with OCD had comorbid bipolar disorder (mainly bipolar II). They found that these patients had a more gradual onset, more episodes of major depression and a higher rate of sexual and religious obsessions and fewer checking obsessions.

A substantial cohort of patients (40–60%) with OCD also have comorbid anxiety disorders, with the most common being panic disorder (12–15%), simple phobia (22–27%), and social phobia (11–18%). It has been suggested that the anxiety disorders represent states of altered risk assessment, and the high rates of comorbidity point to shared pathophysiological mechanisms (Piggot et al., 1994).

A substantial number of patients with OCD also have eating disorders, with lifetime rates of anorexia nervosa of 10–17% and rates for bulimia nervosa of 5–20% (Piggot et al., 1994). Similarly, patients with anorexia nervosa and bulimia nervosa have been reported to have a high incidence of obsessional features. This may have therapeutic implications with some studies suggesting that SSRI's may have preferential efficacy in these patients.

Axis II disorders

Due to changes in the conceptualization and diagnostic criteria of personality disorders, the co-morbidity of personality disorders with OCD has been difficult to elucidate. Nevertheless, in studies using DSM-III or IIIR criteria, personality disorders have been found to be very common in patients with OCD with some studies reporting that over 50% of patients meet the criteria for at least one personality disorder. Avoidant, dependent, histrionic or obsessive compulsive personality disorders appear to be the most common comorbid diagnoses (Piggot et al., 1994).

The relationship between OCD and OCPD has been an area of special interest. For many years the Freudian concept of the 'anal erotic character' dominated thinking about the relationship between OCD and OCPD. Here the disorders were viewed as existing along a continuum; with OCD being the final most severe form of the disorder. More recent evidence suggests that significant differences exist between the two disorders. OCD may be a predisposing factor for the development of OCPD. It has been suggested that patients may develop OCPD as an adaptive mechanism to deal with disorder (Baer & Jenike, 1992), a possibility supported by the observation that OCD often predates the development of OCPD (Baer & Jenike, 1992). Obsessive–compulsive personality disorder occurs less frequently in OCD than previously thought but is still more common in OCD than in either the general population or in patients with major depression or panic disorder.

The role of personality disorders as predictors of outcome has received some study. Concomitant schizotypal personality disorder in particular has been consistently associated with poorer response to medication and behavioural therapy, and in some studies has been shown more likely to be associated with a response to typical neuroleptic augmentation (Ravizza et al., 1995). This is in keeping with studies reflecting dopamine dysfunction in schizotypal personality disorder (Siever, 1994). However, a trial of risperidone did not find a difference in response between those with and without schizotypal personality disorder (McDougle et al., 2000).

Etiology and pathophysiology

OCD is a complex disorder, in which several pathophysiological processes may be involved:

The genetics of OCD

Current data suggest that OCD has a substantial genetic component. Twin studies show concordance rates of approximately 80% in monozygotic twins and only 47–50% in dizygotic twins (Inyoue, 1965; Carey & Gottesman, 1981). Furthermore, several studies have found a greater prevalence of OCD and subsyndromal OCD in parents and first-degree relatives of OCD probands as compared to parents of psychiatrically normal controls (Black et al., 1992; Pauls et al., 1995).

Family studies have also borne out a link with Tourette's syndrome with greater prevalence of OCD in first-degree relatives of probands with Tourette's syndrome regardless of OCD comorbidity. Pauls et al. (Pauls & Leckman, 1986; Pauls et al., 1990) in two studies of Tourette's syndrome probands found familial patterns of Tourette's syndrome, chronic tics, and OCD that were consistent with an autosomal mode of transmission with incomplete penetrance. Two later studies replicated these findings (Van de Wetering, 1993; Eapen et al., 1993).

Taken together, these findings suggest that the risk for developing OCD is heritable and point to at least one form of OCD that is characterized by early onset and association with tic disorders.

Neuroanatomical models of OCD

The current neuroanatomical model of OCD emphasizes the role of cortico-striato-thalamo-cortical (CTSC) circuitry. Alexander et al. (1986, 1990) conceptualized this as being organized into multiple, parallel segregated circuits, which project from the cortex to corresponding striatal subterritories, from there to the basal ganglia, and via the thalamus back to the prefrontal regions from which they originated. Very briefly, these systems function to filter out extraneous input to the cortex, to ensure refined output and to mediate stereotyped rule-based processes without these reaching consciousness.

Modern imaging studies confirm the role of cortico-striato-thalamo-cortical circuitry in OCD.

Structural studies

Several volumetric studies of the caudate have shown structural abnormalities. The nature of the abnormalities described has been inconsistent, with some studies showing increased volume and others decreased volume; it is possible that caudate volume changes over time, with increased volume in the aftermath of streptococcal infection (Giedd et al., 2000), and later shrinkage.

Volumetric changes in the orbital frontal and anterior cingulate regions have been less well studied. Of three studies reported so far, only one (Szezsko et al., 1999) found structural abnormalities (reduced bilateral orbital frontal and amygdala volumes). Functional imaging studies, however, provide more robust evidence for involvement of these structures (see below).

White matter reductions in OCD have been reported and a subsequent replication study confirmed overall white matter reduction but increased opercular volume, which correlated with both severity of OCD and nonverbal immediate memory (Jenike et al., 1996). Finally, thalamic volumes normalize after treatment with paroxetine but not behaviour therapy, perhaps pointing to a different mechanism of action for the two modalities (Rosenberg et al., 2000a).

Studies using magnetic resonance spectroscopy (MRS) have also demonstrated striatal abnormalities. Two studies have found decreased *N*-acetyl-aspartate (NAA) levels in the striatum (Ebert et al., 1997; Bartha et al., 1998), suggesting decreased density of healthy neurons in this region. Furthermore, one of these studies failed to find significant differences in striatal volumes (Bartha et al., 1998), underscoring the purported greater sensitivity of MRS–NAA over current morphometric MRI methods.

Rosenberg's group has also demonstrated abnormalities in a pediatric population. Decreased NAA levels were found in right and left medial thalami, with the decreased levels in the left medial thalamus correlating with increased severity of disease (Fitzgerald et al., 2000). In addition caudate glutamatergic levels were found to be increased in children with OCD (Rosenberg et al., 2000b), but this was found to normalize after treatment with paroxetine, perhaps suggesting that paroxetine treatment is mediated by a serotonergically modulated reduction in fronto-striatal glutamatergic concentration.

Functional studies

Neutral state studies have implicated hyperactivity in the prefrontal cortex and less consistently striatal and cingulate involvement (Baxter et al., 1988; Nordahl et al., 1989; Swedo et al., 1989c; Benkelfat et al., 1990; Machlin et al., 1991; Rubin et al., 1992; Perani et al., 1995). Pre/posttreatment studies also point to involvement of these areas. Decreased activity after medication was found in the medial frontal cortex (Hoehn-Saric et al., 1991), and orbitofrontal cortex (Benkelfat et al., 1990; Swedo et al., 1992c), with one study correlating treatment response to activity in the right frontal cortex. Changes in the caudate and cingulum have also been reported (Benkelfat et al., 1990).

Baxter et al. (1992) found decreased right caudate activity in a group receiving medication as well as a different group receiving behaviour therapy. This was subsequently replicated in a second study of behaviour therapy, which also confirmed correlation between orbitofrontal and caudate activity pretreatment that disappeared posttreatment (Schwartz et al., 1996). These studies confirm that effective treatment of OCD, whether pharmacotherapeutic or psychotherapeutic in nature, is accompanied by specific changes in CTSC circuits.

Why should dysfunction in CTSC circuits lead to OCD symptoms? There is increasing evidence that striatal function is associated with the development, maintenance and selection of motoric cognitive and procedural strategies, this has been variously described as 'habit system' 'response set' and 'procedural mobilization'. Thus, it may be argued that striatal lesions can lead to the inappropriate release of genetically programmed sequences (such as hand-washing, hoarding, etc.).

An early heuristic model (Baxter et al., 1990) postulated that different circuits may be involved in the mediation of different kinds of OCD symptom. According to such a 'striatal topography model', the cognitive symptoms of OCD are mediated by the caudate, motoric symptoms by the putamen, and affective symptoms by paralimbic CTSC circuits. More recent evidence shows involvement of a range of CTSC circuits in OCD; nevertheless it may still be suggested that projections to specific fields or cells mediate different kinds of OCD symptoms.

Rauch et al. have suggested that the intrusive events that are the hallmark of OCD and related disorders represent failure of filtering at the level of the thalamus (Rauch et al., 1985). Information can be processed in two ways explicitly (i.e. consciously) and implicitly (i.e. unconsciously), with implicit operations being primarily processed via cortico-striatal systems. In OCD, pathology in the cortico-striatal pathways may allow this information to gain access to consciousness, presenting as intrusive phenomena. Rauch et al. has shown that the striatum is usually recruited during an implicit sequence learning task, but that in patients with OCD, this fails to occur and instead, medial temporal structures, usually associated with conscious information processing, are recruited (Rauch et al., 1985, 1997, 1998b).

In this model compulsions or tics may represent a compensatory mechanism. These repetitive behaviours may serve to recruit viable cortico-striatal-thalamic circuits, thereby facilitating filtering at the level of the thalamus. The repetitions required would reflect the inefficiency of such mechanisms. This is also consistent with clinical observation that patients often suddenly no longer experience the urge to perform a behaviour, 'as if a switch were turned off'. Presumably, once sufficient repetitions have been performed, a threshold level of filtering is reached and the intrusive stimuli no longer reach consciousness. Rauch et al. (1998a, b) have also demonstrated in functional imaging studies a characteristic pattern of thalamic deactivation with striatal recruitment.

Neuropsychology of OCD

Neuropsychological studies of OCD have demonstrated that the following domains of cognitive functioning are most consistently affected in patients with OCD: visuospatial skill, non-verbal memory, and executive abilities.

Visuospatial skills describe the patient's mental capacity to perceive and manipulate objects in two and three dimensional space (Lezak, 1995). Patients with OCD have been found to be impaired on a number of tests that purport to measure visuospatial memory (Flor-Henry et al., 1979; Insel et al., 1983; Behar et al., 1984; Head et al., 1989; Hollander et al., 1990, 1993; Boone et al., 1991; Christenson et al., 1992; Aronowitz et al., 1994, Savage et al., 1995).

Non-verbal memory refers to the ability to learn and recall new visual objects and images, preferably ones not easily described with words. Again, patients with OCD show impairment on several tests of nonverbal memory (Boone et al., 1991; Zielenski et al., 1991; Christenson et al., 1992; Savage et al., 1993, 1995; Aronowitz et al., 1994; Dirson et al., 1995; Cohen et al., 1996). In particular, their ability to encode new non-verbal information appears particularly affected (Boone et al., 1991; Zielenski et al., 1991; Savage et al., 1993, 1995; Aronowitz et al., 1994; Cohen et al., 1996). Deficits in the ability to retrieve previously stored non-verbal memories have also been described. To put it another way, patients with OCD have difficulty learning new non-verbal material, and once having learnt it, have problems in retrieving that memory.

Underlying both these deficits may be impairment of executive function. Executive function refers to the high-level control processes that modulate more elementary sensory, motor, cognitive, memory and affective functions. It requires the ability to take the overall context of the situation into account and use this knowledge to set priorities, implement strategic behaviour and shift behaviour appropriately as the situation changes (Lezak, 1995).

In general patients with OCD appear to have most difficulty in this last component of executive function, that is, they have trouble changing their behaviour appropriately as the situation changes (Malloy, 1987; Christenson et al., 1992).

This is reminiscent of the symptoms of OCD (Savage, 1998). Take as an example a compulsive checker. The excessive fear that something may happen if he fails to check may be linked to failure to appreciate the overall context of the situation. Checking may also be related to difficulty planning and implementing strategic actions. Continued checking in the face of its failure to reduce anxiety may be related to difficulty in flexibly modifying behaviour

This deficit in executive functioning may underlie the problems with non-verbal memory. If a person has poor executive function, and hence organizational problems, it is likely that they will not be able to break down visual structures into easily recognizable components, and hence find them more difficult to remember. Savage et al. demonstrated exactly this in a study that examined OCD patients' performance on the Rey–Osterreith complex figure test. Patients (and matched controls) were asked to copy a complex figure and then draw it immediately after the figure was removed and 30 minutes later. Patients with OCD showed impairment both in the organizational approach used to copy the figure as well as recall after the figure was removed (both immediate and delayed). Recent work also suggests impaired organizational strategies may mediate deficits in verbal memory as well (Savage et al., 2000).

These findings tie in well with evidence of fronto-striatal dysfunction demonstrated in imaging studies of patients with OCD. Studies of patients with Parkinson's disease and Huntington's disease, both disorders involving striatal degeneration, show evidence of executive dysfunction leading to memory and spatial deficits in these patients,

with deficits in organizational approach similar to those found in OCD (Ogden et al., 1990; Grossman et al., 1993)

Autoimmune pathology in OCD

In a series of landmark studies (Swedo et al., 1989b, 1993), Swedo and colleagues confirmed earlier observations that OCD symptoms were common among children with Sydenham's chorea, and often preceded motor manifestations of the disease. Later work (Swedo et al., 1998) demonstrated that a subgroup had OCD symptoms of abrupt onset, and showed exacerbations that often were associated with demonstrable group A β-hemolytic streptococcus infection. In addition, a subset of children with OCD shows antineuronal antibodies.

Together, these finding have led to the designation of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) (Swedo et al., 1998). Specific criteria include: (i) presence of OCD and/or a tic disorder, (ii) prepubertal onset, (iii) episodic course of symptom severity, (iv) association with group A β-hemolytic streptococcus infection (v) association with neurologic abnormalities.

Autoimmune basal ganglia damage has been identified as an important pathogenic mechanism in Sydenham's chorea (Husby et al., 1976). Furthermore, acute changes in striatal volume parallel the clinical course of PANDAS (Gibofsky et al., 1991). These findings therefore strengthen the case for striatal damage as a pathogenic mechanism for OCD.

Susceptibility to rheumatic fever and hence PANDAS (Gibofsky et al., 1991) may be inherited as an autosomal recessive trait. The B lymphocyte antigen d8/17 appears to serve as a marker for susceptibility to rheumatic fever, occurring in 100% of rheumatic fever sufferers (Khanna et al., 1989), with significantly higher expression in the rheumatic fever patients than in either unaffected first degree relatives or normal controls. As increased D8/17 has not been reported in poststreptococcal glomerulonephritis, it may indicate specific vulnerability to developing rheumatic fever and related complications. Elevated D8/17 expression has been described in patients with childhood onset OCD, Tourette's syndrome and autism, but not in trichotillomania (Swedo & Leonard, 1992; Niehaus et al., 1996; Murphy et al., 1997; Swedo et al., 1997; Chapman et al., 1998).

Neurochemistry and neuropharmacology

A number of neurotransmitter systems appear to play a role in mediating OCD symptoms.

Serotonin and OCD

The serotonergic hypothesis of OCD was first prompted by the observation that serotonergic reuptake inhibitors were more effective in alleviating the symptoms of OCD (Fernandez-Cordoba & Lopez-Ibor, 1967; Zohar & Insel, 1987; Greist et al., 1995b). Whether SSRI's work by correcting some fundamental abnormality on the serotonergic system or whether they modulate an intact system to compensate for underlying abnormalities in OCD is not yet known.

An interesting set of preclinical studies have found that, in order to desensitize the 5-HT1D autoreceptor in orbitofrontal cortex, the administration of relatively high doses of SSRI's for relatively long periods is required (low doses, short duration, and ECT does not have an effect) (Mansari et al., 1995). This work is reminiscent of clinical findings in OCD (see below), and suggests that this receptor may therefore have a particularly important role.

There is also work suggesting that 5-HT-2 receptors are important in OCD. Case reports suggest that certain hallucinogens (psilocybin and LSD), that are potent stimulators of the 5HT2A and 5HT2C receptors, can decrease OCD symptoms (Delgado & Morena, 1998). Conversely, ritanserin, a 5-HT-2 antagonist results in the exacerbation of OCD symptoms (Ergovesi et al., 1992). Arguably, enhancement of neurotransmission through 5HT2A or 5HT2C receptors may be a common pathway for drugs with therapeutic effect in OCD.

Studies of indirect measures of central serotonergic function (such as platelet receptor binding and CSF concentrations of 5HT metabolites) in OCD have been inconsistent. There is somewhat more consistency in studies of serotonergic agonists; OCD symptoms are exacerbated by mCPP (a 5HT1A and 5HTC agonist) (Zohar et al., 1987; Hollander et al., 1991; Piggot et al., 1993) and perhaps by sumatriptan (a 5HT-1D agonist) (Stein et al., 1999). Administration of sumatriptan during functional imaging demonstrated a significant association between symptom exacerbation and decreased frontal activity, arguably consistent with a role for the 5-HT1D receptor in OCD (Stein et al., 1999). Nevertheless, findings with both mCPP (Charney et al., 1988; Ho Pian et al., 1998; Goodman et al., 1996) and sumatriptan (Pian et al., 1998) have not always been consistent, and sumatriptan has poor blood–brain barrier penetration, so that additional work in this area remains necessary.

Dopaminergic systems and OCD

Preclinical studies demonstrate that stereotypic behaviour can be elicited by the administration of dopamine agonists, and decreased by dopamine blockers. Similarly,

complex repetitive behaviours have been described in stimulant abusers (Ellinwood, 1967; Schiorring, 1975). Furthermore cocaine, which potentiates the effects of dopamine by blocking presynaptic uptake has been reported to exacerbate symptoms in patients with OCD and to induce such behaviour in subjects with a family but not personal history of OCD.

As noted earlier, there is also a strong association between OCD and Tourette's syndrome, a disorder for which a dopaminergic basis is well elucidated. For example, the principal dopamine metabolite homovanillic acid (HVA) is decreased in the CSF of patients with Tourette's syndrome (McDougle et al., 1989), and dopamine blockers are a standard form of treatment in TS. Recent imaging studies have demonstrated a significant increase in the number of striatal presynaptic dopamine carrier sites in the caudate and putamen in Tourette's patients (Singer et al., 1991; Malison et al., 1995; Wolf et al., 1996).

Pharmacologic studies in OCD support a potential role for the dopamine system. Only around 50–60% of patients respond to SSRIs, and patients with comorbid tics are particularly likely not to respond (McDougle et al., 1994). However, augmentation of SSRIs with dopamine blockers has been shown effective in both open (Jacobsen, 1995; Stein, 1997b) and controlled trials (McDougle et al., 2000). Typical neuroleptics are particularly effective in OCD patients with comorbid tics (McDougle et al., 1994), while the atypicals appear useful in OCD patients both with and without tics (Stein et al., 1997a, b; McDougle et al., 2000).

Neuropeptides and OCD

Preclinical evidence has linked neuropeptides to repetitive behaviour in animals and initial clinical investigations in OCD patients suggest that they may play a role in modulation of the disorder. Neuropeptides implicated in OCD include arginine vasopressin (AVP), oxytocin, adrenocorticotropic hormone (ACTH), corticotropin releasing factor (CRF), somatostatin, and the opioid system.

Preclinical studies have linked AVP with enhancement of memory acquisition and retrieval and with grooming behaviours. AVP may also inhibit extinction, decreasing the likelihood of changing a behavioural pattern once it has been established. Altemus et al. (1992) found OCD patients had significantly elevated basal levels of AVP and secreted more AVP into plasma in response to hypertonic saline. However, this was not found in a subsequent study (Leckman et al., 1994a). Nevertheless, in children and adolescents with OCD, a negative correlation between symptom severity and AVP levels was found (Swedo et al., 1992a).

Preclinical studies have shown that oxytocin administration markedly increases grooming behaviour. Furthermore, oxytocin has been shown to induce maternal behaviour in female rats, but only in animals primed with estrogen (Insel, 1992). This may be relevant to explaining the increased risk for onset or exacerbation of OCD in pregnancy or the puerperium. Elevated levels of oxytocin (and estrogen) may induce OCD symptoms in a vulnerable subgroup of women. Higher CSF oxytocin levels have been found in adult patients with no family or personal history of tic disorders and oxytocin levels were significantly correlated with Y-BOCS scores (Leckman et al., 1994b). In children, the AVP/oxytocin ratio was negatively correlated with symptom severity (Swedo et al., 1992a). Administration of oxytocin to adults with OCD has, however, had no consistent therapeutic effect (Epperson et al., 1996).

ACTH and CRF are both noted to increase self-grooming in animals. In humans, both basal plasma ACTH and the increase following CRF administration was found to be less in adults with OCD than controls (Bailly et al., 1994). Studies of CRF levels have been inconsistent, with initial reports of elevated CRF in OCD patients not being confirmed in replication studies. In children, no correlation has been found between either CSF ACTH or CRF levels and symptoms severity (Swedo et al., 1992a). As both ACTH and CRF are released in response to stress, it is possible that any elevations found may be a non-specific response to the stress of a chronic illness.

In animals, somatostatin delays the extinction of active and passive avoidance behaviours (which may be similar to the persistent repetition of OCD) and can also produce stereotypic behaviours (Vecsei et al., 1986; Vecsei & Widerlov, 1988). Studies of both adults and children with OCD have found higher CSF somatostatin as compared to normals (adults) and conduct disordered children (Kruesi et al., 1990; Altemus et al., 1993).

Opioids mediate reward signals and it has been postulated that they may be involved in mechanisms that signal successful task completion. Deficiencies in these mechanisms may potentially explain the 'self-doubt' experienced by many patients with OCD. OCD patients have elevated serum antibodies for the dynorphin precursor prodynorphin (Roy et al., 1994). In Tourette's syndrome CSF dynorphin was found to correlate with OCD (but not tic) symptom severity (Leckman et al., 1988). However, no correlation was found between dynorphin levels and symptom severity in children with OCD. Furthermore, challenges with opioid antagonists in OCD have produced inconsistent results (Insel & Pickar, 1983; Keuler et al., 1996).

In summary, preclinical evidence suggests that various neuropeptides may play a role in the pathogenesis of OCD. Differences between results in adult and pediatric popula-

tions suggest developmental factors impact the functioning of the different neuropeptides. However, clinical studies so far have generally produced inconsistent results, and further studies are warranted to elucidate fully the role of these peptides.

OCD spectrum disorders

In recent years a group of disorders has been hypothesized to overlap phenomenologically and neurobiologically with OCD, the so-called OCD spectrum disorders (Hollander, 1993). These potentially include a broad range of conditions including disorders usually first diagnosed in childhood, infancy, or adolescence (Tourette's disorder, autistic disorder, stereotypic movement disorder), somatoform disorders (body dysmorphic disorder, hypochondriasis), and disorders of impulse control not otherwise specified (trichotillomania, pathological gambling). Nevertheless, the characterization of so varied a range of disorders as OCD related remains contentious, with some authors warning against premature and overinclusive classifications (Rasmussen, 1994).

Neurobiological data so far has pointed to several similarities between some of these disorders. Several of the OCD spectrum disorders have shown a selective response to serotonergic agents. Clomipramine has been shown to be superior to desipramine in a range of repetitive behaviours including hair-pulling (Swedo et al., 1989a), nail-biting (Leonard et al., 1991), stereotypic behaviours (Castellanos et al., 1996) and obsessive–compulsive symptoms in autistic disorder (Gordon et al., 1992). Data also indicates the selective efficacy of serotonin reuptake inhibitors (SRIs) for symptoms of body dysmorphic disorder (Hollander, 1993), obsessive–compulsive symptoms in Tourette's (Scahill et al., 1997), and self-injurious behaviour in mental retardation (Mikkelson et al., 1997). Augmentation of SRIs with dopamine blockers may also be useful in some of the disorders. Nevertheless, it should be remembered that SRIs may be selectively effective in disorders with markedly different phenomenology from OCD (such as premenstrual dysphoric disorder (Eriksson et al., 1995)).

There may also be neuroanatomical overlap between OCD and some of the putative OCD spectrum disorders. For example, in Tourette's disorder magnetic resonance imaging (MRI) studies have found abnormalities of the basal ganglia (including the putamen, Singer et al., 1993), and functional imaging studies have demonstrated abnormal activity in frontal-striatal regions. Findings are not precisely those found in OCD, but OCD symptoms in TD may correlate with increased metabolism in orbitofrontal cortex and putamen (Braun et al., 1995). Furthermore, in patients with obsessive–compulsive symptoms, regional cerebral blood flow patterns differed depending on whether a family history of TD was present, and patterns were similar to those seen in TD in patients from TD families (Moriarty et al., 1997).

In trichotillomania there is only limited brain imaging data. The data that does exist suggests that the caudate is not involved (O'Sullivan et al., 1997; Stein et al., 1997b), but that the left putamen may be smaller in trichotillomania than in controls (O'Sullivan et al., 1997). On functional imaging, however, patients with trichotillomania were found to have increased cerebellar and right superior parietal glucose metabolic rates compared to normal controls (Swedo et al., 1991). These authors also found that anterior cingulate and orbital-frontal metabolism correlated negatively with clomipramine response, a result they previously found in OCD. Increased orbital-frontal metabolism may conceivably comprise a compensatory response in both disorders.

Genetic overlap between OCD and TD has been of particular interest in the context of OCD spectrum disorders. Tics are more common than expected in the families of OCD probands, and OCD is more common in the families of TD patients than in those of controls. Furthermore, preliminary work on dopamine receptor polymorphisms suggests differences in OCD patients with and without tics (Nicolini et al., 1998). While trichotillomania and OCD may be more common in the families of trichotillomania probands than in the general population, this seems to be a relatively subtle finding (Lenane et al., 1992). Also, there was no increased prevalence of pathological gambling or eating disorders in families of OCD probands compared with controls (Black et al., 1994).

Neuroimmunological studies also point to the existence of a spectrum of disorders. Swedo et al. (1998) note that in the aftermath of β-hemolytic streptococcal infection, patients may present not only with OCD, but also with a range of other symptoms including tics and hair-pulling (Swedo et al., 1992b). Also, expression of the D8/17 lymphocyte marker appears increased in childhood-onset OCD and Tourette's (Murphy et al., 1997), and in autism (Hollander et al., 1997a), although not in trichotillomania (Niehaus et al., 1996).

Some authors (Stein & Hollander, 1993a, b) have suggested that one way of looking at the OCD spectrum may be in terms of the dimension of compulsivity and impulsivity. This perspective is based on the notion that compulsivity may reflect harm avoidance, whereas impulsivity reflects risk-seeking. Thus OCD falls on the compulsive end of an OCD spectrum, whereas impulsive disorders fall on the impulsive end, with disorders such as

Tourette's, trichotillomania, and obsessive–compulsive personality disorder demonstrating both compulsive and impulsive characteristics.

Serotonin receptor studies appear to provide some evidence in support of this. Whereas OCD appears to be characterized by hyperresponsivity of at least some serotonergic receptors, impulsivity has been strongly associated with serotonergic hypofunction. Similarly, whereas OCD is characterized by frontal hyperactivity on functional imaging, impulsivity is known to be associated with the loss of prefrontal function. Closer examination suggests, however, that such a distinction is overly simplistic. OCD patients may in fact demonstrate impulsive-aggressive symptoms and impulsive patients may have OCD symptoms. Furthermore, patients with OCD may demonstrate serotonergic hypofunction (Barr et al., 1992), and patients with frontal hypofunction may also demonstrate stereotypic symptoms.

One way of reconciling these data may be the presence or absence of compensatory responses. In OCD it is speculated that compensatory neurobiological changes such as upregulation of some serotonin receptors and frontal hyperfunction may occur. In contrast, in impulsive disorders, there is serotonin or frontal hypoactivity, with no compensatory response. Thus, whereas OCD patients characteristically demonstrate resistance to their symptoms, impulsive patients are able only to experience regret or shame after acting out their symptoms. Putative OCD spectrum disorders may involve both compulsive and impulsive features.

Further work is still needed to delineate fully the concept of an OCD spectrum of disorders. Currently, the most convincing evidence is for an overlap between Tourette's and OCD, with that for the other disorders remaining more speculative. In the interim, it may be useful to employ this construct as heuristic in both clinical and research settings.

Treatment of OCD

Treatment options for OCD fall into two main categories: behavioural therapy and medication.

Behavioural therapy

Behaviour therapy for OCD is not new, it was arguably described by Janet in the nineteenth century. The core features of behaviour therapy for OCD are exposure and response prevention, i.e. the subject is exposed to the feared stimulus and is then helped to resist the urge to carry out the compulsion.

The clustering of fears in OCD patients around certain themes (contamination, aggression etc) has been proposed by Seligman to represent 'prepared phobias' (Seligman, 1971) i.e. fears that we are highly prepared to acquire as they were probably linked to improved survival in earlier periods of human history. This ties in with findings suggesting that the basal ganglia are important in the development, maintenance and selection of cognitive and procedural strategies.

The theoretical basis from which exposure and response prevention operates was first proposed by Mowrer (Deese & Hulse, 1967), who stated that anxiety occurred in response to a specific event by classical conditioning. Rituals are engaged in to decrease the anxiety and if successful are reinforced and more likely to occur in the future (operant conditioning). Ritualistic behaviour preserves the fear response by preventing the person from remaining in contact with the anxiety provoking stimulus long enough to habituate. A vicious cycle of anxiety leading to rituals and back to anxiety is set up. As the disease evolves both the anxiety and the rituals becomes generalized to other stimuli.

Outcome studies of behavioural therapy have found it to be effective in the treatment of OCD. Meyer et al. (1974) in a study of 15 inpatients with OCD showed improvement in all, and of 12 followed up only 4 had experienced periods of relapse. Rachman et al. (Foa & Goldstein, 1978) in a crossover trial proved behavioural therapy to be superior to relaxation therapy. These findings have been replicated in USA, Greece and the Netherlands (Boulougaris, 1977; Emmelkamp, 1982; Baer & Minicheiello, 1988), suggesting cross cultural efficacy. Also, gains may be maintained over time. More recently, studies showing that behavioural therapy can be conducted using computer instruction have been undertaken. There is also a growing interest in more cognitive techniques.

Not all patients respond to behaviour therapy. Poor compliance is perhaps the most common predictor of failure; an unsurprising finding given that behavioural therapy demands a great deal of discipline from the patients. Other patients who are likely to have a poor response include those with pervasive checking rituals, overvalued ideation, obsessional slowness and schizotypal personality disorder. (Quality Assurance Project, 1985).

How does behaviour therapy compare to medication? The Quality Assurance Project meta-analysis looked at 71 trials conducted between 1961 and 1984. They found similar effect sizes for behavioural therapy and clomipramine. More recently Van Balkom et al. (1994) replicated and updated this meta-analysis and found equal efficacy for behavioural treatments and SSRIs (Chouinard, 1992).

Pharmacotherapy

Since the differential response of OCD to serotonergic agents was first noted, these have become the mainstay in the pharmacological management of OCD. Two main classes of agents have been found to be effective, clomipramine and the selective serotonin reuptake inhibitors.

Clomipramine is the most serotonergic of the tricyclic antidepressants and was in the fact the first agent shown to have differential efficacy in OCD. Clomipramine has been considered the standard therapy of OCD for years, and remains a useful agent. It is, however, associated with significant cholinergic and adrenergic side effects, which has limited its utility in clinical practice. Fluoxetine, fluvoxamine, sertraline, paroxetine and citalopram have all proven to be superior to placebo in controlled trials, and all are licensed in some parts of the world for use in patients with OCD (Chouinard, 1992; Montgomery et al., 1993; Wheadon et al., 1993; Tollefson et al., 1994; Greist et al., 1995a; Goodman et al., 1996).

Clinical experience suggests that the SRIs are needed in higher doses and for longer periods to produce an effect in OCD. However, in controlled trials the evidence for a dose–response relationship is only partial. Only paroxetine showed a significant dose–response relationship (Wheadon et al., 1993). Citalopram, fluoxetine and sertraline show a trend of better response at higher doses (Wheadon et al., 1993; Montgomery et al., 1993; Greist et al., 1995a), but this was not statistically significant and no dose response relationship was found for fluvoxamine.

The standard regimen is to treat for 10–12 weeks at the maximally tolerated dose. Initial response may take as long as 8 weeks, and maximal response as long as 20 weeks. Once a therapeutic response is achieved, therapy should be maintained for 6 months to a year. Medication should be tapered slowly and restarted should symptoms reoccur. There is some evidence that once a response is achieved patients can be maintained on somewhat lower doses (Pato et al., 1990; Ravizza et al., 1996; Mundo et al., 1997).

Relative efficacy

Meta-analytic studies have suggested that clomipramine is more effective than SSRIs in OCD (Bisserbee et al., 1995; Greist, 1995b; Piccinelli et al., 1995; Stein et al., 1995; Koran et al., 1996a). However, clomipramine was the first agent to be introduced for the treatment of OCD, and subsequent studies may have included more refractory patients, so resulting in a bias against the SSRIs in the meta-analyses. Indeed, direct head to head comparisons of fluoxetine, fluvoxamine, sertraline and paroxetine have shown equal efficacy of SSRIs with clomipramine, with the SSRIs being better tolerated (Piggot et al., 1990; Bisserbee et al., 1995; Koran et al., 1996a, Zohar & Judge, 1996).

Treatment resistance

Up to 60% of patients with OCD do not respond or experience only partial remission (Goodman et al., 1992). Treatment resistance can be defined as having failed an adequate 10–12 week trial of 2 different SSRIs or clomipramine at maximally tolerated doses. Several strategies have been proposed for the management of treatment resistant patients. Augmentation strategies, using tryptophan, lithium, clonazepam, buspirone and inositol, have all been used with varying degrees of success, but there are few positive controlled augmentation studies of these agents (Goodman et al., 1992; Fux et al., 1996).

Augmentation with neuroleptics has been proven effective in controlled studies. As noted earlier, augmentation of an SSRI with haloperidol produced a significant effect in treatment of refractory patients with co-morbid tic disorders and schizotypal personality predicting a response to neuroleptic augmentation (McDougle et al., 1994). The atypical neuroleptics may be effective also in patients without tics (McDougle et al., 2000), and in view of their superior side effect profile, are increasingly being used as augmenting agents.

Intravenous clomipramine has also been used as a strategy in treatment-resistant patients. Both open and controlled trials have shown benefit in patients previously refractory to oral clomipramine, with response being maintained after subsequent treatment with oral clomipramine (Fallon et al., 1992, 1998). Furthermore, intravenous pulse loading with clomipramine has been suggested to produce a faster response than either oral pulse loading or gradual intravenous dosing (Koran et al., 1997, 1998). However, further work is needed to determine the place of intravenous clomipramine in the treatment of OCD.

In pediatric patients, especially those who fulfill the criteria PANDAS, immunomodulatory treatment has been proposed. Several case reports (The Guillain Barré Study Group, 1985; Barron et al., 1992; Allen et al., 1995; Tucker et al., 1996) and a controlled trial (Perlmutter et al., 1999) have suggested that both plasmapheresis and intravenous immunoglobulin produce improvement in OCD symptoms. However, questions remain as to the generalizability of the results (the children studied are not representative of the pediatric population with OCD) and this treatment currently remains in the experimental phase.

Electroconvulsive therapy is generally not thought to be useful in OCD, but there are a few case reports of its efficacy in the elderly and in some treatment refractory patients (Casey & Davis, 1994; Maletzky et al., 1994; Rabheru &

Persad, 1997). Preliminary reports of the efficacy of transcranial magnetic stimulation (Greenberg et al., 1997) suggest that this modality may also have a place in the treatment of OCD, but at this stage it is still an experimental treatment.

Neurosurgery

Neurosurgery is generally limited to patients with severe, intractable OCD who have not responded to an exhaustive array of other available treatment. The four most common procedures used are: cingulotomy, capsulotomy, limbic leucotomy and subcaudate tractotomy (Jenike, 1998). In a review of the literature, Jenike (1998) found that at least partial relief can be obtained by surgery in some patients with malignant OCD. There is some evidence that right sided lesions are more effective. Lippitz et al. (1997, 1999) found that, in patients who had undergone capsulotomy, good outcome was associated with a lesion in small area within the middle of the right anterior limb of the internal capsule. There was no correlation between left sided lesions and outcome.

There is, however, a lack of controlled data about the efficacy of neurosurgery. This is due, in part to the ethical difficulties in finding an acceptable 'placebo' surgery. However, with the newer gamma knife techniques, which do not require craniotomy, such studies may now be feasible. Neurosurgery is not without risks, but these compare favourably with that of stereotactic operations for non-psychiatric indications (Blaauw & Braakman, 1988). The risk of postoperative seizures is estimated at less than 1% (Ballantine, 1985; Jenike et al., 1991). In severely ill patients who have not benefited from any other intervention, neurosurgery should be considered as a treatment option.

Deep brain stimulation is another technique that may be useful in the treatment of severely ill patients with OCD. As with functional surgery for movement disorders, the use of deep brain stimulation is emerging as a possible alternative to ablative lesions for psychiatric indications as well (Nuttin et al., 1999)

Conclusion

OCD is a fascinating and complex disorder that has a markedly disruptive impact on the lives of those who suffer from it. It is comparatively recently that we have begun to unravel the mechanisms underlying this disorder, and much remains to be discovered. Nevertheless, we now know OCD to be a disorder mediated by particular neuroanatomical circuits, and to respond to specific interventions. Future work will undoubtedly extend and better integrate neuroanatomic, neurochemical, neurogenetic and neuroimmunological findings.

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28

Autism and autistic spectrum disorders

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Autism is a neurodevelopmental disorder characterized by the early (before 3 years of age, if not earlier) presentation of deficits in social abilities (and in all abilities that depend upon social abilities) and language (delays and/or inappropriate use) and by repetitive behaviours or apparent obsessions. Approximately 70% of individuals with autism are mentally retarded, and nearly 50% of cases never develop useful speech. These disturbances are lifelong, although they may be modified by education, by circumstances, and perhaps by maturation. Autism is surprisingly common, with an incidence of approximately 1/1000. Although first described in 1943 by Kanner (1943) and in 1944 by Asperger (1944), it came under far more intense scrutiny and saw greater public awareness beginning in the 1970s. Milder forms have been recognized, other conditions (such as the general categories of 'developmental language delays' and 'mental retardation') are now being appreciated as frequently harbouring the diagnosis of autism, and individuals with autism are being more publicly visible, and even in some cases speaking out on their own behalf (e.g. Grandin & Scariano, 1996).

Nevertheless, autism is a confusing condition to many health care professionals. The term 'autism' is confusing partly because its characteristic deficits, in social abilities, communication and language use, and in the flexibility and spontaneity of behaviour, are all domains that are often difficult to assess without a detailed history from good observers, and in which a wide range of normalcy (in development tempo or degree of achievement) is generally allowed. The diagnosis of autism is also confusing to many because the term does not really apply to a single condition or even to a spectrum of severity along a single dimension of disease features. Instead, it describes a set of multidimensional clinical entities that differ in both their specific pattern of features and in the severity of each feature. The term can be used to characterize an award-winning mathematician (Baron-Cohen et al., 1999) as well as a mute, severely retarded child who spins in a corner by himself all day long. Whether such cases have a unifying neurobiologic basis is not yet known. Therefore, the diagnosis of autism is still based on an imperfect phenomenology, not on neurobiology. Because diagnostic standards have also varied over time and across different researchers and clinicians, older data on 'autism' have to be interpreted with caution, whereas information about conditions such as 'childhood schizophrenia' and many examples of 'mental retardation' and 'idiot savants' must now be reinterpreted as possible examples of autistic disorders. Therefore, there is less certain knowledge than one would like about such a relatively common, and frequently devastating, lifelong condition. This chapter will summarize what is reasonably well known or can be reasonably inferred about this condition or conditions, leaving many aspects of the controversies underlying these summaries to the more primary literature. Filipek et al. (1999) review the status of different diagnostic entities and diagnostic criteria and processes. Cohen and Volkmar (1997), Wetherby and Prizant (2000), and Accardo et al. (2000) are recent book-length treatments. Recent general reviews include those by Rapin (1997), Happé and Frith (1996), Minshew et al. (1997), and Bailey et al. (1996), with Ciaranello and Ciaranello (1995) focusing on neurobiology. Piven (1997) and Ingram et al. (2000) review the current knowledge of the genetics of autism. Recent reviews of treatment options include, for behaviour, Heflin and Simpson (1998), Howlin (1998), and Koegel and Koegel (1995), with Zimmerman et al. (2000) reviewing pharmacologic options. Gordon (2000) gives a theoretical overview of the strategies for behavioural treatments and possibly for pharmacological ones as well. Outcome studies have been summarized by Nordin and Gillberg (1998). Sperry (2001) presents the illustrative stories of ten autistic children, followed from childhood through adulthood.

Table 28.1. Diagnostic Criteria for 299.00 autistic disorder

A. A total of six or more items from (1), (2), and (3), with at least two from (1) and one each from (2) and (3)	(1) Qualitative impairment in social interaction as manifested by at least two of the following:	(a) Marked impairment in the use of multiple non-verbal behaviours such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction (b) Failure to develop peer relationships appropriate to developmental level (c) A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g. by a lack of showing, bringing, or pointing out objects of interest) (d) Lack of social or emotional reciprocity
	(2) Qualitative impairments in communication as manifested by at least one of the following	(a) Delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication, such as gesture or mime) (b) In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others (c) Stereotyped and repetitive use of language or idiosyncratic language (d) Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
	(3) Restricted repetitive and stereotyped patterns of behaviour, interests, and activities, as manifested by at least one of the following	(a) Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus (b) Apparently inflexible adherence to specific, nonfunctional routines or rituals (c) Stereotyped and repetitive motor mannerisms (e.g. hand or finger flapping or twisting, or complex whole-body movements) (d) Persistent preoccupation with parts of objects
B. Delays or abnormal functioning in at least one of the following areas prior to age three years	(1) Social interaction (2) Language as used in social communication, or (3) Symbolic or imaginative play	
C. The disturbance is not better accounted for by Rett's syndrome or Childhood Disintegrative Disorder		

Source: From DSM-IV TR (American Psychiatric Association and American Psychiatric Association: Task Force on DSM-IV, 2000). Copyright 2000, American Psychiatric Association. Reprinted with permission.

Defining symptomatology

Terminology is confusing for autism and for the many named conditions that fall under the same term or that have apparent similarities with aspects of autism (autistic spectrum disorder, pervasive developmental disorder, high-functioning autism, Asperger's syndrome, non-verbal learning disability, Rett's syndrome, childhood disintegrative disorder, childhood schizophrenia). Some confusion has arisen because prior classification schemes were often based upon relatively small samples and were also somewhat prescriptive rather than data driven. More recent approaches have emphasized larger-scale surveys and classifications emerging from data clusters and correlations (e.g. Rapin, 1996).

The DSM–IV–TR (American Psychiatric Association and American Psychiatric Association: Task Force on DSM-IV, 2000) currently provides the most accepted definition and classification of autistic conditions; those definitions are reproduced in Table 28.1. (The ICD-10 [World Health Organization, 1993] definitions are very similar, although there are differences that may be important for research classifications.)

The DSM–IV–TR criteria incorporate three key features that define the condition and its relatives.

A defect in social awareness and understanding

Individuals with autism do not respond to other people the way that normal individuals do. Other people may be ignored or treated as though they were objects, or these individuals may fail to appreciate other people's emotional states, feelings, wants, or desires. While they may show some warmth and friendliness, particularly towards family members, even this is markedly reduced compared to normal. For many reasons, the social deficit seems to be a core characteristic of the condition.

A defect in communication

Individuals with autism frequently have delayed or absent speech or, if they have speech capabilities, often do not use these capabilities to communicate effectively. They appear to be unaware of the social uses of speech.

Repetitive and stereotypical behaviours, or fixed and unusual interests

These three characteristics do have a strong tendency to co-occur; they do not seem to be just an arbitrary collection. Some of the behavioural manifestations of autism do occur in other conditions but, in many ways, as Rutter and Bailey (1993) have pointed out, often appear to be more intrinsic to the autistic condition in affected individuals. Studies of children and adults (Wing & Gould, 1978, 1979; Shah et al., 1982; Rutter et al., 1992) and family studies (Bolton et al., 1994; Bailey et al., 1998b; Piven, 2000) have shown that these types of abnormalities tend to co-occur in the same individuals and in milder form in relatives. Nonetheless, these abnormalities still span a wide variety of individual presentations. Several subtypes of the autistic spectrum have either been identified in the literature or seen to be of practical or perhaps research significance (Zimmerman & Gordon, 2000).

Subtypes

Asperger's syndrome

Individuals whose only real deficits are 'qualitative impairments in reciprocal social interaction' with 'restricted, repetitive, and stereotyped patterns of behaviour, interests and activities' (World Health Organization, 1993), without any delays or impairments in language or cognitive development, are given this label. Frequently, these individuals also have a history of delayed motor milestones and motoric clumsiness. (In some classification schemes, these motor impairments are critical for the diagnosis, although it is not clear why they have to be.) In many ways, individuals with Asperger's syndrome can be considered almost the purest form of expression of an isolated defect in social awareness and interaction. As currently defined, the features of the syndrome of non-verbal learning disabilities have a high degree of overlap with those of Asperger's syndrome (Klin et al., 1995), probably representing a failure of precise differentiation. There are many reasons to believe that deficits in social awareness can exist in relatively pure form, apart from any deficits in other non-verbal domains, such as visuospatial functions.

High-functioning autism

Individuals with autistic features, but who have language capabilities and IQs$>$70 (sometimes, performance IQs$>$70), are in this category. The exact characterization of these individuals is controversial, and the upper boundary (with Asperger's syndrome) and lower boundary (with low-functioning autism) are not very distinct. High-functioning autism is now generally distinguished from Asperger's by a history of language delay, which individuals with Asperger's do not have. However, given that the pace of language development has a relatively wide range in normal individuals, the distinction between high-functioning autism and Asperger's may prove to be more of a quantitative difference in many cases than a qualitative one. Relative to individuals with Asperger's, individuals with high-functioning autism have lower verbal IQs and higher performance IQs (Klin et al., 1995).

Low-functioning autism

Generally, this category is reserved for individuals with autism who have low verbal IQs ($<$70). Fifty to 75% of individuals diagnosed as being autistic fall into this category. Approximately 50% of individuals with autism have not just low verbal IQs, but little or no speech. This category is also not precisely defined, partly because the spectrum of verbal abilities is relatively wide and often not easy to categorize in and of itself. For example, a fair percentage of individuals with autism demonstrate echolalia (Howlin, 1982; Roberts, 1989). Frequently, however, speech comprehension is impaired in such cases. IQ in autism is also not well defined (Lincoln et al., 1995), because these children do not necessarily cooperate on the tests, and because their pattern of disabilities prevents standard IQ tests from tapping more central functions.

Autism following regression

Approximately 20–25% of individuals with autism have a history of initially normal development followed by regression. Most often, the parent reports that the child had been developing words, then ceased to add new words and lost the words that he/she had acquired. This finding, most often reported between the age of 18 months and 3 years, has been difficult to study. To the extent that it has been (Rogers & DiLalla, 1990; Kurita et al., 1992; Tuchman & Rapin, 1997; Volkmar et al., 1997), evidence suggests that the actual phenomena may be more complex. Many, if not all, of these children were slower in word acquisition or had some other developmental abnormality or delay preceding the loss of words. In more than half of these children, the loss of words is accompanied by a change in social responsiveness. Regression does not necessarily predict autism, although the best clinical evidence suggests that the risk of autism with this pattern is quite high.

The reasons for this regression are even less clear than the existence of the phenomenon itself. However, a potentially significant possibility is that these cases represent secondary influences causing the autistic spectrum condition. As a result, this group of individuals is under intense scrutiny for possible immunologic and other exogenous etiologies for the autistic spectrum disorder. The best available current evidence has effectively ruled out an association between immunizations and autism in general (Afzal et al., 2000; DeStefano & Chen, 2000). However, the possibility remains that this group is enriched in secondary causes, for which the search continues.

It was once thought that children with regression otherwise followed the typical course of low-functioning individuals. However, there is now clinical evidence that at least some of these individuals can become higher functioning. Autism following regression is categorized here as a separate subtype not because its outcomes are not already categorized, but because its course may help to identify a different cause or causes than is true in other cases of autism.

Broader autism phenotype

The likelihood that autism does not have sharply defined boundaries and may have milder, fragmentary presentations is supported by the evidence for a broader autism phenotype in the relatives of autistic individuals (Bailey et al., 1998b; Piven, 2000). These relatives show a higher incidence of somewhat similar deficits in cognitive functions (relatively lower performance on verbal but not non-verbal IQ scores, poor performance on tests of reading comprehension, rapid automized naming, and executive function, and deficits in pragmatic language and speech), and problems with social cognition (difficulties in accurate interpretation of others' mental states). They suffer more frequently from affective disorders (major depression and anxiety). Relatives of autistic individuals also show a higher frequency of particular personality characteristics (aloofness, rigidity, hypersensitivity to criticism, and anxiety and a history of fewer close friendships) than do those from families without autism. This evidence suggests that there may be elements of autism that can occur in isolation and with less severity.

Autism likely to be secondary to other disorders

Autism has been reliably associated with several other conditions, such as tuberous sclerosis, and less reliably associated with many others (such as fetal alcohol syndrome) (see Table 28.2). Autism is a frequent consequence of tuberous sclerosis (Smalley, 1998). Sixty to 70% of mentally retarded individuals with tuberous sclerosis are autistic as well, and many of these individuals also have epilepsy (Curatolo et al., 1991; Smalley et al., 1992; Hunt & Shepherd, 1993; Gillberg et al., 1994). Particular involvement of the temporal lobes (Bolton & Griffiths, 1997) or of the cerebellum (Weber et al., 2000) has been claimed to be present in those individuals with autistic features. Autism or autistic-like features have also been reported to occur in 15–25% of individuals with Fragile X syndrome (Dykens & Volkmar, 1997; Bailey et al., 1998c). There are scattered reports of associations with other conditions, as noted in Table 28.2, although all have to be interpreted with extreme caution (Dykens & Volkmar, 1997). Severe physical and social deprivation has also been reported to cause autistic-like behaviours (Rutter et al., 1999).

What is also noteworthy about autism's associations is what it is not associated with. Autism has not been associated with focal lesions, even with perinatal focal lesions. Autism and autistic-like features are not seen in other neurodevelopmental conditions, even those with mental retardation. This relative rarity of autism as a secondary consequence of other conditions is part of the evidence for accepting it as an entity in its own right, as difficult as it may be to try to relate its various aspects.

Epidemiology

Prevalence

The prevalence of autism is approximately 1/1000 (Gillberg & Wing, 1999), although it may be as high as 1/500 or even greater, if relatively mild and more circumscribed deficits are included. The exact incidence and prevalence of

Table 28.2. Suspected etiologies or associations of autistic spectrum disorders

Presumed single gene deficit	*HOXA1*, *HOXB1* (Ingram et al., 2000)
Presumed polygenetic	(thought to be most common) (Szatmari et al., 1998; Piven, 2000)
In the context of otherwise known conditions	Fragile X syndrome (Bailey et al., 1998c) Tuberous sclerosis (Smalley, 1998) Phenylketonuria (?) (Dykens & Volkmar, 1997) Angelman syndrome Down's syndrome (rare; see Dykens & Volkmar, 1997) Turner's syndrome (Creswell & Skuse, 1999)
Structural brain anomalies (including those with known genetics)	Neural migration defects Moebius syndrome Joubert syndrome (Holroyd et al., 1991; Ozonoff et al., 1999) Duane syndrome
Toxins	Thalidomide (Stromland et al., 1994) Valproic acid (Williams & Hersh, 1997) Ethanol (Aronson et al., 1997)
Intrauterine infections	CMV (?) (Gillberg & Coleman, 1992) Rubella (?) (Gillberg & Coleman, 1992)
Perinatal cerebral injury	Anoxia–ischemia Hippocampal sclerosis Herpes simplex
Epileptic syndromes	Infantile spasms Lennox-Gastaut syndrome
Environmental (?)	Suspected, not established

Note:
For sources not otherwise referenced, see Dykens and Volkmar (1997), Ingram et al. (2000) and Rapin (2000).

autism are understandably not completely clear and are also controversial. Such estimates require both an appropriate set of screening criteria and a guarantee that all appropriate screening is performed to adequate standards in all of the potential population. Surveys coming closest to these ideals include those reported from Japan (Gillberg, 1995), Nova Scotia (Bryson et al., 1988), and Sweden (Gillberg & Wing, 1999).

In many school districts, the incidence of autism has given the appearance of rising, much to the concern of parents and school officials, probably not because of any change in the actual incidence of the condition (Fombonne, 2001), but instead because of greater awareness and, in some cases, to families moving into regions with allegedly better school systems.

Male predominance

Males are more commonly affected than females, by a ratio of approximately 4:1 overall (Gillberg & Coleman, 1992). This male predominance seems to be particularly true of Asperger's syndrome, where the male:female ratio has been reported to be as high as 10:1 (Gillberg, 1989). Skuse (Creswell & Skuse, 1999; Skuse, 2000) has suggested an explanation for the male predominance in autism; he has posited that a genetic factor that influences other genetic factors responsible for social behaviours is part of the X-chromosome. This factor is functional only on the paternally derived X-chromosome; it is imprinted on the maternal X-chromosome. The X-chromosome of boys can only come from the mother; hence, they become more susceptible to any other factors impairing the expression of genes related to social behaviour. Skuse and his colleagues (Creswell & Skuse, 1999; Skuse, 2000) have shown, in partial support of this hypothesis, that the individuals with Turner syndrome who show autistic features are those with maternal X-chromosomes.

Causative or risk factors

Genetics

The best available evidence is that most cases (if not all) of autism represent genetic disorders (or a genetic predispo-

sition coupled with as-yet-unknown non-genetic factors) (Bailey et al., 1998a; Szatmari et al., 1998; Maestrini et al., 2000; Piven, 2000). In a comparison of monozygotic twins vs. dizygotic twins, autism was present by strict definition in 36–91% of monozygotic twins but in 0% of same-sex dizygotic twins (Bailey et al., 1995). Using a broader definition of cognitive or social abnormalities, 92% of monozygotic twins were concordant compared to 10% of dizygotic twins. It has been suggested that anywhere from 2–20 interacting genes may be involved in the pathogenesis of autism. The strongest evidence for the identity of any one of these genes (which is also evidence that suggests that only one need be at fault) comes from the recent demonstration that the *HOXA1* gene, or perhaps the *HOXB1* gene, is abnormal in a large percentage of individuals with autism (with the frequency of specific mutations in the autistic group ranging from 21–35% (Ingram et al., 2000)). The *HOXA1* gene has been thought to be responsible for the developmental organization of the hindbrain. If this finding is confirmed, it would provide a clue as to why children with autism not infrequently appear to have motor abnormalities of the face and lower cranial nerves, and perhaps why the mental retardation and other defects associated with autism have a very different pattern from those occurring in most other conditions.

The risk to couples who already have one autistic child of having an additional autistic child has been estimated as anywhere from 1.5% to 10–20%, much greater than the general risk of approximately 0.1% (Piven et al., 1990; Jorde et al., 1990; Bolton et al., 1994). Families considering having more children obviously are interested in having a more precise estimate of risk within this almost tenfold estimated range, but it is difficult to refine the estimate more precisely, partly because of the different inclusion criteria used. Broader inclusion criteria are not necessarily incorrect, because of the existence of the broader autism phenotype referred to earlier. However, this broad autism phenotype does lead to an apparent overestimation of the chances of having a child with autism, because children with milder and/or less pervasive abnormalities are also included.

Non-genetic factors

These factors must exist, because the concordance rate even among identical twins is <100% (estimated at 60%, Bailey et al., 1998b). However, at the current time, there is no reliable understanding of what these non-genetic factors can be or how they may operate. Well-publicized cases of 'clusters' of autistic cases have not been proven to be due to any known environmental agent or combinations of agents. Immunization (Wakefield et al., 1998), and more recently, mercury exposure (Bernard et al., 2000) from the carrier used for immunization has been suggested as the 'cause' or contributors to autism. However, not only have these not been proven, there is considerable negative evidence against them (DeStefano & Chen, 2000).

There have been some promising laboratory models of how autism might be acquired. Pletnikov and his colleagues (1999) have shown deficits in social behaviour in juvenile rats who had neonatal infection with Borna disease virus. Bachevalier and colleagues (1994) have shown that some autistic-like behaviours can be seen in monkeys with neonatal injuries to the medial temporal lobes.

As a precaution to researchers in this area, it is perhaps well to keep in mind that, although autism is now known to be the most genetically determined of all the developmental neurobehavioural syndromes, as recently as 1976, genetics were not thought to have a role (Hanson & Gottesman, 1976). The biases and methodologic flaws that led to this erroneous conclusion need to be kept in mind.

Clinical presentation

Initial clinical presentation

Absent or below-average language development is the most common symptom prompting evaluation of these children, but retrospective clinical reports and research studies have suggested that disorders are apparent much earlier in infancy, perhaps as early as 12 months or even earlier. In research studies, the earliest definable feature separating children who will later be diagnosed as autistic from those who would develop normally has been failure of eye contact (based on retrospective review of videotapes of home movies and tapes) (Werner et al., 2000). In retrospect, parents will often note that the infant did not make normal eye contact, did not follow the parent's gaze or pointing (did not seem to have joint attention), and did not point himself.

Clinically, infants with autism are often reported to be irritable, 'colicky', and poor sleepers. Infants may seem to resist being touched, arching the back on contact, or may be unexpectedly passive to touching or holding, even by complete strangers. Early babbling is not abnormal but may not progress, and first words may be delayed, develop at a slower pace than normal, or even seem to be lost by age 2–2½ (see above, 'Autism following regression'). Gross motor development (sitting, crawling, and walking) is not necessarily delayed, although a minority of autistic children will show delayed gross motor development and, later, clumsiness.

The presentation of autism is dependent upon the severity of the defining autistic deficits themselves and

upon the severity of any other associated deficits in sensory function, motor function, or cognition. Many feel that autism can be reliably diagnosed before the age of 2 in most cases. However, it frequently takes much longer to recognize and to be actionable. In some cases, appreciation of autism is delayed until the child enters preschool or school, when more objective individuals can observe and compare behaviours. In fact, more recent awareness of the full diagnostic criteria has meant that some individuals have not been diagnosed until adulthood, when their pattern of social isolation, lack of social understanding, and inappropriate social behavioural responses are identified as being a manifestation of Asperger's syndrome. Social deficits might well be masked by achievement in other areas and by selective isolation and involvement that does not stress those areas of deficiencies.

Other associated findings or conditions

Although the defining symptoms of autism are behavioural, these individuals frequently have a number of other impairments or peculiarities. Many are listed in Table 28.3, although this is far from an exhaustive list; more complete tabulations and references can be found in the general reviews cited earlier and in Rapin (1996) and Leary and Hill (1996). One important limitation of such a list is that most of the available data cannot give individual correlations. Therefore, it is not known what features are related to other features and which are not. There may be clues to the neurobiology in those patterns, but these have not been studied systematically.

The seizures and EEG abnormalities noted in Table 28.3 deserve special mention. Two or more unprovoked seizures (epilepsy) occur in 20–40% of individuals with autism, particularly low-functioning, non-verbal individuals (Rapin, 1997). Seizures are most common in infancy and next most commonly occur in adolescence.

EEG abnormalities have been reported in even a larger proportion of individuals with autism, particularly when extended recordings are done (Tuchman, 2000). The clinical significance of these EEG abnormalities, in the absence of overt seizures, is unclear. Although aggressive antiepileptic treatment and even surgery have been used in such individuals, there is no compelling biological reason to believe that the EEG abnormalities are the primary cause of any of the symptomatology of autism, and there is no empirical evidence that treatment of these abnormalities *per se* actually results in improvement of autistic conditions. However, both of these possibilities are under continued investigation.

Neurobiology

A number of attempts have been made to identify a fundamental behavioural deficit that underlies the surface manifestations of autism. Suggestions include: 'mind-blindness', or a lack of awareness of other people (Baron-Cohen, 1995); executive disorders (Russell, 1997); failures of higher information processing (Minshew et al., 1997); and a failure of central coherence (Frith, 1989), the normal tendency to make consistent scripts for events and situations. Although each of these seems to explain large portions of the autistic disorder, no grand unified behavioural theory seems to be very plausible; the deficits in autism are too diverse and present at too many levels of the neuraxis (and perhaps somatically as well; see below).

Neuropathologic, structural imaging and functional imaging assessments of individuals with autism have been hampered by the relatively small numbers and, in some cases, atypical features of individuals who either are available for postmortem examination or are compliant with imaging studies. Several cooperating research efforts to collect the brains from individuals with autism and controls will undoubtedly help to correct this situation in the future. At the present time, available data have relatively little internal coherence or consistency. It does seem to be a reliable finding that the brains of autistic individuals are either normal sized or slightly larger than average. What elements of cerebral tissue are responsible for the increased size in these individuals is not known. Abnormalities have been reported by macroscopic and/or microscopic neuropathological studies and/or by imaging studies (structural or functional imaging) in the brainstem, cerebellar vermis, medial temporal lobes, and cortex and subcortical structures (e.g. Courchesne, 1997; Kemper & Bauman, 1998; Bailey et al., 1998a; Aylward et al., 1999; Ohnishi et al., 2000), although with considerable differences of opinion between investigators (see, for example, Courchesne, 1997 and Piven & Arndt, 1995). The variability and inconsistencies do suggest that either the reported abnormalities have nothing directly to do with autism itself or that autism may be a byproduct of damage or dysfunction of many different levels and sites in the nervous system. To the extent that autism is a neurogenetic condition, it is almost certain that the chain connecting expressed symptomatology with the underlying genetic defect or defects is likely to be extremely complex (Caviness, 2001).

What is clear about the neuropathology of autism is that no single focal lesion, or even currently used combination of lesions, can reproduce the symptomatology. Bachevalier et al. (1994) have created animal models for some aspects of autism in neonatal monkeys by bilateral ablation of the

Table 28.3. Autism and autistic spectrum disorders: other associated conditions/findings

Physical characteristics	Macrocephaly
	Mid-facial dysmorphic features (e.g. increased inter-pupillary distance) (Bailey et al., 1995)
	Other morphological abnormalities (Rodier et al., 1997; Walker, 1977)
Gastrointestinal disorders	Constipation and/or diarrhea
Sensory disorders	Apparent heightened sensitivity to sound (hyperacusis)
	Seemingly lowered sensitivity to pain
	Abnormal sensory response, increased to decreased (Rapin, 2000)
Motor disorders	Strabismus (Kaplan et al., 1999)
	Oromotor dyspraxia
	Hypotonia with increased joint mobility
	Dysmetria and intention tremor
	Awkward fine motor movements
	Limb apraxias
	Abnormal postures (hands, head, etc.)
	Toe walking
Other neurologic disorders	Sleep disorders with early night wakening (Hoshino et al., 1984)
	EEG abnormalities
	Seizures
	Impaired eye-blink conditioning
Cognitive/behavioural features	Smelling of food and people
	Gaze avoidance 'looking out of the corner of the eye'
	Spinning without dizziness
	Attentional disorders: difficulty holding attention, difficulty diverting attention (e.g. Courchesne et al., 1994)
	Apparent auditory processing deficits (Rapin et al., 1977)
	Apparent relative or absolute superiority (Happé & Frith, 1996) in:
	Visual perception
	WAIS Block design subtest
	Drawing
	Jigsaw puzzles
	Perfect pitch (Heaton et al., 1998)
	Music
	Rote memory
	Lightning calculations
	'Executive function' disorders: disorders of planning, strategy and attention (see above)
	Self-injurious behaviour
	Violence or aggression (goal-directed, or accidental)
	Repetitive, stereotypical behaviours

Notes:
For sources not otherwise referenced, see Happé and Frith (1996), Rapin (1997).

hippocampus, amygdala, or associated structures. This research is encouraging because it also begins to address the issue that lesions in early life may interrupt or redirect development, in addition to whatever deficits for which they may be directly responsible. Certainly, many individual components of the autistic condition can be seen behaviourally in focal brain lesions, even in adults, or seem to occur in other developmental disorders, such as attention–deficit–hyperactivity disorder or Tourette's syndrome, and severe learning disabilities. However, despite these superficial similarities, it remains to be seen whether the seemingly identical overt behavioural abnormalities are caused by the same underlying behavioural impairments or malfunctions.

Although many biochemical and neurotransmitter systems have been considered as possible causes or

contributors to the autistic deficit(s) (Cook, 1990), none have been reliably found to be abnormal, and no treatment of any putative transmitter system has yet been found to be of positive benefit.

Rett's syndrome (Bibat & Naidu, 2001), which has recently been identified as being caused by a mutation of a specific gene (Amir et al., 1999), the methyl-CpG-binding protein-2 gene (*MECP2*) on the X-chromosome, is an instructive example of the behavioural–neurobiologic correlations to be expected for autism. The condition primarily affects girls of all ethnic groups. Initially, there is stagnation of cognitive development, then profound motor and cognitive regression, then partial recovery and stability. Among the behavioural features that Rett's syndrome has in common with autism are loss of language functions, loss of fine motor functions, stereotypic hand movements, constipation, and seizures. (This list is selective; many somatic and neurologic features of Rett's syndrome are not typically seen in autism.)

The *MECP2* gene has been found to have 78 mutations so far in known Rett's syndrome cases (Shahbazian & Zoghbi, 2001). It is now appreciated that there are very mild cases as well as extremely severe cases (probably lethal in most hemizygous males) (Shahbazian & Zoghbi, 2001). Finally, even though the gene is widely expressed throughout the body, the bulk of pathology caused by the mutations seem to be confined to the central nervous system. Even more specifically, the neuropathologic abnormalities that have been described, selective vulnerability of the zona compacta of the substantia nigra, the nucleus basalis of Meynert, the caudate, frontal lobes, and cerebellum, and a distinctive pattern of cerebral cortical abnormalities (Bibat & Naidu, 2001), cannot be easily related to fairly prototypical signs of classic Rett's syndrome. Therefore, Rett's syndrome is further evidence that there must be a bidirectional perspective on these conditions, from the genes up to the neuropathology and behaviour, and from the behaviours and behavioural abnormalities down to the genes, if we are to hope to have a unified account of the neurobiology of these conditions (Caviness, 2001). The situation for autism is likely to be no less complex than that for Rett's syndrome.

Diagnosis

Guidelines for the diagnosis of autistic spectrum disorders have recently been accepted by a number of professional bodies (Filipek et al., 1999, 2000); guidelines are available on the Web (www.aan.com/public/practiceguidelines/autism.pdf). These guidelines divide the diagnosis into an initial screening phase, followed by more specific assessment for individuals identified as high risk for autism or related developmental disorders by the screen. The guidelines for screening reflect in part an increased awareness that developmental delays or idiosyncrasies need to be taken seriously in many cases; children do not necessarily 'grow out of them', as folklore may have taught. Moreover, earlier diagnosis needs to be encouraged because it is likely that, the earlier the intervention, the more positive the eventual outcome.

Several studies have demonstrated that, if a parent expresses concern about a child's development, they are almost always correct; such concerns need to be taken seriously. It is also the case, however, that many parents are not aware or concerned about even apparently obvious developmental delays. Therefore, the physician and health care provider need to have a high suspicion for such abnormalities, even in the absence of parental reports.

One practical problem in making a diagnosis is that the relevant information and assessments are not available at a single time but may be spread out over weeks to months. A related problem is that the relevant information is often in the possession of separate individuals and professions. A speech pathologist may note delayed speech. An occupational therapist may note clumsiness. Parents will realize that the child does not seem to play appropriately and does not have social contact, even with familiar family members. Often, these various observations are treated in isolation without realizing their common origin and interdependent significance.

One important diagnostic quandary is the child who has some features of autism or elements of autistic-like behaviour or dysfunction but does not meet full criteria for autism. Some such individuals seem to overcome these handicaps. Others will express them more persistently and more clearly, and will be more easily classified as autistic. However, regardless of the particular label, each of these elements or dysfunctions is itself a deficit that needs to be addressed by the child's medical and educational system.

Autism is a diagnosis that can be made with a fair amount of certainty, depending on the information base, the severity of the disorder and associated conditions, and the child's age. Moreover, in addition to the diagnosis itself, outcome predictions can be refined by observing the child's response to therapeutic intervention. Outcome itself is probably better, the earlier the intervention. Therefore, overall, it is better for a child to have suspicions aired and to have the appropriate medical and educational mechanisms engaged as early as possible.

Treatments

Autism cannot yet be 'cured' in the way that some other conditions can be cured and eliminated. Given the increasing evidence as to the fundamental nature of autism, it is unlikely that it will be possible to reverse the underlying neurobiologic deficits once they have had a pervasive influence on the developing brain. However, although features of the autistic spectrum disorders are essentially lifelong, this does not mean that they cannot be ameliorated in some way, either by treating the individual or by altering the individual's environment. Behavioural techniques and, to a lesser extent, pharmacological treatments, can improve some aspects of the functioning and adjustment of these individuals.

Behavioural treatments

Even though the basic neurobiologic deficit(s) in autism are not known, there are some basic principles that should guide behavioural treatment attempts (see also Gordon, 2000). Human beings normally have a variety of processes available to them for effecting change in the nervous system as a result of experience, existing at many different neural levels and time scales (Posner et al., 1997). One way of categorizing these processes of learning for behavioural purposes is as follows: at the most basic, least-demanding level, passive correlations can often extract considerable information from the environment, without the necessity for feedback, reward, punishment, or expectation. However, adding feedback, even in just basic rewards or punishments (e.g. food or the withholding of food) vastly increases the rate of learning. This reward/punishment feedback mechanism seems to be a fairly basic and pervasive one; it is evident in non-human animals, and in infants and young children. Some animals, and human children, also have the ability to learn through imitation. Finally, the most complex and subtle forms of learning are perhaps those which are accomplished by mental prediction, assessment of consequences, and selected actions, in essence, fast forwarding different scenarios and examining how they might turn out. The normally functioning human being has all of these mechanisms available to him or her, and all are typically used in almost every learned activity. For example, although learning to play video games involves conscious thought for tactics and strategy, winning or losing activates fundamental learning circuits, and basic perceptual and motor skills are more finely honed by practice, regardless of whether the game is won or lost.

From this perspective, individuals with autism may fail to learn for a large number of reasons: they may lack the perceptual, motoric, or conceptual abilities to understand basic functions and concepts; they may lack the executive abilities necessary to allocate their attention and their efforts; and they may lack the social awareness and needs that help motivate learning. To try to overcome these problems requires exactly the same types of strategies as are used for learning and teaching in general, except they have to be adapted to the narrower abilities of these children, the shorter conceptual leaps that they can take, and to their more constricted motivations. Behavioural treatments can, therefore, logically try to simplify the environment of the child on the one hand and increase the child's capabilities for dealing with that environment on the other.

Although these principles seem fairly straightforward, in the current educational environment, there have actually been a large number of different methods for teaching and training proposed, including Discrete Trial Training (the Lovaas method: Lovaas et al., 1971), the TEACCH method (Schopler et al., 1993; Schopler & Mesibov, 1994), pivotal behaviours (Koegel & Koegel, 1995), floor play (Greenspan, 1992; Greenspan & Wieder, 1998), the Eden method (Holmes, 1997), the Walden approach (McGee et al., 2001), and others (Handleman et al., 2001). There is evidence for the effectiveness of many if not all of these approaches (e.g. Helfin & Simpson, 1998; Howlin, 1998; Rogers, 1998; Sheinkopf & Siegel, 1998; Ozonoff & Cathcart, 1998). However, these various approaches do differ in a number of fundamental assumptions: in the level of functioning (or of functions) for which they are most appropriate; in their basic philosophies as to which are the core or fundamental deficits to be addressed first; and in their adopted methodologies for achieving behavioural changes in those particular functional deficits. Understanding these differences can help identify which approach is best for which child.

Assignment of fundamental deficits

As an example of philosophic differences, the explicit position espoused by Greenspan (1992) might be contrasted with the implicit positions of applied behavioural analysis and discrete trial training approaches (e.g. Lovaas & Taubman, 1981). For Greenspan, 'The primary goal of intervention is to enable children to form a sense of their own personhood, a sense of themselves as intentional, interactive individuals' (Greenspan, 1992). In the applied behavioural analysis tradition, these children have deficits in a number of specific skills. Training is, therefore, directed at improving the specific skills, presumably in the hope that they would coalesce into a better-functioning, complete human being. The evidence from neurobiology would seem

to lend more weight to the implicit applied behavioural analysis position, in that it is generally assumed, with much evidence supporting this, that our mental abilities (including perhaps even our sense of self) are, in fact, a collection of much more specific, discrete, and relatively independent underlying mental functions. If not all of those discrete abilities are present, then normal complete 'personhood' cannot be expected to be achieved. (Autism itself provides examples of how some specific functions can be impaired, while others can be relatively spared.) However, despite this seeming contrast in starting positions, Greenspan's own approach seems to also be focused upon specific functions and abilities (Greenspan & Wieder, 1998), albeit those thought to underlie the development of personhood, and those whose learning can be capitalized upon through special situations and interests in each particular child. This partial convergence of methodologies is perhaps another reason why a comparison of these methods is so confusing for parents and teachers alike.

Methods for achieving behavioural change

Specific methods that have been endorsed range from teacher-imposed, single-trial-at-a-time learning, with rewards (or withholding of rewards) (e.g. Lovaas & Taubman, 1981), to using the child's own spontaneous interests and actions as the basis for instruction (e.g. Greenspan & Wieder, 1998).

From the general perspective on learning discussed above, the ideal learning situation for each individual with autism is not so much a matter of a particular philosophy, but instead, identifying the particular pattern of abilities and disabilities that each individual exhibits at any one point in time, and of choosing the best methods for overcoming those disabilities at that time. For some deficits, in some children, trial-by-trial guidance and rewarding will be necessary (the discrete trial and Lovaas approaches). Other children may have fewer deficits and be more spontaneous and more capable of learning through their own intrinsic devices, with the proper guidance. For these children, approaches that capitalize on these features (such as pivotal behaviours (Koegel & Koegel, 1995) and floor play (Greenspan & Wieder, 1998) may be more appropriate.

A similar approach applies to the question of environmental adaptation. There is an ongoing debate as to whether the environment of these individuals should be simplified or not, to foster learning. For lower-functioning children, environmental adaptations consist of a routinized school environment and a simplified, routinized home environment. Each step involved in, for example, tooth brushing, may be indicated by picture icons as a constant reminder for the child of what is necessary after what. The number of choices may be reduced; commands and comments may be simplified to avoid confusion. For example, a low-functioning child may not apparently recognize that 'sit' and 'sit down' are meant to refer to the same thing.

There is a valid concern that simplification may be counterproductive, especially with higher-functioning children, leading to decreased motivation and to a decreased exposure to the natural variation and richness of a normal environment. This may reduce the child's ability to generalize to new materials or to respond to new situations. Achieving an adequate balance between adequate simplification and productive complexity is an ongoing debate in the teaching of such children. However, it remains the case that many children cannot begin to learn, or learn how to learn, unless they are started in a simplified, structured environment. Even in regular education, the learning environment is made more structured than outside reality usually is. For other children, less simplification and more variety are probably desirable.

In practice, it is often hard to tell many of these methods apart, despite their strong theoretical contrasts. Their goals and methods often seem to overlap and even blend. The overriding principles that need to be kept in mind are that the educational process, and the strategies for education, of any particular individual with autism can and must change with the individual's circumstances. Furthermore, no matter how successful the reported intervention is reputed to be, all interventional strategies must be tested by examination of the actual data for each individual.

Pharmacological treatments

Drugs have not yet been shown to produce improvement in any functions in these individuals. However, there are reasonable expectations, and some data exist that appropriate drug therapy can reduce problem behaviours in at least some individuals (Cook, 1990; Minshew, 2000; Zimmerman et al., 2000). Such behaviours and suggested drug treatment regimens are given in Table 28.4.

Treatment coordination

Regardless of whether behavioural treatments, drug treatments, or both, are used, the treatment of autistic individuals is a constantly changing process that requires different types of expertise at different points in time. Treatment plans must be adapted at any point in time to a particular individual's pattern of abilities and disabilities and to their family and school circumstances. Plans must have goals that are appropriate for that individual's

Table 28.4. Possible pharmacologic treatments for selected disorders in autism

Hyperactivity Distractibility Impulsivity	Stimulant medications	Methylphenidate, 5–60 mg/day in 3–5 divided doses Dextroamphetamine 5–40 mg/day in 3–5 divided doses Adderall, 5–30 mg/kg/day in two divided doses
	Clonidine, 0.1–0.4 mg/day in 2–3 doses or via transdermal skin patch	
	Naltrexone, 0.5–2.0 mg/kg/day in two divided doses	
Rituals Compulsions	Antidepressants SSRIs	Fluoxetine, 5–80 mg/day in 1–2 divided doses or 10–20 mg every other day Paroxetine, 2.5–50 mg/day in 1–2 divided doses Sertraline, 25–200 mg/day in 1–2 divided doses Fluvoxamine, 25–300 mg/day in 1–3 divided doses
	Tricyclic antidepressants	Citalopram, 5–40 mg/day in 1–2 divided doses Clomipramine, 25–200 mg/day in 1–2 divided doses
Aggression Irritability	Sympatholytic agents	Propranolol, 20–320 mg/day in 3–4 divided doses Naldolol, 40–100 mg/day in daily dose
	Anticonvulsants	Carbamazepine to a blood level of 8–12 micrograms/ml Valproate to a blood level of 50–125 micrograms/ml
	Naltrexone, 0.5–2.0 mg/kg in 1–2 divided doses Lithium to a serum level of 0.8–1.2 meq/litre	
	Neuroleptic agents	Risperidone, 0.5–4.0 mg/day in 1–3 divided doses Olanzapine, 2.5–20 mg/day in 1–3 divided doses

Source: Adapted from Minshew (2000). Used with permission.

required functions, current status, and expected trajectory of change. Physicians are not typically involved in this therapeutic process, although their input is critical for justifying it. More typically, the educational process is in the hands of a varying combination of parents, educators, speech pathologists, physical therapists, behavioural psychologists, occupational therapists, and others. For most individuals with autism, it is critical that there be some strong coordinating individual or group that can help to identify goals, prioritize methods, and monitor the progress of any particular program that the child has, eliminating inconsistencies and redundancies, solving unforeseen problems, and trying to capitalize on successes.

Prospects

Although individuals with autism face a lifelong condition, it can be ameliorated in many cases and in many ways. Higher-functioning individuals in particular have a good chance of a successful life; indeed, some of the signature behavioural characteristics of autism can be positives in the right career or career niche. Success in many areas of life is determined less by weaknesses than by strengths, and these individuals may have many strengths. Meanwhile, autism has become an area of enormous interest, both in its own right and for what it can reveal about the mind and the brain and their pathologies and possible treatments.

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29

Attention deficit hyperactivity disorder: spectrum and mechanisms

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Attention deficit hyperactivity disorder (ADHD) is among the most prevalent disorders (3 to 5% of school-age children) treated by physicians who manage children/adolescents, comprising as much as half of child psychiatric practice (Cantwell, 1996). Media attention has been inspired by the extension of the ADHD diagnosis to adults, acknowledgement of frequent comorbidity or antecedent status with respect to other conditions, and concern over the increase in stimulant prescriptions; it may appear that ADHD, or at least its importance, is a novelty. In truth, the essential description of the disorder has a 75-year-long history under a variety of names: 'incorrigibles', 'brain damaged', 'hyperkinetic', and 'Minimal Brain Dysfunction' (Barkley, 1990). Since 1980, the term 'attention' has been the initial and therefore most prominent feature of the names given to the syndrome, either 'attention deficit' alone or combined with 'hyperactivity' (and 'impulsivity') comprising the other central features defining the clinical category (American Psychiatric Association Diagnostic and Statistical Manual, 1994). The current *Diagnostic and Statistical Manual* (*DSM–IV*) lists three subtypes: a combined or full ADHD; a predominantly inattentive; and a predominantly hyperactive/impulsive subtype (*American Psychiatric Association Diagnostic and Statistical Manual*, 1994). Experts suspect that the predominantly hyperactive/impulsive subtype is most often seen in preschool children; there is more controversy about the predominantly inattentive subtype (except when it is only a residual form of the full syndrome, occurring in the adolescent and adult portions of the lifespan); controversial is whether those who present as children with the predominantly inattentive type have a disorder that is quite different. The heterogeneity of ADHD is one of the commonly documented but difficult characteristics of the disorder.

Diagnosis

Hyperactivity may be the first sign to be noticed, obvious in nursery school when not much sustained attention or independent self-control is expected. A small percentage of children diagnosed with ADHD are retrospectively described as difficult right from the moment of birth and as children who 'run rather than walk' as soon as they get up on their feet. Most children with the ADHD diagnosis are also impulsive, which can be in terms of 'on the mind, out the mouth' and is not necessarily gross physical activity or aggressivity. Impulsivity can take the form of not waiting one's turn or thinking before acting, interrupting, talking too much, talking too loud, blurting out whatever comes to mind. Impulsivity is more characteristic of ADHD than is true inattentiveness. Impulsive children may seem clumsy and accident prone because they are uninhibited when exploring the environment in a state of activation/excitation.

Time management, organization of possessions, and sustained on-task effort of any kind present difficulties at any age for people with ADHD. It is often stated that children with ADHD forget what they have for homework, forget to bring in what homework they have done, may bring their homework to school and forget to hand it in, fail to finish things, make careless mistakes, and appear to be in a kind of 'brownian motion' between activities, yet sustain attention on games/play of their own predilection.

Although they appear just 'immature for age' or 'exaggerated children', children with ADHD can make life difficult for everyone around them as well as for themselves, causing disruption and disorganization in homes and schools. Often, they experience social rejection by other children who find their behaviour somewhere between annoying and completely obnoxious, while teachers and parents may regard the children's deportment as belonging

to 'moral turpitude' categories such as irresponsibility, lack of motivation, or laziness. Secondary emotional overlay comes in the wake of rejection and the experience of negative reactions from others, so that anger and frustration may distort the psychosocial adjustment of children with ADHD; they can easily become oppositional, argumentative, and, while denying their own mistakes, attribute the causes of their actions to others. Because children with ADHD do not perform academically up to expectations based on their intellects or talents, because often and repeatedly they are subjected to negative comments, scolding, and punishments, they frequently suffer from poor self-esteem, generating still further disorders like depression and anxiety.

Adolescents and adults with ADHD are more likely to look like the 'predominantly inattentive type' even though, fulfilling full criteria for development of the full syndrome before the age of seven years, they have previously been hyperactive. What persists is a picture of fidgety restlessness, disorganization, forgetfulness, poor boredom tolerance, impatience and a generally 'immature'/disheveled lifestyle. As teenagers, they misplace their possessions, mismanage their time, neglect their homework, and do not achieve the level of self-control considered appropriate for the level of independence craved by most teenagers. Persisting in the adult picture is difficulty setting priorities, managing time, keeping track of possessions, and remembering an agenda. Adult 'hyperactivity' in a sense is persistent in the more time-stretched-out sense of moving frequently, changing primary relationships frequently and changing jobs more frequently than do others of their age.

ADHD is diagnosed at least three times more often in boys than in girls; and this difference, more boys than girls, is even more pronounced among those who are seen in psychiatric rather than pediatric settings. Boys appear more likely to be disruptive, hyperactive, overtly impulsive, and express the comorbidity of oppositional-defiant disorder. Girls are often diagnosed at a later age, and more often with the predominantly inattentive type; close clinical inspection of such girls, however, reveals considerable impulsivity in their leisure behaviours outside of school and a greater degree (than is obvious to the observer) of inhibitory insufficiency in the extent to which they are able to control their mental activities.

Diagnosis of ADHD is complicated by symptoms/signs suggestive of other psychiatric diagnoses and must be distinguished from these or declared comorbid with these. Common comorbidities in childhood are academic learning disabilities and developmental motor coordination disorder. The term minimal brain dysfunction was popular between 1968 and 1980 and was used to describe a mixture of attention deficit hyperactivity disorder symptoms, learning disabilities, and developmental motor coordination disorder (Barkley, 1990). More than 20% of children with ADHD have depressive or anxiety disorders; up to one-third of children with ADHD are aggressive and may receive a formal diagnosis of oppositional-defiant disorder. Some experts believe that the 'externalizing' or acting-out behaviours comprising so-called disruptive 'comorbidity' result from the same underlying failure of behavioural inhibition or impulse control that is fundamental to ADHD. Those whose profiles are complicated by the aggressive, oppositional-defiant, or misconduct symptomatology also have a high rate of alcoholism and drug abuse, sometimes because of antisocial personality, sometimes because of attempts towards self-medication for mood issues (Biederman et al., 1993; Mannuzza et al., 1993). Comorbidity with Tourette's syndrome is discussed in the chapter by Singer, this volume.

There are times when a 'secondary' ADHD gives clues as to the biological basis of the disorder in general; for example, the hyperactive/impulsive group called the 'incorrigibles' were children who suffered brain damage in the wake of the encephalitis lethargica epidemic in the 1920s after World War I. ADHD also occurs secondary to several genetic disorders, head injuries and toxic exposures such as lead poisoning and fetal alcohol syndrome (The Harvard Mental Health Letter, 2000). It is now widely accepted that the core of the disorder is a failure of self-control, most prominently in the sense of behavioural inhibition, inability to respond adequately to routine reward and punishment, and/or deficiencies in what is called 'executive function' (see below). So far, ADHD cannot be diagnosed by any form of neuroimaging, neuropsychological tests, or blood tests.

Differential diagnosis is complicated by the fact that circumstances and situations have to be taken into account in order to rule out that signs/symptoms resembling ADHD result from improper schooling/child rearing, or stress in the form of abuse or neglect. It is sometimes difficult to make a differential diagnosis between bipolar disorder and ADHD (The Harvard Mental Health Letter, 2000). The way in which the child is handled may make the child behave so markedly differently in one situation from another, contemporaneously, that it may be difficult to sort out whether or not the child has the fundamental biological disorder of ADHD; sometimes a child will be perfectly well behaved with a kind but firm teacher, but then be completely out of control in a daycare setting where there is a less structured approach to managing the room. In general, children with ADHD behave better one-to-one, in small groups, or in situations in which the adult management is kind but firm,

and the expectations are clear, as are the consequences of either positive or negative behaviours.

Diagnosis should require a thorough medical/psychiatric history and examination, a neuropsychological/psychoeducational evaluation, and use of questionnaires and rating scales in the context of careful clinical interviews with parents, teachers, and the children themselves. (Unfortunately, this is exceedingly time consuming, so that ideal diagnostic procedures are rarely feasible in today's medical care environment.) Information about family history and about the fine-grained details of home and school life are also important. There may need to be involvement beyond neurologists, psychiatrists, and teachers in the form of information from school counsellors and clinical child psychologists, as well. If there are learning disabilities or language disorders, special educators and language therapists will become participants in the process.

Much of the neurobiological thinking about the disorder has arisen from the fact that certain stimulant drugs in a majority of cases provide striking immediate improvement in the most troublesome and most disruptive symptoms of ADHD; however, response to stimulants is *not* diagnostic of ADHD.

A valid diagnosis of ADHD requires that the problems as quantified on rating scales must be a sufficient number of standard deviations from the mean for the behaviours exhibited by children at that age/level of development. The problems must have begun before the age of seven and must be persistent across time. The requirement that they be pervasive across situations runs into some of the difficulties noted above, but at least in settings similarly structured there should be pervasive problems. It is not that a high level of activity is considered intolerable as long as activity and impulse control are regulated; it is that the child cannot get along with others, obey reasonable requests from parents and teachers, and cannot progress academically because of impersistence. When clinicians follow established guidelines, the diagnosis of ADHD is reliable (NIH Consensus Statement, 1998).

Prognosis

Even the staunchest advocates of a biological interpretation of the basis for attention deficit hyperactivity disorder have been aware of the fact that there are major environmental interactions in the appearance and in the severity of the disorder. The increased demands for sustained attention, and self-control (at an earlier age than decades ago) due to patterns of parental employment, and even the burden of 'virtual reality' distractions may have profoundly influenced attentional and inhibitory capacities and accentuated the perception that a child is inadequate developmentally. Negative parenting practices predict more of the non-compliant and the externalizing behaviours, particularly those that go beyond the age inappropriate and are antisocial (Hinshaw et al., 1997). A persistent misconception is that a biological interpretation of ADHD leads to the conclusion that parenting and schooling do not matter; this prevails even among highly educated persons thinking about the controversies surrounding ADHD. Experience of clinicians is that the child's environment may powerfully influence the prognosis even when there are strong indicators of a biological set of predispositions of ADHD. How the family and the school react to the child, adolescent, and even young adult across the lifespan and how they cope with the problems, seek help and modify the environment for the person with ADHD may be crucial in shaping development; and for all we know, this may be in a very literal brain-development sense as well as the total adaptive sense. Underlying tendencies may be worsened by overly lenient, difficult, inconsistent, or hostile teaching and parenting. The most important complications of ADHD seem to emerge under the worst of circumstances, while optimal parenting and teaching promote strengths in children with ADHD, including positive peer relations (Tannock, 1998).

Neurobiology

Neuropsychology

Since 1980, contemporaneous with the emphasis upon the word 'attention' in the name of the disorder and also a general consensus that psychological processes should guide our understanding of the disorder, neuropsychologists have been struck by analogies between test/assessment behaviours seen in patients with 'frontal lobe' lesions and similar ones in children with ADHD. From this has come a large body of literature focused upon the frontal-lobe-associated construct of 'executive dysfunction' in children with attention deficit hyperactivity disorder, which has itself been the inspiration for a great deal more in the way of study of the normal development of the executive system in childhood. By 1991, a very influential textbook on learning disabilities was constructing a framework in which ADHD was affiliated with frontal lobe, particularly dorsolateral, dysfunction (Pennington, 1991). Executive functions are historically linked to prefrontal, especially dorsolateral, regions and their subcortical,

'domain-general' interconnected regions. The parallel circuits connecting corresponding subdivisions of the frontal lobes and various subdivisions of the basal ganglia have been scrutinized; there is now a general conceptual model to the effect that children with attention deficit hyperactivity disorder, particularly those with the frequent comorbidity of developmental motor coordination disorder, are deficient in one (or more) sectors of the frontal striatal circuitry involving control; there are seen various clinical combinations of motor control, cognitive control, and emotional control deviating from normal developmental attainments. Although there have been both positive and negative findings with respect to each of several tests of executive function in sampled populations with attention deficit hyperactivity disorder, examination of executive functions constitutes a major clinical advance and also inspires the focus of the anatomic imaging work, hypothesis-driven because it measures those structures that are reasonable frontal or basal ganglia 'candidates' implicated in the types of controlled processes on which ADHD-related failures are found (Tannock, 1998; Barkley, 2000).

The executive deficits found have largely been those that involve response inhibition and working memory. As for the adjacent 'motor' domain, there have been many publications on response inhibition in the context of behavioural neurology (Voeller et al., 1991). More recently, eye movements have been studied and a variety of different findings have been forthcoming with respect to antisaccades and remembered saccades (Mostofsky et al., 2000). Clinicians frequently see that tests of executive function, particularly in children, adolescents, and adults with the predominantly inattentive type of ADHD, successfully characterize young patients in a way that is instantaneously recognizable to their parents; however, it has not proven possible to turn around the diagnostic algorithm in such a way that one could classify persons as qualifying for the diagnosis of ADHD on the basis of their executive dysfunctions (Grodzinsky & Barkley, 1999). In his book on ADHD, which is subtitled *The Nature Of Self-Control* (Barkley, 1997), Barkley attempts a linear model explanation of executive function, whereby inhibition is the fundamental and driving precursor of all subsequent developmental executive difficulties, however multiple the manifestations. (Motor control enters into Barkley's thinking as he takes note of the disinhibition on motor examination in the form of overflow movements.) On the other hand, other researchers have suggested that a more pervasive cognitive dysfunction with more proactive organization of components, rather than a precursor deficit restricted to response inhibition, is characteristic of children with attention deficit hyperactivity disorder (Oosterlaan & Sergeant, 1998). Even tests previously thought of as completely within the linguistic domain, such as rapid automatized naming (considered to be one of the best predictors of reading disability) have been shown to be impaired in children with ADHD (Tannock et al., 2000). Furthermore, narrative language skills are not always normal in an ADHD group that is not clinically considered to have language deficits of a more basic nature, because higher order executive function deficits operating upon the domain of language emerge when important prewriting formulation skills are tested (Purvis & Tannock, 1997). Many professionals who specialize in evaluating school problems are now of the opinion, as is the writer of this contribution, that ADHD implies cognitive control issues that do constitute 'true learning disabilities'. The separation between 'learning disabilities' and 'ADHD' is increasingly untenable (Fischer et al., 1990; Cox et al., 1997; Denckla & Cutting, 1999).

On continuous performance tests, particularly of the go/no-go type, most patients with ADHD show prolonged reaction times and a high degree of variability (inconsistency) of their reaction times (Reader et al., 1994). Paradoxically, most patients with ADHD are slow on response preparation, so timed tasks are the most useful ones in corroborating the diagnosis of ADHD. Output under timed conditions with rule-governed control demands brings out deficits in ADHD, as on the letter-word fluency task aptly called Controlled Word Association. Clinicians have found it useful to look at the organizational scores, particularly in a developmental context, from the copying of the Rey Osterrieth complex figure. The California Verbal Learning Test for children also provides a useful opportunity to contrast the level of recall with the learning characteristics and error types. Children with ADHD, who have mainly proactive executive deficits, tend to be poor in strategy (clustering) and also respond less well under free recall conditions than they do when they are given by the examiner the explicit structure of category cues. Those with severe impulsivity make enormous numbers of intrusion errors. The occurrence of repetition errors may indicate poor working memory (Denckla, 1994, 1996).

Neurophysiology of ADHD

Although for many years de-emphasized, recently there has been reborn interest in the epileptiform EEG associated with attention deficit hyperactivity disorder. Epileptiform discharges were reported in a rather large study of children with ADHD, even after all patients with a history of clinical seizures were excluded from the study.

'Definite noncontroversial epileptiform activity' was present in 30%, with epileptiform spike discharges of a focal nature in 24% (temporal/occipital) and generalized spike/waves in 6%. Normal records were found in 47%, but only 28% were completely normal (Hughes et al., 2000). Transcranial magnetic stimulation, when used to study patients with ADHD, indicates immaturity (relative to age-matched peers) in the development of cortical inhibitory pathways; children with ADHD showed reduced intracortical inhibition relative to other children of their age (Moll et al., 2000). Functional magnetic resonance imaging has been used in order to demonstrate altered neuronal activity accompanying relevant response preparation/inhibition tasks; when tested without medication, boys with ADHD showed greater-than-normal activity in the frontal lobe during the more difficult of two tasks requiring response inhibition. Also, the ADHD group showed impaired inhibitory control on both 'easy' and 'hard' go/no-go tasks associated with reduced striatal activation; but they showed improved striatal function when given methylphenidate (Vaidya et al., 1998).

Neuroimaging

Over the past decade, there have been a dozen papers indicating significant regional brain differences in ADHD as determined by quantitative volumetric brain magnetic resonance imaging (MRI). Findings (smaller volumes) have always been more prominent in boys than in girls, but consistently across all studies from all groups is that boys with ADHD have reduced total cerebral volumes compared with controls (boys matched for age and intelligence). Girls with ADHD have not been shown to differ from controls in their total cerebral volume; however, as previously reported in boys with ADHD, girls with ADHD showed similar subtotal volume reductions in bilateral posterior prefrontal brain, bilateral caudate nucleus, left globus pallidus, and posterior inferior cerebellar vermis (F.X. Castellanos, personal communication, 1998). See also MRI volumetrics of Tourette/comorbid ADHD, reviewed by Singer, this volume.

Considerable consensus across studies from different centres reveals the following structures to be smaller in boys with ADHD: frontal regions, caudate, globus pallidus (Aylward et al., 1996; Castellanos et al., 1996; Filipek et al., 1997; Giedd et al., 1994), and posterior inferior cerebellar vermis (Berquin et al., 1998; Mostofsky et al., 1998b). Only one study differed from the majority's emphasis on the anterior structures, reporting additional parietal volume reductions in a group of 15 boys, one-third of whom were said to be stimulant non-responders (Filipek et al., 1997; Semrud-Clikeman et al., 1994). The symptom/sign of disinhibition in children with ADHD correlates with reversed asymmetry of the caudate; measures of attention correlate with right hemisphere white matter volumes (Semrud-Clikeman et al., 2000).

Neurotransmitters implicated in ADHD

Although most research has focused upon dopaminergic mechanisms, recent reviews related to the mechanisms underlying attention deficit hyperactivity disorder provide considerable evidence supporting a noradrenergic hypothesis of ADHD (Biederman & Spencer, 2000). Response to drugs with mixed noradrenergic and dopaminergic pharmacological loci of action have long been the starting point for this hypothesis, albeit the dopamine focus has been dominant. In addition (see genetics section below), although new and controversial, several research publications, with some degree of replication, have found associations between ADHD and two genes, the dopamine transporter and one particular dopamine receptor, D4 subtype (Swanson et al., 2000a). A recent PET study of children with ADHD using the tracer [^{18}F] DOPA indicates unusually high accumulation of that neurochemical in the dopamine-rich region of the high midbrain, while no other dopamine-rich regions significantly differed between groups with and without ADHD (Ernst et al., 1999); this recent PET study was considered to be suggestive of dysfunction at the level of the dopaminergic nuclei in children with ADHD. Noradrenergic activation is documented as essential to the normal operation of attention, especially the arousal infrastructure; the noradrenergic system is well known to be necessary for the modulation of higher cortical functions that include selective attention, vigilance, and executive function in general. Research based upon animal (including primate) models suggests that either too much $\mathcal{L}_1$ receptor or too little $\mathcal{L}_2$ receptor stimulation can impair prefrontal cortex (Arnsten, 2000). Epinephrine itself, linked to adrenomedullary functioning during cognitive testing in boys with diagnosed ADHD, has been reported to be correlated with both parent- and teacher-rated behaviours categorized under 'inattention'. Lower adrenomedullary epinephrine status in individuals with ADHD while they are performing the cognitive 'stress' of schoolwork appears to be associated with the inattentive subtype but not so much with the full syndrome (Anderson et al., 2000).

Serotonin is another neurotransmitter that may play a role, particularly among those children who are prominently aggressive from an early age. Serotonin activity has

also been implicated in working memory performance in some studies of children with ADHD (Gainetdinov et al., 1999; Spivak et al., 1999; Oades, 2000).

Providing transition to the subject of genetics, comparison of the effect of 20 genes that involve dopamine, serotonin, and neuroadrenergic metabolism on quantitative scores in a multivariate linear regression analysis predicting ADHD in a large population indicated that adrenergic genes accounted for more of the variance in ADHD than either the dopaminergic or serotonergic genes combined; but it must be noted that even the six adrenergic genes contributed only 6.9% of the variance, while all genes combined accounted for 11.6% of the variance (Comings et al., 2000).

Genetic basis of ADHD

Genes related to neurotransmitters and neurotransmitter receptors

Molecular genetic studies of ADHD have suggested the possible involvement of one or more dopaminergically relevant genes, either a dopamine transporter gene (associated with a mechanism of excess dopamine reuptake) or the 7-repeat allele of *DRD4* (associated with a reduced sensitivity of the receptor at the postsynaptic level) (Thapar et al., 1999; Swanson et al., 2000a). Neuropsychological tests of attention in those with the 7-repeat allele of *DRD4* gene contradicted the primary hypothesis of this study; those with the candidate abnormal gene (7-repeat allele *DRD4*) seemed to be free of difficulties on the neuropsychological tests, exhibiting average reaction times and consistent responses (Swanson et al., 2000a, b).

The *DRD4* gene and its relationship with ADHD remain controversial. Two negative studies from Israel concern the exon 3 repeat polymorphism (Eisenberg et al., 2000; Kotler et al., 2000) and a study from Ireland concerning the 7-repeat allele was similarly negative (Hawi et al., 2000). On the other hand, there have been several studies documenting *DRD4* variants conferring ADHD risk (McCracken et al., 2000; Barr et al., 2000; Muglia et al., 2000).

The human dopamine transporter gene was further analysed; gene variants that alter levels of DAT expression survive as excellent candidate mechanisms for underlying ADHD as well as, in a less specific fashion, other frequently comorbid associated neuropsychiatric disorders (Vandenbergh et al., 2000). Some evidence for the serotonin HTR 2 A receptor gene as relevant to ADHD opens an entirely new avenue of molecular genetics research on ADHD, leading to speculation that there is a complex interplay in ADHD among neurotransmitter systems rather than strictly emphasis upon the dopamine system (Quist et al., 2000).

Clarifying the genetic architecture of ADHD

Using a sophisticated statistical analysis called latent class analysis in a twin study of school-age children, only two subtypes emerged, one inattentive and the other combined, each of which is a dimensional domain (Neuman et al., 1999). Another twin study suggested that extreme hyperactivity/impulsivity might be genetically and etiologically separable from the usual moderate full syndrome and extrapolated without reservation to families with girls as ADHD probands (Faraone et al., 2000). A common genetic factor (revealed in a large twin pair study) underlies maternally reported and concordant maternal/teacher-reported ADHD; when teacher-only-ADHD is reported, weaker genetic influence is supported and environmental factors loom larger (Thapar et al., 2000).

In multiplex families with ADHD, the gender ratio appeared to be consistent with a genetic model in which a greater loading of familial influences was necessary for the girls to develop ADHD (Smalley et al., 2000).

Treatment

Most of the controversy about the diagnosis of ADHD has emanated from its almost complete identification (in the public mind) with treatment involving stimulant medication. In what is probably the most widely replicated body of literature on psychopharmacology dealing with the pediatric age group it has been shown that methylphenidate (Ritalin) and dextroamphetamine (Dexedrine) provide improvement for between 75 and 90% of children and adults with ADHD. Side effects are few and rarely serious, all being confined to observable effects upon the central nervous system (eating, sleeping, mood, tics). In 1998, the Council on Scientific Affairs of the American Medical Association conducted a 20-year review of the scientific literature and concluded that stimulant drugs were not being prescribed excessively or being misused (The Harvard Mental Health Letter, 2000). Stimulant treatment of ADHD in public schools in Maryland (mainly methylphenidate) is variably prescribed to students for school purposes, being fourfold greater for males than for females, twice as often for white as for minority students, and three times as often for elementary as opposed to high school students. The majority of the children taking stimulant medication had their medical supervision and prescriptions undertaken by pediatricians (63%); when medications other than methylphenidate (Ritalin) were

prescribed, the prescribing physician was a psychiatrist in 29% of such cases (Safer & Malove, 2000). Recent studies on the long-term risk of drug abuse and alcoholism among those who as children were treated with prescription stimulants reaches a conclusion opposite to that of increased risk; rather, the risk for drug abuse in adolescents is lessened by successful childhood stimulant medication treatment of ADHD (Degrandpre & Hinshaw, 2000).

A recent major clinical trial sponsored by the National Institute of Mental Health was conducted at several medical centres and universities for, so far, a 14-month period (MTA Cooperative Group, 1999a). Clear benefits of stimulant medication were documented for carefully diagnosed children with ADHD (who had their medication optimally managed by initial dosage adjustment, monthly family visits to the doctors, and mandatory contact with school personnel). Medication management of this high quality was superior in outcome, in terms of reducing signs/symptoms, to medication-free intensive psychosocial intervention (involving long-term parent training, school consultation, and summer programmes of contingency management/behaviour modification). The careful medication regimen was clearly superior to 'community' standards of stimulant medication treatment lacking the close monitoring and titrating. A lower dose of medication was effective in the group receiving the combined medical and behavioural treatment (MTA Cooperative Group, 1999b).

Medication alone is not even initially effective, when there are comorbid conditions, like learning disabilities, which require remediation. Cognitive interventions for non-academic behaviours are not as useful as contingency management techniques. Schools, following Federal law, must accommodate ADHD as a disability under the Section 504 of the American with Disabilities Act. This is a different law from the one that governs learning disabilities (P.L. 94–142). A 504 Plan for ADHD should feature the following: extended time on tests, frequent breaks on tests, close monitoring, predictable schedules, constant feedback, tangible rewards and response costs; and those with ADHD should be positioned in the classroom close to the teacher and as far as possible from sources of distraction. It appears that the main reason that non-pharmacological treatments do not receive as much focus as pharmacological ones is that they are very demanding of adult time, expertise and effort; and given that the ADHD is chronic, it appears likely that the psychosocial treatments need to be chronic, whatever the modality (Pelham & Gnagy, 1999).

In conclusion, despite fears that 'drugging children' into compliance is the motivation for making the diagnosis of ADHD, there is considerable clinical and research evidence supporting the view that ADHD represents a group of real neurological, mainly neurodevelopmental, disorders involving control processes (motor, cognitive, and emotional). This point of view acknowledges that 'the brain both shapes and is shaped by the environment; underlying psychobiological risk factors can be treated environmentally and some conditions resulting from stressful life events could be dealt with by biological intervention . . .' (Degrandpre & Hinshaw, 2000).

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The neurobiology of drug addiction

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Although neuroscientists have made considerable progress investigating and characterizing the brain regions that are involved in addiction, the integration of this information with clinical practice is still in its infancy. The neurobiology of addiction addresses the dynamic interaction between addictive drugs and the brain, ranging from drug intoxication to chronic neuroadaptations such as withdrawal, tolerance and craving. While psychological, psychosocial and environmental factors play important roles, addiction is primarily a brain disease (Leshner & Koob, 1999), and a greater understanding of its neurobiology should uncover new and effective treatments. Currently, there is an urgent need for medications capable of reducing craving and recidivism, perhaps by reversing brain disruptions associated with chronic substance abuse. Aside from refining treatment, addiction research has also shed light on the brain's reward centres that so dominate our lives. These centres have evolved over millions of years to reinforce feeding, mating, and other survival-related activities. Tampering with brain reward circuitry, through the process of addiction, produces many of the dangerous and lethal consequences that are associated with addictive illness.

Through the development of technological advances, scientists have developed sophisticated probes into the brain regions that are involved in drug reward. Addictive agents affect different neurotransmitter systems at various anatomical sites, creating distinct 'fingerprints' on the reward circuitry. However, the administration of all addictive substances increases extracellular dopamine (DA) levels in the nucleus accumbens (NAc), a location that has been named the 'universal addiction site'. This remarkable fact will be our starting point in a discussion of pathways that interconnect the midbrain, limbic system, and medial prefrontal cortex (PFC). Repeated administration of addictive drugs often produces opposite brain effects, and evidence of impaired DA neurotransmission has been reported with chronic cocaine, opiate, alcohol and marijuana exposure. Other neuroadaptations have also been identified and will be reviewed, by substance, in an attempt to integrate brain mechanisms with clinical phenomena such as drug withdrawal, craving and progression.

The nature of addiction

The hallmark of addiction is a progressive loss of control over drug intake, regardless of negative consequences. The willingness of drug addicts to risk death, disease, incarceration, job loss, financial ruin and family strife may seem counterintuitive. However, when the dynamics of addiction are understood, the lack of control exhibited by drug addicts becomes more comprehensible. A useful framework for conceptualizing addiction has been proposed by Wikler (Wikler & Pescor, 1967), based on classical and operant conditioning theory. In this construct, initial drug use may occur for a number of reasons, including boredom, curiosity, recreation and peer pressure. Drug euphoria, resulting from physiological effects on endogenous reward centres, 'positively' reinforces repeated drug use in the pursuit of pleasure. Over time, neuroadaptations affecting brain reward centres lead to phenomena such as drug withdrawal, craving and dysphoria. These unpleasant states, temporarily alleviated by drugs, 'negatively' reinforce repeated drug use. Craving and withdrawal symptoms can also be triggered by conditioned cues that are associated with drug procurement and drug use. Alternating negative and positive reinforcement drives a viscous cycle of addiction that becomes increasingly entrenched and uncontrollable. Since the cycle of addiction is essentially etched onto the brain's reward substrate, the compulsive drive to use drugs takes on the strength and characteristics of a primary survival drive.

Anatomy and circuitry of endogenous reward centres

Since 'pleasure centres' in the lateral hypothalamus were first discovered by Olds in the 1950s, brain regions supporting electrical and drug self-stimulation have been intensively researched (Bardo, 1998). However, much of what is known about these reward centres is based on animal experiments that may not be easily generalized to humans. Aside from cross-species differences in anatomical, neurotransmitter and molecular systems, it is a wide leap from animal behaviour to human subjective experience. With these caveats in mind, it is apparent that a number of structures with synaptic connections to the medial forebrain bundle are intrinsically involved in drug reward and natural reward states (Wise, 1996). These structures include the DA-rich ventral tegmentum (VTA), PFC, NAc, and elements of the limbic system.

Drugs as diverse as psychostimulants, opiates, alcohol, marijuana, nicotine and phencyclidine (PCP) acutely increase levels of extracellular DA in the NAc (Koob et al., 1998). The shell of the NAc shares embryological and cytoarchitectural similarities with the central nucleus of the amygdala and the bed nucleus of the stria terminalis, comprising what has been termed the extended amygdala (Heimer & Alheid, 1991). The extended amygdala has reciprocal connections with the forebrain, hippocampus, midbrain, ventral pallidum, mediodorsal thalamus and the lateral hypothalamus (Koob et al., 1998). The NAc can be functionally divided into its ventromedial shell, essentially a limbic structure, and its core that is associated with the ventral striatum. The shell is implicated in reward function and the core projects motor-related information to the substantia nigra. The proximity of predominately reward and motor structures within the NAc provides a direct anatomical interface between motivational and behavioural function (Pennartz et al., 1994).

The NAc shell region is composed primarily of medium-sized spiny cells. These neurons utilize GABA as their primary neurotransmitter but may also contain endogenous opioid peptide (EOP) neurotransmitters. EOP neurotransmitters such as dynorphin and enkephalin are contained primarily in output neurons within the NAc. All three classes of opiate receptors are found in the NAc. Agonists for the mu and delta receptors are rewarding in this region, whereas kappa agonists are aversive (Akil et al., 1998). In addition, the activation of mu and delta receptors releases DA, while kappa agonists inhibit DA release. There is evidence that separate populations of NAc neurons in the striatum contain either enkephalin or dynorphin, with enkephalin-containing neurons usually expressing D_2 receptors and dynorphin-containing neurons typically expressing D_1 receptors (Akil et al., 1998). Dynorphin and enkephalin projections are thought to be involved in compensatory actions in response to excessive DA neurotransmission, and alterations in these systems may underlie neuroadaptations associated with opiates, stimulants, and other addictive agents. The presence of opioids and opiate receptors in this universal addiction site is noteworthy.

The NAc receives 'reward circuit' DA projections from the VTA and returns inhibitory reciprocal fibres to this DA-rich centre. DA projections of the reward circuit have complicated actions on medium-sized spiny cells. D_2-mediated effects are inhibitory and reduce the formation of cAMP within NAc target cells (Self et al., 1998). D_1 receptors, on the other hand, stimulate cAMP formation and have a modulatory role that involves either inhibition or excitation, depending on the resting state of NAc target cells. Medium-sized spiny cells tend to be in either an active or inactive state, and D_1 activation causes a prolongation of the pre-existing state (Hernandez-Lopez et al., 1997). Therefore, while D_2 receptor activation inhibits medium-sized spiny cells, D_1 activation can either inhibit or stimulate the firing rates of these output neurons.

The NAc is stimulated by glutamate-containing axons that originate in the PFC, amygdala, hippocampus, and thalamus (Pennartz et al., 1994). The PFC sends massive descending fibres that actually join DA terminals of the reward circuit to form 'dual-synapses' on medium-sized spiny cells (Sesack & Pickel, 1992). Similar convergent DA and glutamate terminals in the NAc have been demonstrated with excitatory inputs from the hippocampus (CA3 area), amygdala and thalamus. Also, the NAc sends reciprocal fibres to each of these glutamatergic areas. Dense glutamate-containing fibres from the amygdala travel via the stria terminalis before converging on the spines and distal dendrites of NAc neurons. Hippocampal projections, possibly involved in reward memory, originate in the subiculum and pass through the fimbria-fornix to target cells in the NAc. Convergent synaptic input from glutamate and DA projections allows for the simultaneous processing of cortical and midbrain reward information by GABA\EOP-containing cells of the NAc.

Aside from glutamate and DA, the NAc is also influenced by other neurotransmitter systems. It receives serotonin terminals from the dorsal and median raphe, and norepinephrine projections from the locus coeruleus and the nucleus tractus solitarius. Cholinergic neurons intrinsic to the NAc synapse on the dendritic shafts of a population of medium-sized spiny cells that do not receive DA projections (Pickel & Chan, 1990). This finding provides evidence that discrete populations of medium-sized spiny cells in

the NAc have different functions. The convergence of DA, GABA, glutamate, EOP, serotonin, norepinephrine and acetylcholine-containing neurons in the NAc allows for complex interactions involving these critical neurotransmitter systems.

The NAc shell sends GABA and opioid-containing projections throughout the reward circuitry. NAc projections extend directly to the lateral hypothalamic and preoptic areas that are involved in the consummatory functions of feeding, drinking, and sexual activity. Morphine is self-administered directly into the lateral hypothalamus, suggesting a role for EOP systems in consummatory reward. Indirect outflow from the NAc passes through the ventral pallidum, a structure intrinsically involved in motivation and drug seeking behaviour (Bardo, 1998). In addition to serving as a relay point to other anatomical regions, the ventral pallidum processes reward information through opioid modulation (Napier & Mitrovic, 1999). The ventral pallidum conveys NAc projections to the pedunculopontine tegmental nucleus, a region composed of large cholinergic cells and smaller glutamate neurons. Cholinergic neurons of the pedunculopontine tegmentum project to the VTA and stimulate nicotinic receptors that are located on DA cell bodies. Implicated in the acquisition of drug-rewarded behaviour, the pedunculopontine nucleus also projects to the amygdala and lateral hypothalamus.

Another important NAc pathway traverses through the ventral pallidum to the mediodorsal thalamic nucleus, an area associated with feelings of fear and anxiety. The mediodorsal thalamus is generally viewed as limbic and has extensive connections to the PFC and anterior cingulate. The anterior cingulate, which also receives direct VTA projections, has numerous functions that include pain perception and the assignment of emotional valence to perceived stimuli. The pallidal–thalamocortical circuit has been termed the 'motive circuit' and is thought to initiate adaptive responses to reward information received from the NAc (Kalivas et al., 1999). The PFC (Grant et al., 1996) and cingulate area (Childress et al., 1999) are hypermetabolic in humans during cocaine cue craving, suggesting that the multisynaptic circuit connecting the NAc, ventral pallidum, mediodorsal thalamus, and cortical regions has an important role in the addictive process. As the neurobiology of craving is further unravelled by additional imaging studies, new treatments for this tenacious negative reinforcer may result.

The amygdala plays a role in reward and reward-related memory. The basolateral nucleus of the amygdala consists largely of glutamatergic pyramidal cells while the central nucleus is mainly populated by GABA-containing projection neurons. As with the NAc, the amygdala is rich in endogenous opioids. The central nucleus of the amygdala, NAc, and bed nucleus of the stria terminalis (extended amygdala) share many characteristics (Heimer & Alheid, 1991). The amygdala sends excitatory glutamatergic axons to the NAc and receives reciprocals from this important reward centre. Preclinical and imaging studies demonstrate that the amygdala is involved in the recognition of emotionally relevant stimuli. Imaging studies in humans have reported hypermetabolism in the amygdala during cocaine cue craving (Grant et al., 1996; Childress et al., 1999), and amygdaloid suppression during cocaine administration (Breiter et al., 1997). Animal studies report that lesions of the basolateral amygdala interfere with the process by which neutral stimuli become secondary reinforcers of cocaine administration and motivate drug-seeking behaviour and cue-induced relapse (Whitelaw et al., 1996). While the basolateral amygdala is involved in the acquisition of cocaine-seeking behaviour, the central nucleus of the amygdala is implicated in alcohol reward and withdrawal. This GABA/EOP-rich region may also be affected by CRF abnormalities that are associated with addiction. CRF is a centrally acting neuropeptide that, aside from its ability to activate the hypothalamic–pituitary–adrenal axis, also mediates behavioural responses to stress. Elevations in CRF are found during withdrawal from many substances (cocaine, opiates, THC, and alcohol) and CRF antagonists reverse aversive affects of alcohol and opiate withdrawal when administered into the central nucleus of the amygdala (Koob et al., 1998).

The VTA is the source of all mesocorticolimbic DA and serves a crucial role in drug reward and in natural drive states, including the procurement of food, fluid, and sex. DA neurons comprise about 85% of the cell bodies in the VTA and display either baseline pacemaker activity, or episodic burst firing when activated. Burst firing occurs during consummatory activity (such as feeding) and later upon exposure to cues associated with these behaviours, suggesting an interesting learning capability of mesocorticolimbic DA neurons (Schultz et al., 1997). The major projection bundles from the VTA extend to the NAc, the frontal lobe (prefrontal and anterior cingulate cortex), and the amygdala. It is not clear how these three important projections and their target sites interrelate on a functional basis through their extensive interconnections.

DA neurons in the VTA are under intensive local and distal regulation, receiving input from GABA, glutamate, acetylcholine, EOP, and serotonergic-containing neurons. Local inhibition is mediated through somato-dendritic D_2 autoreceptors and local GABA interneurons. Inhibitory fibres also project from the NAc (directly and via the ventral pallidum), amygdala and other limbic structures. Glutamatergic projections and cholinergic axons from the laterodorsal

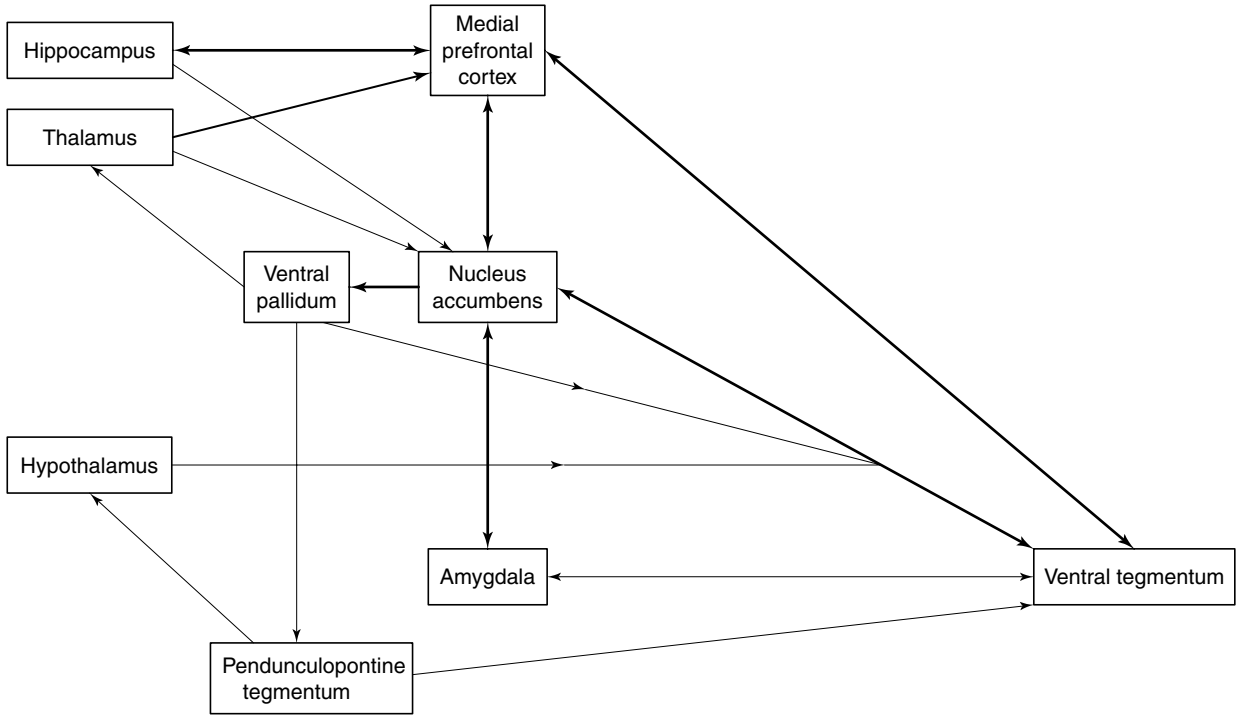

Fig. 30.1. Circuits of the reward centres are schematically represented. Attention is directed to the 'reward circuit' involving DA projections from the VTA to the NAc. The NAc, termed the 'universal reward site' contains GABA\EOP projection neurons and is implicated in all drug reward states. The 'motive circuit' connects the NAc and ventral pallidum with glutamatergic neurons of the thalamus and PFC. Cholinergic projections from the pedunculopontine tegmentum terminate on nicotinic receptors.

tegmental and pedunculopontine nuclei provide excitatory input to the VTA. The activation of inhibitory mu opioid receptors on GABA interneurons of the VTA (and GABA cells projecting to the VTA) releases DA neurons from tonic GABA inhibition (Leshner & Koob, 1999). DA neurons in the VTA also receive direct synaptic input from EOP-containing terminals, and are modulated by the raphe nuclei and the hypothalamus.

Glutamate-containing pyramidal cells in the PFC tonically stimulate VTA neurons, and thereby regulate the basal outflow of DA throughout the limbic system. Glutamatergic terminals synapse directly on DA neurons at the cell body level and activate NMDA and AMPA receptors. These cortical projections and reciprocal DA axons run through the medial forebrain bundle, a tract that has been intensely studied in reward, working memory, and schizophrenia research. DA projections to the PFC form synapses on the dendritic spines and shafts of cortical glutamatergic neurons, modulating their activity (Carr et al., 1999) and completing an interactive loop that is undoubtedly central to reward function. DA projections also modulate local inhibitory circuitry through synaptic connections on cortical GABA neurons. In addition to enhancing working memory, DA projections to the PFC appear to be involved in memory-guided goal-directed behaviour (Durstewitz et al., 2000). PFC pyramidal neurons that receive DA input are also innervated by glutamatergic projections from the hippocampus, a structure that is implicated in memory. The role of memory in the perpetuation of repeated drug use is an essential component of addiction.

The reward circuitry outlined in this discussion is summarized in Fig. 30.1. It is useful to note that there are three major VTA bundles projecting to the NAc, PFC, and amygdala. These structures are extensively interconnected and send reciprocal fibres back to the VTA to form a series of loops within the reward circuitry. The major neurotransmitter systems that comprise these circuits include DA, glutamate, GABA and EOP-containing neurons. Since these neurotransmitters are intimately involved in the acute and chronic actions of addictive substances, researchers have focused on therapeutic agents that directly or indirectly affect their associated neuronal pathways. Given the central modulatory role of mesocorticolimbic DA neurons, intact VTA function is probably crucial

in the normal orchestration of reward circuits. The dysregulation of DA neurons with chronic addiction, combined with target cell neuroadaptations, will be reviewed in the following sections, and may explain many of the clinical aspects of addiction. The next sections will focus on the major classes of addictive drugs with regard to their neurobiology and clinical characteristics.

Central stimulants: cocaine and amphetamine

Historically, central stimulants have caused a number of drug epidemics, especially when perceived to be safe. Stimulants are associated with intense euphoria, well outside the normal range of human experience, and their repeated use leads to rapidly progressive addiction in many individuals. The power of stimulant reward is illustrated by the fact that cocaine and amphetamine are readily self-administered by animals to the point of death, and preferred over sex, food and water (Dackis & Gold, 1985). Aside from producing euphoria, stimulants suppress hunger and food intake, reverse fatigue and increase psychomotor activity. Cocaine is often administered through the intrapulmonary route (as crack), which is the most rapid means of delivery to the brain. The relatively mild withdrawal seen with stimulants, characterized by depressed mood, hypersomnia, hyperphagia, anergia and psychomotor retardation, illustrates that severe physical withdrawal is not crucial in the perpetuation of drug addiction. There is significant evidence that repeated stimulant exposure disrupts the functional integrity of the brain's reward centres.

The rewarding effect of cocaine and amphetamine results from increased DA neurotransmission in reward circuits. Amphetamine promotes the presynaptic release of DA (through reverse transport) while cocaine blocks the dopamine transporter (DAT), a membrane-bound protein that regulates synaptic DA levels (see Fig. 30.2). There is a strong correlation between euphoria and the rate at which cocaine enters the brain and blocks the DAT (Volkow et al., 1999). Cocaine also blocks serotonin and norepinephrine reuptake, and has local anesthetic action on neurons. The acute administration of cocaine and amphetamine dramatically reduces DA neuronal firing in the VTA by activating D_2 autoreceptors. This finding demonstrates that increased DA neurotransmission, not increased DA burst firing, is an essential feature of stimulant euphoria. Also consistent with increased DA neurotransmission during stimulant reward are the findings that DA antagonists block self-administration and reduce euphoric effects (Koob et al., 1998).

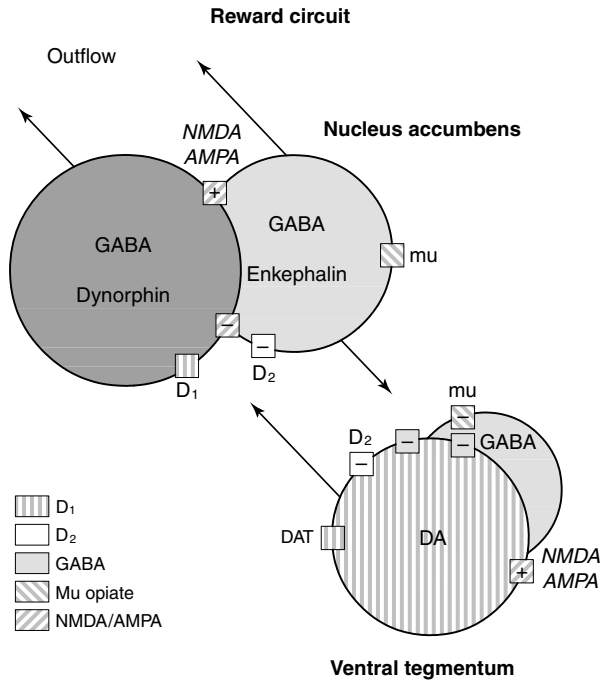

Fig. 30.2. 'Reward circuit' DA projections from the VTA stimulate D_1 and D_2 receptors on dynorphin and enkephalin-containing GABA neurons. Receptor effects (+ or −) are noted, and D_1 effects are modulatory. NMDA/AMPA receptors are excitatory, receiving glutamatergic projections from numerous cortical regions. Heroin acts on mu receptors, releasing DA from tonic inhibition. Cocaine acts on the DAT, increasing DA neurotransmission.

It has been suggested that increased DA neurotransmission cannot entirely explain stimulant reward because DAT knockout mice (lacking the DAT) self-administer cocaine, leading to the speculation that serotonin or norepinephrine systems are involved in stimulant reward. However, DAT knockout animals have high resting levels of extraneuronal DA and may have developed specific brain mechanisms to overcome their genetic deficit. For instance, the norepinephrine reuptake transporter has a high affinity for DA and may play a role in the self-administration of cocaine by these mice. Thus, the balance of evidence continues to support DA as the key neurotransmitter associated with stimulant reward.

Given the importance of DA neurotransmission in stimulant reward, attention is directed toward postsynaptic DA receptors. At least five distinct DA receptors ($D_{1–5}$) have been identified, although D_1 and D_5 receptors (often termed D_1) share many structural similarities, and $D_{2–4}$ receptors (often termed D_2) also have homologous residue sequences. Second messenger systems linked to DA receptors are intimately involved in the reinforcing action of

stimulants. D_2 receptor stimulation inhibits cAMP formation by activating the inhibitory guanine nucleotide binding protein (G_i-protein). If G_i-proteins in the NAc are inactivated with pertussis toxin, stimulant reinforcement is greatly reduced (Self et al., 1998). Therefore, stimulant reward is associated with D_2 inhibition of cAMP within medium-sized spiny cells in the NAc. Opiates also acutely inhibit cAMP in these neurons through mu and delta receptors coupled to G_i-proteins.

Opposing the action of G_i-proteins are G_s-proteins that increase cAMP levels and activate cAMP-dependent protein kinase. Activation of this pathway affects ion channels, neuronal enzymes and even nuclear transcription factors that can change long-term gene expression. It has been theorized that genetic changes are involved in the transformation from drug use to drug abuse. D_1 receptors are coupled to G_s-proteins and their stimulation increases cAMP levels. Therefore, D_1 and D_2 receptors have opposite effects on cAMP formation. Furthermore, cAMP inhibition enhances stimulant reward, while cAMP stimulation has the opposite effect (Self et al., 1998). Repeated cocaine administration increases cAMP levels in the NAc and upregulates D_1 receptors, resulting in a reduced capacity of DA to lower cAMP levels that could underlie tolerance (Self et al., 1998). Reduced D_2 receptors (associated with decreased metabolism in cingulate gyrus and orbitofrontal cortex) have been reported in human cocaine addicts although it is unclear whether these abnormalities are cocaine induced, or represent a pre-existing abnormality that may predispose certain individuals to cocaine dependence (Volkow et al., 1993). Anecdotal evidence from cocaine users suggests acute tolerance within a session and chronic tolerance to subjective effects over time. In a PET study of methylphenidate, another DAT inhibitor, less DA release was observed in cocaine abusers than in normal controls (Volkow et al., 1999). These findings indicate that repeated stimulant administration may render GABA\EOP neurons in the NAc less responsive to D_2-mediated inhibition and more responsive to D_1 effects.

In addition to changes in signal transduction, repeated cocaine exposure has been reported to produce DA depletion. DA depletion has been theorized to underlie the craving and dysphoria associated with cocaine dependence, and may result from the synaptic metabolism of DA during DAT blockade (Dackis & Gold, 1985). Consistent with DA depletion are reports of hyperprolactinemia (a marker for diminished DA tone) (Mendelson et al., 1989), reduced DA release (Volkow et al., 1999) and persistent reductions in DA activity in cocaine addicts (Wu et al., 1997). In addition, preclinical studies show low DA titres in the NAc (Robertson et al., 1991) and reductions in spontaneous VTA neuronal firing (Peoples et al., 1999) after chronic cocaine exposure. DA depletion, in combination with reduced D_2 receptor transduction, could explain the increases in reward thresholds that have been measured after repeated exposure to cocaine (Koob et al., 1998). If DA dysregulation contributes to the craving and dysphoria seen in stimulant addicts, its reversal could improve the recidivism that characterizes stimulant dependence (Dackis & Gold, 1985).

Cocaine craving, a major factor contributing to relapse, can be vigorously triggered by conditioned cues. While rehabilitative approaches advocate the avoidance of 'people, places and things' associated with drug use, this practice is seldom practical for patients immersed in the drug environments of our inner cities. Cue-induced craving has been reported to produce robust limbic activation in cocaine addicts (Grant et al., 1996; Childress et al., 1999), but not in cocaine naïve individuals (Childress et al., 1999), providing a graphic illustration of an acquired brain abnormality. Interestingly, preclinical studies have identified select NAc cells that actually fire in anticipation of cocaine, and this finding may have bearing on cue-induced craving mechanisms (Carelli, 2000). Also, the fact that specific NAc cells fire in anticipation of food and water (Miyazaki et al., 1998) suggests that cocaine has the capacity to recruit brain mechanisms that are normally activated in the presence of survival-related opportunities.

After repeated administration, sensitization develops to a number of toxic and behavioural effects of stimulants. This 'reverse tolerance' is exemplified by kindling in animals (sensitization to the convulsant effects of cocaine) and appears to involve glutamatergic mechanisms. In humans, clear evidence of sensitization is elusive although it has also been proposed to explain the clinical phenomenon of progressively worsening stimulant craving. Amphetamine and cocaine vigorously release glutamate into the PFC, NAc, and several other limbic regions (Reid et al., 1997) through the stimulation of D_1 receptors and, with repeated stimulant use, there develops an increased capacity of the D_1 receptor to release glutamate (Kalivas & Duffy, 1998) (see Fig. 30.3). Sensitization is also associated with D_2 autoreceptor downregulation in the VTA (Li et al., 1999) and supersensitivity of glutamate NMDA receptors (Itzhak, 1995). Stimulant sensitization can be prevented with NMDA antagonists and ablation of the PFC (Li et al., 1999), suggesting an important role for glutamate in this phenomenon. Glutamate depletion has been reported with chronic cocaine administration (Keys et al., 1998), and may result from the overstimulation of glutamatergic neurons.

Excessive brain levels of glutamate can produce neurotoxicity and cell death as a result of Ca^{2+} inflow through

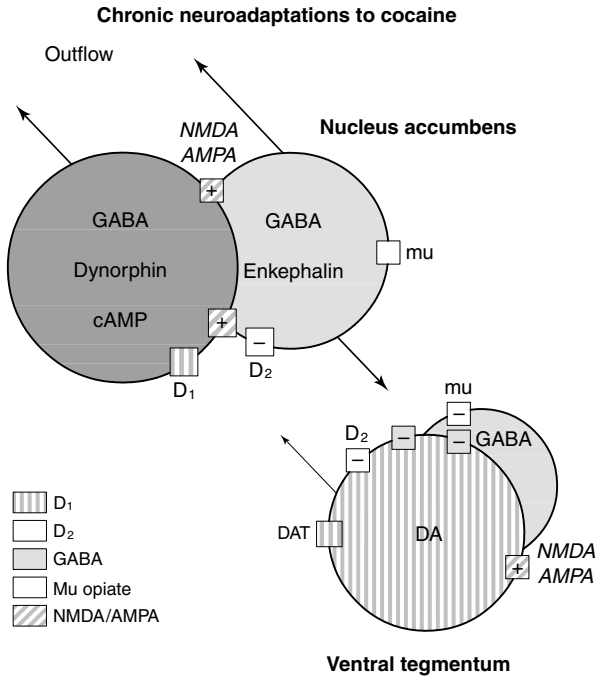

Fig. 30.3. Chronic cocaine exposure results in DA depletion and reduced outflow from the VTA. This effect is compounded by reduced D_2 and increased D_1 receptor transduction, increasing cAMP with NAc neurons. Up-regulation of NMDA/AMPA receptors in the NAc and down-regulation of D_2 autoreceptors contribute to sensitization. The NAc becomes increasingly resistant to VTA inhibition as levels of cAMP rise within GABA\EOP neurons. Over time, these changes may reduce hedonic function and contribute to clinical features of cocaine dependence.

NMDA-gated ion channels. Glutamate toxicity, in combination with focal defects of cerebral perfusion attributed to vasoconstriction (Holman et al., 1991), may account for longstanding neuropsychological impairment reported in some stimulant addicts. Reduced metabolism in the glutamate-rich orbitofrontal cortex has actually been reported during stimulant withdrawal (Volkow & Fowler, 2000). Alterations in glutamate-containing PFC neurons could adversely affect frontal lobe processing, including executive function and the ability to suppress limbic impulses.

Cocaine also affects serotonin, norepinephrine, and GABA-containing neurons. Repeated cocaine administration depletes norepinephrine and serotonin, possibly through increased synaptic metabolism during the blockade of associated membrane transporters. In addition, the stimulation of serotonin ($5\text{-}HT_{1b}$) receptors increases cocaine reward (Parsons et al., 1998). These and other findings may justify research of serotonergic agents in cocaine patients. Cocaine addicts also have benzodiazepine receptor upregulation, strengthening of GABA neurotransmission and enhanced sensitivity to benzodiazepine treatment (Volkow et al., 1998), suggesting likely research opportunities with GABA agents.

Unfortunately, there are no proven pharmacological treatments for stimulant dependence. Cocaine overdose can only be treated by supportive measures and prolonged elimination from the body can result from cocaine's nonlinear pharmacokinetics. The blockade of stimulant reward through neutralizing antibodies to cocaine has been demonstrated in animals and a cocaine vaccine study in humans is under investigation. DA antagonists reduce cocaine euphoria in humans but cause a number of side effects, may worsen craving (Dackis & Gold, 1985), and are unlikely to be acceptable to cocaine addicts. Also, reward blockade would not be expected to ameliorate neuroadaptations of chronic stimulant exposure. Effective detoxification and relapse prevention agents have yet to be identified for psychostimulants, although this is an area of intensive, government-sponsored research. As discussed, GABA/EOP-containing neurons in the NAc receive DA terminals from the VTA and convey reward-related signals to other structures, including regions of the thalamus, PFC, and hypothalamus. Disruption in DA neurotransmission, either through presynaptic DA depletion or postsynaptic transduction changes could drastically affect the orchestration of reward flow in the brain. Current research is being directed toward agents that might reverse DA, GABA, EOP and glutamatergic imbalances that are associated with stimulant addiction.

Opiates

Opiates produce their intensely rewarding effects by activating endogenous opioid receptors, the natural targets of endogenous endorphins, enkephalins, and dynorphins. The genes of mu, delta, and kappa receptors have been cloned, and the former two are involved in opiate reward while kappa receptors may contribute to aversion (Wise, 1996). Mu receptor agonists hyperpolarize medium-sized spiny cells, and this action contributes to their rewarding effect. GABA inhibition also results in DA burst firing with DA release into the NAc. Drug addicts frequently use heroin in conjunction with cocaine (speedballing), a combination that increases NAc extracellular DA by over 1000% (Gerasimov et al., 1999). Although GABA-mediated DA burst firing has been proposed as a mechanism of opiate reward, selective lesions of DA terminals within the NAc do not attenuate IV heroin self-administration (Pettit et al.,

Table 30.1. Intoxication and withdrawal signs and symptoms are listed for several classes of drugs

	Stimulants	PCP	Marijuana	Alcohol/Sedatives	Opiates
Intoxication	Tachycardia	Tachycardia	Tachycardia	Bradycardia	Bradycardia
	Hypertension	Hypertension	Hypertension	Hypotension	Hypotension
	Hyperthermia	Hyperthermia	Hyperthermia	Hypothermia	Hypothermia
	Arousal	Arousal	Paranoia	Sedation	Sedation
	Diaphoresis	Aggression	Diaphoresis	Hypokinesis	Hypokinesis
	Mydriasis	Psychosis	Mydriasis	Ataxia	Pinned pupils
	Hyperkinesis	Ataxia	Ataxia	Slurred speech	Slurred speech
	Euphoria	Salivation	Paranoia	Decreased respirations	Analgesia
	Psychosis	Rigidity	Dry mouth		Head Nodding
	Myoclonus	Red eyes			
	Nystagmus	Nystagmus			
Withdrawal	Bradycardia	Prolonged	Depression	Tachycardia	Tachycardia
	Hypersomnia	Psychosis	Insomnia	Insomnia	Insomnia
	Hyperphagia		Anxiety	Nausea	Nausea
	Depression		Irritability	Anxiety	Anxiety
	Hypokinesis		Anorexia	Hypertension	Hypertension
			Tachycardia	Tachycardia	
				Hyperreflexia	Hyperreflexia
				Diaphoresis	Diaphoresis

Notes:
Note the similarity among alcohol, sedatives, and opiates with regard to intoxication and withdrawal symptoms

1984). This finding demonstrates that opiate reward is not dependent on DA activation, and appears to include two separate (DA-dependent and DA-independent) components. Also consistent with DA-independent opiate reward is the fact that opiates are directly self-administered into a number of brain regions, including the NAc, lateral hypothalamus, amygdala, and the CA3 region of the hippocampus.

Opiates hyperpolarize neurons by increasing the outflow of K^+ through receptor-gated ion channels, and by closing Na^+ channels. As with stimulants, opiates also have the ability to acutely inhibit cAMP through mu and delta receptors coupled to G_i-proteins. Repeated opiate administration has the opposite effect of elevating cAMP levels within NAc cells, and increased cAMP has also been reported in the locus coeruleus, amygdala and thalamus after repeated opiate administration (Terwilliger et al., 1991). The activation of the cAMP pathway renders noradrenergic neurons less sensitive to opiate inhibition, resulting in rebound noradrenergic hyperactivity that has been hypothesized to underlie opiate withdrawal. Increased noradrenergic cAMP has also been reported with chronic stress, and there is an established relationship between stress and recidivism. In addition to noradrenergic effects, chronic exposure to opiates produces DA inhibition. During opiate withdrawal, extracellular DA is reduced in the NAc (Rossetti et al., 1992), and chronic opiate exposure leads to dramatically reduced DA firing rates that persist well beyond physical withdrawal (Diana et al., 1999). DA depletion may contribute to the reward inhibition and dysphoria that has been reported in opiate dependence (Dackis & Gold, 1992; Rossetti et al., 1992).

Opiate addiction has been a significant health problem in this country for many years, especially since the invention of the hypodermic syringe in the nineteenth century. Its poor prognosis is undoubtedly affected by the lure of opiate euphoria, a subjective and physiological state that differs greatly from psychostimulant intoxication (see Table 30.1). These drug states have opposite effects on vital signs, general arousal, libido, aggression, and vigilance. In addition, opiate use typically leads to a state of contentedness that lasts several hours, whereas cocaine use rapidly engenders additional cocaine craving (O'Brien et al., 1992).

A number of treatments are currently available for opiate dependence. Overdose is potentially lethal, usually due to respiratory inhibition, and can be reversed with naloxone, a mu receptor antagonist. Opiate withdrawal offers a classic example of how an understanding of brain mechanisms can uncover new treatments. A large body of clinical and preclinical research predicted the efficacy of clonidine,

an alpha-$_2$ adrenergic agonist, based on its ability to reverse noradrenergic hyperactivity associated with opiate withdrawal. Although alpha$_2$- agonists are effective for opiate withdrawal, patients usually prefer methadone. Heroin detoxification with methadone can be achieved with descending doses in about three days (Dackis & Gold, 1992) and dosing should be guided by clinical signs of withdrawal rather than patient-reported symptoms. Detoxification alone is seldom sufficient treatment and should be provided in concert with drug rehabilitation.

Even after detoxification and rehabilitative treatment, the majority of heroin addicts tend to relapse. Methadone maintenance, the transfer from intravenous heroin to a long-acting oral agonist, can achieve greater retention, reduced heroin use, and lower rates of HIV infection (Sees et al., 2000), viral hepatitis, and bacterial endocarditis. When combined with psychosocial treatment, an adequate dose of methadone can effectively stabilize many otherwise treatment refractory individuals. Two additional replacement agents are available to treat opiate addicts. Levo-alpha-acetylmethadol (LAAM), FDA approved since 1993, is a longer acting opioid that can be administered three times per week. Buprenorphine is a partial mu opiate agonist, an attribute that provides a 'ceiling' effect and diminishes lethality with overdose. Buprenorphine also attenuates the subjective effects of heroin. The availability of methadone, LAAM and buprenorphine provides the clinician with several options in treating these difficult patients.

A final treatment strategy for heroin dependence involves blocking heroin euphoria with naltrexone. Naltrexone has a high affinity for the mu and kappa receptors, and antagonizes neurotransmission by displacing opiate agonists such as morphine, heroin, and methadone. Since opiate receptor blockade produces acute withdrawal in dependent individuals, naltrexone should not be administered prior to the completion of detoxification. Special populations that may benefit from naltrexone are professionals with regular workplace exposure to drugs and probationers who are mandated to treatment (Cornish et al., 1997). Unfortunately, there has been little practitioner interest in this treatment, perhaps due to compliance issues. A long-acting depot form of naltrexone that provides clinically effective blood levels for 30–60 days is currently in clinical trials. It is hoped that this advance will improve medication adherence and reduce impulsive relapses.

THC and PCP

Marijuana is a widely abused substance, particularly by young people. Along with nicotine, another early exposure drug, marijuana has the potential to serve as a gateway to other drugs of abuse, perhaps due to its ability to activate reward circuitry and release DA into the NAc. Also, the persistence of marijuana's metabolites in the urine, combined with the widespread practice of pre-employment drug testing, can prohibitively affect the careers of both habitual and casual users. Marijuana produces drug seeking behaviour and addictive patterns, and its chronic use has been associated with withdrawal symptoms. As with alcohol, opiates, and stimulants, elevations in CRF occur during THC withdrawal (Rodriguez de Fonseca et al., 1997) and chronic exposure to marijuana reduces the firing rates of mesocorticolimbic DA cells (Diana et al., 1998). THC binds the cannabinoid receptor for which an endogenous ligand, anandamide, has been recently isolated (Devane & Axelrod, 1994). Cannabinoid receptors are found in the hippocampus, thalamus, cortex, and striatum, are coupled to G-proteins, and acutely inhibit cAMP levels. THC administration also reduces GABA output and releases DA into the NAc through a Ca^{2+}-dependent mechanism that can be blocked by naloxone (Chen et al., 1990). Therefore, THC appears to activate reward circuitry by stimulating DA and opiate systems. These actions of THC provide a neurochemical rationale for the well-established clinical prohibition of smoking marijuana when attempting recovery from other drugs of abuse.

Phencyclidine (PCP) exerts its rewarding effect through the blockade of NMDA receptors. Originally developed as an intravenous anesthetic, PCP ('angel dust') use was discontinued in humans due to the untoward effects of agitation, delusions, impaired judgment, and violent behaviour. PCP and other NMDA receptor antagonists have been proposed to have potential value in stroke models. The NMDA receptor is a complicated macromolecule that depolarizes neurons by opening gated Ca^{2+} channels, generally in the presence of both glutamate and glycine. This receptor is distinguished from two other glutamate receptor types, AMPA and KA, by its voltage-dependent characteristics, high permeability to Ca^{2+}, and activation of a nitric oxide cascade. PCP rewarding action may result, to some extent, from its ability to directly inhibit NAc medium spiny neurons. As previously discussed, these cells are normally activated by glutamatergic pyramidal neurons of the prefrontal cortex, and modulated by DA projections from the VTA. As a result of GABA inhibition, PCP has been reported to cause neurotoxicity through the release of excessive amounts of acetylcholine in the brain (Kim et al., 1999). Although PCP is not widely used at this time, a reduction in perceived risk could potentially lead to increased use of this dangerous agent. For example, MDMA ('ecstasy') has neurotoxic effects on serotonin neurons (Kosten, 1990) but

is currently popular and has low risk perception. The addictiveness of PCP, a specific NMDA antagonist, demonstrates the importance of glutamate pathways in the neurobiology of addiction.

Nicotine

Nicotine differs from previously discussed substances by its legality and the lack of functional impairment associated with its use. However, the tenacious quality of nicotine, combined with its extensive and serious medical complications, makes it arguably the most lethal of all addictive substances. Nicotine directly accounts for an estimated 400000 deaths per year (Epping-Jordan et al., 1998). Nicotine dependence involves reinforcement, tolerance, and withdrawal, and smokers often cite craving as the greatest impediment to quitting. Substitution therapy with a nicotine patch or nicotine gum has limited effectiveness, perhaps because these routes of administration do not provide the rapid delivery of nicotine seen with the intrapulmonary route. Encouraging results have been found with buproprion, an antidepressant that inhibits the DAT (O'Brien & McKay, 1998).

Nicotine stimulates nicotinic receptors that are located on DA cell bodies in the VTA and on DA terminals in the NAc (Dani & Heinemann, 1996), causing a release of DA into the shell of the NAc. In animal models, nicotine self-administration is reduced by destruction of mesocorticolimbic DA neurons (Corrigall et al., 1992) and by the administration of DA antagonists (Corrigall et al., 1994). Opiate antagonists also reduce nicotine self-administration, suggesting the involvement of both DA and EOP mechanisms. Nicotine withdrawal has been associated with changes in the distribution of nicotine receptors in the brain and with markedly reduced measurements of brain reward (Epping-Jordan et al., 1998). It is possible that a reduction in brain reward contributes to the intense craving characteristic of nicotine dependence. Since nicotine stimulates reward circuits it stands to reason that patients seeking recovery from other drugs might have more success if they quit smoking. Interestingly, 12-step self-help based approaches do not generally advocate nicotine avoidance and research is clearly needed to determine whether nicotine abstinence can improve recovery rates from other addictive agents.

Alcohol and sedative hypnotics

Alcohol has numerous actions on GABA, opiate, glutamate, DA, and serotonin neurotransmitter systems. Unlike other addictive agents with high affinity for membrane-bound proteins, alcohol mediates its effects on ion channels by disrupting the membrane lipid matrix. Alcohol facilitates GABA-mediated neurotransmission by promoting Cl^- influx through $GABA_A$-gated ion channels. This effect on Cl^- influx decreases with repeated alcohol administration, and may contribute to the development of alcohol tolerance (Koob & Weiss, 1992). A number of studies report that GABA neurotransmission is increased during alcohol intoxication and decreased during alcohol withdrawal. Consistent with these findings is the fact that alcohol withdrawal can be reversed with GABA agonists (such as benzodiazepines) and alcohol withdrawal seizures respond to GABAergic anticonvulsants.

The importance of opiate mechanisms in alcohol reward is illustrated by the fact that mu antagonists reduce alcohol consumption, especially when administered directly into the central nucleus of the amygdala (Koob & Weiss, 1992). Also, alcohol administration increases endorphin levels while alcoholics in withdrawal have reduced levels of beta-endorphin (CSF) (Koob & Weiss, 1992). Alcohol-induced DA release into the NAc is blocked by opiate antagonists (Acquas et al., 1993), suggesting an opiate mechanism of this phenomenon. Although the precise mechanism of alcohol's effect on opiate systems in the brain is not known, the appreciation of EOP involvement led to the landmark development of naltrexone as a treatment for alcoholism (Volpicelli et al., 1992).

DA mechanisms are also involved in alcoholism. Rats selectively bred for alcohol preference have an exaggerated DA response to alcohol, whereas D_2 receptor deficient (D_2 knockout) rats show a marked aversion to alcohol (Koob & Weiss, 1992). Alcohol directly and robustly excites DA neurons of the VTA (Brodie et al., 1999), increases DA synthesis and turnover, and releases DA into the NAc (Koob & Weiss, 1992). In addition, DA antagonists applied to the NAc reduce alcohol self-administration (Koob et al., 1998). These findings suggest an important role for DA in alcohol reward. However, the selective destruction of DA terminals in the NAc does not reduce alcohol self-administration (Koob et al., 1998), suggesting an additional DA-independent mechanism in alcohol reward.

Alcohol has chronic actions on DA neurons that are similar to those seen with cocaine and opiates. With chronic alcohol exposure, there is a reduction in DA release (Weiss et al., 1996) and a sustained inhibition of DA firing that persists well beyond the withdrawal state (Diana et al., 1996). This has led to the hypothesis that alcohol-induced DA depletion leads to hedonic inhibition, craving and relapse tendencies of alcoholics (Wise, 1996), as has been proposed with individuals addicted to opiates (Rossetti et

al., 1992), cocaine (Dackis & Gold, 1985), and marijuana (Diana et al., 1998). The high prevalence of depression and suicide in alcoholics and other substance abusers could also result, to some degree, from impaired hedonic function.

Alcohol has additional actions on serotonin, glutamate, and noradrenergic systems. Alcohol preferring rats have reduced levels of brain serotonin, and pharmacological enhancement of serotonin reduces alcohol intake (Koob & Weiss, 1992). However, serotonin depletion also reduces alcohol intake, and serotonergic agents have not been found effective in treating alcoholism (O'Brien & McKay, 1998). Additionally, alcohol reduces NMDA neurotransmission through allosteric blockade of Ca^{2+} and Na^{+} channels, resulting in a reduction of ion current that is linearly related to alcohol intoxication (Lovinger et al., 1989). Conversely, alcohol withdrawal is associated with increased NMDA neurotransmission (Fitzgerald & Nestler, 1995). Alcohol withdrawal may also involve noradrenergic hyperactivity as evidenced by the presence of hypertension, tachycardia, hyperreflexia, diaphoresis, insomnia, tremor, and anxiety (Koob & Weiss, 1992). Detoxification from alcohol is seldom a sufficient treatment for alcoholics and does not eliminate the protracted craving and recidivism that is characteristic of alcoholism. Rehabilitation through professional and self-help approaches should be strongly encouraged with these patients.

Medications currently available for treating alcoholism include detoxification agents, disulfiram, and naltrexone. Detoxification has been reviewed elsewhere (Dackis & Gold, 1992) and generally involves prescribing descending doses of benzodiazepines (or barbiturates) over 3–5 days. Disulfiram inactivates aldehyde dehydrogenase, resulting in high levels of the toxic metabolite, acetaldehyde, when alcohol is consumed. This results in aversive subjective effects that should theoretically discourage drinking. However, double-blind trials have not shown disulfiram to be better than placebo (O'Brien & McKay, 1998) and alcoholics tend to simply discontinue disulfiram and resume drinking. Also, disulfiram does not reverse chronic neuroadaptative changes caused by alcohol and is ineffective against alcohol craving.

Promising results in the treatment of alcoholism have been demonstrated with naltrexone. Naltrexone reduces alcohol consumption and ameliorates craving for alcohol, and its effectiveness may continue beyond the period in which the drug is taken (O'Brien & McKay, 1998). Naltrexone also reduces the rewarding effects of alcohol, presumably by blocking opiate-mediated reward. In spite of numerous studies confirming the efficacy of naltrexone in the treatment of alcoholism, its clinical use is not widespread. Acamprosate, a GABA receptor agonist, is currently under investigation and has been shown to be effective in five studies in Europe (O'Brien & McKay, 1998).

Sedative hypnotics, particularly benzodiazepines, are widely prescribed for anxiety, muscle tension, insomnia, and convulsions. Benzodiazepines, barbiturates, and alcohol produce a similar and characteristic state of reduced anxiety, disinhibition, euphoria, sedation, and hypnosis (Koob & Nestler, 1997). Sedatives facilitate GABA-mediated neurotransmission through allosteric actions on the GABA receptor complex, opening GABA-gated chloride channels. This action serves to inhibit target neurons and, in this regard, sedatives share effects and cross-tolerance with alcohol (Koob & Nestler, 1997). Unlike alcohol, sedatives have no effect on the NMDA receptor. Clinically, it is imperative to maintain a high degree of suspicion for sedative dependence since it is often covert, and withdrawal can be protracted. Successful detoxification from sedatives can be achieved by instituting a descending dose schedule of either phenobarbital (for barbiturates) or long-acting benzodiazepines like chlordiazepoxide (for benzodiazepines), and detoxification may require several weeks duration (Dackis & Gold, 1992). With the exception of treating withdrawal, sedatives should not normally be prescribed to alcoholics due to their addiction potential, similarity in brain action, and ability to reinstate alcohol intake.

In conclusion, extensive research into the neurobiology of addiction has yielded a number of interesting findings and some new treatments. It is evident that addictive drugs with diverse pharmacological and subjective effects activate common reward pathways (see Table 30.2). Increased DA neurotransmission is universally found during drug intoxication, while DA depletion and reduced DA neurotransmission appears to be a feature of chronic addiction. The NAc, thought to be a crucial target of DA projections, is largely composed of GABA/EOP-containing projection neurons. These medium-sized spiny cells convey reward-related information to a number of brain regions known to be associated with motivation and feeling states, including the thalamus, cingulate and frontal cortex, and the hypothalamus. The inhibition of GABA/EOP medium-sized spiny cells occurs in all intoxication states. While GABA/EOP neurons in the NAc are inhibited during drug intoxication, suppression may become increasingly difficult with repeated drug exposure due to molecular changes associated with the cAMP second messenger pathway. Neuroadaptations such as this may contribute to clinical phenomena associated with addictive illness, including tolerance, withdrawal, and hedonic inhibition

Table 30.2. Acute mechanisms of action of major addictive drugs

Alcohol	Facilitates GABA-mediated neurotransmission Antagonizes NMDA-mediated neurotransmission
Amphetamine	Releases DA through reverse transport Releases 5-HT, norepinephrine
Cocaine	Antagonist at DAT, local anesthetic action Antagonist at 5-HT and norepinephrine transporters
Heroin and opiates	Agonist at opiate receptors
Marijuana	Agonist at cannabinoid receptors
Nicotine	Agonist at nicotinic cholinergic receptors
Phencyclidine	Antagonist at NMDA receptors

(see Table 30.3). Since inhibition of medium-sized spiny neurons within the reward centres appears to be an important feature of drug reward, medications capable of altering GABA/EOP function should be high on the list of potential therapeutic agents to be investigated. Although pharmacological treatments for addiction are currently limited, additional treatments may result from a refined understanding of the neuronal and molecular aspects of addiction.

Several lines of evidence support the existence of two separate reward systems in the brain that are activated by different classes of addictive agents. Alcohol and opiates are self-administered even after the chemical ablation of DA terminals (Koob et al., 1998), strongly suggesting the existence of DA-independent reward mechanisms. Also, the intoxication produced by opiates, alcohol, and sedatives differs markedly from that of stimulants, also suggesting the activation of different brain mechanisms. Stimulants and opiates may act on different brain systems that have evolved to reward the procurement and consumption, respectively, of survival needs. Stimulants

Table 30.3. Acute and chronic neurotransmitter effects of addictive substances are indicated. Chronic neuroadaptations are often opposite to acute effects

	Acute actions	Chronic neuroadaptations
Stimulants	Increase DA levels in the NAc Reduce cAMP in the NAc Reduce DA and NE firing rates Decrease GABA firing rates	Deplete DA Increase cAMP in the NAc Increase CRF Increase NMDA receptor sensitivity Reduce D_2 autoreceptor sensitivity Decrease orbitofrontal metabolism Reduce brain reward
Opiates	Release DA into the NAc Reduce cAMP in the NAc DA burst firing Inhibit GABA neurons	Deplete DA Increase cAMP in the NAc NE hyperactivity Increase cAMP in the locus coeruleus Increase CRF
Alcohol	Releases DA into the NAc Decreases NMDA neurotransmission Increases GABA neurotransmission Increases EOP levels Produces DA burst firing	Depletes DA Reduces DA firing rates Increasees NMDA neurotransmission Decreases GABA neurotransmission Reduces EOP levels Increases CRF Reduces brain reward
Nicotine	Release DA into the NAc DA burst firing	Reduces brain reward
Marijuana	Releases DA into the NAc Reduces cAMP in the NAc Blocks GABA output	Depletes DA Increases cAMP in the NAc Increases CRF

promote vigilance, psychomotor and autonomic activation, environmental interaction, and intensification of craving. These activating effects would be desirable in the pursuit of survival goals. Opiates, on the other hand, produce euphoria, behavioural suppression, relaxation, and satiation, and may act on a system designed to punctuate consumption and provide consummatory reward.

Basic science research supports many clinical practices that are currently used in the treatment of addiction. Since all addictive drugs activate reward circuits, and appear to produce similar neuroadaptations with chronic use, reinstatement of addiction is a risk when any addictive agent is used. This notion supports the clinical principle that recovery from one class of addictive drugs is best achieved when all addictive drugs are avoided. The avoidance of cues associated with drug use, a central theme of drug rehabilitation, is strongly supported by PET studies showing limbic activation during cue-induced craving. Reliance on peers and professional caretakers during early recovery may be especially important to counter powerful limbic craving, and compensate for the lack of internal resolve that may result from impaired frontal lobe executive function. Genetic variations affecting the reward circuitry could explain why certain individuals are more likely to develop addiction. The possibility that nicotine use could undermine recovery, through its ability to stimulate the VTA–NAc pleasure circuit, warrants research. Given the biological underpinnings of addiction, clinicians should view addiction as a disease rather than a weakness, and maintain a compassionate and non-judgmental approach to their patients. In addition to being seriously afflicted with a brain disease, drug addicts and alcoholics are often victimized by prejudice and misunderstanding. Hopefully, further elucidation of the neurobiology of addiction will change perceptions, diminish prejudice, and reduce obstacles faced by afflicted individuals who are seeking acceptance and access to medical care.

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Part III

Disorders of motor control

31

Mechanisms of motor control

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Historical overview

The idea that the cortex of the brain could be responsible for the control of movement or indeed that any function could be localized to the cortex is a relatively new one. Until the middle of the nineteenth century it was generally thought that the cerebral cortex was the repository of thoughts and ideas. Nevertheless, Robert Boyle, one of the founders of the Royal Society and originator of the eponymous Boyle's Law, had suggested in 1691 that some aspects of motor function could be localized within the cerebral cortex. Franz Joseph Gall, the father of phrenology, had been a strong advocate of localized function within the cortex, and had suggested that the frontal lobes contained centres for speech some decades before Broca. Observations made by the British neurologist John Hughlins Jackson on patients with focal seizures convinced him that motor activity was localized within the surface of the brain. However, the first experimental demonstration of such localization came with the electrical stimulation experiments of Fritsch and Hitzig in 1870 (Fig. 31.1). They applied galvanic current to the brain of a dog and were able to elicit movements on the opposite side of the body. In 1875 David Ferrier (Ferrier, 1875) did similar experiments on the cortex of the monkey using faradic stimulation. Given the relatively crude methodology employed, the movements elicited by Ferrier through stimulation of different areas conform well to the somatotopic map currently accepted. Sherrington and his colleagues (Leyton & Sherrington, 1917) did a series of detailed experiments, using more refined stimulation methods, on the brains of anthropoid apes to more precisely define the motor and sensory areas of the cortex. Their findings were more detailed than those of Ferrier and not much different from the current standard maps of somatotopic distribution (Fig. 31.2).

Stimulation experiments were also done on the human brain. One of the most dramatic and earliest descriptions

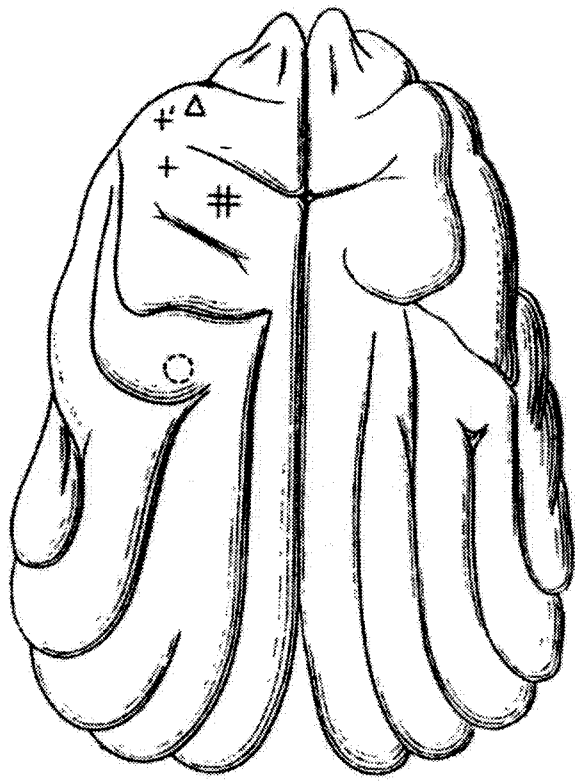


Fig. 31.1. Figure from the classic experiment of Fritsch and Hitzig in 1870. Shows the exposed cortical surface of the dog viewed from above. The symbols denote parts of the surface to which galvanic current was applied and the type of movement elicited in different groups of muscles on the opposite side of the body: # (hindlimb), + (forelimb), +′ (forelimb), △ (neck), ○ (facial). (From Fritsch and Hitzig, 1870, figure 2.)

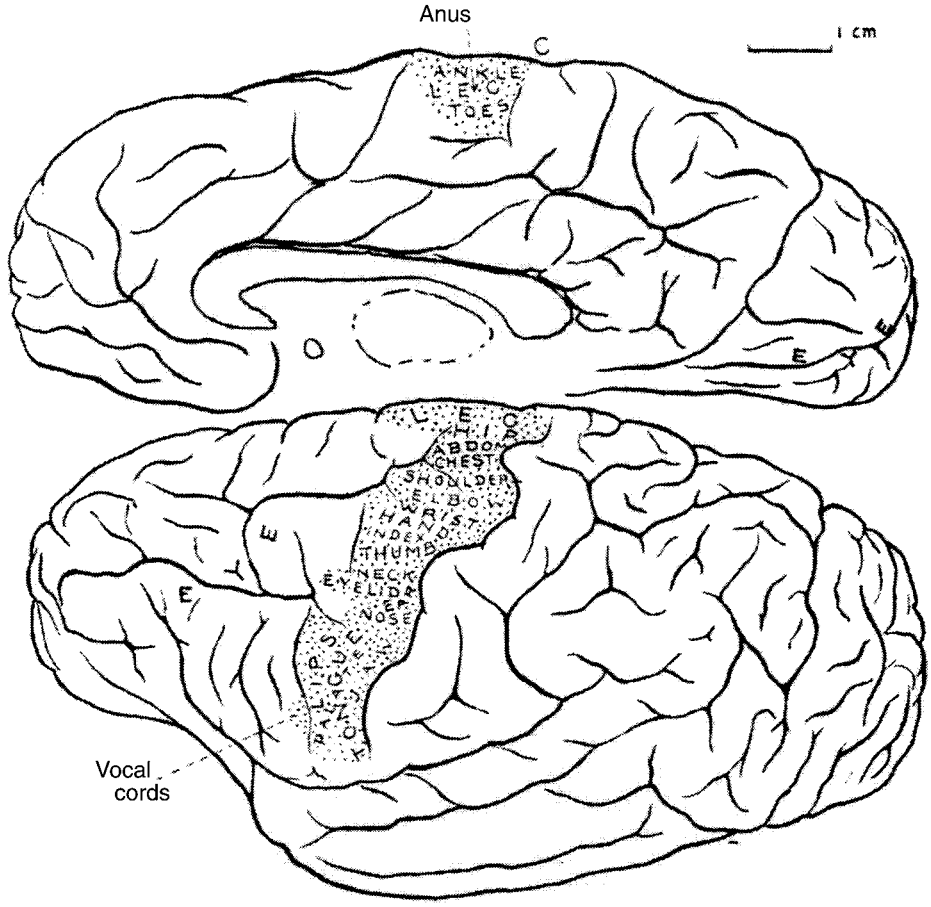


Fig. 31.2. Medial (above) and lateral view of the cortical surface of the brain of the gorilla. Points along the precentral gyrus where stimulation was applied are indicated by dots. The body parts in which movements were elicited following localized stimulation are also shown. (From Leyton and Sherrington, 1917, figure 10.)

of cortical stimulation in a human is to be found in an account by a Dr Bartholow of the Medical College of Ohio (Bartholow, 1874). He describes inserting a needle electrode into the parietal lobe of a patient through a defect in the skull. When current was passed through the electrode, movements were elicited on the opposite side of the body as well as pain and other sensations. Since these pioneering studies, we have gained a much clearer concept as to how the frontal lobes relate to the control of voluntary movement through the use of a variety of investigational techniques.

Investigating the functional properties of motor areas

The are a wide variety of methods that can be used to examine the functional properties of the different motor areas. As already mentioned, most of the earlier data came from electrical stimulation and lesion studies in animals, and from the observation of human subjects with brain lesions following trauma or stroke. After the introduction of extracellular neuronal recording in awake monkeys by Jasper (Ricci et al., 1957) it became possible to more precisely relate dynamic neural activity to aspects of motor behaviour. More recently, the use of functional imaging techniques (Ugurbil et al., 1999), such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), and other approaches such as transcranial magnetic stimulation (Hallett, 2000) has made it possible to study motor areas in the normal human brain in a relatively non-invasive way and at high spatial resolution. The techniques that may be used in the investigation of motor function differ as regards spatial resolution, temporal resolution, and invasiveness and

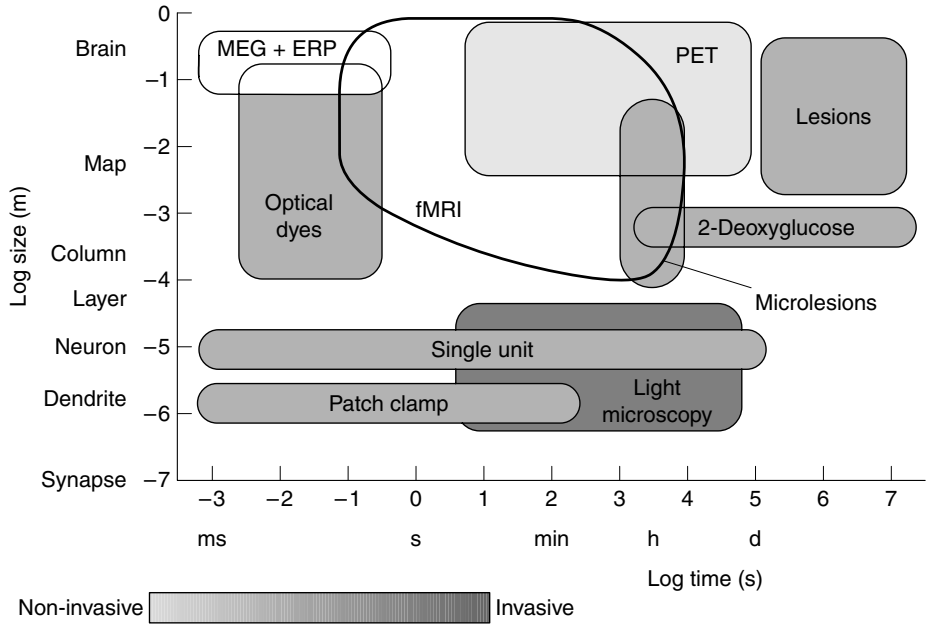


Fig. 31.3. The spatial resolution, temporal resolution, and invasiveness of different experimental techniques used to study the brain. Abbreviations: MEG, magnetoencephalography; ERP, event related potentials; fMRI, functional magnetic resonance imaging; and PET, positron emission tomography. (From Cohen and Bookheimer, 1994, figure 4.)

consequently provide very different types of information (see Fig. 31.3).

Motor cortex and other cortical motor areas

The results of early stimulation studies suggested that the motor portion of the frontal lobe was coextensive with the precentral gyrus, defined cytoarchitectonically as Brodmann area (BA) 4. However with the passage of time it became clear that this narrow view of what constituted 'motor cortex' was not consistent with data from lesion studies (Fulton, 1935) or stimulation experiments in both humans (Penfield & Welch, 1949) and monkeys (Woolsey et al., 1952). We now recognize that the cortical motor areas include both BA 4 and 6. The motor cortex proper or primary motor cortex is in area 4, while several distinct premotor areas, both functionally and anatomically, are located in area 6 (Geyer et al., 2000).

Motor cortex

The motor cortex in BA 4 is designated 'primary' because (i) historically it had been regarded as the only motor area, (ii) its neurons have the most direct and prominent connection to motor neurons in the spinal cord via the corticospinal tract, (iii) it is particularly important for the control of hand and finger movement, and (iv) lesions of this area or its projections frequently result in the most severe motor deficits.

A central question in motor physiology has been whether the motor cortex controls movement by specifying the activation of individual muscles or is primarily involved at a 'higher' level such as the control of whole movements or movement parameters like direction, force, velocity, acceleration etc? This issue of the 'representation' of movement within the motor cortex has been addressed using a variety of different approaches.

Clinical observation

Before the experimental studies of cortical stimulation of Frisch and Hitzig in the dog and Ferrier in the monkey, the neurologist John Hughlings Jackson in 1864 put forward an hypothesis about the cortical representation of movements based on his clinical observations in patients with stroke or convulsions (Jackson, 1864). He noted that, in patients with stroke, or other lesions of the cortex, the main deficit was an inability to perform certain movements rather than weakness in specific muscles and that, even with large lesions, many movements remained intact. There were several components to his hypothesis. He believed that the neural mechanisms of sensorimotor

processes, rather than muscles were represented in the motor cortex: 'The nervous centres represent movements not muscles; cords not notes'. He also believed that all the movements of which an individual is capable are represented in the motor cortex. A direct extension of this is that the hand, for example, a body part capable of a great variety of movements will be more widely 'represented' within the motor cortex, than the leg or the trunk. Jackson conceived of a pattern of overlapping representations of body parts within the motor cortex, the extent of any representation being determined by the repertoire of movements a particular body part possessed.

Cortical stimulation

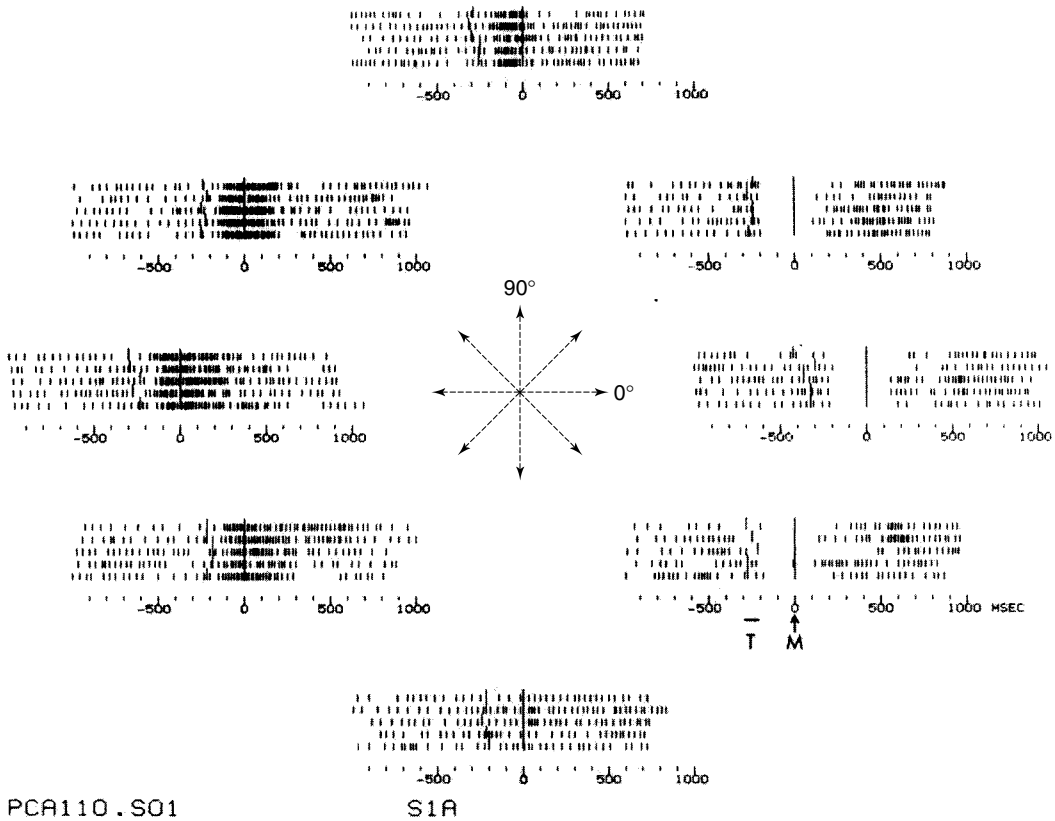
The first direct approach to the issue of representation as conceived by Jackson was through experiments using cortical stimulation, in which electrical stimulation was applied to the cerebral cortex and movements of limbs, joints, and muscles were observed (Penfield & Rasmussen, 1950). These studies showed that the principal body parts were represented separately though not equally, and that the order of this arrangement conformed in a general way to the body surface (somatotopy). However, these studies did not show how movements were represented, merely, that body parts were organized in an orderly way on the cortical surface and that there were direct excitatory connections between the motor cortex and motoneurons in the spinal cord.

Neural recording

The most detailed information to date about the representation of movement has come from neural recording from cells in the motor cortex of subhuman primates during the performance of movement under controlled conditions. Particular attention has been paid to whether the motor cortex plans and codes for movement in spatial terms such as direction and amplitude. In one experiment monkeys were trained to make arm movements from a central starting point to one of eight targets evenly spaced on a circle. During this task a large proportion of cells in the motor cortex were 'tuned' to the direction of movement (Fig. 31.4). Such cells had a preferred direction of movement in which the activity of the cell was highest and the activity decreased progressively as one deviated further from this direction. The interesting question is how cells in the motor cortex with these properties indicate or 'code' the direction of limb movement. Georgopoulos and colleagues (Georgopoulos et al., 1983) proposed, and subsequently demonstrated, that the coding of direction is actually done by a population of cells though the construction of a population vector which predicts the direction of an upcoming arm movement. The concept of the population vector is that for any movement each cell in the motor cortex which is directionally tuned, makes a contribution in its preferred direction, and the magnitude of this contribution is proportional to the angle between its preferred direction and the actual direction of movement. Figure 31.5 (see colour plate section) illustrates this concept for movement in one direction.

These and similar experiments (Alexander & Crutcher, 1990; Ashe & Georgopoulos, 1994; Kakei et al., 1999) suggest that the motor cortex represents movement in terms of the direction of the limb in space rather than on the basis of the activation of individual muscles. This raises the issue of how and at what level the activation of specific muscles, essential for goal directed movement, is achieved. It is likely that during infancy we learn the mapping between the spatial aspects of limb movements and the muscles that need to be activated for those movements to occur. Thereafter, spatial instructions from the motor cortex will automatically activate the appropriate muscles to execute the movement. Recent data which supports this intuitive conclusion comes from experiments in human subjects who were asked to make movements to targets in the presence of a complicated force field opposing the movement (Shadmehr & Mussa-Ivaldi, 1994). At first the movement trajectories were quite disrupted by the force field (Fig. 31.6(*a*)). However, over time, the movement trajectories reverted to those before the force field was imposed (Fig. 31.6(*b*)). The fact that the subjects adapted to the force field and produced smooth straight trajectories although they had received little instruction as to what movements to make suggests that movement is planned in terms of trajectory. To probe exactly how this adaptation was achieved, the force field was suddenly withdrawn (Fig. 31.6(*c*)). Subjects now produced movements with abnormal trajectories (almost the mirror image of the original perturbation) as if they were compensating for the forces they expected to experience. Therefore it is likely that the subjects built an 'internal model' of the forces which mapped the signals being produced by the motor cortex onto the forces being generated by the muscles. Whether one sees a reflection of this internal model in the activity of cells in the motor cortex during motor learning is currently being investigated in a number of laboratories (Gandolfo et al., 2000; Li et al., 2001). What is clear is that one does not see such activity once behaviours have been mastered.

If there is little evidence of a translation of a spatial signal to one indicating muscle activation in the motor cortex then where does this necessary transformation occur? Bizzi and colleagues (Bizzi et al., 1991; Gistzer et al., 1993; Tresch & Bizzi, 1999) have shown in experiments in the frog and rat



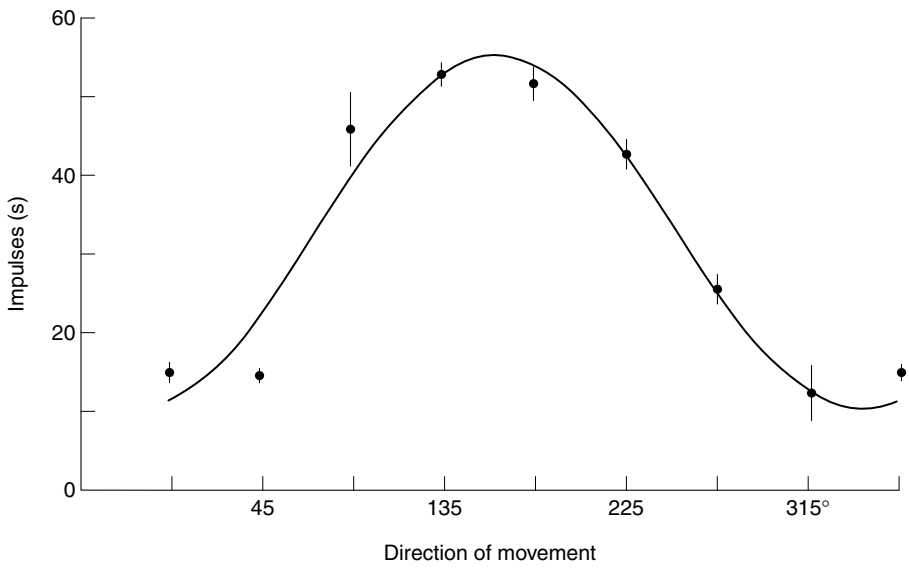


Fig. 31.4. Variation in the frequency of discharge of a single motor cortex cell during movement in different directions. *Upper half*, Each small tick indicates an action potential; the display shows impulse activity during five repetitions (trials) of movements made in each of the eight directions indicated in the centre diagram. Trials are oriented to the onset of movement *M. Lower half*, Direction tuning curve of the same cell; the average frequency of cell activity during the response time and movement time is plotted for each of the eight directions. (From Georgopoulos et al., 1982, figure 4.)

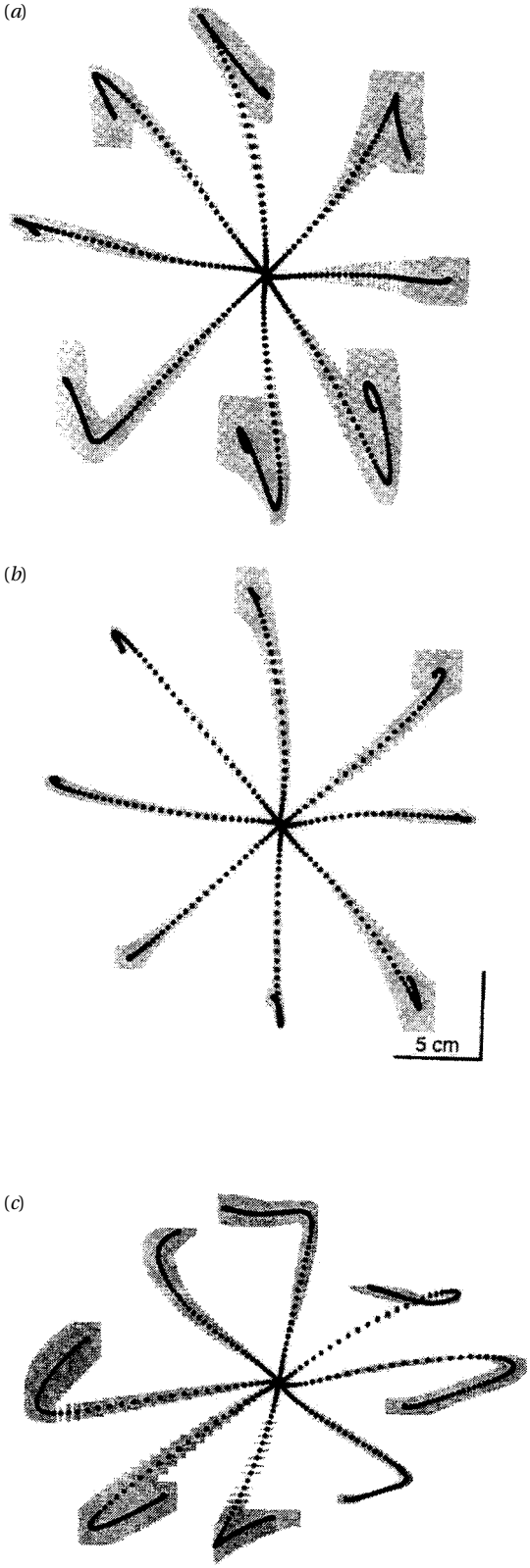


Fig. 31.6. Averages ± SD of hand trajectories during (*a*) the initial exposure to the force field, (*b*) following adaptation to the field and (*c*) after the force field was abruptly withdrawn toward the end of the training period. (From Shadmehr and Mussa-Ivaldi, 1994, modified from figures 9 and 13.)

that a set of 'motor primitives', which could form the basis of activating specific sets of muscles during multijoint movement, can be elicited through microsimulation of the spinal grey matter. These primitives may form the building blocks for voluntary movement by translating spatial signals from the motor cortex into appropriate muscle output. In addition, other spinal interneuronal systems such as the propriospinal system in the cat (Lundberg, 1979) have been shown to be important in the patterned activation of the different muscles required for reaching. Propriospinal neurons at the C3–C4 level in the cat have monosynaptic connections to motoneurons supplying proximal muscles. These propriospinal neurons, in turn, have monosynaptic connections to several supraspinal systems, including the corticospinal tract. Interruption of the projections from the interneurons results in abnormal reaching movements (Alstermark et al., 1981). These propriospinal interneurons may participate in the integration of reaching movements at a spinal level, and effectively translate signals from cells in the motor cortex that relate to the direction of force output of the whole limb (Georgopoulos et al., 1982) into appropriate patterns of muscle activation.

The premotor cortex

If the motor cortex is the most important area for the control of voluntary movement this inevitably raises the issue of the function of the other motor areas in the frontal lobe: the premotor areas (see Fig. 31.7). The functional division between the motor cortex and the other frontal motor areas is not strict nor is there the rigid hierarchy among them that had been previously thought (see Geyer et al., 2000). The motor cortex and premotor areas operate in parallel in the production of movement. Differences in the functional properties among these areas are relative rather than absolute.

Lateral premotor cortex

There are at least two distinct subareas within the lateral premotor cortex in humans: the dorsal (PMD) and ventral (PMV) premotor cortex, and there may be even more based on evidence from subhuman primates (Geyer et al., 2000). There has been a great deal of controversy about the consequences of lesions of the human lateral premotor area. Earlier workers noted a loss of skilled movements, forced

grasping, and spasticity, similar to those deficits seen with motor cortex lesions (Fulton, 1935); while others documented few if any adverse effects of lesions (Walshe, 1935). One consistent finding in humans has been prominent weakness in proximal muscles which led to the suggestion that an important function of the lateral premotor cortex was to place the limb in a position appropriate for action. More detailed work from neural recording in non human primates has pinpointed some clear functional divisions between the two major portions of lateral premotor cortex.

Neurons in the PMV can have both tactile and visual receptive fields (Rizzolatti et al., 1988; Graziano & Gross, 1998). The interesting feature, however, is that the visual receptive fields move with the arm and not with the eyes (Graziano & Gross, 1998). This feature enables the integration of somatosensory, visual and motor information and provides the substrate for the online visual guidance of movement which is now thought to be a prominent function of the PMV. Cells in the PMD show many of the same features as those in the motor cortex such as directional properties (Caminiti et al., 1990). This area may also be the site of the final step in the transformation of visual signals, which are initially coded in retinal coordinates, to a coordinate framework based on the arm (Johnson et al., 1996). The most compelling theory of PMD function is that it is involved in stimulus–response mapping. Neurons in this area integrate information about the properties of the stimulus, including its spatial location, with the attentional state of the subject, and the action or response required, so that we can more effectively interact with our environment.

Medial premotor areas

The medial premotor region contains both the supplementary motor area (SMA) and the cingulate motor areas. The SMA is further subdivided into two regions which are functionally and anatomically distinct, the SMA proper and the pre-SMA which is just anterior to it (Tanji, 1994). The cingulate motor areas in the human may contain up to three separate functional regions (Picard & Strick, 1996).

SMA

Data from subjects with lesions involving the SMA or medial premotor cortex have suggested that an important function of the SMA is in the temporal organization of sequences of movements, particularly when these sequences are produced from memory (Goldberg & Bruce, 1985; Halsband et al., 1993). For example, following a stroke in the medial premotor cortex a concert pianist was no longer able to make transitions smoothly from one note to the next or maintain the relative timing values of the notes although the actual spatial sequence was correct (Foerster,

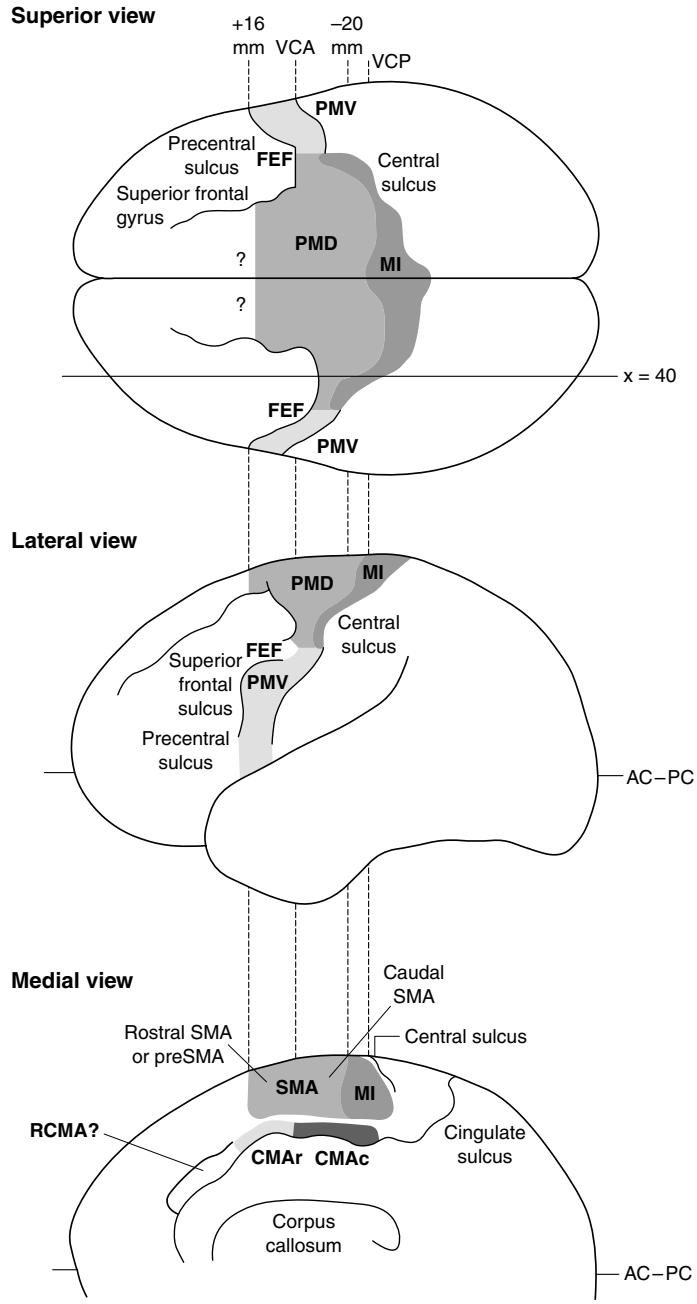


Fig. 31.7. Schematic diagrams of the proposed subdivisions of the cortical motor areas in humans from three different perspectives. AC-PC, anterior commisure–posterior commisure plane; CMAc, caudal cingulate motor area; CMAr, rostral cingulate motor area; FEF, frontal eye fields; M1, primary motor cortex; PMD, dorsal premotor cortex; PMV, ventral premotor cortex; RCMA, rostral anterior cingulate motor area; SMA, supplementary motor areas; VCA and VCP, coronal plane through the anterior and posterior commisure, respectively; $x = 40$, 40 mm from midline. (Adapted from Roland and Zilles, 1996, figure 1.)

1936). The Russian psychologist Luria noted that, although the ability to perform simple movements was preserved following lesions of the medial premotor cortex, there were impairments in complex sequences of movements, particularly when such movements had to be learned (Luria, 1966). In addition, the medial motor areas are involved in the control of bimanual movements; there is strong evidence for this, both from neural recording in monkeys and imaging in humans. The SMA has been subdivided on functional and anatomical grounds into the SMA proper, which has prominent connections to the motor cortex and projections to the spinal cord, and the preSMA which is more closely connected to the prefrontal cortex (Tanji, 1994). PreSMA is more active while learning novel motor behaviours, whereas SMA is prominently involved during the performance of previously learned sequential behaviours. The reports of akinetic mutism following medial premotor lesions in humans are almost certainly due to the involvement of the far anterior portions of the cingulate gyrus which do not have a prominent motor function.

Cingulate motor areas

Three distinct subregions have been defined within the cingulate motor area; all of which are buried in the cingulate sulcus (Picard & Strick, 1996). These comprise a rostral anterior cingulate motor area (RCMA) and two more posterior areas (see Fig. 31.7) divided into cingulate motor area rostral (CMAr) and caudal (CMAc). The RCMA has functions which appear little related to the control of action but is engaged in such operations as spatial attention, working memory, semantic and episodic memory (see Cabeza & Nyberg, 1997) and the online monitoring of performance (Carter et al., 1998). Nevertheless, there are direct projections from the cingulate motor areas to the spinal cord (Dum & Strick, 1991) and in the case of the more posterior areas a substantial number of the neurons project to motoneurons supplying the distal muscles of the upper limb (Dum & Strick, 1991; He et al., 1995). Therefore, these areas, like the motor cortex, may be involved in the control of distal movements. However, the specific function of the cingulate motor area is unclear. In imaging studies of the whole brain, activity within the most posterior cingulate motor areas seems to parallel that within the SMA. There have been few lesion studies restricted to this region, and comprehensive neural recordings have not been performed.

Motor deficits following stroke in humans

The constellation of motor symptoms resulting from stroke in humans seem to be primarily related to damage to the motor cortex or to its subcortical projection fibres (see Rondot, 1969; Rascol et al., 1982; Foix & Levy, 1927; Mohr et al., 1993). Given that vascular lesions generally do not respect cytoarchitectonic boundaries in the brain such statements are approximate at best. While it is not our purpose to treat the various stoke syndromes in any great depth, we can recognise two general types which primarily affect the motor system. The first is the result of infarction of the middle cerebral artery (MCA) or one of its principal branches, the second, the typical lacune, due to small vessel disease in or around the internal capsule.

MCA

Infarction of the main trunk of the MCA often leads to quite a profound deficit with contralateral hemiplegia, hemianesthesia and hemianopia in addition to deviation of the eyes and head toward the lesion. Lesser degrees of infarction such as from occlusion of the upper division of the MCA lead primarily to contralateral motor and sensory deficits which are less severe. There is some controversy as to the expected distribution of weakness in these cases. It has been generally held that the most severe weakness was in the distal arm and lower face and leg in keeping with the principles outlined by Broadbent in the nineteenth century (Broadbent, 1872) and consistent with the areal somatotopic distribution of these body parts on the precentral gyrus. However, this view has been recently challenged particularly by Mohr (Mohr et al., 1993) who maintains that usually proximal and distal movements are equally affected. Monoplegias are extremely rare and when present almost invariably indicate a cortical lesion.

Lacunes

Stroke due to small vessel ischemia in and around the internal capsule is perhaps the most common form of stroke seen clinically. The deficits associated with up to 70% of lacunar strokes are predominantly motor in character and have often been described as representing a form of pure motor stroke (Fisher & Curry, 1965; Rascol et al., 1982). However, it is pure only to the extent that there are not significant deficits in sensation, behaviour, language or vision. Although sensory symptoms may be frequent objective signs are rare. Face, arm and leg are generally equally affected. It has been commonly held that there was a fairly strict somatotopic distribution within the internal capsule. The results of studies correlating radiological lesions with deficits in humans would suggest that this is not the case.

Clinical–physiological interpretation

One of the more striking aspects of the deficits in patients following stroke is that, even in cases in which there is not profound weakness, there is poverty of movement. This seems to fit well with the concept of Jackson that the motor cortex is primarily concerned with movements rather than with muscles; when this representation is disrupted it is the movements rather than the muscles which are affected. The relative lack of correlation between weakness and the general impairment of motor function in patients with stroke has led neurologists to search for other causes. The standard explanation for this lack of correlation is that the motor impairment is primarily related to spasticity (Mizrahi & Angel, 1979; Dietz et al., 1991). Nevertheless, the weight of clinical evidence (Sahrmann & Norton, 1977), in addition to what we currently know about the physiology of motor control, would seem to go against this thesis. Obviously, extreme spasticity can further disrupt the ability to move but numerous studies have failed to find a quantitative relation between the extent of spasticity and the motor deficits.

Recovery of motor function following stroke

Some recovery of motor function is the rule after stroke. The extent and time course of recovery is quite variable and dependent on a host of factors which are not well understood (Twitchell, 1951; Bard & Hirschberg, 1965; Seitz, 1997). The natural history of the recovery from stroke has received less attention than it might have given the social and economic cost of the disorder. Recovery when it does occur generally begins early and is evident first in the proximal muscles (Twitchell, 1951). Patients who make a full recovery do so within the first month and it is not usual to find much additional improvement more than six months after the original stroke. There is controversy as to what constitute reliable prognostic indicators for motor recovery following stroke but prominent spasticity and a long interval from the onset of deficit to the first sign of recovery are not good signs. When recovery does occur, it is invariably associated with cortical reorganization.

Cortical reorganization is a well-described phenomenon following injury. It has been documented in animals following damage to, or disruption of, sensory input (Merzenich et al., 1983) and has been shown to occur in motor cortical areas of non-human primates after amputation, section of motor nerves (Donoghue & Sanes, 1988), or as a result of micro-infarction to adjacent areas of cortex (Nudo et al., 1996; Nudo & Milliken, 1996). Glees and Cole (1950, 1952) were the first to study reorganization in the motor system under controlled conditions. Following experimentally induced lesions of the motor cortex in the monkey, they found, on the basis of cortical stimulation, evidence of reorganization both in areas surrounding the cortical lesion (1950) and also in homologous regions in the other hemisphere (1952). The issue was re-examined more recently by Nudo and colleagues (Nudo et al., 1996; Nudo & Milliken, 1996) who showed that loss of hand and wrist representation after micro-infarcts in the motor cortex of the monkey was restored through reorganization following rehabilitation (Nudo et al., 1996, Fig. 31.8, see colour plate section). Without rehabilitation, although there was reorganization in the motor cortex, the representations in the areas damaged by infarction were not restored. Clearly, restoration of function is not dependent on motor cortex reorganization *per se* and presumably can be mediated by other cortical areas.

Functional imaging studies in humans following stroke have confirmed the suggestion of Glees and Cole (1952) that recovery of function is associated with a re-organization involving lateral premotor areas ipsilateral to the infarct and the motor cortex contralateral to the infarct (Chollet et al., 1991; Weiller et al., 1992; Cramer et al., 1997). Whereas there appears to be abundant data (Brodal, 1972; Kim et al., 1993) to support a role for the motor cortex (contralateral to the lesion) ipsilateral to the motor deficit in the control of movement and consequently its involvement in recovery of function, the evidence for significant reorganization in lateral premotor areas contributing to recovery is not nearly as strong. Recent data (Lewis et al., 1999) suggest that the medial premotor areas, which have prominent corticospinal projections, may make the largest contribution to recovery of function.

Effects of rehabilitation

Studies in normal subjects have shown that cortical motor areas can undergo reorganization on the basis of different patterns of limb or finger use. For example, there is an increased representation of left-hand digits in the motor cortex of string players and the extent of this increase is correlated with the age at which the subjects began to play the instrument (Elbert et al., 1995). The potential for use-dependent changes in cortical representation within the sensory motor system has obvious implications for rehabilitation in patients following stroke. Although spontaneous reorganization of the cortex does occur after experimentally induced cortical stroke in primates (Nudo & Milliken, 1996), this reorganization does not result in

restored movement capacity unless accompanied by specific rehabilitation (Nudo et al., 1996). The technique of constraint-induced movement therapy (or 'forced use'), in which the unaffected limb is restrained in a sling and the impaired one is trained in a series of motor tasks over a two week period, has been shown to lead to long-lasting improvement in function in patients with chronic stroke (Taub et al., 1993; Miltner et al., 1999), and is associated with concomitant changes in cortical excitability (Liepert et al., 2000). The encouraging preliminary results with the technique in both humans and subhuman primates offer hope that it will provide an efficacious form of rehabilitation of motor function in stroke patients when used on a larger scale.

The future: neural signals to control prosthetic devices

One of the more exciting developments for the future is that it may be possible to apply what has been learned about the neural control of movement to enable the use of signals from the intact motor cortex to control prosthetic devices. An even more ambitious project would be the use of neural signals to directly drive muscles, which would clearly be beneficial in patients with spinal cord injury and in a subgroup of patients following stroke.

The idea behind such a development is a relatively simple one and is based on a concept already discussed above: that many cells in the motor cortex are directionally tuned (Georgopoulos et al., 1982) and that a population of such cells can be used to predict the upcoming motor output under a variety of conditions (Georgopoulos et al., 1983, 1986). The issue is how one transforms such neural signals into a coordinated contraction of limb muscles to generate an appropriate motor output (Lukashin et al., 1996; Amirikian & Georgopoulos, 1999). This transformation can be carried out by an artificial neural network, using actual neural signals as an input, which it then recoded as graded muscle activation. For example, Fig. 31.9 shows neural data which were recorded while a monkey exerted force in a particular direction; these data were then used to instruct a model arm to produce the same behaviour.

Other recent experiments suggest that the goal of a neurally driven device is a realistic goal for the future. Chapin and colleagues have sampled neural signals in the cortex and thalamus of the rat and used them to control a relatively simple one-dimensional robot arm (Chapin et al., 1999). While the behaviour used in the experiment was relatively trivial compared to what might be required in real life, the authors also demonstrated that the animal could learn different strategies to control the neurons responsible for the movement of the robot arm. Such plasticity between neural activity in motor cortex and behaviour makes it more likely that patients could eventually learn to control prosthetic devices or even their own muscles. More recently, this work was expanded and extended to the monkey (Wessberg et al., 2000). Neural signals obtained from chronically implanted microwire electrodes in several cortical motor areas were used to predict hand trajectories in three dimensions, and more importantly, could be employed to control a robotic arm in real time. These approaches needs further modification and refinement so that they can be useful for application in humans. The work cited is best regarded as a promising start rather than a final solution.

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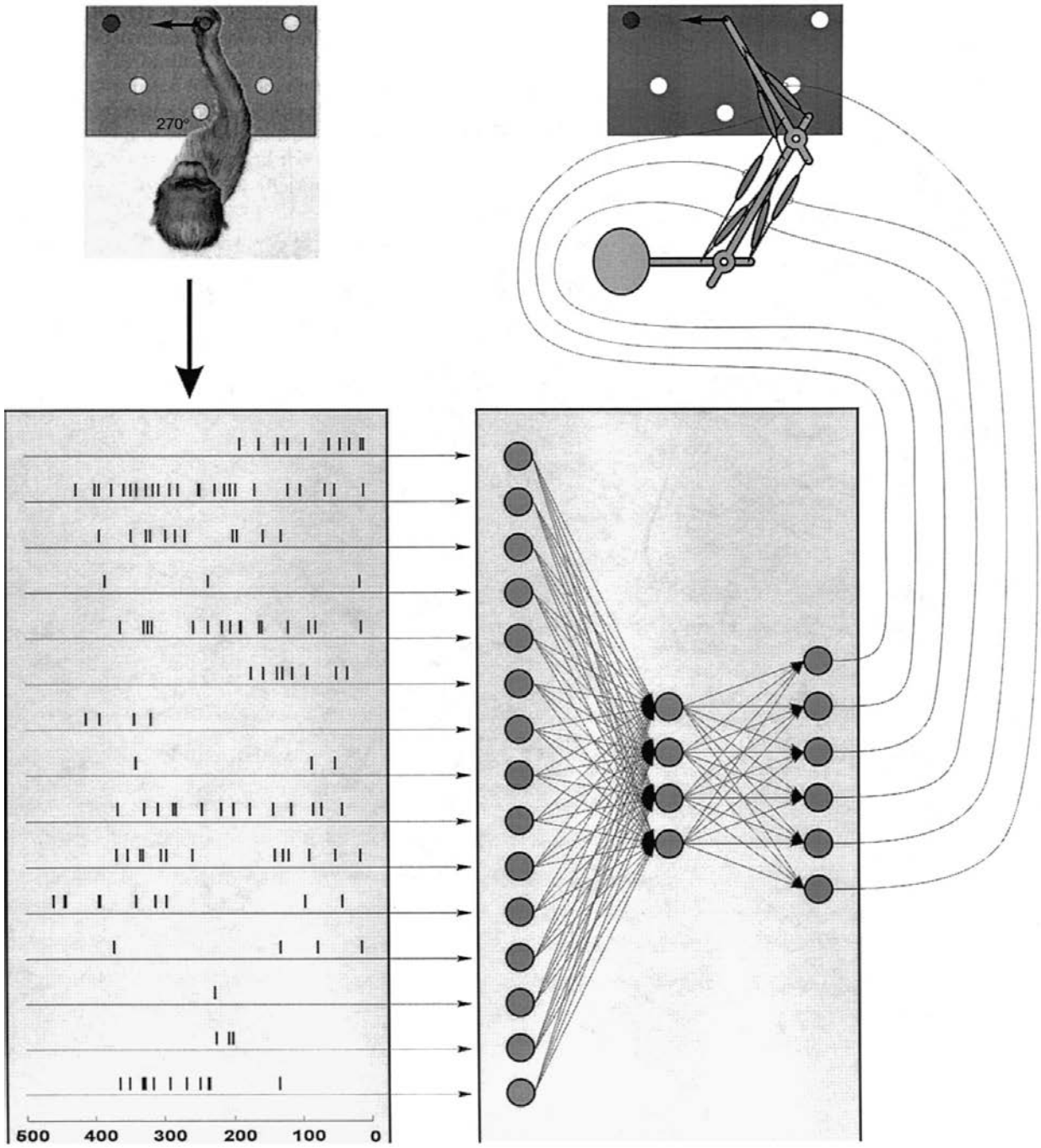

Fig. 31.9. The upper left panel is a sketch of a monkey exerting force in a particular direction. The lower left panel shows the time series of action potentials in 15 separate cells in the motor cortex during the task. The lower right illustrates the three-layered feed forward neural network used to transform the signal and the upper right shows the performance of a model of the arm on the basis of the transformed signals. (From Amirikian and Georgopoulos, 1999, figure 8.)

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32

The apraxias

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Apraxia is a term used to denote a wide spectrum of higher-order motor disorders owing to acquired brain disease affecting the performance of skilled, learned movements with or without preservation of the ability to perform the same movement outside the clinical setting in the appropriate situation or environment. The disturbance of purposive movements cannot be termed apraxia, however, if it results from a language comprehension disorder or from dementia, or if the patient suffers from any elementary motor or sensory deficit (i.e. paresis, dystonia, ataxia) which could fully explain the abnormal motor behaviour (Heilman & Rothi, 1985; Roy & Square, 1985; De Renzi, 1989). The praxic disorder may affect various body parts such as the eyes, face, trunk, or limbs, and may involve both sides of the body (i.e. ideational and ideomotor apraxias), preferentially one side (i.e. limb-kinetic apraxia), or, alternatively, interlimb coordination, as in the case of apraxia of gait.

Apraxias are poorly recognized but common disorders that can result from a wide variety of focal (i.e. stroke, trauma) or diffuse brain damage (i.e. corticobasal degeneration, Alzheimer's disease) (Heilman & Rothi, 1985; Freund, 1992). There are two main reasons why apraxia may go unrecognized. Firstly, many patients with apraxia, particularly ideomotor apraxia, show a voluntary–automatic dissociation, which means that the patient does not complain about the deficit because the execution of the movement in the natural context is relatively well preserved, and the deficit appears mainly in the clinical setting when the patient is required to represent explicitly the content of the action outside the situational props. Secondly, although in apraxic and aphasic patients specific functions are selectively affected, language and praxic disturbances frequently coexist and the former may interfere with the proper evaluation of the latter (Freund, 1992).

Limb apraxias

Liepmann (1920) posited that the idea of the action, or movement formula, containing the space–time form picture of the movement, was stored in the left parietal lobe. In order to carry out a skilled movement, the space–time plan has to be retrieved and associated via cortical connections with the innervatory pattern stored in the left sensorimotorium that conveys the information to the left primary motor area. When the left limb performs the movement, the information has to be transmitted from the left to the right sensorimotorium through the corpus callosum to activate, thereafter, the right motor cortex. Liepmann conceived ideational apraxia as a disruption of the space–time plan or its proper activation, so that it was impossible to construct the idea of the movement; the patient does not know what to do. In contrast, in ideomotor apraxia, the space–time plan is intact but it can no longer guide the innervatory engrams which implement the movement because it is disconnected from them; the patient knows what to do but not how to do it. Finally, limb-kinetic apraxia appears when the disruption of the innervatory engrams interferes with the selection of the required muscle synergies to perform the skilled movement.

Heilman and Rothi (1985) and Rothi et al. (1991) proposed that the 'movement formulae' or 'visuokinesthetic motor engrams' were stored in the left inferior parietal lobule (IPL), and translated into an innervatory pattern in the supplementary motor area (SMA) rather than in the convexity of the premotor cortex (PM). A neuropsychological model was advanced involving specific dissociation of verbal, visual or tactile inputs into an action lexicon (represented in the parietal lobe) in which visuokinesthetic motor engrams programme skilled movements (Rothi et al., 1991).

Table 32.1. Assessment of limb praxis

Intransitive movements:	non-representational (e.g. touch your nose, wriggle your fingers) representational (e.g. wave good-bye, hitch-hike)
Transitive movements:	(e.g. use a hammer, use a screwdriver) under verbal, visual and tactile modalities
Imitation of meaningful and meaningless movements, postures and sequences.	
Multiple step tasks:	(e.g. prepare a letter for mailing)
Tool[a] selection tasks:	to select the appropriate tool to complete a task, such as a hammer for a partially driven nail
Alternative tool selection tasks:	to select an alternative tool such as pliers to complete a task such as pounding a nail, when the appropriate tool (i.e. hammer) is not available
Gesture recognition tasks:	to assess the capacity to comprehend gestures, either verbally (to name gestures performed by the examiner), as well as non-verbally (to match a gesture performed by the examiner with cards depicting the tool / object[b] corresponding to the pantomime)

Notes:
[a] Tool: implement with which an action is performed (e.g. hammer, screwdriver).
[b] Object: the recipient of the action (e.g. nail, screw).
Source: De Renzi (1989); Rothi et al. (1997).

In 1985, Roy and Square refined a praxis model into a conceptual system and a production system. The conceptual system was conceived to contain knowledge of object and tool use and organization of single actions into a sequence. On the other hand, the production system incorporates a sensori motor component of knowledge, as well as encompassing the perceptual motor processes for organizing and executing action. Dysfunction of the praxis conceptual system would give rise to conceptual or ideational apraxia, whereas impairment of the praxis production system would induce ideomotor and limb-kinetic apraxias. At present, however, it is possible to interpret the different types of limb apraxias, particularly ideomotor and limb kinetic apraxias, on the basis of our current knowledge of the modular organization of the brain (Leiguarda & Marsden, 2000).

Evaluation of limb praxis

A systematic evaluation of limb praxis is critical in order: (i) to identify the presence of apraxia; (ii) to classify correctly the nature of limb praxis deficit according to the errors committed by the patient; and (iii) to gain an insight into the underlying mechanism of the patient's abnormal motor behaviour (Table 32.1).

Several types of transitive movements are used in the evaluation of praxis and it is not an uncommon finding that apraxic patients perform some but not all movements in a particularly abnormal fashion and/or that individual differences appear in some but not all components of a given movement. Therefore, the dissimilar complexity and features of transitive movements should be considered in order to analyse and interpret praxic errors accurately. For instance: (i) movements may or may not be repetitive in nature (e.g. hammering versus using a bottle opener to remove the cap); (ii) an action may be composed of sequential movements (e.g. to reach for a glass and take it to the lips in drinking); (iii) a movement may primarily reflect proximal limb control (transport) such as transporting the wrist when carving a turkey, proximal and distal limb control such as reaching and grasping a glass of water, or primarily distal control as when the patient is asked to manipulate a pair of scissors; and (iv) movements may be performed in the peripersonal space (e.g. carving a turkey), in body-centred space (e.g. tooth-brushing), or require the integration of both, such as the drinking action.

Analysis of a patient's performance is based on both accuracy and error patterns (Table 32.2). Three-dimensional motion analysis of the spatio-temporal characteristics of gestural movements has provided an accurate method to capture objectively the nature of the praxis errors observed in clinical examination. Patients with ideomotor apraxia, due to focal left hemisphere lesions (Clark et al., 1994; Poizner et al., 1995), and different asymmetric cortical degenerative syndromes (Leiguarda & Starkstein, 1998), have shown slow and hesitant build-up of hand velocity, irregular and non-sinusoidal velocity profiles, abnormal amplitudes, alterations in the plane of motion and in the direction and shapes of wrist trajectories, decou-

Table 32.2. Types of praxis errors

I. Temporal
S = sequencing: some pantomimes require multiple positionings that are performed in a characteristic sequence. Sequencing errors involve any perturbation of this sequence including addition, deletion, or transposition of movement elements as long as the overall movemen structure remains recognizable.
T = timing: this error reflects any alterations from the typical timing or speed of a pantomime and may include abnormally increased, decreased, or irregular rate of production or searching or groping behaviour.
O = occurrence: pantomimes may involve either single (i.e. unlocking a door with a key) or repetitive (i.e. screwing in a screw with a screwdriver) movement cycles. This error type reflects any multiplication of single cycles or reduction of a repetitive cycle to a single event.

II. Spatial
A = amplitude: any amplification, reduction, or irregularity of the characteristic amplitude of a target pantomime.
IC = internal configuration: when pantomiming, the fingers and hand must be in specific spatial relation to one another to reflect recognition and respect for the imagined tool. This error type reflects any abnormality of the required finger/hand posture and its relationship to the target tool. For example, when asked to pretend to brush teeth, the subject's hand may close tightly into a fist with no space allowed for the imagined toothbrush handle.
BPO = body-part-as-object: the subject uses his/her finger, hand, or arm as the imagined tool of the pantomime. For example, when asked to smoke a cigarette, the subject might puff on his or her index finger.
ECO = external configuration orientation: when pantomiming, the fingers/ hand/arm and the imagined tool must be in a specific relationship to the 'object' receiving the action. Errors of this type involve difficulties orienting to the 'object' or in placing the 'object' in space. For example, the subject might pantomime brushing teeth by holding his hand next to his mouth without reflecting the distance necessary to accommodate an imagined toothbrush. Another example would be when asked to hammer a nail, the subject might hammer in differing locations in space reflecting difficulty in placing the imagined nail in a stable orientation or in a proper plane of motion (abnormal planar orientation of the movement).
M = movement: when acting on an object with a tool, a movement characteristic of the action and necessary to accomplish the goal is required. Any disturbance of the characteristic movement reflects a movement error. For example, a subject, when asked to pantomime using a screwdriver, may orient the imagined screwdriver correctly to the imagined screw but instead of stabilizing the shoulder and wrist and twisting at the elbow, the subject stabilizes the elbow and twists at the wrist or shoulder.

III. Content
P = perseverative: the subject produces a response that includes all or part of a previously produced pantomime.
R = related: the pantomime is an accurately produced pantomime associated in content with the target. For example, the subject might pantomime playing a trombone for a target of a bugle.
N = non-related: the pantomime is an accurately produced pantomime not associated in content with the target. For example, the subject might pantomime playing a trombone for a target of shaving.
H = the patient performs the action without benefit of a real or imagined tool. For example, when asked to cut a piece of paper with scissors, he or she pretends to rip the paper.

IV. Other
C = concretization. The patient performs a transitive pantomime not on an imagined object but instead on a real object not normally used in the task. For example, when asked to pantomime sawing wood, the patient pantomimes sawing on his or her leg.
NR = no response.
UR = unrecognizable response: the response shares no temporal or spatial features of the target.

Source: Rothi et al. (1997).

pling of hand speed and trajectory curvature, and loss of interjoint coordination (Figs. 32.1–32.3). All these studies have evaluated gestures, such as carving a turkey or slicing a loaf of bread, which mainly explore the transport or reaching phase of the movement. However, the majority of transitive gestures included in most apraxia batteries are prehension (reaching and grasping) movements which reflect proximal (transport) as well as distal limb control (grasping). The kinematic analysis of aiming movements in apraxic patients has demonstrated spatial deficits, in particular when visual feedback is unavailable, whereas the analysis of prehension movements has shown disruption of both the transport and grasp phases of the movements as well as transport-grasping uncoupling (Caselli et al., 1999;

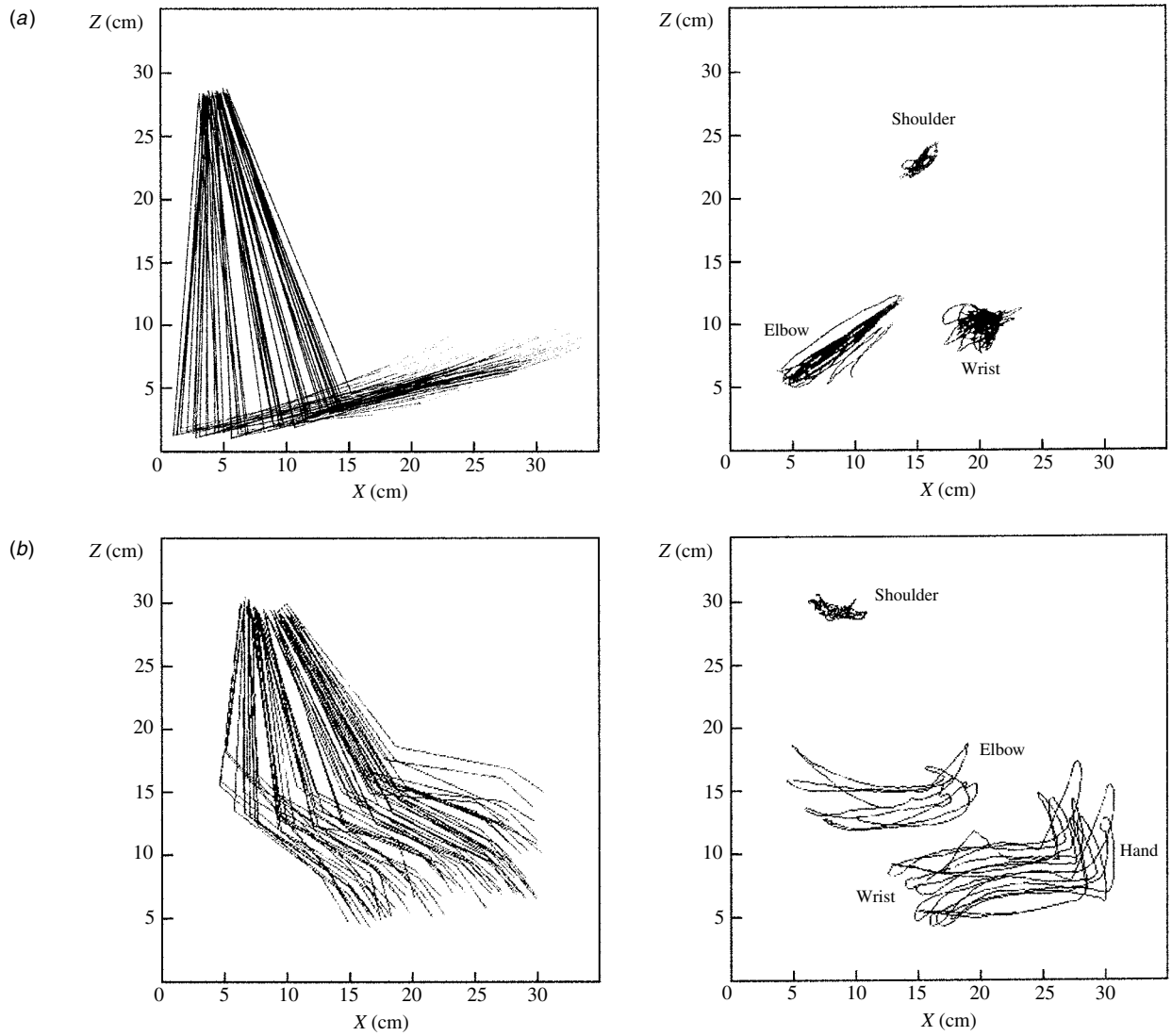

Fig. 32.1. Left: Lateral view of successive arm, forearm, wrist and hand positions during the performance of the bread-slicing gesture. Right: Frontal view of successive cycles of shoulder, elbow, wrist and hand trajectories. (*a*) Control subject. (*b*) Patient with ideomotor apraxia. Wrist trajectories in the control subject are located perpendicular to the goal object and aligned in the sagittal plane with slight vertical and horizontal displacement. The patient's wrist path showed abnormal horizontal displacement. Note also the incorrect orientation of movement axis.

Haaland et al., 1999; Leiguarda et al., 2000). Furthermore, the study of manipulating finger movements has disclosed abnormal workspace and breakdown of the temporal profiles of the scanning movements in patients with limb-kinetic apraxia (Leiguarda et al., 2000). Thus, exploration into the kinematics of reaching, grasping and manipulating provides information regarding the specific neural subsystems involved in patients with different types of limb praxic disorders.

Interhemispheric differences in the control of praxic skills

Apraxia as tested by the imitation of gestures and object use pantomime has been found in about 50% of patients with left hemisphere damage and in less than 10% of those with right hemisphere damage (De Renzi, 1989). Most of the errors exhibited by ideomotor apraxia patients are equally seen in left or right hemisphere-damaged patients

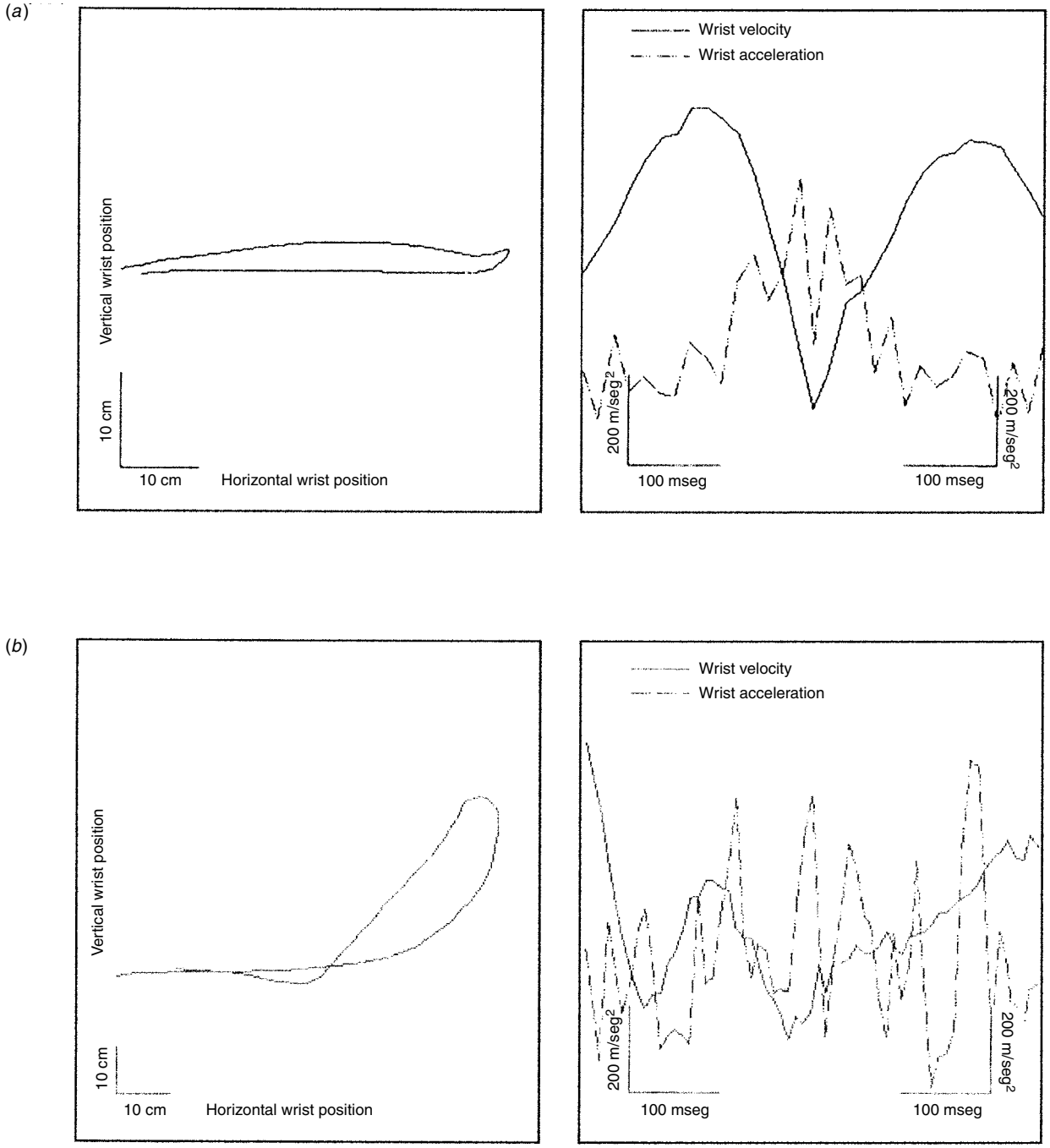

Fig. 32.2. Phase reversal in a control subject (*a*) and in a patient with ideomotor apraxia (*b*). The patient showed an abnormal widening of the wrist path during the reversal phase with a resulting spatial separation of irregular onward and outward path. The spatial distortion corresponds with a grossly disrupted relationship between wrist velocity and wrist acceleration.

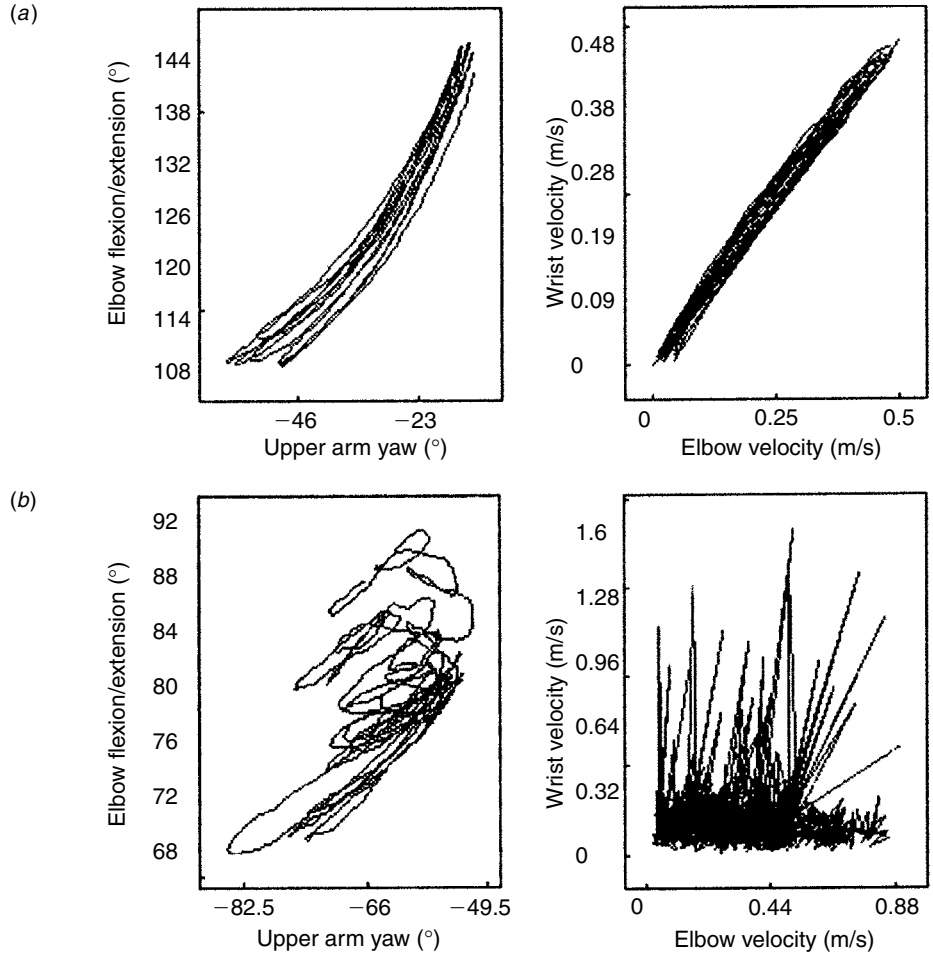

Fig. 32.3. Interjoint coordination (*a*) in a control subject and (*b*) in a patient with ideomotor apraxia. The control subject showed a smooth and linear relationship between elbow flexion–extension and upper arm yaw. As the elbow extended, the upper arm moved laterally across the body in a well-coordinated pattern. In contrast, the patient showed distorted angle–angle relationships owing to poor coordination between elbow flexion–extension and upper arm yaw as well as asynchronous intersegmental joint velocities.

when they pantomime non-representative and representative/intransitive gestures, but are observed predominantly in left hemisphere-damaged patients when they pantomime transitive movements, because it is this action which is performed outside the natural context (Haaland & Flaherty, 1984). Schnider et al. (1997) also emphasized that the left hemisphere motor dominance reflected by ideomotor apraxia refers to spatially and temporally complex movements carried out in an artificial context. Moreover, it has been suggested that, whereas either hemisphere would be able to process intransitive movements as well as transitive movements using tools/objects, the left hemisphere would be dominant not only for the 'abstract' performance (pantomiming to verbal command) of transitive movements but also for learning and reproducing novel movements such as meaningless movements and sequences (Rapcsak et al., 1993). Impairment in sequencing is apparent in left hemisphere-damaged patients when the tasks place demands on memory, but also when the temporal aspects of sequencing, reflecting response preparation and programming, are considered (Harrington & Haaland, 1992). Rushworth et al. (1998) have further proposed that the left hemisphere is not only dominant for learning to select movements in a sequence but also for learning to select a limb movement that is appropriate for the use of an object. Thus, is seems likely that the interhemispheric differences in the control of praxic skills would largely depend on the context in which the movement is performed and on the cognitive requirements of the task; that is, when a single and/or sequence of object-oriented

movements are performed outside the usual context and depend on higher-level cognitive abilities for planning and self-monitoring the action, the left hemisphere emerges as more dominant than the right (Haaland & Harrington, 1996).

Types of limb apraxia

Ideational or conceptual apraxia

In 1905 Pick described a patient who was unable to carry out a series of acts involving the utilization of several objects leading to an action goal (e.g. prepare a letter for mailing), although he was also able to use properly single tools and objects. Liepmann (1908) defined ideational apraxia as an impairment of tasks requiring a sequence of several acts with tools and objects. However, other authors use the term to denote a failure to use single tools appropriately (De Renzi, 1989). To overcome this confusion, Ochipa et al. (1992) have suggested restricting the term ideational apraxia to a failure to conceive a series of acts leading to an action goal, and introduced the term conceptual apraxia to denote deficits in the different types of tool-action knowledge as proposed by Roy and Square (1985). However, a strict difference between ideational and conceptual apraxia is not always feasible, since patients with ideational apraxia not only fail on tests of multiple object use, but may also perform abnormally when using a single object (De Renzi & Lucchelli, 1988).

Patients with ideational or conceptual apraxia exhibit primarily content errors in the performance of transitive movements (see Table 32.2), because they are unable to associate tools and objects with their corresponding action. They may also lose the ability to associate tools with the objects that receive their action; thus, when a partially driven nail is shown, the patient may select a pair of scissors rather than a hammer from an array of tools to perform the action. Not only are patients unable to select the appropriate tool to complete an action, but they may also fail to describe a function of a tool or point to a tool when the function is described by the examiner, even when the patient names the tool properly when shown to him/her. Patients with conceptual apraxia lose the mechanical advantage afforded by tools (mechanical knowledge). For example, when asked to complete an action and the appropriate tool is not available (e.g. a hammer to drive a nail), they may not select the most adequate tool for that action (e.g. a wrench) but rather one which is inadequate (e.g. a screwdriver) (Ochipa et al., 1992). These patients may also be impaired in the sequencing of tool/object use (Pick, 1905; Liepmann, 1920; Poeck, 1983). Patients with ideational or conceptual apraxia are disabled in everyday life, because they use tools/objects improperly, they misselect tools/objects for an intended activity, perform a complex sequential activity (e.g. make express coffee) in a mistaken order or do not complete the task at all (Foundas et al., 1995). Ideational apraxia has been traditionally allocated to the left parieto-occipital and parieto-temporal regions (Liepmann, 1920), although frontal and frontotemporal lesions may also cause ideational (De Renzi & Luchelli, 1988) or conceptual apraxia (Heilman et al., 1997).

Ideomotor apraxia

Ideomotor apraxia has been defined as 'a disturbance in programming the timing, sequencing and spatial organization of gestural movements' (Rothi et al., 1991). Patients with ideomotor apraxia exhibit mainly temporal and spatial errors (see Table 32.2). The movements are incorrectly produced but the goal of the action can usually be recognized. Occasionally, however, the performance is so severely deranged that the examiner cannot recognize the movement. Transitive movements are more affected than intransitive ones on pantomiming to commands and patients usually improve on imitation when performance is compared to responses to verbal commands (Heilman & Rothi, 1985). Acting with tools/objects is carried out better than pantomiming their use, but even so, movements may not be entirely normal. The improvement in performance observed when the patient actually uses the tool/object is due to the advantage provided by visual and tactile-kinesthetic cues emanating from the tool/object and by the fact that in this condition, the patient is performing the movement in a more natural context and therefore less dependent on the left hemisphere. Ideomotor apraxia is commonly associated with damage to the parietal association areas, less frequently with lesions of the PM cortex and SMA and usually with disruption of the intrahemispheric white matter bundles which interconnect them (Leiguarda & Marsden, 2000). Although small lesions of the basal ganglia and thalamus may cause ideomotor apraxia, in the majority of patients the pathology extends to the internal capsule and periventricular and peristriatal white matter (Pramstaller & Marsden, 1996). Most studies examining possible clinico-anatomical correlation for ideomotor apraxia have found a strong association of apraxia with large cortico-subcortical lesions in the suprasylvian, perirolandic region of the left dominant hemisphere, but no specific lesion site which correlated with apraxia. Disruption of cortico-cortical and cortico-subcortical connection due to white matter damage seems essential for the occurrence of apraxia (Kertesz & Ferro, 1984; Alexander

et al., 1992; Schnider et al., 1997; Leiguarda & Marsden, 2000).

Limb-kinetic apraxia

This type of apraxia was originally described by Kleist (1907), who called it 'innervatory apraxia' to stress the loss of hand and finger dexterity due to inability to connect and to isolate individual innervation. The deficit is mainly confined to finger and hand movements contralateral to the lesion, regardless of its hemispheric side, with preservation of power and sensation. Manipulatory finger movements are predominantly affected, but in most cases all movements, either complex or routine, independently of the modality to evoke them, are coarse, awkward, mutilated and 'amorphous' (Liepmann, 1908). Fruitless attempts usually precede wrong movements, which in turn are frequently contaminated by extraneous movements. Imitation of finger postures is also abnormal and some patients use the less affected or normal hand to reproduce the requested posture. The severity of the deficit is consistent, exhibiting the same degree in everyday activities as in the clinical setting; thus, there is no voluntary-automatic dissociation (Liepmann, 1908; Faglioni & Basso, 1985).

Limb-kinetic apraxia has been scantily reported with focal lesions (Faglioni & Basso, 1985); there are two potential explanations: first, most PM lesions also involve the precentral cortex, and, therefore, the contralateral paresis or paralysis precludes the expression of the praxic deficit; and, secondly, bilateral activation of the PM cortex and SMA are often observed with unilateral movements; thus, a unilateral lesion would not be enough for an overt deficit, since bilateral involvement would be most likely necessary. As a matter of fact, all recently pathologically confirmed cases of limb-kinetic apraxia suffered a degenerative process such as corticobasal degeneration and Pick's disease, involving frontal and parietal cortices or, predominantly, the PM cortex (Leiguarda & Marsden, 2000).

Callosal apraxia

Patients with damage to the body of the corpus callosum with or without genu involvement (Liepmann & Maas, 1907; Watson & Heilman, 1983; Graff-Radford et al., 1987; Leiguarda et al., 1989) may develop unilateral apraxia of the non-dominant limb whose characteristics vary according to the type of test given and the lateralization pattern of praxic skills in each patient. Some patients could not correctly pantomime to verbal commands with their left hand, but performed normally on imitation and object use (Geschwind & Kaplan, 1962), whereas others could not use their left hand on command, by imitation or while holding the object (Watson & Heilman, 1983; Leiguarda et al., 1989). Moreover, a few patients could not pantomime to verbal commands and while holding the object, but performed fairly well on imitation (Graff-Radford et al., 1987), or improved over time on imitation and object use (Watson & Heilman, 1983). Thus, the most enduring callosal type of praxic defect is demonstrated when verbal-motor tasks, such as pantomiming to command, are used (Graff-Radford et al., 1987).

Modality-specific or disassociation apraxias

The modality-specific (De Renzi et al., 1982) or disassociation apraxias (Rothi et al., 1991) refer to those types of praxic deficits exhibited by patients who commit errors only, or predominantly, when the movement is evoked by one but not all modalities. Thus, the impairment of patients who performed abnormally only under verbal commands has been attributed to a left hemispheric lesion most likely affecting the audio-verbal inputs to the parietal lobe (De Renzi et al., 1982) or a callosal lesion (Geschwind & Kaplan, 1962). Patients who performed poorly to seen objects, but were able to pantomime gestures normally to verbal command, have also been reported as having lesions interrupting the flow of visual information toward the parietal lobe. On occasion, praxic deficits may be confined to the tactile modality. Finally, patients have been reported who, unlike those with ideomotor apraxia improving on imitation, were more impaired when imitating than when pantomiming to command, or could not imitate but performed flawlessly under other modalities. Deficits may be restricted solely to the imitation of meaningless gestures with preserved imitation to meaningful gestures (De Renzi et al., 1982; Rothi et al., 1991; Ochipa et al., 1994; Goldenberg & Hagmann, 1997).

The anatomofunctional substrates of limb praxis

The fact that most studies exploring possible clinico-anatomical correlations for different types of limb apraxia have failed to unveil a consistent and specific lesion site for the disorder, strongly suggests that praxic functions are distributed across several distinct anatomofunctional neural systems, working in concert but with each one controlling specific processes (i.e. parieto-frontal systems and reaching/grasping, fronto-striatal system and sequential motor events). Damage to these systems would produce selective praxic-related deficits depending on the movement context and cognitive demand of the action.

Parallel parieto-frontal circuits for sensorimotor integration

Recent anatomical and functional studies have identified in primates a series of segregated parieto-frontal circuits,

working in parallel and each one involved in a specific sensorimotor transformation process; that is, their function is to transform the sensory information encoded in the coordinates of sensory epithelia (e.g. retina, skin) into information for movements (Rizzolatti et al., 1998). The transformation process involves parallel mechanisms that simultaneously engage functionally related parietal and frontal areas linked by reciprocal cortico-cortical connections. The posterior parietal cortex comprises a multiplicity of areas, each involved in the analysis of particular aspects of sensory information (i.e. somatosensory, visual, auditory, vestibular). The coordinate system may vary in different parts of the parietal cortex according to the nature of the actions evoked by sensory input. The motor cortex, in turn, is also made up by many areas, each containing an independent body movement representation, and playing a specific role in motor control, according to its afferent and efferent connections. The proposed functions of the main circuits originating from the superior parietal lobule (SPL) include: visual and somatosensory transformation for reaching (MIP-F_2), somatosensory transformation for reaching (PEc/PEip-F_2), somatosensory transformation for posture (PEci-F_3), and transformation of body part location data into information necessary for the control of body part movements (PE-F_1). The circuits originating in the IPL are devoted to visuomotor transformation for grasping and manipulation (AIP-F_5), the internal representation of actions (PF-F_5), coding peripersonal space for limb and neck movements (VIP-F_4), and visual transformation for eye movements (LIP-FEF) (Fig. 32.4) (Rizzolatti et al., 1998).

Selective apraxia-related deficits resulting from damage to the parieto-frontal circuits

Patients with lesions of the postero-superior parietal cortex develop a disorder of visually guided reaching called optic ataxia (Balint, 1909). Some of the patients not only misreach the target but also misshape the hand before grasping and on occasion commit errors in hand orientation (Jeannerod et al., 1994). Freund (1992) has suggested using the term 'visuomotor apraxia' rather than optic ataxia because inaccuracy of the movement (ataxia) is not the sole feature of the disorder, as performance is also misdirected, decomposed and faulty in the execution of its parts. Visuomotor apraxia most likely results from disruption of the parieto-frontal circuit devoted to visual and somatosensory transformation for reaching.

Lesions in the SPL involving circuits that subserve somatosensory transformation for reaching, somatosensory transformation for posture and transformation of body part location data into information for the control of body part movements would explain the external configuration and movement types of praxic errors such as faulty orientation and abnormal limb configuration. Heilman et al. (1986) described a right-handed patient with an apraxia due to a right superior parietal lesion; her performance with the left hand was characterized by minor temporal but gross spatial errors, particularly with the eyes closed; she erroneously moved the arm in space and abnormally oriented the limb in relation to the object. She failed to display visuomotor ataxia, and grasping appeared to be preserved. Selective deficits limited to the grasping phase of the movement that can mirror some of the internal configuration types of praxic errors have also been described in humans with damage to parieto-frontal circuits in the IPL. Jeannerod et al. (1994) reported a patient who, following a bilateral parieto-occipital infarction, showed a severe and bilateral grasping impairment; the hand was widely open, without correlation between grip and object size, and the grasp was awkward and inaccurate. Binkofski et al. (1998) studied patients with lesions involving the anterior bank of the intraparietal sulcus (IPs), possibly the human homologue of the anterior intraparietal area (AIP), who had selective temporal and spatial kinematic deficits in the coordination of finger movements required for grasping a switch with minor disturbances of the reaching phase of the movement. The report of Sirigu et al. (1995) clearly demonstrated the relationship between grasping and praxis. Their patient, with bilateral hypometabolism in the posterior parietal regions, showed a selective praxic deficit for hand postures during grasping objects in the context of utilization gestures, with apparently normal movement trajectories and accurate manual grasp scaling during simple reaching movements. Thus, object attributes are likely to be processed differently according to the task in which subjects are involved. When a subject is requested only to grasp an object but not to use it, the brain extracts the structural attributes of objects (i.e. form, size, orientation) relevant to action to generate the appropriate movement. However, during utilization gestures, in addition to data about object characteristics, prior knowledge about functional properties of objects needs to be integrated into the grasping subsystem to produce an accurate manual grasp (Jeannerod et al., 1995; Sirigu et al., 1995).

Lesions in animals and humans involving areas of the motor cortex making up the parieto-frontal circuits also cause distinct types of praxic-like deficits, though less selectively than those observed with damage to the parietal component of the circuits. Persistent impairment of skilled movement has been observed with damage to the PM cortex. Luria (1980) stressed the 'loss of the kinetic melody',

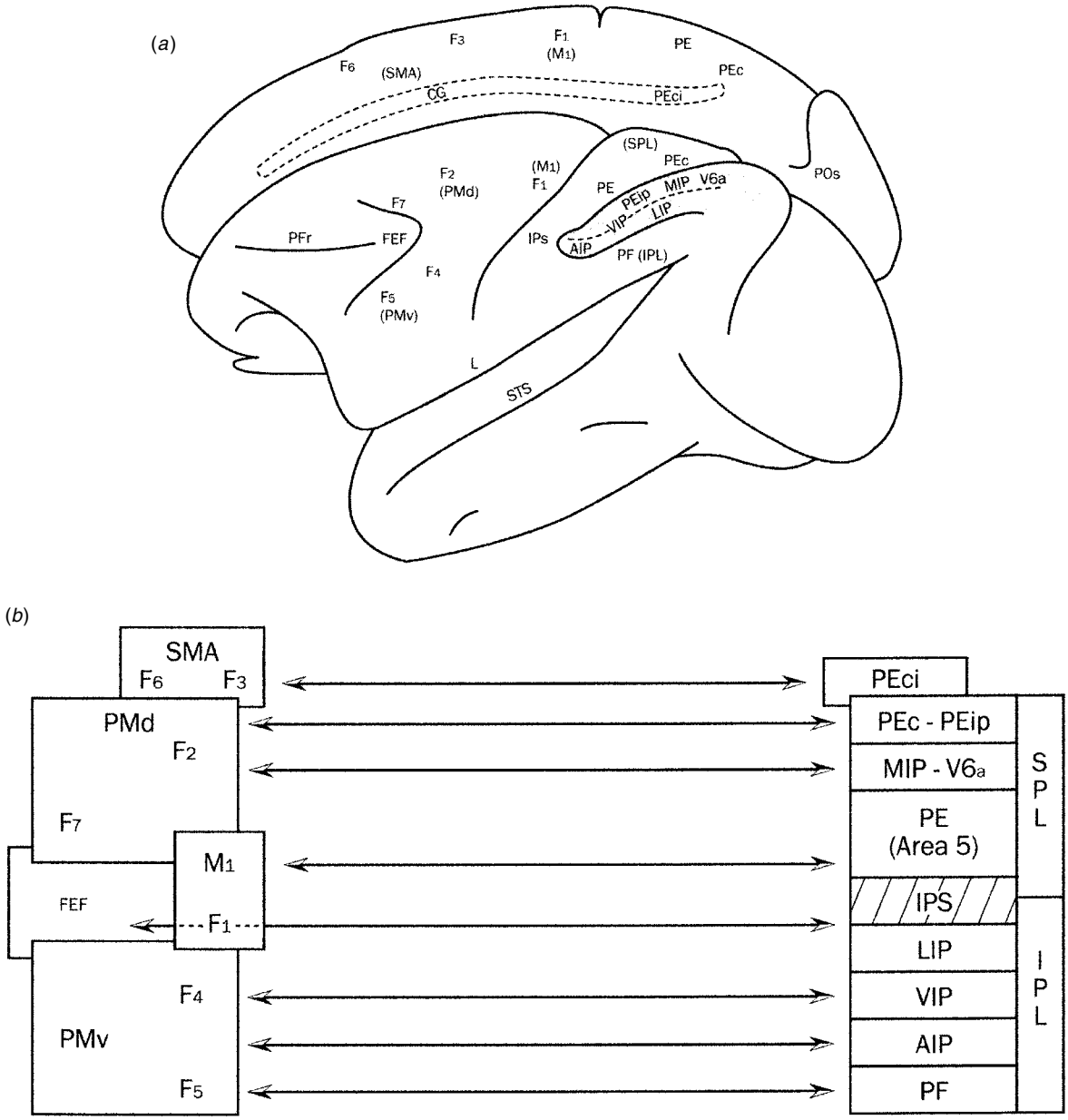

Fig. 32.4. (*a*) Lateral and medial views of the cerebral hemisphere of macaque monkey. The intraparietal sulcus has been opened (shaded grey) to show areas located in its medial and lateral bank. (*b*) Simplified diagram of the organization of the parallel parieto-frontal circuits for sensory-motor integration. The parcellation of the agranular frontal cortex is defined according to Matelli et al. (1985, 1991) studies in monkeys. F1 corresponds to primary motor cortex, F2 and F7 correspond to the dorsal premotor cortex (PMd) and F4 and F5 to the ventral premotor cortex (PMv). F6 and F3 correspond to the pre-supplementary motor area (SMA) and SMA proper, respectively. The arm is represented in F1, F2, F3, F4 and F5 whereas the leg only in F1, F2 and F3. F6 and F7 are almost devoid of corticospinal neurons. In the posterior parietal lobe there are also multiple representations of the arm, leg and face. All parietal areas are defined according to Pandya and Seltzer (1982), except those buried within the intraparietal sulcus (IPs) which are defined according to physiological data (Rizzolatti et al., 1998); AIP, anterior intraparietal area; CG, cingulate gyrus; FEF, frontal eye-field; L, lateral fissure; LIP, lateral intraparietal area; MIP, medial intraparietal area; PE, dorsal part of area 5; PEc, posterior part of PE; PEci, posterior part of cingulate sulcus; PEip, rostral part of the medial bank of IPs; PF, anterior part of the convexity of IPL; POs, parieto-occipital sulcus; PFr, prefrontal cortex; STS, superior temporal sulcus; VIP, ventral intraparietal area; V6a, visual area 6 in the rostral bank of the POs. Monkey IPL is not homologous to human IPL, since it is devoid of Brodmann areas 39 and 40. (Source: Leiguarda & Marsden, 2000.)

resulting in a disintegration of the dynamics of the motor act and of complex skilled movements in patients with PM lesions, which is mainly apparent when the task requires the learning of a new skilled movement. Patients with frontal lobe lesions may exhibit deficits in visually steering the arm accurately, particularly during rapid movements (catch a thrown ball) due to abnormal temporal sequencing of muscular activation (Freund & Hummelsheim, 1985). On the other hand, the cingulate and SMA seem to play a leading role in bimanual interaction since patients with damage to these areas show difficulties whenever the two hands must act simultaneously (i.e. buttoning, tying shoelaces) but experience no trouble with unimanual dexterity (Stephan et al., 1999). In addition, patients with PM lesions exhibit a deficit in conditional motor learning (Halsband & Freund, 1990) which may underlie the inappropriate selection of actions in relation to the context exhibited by apraxic patients (Passingham, 1993).

Fronto-striatal and fronto-parietal systems: sequencing of movements

Patients with apraxia exhibit several types of sequential errors, such as deletions, transpositions, additions, perseverations and non-related types of substitutions (Roy & Square, 1985; Rothi et al., 1997). Functional brain imaging studies have shown that different neural systems are actively engaged in the preparation and generation of a sequential action, depending on whether a sequence has been prelearned or is a new one, and contingent to the complexity of the attentional demands of the task (Grafton et al., 1995; Catalan et al., 1998).

The SMA, primary sensorimotor cortex, basal ganglia (mid-posterior putamen) and cerebellum would be mainly involved in the execution of automatic, overlearned, sequential movements, whereas the prefrontal, PM and posterior parietal cortices and the anterior part of the caudate/putamen would be particularly recruited, in addition to such areas engaged in the execution of simple movement sequences, when a complex or newly learned sequence, which requires attention, integration of multimodal information and working memory processes for its appropriate selection and monitoring, has to be performed (Grafton et al., 1995; Catalan et al., 1998.

Thus, different neural systems would be engaged depending on the type of movement sequence requested to be executed during praxis evaluation. When the sequence is well known or automated, or else performed from memory, the SMA-basal ganglion system would be preferentially recruited. However, most of the sequences used to test praxis are new (e.g. sequencing of movement in the movement imitation test for ideomotor apraxia); or, the content of an otherwise well learned goal-directed action (e.g. multiple sequential use of objects test for ideational apraxia) has to be explicitly represented. In any case, the system made up by the prefrontal, PM and parietal cortices, the striatum and white matter fascicles would be specifically engaged. In addition, it might be possible that within this system there are many different subsystems subserving functionally separate cognitive computations involved in motor sequencing (i.e. timing, motor attention, selection of limb movements and object-oriented responses) which may be selectively damaged by the pathological process and thus produce different types of sequencing impairment in apraxic patients (Harrington & Haaland, 1992; Rushworth et al., 1998).

The temporo-parieto-frontal system: recognition and imitation of actions

Action recognition deficits have been observed in patients with parietal, temporal, frontal and basal ganglion lesions predominantly in the left hemisphere (Ferro et al., 1983; Varney & Damasio, 1987). On the other hand, abnormal performance on imitation has been found in patients with parietal, frontal, temporal, subcortical and basal ganglion lesions (Hermsdöfer et al., 1996). Thus, recognition and imitation of actions seem to be subserved through distributed neural systems preferentially though not exclusively dependent on the left dominant hemisphere. These systems would be made up by several interconnected nodes mainly in the parietal and frontal cortices, but also in the temporal cortex and perhaps subcortical structures, each devoted to preferential functions within each system. Single-unit studies in monkeys and functional neuroimaging studies tend to support these assumptions.

Di Pellegrino et al. (1992) discovered a particular subset of neurones in F5 which discharge during the time a monkey observes meaningful hand movements made by the experimenter, in particular when interacting with objects; they called them 'mirror neurons' and speculated that they belonged to an observation/execution matching system involved in understanding the meaning of motor events as well as in action imitation (Rizzolatti et al., 1998). Neurons with properties similar to those of mirror neurons in F5 are also found in the superior temporal sulcus (STS) in monkeys (Carey et al., 1997). Two other types of neurons, which may contribute to the recognition and imitation of postures and actions, have also been found in the STS. One type encodes the visual appearance of particular parts of the body (i.e. fingers, hands, arms), which combine in such a way that the collection of components can specify a particular meaningful posture or action. The second type

encodes specific body movements, such as walking and turning (Carey et al., 1997). Cells responding to hand–object interaction might also be present in area 7b, located in the rostral part of the IPL, which sends its cortical output to the F5; in turn, area 7b receives projection from the STS region, and the latter is interconnected with the frontal lobe, thus closing a cortical circuit involved in the perception of hand–object interaction. The crucial cognitive role of the STS-7b-F5 network would be the internal representation of actions which, when evoked by an action made by others, would be involved in two related functions, namely, action recognition and action imitation (Rizzolatti et al., 1998).

PET studies in humans support neurophysiological findings in monkeys. Grasping observation markedly increased cerebral blood flow in the cortex of the STS, in the rostral part of Broca's area and in the rostral part of the left IPs on the left hemisphere of right-handed subjects (Rizzolatti et al., 1996; Grafton et al., 1996). Furthermore, the imitation of meaningful actions seems to be mediated by the implicit knowledge about the form as well as the meaning of the gesture, which is processed by regions involved in the planning and generation of actions plus the temporal cortex, whereas imitation of meaningless actions would depend on the decoding of their spatiotemporal layout in the occipito-parietal-PM cortex pathway (Decety et al., 1997), or on the analysis of arbitrary body movements or components (i.e. hand open, finger extended) by cells in the temporal cortex and their corresponding parietal and/or premotor connections (Carey et al., 1997).

Limb apraxias due to dysfunction of the parieto-frontal circuits: higher-order defects of sensorimotor integration

Disruption of parieto-frontal circuits and their subcortical connections, subserving the transformation of sensory information into action, would give rise to most of the praxic errors observed in ideomotor apraxia. Damage to circuits devoted to sensorimotor transformation for grasping, reaching and posture, as well as for transformation of body part location into information necessary for the control of body part movements, would produce incorrect finger and hand posture and abnormal orientation of the tool/object, inappropriate configuration of the arm and faulty orientation of the movement (both with respect to the body and the target of the movement in extrapersonal space), as well as movement trajectory abnormalities. These errors may be similarly observed in the limb contralateral to a left or right parietal lesion, if an associated elemental motor or sensory deficit does not preclude their proper interpretation. However, they would be particularly reflective of ideomotor apraxia, and then also observed in the limb ipsilateral to a left hemisphere lesion, when the patient pantomimes a transitive movement under verbal command. Thus, the praxic quality of the errors in ideomotor apraxia would be determined by the context in which the movement is performed and the cognitive requirements of the task.

Selective praxic deficits may be observed when specific circuits are involved in the parietal or frontal lobes. Damage to the SPL in circuits subserving somatosensory transformation for reaching, posture and movements would produce praxic errors, such as abnormal limb orientation and configuration, resembling those observed in patients with apraxia secondary to superior parietal lesions (Heilman et al., 1986). When the circuits subserving grasping mechanisms are damaged in the IPL, a praxic deficit characterized by a mismatch between finger and hand postures and the object to be grasped will be observed (Sirigu et al., 1995).

Lesions in the PM dorsal cortex and SMA involving the corresponding parieto-frontal circuits will most likely cause milder errors in limb position, configuration, orientation and trajectory than those observed with parietal lesions. These deficits will be more evident in the contralateral limb due to close interrelation between both premotor cortices during movements, although subtle abnormalities may be observed in the limb ipsilateral to a damaged left hemisphere, particularly when the subject pantomimes transitive movements to verbal command. Involvement of the circuits subserving sensorimotor transformation for grasping in the PM ventral cortex may produce some of the ideomotor type of praxis errors confined to hand movements. However, it seems possible that damage to this region of the premotor cortex, particularly when bilateral, would primarily disrupt particular segments of the action and the specificity for different hand and finger movements and configurations. The 'motor vocabulary' necessary for the proper selection of finger and hand movements (Jeannerod et al., 1995) would be impaired and a limb-kinetic type of praxis deficit would appear in the hand contralateral to the more affected hemisphere, regardless of the pattern of cerebral dominance (Leiguarda & Marsden, 2000).

Treatment of limb apraxia

Limb apraxia has a definitive ecological impact on patients' lives, since it interferes with activities of daily living. Patients may use and select tools/objects improperly and may be unable to perform a routine sequential

action. In addition, the presence of limb apraxia may negatively affect the acquisition and use of gestural communication in aphasic patients (Foundas et al., 1995). Furthermore, although the natural evolution of limb apraxia is still unknown, it seems that some aspects of the disorder improve over time, but others are persistent. Therefore, the praxic disorder should be correctly identified and treated together with associated neurological deficits.

Maher and Ochipa have suggested two strategies to manage patients' disability. One is to modify the environment in order to facilitate activities of daily living and to reduce the risk of injuries. The other would be to directly treat specific praxic deficits based on their functional relevance and patients' needs. Although still not well established, preliminary studies indicate that therapeutic gains are restricted to the specific defect or trained activity, and treatment is more effective when implanted into patients' natural environment (Maher & Ochipa, 1997; Goldenberg & Hagmann, 1998).

Distribution of the apraxias in other body parts

Spatial and temporal errors committed by patients with limb (ideomotor) apraxia are remarkably similar to those observed in patients with oral verbal (speech) and oral non-verbal (buccofacial) apraxias which may reflect some common disruption of motor control (Roy & Square-Storer, 1990). Apraxia of speech or verbal apraxia is defined as an articulatory prosodic speech disorder due to 'an impaired ability to program the positioning of the speech musculature . . . and the sequencing of muscle movements' (Darley et al., 1975). The disorder is distinct from aphasia and dysarthria, but often coexists with them, in particular with Broca's aphasia. Apraxic speech is characterized by articulatory errors of different types, slow rate and prosodic deviation or abnormalities of speech rhythm and stress patterns, becoming more evident on longer and phonetically more complex utterances. Frontal (PM), insula, anterior limb of the internal capsule, basal ganglion and parietal damage in the left hemisphere may cause apraxia of speech; the presentation of the motor speech disorder may differ according to lesion location. Both deficits of postural shaping and disruption for sequencing muscle contractions during speech seem to respond to therapy (Square-Storer & Apeldoorn, 1991). Buccofacial or oral non-verbal apraxia is a disturbance of voluntary facial acts; patients exhibit spatial and temporal errors of similar quality to those observed in limb and speech apraxia when performing movements such as sticking out the tongue, blowing out a match or sucking on a straw. Buccofacial apraxia often coexists with Broca's aphasia, but they can be completely dissociated. The disorder is more frequently observed with damage to the frontal and central operculum, insula, centrum semiovale and basal ganglia (Raade et al., 1991).

Apraxia of eyelid opening can be defined as a non-paralytic inability to open the eyes at will in the absence of visible contraction of the orbicularis oculi muscle. Many patients show a forceful contraction of the frontalis muscle and/or a backward thrusting of the head on attempting eyelid opening and use different types of manoeuvres to help open the eyes including opening the mouth, massaging the lids and manual elevation of the lids. Apraxia of eyelid opening can occur in isolation or associated with blepharospasm. Treatment with botulin toxin may be effective in patients with associated blepharospasm and when the disorder is due to a continuation of orbicularis oculi activity following voluntary closure of the eyes (pretarsal motor persistence) but not when it is only the result of involuntary palpebral levator inhibition (Goldstein & Cogan, 1965; Boghen, 1997).

Gerstmann and Schilder (1926) described apraxia of gait as a genuine disturbance of walking due to frontal lesions. However, it remains controversial whether it is a specific disorder or rather it represents a spectrum of higher-order walking syndromes (see Chapter 41). Apraxia of gait is defined as the loss of ability to use the lower limbs properly in the act of walking, which cannot be accounted for by demonstrable sensory impairment or motor weakness (Meyer & Barron, 1960). Gait is characterized by slowness of initiation, loss of balance, 'magnetic attraction of the foot to the ground', and inability to pedal, to kick or to trace a circle with the foot, as well as increased tone (Gegenhalten) and brisk reflexes in the lower limbs with grasping foot responses. The disorder is caused by bilateral damage to the frontal lobes or by white matter lesions interrupting the connections between premotor cortex, supplementary motor area and cerebellum and basal ganglia.

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33

Parkinson's disease

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Movement disorders may be classified as hyperkinetic, characterized by excessive, involuntary movement or hypokinetic, characterized by decreased and slowed movement. First described by James Parkinson in 1817, Parkinson's disease (PD) is the archetypal hypokinetic disorder and the second most common neurodegenerative disorder after Alzheimer's disease. Though incidence and prevalence increase with age, the total estimated incidence is 20/100 000 and prevalence is 150/100 000 (Schapira, 1999). In the United States, approximately one million patients have PD. The estimated societal cost tops $25 billion (Scheife et al., 2000) and is expected to rise as the population ages.

Parkinsonism: classification/clinical symptoms

'Parkinsonism' is a term describing syndromes combining bradykinesia, tremor, muscle rigidity, gait and balance disturbances. The term 'idiopathic PD' traditionally referred to patients exhibiting two or more of the cardinal signs (rest tremor, rigidity and bradykinesia) who responded to levodopa replacement therapy and did not show evidence of other neurologic disease. Given the discovery of inherited dopa-responsive PD, parkinsonian syndromes with good, sustained clinical response to dopaminergic therapy are best termed 'primary PD' (PPD). Infection, drugs, metabolic abnormalities, or other disease states may cause symptomatic parkinsonism. 'Parkinson-plus' (PD-plus) or atypical parkinsonism includes such syndromes as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), Lewy body disease (LBD), the tauopathies (corticobasalganglionic degeneration and frontotemporal dementias), as well as the amyloidopathies (Alzheimer's disease with parkinsonism). These conditions typically exhibit little or no response to levodopa therapy, prominent and early gait and balance disturbance, autonomic and cognitive symptoms (Table 33.1). Table 33.2 lists signs and symptoms occuring in PPD and parkinsonian syndromes. See Chapter 34 for further discussion of the atypical syndromes.

Diagnostic criteria and clinical features for primary Parkinson's disease (PPD)

Although James Parkinson published the first description of the 'shaking palsy' almost 200 years ago, we still have no standardized diagnostic test for PPD. Clinical criteria for PPD vary, but most movement disorders experts agree a patient must demonstrate at least two of the three cardinal signs and experience significant, long lasting (>5 years) improvement with dopaminergic therapy (Gelb et al., 1999). With these clinical criteria and experience, neurologists' diagnostic accuracy can approach 92% (Jankovic et al., 2000). Single photon emission tomography (SPECT) or ^{18}Fluoro-dopa scans may support the diagnosis, but these techniques are currently used largely in research studies and require clinical correlation for an accurate diagnosis (Staffen et al., 2000). Thus, history and clinical exam remain the primary determinants of diagnosis.

PD begins insidiously, often with non-specific complaints of malaise, fatigue or weakness. Since most patients manifest symptoms between ages 55 and 65, these symptoms are often attributed to aging or other disorders, particularly if the typical rest tremor is absent. The asymmetric 'pill-rolling' tremor typical of PPD appears at rest and/or with sustained posture, has a frequency of 4–7 hertz (Hz) and improves with movement of the affected limb. The tremor usually begins in the fingers or hand and spreads

Table 33.1. Classification of parkinsonism

Primary parkinsonism
Idiopathic ('sporadic') PD
Genetic primary PD
Identified mutations (rare)
PARK1 (α-synuclein)
– 2 mutations
PARK2 (Parkin gene mutation)
– multiple polymorphisms
PARK3
Symptomatic parkinsonism
Drugs
Antiemetics (e.g. compazine, metoclopramide)
Neuroleptics
Dopamine depleting agents (reserpine, tetrabenazine)
α-methyldopa
Lithium carbonate
Valproic acid
Fluoxetine
Vascular parkinsonism
Parkinson-plus sydromes
'Alpha-synucleopathies': Multiple systems atrophies and Lewy body dementia
'Tauopathies' (disorders with primary tau pathology): Progressive supranuclear palsy, Corticobasal degeneration, Fronto-temporal dementia
'Amyloidopathies' (disorders with primary amyloid pathology, secondary tau pathology and dementia): Alzheimer's disease with parkinsonism, (Sporadic, APP, PS1 and PS2 related)
Toxins
1-methyl-1, 2, 4, 6-tetrahydropyridine (MPTP)
Manganese
Cyanide
Methanol
Carbon monoxide
Carbon disulfide
Metabolic conditions
Hypoparathyroidism or pseudo-hypoparathyroidism with basal ganglia calcifications
Miscellaneous acquired conditions
Normal pressure hydrocephalus
Catatonia
Cerebral palsy
Repeated head trauma ('dementia pugilistica')
Genetic disorders with parkinsonian features
Wilson's disease
Hallervorden–Spatz disease
Chediack Hagashi disease
SCA-3 spinocerebellar ataxia
X-linked dystonia–parkinsonism (DYT3)
Huntington's disease (Westphalt variant)
Prion disease
Infectious and post-infectious diseases
Postencephalitic PD
Neurosyphilis

Table 33.2. Neurologic signs in selected neurodegenerative disorders

Frequency and intensity of neurologic signs in selected neurodegenerative disorders

	MSA							
	SND	SDS	OPCA	PSP	PD	DLBD	AD	CBGD
Parkinsonism	++++	+++	++	++++	++++	++++	++	++++
Cerebellar signs	++	+	++++	+	0	0	+	+
Pyramidal signs	++	++++	++	+	++	++	+	+
Autonomic failure	++	++++	++	++	++	+	+	++
Cognitive dysfunction	++	+	++	+++	++	++++	++++	++
Oculomotor impairment	+	+	+++	++++	++	++	+	++
Dysarthria	+++	+	+++	+++	++	++	++	+++
Dysphagia	++	+	++	+++	++	++	++	+
Peripheral neuropathy	+	+	++	+	0	0	+	++
Involuntary movements	+	+	++	+	+++	+++	+	++
Prominent gait problem	++++	++++	++++	++++	++	+++	+	+++

Notes:
0 = none; + = uncommon; ++ = common or moderate; +++ = frequent or marked; ++++ = present in nearly all cases or severe.
SND striatal nigral degeneration; SDS = Shy-Drager Syndrome; OPCA = olivopontocerebellar atrophy; PSP = progressive supranuclear palsy; DLBD = diffuse Lewy body disease; AD = Alzheimer's disease; CBGD = corticobasal ganglionic degeneration.
Source: (From Shulman and Wiener, Multiple System Atrophy. In Watts RL, Koller, WC. Movement Disorders 1997, with permission.)

proximally, usually involving the opposite side within 1–2 years. Parkinsonian tremor may appear in the tongue, jaw or facial muscles, but titubation or voice tremor suggests essential tremor. However, in one familial form of PPD essential tremor may occur as an alternate phenotype (Farrer et al., 1999). Such observations have generated comment about the possible relationship between essential and parkinsonian tremor (Deuschl, 2000).

Patients may appear bradykinetic during both 'automatic' (e.g. walking) and 'commanded' tasks (e.g. rapidly alternating hand pronation/supination) as well as activities of daily living and fine motor tasks. Hypophonic speech is a particularly disabling manifestation of bradykinesia.

The rigidity seen in PPD presents as a uniform resistance to passive limb movement. Although subclinical tremor often imparts a 'cogwheel' quality to parkinsonian rigidity, the rigidity does not vary with velocity, thus differentiating it from spasticity. Patients may report 'heaviness' or 'weakness', but rarely complain of 'rigidity'.

Parkinsonian gait is narrow-based and slow, with short shuffling steps, diminished armswing, and *en-bloc* turning. With advancing disease, patients experience increased problems with initiating gait and 'freezing'. Predominant gait symptoms, ataxic gait and significant postural instability early in the course of the illness suggest atypical PD (Table 33.2).

Although PPD is considered a movement disorder, patients experience multiple associated non-motor signs, symptoms and syndromes (Table 33.3). Cognitive, behavioural and mood changes may reflect disruption of the non-motor circuits that parallel the motor circuits of the basal ganglia or involvement of other biogenic amine systems (Alexander et al., 1990).

Symptomatic PD

At one time, postencephalitic parkinsonism accounted for many of the symptomatic parkinsonian cases seen in clinics. However, after the 1918–1930 epidemic, encephalitis lethargica virtually disappeared. Drug-induced, dementia-associated and vascular parkinsonism are now the most common forms of symptomatic parkinsonism (Rajput et al., 1984; Baldereschi et al., 2000).

Dopamine(DA)-blocking and DA-depleting drugs are commonly associated with symptomatic parkinsonism. These include traditional neuroleptics, antiemetic medications (metoclopramide, promethazine, and prochorperazine) and some antihypertensive agents (reserpine and calcium channel blockers cinnarizine and flunarizine). The motor signs of drug-induced parkinsonism are generally symmetric. Rest tremor occurs less commonly than in PPD. The severity of drug-induced parkinsonism correlates with D2 receptor blocking in the basal ganglia. Newer, 'atypical' antipsychotic drugs differ from the traditional neuroleptics in their receptor binding characteristics. Though the

Table 33.3. Common signs and symptoms in Parkinson's disease

Motor
Dystonia
Hypomimia ('masked faces')
Stooped posture
Propulsive/retropulsive gait
Micrographia
'Freezing' or start hesitation
Difficulty arising from a seated position
Autonomic
Constipation
Urinary dysfunction
Erectile dysfunction
Excessive sweating
Orthostatic hypotension
Drooling
Dry mouth (treated patients)
Sensory
Pain/dysesthesia syndromes
Cognitive/psychiatric
Frontal lobe dysfunction
Depression
Anxiety
Sleep
Restless legs syndrome (RLS)
REM-behaviour sleep disorder (RBD)
Excessive daytime somnolence (EDS)

mechanism of reduced extrapyramidal side effects (EPS) associated with atypical antipsychotics is uncertain, it seems related to a higher serotonin to DA blockade ratio and a relatively higher affinity for D3 receptors. Using 'atypical' neuroleptics (clozapine, quetiapine, olanzepine) reduces the risk of drug-induced parkinsonism, but even these atypical agents have been reported to cause parkinsonism (Glazer, 2000; Modestin et al., 2000). Multiple other drugs, including valproate, have been reported to induce parkinsonism, but the mechanism is unclear (Armon et al., 1996; Onofrj et al., 1998).

Although experts agree vascular parkinsonism exists, its precise phenotype is less clear. In general, affected patients have akinetic-rigid 'lower body' symptoms with prominent gait and balance problems. Action tremor is seen more commonly than in PPD. Associated findings include vascular risk factors, atherosclerotic disease, upper motor neuron signs, pseudobulbar palsy, and dementia. Dopaminergic therapy offers little benefit and anticholinergics and amantadine frequently induce hallucinosis or delerium. These clinical signs and evidence of diffuse white matter disease on imaging studies suggest vascular parkinsonism, but postmortem examination is necessary to exclude other causes of parkinsonism.

Etiology: pathology, genetics and pathogenic theories

Gross examination of the brainstem of a patient with PPD reveals the classic loss of pigmentation in the substantia nigra (SN). The basal ganglia (caudate, putamen, globus pallidus) appear normal. On microscopic examination, one sees loss of neuromelanin-containing neurons and gliosis in the substantia nigra pars compacta (SNc). This loss causes DA deficiency in the striatum and in extrastriatal nigral projections to the motor and limbic basal ganglia circuits (Braak & Braak, 2000). The motor portion of the striatum (the putamen) is the earliest and most severely depleted, most likely accounting for the early development of skeletal signs and symptoms.

Large, round, intracellular eosinophilic inclusions, named Lewy bodies (LB) after the neuropathologist who first described them in 1912, are seen in the nigral pigmented neurons as well as multiple other cortical and subcortical locations. These inclusions contain abnormally phosphorylated neurofilaments and have a halo surrounding a core that stains with antibodies to both ubiquitin and α-synuclein. Lewy bodies are found in the SN in about 75% of clinically diagnosed PPD cases and are considered a pathological hallmark for Parkinson's disease. However, LB have also been described in other neurodegenerative diseases including Alzheimer's disease, some prion diseases and diffuse Lewy Body disease (DLBD). They are not present in autosomal recessive juvenile parkinsonism (ARJP) and thus are sensitive, but not specific for PPD.

At least four different mutations (Park1, Park2, Park3, Park4, Table 33.4) have been described in families whose clinical course is consistent with PPD. Two of these mutations (Park1 and Park3) are in genes coding for α-synuclein and an enzyme involved in ubiquitin metabolism. Both ubiquitin and α-synuclein are major components of LB. Mutant proteins may self-aggregate and form the cores of LB or contribute to the selective vunerability of dopaminergic neurons to oxidant stress (Riess et al., 2000; Polymeropoulos et al., 1997). A third mutation, (Park2) (Matsumine et al., 1998) is found in ARJP patients who have not demonstrated LB when autopsied. This lack of LB in ARJP and the finding of DLBD pathology in a Park4

Table 33.4. Genetically mediated dopa-responsive parkinsonism

Gene	Chromosome	Inheritance	Gene product	Phenotype
Park1	4q21–23	AD	missense mutation in α-synuclein	onset <50 years old, rapid progressive, +Lewy bodies
Park2	6q25–27	AR	point mutation or deletion of parkin gene	onset <40 years, dopa-responsive; early motor fluctuations
Park3	2p	AD	?	40% penetrance
Park 4	4p15	AD	missense mutation of ubiqutin carboxy terminal hydrolase L1	PPD and essential tremor phenotypes

affected patient illustrates the difficulty of classifying parkinsonism solely on clinical or pathologic criteria.

Uncertainty surrounding genetic and environmental factors in PPD has been the rule. A small percentage of cases are familial, but the role of heredity in sporadic cases has been questioned. Early twin studies revealed conflicting concordance results and argued against heredity playing a significant role in PPD. However, monozygotic twins in these studies were prematurely classified discordant (Piccini et al., 1999), suggesting genetics may factor in development of some forms of parkinsonism. The 40% penetrance of the Park3 mutation makes it a target of investigation as a 'risk factor' for sporadic PPD.

Though it is not yet clear how mutations in these genes are related to the selective SN cell death seen in PD, other genetic polymorphisms or mutations may also play a role. Kruger et al., reported apolipoprotein E4 combined with a certain α-synuclein allele increases the risk of a person developing PD (Kruger et al., 1999). Furthermore, apoE genotype may modulate the age of PPD onset (Zareparsi et al., 1997).

Oxidative stress, along with mitochondrial dysfunction, excess nitric oxide formation, and inflammatory processes are all considered contributors to accelerated dopaminergic neuronal apoptosis and development of PPD. Increased glutamatergic output from the subthalamic nucleus (STN) may contribute to degeneration of SN_c neurons via excitotoxic mechanisms (Marsden & Olanow, 1998). Inflammatory responses have also been implicated as glial cells may accelerate DA cell loss via release of cytokines (Hirsch et al., 1998). The 30% decrease in mitochondrial complex I activity found in SN neurons in PPD may contribute to a lowered threshold for apoptosis or susceptiblity to environmental toxins (Schapira et al., 1998).

Langston's description of parkinsonism induced by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP, a neurotoxic contaminant of synthetic heroin), suggested environmental toxins could precipitate PPD and lead to the development of the primate MPTP model of PD (Langston et al., 1983). MPTP is converted to MPP+ by monoamine-oxidase-B (MAO-B). MPP+, a mitochondrial complex I inhibitor, is concentrated in dopaminergic cells by the DA re-uptake system. Thus, MPP+ is selectively toxic to the striatal-nigral system, producing motor deficits in humans, non-human primates and a few other species that closely mimic the clinical signs of PPD. These motor symptoms respond to antiparkinson medications. In addition, MPTP-treated animals may develop dyskinesias and dystonic postures, though MPTP-induced tremor is usually seen with posture rather than at rest. As with motor symptoms, MPTP pathology varies from PPD pathology. Notably, LB are not seen (though older primates may show LB-like inclusions) and MPTP damage is selective for the SN_C. The first model to nearly replicate PPD motor signs, MPTP-parkinsonism is currently the standard to which other models are compared and by which new PPD treatments are tested.

Recently, Greenamyre et al. (1999) and Betarbet and Greenamyre (2000) described a new model of PPD based on chronic, low-level exposure of rats to rotenone, a mitochondrial respiratory chain inhibitor, an 'organic' pesticide used in gardening and aquamanagement. This model appears to more closely mimic the time course and neurobiology of PPD than the MPTP model, but its development in primates and confirmation of its validity awaits further study.

Pathophysiology circuit

The basal ganglia are viewed as components of multiple segregated circuits, including motor, oculomotor, associative, and limbic circuits (Alexander et al., 1990). The motor circuit is implicated in the pathophysiology of both hypo- and hyperkinetic movement disorders (DeLong, 1990). It originates from pre- and postcentral sensorimotor fields and includes specific portions of the putamen, the external

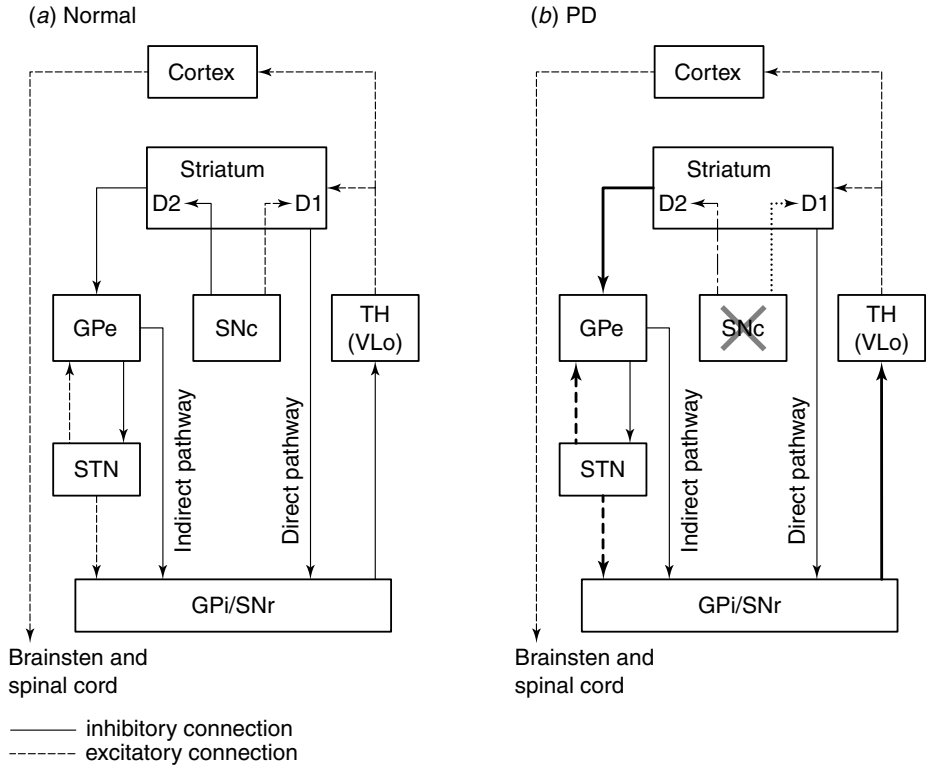

Fig. 33.1. Physiology model of PD. GPe = globus pallidus, external segment; SN_C = substantia nigra, pars compacta; TH = thalamus; VLo = ventrolateral nucleus; STN = subthalamic nucleus; GPi = globus pallidus, internal segment; SNr = substantia nigra, pars reticulata.

(GPe) and internal (GPi) segments of the globus pallidus, the substantia nigra pars reticulata (SNr), the subthalamic nucleus (STN) and portions of the motor thalamus (ventralis lateralis pars oralis, (VLo) and ventralis anterior, (VA)), and returns to the same precentral motor fields from which it originates (Alexander et al., 1990). The striatum (the major input structure of the basal ganglia), influences GPi and SNr (the major output structures), via two routes: a 'direct' pathway from striatum to GPi/SNr and an 'indirect' pathway from the striatum via the GPe and STN (Fig. 33.1).

All the intrinsic connections of the basal ganglia are inhibitory, except for the STN→GPi/SNr pathway, which is excitatory. The dopaminergic nigrostriatal pathway appears to modulate the activity of the two striato-pallidal pathways by activating different DA receptor subtypes (D1 and D2). Thus, DA appears to facilitate transmission in the 'direct' pathway via D_1 receptors and to inhibit transmission in the 'indirect' pathway via D_2 receptors (Albin et al., 1989; Gerfen et al., 1990). Output from GPi/SNr exerts a tonic inhibition on thalamocortical neurons (Yoshida et al., 1972).

Based on this model of intrinsic basal ganglia circuitry, putamenal DA depletion leads to increased mean discharge rates of GPi neurons, excessive inhibition of the thalamic pallidal receiving areas, and correspondingly reduced thalamocortical activity. Consistent with model predictions, single neuron recording studies in parkinsonian animals demonstrated increased tonic discharge rates of GPi neurons and reduced discharge rates in VLo (the pallidal receiving area) (Miller & DeLong, 1988; Filion et al., 1991; Vitek et al., 1994). The observed increases in tonic activity in GPi neurons indicate increased activity in the 'indirect' pathway and decreased activity in the 'direct' pathway in parkinsonian conditions. Increasing striatal inhibition leads to decreased GPe activity, which increases STN activity (Filion et al., 1989, 1991; Bergman et al., 1990). It is proposed that increased STN activity increases GPi output, which, in turn, suppresses thalamocortical activity and leads to dyskinesia and bradykinesia (DeLong, 1990). Consistent with these predictions, temporary or permanent inactivation of the GPi or STN, (in both animal PD models and patients with PPD) is associated with significant improvement in parkinsonian motor signs (Bergman et al., 1990; Wichmann et al., 1994; Lozano et al., 1995; Baron et al., 1996; Gross et al., 1997; Lang et al., 1997; Kumar et al., 1998; Vitek et al., 1998a, b; Volkmann et al.,

1998). Furthermore, this improvement in parkinsonian motor signs coincides with increased cortical metabolic activity (supplementary motor area and dorsolateral prefrontal cortex) (Grafton et al., 1995; Eidelberg et al., 1996; Davis et al., 1997; Samuel et al., 1997; Limousin et al., 1997).

However, this scheme of basal ganglia function (based solely on changes in discharge rate) has several problems. The model predicts that thalamotomy should worsen parkinsonian motor signs by further reducing thalamocortical activity. Contrary to these predictions, most studies report that thalamotomy causes little or no change in bradykinesia, but is highly effective in alleviating parkinsonian tremor and rigidity (Narabayashi, 1986; Montastruc et al., 1994). The model also predicts that pallidotomy should induce excessive involuntary movement (dyskinesias), by disinhibiting the thalamus and increasing thalamocortical activity. However pallidotomy is very effective in alleviating levodopa-induced dyskinesias in addition to improving rigidity, bradykinesia and tremor. These observations are difficult to reconcile with the hypothesis that rate changes alone account for the development of PPD. Many investigators have suggested the observed changes in the pattern of discharge and increased synchronization of neuronal activity reported in animal models and humans with PD play an important role in PPD motor symptoms (Hutchison et al., 1994; Nina et al., 1995; Wichmann & DeLong, 1996; Raz et al., 1997; Vitek, 1997; Vitek et al., 1998).

Changes in pallidal and thalamic receptive field characteristics and neuronal activity patterns (in addition to (or as well as) the levels of neuronal activity) likely provide a significant contribution to the development of parkinsonian motor signs. Disruption of the normal spatio-temporal pattern of cortical neuronal activity may disrupt thalamocortical signal transmission. In the MPTP rodent PD model, improvement of parkinsonian motor signs follows lesioning of the STN. The resulting normalization of pallidal and thalamic neuronal activity (Ryan & Sanders, 1993) coincides with normalization of cortical metabolic activity patterns and improvement in motor signs after stereotactic surgeries in humans with PPD (Grafton et al., 1995; Eidelberg et al., 1996; Davis et al., 1997; Limousin et al., 1997; Samuel et al., 1997). Thus, thalamotomy and pallidotomy are effective in alleviating parkinsonian motor signs because each removes or reduces abnormal neuronal activity that disrupts function in the motor circuit.

Therapeutic principles

The main treatment goals are controlling secondary disability and minimizing associated complications (deconditioning, joint contractures, fractures, etc.) with symptomatic therapy. For all patients, adjunctive therapies including daily stretching and regular physical activity are strongly recommended. Stretching helps maintain flexibility, decreasing the risk of injury from falls, and exercise training may decrease parkinsonian signs (Schenkman et al., 1998; Reuter et al., 1999). Several detailed algorithms for managing early and late PD have recently been published (Olanow & Koller, 1998; Silver & Ruggieri, 1998). The treatment options outlined below fall into three categories: symptom relief, prevention of l-dopa side effects and neuroprotective strategies.

Still considered the most potent symptomatic antiparkinson agent, l-dopa first became widely available in the early 1970s. Although initially administered in high doses without regard to long-term complications, dyskinesias and motor fluctuations were soon observed with chronic l-dopa treatment. Fifty percent of patients with PPD develop dyskinesias after 5 years of l-dopa therapy (Friedman, 1985; Blanchet et al., 1996; Denny & Behari, 1999) and current evidence suggests that the emergence and severity of dyskinesias depend on damaged nigrostriatum exposed to supraphysiologic pulsatile dopaminergic stimulation (Schuh & Bennett, 1993; Chase et al., 1994; Bedard et al., 1999). Younger patients appear more susceptible to motor fluctuations (Quinn et al., 1987; Gibb & Lees, 1988; Giovannini et al., 1991; Pantelatos & Fornadi, 1993; Friedman, 1994; Schrag et al., 1998), and it may be particularly important in younger patients to avoid l-dopa therapy as long as possible. Concerns over such l-dopa-induced side effects and neurotoxicity have led to an ever-increasing emphasis on l-dopa sparing and the early use of DA agonists (Montastruc et al., 1994; Rinne et al., 1998; Rascol et al., 2000; Shulman, 2000).

In addition to priming the basal ganglia for development of dyskinesias, l-dopa neurotoxicity could occur through oxidative stress. L-dopa metabolism generates free radicals, hydrogen peroxide and quinones, all of which can create oxidative stress in dopaminergic neurons. Administering supplemental l-dopa could accelerate or promote apoptotic death of dopaminergic cells. However, evidence from several studies suggests l-dopa delays death in elderly parkinsonian patients about 5 years (Clarke, 1995). Review of the l-dopa toxicity literature (including autopsy cases) found no evidence of l-dopa neurotoxicity in doses comparable to those used clinically (Agid et al., 1999; Weiner, 1999). More recently, Datla et al., provided evidence chronic l-dopa may be protective in 6-hydroxydopamine-lesioned rats (Datla et al., 2001).

The most common side effects of l-dopa are nausea, vomiting, orthostatic hypotension, and hallucinosis. L-dopa is converted to DA in both the periphery and the brain; while l-dopa crosses the blood–brain barrier, DA does not. Combining l-dopa with a peripheral decarboxylase inhibitor (carbidopa) increases the amount of available l-dopa for conversion to DA in the brain. Levodopa conversion to DA in the area postrema is decreased, thereby decreasing nausea and vomiting. Domperidone, a peripheral DA receptor antagonist, may be used as an antiemetic.

Several other agents commonly used for symptomatic management of PPD include DA agonists, anti-cholinergics, amantadine and catechol-*o*-methyl transferase (COMT) inhibitors. Dopamine agonists offer the advantage of directly stimulating postsynaptic DA receptors, thus bypassing the degenerating nigrostriatal nerve terminals. Other advantages include lack of competition with dietary amino acids for absorption and transport into the brain (Rabey, 1995), longer duration of action than standard carbidopa/l-dopa (thus providing more sustained DA receptor stimulation) and lack of auto-oxidation (thus reducing free radical generation and reducing oxidative stress) (Olanow, 1992).

The DA agonists currently used in the United States include ergotamine derivatives (bromocriptine and pergolide) and non-ergolines (pramipexole and ropinirole). Dopamine agonists vary in their affinity for dopamine receptor subtypes and 5-hydroxytryptiline (5-HT) receptors, but none of these compounds has shown clinical superiority in alleviating symptoms. Cabergoline is a long-acting agonist that is clinically available in Europe, but its use in the United States is limited to the treatment of hyperprolactinemia. Apomorphine and lisuride, also available in Europe, have the advantage of parenteral administration. Apomorphine, with its short half-life may be particularly helpful for patients with severe motor fluctuations. The nonergoline structure of ropinerole and pramipexole potentially could limit such side effects as orthostatic hypotension and should decrease the occurrence of pulmonary and retroperitoneal fibrosis associated with ergoline compounds.

Anticholinergic drugs, the first drugs shown to improve parkinsonian symptoms (Duvoisin, 1967), help balance the relative cholinergic excess caused by DA depletion. Though mildly beneficial for rigidity and bradykinesia, anticholinergics are now largely added to target tremor symptoms. Currently used anticholinergics include trihexyphenidyl (Artane), benztropine (Cogentin), and biperiden (Akineton). Ethopropazine (Parsitan) is no longer manufactured in the United States, but can be obtained from Canada and some compounding pharmacies in the United States. Neuropsychiatric and cognitive side effects limit anticholinergic usefulness.

Amantadine, an antiviral agent serendipitously discovered to have anti-parkinson activity, is thought to act by blocking the reuptake of DA into presynaptic neurons, directly stimulating postsynaptic DA receptors, and possibly inhibiting cholinergic activity (Bailey & Stone, 1975; Calne, 1993). More recently, Stoof, et al., recognized that amantadine may act as an NMDA receptor antagonist (Stoof et al., 1992). Amantadine can provide effective monotherapy in early PD, but more importantly provides significant (up to 60%) reduction in dyskinesias (Metman et al., 1999).

As PPD progresses, intracellular DA storage capacity declines and the DA availability becomes more closely tied to circulating blood levels. The COMT inhibitors entacapone and tolcapone have been studied as adjunctive therapy in PD and can extend the duration of l-dopa action by reducing the peripheral degradation of l-dopa. COMT catalyses the breakdown of l-dopa to 3-*o*-methyldopa (3-OMD). Tolcapone and entacapone both inhibit COMT peripherally, and tolcapone also inhibits COMT centrally. Both increase the fraction of l-dopa available to enter the brain. Thus, concomitant l-dopa and COMT inhibitor administration may provide more stable concentrations than can be achieved by fractionating the carbidopa/l-dopa dose or by using controlled release l-dopa formulations.

In addition to symptomatic treatment, neuroprotective strategies are receiving increasing interest. Several clinical trials are in progress to investigate whether DA agonists and such other medications as riluzole could slow PD progression (Dunnett & Bjorklund, 1999). Selegeline was one of the first drugs clinically studied for potential neuroprotection. In the DATATOP study, vitamin E (dosed at 400 IU/day) did not significantly delay the need for l-dopa initiation. Selegeline did delay initiation of l-dopa therapy, but its symptomatic benefit and long washout period confounded this endpoint. Whether selegiline slows the progression of PD remains an unanswered question.

The search for neuroprotection continues with DA agonists and other agents (Marsden & Olanow, 1998; Olanow et al., 1998; Schapira, 1999) Multiple lines of evidence suggest DA agonists may be neuroprotective. Dopamine agonists diminish the need for l-dopa and may therefore minimize the formation of toxic metabolites. In addition, recent evidence suggests that DA agonists have direct antioxidant effects possibly by acting as free radical scavengers (Yoshikawa et al., 1994).

Associated management issues

Coexisting illnesses (e.g. depression, dementia and manic-depressive disorder) can make patients more susceptible to medication side effects and may require the treating neurologist to manage more than the motor manifestations of PPD. Depression, occuring in up to 40% of PPD patients (Cummings & Masterman, 1999), may exacerbate parkinsonian signs and symptoms. Depressed PD patients may be managed similarly to other depressed geriatric patients. Many pharmacists are reluctant to dispense antidepressants to patients who are also taking selegeline, but concern regarding a potential 'serotonin syndrome' interaction is not generally warranted (Heinonen & Myllyla, 1998; Ahlskog, 1999). Patients should also be screened for other medical causes of depression (e.g. hypothyroidism, B12 deficiency).

Patients with cognitive impairment are particularly susceptible to delusions, frank hallucinosis and thought disruption from overstimulation of DA receptors. With a higher ratio of serotonin $5HT_{2a}$ to DA D_2 blockage, the newer atypical antipsychotics clozapine and quetiapine are particularly useful in managing such complications (Juncos, 1999). Electroconvulsive therapy may benefit both depression and parkinsonian symptoms (Anderson et al., 1987).

Along with neuropsychiatric issues, PD patients commonly suffer sleep disruption (Clarenbach, 2000; Larsen et al., 2000; Razmy & Shapiro, 2000). Restless legs syndrome (RLS), a common disorder, responds to DA agents but may be exacerbated by some of the antidepressants used to control depressive symptoms. REM behaviour disorder is a parasomnia commonly seen in PPD. Finally, excessive daytime somnolence and sleep attacks related to dopaminergic therapy are also common in PPD and can be extremely disabling and dangerous (Clarenbach, 2000).

Surgical therapy

Patients with PPD whose motor symptoms can no longer be adequately controlled by medical therapy or who develop intractable drug-induced side effects are candidates for surgical therapy (Fine et al., 2000). Surgical procedures for PD include restorative measures (transplantation using fetal, porcine or retinal tissue), ablative procedures (thalamotomy, pallidotomy and subthalamotomy) and chronic stimulation procedures (thalamic, pallidal, subthalamic).

Although the initial efforts to replace dying dopaminergic neurons with autologous adrenal transplants benefited some patients, such transplants do not offer enough benefit to justify such treatment routinely. Fetal cell transplants seem to offer the best results in animal models and have been tried in humans. Although patients have shown improved bradykinesia and rigidity, freezing and tremor was unaffected and some patients developed severe 'runaway' dyskinesias, even off medications (Fahn, 2000; Freed et al., 2001). Transplant clinical trials thus far have included only patients with advanced PPD, but these patients may not be the ideal candidates for a such a procedure. In the future, transplantation may be a standard therapy, but currently many issues limit it to experimental status.

Thalamotomy is effective for the treatment of Parkinsonian tremor (Tasker, 1998a, b; Linhares & Tasker, 2000). Lesions are generally placed in the cerebellar receiving area, (the ventralis intermedius (V_{im}) nucleus). If extended more anteriorly into the basal ganglia receiving areas (ventralis oralis posterior and ventralis oralis anterior), thalamotomy may also improve rigidity and drug-induced dyskinesias. Thalamotomy is not effective for bradykinesia, freezing, postural instability or the gait disorder associated with PD. Due to an unacceptably high incidence (30–50%) of aphasia, dysarthria or dysphonia, bilateral thalamotomy is not recommended.

A number of studies have demonstrated that pallidotomy is effective for PPD. Lesions within the posteroventral 'sensorimotor' portion of the GPi improve all the cardinal motor signs of PD including tremor, rigidity, bradykinesia, as well as motor fluctuations, drug-induced dyskinesias and dystonia. Although pallidotomy may also improve axial symptoms including gait, balance and freezing, such benefit following unilateral pallidotomy is less consistent than that for appendicular symptoms and many patients lose their benefit 6 months to 2 years postpallidotomy. Bilateral pallidotomy reportedly benefits axial symptoms, but is associated with an unacceptably high incidence of hypophonia. Urinary incontinence and cognitive decline have also been reported following bilateral pallidotomy, though these complications occur less commonly and may result from lesions that encroach on non-motor areas of GPi and/or the internal capsule. Lack of postpallidotomy improvement suggests the patient does not have idiopathic PD or was lesioned outside of the sensorimotor portion of the GPi (Vitek et al., 1998; Eskander et al., 2000).

In recent years, deep brain stimlation (DBS) via implanted electrodes has been employed in place of stereotactic ablation. An implantable programmable pulse generator activates the electrodes. Chronic DBS may reversibly suppress or normalize neuronal activity in neurons by activating an inhibitory interneurons, depolar-

ization block, interupting or normalizing irregular and abnormally bursting activity patterns.

Widely used in Europe, thalamic DBS is now FDA approved for tremor in the United States. Thalamic DBS is effective in the treatment of parkinsonian and other forms of tremor. However, since additional motor symptoms inevitably develop in PPD, pallidotomy or pallidal or subthalamic DBS, should be recommended for PPD patients. Bilateral DBS in the STN or GPi can be performed as a staged procedure or simultaneously. Although some centres support using STN DBS for midline symptoms and GPi DBS for dyskinesias, both procedures are effective in treating the cardinal motor signs of PD and may allow reduced dosing of antiparkinson medications (Burchiel et al., 1999; Krause et al., 2001). Kumar and others have reported benefit lasting 6 to 12 months though the long-term effect of DBS remains ill-defined (Krause et al., 2001).

Future directions: prevention and/or restoration

In the future, treatment strategies will likely provide neuroprotection and neurorescue in PPD (Schapira, 1999). Strategies which decrease iron, lipid peroxidation products and reactive oxygen species accumulation, increase antioxidant concentrations, and improve mitochondrial dysfunction may help accomplish these goals. Such anti-apoptotic agents as the neuroimmunophylins offer another potential avenue of rescue and protection and anti-glutaminergic drugs are being investigated as disease modifying agents. Lastly, transplant studies are currently under way with DA-producing human and pig mesencephalic tissue, genetically engineered dopaminergic cells, and cells expressing trophic factors (GDNF and BDNF). Recently, Kordower et al., successfully delivered glial cell line derived nerve growth factor (GDNF) via a lentiviral injection into the striatum and substantia nigra (Kordower et al., 2000) of rhesus monkeys. The implants successfully expressed GDNF, improved markers of dopaminergic function in MPTP-treated monkeys. Most importantly, the monkeys improved clinically and in quantitative motor testing.

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34

Other extrapyramidal syndromes: parkinsonism-plus and other forms of secondary parkinsonism

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There are numerous other causes of an extrapyramidal syndrome manifesting as parkinsonism apart from Parkinson's disease (see previous chapter). Traditionally, these are listed etiologically as shown in Table 34.1. In this list three broad groups emerge namely that referred to as the parkinsonism-plus syndromes (also called atypical parkinsonian syndromes), the symptomatic or secondary parkinsonian conditions and the hereditary/heredodegenerative disorders (Table 34.1). The parkinsonism-plus syndromes are so called because they are multisystem degenerations and have other features in addition to parkinsonism. This older classification, although useful, has its limitations because the divisions drawn are somewhat artificial and there is a fair amount of overlap in the disorders listed under the different subheadings. For example, additional clinical features can also be present in disorders in the two groups apart from the parkinson-plus disorders and it is being realized that a genetic basis may even underlie parkinsonian disorders thought to be sporadic like progressive supranuclear palsy (PSP). Great advances at the molecular, ultrastructural and genetic level are leading to a newer way of classifying many of these degenerative diseases affecting the basal ganglia causing extrapyramidal syndromes (Dickson, 1997; Spillantini, 1999). Many parkinsonian syndromes can now be viewed as being caused by the genetic or sporadic occurrence of diseases characterized on the basis of cytoskeletal pathology and staining of particular proteins, for example, alpha-synucleinopathies where alpha-synuclein is present (Spillantini, 1999; Goedert, 2001) or taupathies wherein there is deposition of tau protein (Morris et al., 1999a). This way, many of the disorders listed in Table 34.1 can now be reclassified as shown in Tables 34.2 and 34.3 on a molecular basis. Thus PSP and corticobasal degeneration and the inherited condition of frontotemporal dementia parkinsonism as well as dementia pugilistica or encephalitis lethargica from the secondary parkinsonism division are all grouped together as 'taupathies', while multiple system atrophy (MSA) and Parkinson's disease and dementia with Lewy bodies go together as 'alpha-synucleinopathies' (Spillantini et al., 1998a).

It is beyond the scope of this chapter to detail each of the conditions causing parkinsonism listed in Table 34.1, hence this chapter will focus on some of the conditions most likely to be confused with Parkinson's disease, namely progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and multiple system atrophy (MSA) among the parkinsonism-plus syndromes with a brief mention of other related conditions as well as some secondary or symptomatic parkinsonian disorders. The UK brain bank series study looking at a 100 cases diagnosed as having Parkinson's disease in life found that 25 of these had other diagnosis at pathology (Hughes et al., 1992). The most commonly misdiagnosed conditions were atypical parkinsonian disorders, namely progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and vascular parkinsonism (CBD). It is important too for the clinician to recognize the parkinsonism-plus conditions as they usually have a poor response to levodopa replacement treatment and have a bleak prognosis with regard to survival.

Progressive supranuclear palsy (PSP)

Background

PSP is a progressive neurodegenerative condition with the anatomical pathology centred around the basal ganglia and brainstem accounting for its distinctive clinical features. PSP was first recognized as a distinct syndrome by Steele, Richardson and Olszewski in 1963 and their initial

Table 34.1. Classification of parkinsonism

Idiopathic (primary)
Parkinson's disease
Parkinsonism-plus
Progressive supranuclear palsy (PSP)
PSP of the French West Indies (Guadelope)
Multiple system atrophy (MSA)
Striatonigral degeneration (SND/MSA-P)
Shy–Drager syndrome (SDS)
Olivopontocerebellar degeneration (MSA-C)
Corticobasal ganglionic degeneration (CBD)
Dementia syndromes
Parkinsonism–dementia–ALS complex of Guam
Frontotemporal dementia parkinsonism–chromosome 17 (FTDP-17)
Dementia with Lewy Bodies (Diffuse Lewy body disease)
Creutzfeldt–Jakob disease
Alzheimer's disease
Hereditary/heredodegenerative disorders
Wilson's disease
Hallervorden-Spatz disease
Huntington's disease
Neuroacanthocytosis
SCA-3 (Machado–Joseph) and other spinocerebellar ataxias
Lubag (X-linked dystonia–parkinsonism)
Ceroid lipofuscinosis
Hereditary hemochromatosis
Hereditary ceruloplasmin deficiency (Apoceruloplasminemia)
Familial basal ganglia calcification (Fahr's syndrome)
Symptomatic (secondary)
Infectious and postinfectious
Postencephalitic (encephalitis lethargica)
Other encephalitides
Toxins – manganese, cobalt, MPTP, cyanide, CO, methanol, ethanol
Drugs
Dopamine receptor blockers (antipsychotics/antiemetics), dopamine storage depletors, α-methylparatyrosine, α-methyldopa, calcium channel blockers, SSRI's
Vascular–multi-infarct, Binswanger
Brain tumours
Head trauma – including dementia pugilistica
Vascular
Metabolic–hypoparathyroidism, hepatocerebral degeneration
Other – hemiparkinsonism/hemiatrophy, normal pressure hydrocephalus, paraneoplastic

Table 34.2. Conditions characterized by the deposition of tau containing neurofibrillary tangles (taupathies)

Progressive supranuclear palsy (PSP)
Corticobasal degeneration (CBD)
Frontotemporal dementia parkinsonism-chromosome 17 (FTDP-17)
Pick's disease
Post-encephalitic parkinsonism (encephalitis lethargica)
Post-traumatic parkinsonism
Parkinson dementia complex of Guam
Alzheimer's disease
Niemann–Pick type C
Subacute sclerosing panencephalitis

Source: From Morris et al. (1999b).

Table 34.3. Parkinsonian syndromes with alpha-synuclein accumulation (alpha-synucleinopathies)

Lewy body diseases
Idiopathic Parkinson's disease
Inherited Lewy body diseases (mutations of the alpha-synuclein gene, PARK3, PARK4)
Dementia with Lewy Bodies
Halloverden Spatz disease
Multiple system atrophy (MSA)
Striatonigral degeneration
Shy–Drager syndrome
Olivopontocerebellar atrophy

Source: From Goedert & Spillantini (2001).

description has proven to be remarkably accurate (Steele et al., 1964). Despite the distinctive clinical presentation, however, the condition is probably underdiagnosed (Nath et al., 2001).

Clinical aspects

PSP typically occurs late in life usually in the sixth decade with the median age at disease onset between 60 and 66 years (Nath & Burn, 2000). Onset below age 40 years is virtually unknown. A prevalence of 1.4/100 000 had been reported from New Jersey (Golbe et al., 1988) and 1 per 100 000 as per a more national survey from the UK (Nath et al., 2001). A recent cross-sectional study from the UK has shown that the age-adjusted prevalence for PSP was 6.4 per 100 000 (Schrag et al., 1999). There have been only two reported case control studies of PSP both by the same group. The first study sug-

gested that PSP patients were more likely to live in areas of relatively sparse population (Davis et al., 1988). However, a follow-up study failed to identify any particular risk factor except for the likelihood of having completed 12 years of education or more that differentiated PSP patients from matched controls (Golbe et al., 1996). Recently, one study reported a higher prevalence of presymptomatic high blood pressure in PSP patients (81%) compared to Parkinson's disease patients (15%) (Ghika & Bogousslavsky, 1997); however, another subsequent series could not replicate these figures and found this in a much smaller number (24%) of patients with PSP (Fabbrini et al., 1998) . PSP has been considered to be a sporadic condition and in one study of 104 patients, Jankovic et al. (1990) failed to find another affected person among 400 first-degree relatives. However, some reports of familial clustering have appeared in the literature from time to time (Brown et al., 1993; de Yebenes et al., 1995; Tetrud et al., 1996). Recently, 12 families were put together, 8 of whom with probable autosomal dominant inheritance with pathological confirmation in 4 probands (Rojo et al., 1999).

Most patients present with a gait disturbance with a tendency to fall backwards. Indeed 70% of PSP cases would have falls in the first year of the illness. Some may present with a complaint of visual disturbance, particularly when reading or walking downstairs due to lack of control of saccadic eye movements (see below). A growling gruff dysarthria and swallowing difficulty may be associated with presenting symptoms. Despite these disabling presenting features, surprisingly the mean interval from symptom onset to diagnosis of PSP is usually delayed even up to 3–4 years (Maher & Lees, 1986; Golbe et al., 1988). Thus, the average patient with PSP remains undiagnosed for approximately half of the natural history of their disease.

Clinically, most patients have an erect posture in contrast to the flexed posture of Parkinson's disease. Also, unlike Parkinson's disease most signs of parkinsonism in PSP are axial that is involving postural balance, gait and speech with less pronounced distal limb involvement. In contrast to PD, PSP patients have a stiff somewhat broad-based gait quite often marked by start hesitation, freezing and disequilibrium leading to a tendency to fall. There is early loss of postural reflexes as compared to PD (Litvan et al., 1997a). PSP patients, when asked to stand up from sitting, tend to jump up abruptly from the seated position, only to fall back immediately into the chair which has been called the 'rocket sign' and probably results from a combination of postural instability and frontal–subcortical disturbance (Litvan, 1997). Sitting 'en bloc', in which the patient's feet come high off the floor as they sit down, also tends to occur in 30% of cases (Collins et al., 1995). An increase of axial tone with rigidity of the trunk and neck rather than of the limbs is typical and rest tremor is uncommon or does not occur. Bradykinesia is common and affects nearly half the patients by the time of diagnosis and up to 95% of patients during the course of their illness (Verny et al., 1996). Striking frontalis overactivity with markedly reduced blink frequency and hypomimia produce the so-called 'reptilian' stare with regard to facial appearance (Verny et al., 1996). The characteristic feature from which the term 'progressive supranuclear palsy' is derived is the supranuclear gaze problem (Troost & Daroff, 1977). Typically, voluntary down-gaze is slow and incomplete but, when the oculo-cephalic manoeuvre is engaged, full down-gaze is possible. Because up-gaze may be restricted with ageing, and restriction in this direction can also occur with other disorders, downward gaze palsy is more specific for the diagnosis of PSP (Lees, 1987). Some other causes of vertical supranuclear gaze palsy include Whipple's disease (Averbuch-Heller et al., 1999), Niemann Pick type C (Shulman et al., 1995), and other conditions including CBD, prion disease (Brown et al., 1994) and spinocerebellar ataxia (SCA) including SCA2 and SCA3. Square wave jerks, saccadic intrusions when fixing gaze on a stationary object, can also be seen in PSP (Rascol et al., 1991). Unlike corticobasal degeneration, involvement of horizontal saccades occurs only later in PSP (Vidhailhet et al., 1994), a useful differentiating feature. In the late stages, complete supranuclear restriction of eye movements may be seen (Rivaud-Pechoux et al., 2000). Difficulty in eyelid opening may caused by blepharospasm and/or apraxia of eyelid opening. A pseudobulbar palsy occurs in 85–90% of cases, and a frontal lobe-like syndrome sometimes with marked emotional lability is present in 80% of cases with 52% developing this in the first year (Brusa et al., 1980; Verny et al., 1996). Speech and swallowing can be affected early and may be presenting features (Daniel et al., 1995). PSP patients may have stuttering, stammering hypophonic speech. Echolalia, pallilalia and pallilogia can be present. A poor or unsustained response to levodopa is characteristic of PSP (Litvan et al., 1997a). The condition is unfortunately relentlessly progressive with death from disease onset in about 5–6 years (Maher & Lees, 1986; Brusa et al., 1980). An early onset, presence of falls and early down-gaze palsy seems to be associated with a more rapid progression (Santacruz et al., 1998).

Pathology, clinicopathological correlation, tau ultrastructure and genetics of PSP

PSP is characterized pathologically by abundant neurofibrillary tangles (NFTs) which consist of hyperphosphorylated tau and neuropil threads in select basal ganglia and

brainstem regions (Fig. 34.1, see colour plate section). Thus PSP is one of group of tau neurofibrillary disorders (Table 34.2) (Dickson, 1997; Morris et al., 1999a). Tau is a microtubule binding protein which serves to promote and stabilize the polymerization of monomeric tubulin into microtubules. Tau is present mainly in axons and expressed also in glial cells, especially in pathological conditions. In PSP, for example, tau deposition is seen as tufted astrocytes (Fig. 34.2, see colour plate section). The tau protein itself is alternatively spliced from the tau gene with six different types of proteins (isoforms) appearing in normal adult human brain (Morris et al., 1999a). These isoforms differ in the presence of three or four repeated microtubule binding domains (three or four repeat tau) and the extra microtubule binding domain is determined by the inclusion of exon 10 of the tau gene. Tau deposition or dysfunction in these disorders is not thought to be an incidental finding but appears to be the pathogenic cause of neurodegeneration (Hutton et al., 1998; Goedert & Spillantini, 2001).

The main lesions in PSP are in the substantia nigra pars compacta, and reticulata, internal segment of the globus pallidus, subthalamic nucleus, midbrain and pontine reticular formation. Cortical damage and glial pathology is more variable and allows distinction between this disorder from CBD and Pick's disease which have distinctive cortical involvement. The most striking neurochemical abnormality is marked reduction in striatal dopamine, dopamine receptor density, choline acetyl transferase activity and loss of nicotinic cholinergic receptors in the basal forebrain (Young, 1985; Ruberg et al., 1985; Juncos et al., 1991). However, in contrast to the striatum the mesolimbic structures are relatively spared with normal dopamine levels in the nucleus accumbens.

There is a good correlation for PSP between the pathological anatomical substrate and the predominant clinical features. Postural instability is probably due to involvement of the dentate and pedunculopontine nucleus as well as bilateral globus pallidus. Involvement of the substantia nigra, medial pallidum and subthalamic nucleus (Feany & Dickson, 1996) may result in the bradykinesia and limb rigidity. The superior colliculus involvement may account for the increased axial tone. Impairment of vertical saccades is probably due to involvement of rostral interstitial nucleus of Cajal and nucleus of Darkshewitsch and the rostral interstitial nucleus of the medial longitudinal fasciculus (Juncos et al., 1991). Echolalia, pallilalia, grasping and groping behaviour arises from frontal lobe or frontal basal ganglia connections. PSP pathology may affect the spinal cord, and Onuf's nucleus in the sacral spinal cord has been shown to be affected and can result in loss of bladder control and abnormal sphincter electromyogram changes (Scaravilli et al., 2000; Valldeoriola et al., 1995)

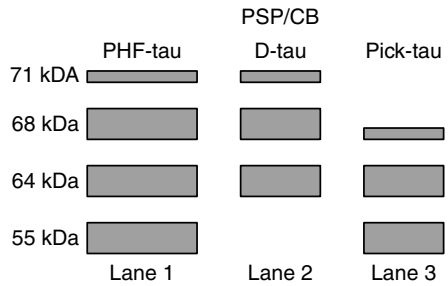

Fig. 34.3. Electrophoretic migration patterns in different taupathies. Lane 1 represents paired helical filament-tau (PHF-tau) characteristic of certain taupathies like Alzheimer's disease and certain forms of frontotemporal dementia linked to chromosome 17 (FTD-17). All six isoforms of tau contribute and a triplet pattern migrating at 68, 64 and 55 kilodaltons is observed. Lane 2 with a doublet pattern migrating at 68 and 64 kilodaltons is observed in conditions such as PSP and CBD. Abnormal tau in both these conditions is composed of four repeat isoforms. Lane 3 shows two bands migrating at 64 and 55 kilodaltons characteristic of conditions like Pick's disease. The tau in this condition is composed of three repeat isoforms. (Courtesy Dr Tamas Revesz, Dept. of Neuropathology, Institute of Neurology, London.)

These changes are associated with nerve cell loss, gliosis, and occasional granulovacuolar or ballooned argyrophilic neuronal degeneration (Jellinger et al., 1995). Ultrastructural and protein chemistry of neurofibrillary tangles allows subdivision of the different taupathies. In contrast to other neurodegenerative disorders with tau pathology like AD, Pick's disease and CBD which are characterized by flame-shaped NFTs, the NFTs of PSP are mainly of the globose type (Fig. 34.1, see colour plate section). They are made up of clusters of straight filaments arranged in circling and interlacing bundles, and have a diameter of 12 to 15 nm (Roy et al., 1974). This filamentous phenotype therefore differs from the paired helical filaments typically found in Alzheimer's disease (Dickson, 1997). Also, on electrophoresis the paired helical filaments of Azheimer's disease are made up of three distinct bands of 55, 64 and 68 kDa and they are composed of all six isoforms of the tau gene, containing both four and three repeat isoforms. In PSP the straight filaments are composed of only two bands at 64 and 68 kDa (Fig. 34.3) and the tau protein is made up only of a subset of tau isoforms consisting only of four repeat tau (Conrad et al., 1997; Morris et al., 1999a). Thus taupathies can be classified according to tau repeat isoforms deposited.

Most cases of PSP are isolated with no family history and it is considered to be a sporadic condition. However, a

number of families have been described with autosomal dominant PSP (Rojo et al., 1999), although neither a linked chromosomal locus nor a causative gene have been identified in any of these (Morris et al., 1999a). As a rare exception recently there has been report of a family with PSP pathology with a novel mutation of exon 10 of the tau gene (Stanford et al., 2000). However, no mutations were identified on sequencing exons 9–13 of the tau gene in over 60 patients with PSP (Baker et al., 1999). This is the area where most of the mutations causing frontotemporal dementia with parkinsonism linked to chromosome 17 had been detected. In fact, no mutations were found on sequencing the entire coding region of the tau gene in any of these PSP patients in whom this was carried out (Baker et al., 1999). Also there appears to be no effect of alpha-synuclein, synphilin, or APOE genotypic variability for the development of PSP (Morris et al., 2000). However, analysis of sporadic PSP cases has led to a suggestion of an association between a polymorphic dinucleotide marker within the tau gene and PSP (Conrad et al., 1997; Higgins et al., 1998, 1999, 2000; Baker et al., 1999; Morris et al., 1999b). In PSP there appears to be an over-representation of the more common allele A0 and the genotype A0/A0 which is not found in PD, MSA or CBD. This may be a predisposing factor to PSP in the same way as as apolipoprotein E e4 allele is in Alzheimer's disease.

Diagnostic tests, diagnostic criteria and differential diagnosis

CT or MRI brain scans of patienst with PSP may show generalized and/or brainstem atrophy mainly of the dorsal midbrain. The degeneration of the superior colliculus gives a flattened appearance of the third ventricle on MRI scans; aqueductal dilatation and increased olivary signal have also been noted (Savoiarda et al., 1994, Schrag et al., 2000). If midbrain atrophy is seen on MRI, differentiation of PSP from PD is possible as MRI is normal but not from other akinetic-rigid syndromes, for example MSA, where similar changes may be present. MR spectroscopy has shown reductions in *N*-acetylaspartate in the lentiform nucleus of PSP patients but not so in PD patients (Federico et al., 1997). Metabolic studies using PET have demonstrated global reduction in cerebral metabolism with particular affectation of the frontal and striatal regions using labelled oxygen or glucose markers (Brooks, 1994). ^{18}F-dopa PET uptake is reduced in the caudate and putamen thus discriminating from PD but not other akinetic-rigid syndromes like MSA which can have a similar picture. Ten to 25% reduction of uptake in caudate and putamen using ^{11}C-raclopride, a D2 receptor ligand, and also for ^{11}C-diprenorphine, an opoid receptor ligand, has been shown in PSP (Brooks, 1994).

Ideal diagnostic criteria for PSP would reliably separate the condition from other akinetic-rigid syndromes, notably Parkinson's disease and also other neurodegenerative disorders with parkinsonism and dementia (Lopez et al., 1999). Many different diagnostic criteria have been proposed to assist the clinician in making an accurate diagnosis of PSP (Lees, 1987; Collins et al., 1995; Tolosa et al., 1994; Litvan et al., 1996a). Of these the National Institute of Neurological Disorders and Stroke and Society for Progressive Supranuclear Palsy, Inc. (NINDS–SPSP) diagnostic criteria are shown in Table 34.4 (Litvan et al., 1996b) which have been validated and also evaluated and found to have good specificity (Lopez et al., 1999). A difficult problem can be with an early case of PSP, before the characteristic clinical features have emerged. The patient may not yet have the typical vertical supranuclear gaze paresis and it is clear that sometimes the development of 'core' diagnostic features may be delayed, or may not occur at all. Thus, in one series comprising 17 pathologically confirmed cases of PSP, 10 of the cases did not have a vertical supranuclear gaze paresis documented antemortem and all 10 of these were misdiagnosed (Daniel et al., 1995). Phenotypic variants for PSP can also cause diagnostic confusion. There have been unusual phenotypes of pathologically confirmed cases, for example, early and severe dementia or that with pure akinesia and unilateral limb dystonia or apraxia leading to a mistaken diagnosis of CBD (Matsuo et al., 1991; Davis et al., 1985; Pharr et al., 1999). PSP is most often clinically misdiagnosed as PD or as cerebrovascular disease (false-negative clinical diagnosis) (Litvan et al., 1996c). In the clinicopathological series of Hughes et al. (1992), mentioned earlier, 25% of the 24 cases clinically diagnosed as having PD, but without Lewy bodies at postmortem, were actually found to have PSP. Conversely, there are pathologically confirmed cases of corticobasal degeneration, multiple system atrophy, dementia with Lewy bodies, prion disease and Whipple's disease, that were clinically misdiagnosed as having PSP (false-positive clinical diagnosis) (Litvan et al., 1996c; Fearnley et al., 1991; Averbuch-Heller et al., 1999). Overall, looking at which factors best differentiate PSP from other related disorders, according to one study, postural instability, leading to falls (typically backwards) within the first year of disease onset, coupled with a vertical supranuclear gaze paresis have been shown to have good discriminatory diagnostic value when comparing PSP with other akinetic-rigid syndromes (Litvan et al., 1997a, b).

Table 34.4. NINDS–SPSP Clinical criteria for the diagnosis of PSP

PSP	Mandatory inclusion criteria	Mandatory exclusion criteria	Supportive criteria
Possible	Gradually progressive disorder Onset age 40 or later Either vertical supranuclear palsy or both slowing of vertical saccades and postural instability with falls <1 year disease onset No evidence of other diseases that could explain the foregoing features, as indicated by exclusion criteria	Recent history of encephalitis Alien limb syndrome, cortical sensory deficits, focal frontal or temporoparietal atrophy Hallucinations or delusions unrelated to dopaminergic therapy Cortical dementia of Alzheimer type Prominent, early cerebellar symptoms or unexplained autonomic dysautonomia	Symmetric akinesia or rigidity, proximal more than distal Abnormal neck posture, especially retrocollis Poor or absent response of parkinsonism to levodopa Early dysphagia & dysarthria Early onset of cognitive impairment including >2 of: apathy, impairment in abstract thought, decreased verbal fluency, utilization or imitation behaviour, or frontal release signs
Probable	Gradually progressive disorder Onset age 40 or later Vertical supranuclear palsy and prominent postural instability with falls <1 year disease onset No evidence of other diseases that could explain the foregoing features, as indicated by exclusion criteria		
Definite	Clinically probable or possible PSP and histopathological evidence of typical PSP		

Source: Adapted from Litvan et al. (1997a).

Management

PSP patients usually do not have significant benefit from dopaminergic medication. In some there may be some initial improvement but this is not sustained. There have been some suggestions that amantadine may be useful with the motor features of PSP but this has not been formally tested in a randomized trial. Cholinergic drugs such as physostigmine have been said to be useful for certain aspects. Following physostigmine administration in PSP patients, a significant reduction in errors of performance was found in four out of seven on neuropsychological tests; however, motor disability was not significantly altered (Blin et al., 1995). Alpha-2 antagonist drugs like idaxozan and efaroxon have been mooted for motor symptoms; however, there is no clear evidence that these are useful (Ghika et al., 1991; Rascol et al., 1998). Botulinum toxin is useful for blepharospasm and less so for levator inhibition or apraxia of eyelid opening. Supportive therapy is the mainstay rather than drug treatment. Physiotherapy and occupational therapy are important to help balance with aids and avoid falls. Early speech therapy and assessment of swallowing function may be helpful in avoiding aspiration and its complications. In some instances feeding may have to be done by means of a percutaneous gastrostomy tube, but such an intervention should take into account the patients and the relatives' wishes with regard to quality of life and how advanced the disease process may be.

PSP in the French West Indies

Clues to the etiology of PSP may come from the recent observation of a large cohort of PSP patients in the small island of Guadelope in the French West Indies (Caparros-Lefebvre et al., 1999). Out of 87 consecutive patients with parkinsonism referred to a single neurological department, 31 had PSP which was a gross over-representation. A case control study established that a higher proportion of the PSP patients, but not the PD patients, consumed herbal teas and tropical fruits. As these are known to contain benzyltetrahydroisoquinolines, this is being considered as the possible exogenous environmental toxin in addition to a possible genetic susceptibility.

Corticobasal degeneration (CBD)

Background

Corticobasal degeneration (CBD), is a rare sporadic neurodegenerative disorder recognized relatively recently with the first description of three patients by Rebeiz, Kolodny and Richardson in 1967. These patients had an asymmetric onset of slow, awkward voluntary limb movement, tremor, dystonic posturing, stiffness, lack of dexterity, and 'numbness or deadness' of the affected limb. The gradual progression of symptoms included gait disorder, limb rigidity, impairment of position sense, and other sensory modalities (Rebeiz et al., 1967, 1968). Cognitive function was said to remain relatively intact (Rebeiz et al., 1967, 1968). A fairly characteristic clinical picture thus emerged. Pathology also was thought to be quite typical with asymmetric frontoparietal cortical atrophy, neuronal loss with associated gliosis, and swollen neuronal cell bodies which were devoid of Nissl substance, thus prompting the descriptive term 'achromatic'. There was considerable loss of pigmented neurons in the substantia nigra in all three patients, variable subcortical neuronal involvement, and secondary corticospinal tract degeneration. Different terms reflecting the cortical and subcortical pathology and the characteristic achromasia appeared in the literature describing clinically similar cases including corticonigral degeneration with neuronal achromasia (Rebeiz et al., 1967, 1968; Lippa et al., 1990), corticobasal ganglionic degeneration (Watts et al., 1985; Riley and Lang, 1988; Greene et al., 1990), corticobasal ganglionic degeneration with neuronal achromasia (Watts et al., 1989), syndrome of progressive rigidity with apraxia (LeWitt et al., 1989) and corticobasal degeneration (CBD) (Gibb et al., 1989; Thompson & Marsden, 1992; Rinne et al., 1994; Wenning et al., 1998), which is the term commonly used now for this condition.

Clinical features

CBD presents in mid to late adult life, with a mean onset of symptoms at 63 years (Wenning et al., 1998). However, cases of CBD have been reported as early as 40 years old and the youngest case with pathologic confirmation was 45 years old. Population prevalence is not known and although both sexes are affected, some have wondered about a slight preponderance of women (Rinne et al., 1994; Schneider et al., 1994; Watts et al., 1997). The clinical phenotype of CBD is well described most recently in three large series of patients (Rinne et al., 1994; Wenning et al., 1998; Kompoliti et al., 1998) one of them with postmortem confirmation (Wenning et al., 1998). The typical presentation is that of an asymmetric progressive akinetic-rigid syndrome poorly responsive to levodopa treatment. The most common initial symptom reported, limb clumsiness, has been observed in 50% of the patients at the first visit in some studies. Rinne et al. (1994) describing a large series of 36 patients with CBD outlined five common types of clinical presentation. The most common presentation was with a 'useless' arm which could be due to combined rigidity, dystonia, akinesia or apraxia, with or without myoclonus. A similar presentation but affecting a leg and presenting as a gait disorder was next most common. Other presentations included a sensory disturbance with pain, or 'clumsiness', or a speech disturbance. Only one patient in this series presented with behavioural changes, and cognitive problems were described as an uncommon presenting feature, being noted only later in the illness. However, of late it is becoming clear that many patients with pathologic findings of CBD may have dementia as the presenting and predominant feature (Grimes et al., 1999).

On examination, limb rigidity or dystonia and focal reflex myoclonus manifesting as an irregular action/postural tremor are the prominent clinical features. Asymmetric limb dystonia is observed in a vast majority of patients (Wenning et al., 1998; Vanek & Jankovic, 2000; Litvan et al., 1997b). The arm is the most frequently affected region and typically is held adducted at the shoulder with flexion of the forearm at the elbow. The fingers are flexed at the metacarpophalangeal joints, often digging into the palms of the hand, sometimes with associated contractures causing fixed posturing (Watts et al., 1997; Vanek & Jankovic, 2000). Akinesia, rigidity and apraxia are the most common findings during the course of CBD (Kumar et al., 1998; Riley & Lang, 2000). Typically, ideomotor and limb kinetic apraxia are seen in patients with CBD with ideational apraxia being less common (Leiguarda et al., 1994). Ideomotor apraxia is manifested by impairment of timing, sequencing, spatial organization, and in copying gestures made by the examiner. In limb kinetic apraxia there is a decrease in dexterity and fine movements. Ideomotor apraxia is usually bilateral and can be tested on the less affected side in advanced cases, as often the severe rigidity and dystonia of the more affected side make apraxia testing virtually impossible (Leiguarda et al., 1994). Orofacial apraxia with impairment of tongue and lip movements is also not infrequent in CBD (Ozsancak et al., 2000). Apart from apraxia, other cortical signs including cortical sensory loss or alien limb phenomenon are often present. The alien limb phenomenon is a failure to recognize ownership of a limb in the absence of visual cues. It is

Table 34.5. Clinical manifestations of CBD

Basal ganglia signs	Cerebral cortical signs	Other manifestations
Akinesia, rigidity	Cortical sensory loss	Postural-action tremor
Limb dystonia	Alien limb phenomenon	Hyperreflexia
Athetosis	Dementia	Impaired ocular motility
Postural instability, falls	Apraxia	Dysarthria
Orolingual dyskinesias	Frontal release reflexes	Focal reflex myoclonus
	Dysphasia	Impaired eyelid motion
		Dysphagia

Source: From Riley et al. (1990).

associated with autonomous activity of the extremity including posturing and levitation. About 40% or so of patients with CBD develop the alien limb phenomenon during the course of the illness, although it is rare on initial presentation (Kumar et al., 1998).

Eye movement abnormalities are also common in CBD and the extraocular movements appear slow and hypometric. Horizontal saccadic latencies are significantly increased in patients with CBD whereas vertical saccades are usually normal at least initially helping to differentiate CBD from PSP (Vidhailet et al., 1994; Litvan et al., 1997b). Slowness of speech production, and dysphonia, echolalia, and palilalia can be present as in PSP and also, like the latter, swallowing disorders are very common, especially in advanced stages.

Riley and colleagues suggested a set of diagnostic criteria for CBD (Table 34.5) (Riley et al., 1990; Riley & Lang, 1993). These consisted of unilateral onset and asymmetric course of an insidious and progressive disorder with the following clinical manifestations which were divided into three main groups: (i) those suggestive of dysfunction of the cerebral cortex namely cortical sensory loss, apraxia, alien limb, frontal release signs; (ii) those attributed to involvement of the basal ganglia namely akinesia, rigidity, limb dystonia, and postural instability and (iii) additional findings which did not localize to either cortex or basal ganglia such as action tremor, hyperreflexia, Babinski signs, oculomotor impairment, dysarthria and dysphagia.

Prognosis

The symptoms are progressive and death usually ensues 5 to 10 years after disease onset. Early onset of bilateral parkinsonism and the presence of a frontal lobe syndrome are associated with shorter survival in CBD patients (Wenning et al., 1998).

Pathology

Superior frontoparietal cortical atrophy in CBD is often asymmetrical and involves perirolandic cortex (Schneider et al., 1994). Microscopic examination reveals neuronal loss and gliosis in cortical and subcortical regions. Superficial spongiosis in atrophic cortical regions is common. Ballooned and achromatic neurons lacking Nissl substance, eosinophilic on H & E staining, and often vacuolar, observed in cortical and subcortical regions are a characteristic feature of CBD (Rebeiz et al., 1968; Watts et al., 1985; Smith et al., 1992). By immunochemistry ballooned neurons do not stain for alpha-synuclein and are sometimes positive for ubiquitin (Smith et al., 1992). However, focal tau immunoreactivity is detected in ballooned neurons as well as in neurofibrillary tangles, neuropil threads, grains, glial, and neuronal inclusions seen in this condition (Dickson, 1999; Feany & Dickson, 1996). They are frequently identified on silver stain preparations and on tau immunohistochemistry within cortical neurons, and subcortical structures including the basal ganglia, and brainstem nuclei. The locus ceruleus, raphe nuclei, tegmental grey matter, and substantia nigra have frequent neurofibrillary lesions that are tau immunoreactive (Feany & Dickson, 1996). Tau pathology in glial cells is also expressed in CBD (Dickson, 1999; Feany & Dickson, 1996). Tau-positive astrocytic plaques are argyrophilic structures identified in many cases of CBD. They are thought to be characteristic of CBD although they have also been observed in PSP (Dickson, 1999).

There appears to be considerable neuropathological overlap between Pick's disease, progressive supranuclear palsy (PSP), and CBD (Dickson, 1999; Gearing et al., 1994). All three conditions may have ballooned neurons along with variable degeneration of the substantia nigra, basal ganglia, and tau-positive inclusions (Gearing et al., 1994; Schneider et al., 1994). However, the temporal cortex as

well as the hippocampus that are usually involved in Pick's disease are spared in CBD and Pick bodies, which are characteristic of Pick's disease, are rarely observed in CBD. Also in CBD astrocytic tau plaques are seen, while in PSP there are tufted astrocytes (Fig. 34.2, see colour plate section) with tau within the distal and proximal processes (Dickson, 1999). Electrophoretic pattern of tau can separate Pick's disease from CBD, PSP (and frontotemporal dementia). Only Pick's disease has two bands migrating at 64 and 55 kdalton while in the others there are 60 and 64 kdalton bands (Fig. 34.3) (Dickson, 1999; Dickson et al., 2000). Both CBD and PSP have four repeat tau (Dickson et al., 2000).

It appears to be a sporadic condition, although rare familial cases have been reported and there is a suggestion that like PSP those with the specific tau haplotypes may be at risk factor for CBD (Di Maria et al., 2000; Houlden et al., 2001). Tau sequencing in 57 neuropathologically confirmed cases failed to reveal the presence of pathogenic mutations; however, analysing tau polymorphisms in CBD cases vs. controls the frequency of H1, H1/H1 was significantly increased. CBD and PSP thus seem to share a common genetic risk factor (Houlden et al., 2001).

Differential diagnosis

The characteristic features of CBD are so distinctive that it is often possible to make a confident clinical diagnosis (Feifel et al., 1994; Litvan, 1997). However, prototypic phenotypes may have atypical (non-CBD) pathology (Boeve et al., 1999; Bhatia et al., 2000). Examples of these CBD look-alikes include vascular lesions, leukodystrophies, Pick's and Alzheimer's disease, PSP and other etiologies (Bhatia et al., 2000). On the other hand, there are also examples of atypical phenotypes, for example presenting with early dementia, who have classic CBD pathology (Bergeron et al., 1996). CBD appears to be underdiagnosed, particularly in the early stages of presentation (Wenning et al., 1998; Litvan et al., 1997b). When it presents with the motor disorder phenotype, PSP is the commonest misdiagnosis (Litvan et al., 1997b). Differentiating the two can be difficult; however, CBD patients presented with lateralized motor (e.g. parkinsonism, dystonia or myoclonus) and cognitive signs (e.g. ideomotor apraxia, aphasia or alien limb), while PSP patients often had severe postural instability at onset, symmetric parkinsonism, vertical supranuclear gaze palsy, speech and frontal lobe-type features. Litvan et al. (1997b) have suggested that limb dystonia, ideomotor apraxia, myoclonus, and asymmetric akinetic-rigid syndrome with late onset of gait or balance disturbances were the best predictors for the diagnosis of CBD.

However, as mentioned recently, it has become clear that a fair proportion of patients with pathological proven CBD may have dementia as their presenting and/or as the main feature (Grimes et al., 1999). Thus conditions like Pick's disease, Alzheimer's disease and frontotemporal dementia which can have some extrapyramidal manifestations also come into the differential (Boeve et al., 1999; Litvan et al., 1997b).

Radiographic studies may help but are not by themselves diagnostic. Cortical asymmetry with fronto-parietal atrophy on CT or MRI may suggest CBD. Compared with CBD, MRI in patients with PSP shows atrophy in the midbrain (Schrag et al., 2000). AD, on the other hand, may be differentiated from CBD by recognizing diffuse temporal and hippocampal atrophy. CBD patients show a global reduction of oxygen and glucose metabolism demonstrated by FDG positron emission tomography (PET) scans most prominent in the cerebral hemisphere contralateral to the most affected limb (Brooks, 2000). There is a corresponding reduction of CBF most evident in the frontoparietal, medial frontal, and temporal cortical regions (Okuda et al., 1999; Laureys et al., 1999; Sawle et al., 1991). Dysfunction of the nigrostriatal dopaminergic system has been demonstrated by decreased ^{18}fluorodopa (F-Dopa) uptake in the striatum with PET, and reduced postsynaptic striatal D2 receptor binding of [^{123m}I]-iodobenzamide (IBZM) on SPECT scanning. Caudate and putamen are similarly affected in CBD, whereas in PD F-Dopa uptake is selectively reduced in the putamen (Brooks, 2000). The characteristic pattern of asymmetrically reduced frontoparietal cerebral cortical metabolism and/or CBF coupled with bilateral reduction of F-Dopa uptake in the caudate and putamen provides strong supportive evidence in a patient with a clinical diagnosis of possible CBD (Brooks, 2000).

Therapy

Pharmacotherapy for CBD has generally been of limited benefit. CBD patients show limited or no beneficial response to carbidopa/levodopa and other dopaminergic agents. However, these drugs are worth trying as some improvement in clinically diagnosed CBD occurred in 24% of patients receiving carbidopa/levodopa in one report (Kompoliti et al., 1998). Dopamine agonists provide less clinical improvement than carbidopa/levodopa and are more likely to produce side effects. Clonazepam can be beneficial for treatment of the action tremor and myoclonus. Baclofen and tizanidine may improve rigidity and tremor, but they have only a modest effect. Anticholinergics have been reported to yield benefit in a

small number of patients but their benefit wanes quickly and they are poorly tolerated (Kompoliti et al., 1998). Likewise, amantadine is of little or no benefit and may produce side effects. Botulinum toxin injections may be useful in the treatment of painful focal upper limb dystonia and blepharospasm (Vanek & Jankovic, 2000).

As for PSP, other aspects of patient care, not involving pharmacotherapy, are important for these CBD patients and their carers. Physiotherapy is useful for maintenance of mobility and may help prevent contractures. Speech therapy may help optimize speech function and guard against aspiration secondary to swallowing difficulty. Unfortunately, the disease is relentlessly progressive to a state of bilateral rigid immobility, and the patients usually die from aspiration pneumonia or urinary tract infection.

Frontotemporal dementia parkinsonism-chromosome 17

Frontotemporal dementia is a condition characterized by a behavioural disorder of insidious onset and variable progression. Clinically, its early features reflect frontal lobe dysfunction characterized by personality change, worsening memory and executive functions, and stereotypical and perseverative behaviour. Parkinsonism, postural instability and supranuclear gaze palsy are other characteristics showing similarities to other taupathies like PSP and CBD. Progressive dysphasia is prominent in some kindreds and signs of anterior horn disease may also be distinctive features. The condition can be rapidly progressive with the parkinsonism being unresponsive to levodopa therapy.

Pathologically, there is degeneration of the neocortex with marked frontal and temporal lobe atrophy and involvement of the subcortical basal ganglia and brainstem nuclei which led to the use of the term pallido-ponto-nigral degeneration (PPND) to describe some of these families (Wzolek et al., 1992). In cases where family aggregation is observed, it is inherited as an autosomal dominant, age-dependent disorder. Other terms for such families had included familial Pick's disease and disinhibition–dementia–parkinsonism–amyotrophy complex (Wilhelmsen–Lynch disease). However, there was linkage to chromosome 17q21 in many of the different kindreds (Lynch et al., 1994, Wilhelmsen et al., 1994; Wijker et al., 1996; Reed et al., 1998) described above, which led to the search of primary genetic etiology of these conditions. It became clear that, in all such families there was significant tau deposition in those where there was pathology, and they were all related disorders now called frontotemporal dementia parkinsonism-17 (FTDP-17). The link with tau was further established, as the tau gene was known to be located on chromosome 17q and it is clear tau gene mutations cause FTDP-17 (Poorkaj et al., 1998). Hutton et al. (1998) described three missense mutations and three mutations in the 5′ splice site of exon 10. Subsequently, many more different mutations have been found associated with FTDP (Dumanchin et al., 1998; Spillantini et al., 1998a, b; D'Souza et al., 1999). The location of most mutations in the microtubule binding region of the tau gene (Dumanchin et al., 1998) suggests that disruption of this process is likely to be central to the neurodegenerative process. It has also confirmed that abnormal tau deposition in this disorder leads to neurodegeneration (Spillantini et al., 2000). An other possibility is a proapoptotic effect by the tau mutations (Furukawa et al., 2000). Bird et al. (1999) in a clinical pathological comparison of three families with frontotemporal dementia and with an identical mutation in the tau gene (P301L) found marked clinical and pathological variabity in these families. This suggested that unidentified environmental and/or genetic factors were producing phenotypic variability on the background of an identical mutation. PET scanning in kindreds said to have pallido-ponto-nigral degeneration type of FTDP-17 showed a reduction of Fluoro-dopa uptake, which affected both caudate and putamen (Pal et al., 2001). 11C-Raclopride scans showed normal to elevated striatal D2-receptor binding and cerebral glucose metabolism globally reduced but with maximal involvement of frontal regions (Pal et al., 1999). The fact that there was severe presynaptic dopaminergic dysfunction with intact striatal D2 receptors in these patients suggested that the dopa unresponsiveness is probably a result of pathology downstream to the striatum. The pattern of presynaptic dysfunction contrasts with that seen in idiopathic parkinsonism, where the putamen is affected more than the caudate nucleus, but is similar to that in other atypical Parkinsonian conditions such as PSP. The differential diagnosis is from other conditions presenting with dementia and parkinsonism like Pick's disease, PSP, CBD and rarely Alzheimer's. A family history is usually lacking in these disorders compared to FTDP-17. However, rarely familial CJD or prion disease can present with a phenotype of FTDP-17. Recently, a family with CJD associated with a point mutation at codon 183 of the prion protein gene presented at median age of 44 years with behavioural disturbances as the predominant presenting symptom. Eight of the nine patients manifested parkinsonian signs and dementia thus resembling FTDP-17 (Nitrini et al., 2001).

Multiple system atrophy (MSA)

Background

Multiple system atrophy (MSA) is a sporadic progressive degenerative neurological disorder characterized clinically by the combination of varying degrees of parkinsonism, autonomic dysfunction and impaired cerebellar function (Quinn, 1989). Early descriptions focused on the most conspicuous clinical manifestation, so that it was variously described as striatonigral degeneration (SND), (predominant parkinsonism with a poor response to levodopa), Shy–Drager syndrome (SDS) (parkinsonism and/or cerebellar syndrome with predominant autonomic dysfunction) and sporadic olivopontocerebellar atrophy (sOPCA) (predominant cerebellar dysfunction). Although sOPCA was described in 1900 by Dejerine and Thomas, it was not until the 1960s that other presentations of MSA were documented by Shy and Drager (1960), Adams et al. (striatonigral degeneration, 1961) and Graham and Oppenheimer (1969). The term MSA thus describes a syndrome with features overlapping with SDS, SND and sOPCA (Quinn, 1989). The discovery of the characteristic histology marked by the glial cytoplasmic inclusions by Papp and Lantos in 1989 which are present in all these three types defined MSA as a clinico-pathological entity. MSA seems to be greatly under-recognized and, in one series of 35 pathologically proven cases of MSA, 30% had an incorrect diagnosis of Parkinson's disease (PD) at the time of death (Wenning et al., 1995).

The population prevalence of MSA has been estimated at 4.4 per 100 000, thus representing 2.4% of cases of parkinsonism (Schrag et al., 1999). The disease affects both men and women usually starting in the sixth decade, the median age at onset being 54 years. Onset before age 30 years has not been described and the incidence of the disease appears to decline after peaking in the early 50s. Median survival from first symptom to death was 9.5 years in one large clinical series (Wenning et al., 1994) but only 6.2 years in a large retrospective meta-analysis of pathologically proven cases from the literature (Ben Shlomo et al., 1997).

Clinical features

The clinical features and their frequency are listed, from a report of 203 pathologically verified cases of MSA, in Table 34.6 (Wenning et al., 1997). Bradykinesia, rigidity, and postural and rest tremor as well as dysequilibrium and gait unsteadiness characterize the parkinsonism associated with MSA. Although 67% of patients have resting tremor, a

Table 34.6. Clinical features in 203 cases of MSA

Features	Frequency (%)	CI (95%)
Autonomic symptoms		
Urinary incontinence	55	(48–62)
Postural faintness	51	(44–58)
Impotence	47	(37–56)
Recurrent syncope (>2)	18	(12–23)
Urinary retention	18	(13–24)
Fecal incontinence	12	(8–17)
Parkinsonism		
Akinesia	83	(77–88)
Tremor*	67	(60–73)
Present at rest	39	(32–46)
Pill-rolling	8	(5–12)
Jerky	3	(1–6)
Not specified	25	(18–32)
Rigidity	63	(56–70)
L-Dopa response		
Best Poor	72	(62–83)
Good	28	(17–38)
Last Poor	95	(75–92)
Good	5	(1–12)
Dyskinesias	27	(17–38)
Orofacial	15	(8–25)
Limbs	10	(4–19)
Fluctuations	24	(15–35)
Cerebellar signs		
Gait ataxia	49	(42–56)
Limb ataxia	47	(40–54)
Intention tremor	24	(18–30)
Nystagmus	23	(18–30)
Pyramidal signs		
Hyperreflexia	46	(39–53)
Extensor plantar response	41	(34–48)
Spasticity	10	(6–15)
Other features		
Intellectual deterioration		
Mild	22	(17–29)
Moderate	2	(1–5)
Severe	0.5	(0–3)
Stridor	13	(9–18)
Dystonia	12	(8–17)
Anisocoria	8	(5–12)
Contractures	7	(4–11)

Notes:

* Some patients had more than one type of tremor.

CI, confidence interval.

Source: From Wenning et al. (2001).

classic pill rolling rest tremor typical of PD is almost never or very rarely (8%) present in MSA patients. Up to 90% of patients with the parkinsonian presentation (MSA-P) treated with levodopa do not have a sustained response over the long term although there may be some initial benefit. Also unusual levodopa-induced dyskinesia often involving the orofacial region, as a dystonic grimacing of one side of the face, occur in MSA (Wenning et al., 1994). The cerebellar disorder consists of gait ataxia commonly leading to early falls when associated with the extrapyramidal loss of postural reflexes. Limb kinetic ataxia, scanning dysarthria and cerebellar oculomotor disturbances are other features of cerebellar dysfunction. Autonomic failure in MSA is manifested predominantly as symptomatic orthostatic hypotension which is defined as a 20 mm Hg fall of systolic or 10 mm Hg fall of diastolic blood pressure. Erectile disturbance is common and may be the earliest feature of MSA in males. Other features include increased constipation, hypohidrosis or anhidrosis. Urinary bladder disturbances are also common including urinary urgency, frequency, nocturia and urge incontinence.

Mild cognitive problems occur in about 22% of cases but moderate to severe dementia rules against the diagnosis of MSA. Apart from the main features mentioned above, softer signs or 'red flags' as they are called by Quinn (1995) often indicate the diagnosis. These include REM sleep behaviour disorder, inspiratory sighs, snoring, stridor, myoclonus, contractures and the so-called disproportionate anterocollis where the head is severely flexed forward with a fairly upright stance or/and the 'Pisa' syndrome where the patient leans to one side. Diagnostic criteria for MSA (Gilman et al., 1998) are shown in Tables 34.7, 34.8 and 34.9, which have to be used together.

Differential diagnosis

The difficulty most commonly faced is to differentiate MSA from PD or PSP. Colosimo et al., in 1995 attempted to identify factors that could assist in the early differentiation of MSA-P from PD and PSP and suggested that, in patients with symmetric onset, rapid progression, lack of tremor, orthostasis and little benefit from levodopa the diagnosis of MSA should be very carefully considered (Colosimo et al., 1996). Wenning et al. (2000) posing the same question developed a model based on the emergence of features within the first five years of the illness. The four features selected included: presence of autonomic features (2), poor initial response to levodopa (2), early fluctuations (2) and initial rigidity (2). Of note, 23% of PD subjects' initial response to levodopa was poor, while 58% of MSA cases had a poor response. Dementia and psychiatric symptoms were more common in PD than MSA. Speech impairment and axial instability were almost universal in the MSA cases. Autonomic failure occurred in 84% of the MSA cases but also in 26% of the PD cases. These findings should be considered when making the diagnosis in a given patient.

Diagnostic investigations

The diagnosis of MSA is thus largely clinical, based on the history and examination. No investigation is diagnostic by itself but diagnostic tests may help in supporting the clinical impression and help with excluding the differential diagnosis. In patients with urogenital complaints, external sphincter electromyography frequently shows prolonged and polyphasic muscle potentials consistent with deinervation and reinervation of voluntary sphincter muscles. However, sphincter EMG is a sophisticated technique that is not widely available. Also, because interpretation of the results requires great caution, since it may be affected by previous traumatic childbirth, abdominal, rectal, or retropubic prostatic surgery, and also since it is often abnormal in PSP (Valldeoriola et al., 1995) it is not particularly helpful in distinguishing between MSA and PSP. Nonetheless, if correctly undertaken and interpreted, the presence of an abnormal sphincter EMG can still be a useful ancillary investigation pointing away from idiopathic PD (Palace et al., 1997; Tison et al., 2000).

CT brain scans may show infratentorial atrophy in MSA patients. In almost 90% of patients with MSA brain, MRI shows characteristic changes in the striatum, brainstem and cerebellum (Schrag et al., 1998, 2000; Schultz et al., 1999). In T_2-weighted images there is frequently a hyperintense signal seen adjacent to the posterolateral putamen which itself displays a hypointense signal due to atrophic changes. What is the morphological basis of the hyperintense band is not entirely certain but it may be due to activated microglia seen adjacent to atrophic putamenal tissue. This appearance is a useful diagnostic marker with an estimated sensitivity of 93% and specifity of 88%. Another characteristic appearance is the so called 'hot cross bun' sign of MSA (Fig. 34.4); on T_2-weighted images of the brainstem, a hyperintense signal in the shape of a cross seen in the pons (Schrag et al., 1998). MR spectroscopy has shown reduced *N*-acetylcysteine as a metabolic correlate of neuronal cell loss in MSA (Davie et al., 1995) but, as yet, this has limited diagnostic value in a given patient. Functional imaging may be a useful adjuvant in support of the diagnosis but the changes are not specific

Table 34.7. Diagnostic categories of MSA

I. Possible MSA
One criterion plus two features from separate other domains. When the criterion is parkinsonism, a poor levodopa response qualifies as one feature (hence only one additional feature is required)

II. Probable MSA
Criterion for: autonomic failure/urinary dysfunction plus poorly levodopa responsive parkinsonsim or cerebellar dysfunction

III. Definite MSA
Pathologically confirmed by the presence of a high density of glial cytoplasmic inclusions in association with a combination of degenerative changes in the nigrostriatal and olivopontocerebellar pathways

Table 34.8. Exclusion criteria for the diagnosis of MSA

I. History
Symptomatic onset under 30 years of age
Family history of a similar disorder
Systemic disease or other identifiable causes for features listed in Table 34.7
Hallucinations unrelated to medication

II. Physical examination
DSM criteria for dementia
Prominent slowing of vertical saccades or vertical supranuclear gaze palsy
Evidence of local cortical dysfunction such as aphasia, alien limb syndrome, and parietal dysfunction

III. Laboratory investigation
Metabolic, molecular genetic, and imaging evidence of an alternative cause of features listed in Table 34.3

Source: From Gilman et al. (1998).

Table 34.9. Clinical domains, features and criteria used in the diagnosis of MSA

I. Autonomic and urinary dysfunction
A. Autonomic and urinary features
   1. Orthostatic hypotension by (20 mm Hg systolic or 10 mm Hg diastolic)
   2. Urinary incontinence or incomplete bladder emptying
B. Criterion for autonomic failure or urinary dysfunction in MSA
Orthostatic falls in blood pressure by (30 mm Hg systolic or 15 mm Hg diastolic) or urinary incontinence (persistent, involuntary partial or total bladder emptying, accompanied by erectile dysfunction in men) or both

II. Parkinsonism
A. Parkinsonian features
   1. Bradykinesia (slowness of voluntary movement with progressive reduction in speed and amplitude during repetitive actions)
   2. Rigidity
   3. Postural instability (not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction)
   4. Tremor (postural, resting or both)
B. Criterion for parkinsonism in MSA
   Bradykinesia plus at least one of items 2 to 4

III. Cerebellar dysfunction
A. Cerebellar features
   1. Gait ataxia (wide based stance with steps in irregular length and direction)
   2. Ataxic dysarthria
   3. Limb ataxia
   4. Sustained gaze-evoked nystagmus
Criterion for cerebellar dysfunction in MSA
Gait ataxia plus at least one of items 2 to 4

IV. Corticospinal tract dysfunction
A. Corticospinal tract features
   1. Extensor plantar responses with hyperreflexia
B. Corticospinal tract dysfunction in MSA: no corticospinal tract features are used in defining the diagnosis of MSA

Notes:
A feature (A) is characteristic of the disease and a criterion (B) is a defining feature or composite of features required for diagnosis.

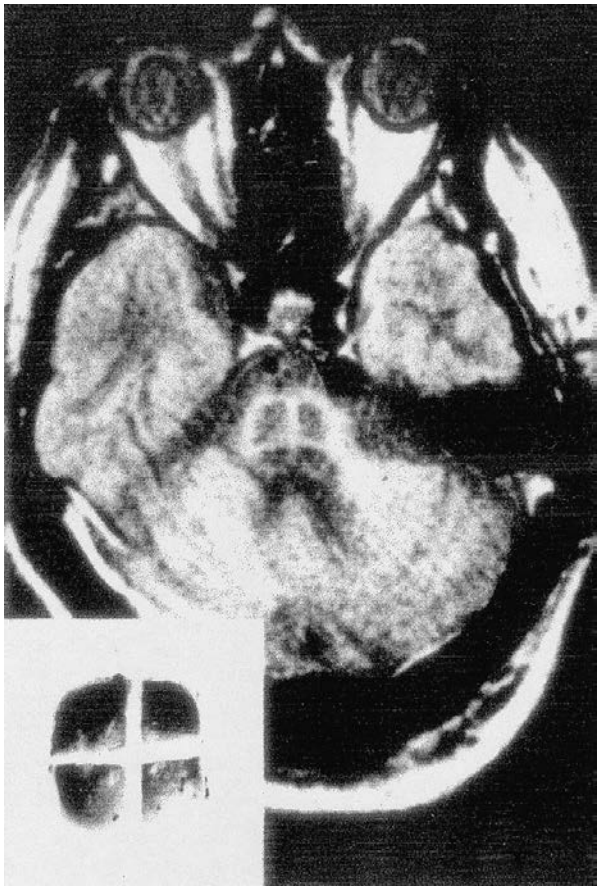

Fig. 34.4. MRI T_2-weighted image of the brainstem in a patient with multiple system atrophy showing infratentorial atrophy and typical signal change in the pons in the form of a cross resembling that seen on hotcross buns (inset) which are baked typically over Easter. (Courtesy Prof. Niall Quinn, Institute of Neurology, Queen Square, with permission from Journal of Neurology, Neurosurgery and Psychiatry.)

for MSA. IBZM SPECT shows reduced striatal dopamine D2 receptor binding in MSA and may predict l-dopa unresponsiveness with these patients turning out to have either MSA-P or PSP (Schulz et al., 1994; Schwarz et al., 1998). However, dopamine transporter ligands such as beta CIT so far are not particularly useful for the differential diagnosis (Brucke et al., 1997; Pirker et al., 2000). Fluorodopa PET scanning shows reduced uptake both in the putamen and caudate, a pattern different from PD but which may be seen with other atypical parkinsonian conditions like PSP or CBD. Increased striatal binding of both D2 and D1 receptor ligands (11C-SCH 23390) has been noted (Brooks et al., 1992; Momose et al., 1997; Shinotoh et al., 1993). On the other hand, there is decreased uptake in the putamen and caudate with opiod receptor ligand ^{11}C-diprenorphine (Burn et al., 1995). Specialized imaging can thus suggest that the patient has an atypical parkinsonian condition and not Parkinson's disease but cannot definitely differentiate between the different atypical parkinsonian disorders.

Pathology

Pathologically, there is neuronal loss and gliosis in substantia nigra, striatum (mainly posterior putamen), inferior olives, cerebellar Purkinje cells and pontine nuclei, and the intermediolateral cell columns and Onuf's nucleus of the spinal cord, to varying degrees according to clinical emphasis (Terao et al., 1994; Daniel, 1992). The current nomenclature is MSA-P, in which parkinsonism is more prominent, and MSA-C, in which cerebellar dysfunction is more prominent. The identification of a common pathology, the presence of glial cytoplasmic inclusions (GCIs) in oligodendrocytes (Papp et al., 1989), in these syndromes confirmed the suspicion that these disorders are manifestations of the same process. Glial inclusion formation which is thus characteristic of MSA has been added to the consensus diagnostic criteria of definite MSA (Gilman et al., 1998). GCIs are argyrophilic and half-moon, oval or conical in shape (Fig. 34.5, see colour plate section). They are distributed selectively in the basal ganglia, supplementary and primary motor cortex, reticular formation, bases pontis, the middle cerebellar peduncle and the cerebellar white matter (Lantos, 1998; Papp & Lantos, 1994). The origin of the GCIs is not known, but they are known to consist of filaments 20–30 nm in diameter and are antigenic for ubiquitin and tau (Lantos, 1998). The tau in MSA, however, resembles nomal adult tau (Cairns et al., 1997; Spillantini et al., 1998a, b; Takeda et al., 1997). Recently, alpha-synuclein has been observed in both neuronal and glial cytoplasmic inclusions in MSA brains (Fig. 34.3) (Wakabayashi et al., 1998; Arima et al., 1998; Tu et al., 1998). This has led to the notion that MSA belongs to the group of synucleinopathies like PD and DLB (Spillantini, 1999). What the role of alpha-synuclein is in the pathogenesis of MSA is not clear. Usually, this protein is found in the soluble fraction of neuronal cytoplasm, however in pathological states for example MSA, alpha-synuclein forms insoluble aggregates. Whether this is a primary event or a secondary epiphenomenon of MSA pathology remains to be discovered.

MSA is known to be a sporadic condition and abnormalities of alpha-synuclein gene causing autosomal dominant Parkinson's disease (A53T and A30P) have not been found in confirmed cases of MSA (Ozawa et al., 1999; Kruger et al.,

1998) suggesting that these mutations are not the pathogenic cause of MSA.

Therapy

Although MSA patients have a poor or unsustained response to levodopa almost 30% do have some benefit initially and hence it is worth trying (Wenning et al., 1994). In fact as per one report about 5% of cases still responded to levodopa after 5 years of treatment (Wenning et al., 1994). Patients with MSA also develop dyskinesias but unlike PD these are dystonic and often involve the face (Wenning et al., 1994). Dopamine agonists are generally not beneficial and poorly tolerated. Amantidine has not been found to be useful (Colosimo et al., 1996). The parkinsonian features of MSA are not helped by stereotactic surgery including pallidotomy and subthalamic nucleus stimulation and, in fact, the suspicion of MSA is a contraindication for these procedures. Management of orthostatic hypotension can be difficult. Increased salt intake, elastic stockings and head-up tilt of about 30 degrees are useful physical measures. Drugs like fludrocortisone, ephedrine and octreotide may be useful. For bladder urgency and urge incontinence, oxybutinin can be helpful. Physical therapy including use of walking aids and speech as well as occupational therapy can be very useful in these cases usually more so than drug treatments.

Dementia with Lewy bodies (DLB)

This condition which used to be called diffuse Lewy body disease has recently been defined as a clinical pathological entity (McKeith et al., 1996) in a consensus report of an international consortium. The syndrome is characterized by cognitive deficit and parkinsonism. Onset age is between 50 and 85 years. Cognitive impairment in DLB resembles that seen in Alzheimer's disease (AD), but memory loss is less marked early on; however, differentiation on clinical grounds alone may be difficult. Fluctuations in cognitive state often present as confusional states. Pathologically there are Lewy bodies, alpha-synuclein immunoreactive Lewy neuritis and neuronal loss in the neocortex and subcortical nuclei. Thus dementia with Lewy bodies is a synucleinopathy (Spillantini, 1999). Diffuse and neuritic amyloid plaques and neocortical neurofibrillary tangles can also be seen in about a quarter of cases. What is the relationship between Lewy bodies and the Alzheimer's type of change is still unresolved. However, it is clear that the clinical syndrome of dementia, psychosis and autonomic failure can occur with the presence of Lewy bodies alone (without significant Alzheimer's changes). Compared to Alzheimer's disease on formal neurospsychometry, attention and working memory appears to be disproportionately impaired in DLB, and these patients are worse off in visuospatial and constructional tasks and perception (Gnanlingham et al., 1997; Calderon et al., 2001). About 80% with DLB will develop extrapyramidal features in the course of the disease (McKeith et al., 1996). The parkinsonism in DLB may differ somewhat from PD, with symmetrical signs, uncommon resting tremor, frequent myoclonic jerks and an unpredictable response to levodopa. Recurrent visual hallucinations, depression and delusions are common, as is a REM sleep disorder which may precede the other features (Boeve et al., 1999). Autonomic dysfunction can be present leading to syncope and falls. The clinical criteria for the diagnosis of DLB have been suggested (McKeith et al., 1996). In addition to the progressive cognitive decline, two of the following are required for the diagnosis of 'probable' DLB (one for possible DLB): (i) Fluctuating course with pronounced variations in attention and alertness; (ii) recurrent, well-formed visual hallucinations and (ii) motor features of parkinsonism. Supportive features (not required for the diagnosis) include repeated falls, syncope, transient loss of consciousness, neuroleptic sensitivity, systematized delusions and hallucinations in other modalities. Clinically, differentiation from other Parkinsonian-plus syndromes can be difficult. Both MSA, if the autonomic features are present, and PSP, if there is dementia and supranuclear gaze palsy which can sometimes be seen in DLB (Lewis & Gawel, 1990), can come into the differential as can different dementing disorders including Alzheimer's and Pick's disease and corticobasal degeneration to name a few. However, as yet there are no specific antemortem biological markers for DLB and the clinical differentiation between these disorders remains a diagnostic challenge. Recent advances in structural and functional imaging can be useful but not definitive in making the diagnosis. Structural brain imaging shows generalized atrophy in DLB and in 50% or so the medial temporal lobe appears to be relatively preserved unlike Alzheimer's disease (Barber et al., 1999). Dopaminergic dysfunction in DLB can be shown by SPECT studies using dopamine transporter and this may help differentiate it from AD (Walker et al., 1999) but not from other parkinsonian syndromes.

Secondary/symptomatic parkinsonism

These are listed in Table 34.1 and some of them will be discussed in the section below.

Postencephalitic parkinsonism (PEP) and other infections

Encephalitis lethargica or postencephalitic parkinsonism (PEP) occurring after the pandemics of influenza beween 1918 and 1926 is well recognized (Calne & Lees, 1988). The parkinsonism in these cases usually occurred after a latent period, sometimes of many years. The presence of associated features such as oculogyric crises, blepharospasm and rarely, chorea, tic, and dystonia helped differentiate this disorder from PD. However, there appear to be many similarities between PEP and PSP and the Parkinson–dementia complex of Guam both clinically and pathologically (Geddes et al., 1993). Neuropathologists have great difficulty differentiating PSP and PEP on postmortem brains (Geddes et al., 1993). However, when clinical data is available, the sensitivity and reliability of diagnosis of PEP improves significantly (Litvan et al., 1996a, b). All three conditions display neurofibrillary tangles in subcortical and cortical areas and therefore a common etiology has been suspected but seems unlikely. New sporadic cases of PEP still occur rarely (Howard & Lees, 1987). However, other types of encephalitis such as Japanese B encephalitis in south east Asia, Western Equine encephalitis and others can also cause parkinsonism. Unlike encephalitis lethargica where there was a long latency period, in Japanese B and others, mentioned earlier the parkinsonism appears as the acute phase is resolving. Creutzfeldt–Jacob disease can present as a rapidly progressive parkinsonian syndrome with dementia and myoclonus associated (Brown et al., 1993). Parkinsonian signs and dementia resembling FTDP-17 have been described in a familial CJD with prion gene mutation (Nitrini et al., 2001).

Drug-induced parkinsonism

Perhaps the commonest secondary cause of parkinsonism is due to drugs. Neuroleptic drugs or dopamine receptor blockers are the usual culprit. Mostly, these drugs have been used to treat psychosis or other psychiatric disorders but it is important to remember that these drugs can be used for other indications, for example metoclopromide which is used to treat gastrointestinal symptoms and is a powerful D2 receptor blocking agent. The prevalence of neuroleptic-induced parkinsonism is estimated variably from 5% to 60% in those treated with these drugs. Female more than male, age, and possible genetic tendency are possible risk factors. Neuroleptic drug may be unmasking latent Parkinson's disease. One study by Rajput et al. (1982) showed that some patients who recovered from neuroleptic-induced parkinsonism had pathological changes of PD on postmortem.

Also, apart from neuroleptics, calcium channel blockers like cinnarazine and flunnarazine and even serotonin reuptake inhibitors (SSRIs) can induce parkinsonism.

Vascular parkinsonism

The clinical features here are fairly characteristic with gait difficulty freezing being the prominent feature as well as postural reflex impairment. Apart from that urinary and cognitive symptoms may be present. As there is no true bradykinesia involving the upper limbs some refer to this condition as a form of pseudo-parkinsonism (Quinn, 1995). There is usually no tremor and the response to levodopa is poor. Imaging will show multiple lacunes involving the basal ganglia. Rarely, a frontal tumour like a meningioma or other mass lesion may present with a similar clinical picture. Removal of the tumour can lead to resolution of the parkinsonian features, which must be caused by indirect pressure effects on the dopaminergic nigrostriatal pathway.

Toxins

A variety of toxins and heavy metals can cause parkinsonism. Exposure to manganese causing toxicity in miners without proper protective gear produces an atypical parkinsonian syndrome manifested as akinesia, postural reflex loss usually without tremor (Pal et al., 1999). There are dystonic features affecting the feet and legs and causing a peculiar gait with the patients walking on their toes, referred to as 'cock-walk'. The early phase of the intoxication may be characterized by psychic, non-motor signs. The neurological syndrome does not respond to levodopa. If these extrapyramidal findings are present, they are likely to be irreversible and even progress after termination of the exposure to manganese (Pal et al., 1999). Imaging of the brain may reveal MRI signal changes in the globus pallidus, striatum, and midbrain. Positron emission tomography reveals normal presynaptic and postsynaptic nigrostriatal dopaminergic function (Pal et al., 1999). Gliosis in the pallidal segments underlies the well-established phase of the intoxication. The mechanism of toxicity is not clear and oxidative stress is considered as a possibility.

Carbon monoxide, cyanide, MPTP, n-hexane and organophosphates (Bhatt et al., 1999) all can produce a parkinsonian syndrome. Bhatt et al. (1999) described five patients with exposure to organophosphates who acutely

developed an atypical parkinsonian syndrome poorly responsive to levodopa which reversed in four patients completely after withdrawal from exposure and one patient experienced repeated episodes of parkinsonism with inadvertent re-exposure.

Trauma

A direct link between trauma and parkinsonism has been long debated (Stern, 1991; Jankovic, 1994). However, it is widely accepted that repeated head injury for example in boxers leads to what is described as the chronic traumatic brain injury (CTBI) syndrome (Jordan, 2000). This presents with varying degrees of motor, cognitive, and/or behavioural impairments. Parkinsonism is a feature of the motor syndrome, along with gait imbalance and loss of postural reflexes. The severe form of CTBI is referred to as 'dementia pugilistica'. The diagnosis of CTBI is dependent upon documenting a progressive neurological condition that is consistent with the clinical symptomatology of CTBI attributable to brain trauma and unexplainable by an alternative pathophysiological process (Jordan, 2000). Pathologically, CTBI shares many characteristics with Alzheimer's disease (i.e. neurofibrillary triangles, diffuse amyloid plaques, acetylcholine deficiency, and/or tau immunoreactivity) (Jordan, 2000). The mainstay of treatment of CTBI is prevention; however, medications used in the treatment of Alzheimer's disease and/or parkinsonism could be tried, although no controlled trials have been done.

More contentious is the notion that head injury can cause or precipitate Parkinson's disease. Although trauma is mentioned in epidemiological studies, there is only a weak causal relationship between trauma and PD as a result of recall bias, time between injury and onset of the condition and other factors. Long-term prospective data fail to corroborate an increased incidence of PD among a cohort of head injury patients (Williams et al., 1991). There are some exceptions. Recently, Bhatt et al. (2000) reported three patients who developed a rapidly evolving post-traumatic akinetic-rigid syndrome following head injury, the clinical manifestations of which were similar to parkinson's disease, including response to levodopa. In all three cases imaging studies showing traumatic damage to the substantia nigra; however, the parkinsonian syndrome appeared only after a delay of 1–5 months after the injury. However trauma remains a rare cause of parkinsonism. Cardoso & Jankovic (1995), have proposed that even peripheral injury can result in movement disorders including parkinsonism. However, not all agree with this assumption. For example, recently there was a report of parkinsonism following electric injury to the hand (Morris et al., 1998) but this claim was refuted by Quinn and Marganore (2000), who suggested that this was a coincidence.

Hereditary/heredodegenerative disorders

These have been listed in Table 34.1 and many of these disorders are detailed elsewhere in other chapters. A few conditions will be mentioned briefly here. About 10% or 50 of patients with Huntington's disease present with an akinetic rigid syndrome rather than chorea and this is often referred to as the Westphal's variant. This presentation is more common in the juvenile onset cases who are more likely to have inherited the CAG triplet repeat disorder from their fathers.

Wilson's disease usually presents with dystonia, imbalance, dysartria, and psychiatric or cognitive disturbances. Sometimes they may manifest with parkinsonism and all juvenile onset parkinsonian patients must have serum copper and ceruloplasmin assay and a slit-lamp examination for presence of Kayser–Fleischer rings. It is important not to miss this potentially treatable disorder. Copper chelating agents like D-penicillamine can be very effective.

Neuroacanthocytosis mostly occurs as a neurological syndrome with chorea, personality change, orofacial dyskinesias or dystonia causing feeding difficulty and self-mutilation, and often absent tendon reflexes due to an axonal peripheral neuropathy (Hardie et al., 1991). Rarely, parkinsonism may be the predominant feature rather than the chorea (Peppard et al., 1990) and sometimes there can be progression from an earlier hyperkinetic disorder to a later parkinsonian state (Stevenson & Hardie, 2001). Diagnosis requires the demonstration of acanthocytes in a peripheral blood smear and serum creatine kinase is frequently elevated.

Hallervorden–Spatz syndrome usually presents in childhood predominantly as a dystonic syndrome often with associated dementia, psychiatric disturbances and retinal pigmentary changes. Rarely, onset in adolescence or adulthood may be with predominant parkinsonism. Pathologically there are spheroids seen and there is deposition of iron in the globus pallidus and zona reticulata of the substantia nigra. The diagnosis may be indicated by MRI changes due to the iron deposition producing the typical 'eye of the tiger' sign with a zone of decreased intensity (due to iron) with hyperintensity on T_2-weighted images. Treatment is only symptomatic and not usually beneficial.

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35

Tremors

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Tremor, the most common movement disorder, is defined as a rhythmic, oscillatory movement of a body part produced by alternating or synchronous contractions of agonist and antagonist muscles. It ranges from a normal, barely noticeable, physiologic phenomenon to a severe, disabling movement disorder. Tremors can be classified according to their phenomenology, distribution, frequency, amplitude or etiology (Deuschl et al., 1998). Phenomenologically, tremors are subdivided into two major categories: rest tremors and action tremors. Rest tremors occur when the body part is fully supported against gravity and not actively contracting. In contrast, action tremors manifest during voluntary muscle contraction on an antigravity posture (postural tremor) or a goal-directed movement (kinetic tremor) (Table 35.1). This phenomenologic classification is far from ideal since there are many overlapping features among different tremors, but it remains the most widely accepted classification.

Rest tremor is present predominantly in Parkinson's disease (PD). It may also occur in other conditions such as different forms of parkinsonism, severe essential tremor (ET) and midbrain lesions. Postural tremors are typical of physiologic tremor, enhanced physiologic tremor, and ET. Task- or position-specific tremors are action tremors that occur only during specific motor activities, such as writing ('primary writing tremor') or maintaining at a certain posture. Kinetic tremors exist in cerebellar or midbrain disorders. Isometric tremor is seen during a voluntary isometric contraction, such as making a tight fist or contracting abdominal muscles. Tremors associated with dystonia, myoclonus, tardive dyskinesia, and other movement disorders may exhibit mixed phenomenology. Other disorders that produce rhythmic, but not necessarily oscillatory movements include segmental myoclonus, myorhythmia, asterixis, fasciculations, clonus, epilepsia partialis continua, shivering, head bobbing, and titubation. In this chapter we will first review the current notions of the tremor pathophysiology and then discuss the clinical features and treatment of the different types of tremors.

Pathophysiologic mechanisms of tremors

The broad clinical spectra of tremors suggest that different pathophysiologic mechanisms underlie various forms of tremors. Based on a large body of evidence from experimental and clinical physiologic studies, tremors originate from two types of mechanisms: (i) central and (ii) peripheral. The central oscillators consist of neuronal networks with auto-rhythmic properties and spontaneous bursting propagated through central nervous system (CNS) motor pathways. The peripheral components of tremors are influenced by mechanical characteristics of the affected body parts (muscles, tendons, and joints) and sensorimotor reflex mechanisms (Hallett, 1998). With the development of novel electrophysiologic and functional imaging techniques, the knowledge of mechanisms of tremors has been significantly advanced in recent years.

Intracellular recordings of certain neurons reveal autorhythmic (pacemaker) properties. Studying neurons of the inferior olive, Llinas and colleagues (Llinas, 1988) demonstrated that, as a result of low-threshold Ca^{2+} conductance, these neurons generate action potentials (low-threshold spike or LTS) at subthreshold depolarization. A fast action potential, generated by Na^{+} current into the cell body, is followed by a slow, high-threshold Ca^{2+} spike that activates prolonged (80–100 ms) K^{+}-mediated hyperpolarization. This is followed by an abrupt rebound response mediated by a low-threshold Ca^{2+} conductance large enough to generate a second Na^{+}-dependent action potential. The cycle then repeats, resulting in rhythmical bursting. Other CNS regions besides inferior olivary also

Table 35.1. Classification and differential diagnosis of tremors

Rest tremors (Typical 3 to 6 Hz)	Action tremors
Parkinson's disease	*Postural tremor*
Other parkinsonian syndromes	*Physiologic tremor*
Multiple system atrophies (SND, SDS, OPCA)	*Enhanced physiologic tremor*
Progressive supranuclear palsy	(Typical 8–12 Hz)
Cortical–basal–ganglionic degeneration	(a) Stress-induced: emotion, exercise, fatigue, anxiety, fever
Parkinsonism–dementia–ALS of Guam	(b) Endocrine: hypoglycemia, thyrotoxicosis, pheochromocytoma, adrenocorticosteroids
Diffuse Lewy body disease	(c) Drugs: beta agonists (theophylline, terbutaline, epinephrine, etc), dopaminergic drugs (levodopa, dopamine agonists), stimulants (amphetamines), psychiatric drugs (lithium, neuroleptics, tricyclics) methylxanthines (coffee, tea), valproic acid, cyclosporin, interferon
Progressive pallidal atrophy	(d) Toxins: Hg, Pb, As, Bi, Br, alcohol withdrawal
Heredodegenerative disorders	
Huntington's disease	*Essential tremor*
Wilson's disease	(Typical 4–8 Hz)
Neuroacanthocytosis	(a) Autosomal dominant
Hallervorden–Spatz disease	(b) Sporadic
Gerstmann–Strausler–Scheinker disease	
Ceroid lipofuscinosis	*Postural tremor associated with*
Secondary parkinsonism	(a) Dystonia
Toxic: MPTP, CO, Mn, methanol, cyanide, CS_2	(b) Parkinsonism
Drug-induced: dopamine receptor blocking drugs (neuroleptics, the 'rabbit syndrome'), dopamine depleting drugs (reserpine, tetrabenazine), lithium, flunarizine, cinnarizine	(c) Myoclonus
	(d) Hereditary motor–sensory neuropathy (Roussy–Levy)
	(e) Kennedy's syndrome (X-linked spino–bulbar atrophy)
Vascular: multi-infarct, Binswanger's, 'lower body parkinsonism'	*Task- or position-specific tremors*
Trauma: pugilistic encephalopathy, midbrain injury	(a) Handwriting
Tumour and paraneoplastic	(b) Orthostatic
Infectious: postencephalitic, fungal, AIDS, SSPE,	(c) Other (e.g. occupational) task-specific tremors
Creutzfeldt-Jakob disease	
Metabolic: hypoparathyroidism, mitochondrial	*Kinetic (intention, terminal) tremors*
Cytopathies, chronic hepatic degeneration	(Typical 2.5–4 Hz)
Normal pressure hydrocephalus	(a) Cerebellar disorders (cerebellar outflow): multiple sclerosis, trauma, stroke, Wilson's disease, drugs, toxins
Spasmus nutans	(b) Midbrain lesions
	Isometric tremor
	Muscular contraction during sustained exertion
Tremors with mixed phenomenology	*Miscellaneous tremors and other rhythmic movements*
A Parkinson's disease and other parkinsonian syndromes (rest and postural)	A Myoclonus: rhythmical segmental myclonus (e.g. palatal), oscillatory myoclonus, asterixis, mini-polymyoclonus
B Essential tremor (postural and kinetic) Severe essential tremor (postural and rest)	B Dystonic tremors
	C Cortical tremors
C Midbrain (rubral) tremor (postural, kinetic and rest)	D Epilepsia partialis continua
D Tardive tremor (rest, postural and kinetic)	E Nystagmus
E Myorhythmia (rest and kinetic)	F Clonus
F Neuropathic tremor (postural or rest)	G Fasciculations
G Psychogenic tremor (rest, postural or kinetic)	H Shivering
	I Shuddering attacks
	J Head bobbing (3rd ventricular cysts)
	K Aortic insufficiency with head titubation

contain neuronal networks with self-generating bursts of activities. For example, high-frequency oscillations are induced in local cortical circuits from cortex-striatum-mesencephalon organotypic cultures (Plenz & Kitai, 1996). Neurons from the subthalamic nucleus and external globus pallidus generate synchronized oscillating bursts at 0.4, 0.8 and 1.8 Hz in cell cultures.

Different types of tremors originate from different central oscillators. By studying awake decerebrate monkeys, Lamarre (1984) found two different types of rhythmic discharges from two different regions: 3 to 6 Hz spontaneous rhythmic discharges in the ventral thalamus and 7 to 12 Hz discharges in the olivo-cerebellar system. The 3 to 6 Hz thalamic neuron discharges were facilitated by a lesion in the ventromedial tegmentum of the midbrain. Such thalamic deafferentiation was thought to express parkinsonian rest tremor.

Central mechanisms

Central oscillators are thought to play a major role in the generation of rest tremor in PD, with only minimal contribution from the peripheral mechanical-reflex mechanisms. Rest tremor can be produced in a monkey treated with the neurotoxin 1-methyl-4-phenyl-1, 2, 3, 6- tetrahydropyridine (MPTP) which damages dopaminergic neurons in SN pars compacta (SNpc) (Bergman et al., 1994). The investigators demonstrated that subthalamic nucleus (STN) and globus pallidus interna (GPi), the outflow nucleus from the basal ganglia, were overactive in the monkeys with MPTP-induced parkinsonism (Blandini et al., 2000). According to a model of the basal ganglia circuitry, the degeneration of SNpc and reduced striatal dopamine (DA) result in excessive inhibition from striatal neurons that project to globus pallidus externa (GPe) and consequent disinhibition of the subthalamic nucleus (STN) via indirect pathway (Obeso et al., 2000). The nigrostriatal denervation decreases inhibition of globus pallidus interna (GPi) via the direct pathway. The combined effects of increased activity of the indirect pathway and decreased activity of the direct pathway result in increased activity of the STN and GPi. Since the outflow pathway from the GPi to the thalamus is mediated by the inhibitory neurotransmitter gamma-amino-butyric acid (GABA), the increased GPi activity in PD results in overinhibition of the thalamo-cortical-spinal pathway, clinically expressed as bradykinesia and tremor. The latter is presumably due to an inhibition of those thalamic neurons that normally suppress the oscillators in the ventral thalamus 'unmasking' the normally suppressed pacemakers. The 3 to 6 Hz spontaneous bursts from ventral thalamus are transmitted via the thalamo-cortical-spinal circuitry to the spinal motor neurons leading to synchronization of motor unit discharges, manifested as tremor. This model is used to explain the physiologic basis of surgical treatment of PD by thalamotomy, pallidotomy and deep brain stimulation (DBS).

Unlike PD, there are no morphologic or biochemical abnormalities found in autopsied brains of patients with ET (Rajput et al., 1991). Clinical physiologic studies demonstrate that the frequency of ET is not affected by mass loading to the studied limb. This indicates that central oscillators but not stretch reflex or limb mechanics play a major rolesin ET (Hallett, 1998). Tremorgenic oscillators in the CNS, possibly in those brainstem nuclei projecting to the cerebellum, are believed to be responsible for the tremor of ET. This is supported by the finding that harmaline, a monoamine oxidase inhibitor that causes tremor similar to human ET in animal models, induces rhythmic activities in the olivo-cerebellar system (Wilms et al., 1999). Metabolic PET studies (Wills et al., 1994) and functional MRI (Bucher et al., 1997), however, suggest that the tremor generators for ET reside in bilateral cerebellum and red nucleus. Cerebellar involvement in ET is also supported by subtle signs of cerebellar dysfunctions, impaired tandem gait, postural instability, kinetic tremor in advanced stage of ET, and disappearance of ipsilateral ET after cerebellar infarct (Deuschl et al., 2000). Alcohol reduces the amplitude of ET possibly by inhibiting cerebellar hyperactivity, as demonstrated by PET studies during tremor (Boecker et al., 1996). However, some argue that cerebellar dysfunction is not specific for ET since other forms of tremors such as PD, neuropathic tremor, and orthostatic tremor (see below) are associated with an increase in cerebellar blood flow on PET (Boeker & Brooks, 1998). Thalamus has been also postulated to play a role in ET either because it contains populations of pacemaker neurons or because it simply relays rhythmic discharges from the cerebello-olivary pathway to the motor cortex and then to the spinal cord, synchronizing the motor neuron pool and thus producing the oscillatory movement (Hua et al., 1998). The involvement of thalamus in ET is supported by the observation that thalamotomy and thalamic stimulation improve ET (Ondo et al., 1998).

Ever since the classic descriptions by Holmes (1917) that cerebellar injuries cause hypotonia, ataxia, and kinetic tremor, this form of tremor has been related with dysfunctions of cerebellum and its outflow pathways. Lesions in the midbrain (red nucleus) are associated with a slow, 2 to 3 Hz frequency tremor, sometimes referred to as myorhythmia. Higher brain stem (midbrain, pons) lesions lead to tremor at 5–7 Hz, and lower brainstem lesions produce a faster frequency at 8–11 Hz. Several anatomic–

physiologic studies have demonstrated that disruptions of the dentatorubrothalamic outflow pathway induce kinetic tremor. Such lesions result in error timing on contractions of the agonist and antagonist muscle groups.

Peripheral mechanisms

The limb muscle coupled with bones, tendons and joints is virtually a mechanical spring system that resonates and vibrates at its natural frequency. The resonant frequency varies from different joints and is inversely related to the mass of the body part. Walsh (1992) formulated an equation to calculate this frequency of vibration (f_0): $f_0 = 1/(2\pi)(K/J)^{1/2}$, where K is the stiffness exerted on a structure and J is the moment of inertia. Several factors may modify the resonance. Ballistocardiac effect influences the frequency and amplitude of peripherally generated tremors. Loading the extremity with weight mass reduces the resonant frequency. This oscillation of the muscle–joint coupling is the major contributor to physiologic tremor with typical frequency at 8 to 12 Hz. Muscle spindle primary afferent ending receptors are very sensitive, particularly in contracting muscles with α-γ co-activation, sending signals to the spinal cord and eliciting a stretch reflex. With appropriate timing, the stretch reflex produces synchronization of spinal motor neurons and generation of muscle contraction. The contraction induces another stretch reflex, and the cycle repeats itself, resulting in an oscillatory movement (McAuley & Marsden, 2000). The stretch reflex–muscle spindle feedback is controlled and modified by central oscillators and other supraspinal influences. The presence of stretch reflex loop is essential for enhanced physiologic tremor; tremors of PD and ET are much less dependent on the peripheral stretch reflex.

Clinical features and treatments of tremors

Rest tremors

Rest tremor is an oscillatory movement of a body part when that part is supported against gravity. By definition, rest tremor disappears or diminishes during voluntary muscle contraction or movement. It is difficult, however, to apply this definition to certain body parts such as lips, chin and face that are often involved in rest tremor. It should also be emphasized that all tremors, including rest tremors, disappear when the body part is at a complete rest state or during sleep and hand rest tremor is typically exacerbated when a patient with PD walks. The classical clinical picture of PD rest tremor is an asymmetric onset of 3 to 6 Hz supinating-pronating (pill-rolling) hand oscillation. Other body parts frequently involved by PD tremor include individual fingers, lips, jaw, tongue, legs and feet. Head tremor, which is typical for ET, however, is rarely seen in PD. About 70% of PD patients present with rest tremor and nearly all patients with PD manifest tremor some time during the course of their illness (Hughes et al., 1993). Patients with tremor-dominant form of PD generally have a younger age at onset, relative sparing of cognition, slower progression and more favourable prognosis than PD patients with postural instability and gait difficulty, or PIGD (Jankovic et al., 1990). The amplitude varies between different patients and may vary from minute to minute in the same patient. When PD patients hold their arms outstretched horizontally in front of their body, the rest tremor usually disappears. In some patients the tremor reappears after a latency of several seconds (up to a minute). Although this tremor occurs during maintenance of a posture, this 're-emergent tremor' shares the same mechanisms with rest tremor because its amplitude and frequency are both similar to those of rest tremor (Jankovic et al., 1999).

While PD is the most common cause, there are many other etiologies including secondary parkinsonism and parkinsonism-plus syndromes presenting with rest tremor (Table 35.1). Advanced ET can also cause rest tremor. Although some authors argued that the coexistence of PD and ET simply represents a chance of occurrence of two common diseases (Pahwa & Koller, 1993), there is a growing body of evidence that the presence of ET is a risk factor for later development of PD (Jankovic, 2000). Several autosomal dominant families have been described in which some members have ET and others have PD (Jankovic et al., 1995; Findley, 2000).

Treatment

The discussion of treatment of rest tremors is beyond the intended scope of this chapter, but it is essentially the same as treatment of PD (Jankovic & Marsden, 1998). For a summary of treatment options on different types of tremors, please refer to Table 35.2. The choices of medical treatment of PD rest tremor include dopamine replacement with levodopa, dopamine receptor agonists, amantadine, and anticholinergic agents. Clozapine, an atypical neuroleptic (Ceravolo et al., 1999) and mirtazapine, an antidepressant with both noradrenergic and serotoninergic properties (Pact & Giduz, 1999) have been also found effective. Local injections of botulinum toxin (BTX) into the affected muscles reduce the tremor amplitude (Jankovic et al., 1996). The antitremor action of BTX is not well understood, but has been attributed to the action of BTX on the extrafusal and intrafusal motor fibres, reducing

Table 35.2. Medical treatment of tremor variants

Variant	Treatment		
Rest tremor	T, L, PH	BTX	DBS
Postural hand/arm tremor	P, PRI, A, PH	BTX	DBS
Head tremor	C, PRI, P	BTX	
Voice tremor	P	BTX	
Facial/tongue tremor	P, PRI, L	BTX	
Task-specific tremor	T, P, PRI	BTX	
Orthostatic tremor	G, C, PRI, PH, L		
Kinetic hand/arm tremor	C, P, PRI, BU, PH	BTX	DBS

Notes:
A = Alprazolam.
BTX = Botulinum toxin.
BU = Buspirone.
C = Clonazepam.
DBS = Deep brain stimulation.
G = Gabapentin.
L = Levodopa.
P = Propranolol.
PH = Phenobarbital.
PRI = Primidone.
T = Trihexyphenidyl.

spindle afferent input to the spinal cord. This restores presynaptic inhibition between antagonist muscles and reduces tremor (Modugno et al., 1998). While BTX injections may be quite effective in the treatment of parkinsonian rest tremor, it is particularly useful in ET and in dystonic tremor (see below).

For drug-resistant and disabling tremors, several surgical treatment options include thalamotomy, pallidotomy and high frequency deep brain stimulation (DBS) of the STN or GPi (Jankovic, 1999; Lang, 2000). Ventral lateral thalamotomy involving the nucleus ventralis intermedius (VIM) used to be the most popular choice of surgical options, but now VIM DBS (in ET), GPi DBS and STN DBS (in PD) are far more common. Patients can turn the pulse generator (stimulator) on or off by applying a magnet over the area where the stimulator is subcutaneously implanted, usually in the upper chest. These procedures have the advantage over the ablative procedures because the stimulating parameters can be customized to each patient and they are safer and more effective than the traditional thalamotomy (Schuurman et al., 2000). While VIM DBS reduces contralateral tremor in about 46–92% of patients (Ondo et al., 1998; Koller et al., 1999), GPi or STN DBS offers the possibility of improvement on tremor and other parkinsonian features as well, including levodopa-induced motor complications (Krack et al., 1998; Krauss et al., 2001). Rare complications of DBS are hemorrhage, seizures, contralateral hemiparesis, dysequilibrium, and infection due to foreign bodies (stimulating electrode, the pulse generator and their connections).

Action tremors

Physiologic tremor

Physiologic tremor is universally present in all people, but it is not considered pathological, until it interferes with social or occupational (fine motor) activities. Many factors may exacerbate the amplitude of physiologic tremor, including endogenous factors such as emotional stress, anxiety, fatigue, hypoglycemia, endocrine effects (e.g. hyperthyroidism, hyperadrenergic states in response to hypoglycemia); exogenous CNS stimulants such as caffeine, amphetamines, beta-agonists, lithium, neuroleptics, anticonvulsants, and tricyclic antidepressants (Diederich & Goetz, 1998). Delirium tremens, the tremor induced by acute alcohol withdrawal, is a variant of enhanced physiological tremor. Enhanced physiologic tremor is usually reversible after causative agents are removed. Chronic use of certain drugs, such as the neuroleptics, however, can produce persistent parkinsonian or tardive tremor. Tardive tremor is manifested by a mixture of rest, postural and kinetic tremor with a frequency of 3 to 5 Hz (Stacy & Jankovic, 1992). In contrast to parkinsonian tremor, tardive tremor improves rather than worsens with anti-dopaminergic agents such as tetrabenazine, a dopamine depleting and dopamine receptor blocking drug.

Several studies have demonstrated an overlap in physiologic characteristics between physiologic and isometric tremors. Isometric tremors usually do not require treatment with the exception of orthostatic tremor (Deuschl et al., 1998) (see below).

Treatment

In most cases, enhanced physiologic tremors are reversible and the treatment strategies should focus on elimination of the triggering factors such as anxiety, caffeine, drugs (e.g. lithium), hyperthyroidism, pheochromocytoma, and hypoglycemia. If tremor is embarrassing or troublesome, beta adrenergic blockers (propranolol or nadolol) and benzodiazepines may be useful (Wasielewski et al., 1998).

Essential tremor

ET is characterized by postural or kinetic tremor with frequency usually at 4 to 8 Hz, but sometimes may be as high as 12 Hz (Jankovic, 2000b). Head tremor has a slower frequency at 2 to 8 Hz. The amplitude and frequency of ET are less dependent on position of the limb or mass loading, different from those of physiologic tremor. Although the term 'benign essential tremor' is still used in the literature,

it is important to recognize that ET can be very disabling. The tremor may interfere with eating, speaking, writing, daily activities and cause social embarrassment leading to social withdrawal.

Various epidemiologic studies show prevalence rates ranging from 0.4 to 5.6%, depending on different methodologies, diagnostic criteria and study populations (Louis et al., 1998). The age at onset appears to be a bimodal distribution, with peaks at the second and sixth decades (Lou & Jankovic, 1991). Since there are no physiologic, genetic or biological markers for ET, the diagnosis is based on clinical criteria. According to one set of criteria, definite ET is a bilateral postural tremor, with or without kinetic component, involving hands or forearms persistent for more than 5 years (Jankovic, 2000b). The tremor may be asymmetrical and other body parts may be affected. Other causes of tremor must be excluded. Probable ET includes the same criteria as of definite ET, but tremor may be confined to one body part and the duration is greater than 3 years. Primary orthostatic tremor, isolated voice, tongue, chin tremors, position- and task-specific tremors must be excluded. There are two types of possible ET. Criteria for type 1 possible ET are the same as of probable ET, but patients may exhibit other neurologic disorders (parkinsonism, dystonia, myoclonus, peripheral neuropathy, restless legs syndrome, or mild extrapyramidal signs). Type 2 possible ET consists of a monosymptomatic and isolated tremor of uncertain relationship to ET. It includes position- and task-specific tremors such as occupational tremors (primary writing tremors), primary orthostatic tremor, isolated voice, chin, tongue, leg tremor and unilateral postural hand tremor. Core and secondary criteria were proposed to facilitate a practical approach to the diagnosis of ET (Elble, 2000). Core criteria include bilateral action tremor of the hands and forearms (but not rest tremor), absence of other neurologic signs (except for the Froment's sign), and isolated head tremor without signs of dystonia. Secondary criteria include long duration (>3 years), positive family history, and beneficial response to alcohol. There are diagnostic red flags which indicate diagnoses other than ET, such as unilateral tremor, leg tremor, rigidity, bradykinesia, rest tremor, gait disturbance, focal tremor, isolated head tremor with abnormal posture (head tilt or turning), sudden or rapid onset, and on drug treatment that may cause or exacerbate tremor.

Upper extremities are involved most frequently in ET, typically manifesting a 4 to 8 Hz symmetrical hand tremor. Similar to enhanced physiologic tremor, emotion, stress and fatigue make ET worse. Head is another body part frequently affected, either in a form of anterior–posterior oscillation (yes–yes nodding) or lateral, side-to-side (no–no shaking) oscillation at 2–8 Hz. Body parts also affected by ET include larynx (voice), jaw, lips, face and tongue. The lower extremities are rarely involved (Lou & Jankovic, 1991; Elble, 2000). ET often develops insidiously and progresses slowly, becoming more severe over years. The prevalence increases with age, affecting 5% to 14% of people above 65 years old (Brin & Koller, 1998). Older patients tend to have lower frequency (4–12 Hz) than younger patients (8–12 Hz) (Elble, 2000). Because the frequency of physiologic tremor is similar to ET, it may be difficult to differentiate mild ET from enhanced physiologic tremor. The way to differentiate is that mass loading of the limb decreases the frequency of physiologic tremor, but not ET.

ET is a genetic disorder inherited as an autosomal dominant pattern. The frequency of positive family history among first-degree relatives ranges from 17% to 100%. These wide variations in reported family histories are mostly due to different methodologies used to ascertain ET among family members and different characteristics of study populations (Findley, 2000). Based on studies of large ET families, Higgins et al. (1998) found a marker on chromosome 2p22–p25, termed *ETM*. The ET gene locus, *FET1*, on chromosome 3q13 (Gulcher et al., 1997), was mapped in other families with ET. Although classic ET is a monosymptomatic disorder without other neurologic signs and symptoms, in some patients and families ET is associated with parkinsonism, dystonia and other neurologic disorders. In one such family, the disorders (ET, parkinsonism, or both) were linked to chromosome 4p14–16.3 (Farrer et al., 1999). It is anticipated that there will be more gene loci and mutations identified in tremor families which will eventually lead to a genetic classification of ET.

Task- or position-specific tremors represent either variants (forme fruste) of ET or dystonia (Jankovic, 2000). The patients experience tremor when performing fine-coordinated motor activities, such as writing, playing a musical instrument, golfing or holding objects in certain positions (Bain et al., 1995). The pathophysiology of these tremors is not clear. One possibility is an abnormal CNS response to muscle spindle input from forearm muscles. Isolated voice, tongue and chin tremors also have features that seem to overlap with focal dystonia (Deuschl et al., 2000). Although many patients with dystonia have a postural tremor that is phenomenologically identical to ET, this tremor does not appear to be associated with the known GAG deletion in the *DYT1* gene (Dürr et al., 1993). Orthostatic tremor, another position-specific tremor, is characterized by a rapid (14–16 Hz) frequency tremor present in the legs while standing or during isometric contraction of trunk muscles. It is associated with 'vibration' in the legs, calf cramps and a feeling of unsteadiness after

standing for a few minutes (Heilman, 1984). Jaw and other cranial muscles may occasionally be involved. Electrophysiologic recordings from the legs show bilateral coherence supporting the notion that this type of tremor is generated from a single central oscillator (McAuley et al., 2000).

Treatment

The choice of treatment for ET largely depends on the severity of the tremor and how it interferes with patient's daily activities. The antitremor medications decrease tremor amplitude but not frequency. In addition to medical treatment, factors affecting tremor such as drugs, alcohol, caffeine, anxiety, or temperature should be eliminated or minimized whenever possible. The main therapeutic options for ET include beta-adrenergic blockers and primidone (Koller et al., 2000). The beta-adrenergic blockers, especially propranolol, have been considered the treatment choice since the early 1970s. The other beta-blockers (metoprolol, nadolol and timolol) seem to be less effective than propranolol. The pharmacological mechanism of beta-blockers in the treatment of ET is not clear. Since there is no direct correlation between lipid solubility (and consequent ability to cross the blood brain barrier) and their efficacy, peripheral mechanisms seem to play a key role in reducing tremor (Guan & Peroutka, 1990). Beta-blockers are generally well tolerated, but may cause excessive daytime drowsiness, fatigue, erectile dysfunction and depression. They should not be prescribed in patients with diabetes, asthma or congestive heart failure. The efficacy of primidone in reducing tremor amplitude is about 40–50%, similar to that of propranolol. The drug is metabolized into phenylethylmalonamide (PEMA) and phenobarbital. Neither PEMA nor phenobarbital seem to have an independent antitremor activity, suggesting that the parent compound is the active drug (Sasso et al., 1991). The most common side effect is excessive daytime drowsiness, and up to 25% of patients, particularly the elderly patients, experience an acute reaction that is manifested by nausea, vomiting, sedation, confusion and ataxia. This idiosyncratic reaction may be prevented by initiating the drug with a very low dose (e.g. 25 mg at bedtime) followed by a slow and gradual titration over several weeks (up to 750 mg per day in 3 divided doses).

Many patients with ET report transient improvement of tremor after alcohol ingestion. Some use alcohol (often not judiciously) at social events to ameliorate tremor (Koller et al., 2000). Benzodiazepines, especially clonazepam, are also used to reduce ET. Other drugs with antitremor effect include the antiepileptic drugs gabapentin and topiramate (Ondo et al., 2000). Orthostatic tremor responds well to clonazepam, gabapentin and perhaps levodopa (Wills et al., 1999). BTX injections into the muscles involved in the generation of tremor have been found to be beneficial (Jankovic et al., 1996). BTX is particularly useful in controlling head tremor, which usually does not respond well to other medical therapies. Vocal and palatal tremors are also effectively treated with BTX injections. Kaji et al. (1995) showed that local injection of lidocaine into the target muscle produced peripheral deafferentiation and transient reduction in the amplitude of postural tremor (as well as focal dystonia, such as writer's cramp).

Neurosurgical intervention should be reserved only for those patients with severe ET who are disabled or functionally impaired despite optimal medical therapies. While thalamotomy was the surgical treatment of choice in the past, in recent decades DBS of the ventral intermediate (VIM) nucleus of the thalamus has become the surgical treatment of choice because it is safer and more effective (Schuurman et al., 2000). Besides VIM, chronic cortical stimulation may improve contralateral action tremor, but this is not a practical treatment modality (Nguyen et al., 1998). Subthalamic nucleus is currently being investigated as a target for refractory proximal ET (Kitagawa et al., 2000).

Kinetic tremor

Kinetic tremor, formerly named 'intention' tremor, is a form of action tremor in which the oscillation occurs when voluntary contraction of muscles produces a goal-directed movement (e.g. finger-to-nose). This tremor has been referred as 'midbrain' or 'rubral' tremor although CNS areas, especially thalamic lesions, may present a similar clinical picture (Vidailhet et al., 1998). Diseases affecting the cerebellum or the cerebellar outflow pathways cause not only kinetic tremor, but also ataxia, dysmetria and other cerebellar signs (Deuschl et al., 2000). 'Titubation', which is a slow rhythmic oscillation of whole body or head with increasing amplitude on movement, is associated with cerebellar dysfunction (San Pedro et al., 1998). Kinetic tremor is often unilateral, present on the side ipsilateral to the cerebellar lesion, with a slow frequency raging between 2 and 5 Hz. Amplitude is medium to coarse, and is more robust when approaching the target (terminal tremor). Disorders commonly causing kinetic tremor include multiple sclerosis (MS), Friedreich's ataxia, stroke, trauma, and Wilson's disease. Alcohol abuse and toxicity due to various anticonvulsants (phenytoin and valproic acid) may also induce kinetic tremor.

Myorhythmia is a special type of tremor that is characterized by a slow 1 to 3 Hz frequency, continuous or intermittent rhythmic movement existing at rest and persisting during activity. It has irregular presentations mixed with

rest, kinetic and postural tremors and is not as rhythmic as other tremors (Deuschl et al., 1998). It is often accompanied by ataxia and ipsilateral 3rd nerve palsy. This slow tremor arises from lesions in the red nucleus, midbrain, cerebellum or thalamus with secondary interruption of various pathways. It is also associated with palatal myoclonus due to an interruption of the dentato-rubro-olivary pathway (Yanagisawa et al., 1999). Etiologies of myorhythmia include cerebellar degeneration, ischemic or hemorrhagic lesions, Whipple's disease and Wilson's disease. Autopsy and PET studies suggest that the combination of rest and kinetic tremors is typically associated with disruptions in both cerebello-thalamic and nigrostriatal systems (Remy et al., 1995).

Treatment

Before selecting a symptomatic therapy for the kinetic tremor, it is important to thoroughly evaluate the patient in search of an etiology-specific treatment. Of all different tremors, kinetic tremor is the most resistant to symptomatic pharmacologic therapy. No drug has been found to provide a reliable benefit (Wasielewski et al., 1998). Clonazepam, which works on both serotoninergic and GABA systems, is used frequently for symptomatic relief. Buspirone, a 5-HT1A agonist and odansetron, a 5-HT3 antagonist were reported effective in improving cerebellar tremor (Lou et al., 1995; Rice et al., 1997). Tetrahydrocannabinol and cannabinoids may improve spasticity and tremor in patients with multiple sclerosis (Baker et al., 2000). Surgical treatment is less effective in kinetic tremor, but for some incapacitating kinetic tremors, surgical intervention, such as VIM DBS, may be the only option (Schulder et al., 1999; Taha et al., 1999).

Miscellaneous tremors

Tremors associated with peripheral neuropathy

Tremors often accompany peripheral neuropathies, particularly the dysgammaglobulinemic neuropathies, and hereditary motor–sensory neuropathies (Cardoso & Jankovic, 1993). Since the amplitude of tremor in patients with hereditary motor–sensory neuropathy does not directly correlate with the severity of motor weakness, sensory loss, or slowing of nerve conduction, the mechanism of the tremor may be pathophysiologically independent of the neuropathy. Peripheral injuries induce tremor, whether or not associated with reflex sympathetic dystrophy or the complex regional pain syndrome (Cardoso & Jankovic, 1995). There is growing evidence of central reorganization in response to altered peripheral input that may underlie peripherally induced tremors (Jankovic, 2001).

Psychogenic tremor

Psychogenic tremor sometimes can be difficult to differentiate from neurologic ('organic') tremor, but several series have provided useful diagnostic criteria (Deuschl et al., 1998). These include: (i) sudden onset, (ii) spontaneous remission, (iii) various combinations of different types of tremors, (iv) changing amplitude and frequency, (v) tremor increases with attention and decreases with distraction, (vi) poor response to antitremor drugs, (vii) selective disability, (viii) entrainment of the tremor with voluntary repetitive movement, (ix) absent finger tremor, and (x) remission with psychotherapy. Many patients with psychogenic tremor not only have abrupt onset but also present with maximal disability at onset (Kim et al., 1999). Some additional or associated features may help diagnose psychogenic tremor, such as false weakness, false sensory symptoms, multiple somatizations, self-inflicted injuries, bizarre movements or pseudoseizures, and subtle or obvious psychiatric illness. The management of patients with psychogenic tremor is often challenging and should include careful exploration of psychological as well as physical factors that may be contributing to the tremor. By helping the patient provide insight into the psychodynamics of the tremor, the physician may successfully treat not only the tremor, but also the underlying psychological disturbance. Antidepressant medications often play an ancillary role. Prognosis varies from poor to complete remission, largely depending on the insight of the patient and the family.

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Myoclonus

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Myoclonus is defined as shock-like involuntary movements. Most often these are due to brief bursts of muscle activity, resulting in positive myoclonus. Jerks, however, may also result from sudden short inhibitions of ongoing tonic muscle activity, termed negative myoclonus or asterixis. Myoclonus may be physiological, such as hiccups, or due to a variety of hereditary or acquired conditions. In particular, it may be seen in primary generalized epilepsy, but as this syndrome is dominated by epilepsy rather than myoclonus, it will not be considered further here.

Clinical overview of physiologically based classification

Although etiological classifications have not proven very useful in predicting the response to drugs, electrophysiological investigations have been able to distinguish several different pathophysiological mechanisms with therapeutic implications. To a large degree, the pathophysiological type of myoclonus can be suspected on clinical grounds. The most useful clinical distinction is between generalized, multifocal and focal/segmental jerks. Generalized myoclonus involves the majority of the body in a synchronous jerk. It may spare the face and be predominantly axial, as in propriospinal myoclonus, or include the face, as in brainstem myoclonus. The latter may only consist of reflex jerks, as in exaggerated startle/hyperekplexia, or may also involve prominent spontaneous jerks as in brainstem reticular reflex myoclonus. A useful confirmatory sign of a brainstem origin is the presence of jerks in response to auditory stimulation, particularly unexpected sounds. Multifocal myoclonus involves different parts of the body at different times. There may also be the occasional generalized jerk, but the clinical picture is dominated by multifocal jerks. Such patients may be divided into those in whom the distal limbs are especially involved, and are likely to have cortical myoclonus, and those in whom the jerks are most noticeable proximally, particularly round the shoulders. These are likely to have essential myoclonus. Helpful confirmatory signs of cortical and essential myoclonus are an exacerbation of jerking upon voluntary action and the presence of dystonic posturing, respectively. Focal/segmental jerks are the most obscure as they may arise at virtually any level of the nervous system, including the spinal cord.

Clinical suspicion of particular pathophysiological types of myoclonus can be supported by simple investigation. Epileptic EEG abnormalities are suggestive of a cortical origin, as are giant cortical SEPs following median or tibial nerve stimulation. EMG studies are useful in focal myoclonus as signs of segmental denervation often accompany spinal segmental myoclonus. Similarly, imaging of brain and spinal cord can be very helpful in demonstrating the structural lesion that often accompanies generalized or focal myoclonus.

Cortical myoclonus

Pathophysiology

Cortical myoclonus is the result of an abnormal discharge in the sensorimotor cortex, and rapidly conducting corticospinal pathways. It may consist of reflex myoclonus, spontaneous jerks or myoclonus elicited by voluntary action, and tends to be focal or multifocal. It is characterized by brief bursts of electromyographic activity (EMG), usually less than 70 ms in duration. EMG bursts are preceded by pathological enlargement of the cortical components of the sensory evoked potential in reflex jerks, or a time-locked cortical correlate in the electroencephalographic activity (EEG) in action or spontaneous myoclonus

(Fig. 36.1). In each case the relevant EEG wave precedes the EMG burst by an interval more or less appropriate for conduction in the fastest corticospinal pathways. For the intrinsic muscles of the hand, this interval is about 20 ms. Although the EEG waves prior to the jerks are often several tens of microvolts in amplitude, averaging techniques, such as backaveraging, are usually necessary to identify their morphology and distribution.

Some patients may also have cortical negative myoclonus, either action induced or reflex. In this a brief silencing of muscle activity occurs preceded by a cortical wave. Sudden lapses in posture result, particularly noticeable during gait, and tend to be more resistant to drug treatment than positive reflex or action myoclonus. In addition, in some patients with multifocal myoclonus, myoclonic activity spreads within and between the sensorimotor cortices, so that bilateral or generalized jerks also occur. Spread is somatotopic, and cranial nerve innervated muscles are activated rostro-caudally, unlike the caudo-rostral activation seen in hyperekplexia.

The cortical inhibitory processes, which would normally keep spread in check, are deficient in cortical myoclonus. This can be shown in vivo using the technique of transcutaneous stimulation of the motor cortex (Brown et al., 1996). A conditioning magnetic shock to either the ipsilateral or contralateral motor cortex normally inhibits the response to a succeeding test shock, demonstrating the presence of both cortico-cortical and transcallosal inhibition in healthy subjects. Both types of inhibition are severely impaired in patients with cortical myoclonus and evidence of cortical spread of myoclonic activity.

Etiology and clinical features

Cortical myoclonus is most marked in the distal limb, and in focal forms is usually confined to this site. If widespread, myoclonus is multifocal, with or without additional bilateral or generalized jerks. The latter are associated with more marked disability. Reflex jerks may be elicited by touch and tap, or visual stimuli. Marked sensitivity to photic stimulation suggests Unverricht–Lundborg disease. Sensitivity to auditory stimuli suggests a startle syndrome, although some patients may have a combination of cortical myoclonus and pathological startle. Multifocal jerks occurring with voluntary action are very suggestive of a cortical origin for the myoclonus. As well as involving arm function, jerks may affect speech and gait. Extraocular muscles are spared.

Focal cortical myoclonus is usually due to vascular or neoplastic lesions of the sensorimotor cortex. When spontaneous jerks are frequent, focal cortical myoclonus is

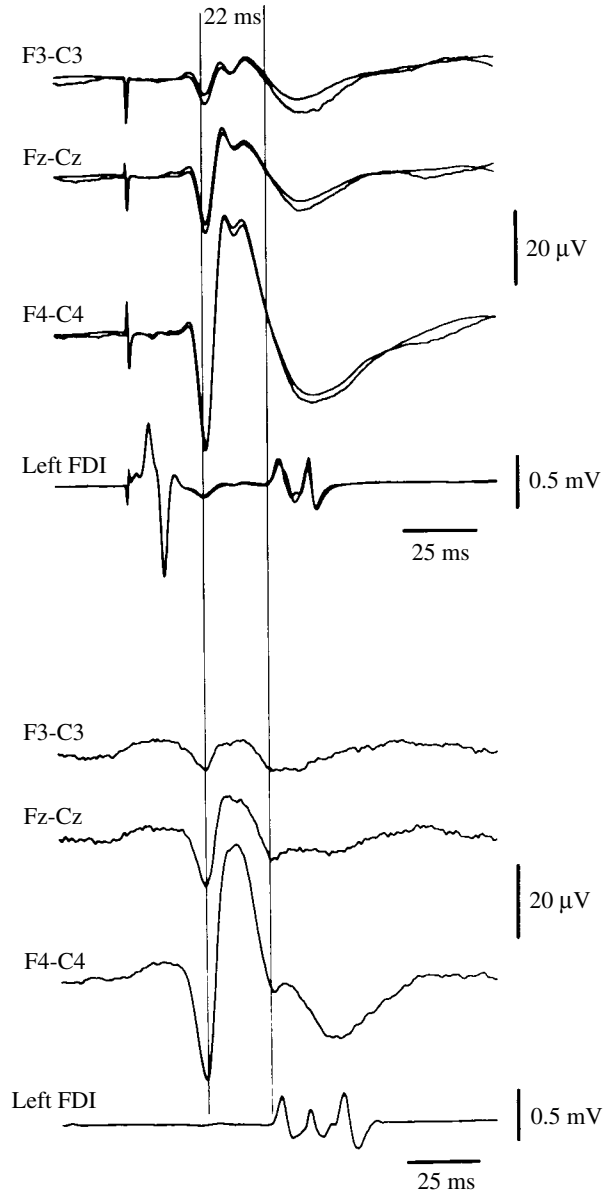

Fig. 36.1. (*a*) Cortical sensory evoked potentials to electrical stimulation of the left ulnar nerve at the wrist. (*b*) Backaveraged EEG activity preceding voluntary action jerks in a patient with coeliac disease and cortical myoclonus. A giant EEG wave is recorded, largest contralateral to the stimulated or moved hand. The positive (downgoing) component of the wave precedes the reflex response (*a*) or action jerk (*b*) by 22 ms, an interval appropriate for conduction from motor cortex to hand via the fastest pyramidal pathways. (Reprinted from Bhatia et al., 1995, with permission.)

often called epilepsia partialis continua. Multifocal myoclonus may occur in posthypoxic encephalopathy, as first described by Lance and Adams (1963), or as part of a progressive illness, as in the syndromes of progressive myoclonic ataxia and progressive myoclonic epilepsy. Causes with a genetic basis usually have an onset before the age of 20. Progressive myoclonic ataxia describes those patients with prominent myoclonus and ataxia, but little in the way of epilepsy or progressive dementia. The term encompasses the Ramsay Hunt syndrome. Progressive myoclonic ataxia is most commonly due to Unverricht–Lundborg disease, mitochondrial encephalopathy or coeliac related encephalopathy. The latter usually comes on in middle-age or later and enteric coeliac disease may be asymptomatic (Bhatia et al., 1995). The diagnosis is confirmed by small bowel biopsy. Unverricht-Lundborg disease is due to mutations in the gene on chromosome 21q that codes for cystatin B, an inhibitor of cysteine protease. The mitochondrial encephalopathy associated with myoclonus is usually the MERRF syndrome of myoclonus, epilepsy and ragged red fibres. This is typically due to point mutations in the mitochondrial gene that codes for tRNA (Lys). An elevated CSF lactate level is suggestive of the diagnosis, which can often be confirmed by mitochondrial DNA analysis of blood.

Progressive myoclonic epilepsy describes those patients with myoclonus, severe epilepsy and relentless cognitive decline. The commonest causes are sialidosis, Lafora's disease, lipidosis, neuronal ceroid lipofuscinosis, dentato-rubro-pallido-luysian atrophy and Huntington's disease, although mitochondrial encephalopathy can also be responsible. Dentato-rubro-pallido-luysian atrophy and Huntington's disease are due to CAG triplet repeat expansions on chromosome 12p and 4, respectively. Sialidosis is due to mutations in the sialidase gene and confirmatory tests include assays for urine oligosaccharides and fibroblast α-neuraminidase. Juvenile neuronal ceroid lipofuscinosis is caused by mutations in the CLN3 gene, a gene of unknown function that encodes a 438-amino acid protein of possible mitochondrial location. The remaining forms of neuronal ceroid lipofuscinosis and Lafora disease have been mapped by linkage analysis but the corresponding gene defects are still unknown. Lafora disease is an autosomal recessive storage disease characterized by polyglucosan acid-Schiff positive inclusions (Lafora bodies) in cells of brain, liver, muscle and skin, in sweat gland ducts.

Cortical myoclonus may also be a relatively minor aspect of several degenerative diseases, where the clinical picture is dominated by other features. Examples are multiple system atrophy and Alzheimer's disease. Multifocal myoclonus, particularly of the hands, may be present in corticobasal degeneration, but it seems likely that the myoclonus in this condition is subserved by different pathways to classical cortical myoclonus. In particular, cortical sensory evoked potentials are not giant, and the latency of reflex responses is very short, raising the possibility of a direct relay of somatosensory afferent input to the motor cortex without involvement of the sensory cortex. Patients with Creutzfeldt–Jacob disease usually have myoclonus, which at least in some cases has a cortical origin.

Pharmacology and treatment

Drug treatment is primarily aimed at bolstering deficient inhibitory processes. In particular, a reduction of 25 to 50% of GABA levels has been reported in the cerebrospinal fluid of patients with posthypoxic myoclonus and progressive myoclonic epilepsy, and GABAergic drugs form the cornerstone of treatment. Of these sodium valproate is the most effective, and increases cortical GABA levels as well as potentiating GABA postsynaptic inhibitory activity. The drug is introduced slowly, with most patients needing doses of 1200 to 2000 mg/day. Transient gastrointestinal upset may occur during initial treatment, usually with nausea and vomiting, but sometimes with abdominal pain and diarrhea. Hair loss, tremor, hepatotoxicity and drowsiness may also occur.

Benzodiazepines and barbiturates facilitate GABAergic transmission by effects on the GABA receptor–ionophore complex. Clonazepam is the most useful antimyoclonic agent. Large doses of clonazepam are often necessary (as much as 15 mg/day). Undue drowsiness and ataxia are the only major side effects and can be largely overcome by gradually increasing the dosage. Abrupt reductions and withdrawls can result in a marked deterioration in myoclonus and withdrawal fits. Tolerance may develop over a period of several months in some patients. Primidone and phenobarbital are occasionally useful.

Piracetam is structurally similar to GABA, but it does not elicit specific GABAergic effects nor modify GABA levels in the brain, and its mechanism of action remains unclear. The drug's effectiveness is largely limited to cortical myoclonus, regardless of aetiology. This suggests that, where possible, electrophysiological assessment of the physiological type of myoclonus should be undertaken before considering treatment with the drug. Piracetam is well tolerated and does not alter blood levels of other anticonvulsants. In particular, it is non-sedating. It is usually prescribed as add-on therapy, but can be effective when given alone. Therapeutic dosages range between 2.4 g and 21.6 g. Abrupt withdrawal of piracetam has been associated

with a severe worsening of myoclonus and seizures in a minority of patients.

Disturbances of serotoninergic function have also been incriminated in cortical myoclonus. CSF concentrations of the principal metabolite of serotonin, 5-hydroxyindoleacetic acid, are reduced in these patients. However, treatment with serotonin precursors like 5-hydroxytryptophan, is poorly tolerated and, nowadays, only used as a last resort.

Phenytoin and carbamazepine are rarely helpful. In some patients, particularly those with Unverricht–Lundborg disease, phenytoin may exacerbate myoclonus. Carbamazepine may worsen myoclonic seizures. Vigabatrin, an irreversible inhibitor of GABA transaminase, surprisingly does not seem very useful. It may lead to a paradoxical increase in myoclonus in some patients, or, occasionally, myoclonus in its own right.

In summary, the treatments of first choice in cortical myoclonus are sodium valproate and clonazepam. However, most patients only gain adequate relief from their myoclonus when drugs are used in combination (Obeso et al., 1988). Gait disturbance tends to be the most resistant feature and a bouncy unsteady gait with frequent falls may persist despite control of action and reflex myoclonus in the upper limbs. The combination of clonazepam, primidone and either sodium valproate, piracetam or both may be necessary to provide substantial relief of myoclonus. Polytherapy is generally well tolerated, but doses may be limited by ataxia and drowsiness. Piracetam has particular advantages in these circumstances, as its addition to existing treatments is rarely accompanied by sedation.

Prognosis

Prognosis is dictated by the underlying condition. However, two conditions merit particular comment. The progressive myoclonic ataxia associated with coeliac disease often starts in the foot, slowly spreading to the other foot and upper limbs. Most patients become wheelchair bound or die within 2 years, regardless of dietary restriction (Bhatia et al., 1995). In posthypoxic myoclonus the disability following the hypoxic event is often severe, but it has recently been realized that late improvement in the myoclonic syndrome and the level of disability can occur years after onset (Werhahn et al., 1997). Some patients are eventually able to discontinue antimyoclonic medication and to walk unaided. Cognitive deficits are found in about half, but are usually mild. Epilepsy may be a problem in the first year, particularly during the initial period of posthypoxic coma, but thereafter only persists in the minority of cases. Other neurological deficits are rare.

Table 36.1. Diagnostic criteria for hereditary essential myoclonus

Onset under 20 years old
Males and females equally affected
Myoclonus with a benign course, compatible with a life of normal span
Dominant mode of inheritance, but with variable severity
Absence of seizures, dementia, gross ataxia and other neurological deficits
Normal EEG

Myoclonus in association with dystonia

Essential myoclonus

Essential myoclonus is commonly inherited as an autosomal dominant trait with variable penetrance and expression, when it is termed hereditary essential myoclonus (the terms essential familial myoclonus, familial myoclonia, ballistic overflow myoclonus and benign essential myoclonus have also been used). The diagnostic criteria for this condition have been set out by Mahloudji and Pikielny (1967), and are summarized in Table 36.1. The jerks are present at rest, but become more marked with action. They are worst around the neck and proximal arms, and may dramatically improve with alcohol. In many cases there is also evidence of dystonic posturing or a family history of dystonia. Sporadic cases are very similar and may be examples of hereditary essential myoclonus with incomplete penetrance, new mutations or truly sporadic phenocopies.

Myoclonic jerks arise from a distortion of the normal reciprocal activation pattern of ballistic movements, so that muscle activity is no longer restricted to appropriate muscles. EMG activity may also be prolonged, with conspicuous cocontraction. Stimulus sensitivity is not a prominent feature, although jerks can sometimes be provoked by unexpected loud noises. Cortical somatosensory evoked potentials are normal. Back-averaging of the EEG activity preceding jerks reveals no cortical correlate or an unusual generalized wave preceding the jerks by a longer interval than seen in cortical myoclonus.

The available but limited pharmacological evidence suggests a cholinergic–serotoninergic imbalance. Thera-

peutic trials have shown moderate benefit from benztropine mesylate and 5-HTP, although the latter is poorly tolerated. The deterioration of the myoclonus following parenteral physostigmine also supports a relative cholinergic overactivity. Antiepileptic treatments are not helpful, with the possible exception of clonazepam. Drug treatments generally fail to match the amelioration seen with alcohol, and as a result there is a real danger of alcoholism in this condition. Deep brain stimulation of the globus pallidus interna may be considered in intractable cases.

Myoclonic dystonia

Some families with idiopathic dystonia may have family members with jerks (termed myoclonic dystonia), but myoclonus is not found in the absence of dystonia and does not show a dramatic response to alcohol, distinguishing these families from those with hereditary essential myoclonus (Quinn, 1996).

Brainstem myoclonus and the startle syndrome: segmental

Brainstem myoclonus usually leads to generalized myoclonic jerks, as in brainstem reticular reflex myoclonus and hyperekplexia. Focal forms are rare, although diaphragmatic myoclonus may arise in the rostral medulla. Palatal myoclonus is best considered as a form of tremor.

Hyperekplexia/startle syndrome

The most striking clinical characteristic of the generalized forms of brainstem myoclonus is the exaggerated motor response to unexpected auditory and, sometimes, somesthetic and visual stimuli. Hyperekplexia is the commonest cause of the startle syndrome. It may be idiopathic, inherited as an autosommal dominant condition, or symptomatic. There is now general agreement that the response in hereditary and symptomatic hyperekplexia is a pathological exaggeration of the normal startle reflex (Brown et al., 1991b; Matsumoto et al., 1992). Both types of response are the result of activity in a common reflex centre in the lower brainstem. Thus (when allowance is made for the blink reflex which is usually elicited concurrently) the first EMG activity in the startle is recorded in sternocleidomastoid, with other cranial, trunk and limb muscles following in an orderly fashion, as myoclonic activity spreads up the brainstem and down the spinal cord (Fig. 36.2). Caudal muscles are recruited relatively slowly, and involvement of the

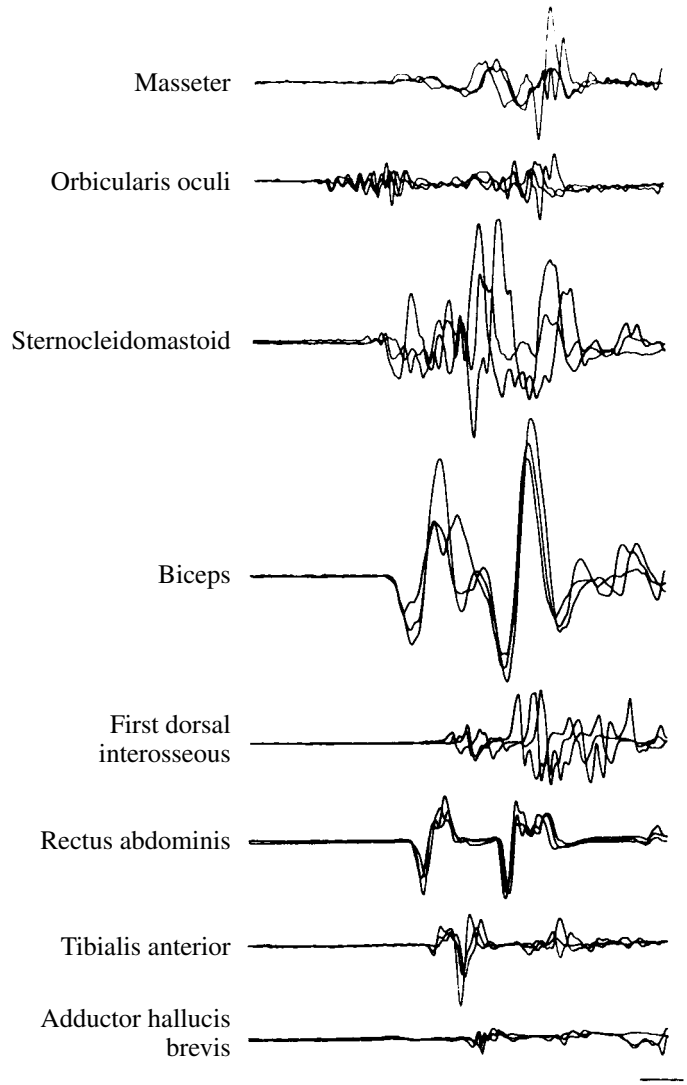

Fig. 36.2. The EMG activity in the abnormal startle response elicited by auditory stimulation in a patient with symptomatic hyperekplexia. The unrectified EMG activity in three single trials is superimposed. Each trial was started at the point of presentation of a 124 dB tone. Following the normal auditory blink reflex, EMG activity was recorded first in sternocleidomastoid, and then later in masseter and trunk limb muscles. The latencies to the intrinsic hand muscles of the hand and foot were disproportionately long. The horizontal calibration line represents 20 ms. The vertical calibration line represents 0.5 and 4.0 mV for the upper three channels, and the lower five channels, respectively. (Reprinted from Brown et al., 1991a, with permission.)

intrinsic hand and foot muscles is disproportionately delayed.

The reflex jerks to auditory, somesthetic or visual stimuli involve many muscles, both proximal and distal, bilaterally and synchronously to produce a sudden shock-like movement usually involving a grimace, abduction of the arms, and flexion of the neck, trunk, elbows, hips and knees. Thus the reflex jerks resemble the normal startle reaction in general character, although, clinically, they are greatly exaggerated in amplitude, more extensive in distribution and habituate poorly. Somesthetic stimuli are most effective when applied to the mantle area; that is the head, face and upper chest.

Many patients also exhibit generalized tonic spasms with unexpected stimuli, and it is these that lead to frequent injury and which are the most disabling feature of the condition. The pathophysiology of these tonic spasms is not known. They may be a brainstem phenomenon or the result of activity in the motor and supplementary motor cortex, as in startle epilepsy. Tonic spasms consist of generalized stiffening, lasting a few seconds, usually in response to unexpected somesthetic or acoustic stimuli. During these tonic spasms patients are unable to take any protective action and, if erect, fall stiffly to the ground, without losing consciousness. When present, tonic spasms tend to dominate the clinical picture. The tonic episodes are quite different to the brief, generalized startle reflexes seen in these patients and occur less frequently than the latter. They are also distinct from the tonic spasms of multiple sclerosis, which are usually painful, unilateral and rarely stimulus sensitive.

In addition, patients may experience excessive jerking, particularly during or going off to sleep. These paroxysms of jerking involve repetitive flexion of all four limbs, especially the legs. They are usually spontaneous. Consciousness is preserved in diurnal attacks, although jerking may be severe enough to cause incontinence of urine. The pathophysiology of the episodes of jerking, like that of the tonic spasms, is unclear.

Carbamazepine, phenytoin and the benzodiazepines, particularly clonazepam, form the mainstay of treatment, which is directed at the disabling tonic spasms rather than the exaggerated startle responses.

Hereditary hyperekplexia

Hereditary hyperekplexia is due to a mutation in the alpha$_1$ subunit of the glycine receptor, which may lead to altered ligand binding or disturbance of the chloride ion-channel part of the receptor (Shiang et al., 1993). Gycine receptors are widely distributed within the central nervous system, and this change in the alpha$_1$ subunit may account for the range of abnormalities which can be present in this condition. Stiffness and apneic attacks as a baby, hyperreflexia, a hesitant wide-based gait, epilepsy, and low intelligence may occur in addition to an exaggerated startle, tonic spasms and paroxysms of jerking.

The clinical and electrophysiological findings vary between members of the same family, and many relatives may only have an excessive startle reaction, without other neurological abnormalities. The mutation in the glycine receptor is rarely found in these minor forms, despite its presence in more affected relatives and it is possible that these minor forms represent a normal variant or 'copied' behaviour.

Acquired hyperekplexia

Clinically, idiopathic and symptomatic hyperekplexia are usually only distinguished from hereditary hyperekplexia by the absence of a family history and the presence of any signs attributable to the underlying disease in symptomatic forms. Patients have an exaggerated startle reflex, with or without tonic spasms and paroxysms of jerking. Tonic spasms are occasionally complicated by laryngeal spasm, with the risk of respiratory arrest. So far, sporadic cases have not been found to have mutations in the glycine receptor. Symptomatic hyperekplexia is usually due to brainstem disease, such as infarct, hemorrhage or encephalitis.

Startle epilepsy

Startle epilepsy can readily be distinguished from hyperekplexia, although similar pathophysiological mechanisms may operate in the tonic episodes of each condition. Startle epilepsy is seen in the setting of early brain damage, usually perinatal anoxia (Chauvel et al., 1992). Most patients have a hemiparesis, and mental retardation is common. Seizures begin in childhood or adolescence, and tend to be frequent. They consist of tonic spasms, lasting up to 30s, with preservation of consciousness. The spasms are typically asymmetrical and predominatly involve the paretic limbs. They may be elicited by unexpected auditory, visual or somesthetic stimulation, or occur spontaneously. Other seizure types occur in about a quarter of patients. Cranial imaging is abnormal in the majority of cases, usually showing unilateral atrophy involving the lateral central and pericentral cortex. The interictal EEG is generally abnormal with localized or diffuse slow waves and spikes. Ictal scalp-recorded EEG shows a fast low amplitude discharge often preceded by a high voltage spike at the vertex. Using depth electrodes the tonic seizures have been shown to originate in the motor or supplementary motor cortex.

Brainstem reticular reflex myoclonus

This rare form of generalized myoclonus may occur in posthypoxic encephalopathy, brainstem encephalitis and uremia. It responds to anticonvulsant drugs, particularly clonazepam and sodium valproate. Clinically, it is distinguished from hyperekplexia by the frequent occurrence of spontaneous, as well as reflex jerks to auditory and somesthetic stimulation. The latter is most effective over the distal limbs, rather than the mantle area typical of hyperekplexia. The basic pattern of muscle recruitment in the jerks is similar to that recorded in hyperekplexia in so far as activity seems to spread from the caudal brainstem (Hallett et al., 1977). EMG activity is recorded first in trapezius and sternocleidomastoid, and later in other cranial, trunk and limb muscles. The relative latencies to onset of reflex EMG activity in these muscles increases with the distance of their respective segmental innervations from the lower brainstem.

These generalized jerks are therefore believed to arise in the reticular formation of the caudal brainstem. Despite this, several important electrophysiological distinctions exist between brainstem reticular reflex myoclonus and hyperekplexia, making it likely that their origins within the bulbopontine reticular formation are different. The difference between the relative latencies of trunk and limb muscles is small in the jerks of brainstem reticular reflex myoclonus, indicating that the spinal motor pathways are rapidly conducting, with velocities comparable to those of rapidly conducting pyramidal pathways. This is in contrast to the findings in hyperekplexia. Also, in reticular reflex myoclonus the relative latencies of the intrinsic hand and foot muscles are not disproportionately prolonged, as in hyperekplexia.

Startle responses with unknown physiology

There remain several other conditions in which an exaggerated startle is a prominent feature, but the physiology of the motor response is unclear. Infantile GM2 gangliosidosis (Tay–Sachs and Sandhoff's diseases) is characterized by hypotonia, irritability and abnormal startle responses in infancy. Developmental regression, progressive blindness with a cherry red macular spot, deafness, seizures and spasticity ensue. Death usually occurs before the third year. The physiology of the abnormal startle is unknown in this condition, but a relationship to the normal startle or Moro response seems unlikely as the motor response consists of a sudden extension of the arms, head and trunk.

Tics in Gilles de la Tourette's syndrome usually are spontaneous, but sometimes may be triggered by external stimuli and may have the appearance of an exaggerated startle response. They rarely represent a diagnostic problem as the other clinical features of Gilles de la Tourette's syndrome are distinctive. In jumping, latah and myriachit unexpected sensory stimulation leads to an initial violent start followed by automatic speech or behaviour, such as echolalia, echopraxia or the assumption of a defensive posture.

Spinal myoclonus

The spinal cord possesses both local segmental organization and long propriospinal pathways linking activity across many segments. Pathological activity in either system can lead to myoclonus. Very rarely, focal myoclonus may be due to a lesion of the spinal root, plexus or peripheral nerve.

Propriospinal myoclonus

In this form of myoclonus a spinal myoclonic generator recruits axial muscles up and down the spinal cord via long propriospinal pathways (Brown et al., 1991a; Schulz-Bonhage et al., 1996). The disorder generally develops in middle age, and follows cervical trauma, albeit mild, in about half of cases. Its course is relatively benign, with a history of involuntary jerking stretching back up to 25 years. Spontaneous remission is unusual. Myoclonus usually takes the form of axial flexion jerks involving the neck, trunk, and hips, although a minority of patients may have truncal extension jerks. It may occur spontaneously, particularly on lying flat, or be precipitated by somesthetic stimuli. Myoclonic EMG activity usually consists of repetitive bursts with a frequency of 1–7Hz. EMG bursts can be quite long, lasting several hundred milliseconds. The jerks may be stimulus sensitive, particularly to taps to the abdomen, biceps or patella tendons. The orderly recruitment of rostral and caudal segments from a given spinal focus often confirms a spinal origin for the myoclonus (Fig. 36.3), although it is not always possible to distinguish such a pattern of activation. Clonazepam has proven the most effective treatment for propriospinal myoclonus, and leads to partial improvement in over half of patients. Other anticonvulsants have been largely unhelpful.

Segmental spinal myoclonus

Segmental spinal myoclonus is often symptomatic of an underlying structural lesion, such as an intrinsic or extrinsic

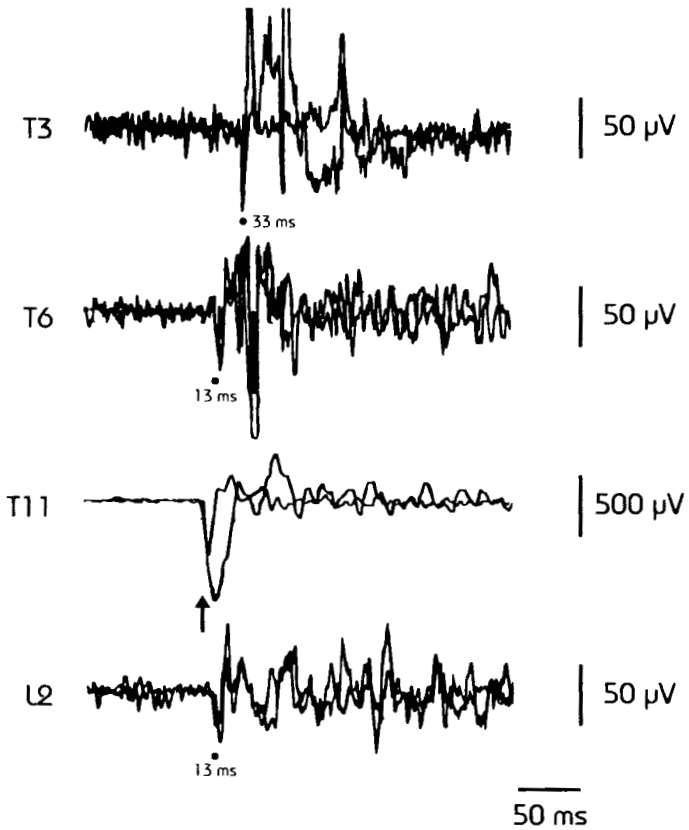

Fig. 36.3. EMG recordings from erector spinae at various vertebral levels from the second lumbar vertebra (L2) to the third thoracic vertebra (T3) in a patient with stimulus-sensitive propriospinal myoclonus. Two recordings are superimposed. Jerks were elicited by tapping the electrode overlying T11 (arrowed). Latencies are given with respect to the stimulus artefact at T11. Propagation occurs away from the lower thoracic level. (Reprinted from Schulze-Bonhage et al., 1996, with permission.)

malignancy or syringomyelia, or of viral or paraneoplastic myelitis (Brown, 1994). It is confined to one or a few contiguous myotomes, and is most often rhythmic, the frequency of the jerks varying between 1 and 2 per minute to 240 per minute. EMG bursts may be up to 1000 ms in duration. Clues to a spinal origin are the independence from supraspinal influences and persistence of myoclonus in sleep. The condition may or may not be stimulus sensitive.

Segmental spinal myoclonus is believed to result from the isolation of spinal motoneurones from inhibitory influences or from direct cellular injury. Treatment is that of the underlying cause, where this is possible. Symptomatic treatment is only moderately effective. Clonazepam is the drug of first choice and, in dosages of up to 6 mg daily, may diminish or abolish myoclonus.

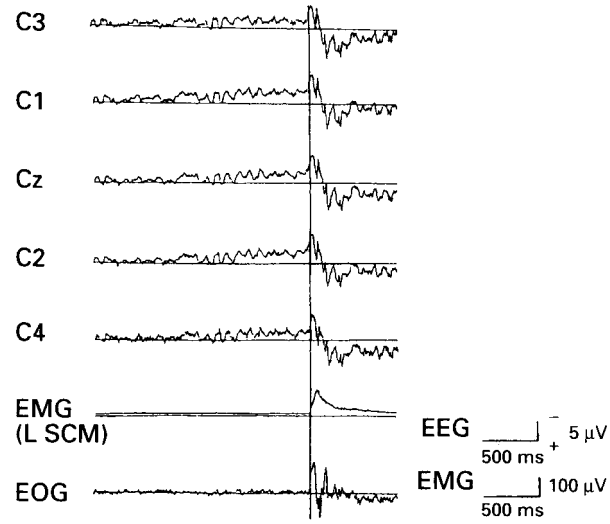

Fig. 36.4. Records from a patient with psychogenic myoclonus. EEG activity has been realigned to the onset of the jerk recorded in left sternocleidomastoid (L SCM) and then averaged to give the 'backaveraged EEG'. This shows a slow negative wave (the Bereitschaftspotential) starting 1.3 seconds before the EMG onset. Compare this wave to the brief, giant wave, which precedes cortial myoclonus by 20 or so milliseconds in Fig. 36.1. (Reprinted from Terada et al., 1995, with permission.)

Diazepam, carbamazepine and tetrabenazine have been useful in occasional cases.

Psychogenic myoclonus

Clinical features suggestive, but not diagnostic, of a psychogenic origin are the sudden onset of an inconsistent and variable movement disorder, which does not overly trouble the subject. Additional clues are the lessening of movements when distracted and, conversely, a dramatic increase in severity and complexity of movements during direct observation, settling again when no longer under direct observation. The absence of signs of organic neurological disease and the unusual nature of the movements are also suggestive, but not necessarily diagnostic of a psychogenic etiology. More convincing is the disappearance of the movement disorder when supposedly unobserved or following suggestion and placebo. The typical indicators of a conversion disorder, such as psychological precipitants, multiple somatizations and secondary gain may or may not be present.

The electrophysiological pattern of psychogenic jerks is indistinguishable from that of voluntary movements. In particular, EMG burst duration is almost always longer

than 70ms (unlike cortical myoclonus) and may involve a triphasic activation of agonist and antagonist muscles. The pattern of recruitment of muscles with different segmental origins is variable, and the latencies of reflex jerks are long. In patients with spontaneous jerks good electrophysiological evidence in favour of psychogenic myoclonus is the presence of a slow negative wave (Terada et al., 1995), the Bereitschaftspotential, in the EEG backaveraged from the jerks (Fig. 36.4).

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Dystonia

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Dystonia is a movement disorder characterized by sustained involuntary muscle contraction causing abnormal twisting, repetitive movements or posturing that tend to have a directional predominance. Descriptions of dystonic patients, who were often believed to be hysterical, first appeared at the beginning of the twentieth century (Zeman & Dyken, 1968). In 1908, Schwalbe ascertained the hereditary nature of the illness and its variable expression (Schwalbe, 1908). The term 'dystonia musculorum deformans' was first used by Oppenheim (1911), while Mendel and Flateau, emphasizing the twisted posture, called the disease 'torsion dystonia' or 'torsion spasm' (Flateau & Sterling, 1911; Zeman & Dyken, 1968).

After a period of relative inattention, interest in dystonia revived in the 1970s with a fuller delineation of the symptomatology allowing the recognition of focal forms. More recent technological developments have culminated in the identification of genetic mutations underlying generalized torsion dystonia, dopa-responsive dystonia, and some focal dystonias. New therapies have been developed including botulinum toxin injections, stereotactic surgery, and deep brain stimulation.

Classification

Dystonia can be classified by etiology, by the body area involved, and by the age of onset. The division by etiology into primary (idiopathic) and secondary (symptomatic) dystonia provides a schema for evaluating the patient. The classification by affected region is especially useful for the primary dystonias, where the epidemiology, prognosis, treatment and genetics differ by dystonia type. Classifying dystonia by age of onset is also most applicable to primary dystonia, where it serves to separate idiopathic generalized torsion dystonia of childhood onset from the focal dystonias which typically present in adulthood.

A classification suggested by Fahn et al., divides dystonias into primary dystonia, 'dystonia-plus' syndromes in which dystonia combines with other neurological symptomatology, secondary dystonia where an underlying pathological process causing dystonia can be identified, and heredofamilial dystonia in which there is an underlying neurodegenerative disorder (Fahn et al., 1998).

Signs and symptoms

Idiopathic dystonia often first manifests as a feeling of discomfort or stiffness in the affected body part. Abnormal movement ensues and initially may only be apparent when performing specific acts, interfering with smooth and accurate performance. As it progresses, dystonia occurs with other voluntary movements and may eventually be present even at rest. Dystonic muscles may hypertrophy; fixed contractures and deformity occur in severe cases. Dystonia disappears during sleep. Prolonged muscle spasm can lead to aching, but severe pain is generally absent except in cervical dystonia.

Dystonia may be the sole movement disorder present or it may be accompanied by postural or action tremor (Cohen et al., 1987; Jedynak et al., 1991; Lou & Jankovic, 1991; Dubinsky et al., 1993). As shown in the Fig. 37.1, some patients have 'gestes antagonistes' or tricks whereby a simple touch or movement temporarily relieves the dystonia. Primary sensory function assessed by routine neurologic examination, strength, muscle tone, and reflexes are normal in idiopathic dystonia. The presence of such neurologic signs should therefore suggest another diagnosis.

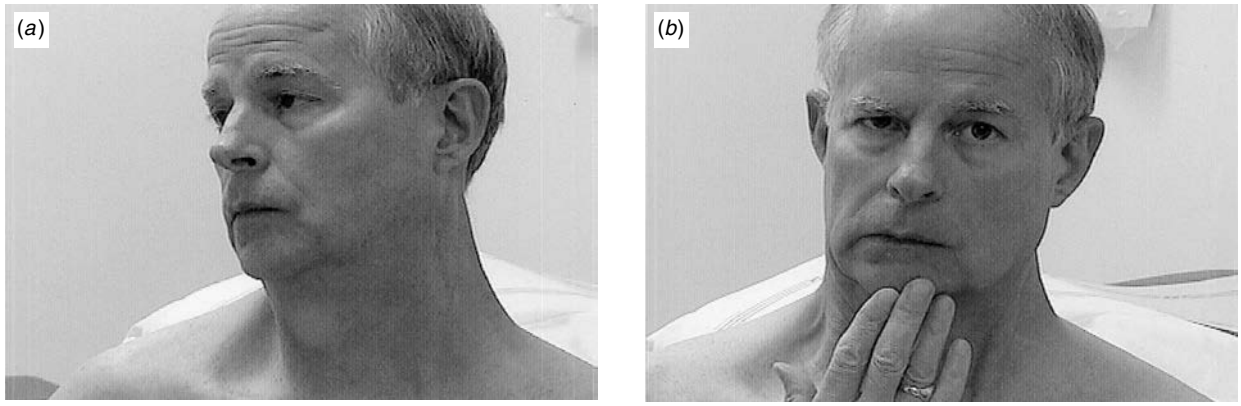

Fig 37.1. (*a*) Resting position of the head in a patient with torticollis. (*b*) Resting position of the head during the geste antagoniste. A light touch to the chin allows the head to return to a forward position.

Primary dystonias

The generalized dystonias include idiopathic torsion dystonia (formerly called 'dystonia musculorum deformans') and 'dystonia-plus' syndromes such as dopa-responsive dystonia, paroxysmal choreoathetosis/dystonia, rapid onset dystonia/parkinsonism and myoclonic dystonia.

Idiopathic generalized torsion dystonia (early-onset torsion dystonia) typically presents between ages 6 and 12, almost always before age 24 (Marsden & Harrison, 1974; Bressman et al., 2000). The first sign in many patients is limb involvement (Bressman et al., 2000), such as gait impairment due to foot flexion and inversion. When dystonia presents with early onset and limb involvement, it is especially likely to progress and become generalized, but affects the cranial muscles in only 11% of patients. Symptoms usually stabilize after 5–10 years. While patients often become wheelchair bound, lifespan is nearly normal. Remissions lasting hours to years occur in up to 20% of patients.

Early-onset generalized torsion dystonia is most frequently an autosomal dominant disease with a reduced penetrance. In the most common form, DYT1, the clinical expression is highly variable and members of the same family may have focal rather than generalized symptoms. The gene underlying this disorder has been identified and will be discussed below.

Dopa-responsive dystonia (DRD) is a less common form of generalized dystonia characterized by childhood-onset, diurnal variation and exquisite sensitivity to low doses of l-dopa (Segawa et al., 1976; Nygaard et al., 1990). In this disorder, dystonic symptoms progressively worsen during the day and improve with sleep. The presence of spasticity and mild hyperreflexia in some patients may lead to the mistaken diagnosis of cerebral palsy. Parkinsonism may develop later in the course. Genetic mutations underlying both autosomal dominant and autosomal recessive forms of DRD have been identified and will be discussed below.

In paroxysmal dystonic choreoathetosis (PDC), attacks of generalized dystonia sometimes accompanied by choreoathetosis begin in infancy or childhood. In kinesigenic dyskinesia, brief attacks follow exercise or movement. In the rarer non-kinesigenic PDC, episodes are precipitated by alcohol, stress or caffeine and last minutes to hours (Bhatia, 1999). Patients are asymptomatic between attacks.

Myoclonic dystonia is an autosomal dominant disease with myoclonus and dystonia beginning in adolescence (Quinn et al., 1988; Klein et al., 1999). Both symptoms may respond dramatically to alcohol ingestion. Unlike early-onset idiopathic generalized torsion dystonia, it typically spares the legs.

Focal dystonias

Focal dystonias are named by the predominant site of involvement. The extent to which the various forms of focal dystonia share genetic or physiological underpinnings is unknown. Focal dystonia can be the presenting feature of generalized dystonia, but especially in later-onset cases, tends to remain focal.

Cervical dystonia (spasmodic torticollis) is the most common focal dystonia with approximately 9 cases/100 000 population (Nutt et al., 1988). Women are more often affected than men and the usual age of onset is 40–60 years (Jankovic et al., 1991). Cervical dystonia is named by the direction of head movement. The most common pattern is torticollis, where the head turns to one

side due in part to overactivity of the opposite sternocleidomastoid muscle. In retrocollis, the head tilts backward due to over-contraction of neck extensors such as splenius capitus. In anterocollis the neck is flexed due to hyperactivity of the anterior scalenes and sternocleidomastoids. Laterocollis, head tilt, and other patterns are less common. Cervical dystonia is often accompanied by tremor and shoulder elevation. Unlike other focal dystonias, cervical dystonia is often painful.

Patients with blepharospasm often first complain of uncomfortable sensations in or around the eyes. Bilateral involuntary eye closure ensues leading to visual impairment, and, at worst, functional blindness. In Meige syndrome, blepharospasm combines with oromandibular dystonia where the abnormal movements encompass the jaw, face, and neck.

Dystonia of the vocal cords is called spasmodic dysphonia. The most common form is adductor spasm, in which dystonia of the thyroarytenoid muscles produces a hoarse, choked voice. The less common abductor spasm is due largely to cricoarytenoid dystonia and leads to an intermittent soft, whispery voice.

Focal hand dystonia often arises in those whose work entails repetitive small hand movements or following a period of particularly excessive hand use. The initial sign may be a feeling of tightness or stiffness in the affected limb. As the dystonia develops, abnormal hand posture may become apparent accompanied by loss of speed, impaired movement fluency, and inaccurate motor control. At its onset, limb dystonia may be task-specific, i.e. present only during a particular action such as writing or playing a musical instrument. Other movements, even those utilizing the same muscles, can be performed normally. In some patients, the dystonia progresses to include other activities and at times, may become obvious even at rest. When limb dystonia involves the contiguous proximal limb girdle musculature, it is called segmental dystonia.

Hemidystonia, in which only half of the body is affected, is often secondary to structural brain damage (Marsden et al., 1985).

Secondary dystonia

Dystonia can be part of the symptomatology of a wide range of metabolic and degenerative diseases, can accompany or follow brain damage, or be caused by medications (Table 37.1). When identifiable brain lesions are present in patients with symptomatic dystonia, the basal ganglia, especially the putamen, are likely to be involved (Marsden et al., 1985; Bhatia & Marsden, 1994; Kostic et al., 1996; Lehericy et al., 1996). Conversely, dystonia is the most common movement disorder associated with basal ganglia damage (Bhatia & Marsden, 1994). Dystonia can occasionally arise from damage in the thalamus, subthalamic area, brainstem, or with posterior fossa or cervical lesions (Jankovic & Patel, 1983; Lee & Marsden, 1994; Cammarota et al., 1995; Jho & Janetta, 1995; Krauss et al., 1997).

Dystonia is part of the symptomatology of several known basal ganglia diseases. It is seen with Parkinson's disease and other parkinsonian and degenerative disorders such as X-linked dystonia/parkinsonism (Lubag), rapid-onset dystonia–parkinsonism, and corticobasal ganglionic degeneration. In Wilson's disease, dystonia may arise before tremor or cerebellar signs. Neuroleptic medications are a common cause of both acute dystonic reactions and tardive dystonia, especially in the psychiatric population.

Table 37.1. Dystonia in association with other disorders and causes of secondary dystonia

Degenerative and metabolic diseases
Parkinson's disease
Parkinsonian syndromes
Lubag
Machado-Joseph
Corticobasalganglionic degeneration
Dentato-rubro-pallido-luysian atrophy
Huntington's disease
Hallervorden Spatz disease
Wilson's disease
Gangliosidoses
Lipidoses
Amino acidurias
Leigh's disease
Injury or toxicity
Perinatal birth injury/ cerebral palsy
Head trauma
Peripheral trauma
Cervical cord injury
Post-encephalitis
Post-hypoxia
Poisoning (manganese, cyanide, methanol, carbon monoxide)
Pontine and extrapontine myelinolysis
Brain tumour
Multiple Sclerosis
Psychogenic
Medications
Neuroleptics,
Anticonvulsants
Antidepressants
L-dopa

Table 37.2. Genetics of dystonia

Genotype	Location	Mutation	Phenotype
DYT1	9q34	GAG deletion in Torsin A	Early-onset generalized dystonia
DYT2	Unknown	Unknown	Autosomal recessive dystonia in Gypsies(Gimenez-Roldan et al., 1988)
DYT3	Xq13.1	Unknown	X-linked dystonia/parkinsonism (Lubag)
DYT4	Unknown	Unknown	Hereditary whispering dystonia in an Australian family (Parker, 1985)
DYT5	14q22.1-22.2	GTP cyclohydrolase I	Dopa-responsive dystonia-autosomal dominant
	11p15.5	Tyrosine hydroxylase	Dopa-responsive dystonia-autosomal recessive
DYT6	8p21-q22	Unknown	Phenotype intermediate to early- and late-onset dystonia in Mennonites
DYT7	18p	Unknown	Adult-onset torticollis and spasmodic dysphonia
DYT8	2q33-35	?channelopathy	Paroxysmal non-kinesigenic dystonic choreoathetosis
DYT9	1p	Unknown	Paroxysmal choreoathetosis with episodic ataxia
DYT10	16p11.2-q12.1	Unknown	Paroxysmal kinesigenic dystonic choreoathetosis
DYT11	11q23	Dopamine receptor D2	Myoclonic dystonia
DYT12	19q13	Unknown	Rapid onset dystonia-parkinsonism

Post-hemiplegic dystonia follows ischemic brain damage or trauma and is probably due to aberrant cerebral reorganization. Extrapontine myelinolysis, a neurologic disorder caused by rapid correction of hyponatremia, frequently affects the basal ganglia and dystonia often develops weeks to months after the initial brain insult (Wu & Lu, 1992; Seiser et al., 1998).

Dystonia, especially hemidystonia, can follow head trauma with a latency of months to years (Krauss et al., 1992, 1996). The contralateral basal ganglia and thalamus are the most frequent lesion sites in post-traumatic dystonia (Lee et al., 1994).

There is also an association between peripheral trauma and the development of dystonia (Schott, 1985; Jankovic & Van Der Linden, 1988). Bhatia et al. reported a history of trauma to the dystonic body part within 3 months preceding the onset of dystonia in 39% of patients with primary axial dystonia (Bhatia et al., 1997). Similarly, peripheral trauma appeared to trigger the onset in up to 20% of cases with idiopathic generalized torsion dystonia reported by Fletcher et al. (1991). Tarsy identified differences in cervical dystonia developing immediately after trauma from that developing later and from idiopathic torticollis (Tarsy, 1998). Acute onset torticollis reached maximal intensity within days of the injury, had a more fixed posture, no relief with sensory tricks, and poorer response to botulinum toxin injection.

Dental procedures and facial trauma can trigger oromandibular dystonia, even in areas of the face and oropharynx not directly traumatized. These patients often have pain and dysesthesia as well as dystonia (Sankhla et al., 1998; Schrag et al., 1999).

Dystonia is no longer considered a hysterical disorder, but can be psychogenic in some patients. Psychogenic dystonia should be suspected when there is no identified underlying cause, abrupt onset, rapid progression to fixed posture, prominent pain, other psychogenic neurologic signs, and multiple somatizations (Lang, 1995).

Secondary dystonias can be recognized by the clinical setting and by the presence of neurological signs other than dystonia. Evaluation for treatable form of dystonia, such as Wilson's disease, should be undertaken in all patients in whom an etiology is not apparent.

Epidemiology

Nutt et al. (1988) found a prevalence of generalized dystonia of 3.4/100000 and focal dystonia of 29.5/100000 in Rochester, Minnesota in 1980. The European Dystonia Study Group found that, except for writer's cramp, segmental and focal dystonias are more common in women, but that men tend to have an earlier age of onset (Epidemiologic Study of Dystonia in Europe Collaborative Group, 1999).

Genetics

Table 37.2 summarizes the identified dystonia genes.

Idiopathic torsion dystonia

Early-onset idiopathic torsion dystonia is most often an autosomal dominant disorder with 30–40% penetrance.

Ozelius et al., first reported the localization of the gene (DYT1) for this disorder to chromosome 9q34 in 1989 (Ozelius et al., 1989). In 1997, the same group identified the gene itself (Ozelius et al., 1997). Early-onset torsion dystonia is caused by a GAG deletion in the DYT1 gene resulting in the loss of a glutamine residue from a conserved region of an ATP binding protein, Torsin A. Although the function of Torsin A is not known, it is structurally related to heat shock proteins. Torsin A is expressed in the substantia nigra pars compacta, the major source of dopaminergic neurons projecting to the basal ganglia (Augood et al., 1999).

The DYT1 mutation is present in 2.7/100000 Ashkenazi Jews but only in 0.5/100000 of the general population. Early-onset idiopathic torsion dystonia in Ashkenazi Jews appears to have arisen from a single founder mutation (Risch et al., 1995). The GAG deletion in the Torsin A gene is responsible for 60–75% of cases of early-onset idiopathic dystonia. The DYT1 mutation can be associated with atypical phenotypes in different members of the same family, such as postural hand tremor or stuttering (Slominsky et al., 1999).

Less is known about the genetics of adult-onset idiopathic dystonias. Up to 25% of patients with focal dystonias have other affected family members and these disorders may also be autosomal dominant with incomplete penetrance and variable phenotypic expression (Waddy et al., 1991; Stojanovic et al., 1995; Leube et al., 1997). The DYT1 mutation is not involved (Valente et al., 1998). There is similarly no evidence that the DYT1 founder mutation plays a role in the development of secondary dystonia (Bressman et al., 1997).

Dopa-responsive dystonia

Dopa-responsive dystonia (DRD) can be an autosomal dominant or recessive disorder. Autosomal dominant DRD is caused by mutations on chromosome 14q22.1–22.2 in the gene for the tetrahydrobiopterin (BH4) biosynthetic enzyme, GTP cyclohydrolase I (GCH1). BH4 is a required cofactor for tyrosine hydroxylase, the first enzyme in the synthesis of dopamine from tyrosine. These patients therefore have low basal ganglia neopterin and biopterin levels. Putaminal tyrosine hydroxylase levels may also be low (Furukawa & Kish, 1999; Furukawa et al., 1999; Ichinose & Nagatsu, 1999). More than 30 mutations have been reported in the GCH1 gene, but the specific mutation does not predict the clinical picture. As with idiopathic early-onset dystonia, there is marked phenotypic variation even in the same family. Mutations in the tyrosine hydroxylase gene itself have been found in patients with autosomal recessive DRD (Nygaard et al., 1990; Ichinose & Nagatsu, 1999).

Other dystonias

Almasy et al. (1997) identified DYT 6 in the pericentromeric region of chromosome 8 in 2 Mennonite families with a phenotype intermediate to that of early and late-onset dystonia. Leube et al. (1996) identified DYT7 on chromosome 18p in a single pedigree from northwest Germany with adult-onset spasmodic torticollis and spasmodic dysphonia.

Autosomal dominant paroxysmal non-kinesigenic dystonic choreoathetosis has been mapped to chromosome 2q31–36 and, similar to other paroxysmal movement disorders, may be a channelopathy (Fink et al., 1997; Jarman et al., 1997; Matsuo et al., 1999). Paroxysmal kinesigenic dystonic choreoathetosis appears to localize to chromosome 16 (Bennett et al., 2000). Myoclonic dystonia is associated with a mutation in the dopamine D2 receptor on chromosome 11 (Klein et al., 1999). The area of the X-chromosome linked to the DYT3 gene associated with X-linked dystonia/parkinsonism is being narrowed (Nemeth et al., 1999). Rapid onset dystonia-parkinsonism is a rare autosomal dominant disease in which dystonia and parkinsonism evolve over hours or days. This disorder has been linked to chromosome 19q13 (Brashear et al., 1998; Kramer et al., 1999). Despite the progress made to date, idiopathic dystonias appear to have wide genetic heterogeneity and the presently identified genes cannot account for most cases (Jarman et al., 1999).

Pathology

While isolated cases of neuronal loss and gliosis have been reported (Zeman & Dyken, 1968; Zweig et al., 1988), routine pathological examination is generally unrevealing in idiopathic dystonia (Zeman, 1970; Hornykiewicz et al., 1986; Gibb et al., 1988; Furukawa et al., 2000). X-linked dystonia–parkinsonism, however, has been associated with a mosaic pattern of striatal gliosis (Altrocchi & Forno, 1983; Gibb et al., 1992; Waters et al., 1993), and hypopigmentation of dopaminergic cells in the substantia nigra may be seen in dopa-responsive dystonia (Rajput et al., 1994).

Becker et al. (1999) recently reported increased copper and a trend towards increased manganese in the globus pallidus and putamen in idiopathic adult-onset dystonia. These changes in metal deposition may explain the increased basal ganglia echogenicity on transcranial sonography in patients with idiopathic dystonia reported

by Naumann and Becker (Naumann et al., 1996; Becker et al., 1997). Naumann et al. (1998c) failed to find changes in *N*-acetyl aspartate/creatine-lactate/creatine ratio in focal hand dystonia, suggesting no neuronal loss or change in aerobic metabolism.

Neurochemistry

Although a unifying neurochemical abnormality has not been identified in dystonia, dopamine is likely to be involved. Dystonia is part of the symptomatology of other disorders with dopaminergic dysfunction such as Parkinson's disease, myoclonus-dystonia, dopa-responsive dystonia, rapid-onset dystonia parkinsonism, and X-linked dystonia–parkinsonism. Dystonia also arises with l-dopa treatment in Parkinson's disease patients. Neuroleptic medications, which are dopamine antagonists, can cause both acute and tardive dystonia.

Direct measurement of neurotransmitters and their metabolites in cerebrospinal fluid (CSF) or pathological specimens have given inconsistent results. Low CSF levels of homovanillic acid (HVA), the major metabolite of dopamine, have been found in isolated cases of idiopathic dystonia (Tabaddor et al., 1978; Ashizawa et al., 1980), but are usually normal (Marsden & Harrison, 1974). CSF HVA is low in dopa-responsive dystonia, and rapid-onset dystonia–parkinsonism (Nygaard et al., 1990; Brashear et al., 1998). Hornykeiwicz also found decreased striatal dopamine in a single patient with idiopathic dystonia (Hornykiewicz et al., 1986). In contrast, striatal dopamine and HVA concentrations were normal in a single patient with the DYT1 mutation reported by Furukawa et al. (2000).

In vivo positron emission tomography (PET) and single photon emission tomography (SPECT) studies have similarly given inconsistent results. Kishore et al., found elevated D2 receptor binding in the striatum in both patients and asymptomatic gene carriers of dopa-responsive dystonia (Kischore, 1998), and Leenders et al. (1993) found increased striatal uptake of C11-methyl-spiperone contralateral to dystonia in 6 focal dystonia patients. Perlmutter et al. (1997a), however, found decreased F18-spiperone binding in the putamen in idiopathic blepharospasm and oromandibular dystonia, and Naumann et al. (1998a) found decreased D2 receptor binding in the striatum of patients with torticollis. In the same study, Naumann found normal presynaptic tracer uptake; however, Playford et al. (1993) reported decreased F18-dopa uptake in the putamen in idiopathic dystonia. Vidailhet et al. (1999) found decreased F-dopa uptake in the striatum of patients with dystonia secondary to midbrain strokes that paralleled the severity of the dystonia.

Animal studies have also implicated dopamine. In MPTP-poisoned animals, dystonia appears before the onset of parkinsonian symptoms. In these animals, Perlmutter et al. (1997b) found that the dystonic phase was associated with a 98% decrease in dopamine in the ipsilateral caudate and putamen and decreased D2 receptor number bilaterally, which increased as the dystonia improved. In the spontaneously dystonic hamster, D1 and D2 binding are decreased in the dorsomedial striatum as well as in limbic structures (Nobrega et al., 1999).

Although the strongest evidence is for dopaminergic dysfunction, other neurotransmitters may be involved. Jankovic and Patel (1983) and Hornykiewicz et al. (1986) found abnormalities of several neurotransmitters, especially norepinephrine, in patients with idiopathic dystonia. The dystonic dt rat has more marked changes in norepinephrine than dopamine (Richter & Loscher, 1998). The response of some dystonia patients to anticholinergic medications raises the possibility of an abnormality in acetylcholine function or in interactions between dopaminergic and cholinergic pathways.

Both decreased activity in the D2-mediated indirect pathway (Perlmutter et al., 1997a; Todd & Perlmutter, 1998) and increases in the D1-direct pathway (Eidelberg et al., 1995; Karp et al., 1999) in the basal ganglia have been proposed as underlying dystonia. Either condition would lead to impaired thalamic inhibition by the globus pallidus and thus to excess thalamic stimulation of the cerebral cortex. Rather than being due to an absolute underactivity or overactivity in either pathway, dystonia may arise from an imbalance between the two.

Animal models

There are two animal lines with spontaneously-arising dystonia. The dt rat develops generalized dystonia after a period of normal motor development which worsens with stress and disappears during rest (Richter & Loscher, 1998). Similar to human idiopathic dystonia, cerebral gross and microscopic pathology are normal. Studies in these rats have suggested cerebellar and noradrenergic dysfunction. In the dystonic hamster (dt^{SZ}), dystonia is precipitated by stress and worsened by selective dopamine uptake inhibitors and intrastriatal injection of dopamine agonists (Rehders et al., 2000). During dystonic attacks, dopamine transporter binding is decreased in the nucleus accumbens and ventral tegmental area (Norbrega, 1999).

Dystonia can be induced in otherwise normal animals. Matsumura et al. (1991) showed that local application of bicuculline, a GABA antagonist, onto motor cortex caused disordered movement and changed the EMG pattern from reciprocal activity of antagonist muscles to co-contraction. At the cellular level, there was a loss of cell directionality and conversion of silent cells into active ones (Matsumura et al., 1992). Guehl et al., used bicuculline injections into the ventrolateral (VL) thalamus to produce dystonia (Guehl et al., 2000). In these animals, injections into the rostral VL thalamus caused severe dystonic posturing, difficulty performing a sequential motor task, and, by EMG, prolonged muscle bursts with co-contraction of antagonist muscles. Injection into the caudal VL thalamus led to dystonia with myoclonus. Byl et al. (1996) showed that repetitive hand movements in monkeys could induce a motor dysfunction similar to dystonia associated with enlargement and overlap of somatosensory neuron receptive fields for the fingers in primary sensory cortex (Topp & Byl, 1999). A role for aberrant plasticity in the development of dystonia is also supported by studies in rats, where facial palsy coupled with mild dopamine deficiency induced by unilateral injection of 6–OH-dopamine caused blepharospasm with increased excitability of the blink reflex (Schicatano et al., 1997).

Physiology

Dystonic movements have been studied electromyographically since the mid-twentieth century (Herz, 1944; Tournay & Paillard, 1955). They are characterized by cocontraction of agonist/antagonist muscles with loss of normal alternation, prolonged duration of muscle bursts with superimposed shorter, repeated bursts of activity, lack of selectivity for individual movements, overflow of contraction to muscles not normally activated by the task being performed, and failure of some muscles to activate voluntarily (Cohen & Hallett, 1988; Berardelli et al., 1998). The time needed to switch between components of a voluntary complex motor task is increased (Agostino et al., 1992). Using cross-correlational analysis, Farmer et al. (1998) showed that dystonic cocontraction is distinct from voluntary cocontraction and is due to abnormal presynaptic synchronization of antagonistic motor pools.

Reciprocal inhibition is a process by which activation of a muscle suppresses activity in its antagonist. Deficient reciprocal inhibition, which could result in co-contraction of antagonist muscles, has been demonstrated in patients with generalized dystonia, writer's cramp, spasmodic torticollis, and blepharospasm (Rothwell et al., 1983; Nakashima et al., 1989a; Panizza et al., 1989, 1990; Deuschl et al., 1992; Chen et al., 1995; Valls-Sole & Hallett, 1995). Deficient inhibition can also be demonstrated in the blink reflex in blepharospasm, generalized dystonia, spasmodic torticollis, and spasmodic dysphonia, in some cases even in the absence of clinical eyelid involvement (Berardelli et al., 1985; Cohen et al., 1989). Similar abnormalities are seen in perioral reflexes (Topka & Hallett, 1992) and exteroceptive silent periods (Nakashima et al., 1989b). Although reduction of spinal cord and brainstem inhibition are present in dystonia, the fundamental physiological disturbance is more likely to be in supraspinal commands.

Several lines of evidence point to dysfunction of the cortical motor system in dystonia. Movement-related cortical potentials with self-paced finger movements in patients with arm dystonia show a diminished amplitude of the NS component, thought to be generated in the motor cortex (van der Kamp et al., 1995; Deutschl, 1995). Changes both in premotor potential peak amplitude and in localization were found by Feve et al. (1994) in more severely affected secondary and idiopathic dystonia patients. Yazawa et al. (1999) found that the premotor potential preceding voluntary wrist relaxation was also decreased in amplitude. The contingent negative variation, an EEG potential generated in a warned, reaction time task, is similarly deficient with head turning in patients with torticollis (Kaji et al., 1995b) and with hand movement in patients with writer's cramp (Ikeda et al., 1996; Hamano et al., 1999). A localized deficiency of event-related desynchronization in the beta frequency range of the EEG before unilateral movement in patients with writer's cramp confirmed a focal abnormality of the contralateral sensorimotor regions (Toro, 1993). These studies demonstrate abnormalities in cerebral preparation for movement in dystonia (Berardelli et al., 1998).

Other evidence of cerebral dysfunction in dystonia comes from cerebral blood flow studies. Ceballos-Baumann et al. (1995) found depressed activity of the caudal SMA and bilateral sensorimotor cortex, with overactivity of the contralateral lateral premotor cortex, cingulate, dorsolateral prefrontal cortex, and lentiform nucleus with self-paced movements and handwriting in patients with dystonia (Ceballos-Baumann et al., 1997). Magyar-Lehmann et al. (1997) found increased glucose metabolism bilaterally in the lentiform nucleus in patients with torticollis. Ibanez et al. (1999) found deficient activation of somatosensory cortex, premotor cortex, cingulate, and SMA during writing and with sustained hand muscle contraction in patients with writer's cramp. Eidelberg et al. (1995) found increased metabolic activity of contralateral lentiform nucleus, pons, and midbrain which was dissociated from thalamic activity and correlated with symptom severity in patients with unilateral dystonia.

Hyperexcitability of motor cortex can be demonstrated by transcranial magnetic stimulation (TMS). Ikoma et al., showed that motor threshold and motor evoked potential (MEP) amplitude were normal; with increases in the level of background contraction, however, there was an abnormal increase in MEP size with increasing stimulus intensity in writer's cramp (Ikoma et al., 1996). They and Byrnes et al. (1998) also found enlarged motor maps for dystonic muscles suggesting cortical reorganization. Hyperexcitability of the motor cortex may arise from deficient intracortical inhibition. Ridding et al. (1995) and Siebner et al. (1999) demonstrated less inhibition of MEPs elicited by dual stimulus and repetitive TMS in patients with focal hand dystonia. Chen et al. (1997) found similar defective inhibition at long interstimulus intervals with sustained background contraction only in the symptomatic hand in writer's cramp. A shortening of the silent period elicited by TMS in dystonia patients also indicated defective inhibition (Ikoma et al., 1996; Chen et al., 1997; Filipovic et al., 1997; Rona et al., 1998; Curra et al., 2000). Taken together, these results suggest relative overactivation of prefrontal motor planning areas and underactivation of inhibitory sensorimotor areas in dystonia (Berardelli et al., 1998).

Although dystonia is a movement disorder, abnormalities of sensory systems may contribute (Hallett, 1995). While the routine sensory examination is normal, subtly abnormal kinesthesia may be present (Grunewald et al., 1997). In some cases, ill-defined abnormal sensations may elicit or accompany dystonic movements, as in patients with blepharospasm who have photophobia or eye irritation (Ghika et al., 1993). Sensory gestes can temporarily relieve dystonia. Aberrant sensory feedback may contribute to the development of dystonia following peripheral trauma. Sensory dysfunction in dystonia may arise at the level of the processing of muscle spindle input. Kaji et al. (1995b) found that vibration induced dystonia in patients with hand cramp, which could be reversed by cutaneous stimulation similar to the sensory geste or by lidocaine block. PET and evoked potential studies have detected abnormal brain responses to somatosensory input in dystonia (Tempel & Perlmutter, 1990; Reilly et al., 1992; Tempel & Perlmutter, 1993; Tinazzi et al., 1999, 2000). Cortical sensory maps for individual fingers may be distorted and temporal discrimination impaired (Bara-Jimenez et al., 1998, 2000). Intracerebral recordings have shown expanded thalamic sensory receptive fields (Lenz et al., 1999).

Basal ganglia dysfunction may underlie the cortical abnormalities. Direct recording from neurons in patients with primary dystonia undergoing neurosurgical procedures have found lowered firing rates, enlarged sensory receptive fields, and irregular discharge patterns in the basal ganglia (Vitek et al., 1998a). Defects in the TMS-elicited silent period have been found in diseases known to involve the basal ganglia, such as Parkinson's disease and Huntington's chorea (Roick et al., 1992; Priori et al., 1994). Bromocriptine can increase intracortical inhibition in normal subjects, demonstrating dopaminergic influences on cortical function (Ziemann et al., 1997).

Although most evidence points to the basal ganglia as the fundamental site of dysfunction in dystonia, abnormalities can also be found the thalamus, an area where sensory and motor functions converge. As noted above, bicuculline injections into the thalamus can produce dystonia (Guehl et al., 2000). Recordings made during thalamic surgery in patients with secondary dystonia show sensory reorganization (Lenz & Byl, 1999; Lenz et al., 1999). Thalamotomy lesions in the Vim or Vop nuclei can treat dystonia in some patients.

Treatment

Since the etiology of dystonia is not yet known, its treatment remains symptomatic. Current therapeutic options include oral medications, chemodenervation, peripheral nerve or muscle surgery, and brain neurosurgical procedures. Often despite optimal management, there are residual dystonic symptoms. Oral medications are most useful in generalized, hemi-, segmental, and severe cervical dystonia. Focal dystonias are often well controlled with botulinum toxin injections. This approach is less successful in the treatment of widespread dystonic symptoms because toxic doses would be required. Surgery is reserved for medication-refractory dystonia. Physical therapy, occupational therapy and alternative treatments can be combined with pharmacotherapy or surgery. The management of secondary dystonias is similar to that of primary dystonias, except where specific treatment is available for an underlying disorder such as Wilson's disease.

Pharmacotherapy

Dopaminergic agents

Although dopamine dysfunction likely plays a role in the etiology of dystonia, neither dopaminergic agonists nor antagonists are generally effective treatments. An important exception is dopa-responsive dystonia (DRD), in which symptoms are well-controlled with low doses of l-dopa. The response of DRD is also remarkable in that it can be sustained for years without the medication side effects

common in Parkinson's disease patients. Although DRD usually presents in childhood with lower limb involvement, atypical presentations during adulthood have also been described (Steinberger et al., 1998, 1999). Patients with idiopathic dystonia should therefore have a trial of L-dopa treatment (Bandmann et al., 1998; Jankovic, 1998).

Antidopaminergic medications

While dopamine receptor antagonist medications, such as the conventional neuroleptics may be particularly useful in suppressing tardive dystonia (Kang et al., 1986), they may also benefit patients with idiopathic generalized or focal dystonia (Fahn, 1987; Lang, 1988). Their use, however, is often complicated by significant side effects such as parkinsonism, which may require the concomitant use of anticholinergic drugs. Sedation and depression are also common. More seriously, typical neuroleptics can cause neuroleptic malignant syndrome or permanent tardive dyskinesia. The efficacy of newer neuroleptics, such as risperidone, has not yet been fully evaluated. Clozapine, an atypical neuroleptic agent, is useful in treating tardive dystonia (Trugman et al., 1994; Wolf & Mosnaim, 1994; Adityanjee & Estrera, 1996; Raja et al., 1996) and, in a small open-label trial, also helped patients with idiopathic generalized and focal dystonia (Karp et al., 1999).

Approximately 25% of dystonia patients benefit from dopamine depleting agents such as reserpine or tetrabenazine (Greene et al., 1988; Jankovic & Beach, 1997). These drugs, however, can cause intolerable sedation and depression, limiting their use.

Anticholinergic agents

Although their mechanism of action in treating dystonia is not known, anticholinergic medications are often the most effective oral drugs. Approximately 50% of children and 40% of adults with idiopathic dystonia benefit from trihexiphenidyl, although high doses may be required (Fahn, 1983). The use of anticholinergic medication is limited by side effects, many of which are dose-related. Systemic side effects include blurred vision, dry mouth and constipation. The elderly are particularly susceptible to central side effects such as sedation, confusion and short-term memory loss.

Muscle relaxants and antispasmodics

Clonazepam and other benzodiazepines are rarely adequate to treat dystonia when used as sole agents (Greene et al., 1988), however they are often used as adjunctive therapy. There have been no controlled trials of clonazepam as an antidystonic agent, but some anecdotal evidence supports its efficacy in dystonic tremor (Davis et al., 1995). Side effects of benzodiazepines include sedation, depression, and drug dependence.

Muscle relaxants and antispasmodics such as baclofen or possibly tizanidine may also help patients with severe or generalized dystonia. Similar to benzodiazepines, they are not very effective when used alone, but may contribute to dystonia relief when combined with other medications (Greene et al., 1988). Side effects of oral baclofen and tizanidine include sedation, dizziness, weakness, and fatigue.

Baclofen can also be administered as a continuous intrathecal infusion via an implanted pump, which delivers a high dose directly into the spinal fluid, thereby limiting systemic adverse effects. This approach improves spasticity and there is some evidence of efficacy in dystonia, although higher doses may be required (Penn et al., 1995; Albright et al., 1996; Ford et al., 1996, 1998a; Siebner et al., 1998). Ford et al. (1996) retrospectively reviewed 13 patients undergoing baclofen pump implantation. After a mean of 21 months, 55% patients had continued benefit, but only 27% had sustained improved function. Thirty-eight per cent had severe, treatment-related complications. Penn et al. (1995) tried intrathecal baclofen in five patients who had failed oral baclofen. Three patients with generalized or secondary dystonia had mild or brief improvement, while two with focal leg dystonia had marked improvement. Unfortunately, some patients who initially respond become tolerant to intrathecal baclofen and lose benefit over time. Because pump implantation is associated with significant morbidity, including infection, CSF leaks, baclofen over-infusion, meningitis, lethargy and skin erosion, it should only be undertaken if there is a good response to a test drug infusion before pump insertion and after carefully weighing the risks and benefit (Ford et al., 1998a).

Botulinum toxin

Dr Alan Scott pioneered the use of intramuscular injection of small doses of botulinum toxin to treat strabismus (Scott, 1981). Its success in treating ocular disorders associated with muscular overcontraction led to successful trials in dystonia. Botulinum toxin has become the first line of treatment for focal dystonia.

Botulinum toxin is the most potent biological toxin known. It acts presynaptically, blocking the release of acetylcholine at the neuromuscular junction, thereby chemically denervating the muscle. There are seven distinct botulinum toxin serotypes which cleave SNAP-25, a protein needed for acetylcholine vesicle fusion with the presynaptic membrane, synaptobrevin-2/VAMP, a compo-

Table 37.3. Botulinum toxin serotype sites of action

Serotype	Site of Action
Type A	SNAP-25
Type B	VAMP/ synaptobrevin
Type C	Syntaxin 1A, 1B
Type D	SNAP-25; VAMP/synaptobrevin
Type E	SNAP-25
Type F	VAMP/ synaptobrevin
Type G	VAMP/ synaptobrevin

nent of the synaptic vesicle membrane or syntaxin, a plasma membrane-associated protein (Table 37.3) (Tsui, 1996). Since type A has been the only form commercially available until recently, the discussion below centres on clinical experience with this serotype. Type B toxin, recently marketed, differs in dosage and possibly duration of action and frequency of adverse effects. Although type F has been studied in limited clinical trials, it will not be commercially developed.

During preparation for clinical use, botulinum toxin is precipitated with hemaglutinin and other proteins. The weight of the drug therefore does not correlate well with clinical potency. Botulinum toxin dose is, rather, quantified in terms of the mouse unit (MU) defined as the LD50 for 18–20 gram female Swiss-Webster mice injected intraperitoneally. Extrapolating from data on intramuscular injection in monkeys, the human LD50 is estimated to be 40 MU/kg for type A toxin (Scott & Suzuki, 1988). When used to treat dystonia, benefit from botulinum toxin becomes apparent within 2 weeks, peaks between 2 and 6 weeks, and wears off about 10–12 weeks after injection, although the time course varies widely. Regardless of the response duration, repeated injections are needed to maintain benefit. There are presently two commercially available preparations of botulinum toxin type A, Botox®(Allergan, Inc, USA), and Dysport® (Speywood Pharmaceuticals, England). The doses of these two products are not equivalent. Due to differences in preparation, Botox® is approximately 3–5 times as potent as Dysport® (Tsui, 1996). Botulinum toxin can effectively treat all forms of focal dystonia including blepharospasm (Scott et al., 1985), cervical dystonia (Jankovic & Schwartz, 1990), oromandibular dystonia (Hermanowicz & Truong, 1991), and limb dystonia (Karp et al., 1994), but is less successful if large muscles or many body areas are involved.

Up to 10% of patients receiving the original type A botulinum toxin preparations develop clinical resistance due to the formation of blocking antibodies. The incidence of antibody formation in patients receiving the newer toxin preparations is not yet known. Sensitization is especially likely in patients who receive large doses and frequent injections. Patients who lose response to repeated injections should be tested for the presence of antibodies. The currently available immunoassay has high specificity, but variable sensitivity; a rabbit bioassay correlates better with clinical resistance (Borodic et al., 1996). The absence of weakness following a trial injection into a non-dystonic muscle, such as the frontalis, can also be used to demonstrate loss of toxin efficacy (Hanna & Jankovic, 1998).

There is little immune cross-reactivity between botulinum toxin types. Therefore, in the face of antibody development, patients may be switched to another serotype. Resumption of clinical benefit has been demonstrated in patients with antibodies to type A toxin who are switched to type F or type B (Tsui et al., 1995; Borodic et al., 1996; Chen et al., 1998; Sankhla et al., 1998a). Plasmapharesis was used in a single patient with botulinum toxin resistance to decrease antibody burden (Naumann et al., 1998c). The patient was able to benefit from a subsequent injection. Duane et al. (2000) used mycophenolate, an immunosuppressant, to maintain non-detectable antibody titers and botulinum toxin responsivity in three patients with cervical dystonia and previous loss of response. It is not yet known if either of these latter approaches to botulinum-toxin resistant patients will be practical for long-term management.

The most common side effect of botulinum toxin injections is greater weakness than intended in the injected or contiguous muscles. To help avoid spread, small volume injections into multiple sites are preferable to a single large injection. Weakness is always transient, typically resolving in a matter of weeks. Dysfunction due to excessive weakness depends on the location of injection. For example, injection of the anterior neck muscles may lead to dysphagia. Ptosis and diplopia may result from injections around the eyes. Weakness is rarely a problem with lower limb injections. Although electrophysiological changes in neuromuscular junction function in muscles remote to the injection site can be demonstrated (Girlanda et al., 1992), there are few clinically significant systemic side effects. Transient low-grade fever, malaise, fatigability and flu-like symptoms have been noted (Tsui et al., 1986). Other rare adverse reactions to botulinum toxin include allergic reactions and a Guillain–Barré-like syndrome (Haug et al., 1990; LeWitt & Trosch, 1997). Neuromuscular disorders, such as myasthenia gravis, Eaton–Lambert syndrome, amyotrophic lateral sclerosis and the concomitant use of aminoglycosides are relative contraindications to using botulinum toxin. The safety of botulinum toxin in pregnancy and during nursing has not been evaluated.

Neuroablative drugs

Intramuscular injection of phenol permanently destroys the surrounding peripheral nerve and muscle tissue (Gracies et al., 1997). Although phenol is less expensive than botulinum toxin, its use requires additional precautions. Phenol injection is painful. It can only be used on motor nerves, as destruction of sensory nerves can lead to severe, persistent dysesthesia. Two pilot studies showed benefit in three of five patients with torticollis (Massey, 1995; Garcia Ruiz & Sanchez Bernardos, 2000). Although effects were longer lasting than those of botulinum toxin, repeated phenol injections were sometimes necessary.

Doxorubicin is an antimitotic drug that destroys muscle. Wirtschafter et al., injected this medication to treat 18 patients with blepharospasm (Wirtschafter, 1991; Wirtschafter & McLoon, 1998). Of ten patients able to complete a series of up to ten injections, nine had remission lasting longer than one year. Caution is warranted, however, because of significant adverse effects including skin ulceration, pigmentary changes, urticaria and diplopia.

Local anesthesia

Noting the possible sensory contributions to dystonia discussed above, Kaji et al. (1995b) injected lidocaine at doses that blocked muscle spindle afferents. Thirteen of 15 patients had clinical improvement lasting up to 24 hours. Benefit was prolonged up to 21 days if 10% ethanol was injected at the same time. The utility of oral mexiletine for the treatment of dystonia is currently being explored (Ohara et al., 1997, 1998).

Peripheral surgery

Dystonia surgery is usually reserved for those patients who are refractory to medical management, develop antibodies to botulinum toxin, or desire a more permanent solution.

Several techniques have been employed to treat cervical dystonia, including rhizotomy, peripheral denervation of the spinal accessory nerve, ramisectomy and myectomy (Lang, 1998). An early surgical approach combined anterior cervical rhizotomy with selective resection of the spinal accessory nerve (Hamby & Schiffer, 1969; Gauthier et al., 1988). Hernesniemi et al. reported 23 patients with spasmodic torticollis, 11 of whom underwent SCM myotomy and 12 of whom had cervical rhizotomy (Hernesniemi & Keranen, 1990). Only two of the myotomy patients reported subjective improvement lasting up to 4 years after surgery. The remainder of the patients had poor response. Complications of both procedures were significant, including neck and shoulder weakness, neck instability, pain and dysphagia (Horner et al., 1992; Lang, 1998). Myectomy or myotomy of the trapezius muscle similarly achieved only moderate improvement (Hernesniemi & Keranen, 1990; Krauss et al., 1999).

Peripheral denervation and selective sectioning of the spinal accessory nerve are more successful in treating cervical dystonia, but also entail significant complications including sensory loss or hyperesthesia, weakness of the trapezius, and dysphagia (Bertrand et al., 1987; Bertrand, 1993). Ford et al. (1998b) conducted a retrospective study of selective ramisectomy in botulinum toxin-resistant cervical dystonia patients. One-third of 16 patients had at least moderate benefit, but all except one remained unable to work. Given the limited benefit and the high frequency of adverse effects and dystonia recurrence, such procedures should be reserved for patients with severe, refractory cervical dystonia.

Peripheral nerve surgery, such as carpal tunnel release, is generally not helpful in limb dystonia. Ulnar nerve transposition, however, may benefit the occasional patient whose hand dystonia may be secondary to an occult ulnar neuropathy (Ross et al., 1995; Charness et al., 1996). Tendonotomy or even limb amputation have been performed for severe, disabling limb dystonia (Moberg-Wolff, 1998).

Myectomy of the orbicularis oculi and neurectomy of the facial nerve have been used for blepharospasm. Up to 90% of patients initially have improved visual function with such procedures, but blepharospasm recurrence is common. Forty-six per cent of the patients reported by Chapman et al. (1999) who benefited from myectomy required botulinum toxin injections within 5 years of surgery. Side effects of myectomy include forehead numbness, chronic periorbital lymphedema, keratitis, ptosis, and lid retraction (Lang, 1998).

Sectioning of the recurrent laryngeal nerve benefits many patients with adductor spasmodic dysphonia (Schiratzki & Fritzell, 1988; Fritzell et al., 1993). Symptom recurrence, often attributed to nerve fibre regeneration, is common after surgery, and may require an additional procedure or botulinum toxin injections (Ludlow et al., 1990).

Thalamotomy, pallidotomy and deep brain stimulation

Stereotactic neurosurgery was used to treat dystonia as early as the 1950s. In 1979, Cooper reviewed his 20-year experience with thalamotomy for primary and secondary generalized dystonia (Cooper, 1979). Most patients had bilateral procedures. Seventy per cent had subjective improvement. In the series reported by Andrew et al. (1983), 64% of 55 patients with focal or generalized dystonia improved after thalamotomy, but benefit persisted

longer than a year in only 25%. Lesioning the contralateral thalamus was especially helpful in hemidystonia. Bilateral thalamotomy was more successful than unilateral in patients with torticollis. In Tasker's review of 56 patients with lesions in either the ventral intermediate or posterior ventral oral nucleus of the thalamus operated on between 1961 and 1985, 34% of those with secondary dystonia and 32% with primary generalized dystonia had at least 50% improvement in their symptoms (Tasker et al., 1988). Unfortunately, symptoms recurred in most patients following surgery; the longest remission was six years. Thalamotomy complications were frequent and included hemiparesis, numbness, dysarthria and dysphagia. Adverse effects were more common with bilateral procedures. Overall lack of uniformity in technique, target and patient selection led to a wide range of outcomes and the procedures were largely abandoned.

Recent stereotactic advances have led to a revival in neurosurgical approaches to treating dystonia. Surgical targets for dystonia are largely the thalamus and internal globus pallidus (GPi), components of the fronto-basal ganglionic-thalamo-cortical circuit that appears to be involved in the generation of dystonia (Lenz et al., 1998; Vitek, 1998; Vitek et al., 1998a, b).

Initially shown beneficial in Parkinson's disease, pallidotomy has more recently been applied to the treatment of dystonia. Ondo et al. (1998) reported improvement lasting up to 9 months in 8 patients with primary and secondary generalized dystonia. The patients with idiopathic dystonia had greater benefit than those with secondary dystonia. Lozano et al. reported improvement in single cases of patients with idiopathic or symptomatic childhood-onset dystonia with bilateral GPi procedures (Lozano et al., 1997; Lin et al., 1998, 1999; Lai et al., 1999). Complications from pallidotomy including hemiparesis, hemianopsia, dysarthria, dysphagia, cognitive and mood disorders were more common with bilateral procedures.

Ablative techniques such as pallidotomy and thalamotomy leave permanent lesions in the target structure. Many physicians therefore now prefer deep brain stimulation (DBS), which entails the implantation of electrodes in the same brain targets. Activation of the electrodes suppresses neuronal firing. The electrodes are controlled by a stimulator implanted under the skin which can be turned on or off at will. Stimulus parameters can be adjusted to those providing maximal relief of symptoms with minimal adverse effects. If needed, the electrodes and stimulator can be repositioned or removed.

Kumar et al., used bilateral GPi DBS to treat generalized dystonia and found significant improvement that was sustained for at least one year (Kumar et al., 1999). Interestingly, PET scanning 1 year after surgery showed a decrease in previously hyperactive motor cortex activity. Tronnier et al., reported GPi DBS in three patients with generalized dystonia, two with idiopathic and one with secondary dystonia (Tronnier & Fogel, 2000). Both patients with idiopathic dystonia had marked improvement, while the patient with secondary dystonia had only moderate improvement. Symptomatic dystonia may however also respond to DBS. Loher reported a single patient with post-traumatic hemidystonia who had improvement in dystonic symptoms sustained for at least four years (Loher et al., 2000).

Deep brain stimulation can also target the thalamus. A case study of hemidystonia secondary to a thalamic lesion reported marked benefit from ventroposterolateral nucleus stimulation (Sellal et al., 1993). Benabid et al., however, found only mild improvement with nucleus ventralis intermedius stimulation in two patients with idiopathic dystonia (Benabid et al., 1996).

There is more limited experience with stereotactic procedures for focal dystonia. Individual case reports have shown mixed results in treating limb dystonia and blepharospasm with thalamotomy (Goto et al., 1997; Iacono et al., 1998).

Ancillary therapies

Ancillary non-pharmacological, non-surgical therapies such as physical and occupational therapy help many dystonic patients maintain as much function and mobility as possible. Splints and neck braces in patients with limb or cervical involvement may be helpful. Biofeedback benefited a single patient with writer's cramp reported by O'Neill et al. (1997). Specific large muscle EMG biofeedback eased writing in 10 of 13 writer's cramp patients with proximal muscle involvement reported by Deepak et al. (Deepak & Behari, 1999). Biofeedback, acupuncture, massage and other alternative therapies may increase patient comfort, but their use in dystonia has not been studied systematically. Our patients have had mild relief of dystonia-associated pain, but no sustained benefit from acupuncture. Since these therapies may offer some relief to individual patients and since they can be safely combined with medical or surgical treatment, physicians should consider their use.

Conclusions

Dystonia is a hyperkinetic movement disorder characterized by sustained or tremulous twisting or turning postures. Physiologic and pharmacologic data suggest dopaminergic dysfunction of the basal ganglia and

defective cerebral inhibition at several levels. Optimal management takes advantage of oral medications, chemodenervation, and ancillary, non-pharmacologic therapies. Surgery and deep brain stimulation are currently reserved for medically refractory dystonia. As our understanding of the genetic, physiologic, and biochemical bases of dystonia grows, more specific, curative therapies may well become available.

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38

Tourette syndrome

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In 1885 George Gilles de la Tourette, a Parisian neuropsychiatrist, described nine patients with a chronic disorder characterized by the presence of multiple motor and vocal tics. He recognized many of the salient clinical features of the syndrome that today bears his name, including its onset in childhood, the tendency of tics to wax and wane, and the presence of a variety of comorbid neurobehavioural problems such as obsessive–compulsive symptoms, anxieties, and phobias. Nevertheless, Gilles de la Tourette (1885) and his mentor Charcot attributed this disorder to a form of 'hereditary insanity' and felt it was a degenerative disorder with 'no hope of a complete cure'. Today, Tourette syndrome (TS) is considered a complex neuropsychiatric disorder with a wide spectrum of behavioural manifestations and psychological comorbidities.

Clinical features

Tics are the cardinal feature of TS. They encompass a wide variety of involuntary movements and sounds and are formally defined as involuntary, sudden, rapid, brief, repetitive, non-rhythmic stereotyped movements or vocalizations. Motor tics consist of involuntary movements and are subdivided into simple and complex subtypes. Simple motor tics are movements of single muscle groups. Examples include eye blinking, head jerking, and facial twitching. Complex motor tics consist of a coordinated pattern of movements that may be non-purposeful (facial or body contortions) or appear to be more purposeful but actually serve no purpose (touching, smelling, jumping, obscene gestures). Copropraxia describes the presence of obscene gestures, whereas echopraxia is the imitation of the gestures of others as a tic manifestation. Phonic (vocal) tics involve the production of sound. Simple phonic tics include sniffing, grunting, and throat clearing. Complex phonic tics involve the production of partial or complete words, phrases, or sentences. Palilalia is the repetition of one's own words and echolalia is the repetition of words of another person. Coprolalia is a dramatic type of tic that consists of the involuntary utterance of obscene words and phrases. Although once considered necessary for the diagnosis of TS, coprolalia occurs in only a small minority of patients with TS (Goldenberg et al., 1994). Tics are commonly misdiagnosed as other problems such as chronic respiratory symptoms, visual problems, asthma, allergies and anxiety.

Several features differentiate tics from other movements, including their variability, duration, exacerbating factors, supressibility, diminution during sleep, subjective perceptions and associated disturbances. Tics typically wax and wane in severity and may not be apparent during a routine office visit. As one tic fades, another may take its place. Several tics may occur at one time, or there may be a quiescent period with no tics noticed. A videotape of the movements is often helpful when the diagnosis is in question. Tics evolve over time and vary in their temporal pattern. Often exacerbated by fatigue, anxiety, and stress, tics may lessen during periods of relaxation. Although they are not usually evident on casual observation during sleep, they are present on polysomnograms. Most individuals are able briefly to suppress their tics. During the period of voluntary suppression, patients frequently describe a build-up of 'inner tension' that is relieved when the tic occurs or the effort to suppress the tics is discontinued. Tics are often preceded by a 'feeling' or sensory phenomenon, labeled a premonitory urge or sensory tic.

Infrequently tics can be mistaken for other movements or disorders. Stereotypies are involuntary, patterned, purposeless, repetitive, rhythmic movements that can be simple or complex. They often occur in the setting of

mental retardation, pervasive developmental disorders, and other syndromes of brain dysfunction, but can also occur as a normal developmental feature of childhood. Mannerisms are an individual's embellishments of otherwise intentional normal movement patterns (e.g. baseball player at bat). Compulsions are behaviours that are experienced as alien but necessary to fulfil an inner 'need.' There is significant comorbidity of obsessive–compulsive disorder with TS, and sometimes it may be difficult to distinguish between compulsive movements and tics (Miguel et al., 1995). Seizures are occasionally confused with complex motor tics, but are distinguished from them by non-suppressible prolonged movements, loss of awareness, postictal state, and abnormal electroencephalogram. Myoclonus, tremor, dystonia, and chorea are usually clearly distinguishable from tics by observation. Sydenham's chorea (SC), which occurs in the same age group as TS, can have tics as part of the presenting motor disorder. A wide range of conditions, drugs and toxins have been associated with tics (Table 38.1). A spectrum of movements that are not tics may also occur in patients with TS. For example, it is possible that some movements may be drug-induced (akathisia, dystonia, chorea, parkinsonism) or associated with comorbid conditions such as obsessive–compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), or antisocial behaviour (Kompoliti & Goetz, 1998).

Although the diagnosis of a tic disorder typically requires an age of onset before 18 to 21 years, the mean age of onset for tics in TS is between 6 and 7 years (Shapiro & Shapiro, 1982). Seventy-five per cent of patients have symptoms by 11 years. Infrequent cases of adult-onset tics have been reported (Chovinard & Ford, 2000). Often tics come to attention gradually, but on occasion there is an apparently explosive onset (Singer et al., 2000). Boys are three times as likely as girls to be diagnosed with TS. The most common presenting tics are those classified as simple motor tics, e.g. eye blinking, facial and head movements. Vocal tics are uncommon as a presenting symptom (Shapiro & Shapiro, 1982). Tics are usually most severe during late childhood and early adolescence (8 to 12 years). More complex tics, including coprolalia, may develop several years after the initial tic appeared (Shapiro & Shapiro, 1982). About one-third of patients with TS will have complete remission of their tics during late adolescence, and a significant improvement in tic severity is seen in an additional third of patients (Erenberg et al., 1987; Bruun, 1988; Bruun & Budman, 1993). The remaining one-third will continue to have significant tics into adulthood. Childhood tic severity is not a good predictor of tic severity later in life.

Table 38.1. Conditions in which tics may be seen

Chromosomal abnormalities	9p mosaicism
	XXX
	Fragile X
	XXY
	XYY
Developmental disorders	Static encephalopathies
	Cerebral palsy
	Autistic spectrum disorders
Neurodegenerative disorders	Huntington's chorea
	Lesch–Nyhan syndrome
	Hallovorden–Spatz
	Neuroacanthocytosis
	Subacute sclerosing panencephalitis
	Wilson's disease
	Primary dystonia
Drugs	Tardive dyskinesia (tardive Tourette)
	Dopaminergic drugs
	CNS stimulants
	Carbamazepine
	Phenobarbital
	Phenytoin
	Lamotrigine
	Clomipramine
	Wellbutrin
	Cocaine
Infections	Encephalitis (para or post)
	Lyme infection
	Sydenham's chorea
	Creutzfedt–Jakob disease
	HIV
	Neurosyphilis
Trauma	Head trauma
	Stroke
	Cardiopulmonary bypass with hypothermia
Toxins	CO poisoning
	Wasp-venom encephalopathy
	Lead poisoning
	Gasoline inhalation
Metabolic disorders	Citrullinemia
Other conditions reported to have tics	Duchenne muscular dystrophy
	Tuberous sclerosis
	Anorexia nervosa
	Type 1 neurofibromatosis

Source: From Fahn & Ehrenberg (1988).

Table 38.2. Diagnostic criteria for Tourette syndrome (TS Classification Group)

(i)	The presence of multiple motor and at least one vocal (phonic) tics
(ii)	A waxing and waning course with tics evolving in a progressive manner
(iii)	The presence of tic symptoms for at least 1 year
(iv)	Onset before age 21
(v)	Absence of a precipitating illness, e.g. encephalitis, stroke or degenerative disease
(vi)	Observation of tics by a knowledgeable individual

Diagnostic criteria

Tic disorders are classified into transient and chronic forms. Transient tic disorder is quite common, affecting 5–24% of school children. By definition, the disorder lasts less than 1 year and typically involves only a few motor or vocal tics. Chronic tic disorders (CTD) are diagnosed after a duration of at least 1 year and include chronic motor tic disorder, chronic vocal tic disorder, Tourette syndrome, and Tourette disorder. To meet the diagnosis of chronic motor (or phonic) tic disorder an individual must have either several motor (or several phonic tics), but not both. Chronic motor/phonic tic disorder is a heritable trait (often occurring in families with TS) and responds similarly to TS therapies. Non-specific tic disorder is a category in the DSM IV that encompasses chronic tic disorders that do not meet criteria for CTD or TS (APA, 1994). Terms often used for this category include Tourettism, Tourette-like, or secondary tic disorder.

Criteria for *Tourette syndrome* have been developed by the Tourette Syndrome Classification Group and are set out in Table 38.2 (1993). The DSM IV criteria for Tourette disorder (TD) are similar to those for TS, with several additions including an 'impairment' criterion requiring that 'marked distress or significant impairment in social, occupational, or other important areas of functioning' be present (APA, 1994). Furthermore, the DSM IV requires an age of onset before 18 years and a tic-free interval that is not longer than 3 months. Coprolalia, echolalia, and copropraxia are not inclusion criteria in either TS or TD, nor is there a requirement for coexisting comorbid features. Since the duration of tics is an essential criterion for tic disorder diagnosis, individuals presenting with a brief history of tics are called 'tic disorder-diagnosis deferred' while awaiting further temporal observation. Accurate distinction of a chronic tic disorder into CTD, TS, or non-specific tic disorder is important for research investigations, but has little relevance for discussion of outcome or treatment.

Rating scales

Although the diagnosis of tics is generally straightforward, it is challenging to rank tics objectively in terms of symptom severity and their impact on quality of life. Several questionnaires and rating scales have been developed for this purpose. Self-report checklists such as the Tourette Syndrome Questionnaire (TSQ) (Jagger et al., 1982) and the Tourette Syndrome Symptom List (TSSL) (Cohen et al., 1980) are easy to administer. The Tourette Syndrome Severity Scale (TSSS) (Shapiro & Shapiro, 1984; Shapiro et al., 1988), the Hopkins Motor and Vocal Tic Scale (Walkup et al., 1992), and the Yale Global Tic Severity Scale (YGTSS) (Lechman et al., 1989) are three different scales that are based on patient observation and historical information. The TSSS and YGTSS take into account not only the phenomenology of tics but also their impact on quality of life. Video-based rating systems offer the advantage of video replay for reliable tic assessment, but may be difficult to obtain in a busy office setting. The Rush Video-based Tic Rating Scale is a 10-minute film protocol that includes near and far body views obtained with the patient relaxed with and without the examiner present. It has recently been suggested that videos obtained in the home environment, rather than the physician's office, may be more accurate indicators of tic severity (Goetz et al., 1999). Other common questionnaires used to assess neuropsychiatric comorbidities include the Child Behaviour Checklist (Achenbach, 1991), Parent Symptom Questionnaire for ADHD (Conners, 1970), and the Child Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Goodman et al., 1989a, b).

Associated behaviours and psychopathology

Individuals with TS frequently manifest other behavioural and psychiatric problems. The most common comorbidities are attention deficit hyperactivity disorder (ADHD) and obsessive–compulsive disorder (OCD) and this diagnosis is often referred to as the 'TS triad.' In addition to these typical findings, the scope of comorbidity includes anxiety disorders, bipolar and non-bipolar mood disorders, and episodic behaviour disorder (Table 38.3). In several studies, severely ill patients with tic disorders have been shown to be more impaired by their non-tic

Table 38.3. Frequency of comorbid conditions in TS

OCD	30–70%
ADHD	50–75%
Anxiety disorders	20–80%
Mood disorders	20–80%
Episodic control disorders	25%
Sleep problems	12–62%
Academic difficulties	50%

symptoms than by their tics (Coffey et al., 2000; Robertson, 2000). Rates of comorbidity vary depending on the clinical setting in which individuals are seen, i.e. patients seen in a psychiatry clinic are more likely to be diagnosed with comorbid psychiatric conditions than if they are seen in a neurologist's office.

Obsessive–compulsive disorder

Obsessions are defined as recurrent ideas, thoughts, images, or impulsions that intrude upon conscious thought and are persistent and unwelcome (ego-dystonic). Compulsions are repetitive, seemingly purposeful, behaviours usually performed in response to an obsession, or in accord with certain rules, or in a stereotyped fashion. Obsessive–compulsive behaviours (OCB) become a disorder (OCD) when activities are sufficiently severe to cause marked distress, take up more than 1 hour of the day, or have a significant impact on normal routine, function, social activities, or relationships. The incidence of OCB in TS is typically reported to be from 30–70% (Frankel et al., 1986; Comings & Comings, 1987d; Kano et al., 1997; King et al., 1999). Obsessive behaviours generally emerge several years after the onset of tics, usually during early adolescence. Comorbidity with OCD is associated with a more severe tic phenotype (de Groot et al., 1997). In one study, subjects with more severe tics, notably coprolalia, were more likely to have OCB (Kano et al., 1997). Studies comparing OCB in persons with and without TS have suggested clinical differences. In patients with TS, obsessions may have sexual, violent, religious, and/or aggressive themes, and compulsions include a need for order or routine and a requirement for things to be symmetrical or 'just right.' Hence, compulsions typically involve arranging, ordering, hoarding, touching, tapping, rubbing, counting, checking for errors, and 'evening-up' rituals. In contrast, in pure OCD, obsessions are predominantly concerned with contamination, dirt, germs, being neat and clean, fear of errors, bad happenings, or illness, and compulsions tend to involve cleaning and washing (Robertson, 2000). Biological differences have reported between pure OCD and TS–OCD groups based on levels of CSF oxytocin (Leckman et al., 1994). Patients from both groups, however, have premonitory sensations and urges. Obsessive–compulsive behaviours are associated with a preceding trigger of anxiety or fear rather than a true sensation (itch, tightening, tingling) or a feeling of tension before a tic. After the action is performed, there is a brief relief from the trigger. Despite these differences, it may be difficult to distinguish whether actions such as touching, tapping, and picking represent tics or compulsions. Because of similarities in features, many investigators believe complex tics and compulsions represent a clinical spectrum of symptoms with many overlapping features. The concept that tics and obsessive–compulsive symptoms represent a continuum is supported by evidence that there is a genetic association between OCD and TS. Nevertheless, OCD is etiologically heterogeneous and not all cases are associated with a chronic tic disorder. The pharmacologic treatment of tics and OCD is distinctly different.

Attention deficit hyperactivity disorder (ADHD)

ADHD (see also Chapter 29) is characterized by impulsivity, hyperactivity, and a decreased ability to maintain attention. The disorder is common in TS probands and is reported to affect about 50–75% of referred TS cases (Golden, 1984; Comings & Comings, 1987a; Matthews, 1988; Comings, 1990; Walkup et al., 1999). Often children are diagnosed with ADHD before the onset of tics. ADHD typically begins about age 4–5 years and in TS patients, usually precedes the onset of tics by 2 to 3 years. Its appearance is not associated with the concurrent severity of tics, although ADHD is common in patients with more severe tic symptoms. Associated ADHD appears to be the most important contributing factor to poor school performance in a child with TS (Park et al., 1993; Abwender et al., 1996). Comparisons between children with ADHD-only and TS+ADHD have suggested that mood and anxiety problems were associated with ADHD and not the presence of tics (Spencer et al., 1998). Investigators have also suggested that some of the apparent increases in personality disorders in adults with TS are secondary to the presence of childhood ADHD (Robertson, 2000). Impairments in TS patients with ADHD appear to differ quantitatively and qualitatively from those observed in patients with primary ADHD without tics: those with primary ADHD have significantly more impairment on tests that measure visual search and mental flexibility, have slower reaction times, and make fewer correct

responses on both simple and choice reaction time tasks (Silverstein et al., 1995). Whether a genetic relationship exists between TS and ADHD remains controversial. Pauls and colleagues have suggested that there may be two distinct populations of TS patients with comorbid ADHD: (i) those with onset of ADHD before the onset of tics; and (ii) those, possibly genetically associated, with onset after, or in concert with, the onset of tics (Pauls et al., 1993).

Other psychopathologies

Several studies have shown an increased incidence of anxiety and depression in patients with TS (Comings & Comings, 1987a, b; Robertson, 1989; Coffey et al., 1992; Robertson et al., 1993). Although the incidence of generalized anxiety disorder in TS subjects (range 19 to 80%) exceeds that in controls, some investigators believe that symptoms, especially separation anxiety, may be secondary to moderate or severe TS (Coffey et al., 1992; Robertson, 2000). TS patients also have a higher prevalence of depression than do controls. Some investigators believe that depression correlates positively with earlier onset and longer duration of tics, whereas others find no correlations between depression and the number of tics. Genetic studies show that major depressive disorder is genetic but that TS and this disorder are unrelated (Pauls et al., 1994). Personality disorders are more common in TS, but this increase has been attributed to long-term outcome of childhood ADHD (Robertson et al., 1997). Sudden, unpredictable, explosive outbursts of anger, irritability, temper, and aggression have been reported in about 25% of clinically referred patients with tic disorders (Comings et al., 1989; Wand et al., 1993; Budman et al., 2000). These explosive outbursts occur more frequently in children and resemble intermittent explosive disorder. Their presence appears to correlate highly with the combined comorbidity of ADHD and OCD (Santangelo et al., 1994; Park et al., 1996). A variety of other behavioural/emotional problems have been identified, including aggressiveness, immaturity, withdrawal, conduct disorder, oppositional defiant disorder, and somatic complaints (Singer & Rosenberg, 1989; Walkup et al., 1992, 1995). Whether these disorders are related to tic severity, are secondary to the presence of ADHD, or are the result of having a stigmatizing disorder is unclear.

Sleep problems

Sleep disturbances, including somnambulism (sleep walking), night terrors, nightmares, talking in sleep, restlessness, and difficulty falling asleep, have been reported in 12 to 62% of patients with TS (Comings & Comings, 1987f; Allen et al., 1992). Studies with polysomnographs have revealed decreased rapid eye movement sleep, but have not shown consistent abnormalities in delta sleep (Mendelson et al., 1980; Glaze et al., 1983). The use of sleep behaviour questionnaires has confirmed that patients with TS have an increased incidence of insomnia, dreams, required bedtime rituals, and parasomnias (Allen et al., 1992). This study found that the incidence of sleep problems was significantly increased in patients with comorbid ADHD, however, suggesting that ADHD may be a significant determinant for sleep problems in TS. Overlapping clinical and pathologic features have been proposed to exist between individuals with TS and the restless legs syndrome. Both groups have excess periodic leg and arm movements during sleep (Voderholzer et al., 1997).

Academic difficulties

Several studies have shown that learning problems are common in children with TS (Hagin & Kugler, 1988; Burd et al., 1992) and that TS is more prevalent in children in special education classes (Comings et al., 1990; Kurlan et al., 1994b). Individuals with TS typically have normal levels of intellectual functioning, although there may be a discrepancy between performance and verbal IQ, an impairment of visual perceptual achievement, or a decrease in visual–motor skills. Learning difficulties have been reported in up to 51% of children with TS, but are most common in those with both TS and ADHD. Several studies have identified differences in neuropsychological and neuromotor capabilities between children with TS only and those with TS + ADHD. For example, children with TS only had higher full scale IQ scores than did children with TS + ADHD (Faraone et al., 1993; Schuerholz et al., 1996). In a study designed to determine whether a discrepancy-based learning disability was associated with a specific subset of TS patients, results showed that comorbid ADHD accounted for the increased incidence of learning disabilities (Schuerholz et al., 1996). Children without ADHD also performed better on tests of executive function. Nevertheless, individuals with TS, irrespective of the presence of ADHD, often require extra time to complete their assignments. This difficulty has been associated, in part, with a linguistic executive dysfunction that affects the speed and efficiency of memory search. For example, a group of bright children with TS only and no learning disabilities had slowed responses on measures of executive function, especially those that were timed. Most notable was slowing on the Letter Word Fluency Task, which

requires the ability to search memory efficiently. TS boys, compared to age-matched controls, had slowed reaction time during a continuous performance test (Shucard et al., 1997), but the effect of comorbid variables was not measured. In patients with TS without ADHD, school difficulties may be related to tic severity, the use of tic-suppressing medicine, executive dysfunction, a direct consequence of having a stigmatizing disorder, or other psychopathologies (Singer et al., 1995).

Epidemiology

Tourette syndrome occurs worldwide, with increasing evidence of common features in all cultures and races. The true incidence and prevalence of TS have yet to be accurately determined. Among the multiple factors accounting for inconclusive estimates are the following: mildly affected individuals do not seek medical care; the diagnostic criteria have evolved over time; TS symptoms vary in their intensity and severity; misdiagnosis of TS by practitioners; and estimates are influenced by selection and attribution bias. In a retrospective review of medical records in Rochester, Minnesota over 12 years, the calculated incidence from identified cases was 0.46 per 100 000 or 1000 new cases annually in the United States (Lucas et al., 1982). The estimated prevalence of TS has varied greatly in individual studies; estimates of 49.5 (65), 23 (72), 5.2 (73), 2.9 (9), and 0.7 (10) per 10 000 in school age children and adolescents. More recent studies, however, have suggested a prevalence rate of approximately 1% of school-age children. A study of 13- to 14-year-old mainstream British students revealed a prevalence of 299 per 10 000 children with mild to severe tics. The validity of this study has been questioned, however, because this population was not reassessed or formally diagnosed by an expert (Shapiro & Shapiro, 1982). In Houston, Texas, investigators found a prevalence rate of definite TS or TS by history in 0.7% of students (Kadesjö & Gillberg, 2000), in Sweden the prevalence was estimated at up to 1.1% of school-aged children (Hanna et al., 1999) and in Rochester NY up to 3.5% of school-aged children (Kinlan et al., 2001). All authors suggest that mild TS is more common than was previously recognized. In adult populations, prevalence estimates have been much lower (Coffey et al., 1992), presumably because the natural history is that tics become less severe after adolescence. Investigators have also shown that children in special school populations have an increased prevalence of tic disorders (Comings et al., 1990), as do children with autism, Asperger syndrome, and autistic spectrum disorders (Baron-Cohen et al., 1999).

Genetics

Although Georges Gilles de la Tourette suggested that TS is an inherited disorder, the precise pattern of transmission and the identification of the gene remain elusive. Strong support for a genetic disorder is provided by studies of monozygotic twins, which show an 86% concordance rate with TS as compared to 20% in dizygotic twins (Price et al., 1985; Hyde et al., 1992). Earlier proposals suggesting a sex-influenced autosomal dominant role of inheritance with variable expressivity as either TS, chronic tic disorder, or OCD (Pauls & Leckman, 1986) have been seriously questioned. Other investigators have proposed hypotheses of a single major locus in combination with a multifactorial background, i.e. either additional genes or environmental factors (Walkup et al., 1996). The search for a genetic site is being actively pursued, but to date no reproducible locus has been identified. In a systematic genome scan of 76 affected sib-pair families with a total of 110 sib pairs, the multipoint maximum likelihood scores for two regions (4q and 8p) showed a trend, but did not reach acceptable statistical significance (The Tourette Syndrome Association, 1999). Linkage analysis in a large French Canadian family showed a LOD score of 3.24 for chromosome 11 (11q23), which replicated findings described in a South African population (Simonic et al., 1998; Merette et al., 2000). A region on chromosome 19p has also been implicated in a genome scan of multigenerational families and three of five patients with a fragile site at 16q22–23.37 had TS. Linkage studies to candidate genes associated with specific synaptic markers, including dopamine D1–5 receptors, have not found a consistent linkage to a large variety of factors (Barr et al., 1997, 1999a; Brett et al., 1997; Hebebrand et al., 1997; Devor et al., 1998; Thompson et al., 1998; Stober et al., 1999). Several variables have been proposed to explain the unsuccessful genome search, including problems defining the phenotype, inaccurate diagnostic assessment, improper ascertainment methods, and problems with genetic modelling and data analysis. Nevertheless, some investigators have suggested that TS is not genetic, but rather represents a common disorder in the general population (Kurlan, 1994). Further complicating our understanding of TS genetics is the controversial issue of genomic imprinting (sex of the transmitting parent may affect the clinical phenotype) (Furtado & Suchowersky, 1994; Lichter et al., 1995; Eapen et al., 1997) and bilineal transmission (genetic contribution from both sides of the family (Comings et al., 1989; Kurlan et al., 1994a; McMahon et al., 1996; Hanna et al., 1999; Lichter et al., 1999). For example, it has been shown that paternal transmission of the affected gene leads to increased vocal

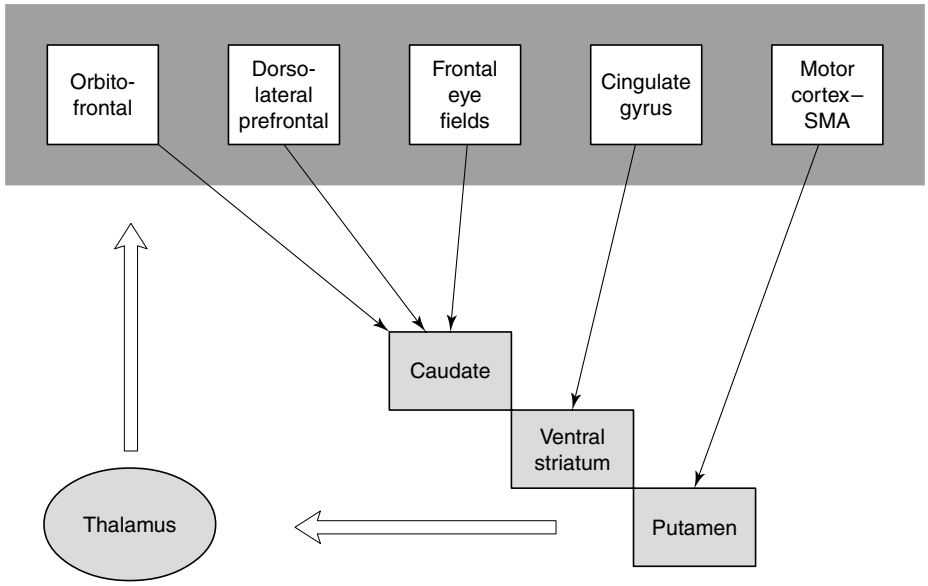

Fig. 38.1. Postulated frontal–subcortical pathways involved in Tourette syndrome.

tics and ADHD, whereas maternal transmission is linked to greater motor tic complexity and obsessive compulsive symptoms (Lichter et al., 1995). Additionally, one study estimates bilineality for tics, OCD, and ADHD to be 26% in TS families, further complicating interpretation of genetic data (Hanna et al., 1999). Studies also emphasize that factors other than genetic dose effects, such as genetic heterogeneity, epigenetic factors, and gene-environment interactions, may play an important role in determining tic severity in TS. A hypothesized role for environmental factors, especially infections, in the presentation or exacerbation of tics and OCD (Swedo et al., 1998) remains a controversial issue awaiting more definitive evidence (Kurlan, 1998).

Pathophysiology

Neuroanatomy

The exact neuroanatomic localization of TS remains unknown. Published postmortem studies are limited to seven cases; one suggested arrested development of the striatum and four showed a reduction in dynorphin-like immunoreactivity in the striatal projections to the globus pallidus and ventral pallidum (Richardson, 1982; Haber & Wolfer, 1992). Routine non-invasive neuroradiographic studies (CT and MRI) have identified only isolated defects that are considered to be incidental non-specific findings, unrelated to the basic pathology. Nevertheless, several publications have described localized lesions in the striatum, globus pallidus, and gyrus rectus of the left frontal lobe associated with clinical tics (Singer & Walkup, 1991). Neuropathologic and radiographic investigations have shown abnormalities in persons with secondary tics (Tourettism). For example, in a postmortem study of encephalitis lethargica, subjects with acquired tics had an array of small focal lesions in the central grey matter that extended into the midbrain tegmentum (Wohlfart et al., 1961; Sacks, 1982). Tourette-like symptoms also appear in association with a variety of acute and chronic neurologic disorders (see Table 38.1).

Although the exact neuroanatomic localization for tics has yet to be established, a series of parallel frontal subcortical circuits that link specific regions of the frontal cortex to subcortical structures (Alexander et al., 1986; Alexander & Crutcher, 1990; Cummings, 1993) provide a unifying framework for understanding the interconnected neurobiologic relationships that exist between ADHD and movement disorders (see Fig. 38.1). In brief, the striatum is distinguished by the presence of several structurally and functionally distinct subcortical and cortical circuits that are shared by the frontal lobe, striatum, globus pallidus, and thalamus. Each of these circuits has been associated with a behavioural abnormality seen in TS. The motor circuit, a potential site for generation of tics, originates primarily from the supplementary motor cortex and projects to the putamen in a somatotopic distribution. The

oculomotor circuit, a potential site of origin for ocular tics, begins primarily in the frontal eye fields and connects to the central region of the caudate. The dorsolateral prefrontal circuit links Brodmann's areas 9 and 10 with the dorsolateral head of the caudate and appears to be involved with executive function and motor planning. Dysfunction of this pathway could lead to attentional difficulties such as ADHD. The lateral orbitofrontal circuit originates in the inferolateral prefrontal cortex and projects to the ventromedial caudate. Orbitofrontal injury is associated with OCD, personality changes, disinhibition, irritability and mania. Lastly, the anterior cingulate circuit arises in the anterior cingulate gyrus and projects to the ventral striatum (olfactory tubercle, nucleus accumbens, and ventral medial aspect of the caudate and putamen) which receives additional input from the amygdala, hippocampus, and entorhinal and perirhinal cortex. Mutism, apathy and OCD are associated with this circuit. An important aspect of a circuit hypothesis is that lesions in one part (e.g. globus pallidus) of the circuit could produce signs and symptoms similar to those caused by a lesion in another region of the circuit (e.g. prefrontal cortex).

Direct evidence for pathophysiologic involvement of frontal subcortical circuits, especially the basal ganglia, in TS is derived from volumetric MRI studies (Peterson et al., 1993; Singer et al., 1993), area measurements of the corpus callosum (Peterson et al., 1993; Baumgartner et al., 1996), functional imaging of glucose metabolism and blood flow (Riddle et al., 1992; Baxter & Guse, 1993), oculomotor paradigms (Farber et al., 1999; Dursun et al., 2000; Mastofsky et al., 2001), and neuroimaging studies in subjects with ADHD and OCD (Aylward et al., 1996; Trivedi, 1996). For example, volumetric MRI studies in TS have shown significant differences in the symmetry of the putamen and lenticular region in boys (Singer et al., 1993) and a reduction in the size of these structures in adults (Peterson et al., 1993). On the basis of a quantitative MRI study of monozygotic twins, other investigators have suggested that, rather than an abnormality of the lenticular region, the caudate may be the important site (Hyde et al., 1995). A recent study in girls, however, showed no significant differences in basal ganglia or corpus callosum size between those with and without TS, suggesting that there may be gender differences in the neurobiologic manifestations of TS (Mostofsky et al., 1999; Zimmerman et al., 2000). Functional imaging studies have identified abnormalities in glucose metabolism and perfusion of the basal ganglia, especially on the left (Riddle et al., 1992; Stoetter et al., 1992; Baxter & Guse, 1993). In the HMPAO SPECT study of Riddle et al. (1992), TS was associated with a 4% reduction of blood flow to the left putamen and globus pallidus. In a small number of TS patients, event-related $[^{15}O]H_2O$ PET combined with time-synchronized audio and videotaping, identified aberrant activity in interrelated sensorimotor, language, executive, and paralimbic circuits (Stern et al., 2000). Transcranial magnetic stimulation (TMS) in children with tic disorders identified a shortened cortical silent period (Ziemann et al., 1997), suggesting a reduced motor inhibition believed to be at the level of the basal ganglia. In preliminary functional MRI studies, Peterson et al. (1998) compared images acquired during periods of voluntary tic suppression with those acquired when subjects were allowed spontaneous expression of their tics. Significant changes in signal intensity were seen in the basal ganglia and thalamus, as well as in connected cortical regions. Lastly, functional MRI imaging of five patients with TS during finger tapping showed an increased area of cerebral activation in both sensorimotor cortex and supplementary motor area as compared to these areas in healthy subjects (Biswal et al., 1990).

Neurochemistry

The distribution of classical neurotransmitters within the basal ganglia's frontal–subcortical circuits raises the possibility that a variety of transmitters are involved in the pathobiology of TS (Graybiel, 1990; Graybiel et al., 1994). In general, current hypotheses are based on extrapolations from clinical trials evaluating the response to specific medications; from studies of CSF, blood, and urine in relatively small numbers of patients; from SPECT and PET investigations; and from neurochemical assays on a limited number of postmortem brain tissues (Singer, 1997; Singer & Wendlandt, 2001). Genetic linkage analyses have also been performed in an attempt to identify specific candidate genes that are associated with components of neurotransmission. To date, the dopaminergic, GABAergic, cholinergic, serotoninergic, noradrenergic, and opioid systems have all been implicated. Which, if any, of these systems is the primary pathologic factor remains to be determined. Since many transmitter systems are interrelated in the production of complex actions, it is indeed possible, if not probable, that imbalances exist among several transmitter systems. Moreover, investigators must vigorously pursue mechanisms that could unify findings of alterations within multiple transmitter systems, i.e. such possibilities as second-messenger pathways, vesicle release proteins, channel abnormalities, or synaptic membrane dysfunction. Furthermore, any hypotheses about specific neuro-

transmitter deficiencies must account for variability in tic manifestations, fluctuating symptoms, and potential resolution in adulthood.

Neurochemical studies on postmortem tissues are limited to four TS cases. Singer et al. (1991) found a significant elevation of striatal [^{3}H]mazindol binding suggesting an elevation of dopamine transporter sites. Additionally a reduction in cyclic AMP was observed in cerebral cortex (Singer et al., 1990), but subsequent investigations identified no specific abnormality within several second messenger pathways (Singer et al., 1995a). Anderson et al. (1992) evaluating the same cases, compared levels of catecholamines, serotonin (5-HT), amino acids, and metabolites in 13 brain regions. Results showed reductions of 5-HT, tryptophan, and 5-hydroxyindoleacetic acid in subcortical structures, decreased glutamate levels in the globus pallidus and substantia nigra pars reticulata, and diminished glycine levels in substantia nigra pars reticulata. These data would suggest the possibility of altered serotoninergic transmission in the striatum and a reduced influence of glutamate in subthalamic efferent pathways. Because of the small number of available postmortem samples, emphasis has shifted to studies by in vivo neurochemical imaging. Dopaminergic hypotheses, including abnormalities of both pre- and postsynaptic function (supersensitive postsynaptic dopamine receptors, dopamine hyperinnervation, abnormal presynaptic function, or excessive release of dopamine) have been studied by PET and SPECT techniques. Overall, studies of D2 dopamine receptors have not consistently shown significant differences between TS patients and controls. Nevertheless, several investigations have supported the hypothesis that the dopamine receptor is involved in the neurobiology of TS (Wolf et al., 1996; Wong et al., 1997; Muller-Vahl et al., 2000). Similarly, attempts to provide support for a postulated dopamine hyperinnervation hypothesis by PET or SPECT binding have resulted in contradictory reports (Maison et al., 1995; Heinz et al., 1998). Studies evaluating dorsal striatal dopaminergic innervation by use of in vivo measures of vesicular monoamine transporter type 2 (VMAT2) binding, however, do not support the concept of increased striatal innervation. The possibility that deficits in a variety of presynaptic dopamine functional elements play a role has been supported by higher accumulations of [^{18}F]fluorodopa in the left caudate nucleus and right midbrain compared with levels in control subjects (Ernst et al., 1999). Lastly, increased intrasynaptic dopamine release from the putamen has been proposed, based on kinetic modelling of [^{11}C]raclopride binding after pretreatment with a central stimulant (Singer et al., in press). A [^{125}I]-CIT SPECT binding study has reported a negative correlation between overall tic severity and binding in the midbrain (serotoninergic) and thalamus (serotonin or noradrenergic) (Heinz et al., 1998). The authors suggest that serotoninergic transmission is a modifying, but not causal, factor in the pathogenesis of tics. In summary, available data have not confirmed a definite consistent abnormality of synaptic neurotransmission.

Neuroimmunology

Recently it has been proposed that TS, like Sydenham's chorea (SC), may be part of an immune-mediated neurologic response to a Group AB-hemolytic streptococcus infection (GABHS). SC is a major manifestation of rheumatic fever, along with carditis, migratory polyarthritis, erythema marginatum, and subcutaneous nodules. Typically, systemic manifestations of rheumatic fever occur 1–5 weeks after a GABHS pharyngitis, whereas chorea, which may be the sole manifestation, occurs from 2–6 months after antecedent infection. The pathophysiology responsible for the chorea has been speculated to be autoimmune, probably due to 'molecular mimicry,' i.e. shared antigens by the bacteria and host organs (Cairns, 1988; Stollerman, 1991).

The proposed spectrum of neurobehavioural disorders associated with GABHS infection has been expanded to include some children with TS and/or OCD termed 'pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection' (PANDAS) (Swedo et al., 1997, 1998). A possible association between GABHS and tics was initially proposed in case reports describing the explosive onset of tics after a preceding streptococcal infection (Kondo & Kabasawa, 1978; Matarazzo, 1992; Kiessling et al., 1993). More recently, Swedo and colleagues proposed diagnostic criteria that include: the presence of OCD and/or tic disorder; prepubertal age at onset; sudden, 'explosive' onset of symptoms and/or a course of sudden exacerbations and remissions; a temporal relationship between symptoms and GABHS; and the presence of neurologic abnormalities, including hyperactivity and choreiform movements. Volumetric MRI analysis in 34 children with PANDAS showed that the average size of the caudate, putamen, and globus pallidus, but not thalamus or total cerebrum, was significantly greater in the affected group than in 82 healthy children (Gredd et al., 2000). In a study of first degree relatives of children with PANDAS, the rates of tic disorders and OCD were similar to those published for tic disorders

and OCD (Lougee et al., 2000). The authors suggest that this supports the hypothesis of an environmental trigger in a genetically vulnerable population. An immune-mediated mechanism involving molecular mimicry has been proposed for PANDAS (i.e. antibodies produced against GABHS cross-react with neuronal tissue in specific brain regions), similar to the Sydenham's chorea model. Indirect support for this hypothesis is derived from the response of a small number of patients with PANDAS to two forms of immunotherapy, intravenous immunoglobulin (IVIG) and plasmapheresis (PEX) (Perlmutter et al., 1999); the documentation of antineuronal antibodies in patients with TS (Singer et al., 1998); and the development of dyskinesias (paw- and floor-licking, head- and paw-shaking) and phonic utterances in rodents after the microinfusion of dilute IgG from TS subjects into their striatum (Hallett et al., 2000).

The existence of PANDAS, however, remains controversial (Kurlan, 1998). For example, no prospective epidemiologic study has confirmed that an antecedent GABHS infection is specifically associated with either the onset or exacerbation of tic disorders or OCD. Subjects with PANDAS lack other stigmata of streptococcal infection, such as rash, arthritis, or valve disease. Diagnostic criteria established for PANDAS are also potentially confounded by the phenotypic variability commonly associated with tic disorders: a normal fluctuation in the frequency and severity of symptoms; exacerbation of tics by stress, anxiety, fatigue, and illness; the occurrence of 'sudden, abrupt' onset and/or recurrence of tics in non-PANDAS subjects (Singer et al., 2000); a variable response to pharmacotherapy; and the lack of a precise definition for choreiform movements. Additionally, longitudinal laboratory data, rather than studies that utilize only a throat culture or only a single antistreptolysin O (ASO) or antideoxyribonuclease B titre, are necessary to confirm the presence of a prior GABHS infection.

Evidence to support an immune-mediated hypothesis for PANDAS also remains largely circumstantial. For example, although plasmapheresis was claimed be beneficial, the therapeutic response did not parallel to the rate of antibody removal, it is unclear how peripheral changes affect events across the blood–brain barrier, and the mechanism for the beneficial response remains undetermined. Additionally, despite reported higher antineuronal antibody values in children with neurobehavioural problems and/or movement disorders including tics (Husby et al., 1976; Kiessling et al., 1992; Singer et al., 1998), the sensitivity and specificity of these studies remain a major issue. Antineuronal antibodies are present in control groups and Western blot analyses suggest that there are multiple differences in antibody repertoires in children with TS (Wendlaudt et al., 2001). Longitudinal studies will be required to clarify the current controversies.

Table 38.4. Tic-suppressing medications

Non-neuroleptics
Clonidine
Guanfacine
Baclofen
Clonazepam
Neuroleptics
Pimozide
Fluphenazine
Haloperidol
Trifluphenazine
Atypical neuroleptics
Risperidone
Olanzapine
Ziprasidone
Alternatives
Botulinum toxin
Tetrabenazine
Pergolide
Nicotine
THC

Treatment

Treatment of TS must take into account not only the severity of tics but the significance of comorbid academic, social, and neuropsychiatric problems. The symptom causing the most difficulty for the patient must be targeted first. The mere presence of tics does not in itself justify initiation of pharmacotherapy (Table 38.4). Medications should be targeted and reserved only for those problems that are functionally disabling and not remediable by non-drug interventions.

Patients with tics that are not causing any psychosocial or physical problems (i.e. no loss of self-esteem, no peer problems, no difficulty participating in academic, social, and after-school activities, no disruption of classroom setting, and no musculoskeletal problems) should be counseled and observed for the progression of symptoms. A variety of behavioural treatments including conditioning techniques, relaxation training, biofeedback, and hypnosis have been utilized as alternative therapeutic approaches for tics with variable short- and long-term success (Turpin, 1983; Bergin et al., 1998).

Tic-suppressing medications can be broadly divided into a 'mild' (non-neuroleptic) group and the neuroleptics (typical or atypical). Initial treatment of tics generally begins with non-neuroleptics. This category includes clonidine, guanfacine, baclofen and clonazepam. Clonidine can be especially effective in individuals with relatively mild tics who also have ADHD with aggressive features or poor impulse control. There is some suggestion that motor tics are more effectively suppressed with clonidine than are vocal tics (Leckman et al., 1985, 1991; Goetz et al., 1987). For tics alone, a BID dosing schedule is often adequate. For patients with comorbid ADHD, a QID schedule is often necessary for a consistent therapeutic effect. Common side effects include drowsiness, dry mouth, itchy eyes, postural hypotension, bradycardia and headaches. Clonidine should be tapered gradually to avoid rebound tic exacerbation and hypertension.

Individuals who fail initial therapy or who present with severe tics may benefit from neuroleptic or atypical neuroleptic medications. Neuroleptics, D2 dopamine receptor antagonists, are the most effective tic-suppressing agents (about 70–80% effective), but side effects may limit their usefulness. Side effects include weight gain, dysphoria, movement abnormalities (acute dystonic reactions, bradykinesia, akathisia, tardive and withdrawal dyskinesias), depression, and poor school performance. Haloperidol has historically been the most frequently used neuroleptic in this class, but more recently it has been replaced by pimozide because of greater tolerability (Shapiro et al., 1989; Sallee et al., 1997). Before initiating treatment with pimozide, an ECG should be obtained in order to identify a prolonged Q–T_c interval, a contraindicating factor. Other neuroleptics used in TS include fluphenazine and trifluoperazine.

The atypical neuroleptics were designed to decrease the extrapyramidal side effects common to most D2 receptor antagonists. As a group, risperidone, olanzapine, ziprasidone, clozapine, and quetiapine all have greater affinity for 5-HT2 (serotonin) receptors than for D2 receptors. Of these, risperidone and olanzapine have been used most extensively in TS. Risperidone may be most beneficial when tics occur with comorbid OCD (Robertson et al., 1996). A recent study has identified equal efficacy in the suppression of tics with use of either risperidone or pimozide (Beuggeman et al., 2001). In several studies olanzapine has been shown to be generally well tolerated and beneficial for tics (Bengi & Semerci, 2000; Onofrj et al., 2000; Stamenkovic et al., 2000).

Several additional pharmacotherapies have been proposed as tic-suppressing agents. Tetrabenazine, a dopamine antagonist that depletes presynaptic storage of dopamine and blocks postsynaptic dopamine receptors, has effectively suppressed tics (Jankovic et al., 1984; Jankovic & Beach, 1997). Dopamine agonists, such as pergolide, somewhat unexpectedly improved tics at approximately one-tenth the dose used for treatment of Parkinson's disease (Lipinski et al., 1997). Nicotine, in gum or patch form, has been shown to have brief beneficial effects when used in conjunction with neuroleptics (Dursun & Reveley, 1997; Sanberg et al., 1988, 1989, 1997). In uncontrolled trials, marijuana and delta-9-tetrahydrocannabinol, the major psychoactive component of marijuana, have been reported to be beneficial (Muller-Vahl et al., 1999, 2000). Botulinum toxin, which reduces muscle activity by inhibiting acetylcholine release at neuromuscular junctions, has been shown not to only reduce tics but also the premonitory urge associated with the tics (Kwak et al., 2000). Suggestions that Botox® produces a universal improvement in simple tics (Trimble et al., 1998; Awaad, 1999) have not been supported in all studies (Marras et al., 2000). Several patients with coprolalia have been successfully treated with injections either into a single vocal cord or both thyroarytenoid muscles (Scott et al., 1996; Trimble et al., 1998). Penicillin and immune therapies including IVIG and plasmapheresis for PANDAS are currently under investigation. Neurosurgical interventions for severe intractable tics are rarely indicated. Procedures used have included focal lesions of frontal, cingulate, thalamic, and cerebellar areas (Rauch et al., 1995). Thalamic deep brain stimulation, a modern stereotactic treatment proposed for use in other movement disorders, has been suggested as a potential therapy for the control of tics.

ADHD

Although psychostimulant medications are generally regarded as the treatment of choice for ADHD, their use in children with TS was controversial because of their proposed potential to provoke or intensify tics in a substantial minority. Several new reports providing additional information on the question of the role of stimulants in worsening tic disorders can be summarized as follows: there is strong evidence that stimulants have a beneficial effect on ADHD and, in most children receiving low-moderate doses of methylphenidate, there appears to be no clinically significant effect on tics (Lowe et al., 1982; Castellanos et al., 1997; Gadow et al., 1999; Nolan et al., 1999; Law & Schachar, 1999). Tics may fluctuate but usually do not require pharmacologic adjustments. Other medications suggested for the treatment of ADHD symptoms in children with TS include clonidine, guanfacine, desipramine, deprenyl, and nortriptyline. In the occasional situation where a stimulant is required for attendance in school or

performance at work and tics remain constant, stimulants and tic-suppressing medications are given simultaneously.

OCD

Over the past decade the treatment of OCD has expanded, with the addition of a variety of serotonin reuptake inhibitor antidepressants including fluoxetine, fluvoxamine, clomipramine, paroxetine, and sertraline. These medications, also effective in anxiety disorders, can sometimes be helpful in addressing the stress associated with the stigma of a chronic tic disorder.

In conclusion, although much is known about TS and related disorders, much remains to be done. Tourette syndrome is a chronic neuropsychiatric disorder that has been recognized for well over a century. Although defined by the presence of vocal and motor tics, comorbidities, such as OCD and ADHD, often cause more significant impairment than the tics. TS is considered to be an inherited disorder, although the precise pattern of transmission and the identification of the gene remains elusive. Genetic heterogeneity, epigenetic factors and gene–environmental interactions may play an important role in phenotypic expression. Evidence supports involvement of frontal–subcortical circuits and synaptic neurotransmission. Nevertheless, the precise localization and specific subcellular mechanism have yet to be determined. Pharmacotherapy is available for tic suppression, but is strictly symptomatic, not universally effective, and often limited by side effects.

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39

Cerebral palsy

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Cerebral palsy (CP) is a clinical diagnostic term referring to a group of upper motor neuron syndromes secondary to disorders of early brain development (Johnston, 1998a). In addition to primary impairments in motor function, there may be associated problems with speech, cognition, epilepsy, visual impairment seizures and orthopedic deformities. Although CP is considered non-progressive, neurological findings may change or progress over time (Saint Hilaire et al., 1991; Scott & Jankovic, 1996).

CP is the most prevalent and costly form of chronic motor disability that begins in childhood. Although comprehensive longitudinal studies are limited, the majority of affected children live into adulthood (Crichton et al., 1995). In the United States, financial costs of care are estimated to be in the billions of dollars (Kuban & Leviton, 1994). The non-economic impact on affected individuals and their families is substantial (Murphy et al., 2000).

At the end of the nineteenth century, William Osler published his lectures on *The Cerebral Palsies of Children,* with a CP classification based on neuroanatomy, etiology and extremity involvement. 'Dividing the motor path into an upper corticospinal segment, extending from the cells of the cortex to the grey matter of the cord, and a lower spinomuscular, extending from the ganglia of the anterior horns to the motorial end plates, the palsies which I propose to consider have their anatomical seat in the former, and may result from a destructive lesion of the motor centres, or of the pyramidal tract, in hemisphere, internal capsule, crus or pons' (Osler, 1987). The current concept of CP is built on Osler's description, using imaging techniques, molecular genetic probes and measurement tools to further etiological understanding, improve classification and refine treatment options (Hoon & Melhem, 2000; Brunstrom et al., 2000).

Several strongly conflicting theories of causation have been proposed. In the mid-1800s, Sir William Little suggested that most CP was related to difficulties with delivery, a view which has had legal ramifications extending to the present time (Little, 1861). Approximately 50 years later, Sigmund Freud offered an alternative hypothesis that cerebral palsy reflected 'symptoms of deeper underlying influences which have dominated the development of the fetus' (Freud, 1968). Recent epidemiological studies indicate that most cases are related to prenatal disorders of genetic and environmental origin (Hagberg et al., 1996; Palmer et al., 1995). A small but distinguishable group results from perinatal hypoxic–ischemic insults, and a third group from injury in early childhood.

Modern neuroimaging techniques, including cranial ultrasound, computerized tomography (CT) and magnetic resonance (MR) imaging, provide clues to the timing and pathogenesis in 70–90% of patients (Truwit et al., 1992; Hoon, 1995). The ongoing development of advanced nuclear magnetic resonance methods, including diffusion-weighted imaging (Inder et al., 1999a; Johnson et al., 1999), diffusion tensor imaging (Mori et al., 1999) and MR spectroscopy (Shu et al., 1997; Novotny et al., 1998), hold promise to further etiological understanding.

Neuroimaging studies, including brain MR imaging, have demonstrated links between specific CP syndromes and patterns of selective vulnerability of specific components of developing motor systems (Dammann & Leviton, 1997; Nelson et al., 1998). These patterns are related to age-dependent changes in cellular metabolism, neuronal connectivity and circulation (Johnston, 1998b). Important examples readily seen with MR imaging include white matter vulnerability between 24 and 34 weeks, termed periventricular leukomalacia (PVL), as well as neuronal vulnerability at term (Okumura et al., 1997; Menkes & Curran, 1994).

Effective management of patients with CP requires the participation of a team of physicians, clinicians and thera-

pists that provides careful, continuing neurodiagnostic evaluation along with therapeutic intervention to manage tone and other rehabilitative needs. Coordination of services with community based clinicians is also required to ensure that affected individuals have full opportunities to learn in school and participate in society.

Epidemiology

The overall prevalence of CP in developed countries is 2–3/1000 (Murphy et al., 1993; Hagberg et al., 1996). This figure has remained relatively constant over the last two decades, despite dramatic improvements in obstetrical and neonatal intensive care. This suggests that obstetrical interventions such as tocolysis (medication to slow or stop labour, eg, ritodrine, magnesium), the increased rate of Caesarean section and fetal heart rate monitoring have had little impact in reducing the incidence of CP (Canadian Preterm Labor Investigators Group, 1992; Scheller & Nelson, 1994; Parer & King, 2000).

Prematurity is strongly associated with CP (Surveillance of Cerebral Palsy in Europe, 2000). The improved survival of very low birthweight infants has led to an absolute increase in the number of children with the disorder. A second related factor is the recent increase in multiple births; there is a tendency for these infants to be low in birthweight, with a consequent increased risk of developing CP (Grether et al., 1993). Overall, while most premature infants develop normally, concerns have been expressed that one undesirable result of the success of neonatal medicine is the increased survival of children with severe neurodevelopmental handicaps, including CP (Hack & Fanaroff, 1999; Colver et al., 2000).

However, births at term are far more numerous than premature births and the majority of children with CP are born full term. Studies based on the NIH Perinatal Collaborative Project indicate that in more than 80% of cases, CP is associated with disorders of prenatal origin (Nelson & Ellenberg, 1986). Major risk factors for CP, in addition to low birthweight and prematurity, include maternal infections and/or fever at term, endocrine disturbances such as hypothyroidism and other factors listed in Table 39.1.

Table 39.1. Epidemiological factors associated with cerebral palsy

Maternal	Fetal/neonatal
History of fetal loss	Congenital malformations
Long interval between menstrual cycles	Fetal growth retardation
	Twin gestation
Low socioeconomic group	Abnormal fetal presentation
Mental retardation	Nuchal cord
Fever in labour	Prematurity
Chorioamnionitis	Premature separation of placenta
Febrile urinary tract infections	
Thrombophilic disorders	Newborn encephalopathy
Thyroid disorders	

Table 39.2. Common cerebral palsy syndromes

Bilateral spasticity	Extrapyramidal (dyskinetic)
Spastic diplegia	Bradykinesia
Spastic quadriplegia	Dystonia
Unilateral spasticity	Choreoathetosis
Spastic hemiplegia	Hemiballismus

Cerebral palsy syndromes

CP can be classified into four broad groups based on differences in tone and limb involvement: bilateral spasticity, unilateral spasticity, extrapyramidal (dyskinetic) and hypotonia/ataxia, and further subcategorized into clinically recognizable syndromes such as spastic diplegia (Table 39.2). These syndromes often have differing etiological antecedents (Table 39.3) and relatively distinct clinical features (Table 39.4).

The majority of patients with CP have relatively symmetric upper motor neuron involvement, with spasticity being the primary neurologic abnormality. Most of these individuals have either spastic diplegia or spastic quadriplegia depending on whether the lower limbs are preferentially involved (diplegia) or whether all four extremities are heavily involved (quadriplegia). A smaller group with unilateral spasticity is referred to as hemiplegic CP.

Patients with abnormalities of tone and posture associated with basal ganglia involvement are classified as extrapyramidal (dyskinetic) CP. They usually have rigidity rather than spasticity, variability in truncal and appendicular tone, and additional manifestations of basal ganglia involvement including bradykinesia, dystonia, choreoathetosis or hemiballismus.

A small group of patients with atypical features such as hypotonia and or ataxia are classified with hypotonic/ataxic CP. Many patients with this type of congenital motor disorder, along with a substantial portion of the extrapyramidal

Table 39.3. Common causes of cerebral palsy by syndrome

Spastic diplegia	Spastic quadriplegia	Hemiplegia	Extrapyramidal
PVL[a]	PVL[a] (Severe)	Stroke[d]	Near-total asphyxia
Hereditary spastic paraparesis	Multicystic encephalomalacia[b]	Periventricular hemorrhagic infarction[e]	Kernicterus
HIV	Genetic-developmental[c]	Genetic-developmental[f]	Genetic-metabolic[g]
	Hydrocephalus		Hypothermic circulatory arrest (heart surgery)

Notes:
[a] Secondary to hypoxia–ischemia, maternal infection, fetal/neonatal infection and endocrine/metabolic disorders in the mother or fetus (e.g, thyroid disorder); [b] secondary to partial prolonged asphyxia, intrauterine infection, bacterial meningitis, non-accidental trauma; [c] holoprosencephaly, neuronal migration disorders, agenesis of the corpus callosum; [d] secondary to thrombophilic disorders, embolic disorders, trauma, infection; [e] (Grade 4 IVH); [f] unilateral schizencephaly; [g] mitochondrial disorders, methylmalonic aciduria, glutaric aciduria, type I Huntington disease, Hallervorden–Spatz.

Table 39.4. Clinical features of cerebral palsy

	Spastic diplegia	Spastic quadriplegia	Hemiplegia	Extrapyramidal	Hypotonia/ataxia
Tone	Spasticity	Spasticity	Spasticity	Rigidity	Hypotonia
Extremity involvement	LE > UE	LE = UE	Unilateral	UE > LE	UE = LE
Movement disorders	Clonus, spasms, toe walking	Clonus, spasms	Clonus, spasms	Dystonia, chorea, athetosis	Ataxia
Speech/swallowing	Mild impairment	Impaired	Intact	Impaired or absent speech	Variable
Cognitive impairment	Mild–moderate, learning disorders	Moderate–severe	Intact to mild	Intact to moderate	Variable
Associated problems	Strabismus, orthopedic deformities	Orthopedic deformities, epilepsy	Epilepsy	Orthopedic deformities Genetic–metabolic disorders	Undiagnosed genetic–metabolic disorders

group, have undiagnosed genetic/metabolic disorders including disorders of mitochondrial energy metabolism.

Spastic diplegia

Spastic diplegia is the clinical syndrome with spasticity greater in the legs than the arms, seen most commonly in children born prematurely. As premature infants usually receive careful developmental follow-up after discharge from the NICU, those with spastic diplegia are often identified during the first 6–12 months of life with signs of delayed motor development.

Spastic diplegia is primarily a disorder of developing white matter and is nearly always associated with neuropathological and neuroimaging findings of PVL. PVL is characterized by destruction of cerebral white matter in regions near the lateral ventricles. It consists of areas of focal necrosis with complete cellular loss, and surrounding regions with selective glial cell injury. PVL is easily demonstrated on MR imaging either as characteristic 'squared off', enlarged ventricles or as moderate ventricular enlargement with periventricular gliotic scarring, as seen on T_2-weighted sequences (Fig. 39.1). PVL is typically more prominent in the posterior ventricular system, particularly in the periatrial area, and is associated with thinning of the corpus callosum.

PVL is strongly associated with premature birth, with the highest incidence at 28 weeks gestation; later in gestation the incidence markedly declines, becoming far less frequent after 32 weeks gestation. While most children with PVL are born prematurely, a few are born at term. It is very likely that most of these children acquired PVL earlier

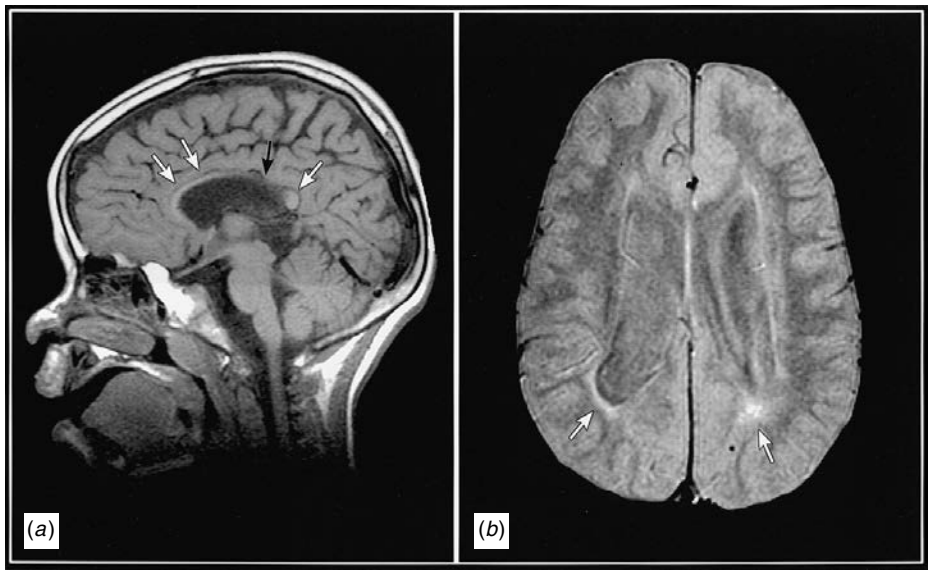

Fig. 39.1. These MR images obtained in childhood show the MR imaging findings of PVL. (*a*) Marked thinning of the corpus callosum (white arrows) with area of complete loss (black arrow); (*b*) Ventriculomegaly with scalloped irregular borders and periventricular gliosis (white arrows). Clinically the child had severe motor and cognitive impairments. (These images were previously published in Hoon & Melhem, 2000.)

during gestation (Miller et al., 2000). Preferential involvement of myelinating corticospinal fibres closest to the ventricles, which control the lower extremities, explains the greater involvement of the legs than the arms in spastic diplegia.

Considerable clinical and experimental evidence indicates that PVL and associated spastic diplegia reflect the selective vulnerability of immature oligodendroglia to stressors such as hypoxia–ischemia or infection at a critical period in their development (Dammann & Leviton, 1997). In many premature infants, PVL is probably produced by reductions in blood flow to marginally perfused periventricular regions as a result of dysfunctional vascular regulatory mechanisms related to prematurity and other contributing factors, including respiratory distress syndrome/prolonged mechanical ventilation, sepsis and necrotizing enterocolitis (Volpe, 1997). Experimental evidence suggests that glutamate released during ischemic episodes may trigger excitotoxic injury in immature oligodendroglia, in part because these cells are less protected from oxygen free radical damage than more mature oligodendroglia (Oka et al., 1993).

Infection, especially gram-negative infection, in either the mother or infant has also been associated with PVL based on clinical and experimental evidence. PVL has been reported to be more frequent in infants whose mothers had febrile urinary tract infections during pregnancy and in infants with sepsis related to necrotizing entercolitis. PVL may also be associated with thyroid or other endocrine metabolic disturbances.

In contrast, low grade (I–II) intraventricular bleeding does not appear to be a strong predictor of motor disability or PVL (Paneth, 1999). However, periventricular hemorrhagic infarction associated with grade IV hemorrhage is often associated with unilateral white matter destruction and asymmetric spasticity (Volpe, 1995).

MR imaging is quite sensitive and specific for PVL associated with spastic diplegia, and is useful for ruling out other causes of motor dysfunction. MR imaging is useful even in older patients with PVL since the changes appear to be permanent. Evidence from quantitative brain MR studies suggests that ventricular enlargement with PVL correlates with greater motor and cognitive impairment related to loss of white matter connections among different regions of the cerebral cortex (Melhem et al., 2000). Quantitative MR imaging is also useful for detecting neuronal abnormalities that may coexist with PVL (Inder et al., 1999b). By contrast, CT scanning is relatively insensitive to PVL, showing only the most severe involvement as enlargement of the ventricles with the characteristic 'squared-off' ventricular profile.

Cranial ultrasound is often informative in the newborn period when the anterior fontanel remains open. Cranial ultrasound can often detect the progression from

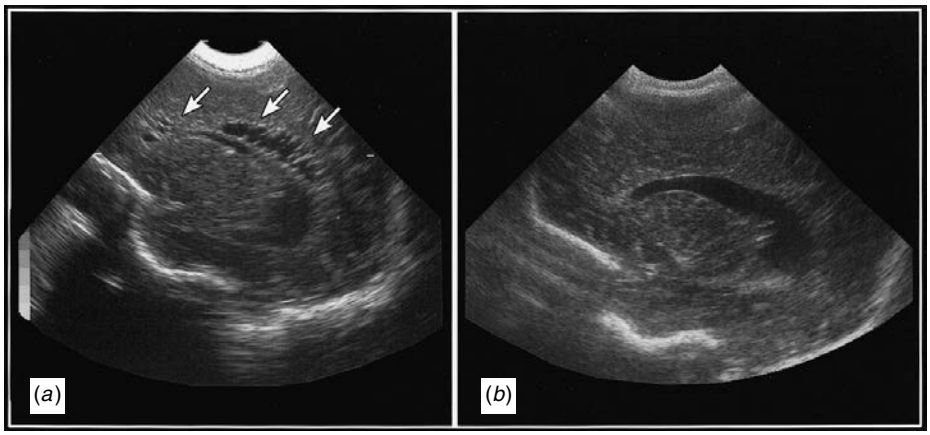

Fig. 39.2. These images show the evolution of cystic PVL on sagittal cranial ultrasound images in a 27 week infant. (*a*) Hypoechoic areas corresponding to cystic degeneration in periventricular white matter at 2 months of age (white arrows); (*b*) Resolution of the cysts with compensatory ventriuculomegaly at 6 months of age. The findings in Panel A carry a risk for CP which approaches 100%. (These images were previously published in Hoon & Melhem, 2000.)

periventricular enhanced signal intensity to cyst formation to ventricular enlargement that can occur during the postnatal period in premature infants (Fig. 39.2). Persistent ventriculomegaly seen on ultrasound in premature infants is a strong risk factor for CP, probably because it reflects loss of periventricular white matter (Paneth et al., 1994).

Spastic quadriplegia

Spastic quadriplegia is the pattern of bilateral spasticity affecting all four extremities. It is the result of a broader range of pathological insults than spastic diplegia, including severe PVL, multicystic encephalomalacia, genetic/developmental brain malformations and hydrocephalus. As with other forms of CP, low birthweight, prematurity and complicated neonatal course are important risk factors. Delayed motor development in the first year is usually more prominent than in spastic diplegia.

In the subgroup with severe PVL, extensive white matter involvement leads to disruption of arm as well as leg fibres as they descend from the motor cortex. These children are often born very prematurely. Some may have also sustained posthemorrhagic hydrocephalus with pressure-related disruption of white matter.

Patients in a second major subgroup have relatively symmetric destructive lesions of the cerebral cortex. One important type of destructive lesion is multicystic encephalomalacia, which refers to multiple cystic cavities in the cortex separated by glial septations. It results from diffuse insults occurring from late gestation through infancy (Barkovich, 2000). It can be produced by intrauterine infections, partial prolonged hypoxia–ischemia, perinatal herpes simplex, bacterial meningitis, or non-accidential trauma during infancy. Parasagittal watershed infarctions associated with hypotension in sick term infants may present as quadriplegia with more weakness in the shoulders and upper extremities (Pasternak, 1987).

A third subgroup includes patients with genetic/developmental brain malformations, such as holoprosencephaly, lissencephaly, pachygyria and agenesis of the corpus callosum which commonly lead to microcephaly and spastic quadriplegia. TORCH infections (toxoplasmosis, rubella, cytomegalovirus, herpes, and other bacterial and viral) can also result in pachygryria, with similar clinical findings. Brain MR imaging is very useful for distinguishing these disorders, some of which have specific recurrence risks (Hoon & Melhem, 2000). CT is still useful for detecting intracranial calcifications.

A final common subgroup includes those with fetal or neonatal hydrocephalus, reflecting a variety of pathologies affecting the development and maintenance of CSF pathways, including aqueductal stenosis and Dandy Walker syndrome. Outcome is related to the presence and severity of associated anomalies (Pretorius et al., 1985) as well as the need for multiple shunt revisions.

Hemiplegic cerebral palsy

One-third of patients with CP have unilateral spasticity, termed hemiplegic CP, which usually affects the arms more than the legs. A higher proportion of these infants are born at term than in groups of patients with diplegia or quadri-

Table 39.5. Thrombophilic disorders associated with vascular occlusions in CP

Factor V Leiden
N-Methylene-tetrahydrofolate reductase deficiency
Prothrombin mutation
Deficiency of Protein S, Protein C, or Antithrombin III
Anticardiolipin antibodies

plegia. Several studies indicate that most term infants with hemiplegic CP sustained cerebral infarctions or strokes prior to birth (Scher et al., 1991; Nelson, 1991). Neuropathological and neuroimaging studies demonstrate the presence of wedge-shaped lesions suggesting vascular infarctions or irregularities in the periventricular white matter (Taudorf et al., 1984). In a large postmortem study of cerebral infarctions in neonates, arterial vascular occlusions were found to be the most common lesion, and the most common associated cause was sepsis with or without disseminated intravascular coagulation (Barmada et al., 1979). Venous sinus thrombosis is probably also a significant cause of hemiparesis, though it has been difficult to identify until the era of modern neuroimaging.

In a study of focal white matter necrosis in infants, markers for infection are prominent risk factors as are congenital malformations, placental vascular malformations, multiple births and maternal and intra-amniotic infections (Leviton & Paneth, 1990). Prenatal white matter necroses and hemipareses have also been found to be associated with polyhydramnios, and the in utero death of one twin. In premature infants, hemiparetic CP can be produced by Grade IV intraventricular hemorrhages with periventricular white matter infarction due to venous infarction. Overall, hemiparetic CP is far more likely than other syndromes to be caused by infarctions secondary to vascular occlusions.

Recently, inherited thrombophilic disorders such as Factor V Leiden have been recognized to be a significant cause of vascular occlusions in fetuses and infants, and may be nearly as frequent as infection as a precipitating cause of hemiparetic CP (Thorarensen et al., 1997) (Table 39.5). Recent studies suggest that Factor V leiden may be responsible for obstetrical complications in mothers such as preeclampsia, as well as for bleeding disorders and strokes in infants (Harum et al., 1999). In one study of mothers with complicated pregnancies, acquired or inherited thrombophilic disorders were diagnosed in more than half of these women (Kupferminc et al., 1999). These studies suggest that patients with hemiparetic CP should be evaluated carefully for possible thrombophilic disorders, which may carry a recurrence risk in subsequent pregnancies.

A third group of disorders which may cause hemiplegia is schizencephaly, some forms of which may have a genetic etiology (Brunelli et al., 1996). Unilateral schizencephaly is associated with hemiplegic CP, while bilateral schizencephaly results in spastic quadriplegia.

Brain MR imaging is the most useful diagnostic modality in patients with hemiplegia. It provides clear distinction between vascular insults which are lined with gliotic white matter and the grey matter lining seen in schizencephaly (Candy et al., 1993).

Extrapyramidal cerebral palsy

Approximately 20% of patients with CP have a prominent extrapyramidal syndrome with rigidity more than spasticity and involvement of the upper extremities more than lower extremities. It is usually associated with a marked reduction in speech production but relatively preserved intelligence. Most of these individuals have an overall reduction and slowing of movement (bradykinesia), but some have hyperkinetic disorders including chorea, athetosis, dystonia and hemiballismus. (An additional group of children have spastic diplegia or quadriplegia associated with extrapyramidal signs, and are referred to as having a 'mixed' CP.)

The entire group of patients with extrapyramidal CP is quite heterogeneous because of the wide spectrum of acquired and inherited disorders of the basal ganglia responsible for the syndrome (Hoon et al., 1997). In some patients the motor disability remains stable over time, while in others there is progressive neurological decline. This important distinction may require careful, repeated neurological examinations to establish.

One important subgroup of extrapyramidal CP patients results from selective injury to the basal ganglia, especially the putamen and thalamus, occurring in acute near-total asphyxia in the last few weeks of a term gestation (Johnston & Hoon, 1998). Several authors have reported the neuroimaging picture of basal ganglia injury in these patients, with MR imaging proving to be particularly helpful (Menkes & Curran, 1994; Pasternak & Gorey, 1998). Early MR imaging, within a few weeks of injury, often shows increased signal on T_1-weighted images in the caudate, putamen and thalami while follow-up is more likely to show enhanced T_2-weighted signal in the posterior portion of the putamen and lateral thalami. The peri-rolandic cerebral cortex is sometimes involved as well. The selective vulnerability of these regions may reflect hyperactivity of prominent excitatory glutamate-containing neurons that

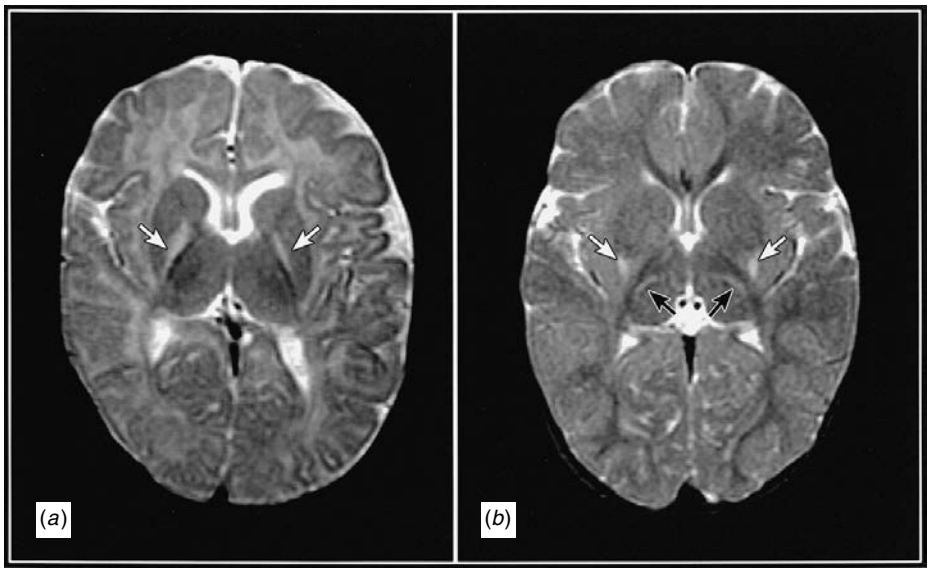

Fig. 39.3. MR images from two infants with clinically similar neonatal encephalopathies, including seizures and ventilatory failure. (*a*) Globus pallidus hyperintensities (white arrows) seen in bilirubin encephalopathy; (*b*) Putaminal (white arrows) and thalamic (black arrows) hyperintensities seen in perinatal hypoxic–ischemic encephalopathy. Both result in extrapyramidal CP.

connect these regions with the cerebral cortex in reciprocal circuits. This pattern of selective vulnerability has also been reproduced in animal models of hypoxia–ischemia. MR imaging can provide strong evidence that hypoxic–ischemic injury to the basal ganglia from asphyxia is responsible for extrapyramidal CP in some patients.

Other patients with extrapyramidal CP may have heterogeneous disorders that require careful diagnostic evaluation. This subgroup of patients is most likely to contain undiagnosed metabolic–genetic disorders, where careful follow-up is important to detect changes that may reflect a progressive disorder. MR imaging can readily distinguish patients with extrapyramidal CP associated with lesions in the globus pallidus from those with putaminal injury in asphyxia. Pallidal injuries are common in kernicterus from hyperbilirubinemia (Fig. 39.3), but may also be caused by mitochondrial disorders with or without lactic acidosis. Some patients with extrapyramidal CP may have pallidal injury after heart surgery as infants (Kupsky et al., 1995). These patients are more likely than others to have hyperkinetic disorders such as chorea or hemiballismus.

Patients with degenerative disorders that affect the globus pallidus, such as Hallervorden–Spatz disease, may progress at such a slow rate initially that they appear to have idiopathic extrapyramidal CP. Other disorders that can present as undiagnosed CP include glutaric aciduria Type I and juvenile Huntington disease, both of which have prominent basal ganglia lesions on MR imaging (Morton et al., 1991; Lenti & Bianchini, 1993). Methylmalonic aciduria can also present with prominent lesions of the globus pallidi after metabolic 'strokes' (Heidenreich et al., 1988). Patients with other, more obscure disorders of intermediary or neurotransmitter metabolism, or of idiopathic or genetic dystonia, may present initially as extrapyramidal CP. Rarely, patients with a defect in GTP cyclohydrolase (Segawa's disease or dopa-responsive dystonia) may present with severe idiopathic extrapyramidal CP early in life (Korf, 1998).

Because of the diverse nature of disorders that can present as extrapyramidal CP, this group of patients requires careful diagnostic evaluation. The etiological evaluation should include brain MR imaging, urine organic acids, plasma amino acids, lactate and chromosomes. Evaluation of CSF biopterin, neurotransmitter and amino acid metabolism is often indicated, especially in patients with idiopathic extrapyramidal CP with normal MR scans. Careful follow-up is important as many of these patients progress or change over time. Furthermore, patients with extrapyramidal CP secondary to acquired lesions such as asphyxia may progress or display new movement disorders including dystonia in teenage or adult years, probably due to continuing reorganization of the nervous system.

Hypotonic/ataxic cerebral palsy

A few patients with congenital motor disorders present predominantly with hypotonic truncal tone, delayed

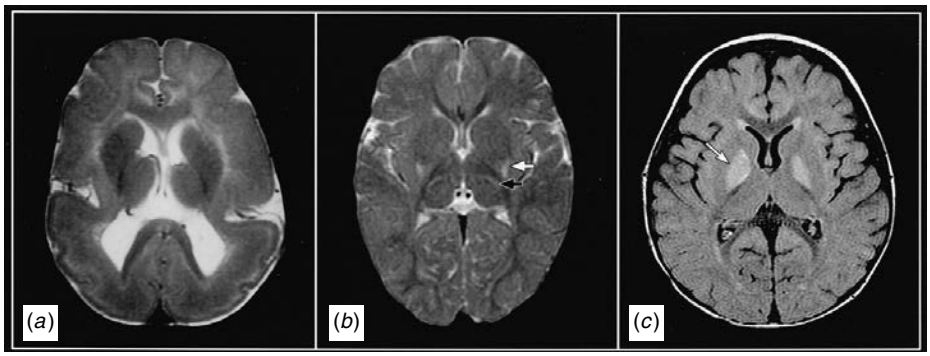

Fig. 39.4. MR images from three children presenting with severe CP. (*a*) Lissencephaly in Miller–Dieker syndrome; (*b*) perinatal hypoxic–ischemic encephalopathy (from Fig. 39.3), and (*c*) methymalonic acidemia with globus pallidus hyperintensities (white arrows).

motor milestones and an abnormal gait with an ataxic appearance (Dubowitz, 1980). These patients are distinguished by the lack of lower motor neuron signs, suggesting a disorder of upper motor neurons. Like extrapyramidal CP, this is a very heterogeneous group, which probably contains many patients with undiagnosed genetic-metabolic disorders. This group is probably the least likely of all the cerebral palsy syndromes to be caused by an acquired condition such as asphyxia. Careful neurodiagnostic evaluation of these patients is also indicated with MR as well as metabolic testing. Recognized disorders include congenital malformations of the cerebellar vermis with mega-cisterna magna, mitochondrial disorders, carbohydrate-deficient glycoprotein disorder, disorders of neurotransmitter metabolism, and Joubert's syndrome. Periodic re-evaluation of these children is indicated.

Diagnostic evaluation

The evaluation of patients with motor delay should begin with a careful history, including details of the prenatal, perinatal and postnatal course. Maternal perception of decreased fetal movement is an important sign of prenatal onset. If there is no history of an acute neonatal encephalopathy, then the etiology is not related to perinatal events. Family history is important to identify those with potential genetic disorders. The review of systems should include questions about vision, hearing, snoring, feeding, bowel and bladder function as well as any cardiac and pulmonary problems. The neurological examination should be comprehensive, including careful observation for adventitious movements, including chorea, athetosis, hemiballismus and dystonia.

An assessment of functional abilities should be obtained, and measures of cognitive function whenever possible. The functional assessment of children with CP is best done in conjunction with skilled physical and occupational therapists. Children may be classified both by the extent of mobility aids required (from point canes to wheelchairs), as well as by their ability to ambulate independently in various settings (from home to gymnasium to community). Physical therapists can be of great benefit here, recommending appropriate aids to mobility as well as setting functional goals for the child, which will foster independence. The cognitive evaluation should be done by a neuropsychologist experienced in the assessment of intelligence in motor impaired patients to provide an accurate reflection of abilities.

The diagnostic evaluation should commence with an MR imaging study (Fig. 39.4). Findings from this study can often be used to determine the need for additional testing. For example, in a child with extrapyramidal CP and imaging abnormalities in the globus pallidus, a comprehensive evaluation for genetic–metabolic disorders should be completed. In those with developmental brain malformations including neuronal migration disorders such as lissencephaly and schizencephaly, specific molecular testing may be important to identify an etiology and to determine recurrence risk (Gleeson et al., 2000).

Depending on the clinical setting, there are a number of other diagnostic modalities. All children with CP should have an ophthalmological evaluation by a specialist experienced in CP. This is important both because of the large number who have refractive errors as well as the potential diagnostic clues which can be identified from a dilated examination of the optic nerve and retina.

Based on clinical examination, if there is evidence to suggest a genetic etiology, a karyotype as well as specific molecular probes should be obtained. If there is evidence of rigidity on examination, a disorder of energy production involving mitochondrial function should be considered,

with a lactate, plasma amino acid and urinary organic acid profile obtained. If there is significant ataxia, the cerebellum should be carefully assessed on MR imaging, with testing to include various forms of SCA as well as carbohydrate deficient glycoprotein disorders; Angelman syndrome should also be considered.

If the initial diagnostic work-up is unrevealing, ongoing clinical follow-up may reveal further information that will assist in diagnosis and clinical care. While many parents seek 'closure' of the search for cause so that they can proceed with rehabilitation, most nevertheless remain interested in establishing the cause, and will continue with a carefully orchestrated ongoing diagnostic search.

Associated impairments

While CP refers primarily to the motor involvement, affected individuals frequently have a range of associated impairments (Table 39.3). Up to half of children with CP have mental retardation. A third have seizure disorders. Learning disabilities are also linked with CP. Impairments in hearing and vision should also be considered, as well as disorders of speech, swallowing and feeding.

Furthermore, for the affected child, there may be social and emotional limitations. These children often have a difficult time once they become aware of differences from their peers. It is important for families to encourage them to develop skills in other areas, which may include horseback riding, and in other forms of therapeutic recreation. This will promote a sense of confidence and self-esteem.

While educational opportunities are often available until age 21 under the provisions of the Individuals with Disabilities Education Act (IDEA), rehabilitative and supportive services are less well organized in adulthood. Despite the American with Disabilities Act, barriers to employment continue to exist.

Rehabilitation

There are a number of rehabilitative motor interventions for individuals with CP. Depending on the clinical situation, the rehabilitative goals may be ease of care, preventing orthopedic deformities or facilitating function. The specific goals of affected individuals and their families should be carefully considered in formulating rehabilitation plans.

In young children, the mainstays of rehabilitation are occupational and physical therapy (Bartlett & Palisano, 2000). These techniques serve to lessen the effects of inhibitory reflexes and to facilitate the acquisition of gross and fine motor skills. They may also have benefit in other areas of development including language, and the promotion of confidence and self esteem.

In children with spasticity, there may be progressive orthopedic deformities. In the past, surgeries were done in a sequential fashion, one at a time. However, more recently, multiple soft tissue and/or bone procedures have been conducted simultaneously (Fabry et al., 1999). Initially, soft tissue releases are usually employed for those with contractures. Bony procedures to the leg, hip and spine may also be required. Whether pharmacological interventions will lessen the need for orthopedic surgery is unclear at this time.

For patients with localized spasticity, botulinum toxin has been effectively utilized to improve gross and fine motor abilities (Wissel et al., 1999; Koman et al., 2000). Beneficial effects are related to the temporary weakening of specific muscle groups interfering with function. Botulinum injections are extremely safe, with effects lasting up to three to four months.

A range of oral pharmacological agents has been effectively utilized to diminish spasticity (Pranzatelli, 1996). Diazepam has been employed in the past, although concerns over cognitive side effects limited its use. More recently, baclofen has been preferentially used, recognizing that there are less cognitive side effects from this drug. However, patients should be cautioned against abruptly discontinuing baclofen, which can precipitate hallucinations or seizures. Depending on the clinical situation, other antispasticity agents such as dantrolene and tiazadine can be used.

For patients with extrapyramidal CP, pharmacological agents modulating dopamine action in the striatum have been effectively utilized. For those with chorea, drugs to deplete dopamine such as reserpine, tetrabenazine, clonzapam and carbamazepine have been used. For patients with dystonia, athetosis or bradykinesia, drugs to increase dopamine flux including trihexyphenidyl and levodopa (usually administered with carbidopa) have been effectively employed.

Recently, intrathecal baclofen, delivered by a programmable pump placed in the abdomen connected to a catheter ending in the intrathecal space, has been employed for patients with spasticity of spinal as well as cerebral origin (Penn & Kroin, 1985; Albright et al., 1993). Studies have indicated that intrathecal baclofen effectively reduces spasticity (Gilmartin et al., 2000), and may be of benefit in improving function (Latash & Penn, 1996). Intrathecal baclofen has also been reported to be of benefit in dystonic CP (Albright et al., 1996). Complications of this

therapy include catheter kinking as well as infection, possibly requiring replacement of the catheter or pump.

Selective dorsal rhizotomy, a neurosurgical procedure in which a percentage of sensory rootlets in the LS spine are cut, is felt by some groups to be an effective intervention for spastic diplegia (Park & Owen, 1992). In carefully chosen patients with relatively pure forms of spastic diplegia, this procedure reduces spasticity and improves function (Steinbok et al., 1997). However, other groups have reported no benefit from this procedure over intensive physical therapy (Graubert et al., 2000). Furthermore, there may be both short- and long-term complications from this procedure (Abbott, 1992; Tuir & Kalen, 2000).

Recently, there has been interest in stereotactic neurosurgical procedures similar to those performed for Parkinson disease (De Salles, 1996). Preliminary work indicates that in carefully selected patients, the severity of dystonia and hemiballismus may be decreased. Depending on the clinical setting, both ablative as well as neural stimulation procedures may be done.

Because therapies have not achieved all the goals that families want for their children or for themselves, parents and those affected may seek alternative therapies. Such therapies are wide ranging, from herbal remedies to hyperbaric oxygen. While some may be beneficial, each should be carefully considered. Care should be taken as some herbs may have significant toxicities, and with regard to hyperbaric oxygen tanks, there have been concerns that high oxygen tension may damage developing white matter pathways (Huang et al., 2000).

Prognosis

Families as well as affected individuals often seek information about long-term prognosis so that appropriate medical, financial and life care plans can be made. They may also worry about whether other family members are at risk. The key step to providing information in these matters is to conduct a comprehensive etiological evaluation at the time that the diagnosis of CP is made. Such a work-up can provide specifics of prognosis and recurrence risk when a recognized genetic or metabolic disorder is identified, as well as reassurance when a sporadic cause is identified.

Given the progressive nature of some CP syndromes, ongoing medical follow-up is required both for the individual patient, as well as to establish guidelines for groups of patients. For example, some adults with extrapyramidal CP are at risk for progressive cervical spine disease, which if untreated can lead to sudden quadriplegia (Harada et al. 1996) (Fig. 39.5). Others may develop progressive neurological symptoms necessitating new treatment modalities (Scott & Jankovic, 1996).

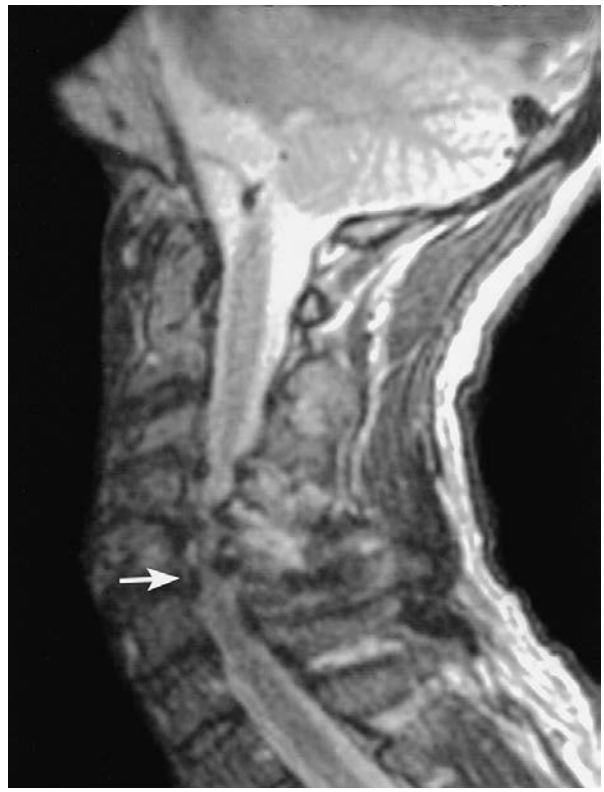

Fig. 39.5. MR image from an adult with extrapyramidal CP, who sustained cord compression (white arrow) from repetitive head movements used to control a communication system.

In conclusion, advances in neurobiology, as well as brain imaging, have expanded the understanding of the pathogenesis of CP. Combining imaging techniques with clinical examination can refine classification and establish homogeneous groups so that rehabilitative interventions can be more effectively assessed.

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Gait and balance disorders

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Walking requires two capabilities: maintenance of balance (protection of upright stance via anticipatory and reactive postural mechanisms) and movement through the environment via locomotion. Postural responses and locomotion are dependent upon all levels of the nervous and musculoskeletal systems. Consequently, gait and balance disorders are common manifestations of many diseases.

The clinician commonly thinks of gait disorders in terms of walking pattern, emphasizing the movements of the legs. And literally this is correct; 'gait' is defined by Webster's *Third International Dictionary* as the 'manner of walking' or 'sequence of foot movements.' Accordingly, the neurological exam emphasizes evaluation of strength, tone, coordination, sensation and reflexes of the limbs. The result is that clinical neurology focuses on locomotion.

The importance of balance or equilibrium to walking is not recognized or explicitly acknowledged. Yet balance is the key and critical element in safe ambulation. Many so-called gait disorders are in reality balance disorders, not disorders in the sequence of foot movements. For example, Bruns' 'frontal ataxia' (Bruns, 1892) and van Bogart and Martins' 'apraxia of gait' (1929) are descriptions of patients who could not even stand independently. Although impairments of gait or locomotion can sometimes be separated from impairments of balance or postural equilibrium, locomotion and balance are more often inextricably intertwined (Mori, 1987). Thus, classifications need to consider disorders of both gait and balance.

The aim of this chapter is to present a classification scheme for gait and balance disorders. We first consider a classification based on neurological functions required for purposeful ambulation using Hughlings Jackson's hierarchical scheme of lower, middle and higher functions. This classification suggests the range of neurological impairments that can disrupt ambulation and the relationships among various gait and balance disorders.

Patients' walking and balance patterns do not necessarily reflect impairments in neural functioning but rather the patient's compensatory strategies for coping with the impairments. Different impairments may elicit common compensatory strategies. For this reason, classification by impairments is inadequate for clinical diagnosis. The second portion of our classification scheme considers the common compensatory strategies as clinical patterns or syndromes for which there are differential diagnoses. Problems with ambulation are separated into clinical patterns or syndromes that are predominantly disorders of balance and those that are predominantly disorders of locomotion, recognizing that in most diseases, both postural control and locomotion are affected to some extent. Because falls are a common presenting complaint, we offer a separate classification for fall patterns.

Physiology of locomotion and postural control

The temporal and spatial sequence of contractions of leg muscles for locomotion are programmed at the spinal cord level by central pattern generators (CPGs) (Grillner & Wallen, 1985). Well-patterned hind leg stepping responses can be elicited by treadmill stimulation in cats with total thoracic cord transection (Grillner & Wallen, 1985) and in the legs of humans with paraplegia and quadriplegia (Dietz et al., 1994). This spinal stepping can be activated by sensory stimulation resulting from treadmill motion and by non-specific dorsal root sensory stimulation. The CPGs are normally activated by descending pathways arising in brainstem locomotor centres (Orlovsky & Shik, 1976). Electrical stimulation of the brainstem locomotor centres will produce stepping and, at higher intensity, trotting and running movements of the legs of cats and monkeys (Eidelberg et al., 1981). Cerebellum, basal ganglia and

primary motor areas refine and adapt locomotion to varying conditions such as for precision walking on the rungs of a horizontal ladder (Armstrong, 1988). Other cortical areas coordinate locomotion with the individual's voluntary or purposeful actions.

The neuroanatomical control of posture is less well understood than is locomotion. The isolated spinal cord does not have postural responses. The hindlimbs of paraplegic cats can support the weight of the trunk with background muscle tone but do not respond to postural perturbation to prevent a fall (Macpherson & Fung, 1999). Postural support must be provided for the spinal cats walking on a treadmill (Grillner & Wallen, 1985) indicating that postural responses must be mediated through centres above the spinal cord. Coordinated postural responses can be elicited from brainstem. Evidence for brainstem programming of postural control comes from the studies in intact cats with implanted electrodes in dorsal and ventral tegmental regions of the pons. Stimulation of the ventral tegmental region would make a lying cat stand up and then begin walking. Stimulation of the dorsal tegmental region reversed this effect; a walking cat would first stop and then would lie down (Mori, 1987). Thus, at least some postural responses appear to arise from the brainstem.

Higher centres are presumed to adapt postural control to the environment and to the individual's needs. For example, frontal cortical areas coordinate anticipatory postural adjustments that precede and accompany any voluntary movement to protect postural stability. These adaptations require accurate neural maps of the body in relation to the earth's gravitational field, the support surface and the immediate environment as well as the relation of various body segments to each other. These maps are synthesized from information obtained from a variety of sensory modalities (Horak & Macpherson, 1996). Somatosensory information from proprioceptors in muscles and joints is the most important for coordination of posture and gait, including triggering rapid postural responses. Cutaneous information provides information about the contour and characteristics of surfaces, the pressure under the feet in contact with support surfaces, and a stable reference for posture. Vestibular information helps control trunk and head orientation in space, as well as stable gaze during locomotion. Vision is primarily used in a predictive manner to avoid obstacles and plan trajectories and step placement during gait. In addition to online sensory information, postural responses are modified and adapted to behaviour goals by context, previous experience and expectation.

Systems classification of gait and balance syndromes

A hierarchical classification, modelled after Hughlings Jackson's approach, considers three levels of neural function controlling gait and balance; lower, middle and higher levels (Table 40.1). 'Lower' to 'higher' correlates with 'simpler' to 'more complex' neural processing. It will be apparent that clinicians are most comfortable diagnosing disorders caused by neurological dysfunction arising at lower levels and motor dysfunction at the middle level of this classification. The effects of sensory disorganization and higher neurological dysfunction on balance and gait are less well defined clinically. We emphasize these less recognized and problematic disorders in the text and references. It is important to note that a given disorder may produce balance and gait dysfunction by effects at several levels. For example, mild to moderate parkinsonism is envisioned as causing mid-level dysfunction by reducing the force generation for balance and locomotor synergies. More severe parkinsonism may also affect higher level functions such as adaptation of balance synergies to environmental conditions and coordination of synergies.

Lower level

The lower level has three components. The first component consists of the intrinsic locomotor synergies (CPGs) programmed in the spinal grey matter and the postural responses programmed in the brainstem. These locomotor and postural synergies are the building blocks of successful ambulation. A patient with complete spinal cord section may have no behavioural evidence of locomotor synergies because they lack the necessary facilitation to elicit them. Spinal lesions may also injure CPGs disrupting spinal locomotor synergies and thereby timing of muscle contractions required for locomotion although frequently other neurological dysfunctions from higher spinal and brainstem lesions complicate interpretation. Lower level synergies may be disinhibited by higher lesions so that spinal stepping (Dietz et al., 1994) and decerebrate, tonic neck and perhaps grasp responses may emerge. Another possible abnormal postural response in humans resulting from disinhibition is the involuntary hyperextension or pushing the centre of mass behind the base of support seen in some patients upon standing.

The second component of the lower level is the primary sensory modalities with which the person locates themself with respect to the support surface, the gravitational field, and the immediate environment and also senses the relative

Table 40.1. Neural systems/anatomical classification

I. LOWER LEVEL

A. Spinal locomotor and brainstem postural synergies

1. Absence of synergies
2. Abnormal spatial–temporal organization of synergies
   a. Spinal cord lesions disrupting CPGs
3. Disinhibition of synergies with higher lesions
   a. Spinal stepping
   b. Decerebrate posturing, tonic neck responses
   c. Hyperextension, pushing backwards

B. Primary Sensory Input (vestibular, visual, somatosensory)

1. Absent or distorted input
   a. Veering ataxia of acute vestibular lesions
   b. Sensory ataxia with loss of proprioception from peripheral nerve or posterior column lesions
   c. Veering, careful gait of newly blind

C. Force Production (muscle and nerve)

1. Weakness
   a. Steppage gait (foot drop) of peripheral nerve lesions
   b. Waddling gait of muscular dystrophies and polymyositis with involvement of proximal muscle
   c. Hyperextended knees with quadriceps weakness

II. MIDDLE LEVEL

A. Perception/Orientation (organization of primary sensation into spatial maps of body in gravitational field by parietal cortex, putamen, premotor cortex and their subcortical connections)

1. Distorted spatial maps
   a. Central vestibular lesions of brainstem and thalamus
   b. Parietal lesions and 'pusher syndrome'
2. Distorted maps or neglect of spatial information
   a. Thalamic astasia
   b. Putaminal astasia
   c. Progressive supranuclear palsy?
   d. Non-dominant parietal lesions?

B. Force Scaling (modulation of force for optimization of postural and locomotor synergies by basal ganglia, cerebellum and primary motor cortex)

1. Movement disorders
   a. Hypo- and hyperkinetic disorders of basal ganglia origin
   b. Hypermetric and dysmetric disorders of cerebellar origin
   c. Spasticity and clumsiness from corticospinal system damage

III. HIGHER LEVEL

A. Synergy selection, coordination and adaptation of locomotor and postural responses (less conscious functions) mediated by frontal lobe and subcortical connections.

1. Dyscoordination of voluntary movement and postural responses
   a. Reduction or loss of anticipatory responses with frontal lobe lesions
2. Altered inhibition or excitation of lower postural and gait synergies
   a. Hyperextension and pushing centre of mass behind support
   b. Freezing with frontal, subcortical and basal ganglia lesions
3. Adaptation of postural synergies to conditions
   a. Postural inflexibility of advanced parkinsonism
   b. Inability to use experience to anticipate appropriate magnitude of postural responses in cerebellar disease
   c. Appropriate slowing, shortening of stride and en bloc turns with perceived postural instability
4. Inappropriate sequencing of postural synergies
   a. 'Apraxia' of postural shifts as from lying to sitting and sitting to standing

Table 40.1 (*cont.*)

B. Cognitive (attention and insight for adaptation to person's goals and limitations (more conscious functions) mediated by all cortical regions
1. Impaired attention
a. Falls related to centrally active medications, delirium and dementia
2. Imparied insight
a. Falls related to inappropriate behaviour in dementia
b. Psychogenic gait disturbances

positions of various limb segments, trunk and head. Under most conditions, the information from the visual, vestibular and proprioceptive sensory systems is redundant so that an accurate spatial sense is possible with input from just one or two of the sensory systems. The disequilibrium of acute and chronic vestibular dysfunction and the sensory ataxia associated with proprioceptive dysfunction are examples of gait and balance disorders associated with reduced, unbalanced and disordered sensory input.

The third component of the lower system is the musculoskeletal system and peripheral motor nerves connecting it to the CNS. These tissues are responsible for generating forces to preserve balance and to move in space. Damage or disease affecting these structures, the effectors of postural and locomotor strategies, will obviously alter the execution of the strategies. Skeletal deformities, arthritis, muscle disease and peripheral motor neuropathies will affect gait and postural responses. For the neurologist, the waddling gait and locked knees of muscular dystrophies and polymyositis and the steppage gait of peripheral neuropathies such as Charcot Marie Tooth disease are prime examples of this type of dysfunction.

Middle level

At the middle level there are two components. The first component is composed of the neural structures that integrate sensory information into spatial maps. This function probably takes place in many areas of the brain. Spatial maps concerned with motor function have been identified in the putamen and premotor cortex. Maps concerned with visual function exist in frontal eye fields and the superior colliculus. Surprisingly, the parietal lobes appear to be more important in creating the spatial maps which may actually reside elsewhere in the brain (Gross & Graziano, 1995). Distorted maps can result in body tilt or lean or inappropriately asymmetrical postural responses. Examples of this type of disorientation are the altered perception of visual and postural verticality that may accompany lesions of central vestibular connections (Dieterich & Brandt, 1993; Bisdorff et al., 1996) and parietal lesions (Karnath, 1994; Karnath et al., 2000). Other candidates for this type of dysfunction in orienting in space are progressive supranuclear palsy, thalamic astasia (Marsden & Gorelick, 1988) and putaminal astasia (Labadie et al., 1989) syndromes in which patients appear to be either unaware of postural vertical or indifferent to this information. As patients with these clinical syndromes have not been studied carefully, it is not known if these syndromes are attributable to lack of synthesizing information into maps or to sensory neglect, motor neglect, or other types of dysfunction.

The second component of the middle level function is the precise modulation of force for optimal locomotor and postural control. The central motor system has this role. Basal ganglia, cerebellum and cortical motor areas sharpen and adapt locomotor and postural coordination but do not create the synergies. The clinical manifestations of dysfunction at this level are parkinsonism (slow/bradykinetic and stiff/rigid postural and locomotor synergies), hyperkinetic movement disorders (involuntary movements superimposed on normal strategies), ataxia (hypermetric and dysmetric synergies) and spasticity (slowed, stiff and imprecise synergies). These clinical syndromes are a distortion, not loss, of appropriate postural and locomotor synergies caused by the imprecise execution of appropriate synergies. Skilled and precise voluntary stepping are impaired; walking a line or performing a dance step become challenging.

Higher level

At the higher level, two components are hypothesized. The first largely operates at an unconscious level. It is responsible for selecting, accessing and coordinating the appropriate brainstem and spinal synergies for balance and walking. The selection of synergies is based on the information about the body, its location in space and the goals

of the individual. Sensitivity to context is an important component of this function. For example, balance and locomotor synergies should be different for walking on a slick versus a non-slippery surface and for responding to a postural perturbation when holding onto a support versus when standing without a handhold. Anticipatory postural responses that accompany voluntary movements to prevent postural perturbations caused by the voluntary movements may be impaired by lesions of premotor or supplementary regions (Massion, 1992).

A second group of higher level problems is with disinhibition of inappropriate postural responses and inability to elicit appropriate locomotor synergies. The tendency for some patients to push their centre of mass behind their support base may be an example of disinhibition of an inappropriate postural tone. It may be seen with frontal lesions, deep white matter lesions and severe parkinsonism (which may induce frontal dysfunction). Freezing appears to be disturbed access to locomotor synergies and is associated with the same array of frontal, subcortical white matter and basal ganglia lesions (Yanagisawa et al., 1991; Achiron et al., 1993; Giladi et al., 1997).

A third group of higher level problems relates to the ability to adapt to changes in environmental conditions and to predict appropriate responses. Subjects with basal ganglia disease have difficulty adapting postural synergies to changes in support surfaces (Horak et al., 1992) and subjects with cerebellar disease have difficulty adapting postural synergies based on prior experience (Horak & Diener, 1994). A gait that is often considered as abnormal and variously termed senile, elderly or cautious gait, is the slowed, short stepped gait with *en bloc* turns. However, this gait pattern is an appropriate response to perceived instability and shows that at least some of the higher level function is intact.

A fourth group of higher level problems is totally deranged synergies that may fit the concept of apraxia. Although the term 'apraxia of gait' is in common use, its appropriateness and clinical definition are problematic (Nutt et al., 1993). However, the term 'apraxia of balance' may be justified for righting responses that are entirely disrupted and ineffective. Inappropriate righting responses such as trying to arise from a chair without bringing the feet underneath the seated body, and bizarre postural responses upon standing may be associated with frontal lobe lesions and deep white matter lesions (Bruns, 1892; van Bogart & Martin, 1929; Meyer & Barron, 1960; Petrovici, 1968; Thompson & Marsden, 1987; Nutt et al., 1993). What is commonly termed apraxia of gait is subsumed under freezing and apraxia of balance in our classification.

A second component of the highest system operates at a more conscious level to modify locomotor synergies. It is responsible for precision stepping such as on stepping stones or performing unfamiliar dance steps. If there are lower and middle level postural and locomotor difficulties, this higher level compensates as best it can to allow ambulation within the constraints imposed by the lower level dysfunction. Under these circumstances, walking and balance are elevated from operation at the largely unconscious level to operation at a conscious level. The more balance and gait are under conscious control, the more attention is required. In this situation, balance and gait deteriorate when attempting a simultaneous, cognitive task such as conversation, searching for keys in a pocket or carrying a fragile object (Wright & Kemp, 1992). Falls occur in older patients who do not direct sufficient attention to walking and balance or who do not have the insight to avoid posturally challenging situations. This may be the reason that dementia and centrally active drug use in the elderly emerge in epidemiological studies as predisposing factors to falls (Tinetti et al., 1988; Salgado et al., 1994).

Psychogenic gait disorders would also be seen as representative of dysfunction at this higher level (Keane, 1989; Lempert et al., 1991).

Classification of balance and gait disorders by clinical patterns

The postural responses and locomotor patterns that the clinician observes are not the direct consequence of the neurological impairments but instead reflect the compensatory strategies the patient uses to cope with the impairments. Impairments at different levels may invoke clinically similar compensatory postural and gait patterns. For example, a hyperextended, locked knee to prevent knee buckling in stance may be a compensatory strategy for weak quadriceps muscles, hypermetric synergies from a cerebellar disorder or lack of proprioceptive feedback in an individual with profound somatosensory loss.

The pattern classification assumes that there are gait and balance features that define different strategies for which there is a limited differential. The patterns or syndromes are not exclusive; a patient may demonstrate more than one abnormal pattern.

The classification is based on the history and observation of gait and postural responses. History is particularly important for patients with falls, as they are generally not directly observed. Gait and balance features are observed not only during stance and gait, but also during transitions from sit to stand and turning, when balance is challenged by walking in tandem with a narrow base of support, and responding to postural perturbations such as the 'pull test.'

Table 40.2. Fall patterns

1. Collapsing (akinetic seizures, syncope, orthostatic hypotension)
2. Toppling
   a. Drifting into a fall while standing
   b. While changing position/posture
   c. Weaving from side to side or in all directions until falling
3. Tripping
4. Freezing
5. Falling in specific situations or with concurrent sensory symptoms
6. Non-patterned

The perceived limits of stability can also be evaluated by examining how far the subject can lean forward and backwards in standing and laterally in sitting. Ability to maintain orientation with limited somatosensory information can be evaluated by standing on compliant foam with eyes open and closed. These features will describe gait and balance patterns. Each pattern will have a differential. Other clinical features derived from the neurological exam, imaging and laboratory testing will help differentiate between causes of a given pattern but are not used to define the pattern. The proposed pattern classification has three categories; fall patterns, disequilibrium patterns and gait patterns.

Fall patterns

Fall patterns (Table 40.2) are based on history. The first distinction is between falling because of loss of postural tone and falls with retained tone. 'Collapsing in a heap' is a common description of falls from loss of postural tone. Akinetic seizures, negative myoclonus, syncope, otolithic crises and orthostatic hypotension cause collapsing falls. The recognition of the collapsing fall syndrome is an important distinction as the differential, diagnostic tests and treatments are very different from the other falls to be considered below.

In falls with retained muscle tone, the patient falls in some direction and does not just collapse. It may be helpful to distinguish whether the patient actually falls to the ground or has 'near-falls.' 'Near-falls' suggest that the patient recognizes when they are out of equilibrium and performs a late or inadequate postural response. In contrast, patients who consistently fall to the ground clearly have grossly inadequate postural control or are unaware, until too late, that equilibrium has been compromised. Patients and their caregivers can often provide helpful information regarding the environmental situation, task attempted and type of fall pattern. It is also useful to re-enact the circumstances that led to a fall during the clinical exam.

Toppling falls are falls where the patient 'topples like a falling tree.' They may occur when the subject is just standing as seen in progressive supranuclear palsy or thalamic and putaminal astasia (Masdeu & Gorelick, 1988; Labadie et al., 1989) or when the subject is changing position as is characteristic of parkinsonism. In these disorders there is often inadequate or no effort to arrest the fall. Patients with cerebellar disease may weave about when standing and fall in any direction but have protective responses.

Tripping falls occur because the feet do not clear the support surface adequately. The falls are generally forward. Foot drop, spasticity and parkinsonism are common causes of tripping falls.

Freezing falls occur when the feet do not move quickly enough to stay under the falling forward centre of mass. The patients typically fall forward on to their knees and outstretched arms.

Falls that occur only when the patient is experiencing vertigo, in the dark, or in sensory conflict situations such as when surrounded by moving objects, suggest a peripheral or central vestibular deficit. Falls when walking on uneven surfaces suggest inadequate sensory information for control of balance, especially somatosensory loss as occurs with peripheral neuropathy and dorsal column disease. In these sensory type falls, patients generally recognize their spatial disorientation and attempt to use their arms to grab onto stable objects or voluntarily sit down to prevent injury.

Finally, non-patterned falls, falls that do not seem to fit a consistent pattern, may represent failure of attention and insight producing carelessness as can occur in dementia.

Disequilibrium syndromes

Disequilibrium syndromes (Table 40.3) are characterized by impairments of balance that markedly impede or preclude locomotion. They are identified by inspection of arising, standing with eyes open and closed, standing on foam, walking, tandem walking, turning, response to postural perturbation and limits of stability while standing and sitting.

Disequilibrium can result from dyscoordination within postural synergies; the relative timing of postural muscle contractions is inappropriate. The clinical consequence is buckling and excessive motion of joints. Cortical lesions and partial spinal cord lesions can produce abnormal timing of postural responses. An example of a dyscoordi-

Table 40.3. Disequilibrium patterns

1. Dyscoordination: excessive motion, buckling, etc. of limb segments caused by disordered timing affecting temporal patterns of body segment movements
2. Dysmetric (hypermetric): excessive sway and over-reaction to postural disturbance caused by correct timing but inappropriately large movements
3. Hypometric: postural responses are too small because force develops slowly
4. Sensory deprivation: situation-dependent disequilibrium related to circumstances that limit sensory input
5. Sensory disorganization: apparent disregard for postural vertical leading to drifting off balance or distorted perception of verticality causing active moving into unstable postures
6. Apraxic: completely abnormal or inappropriate postural responses

nated pattern is the delayed onset of postural responses in gastrocnemius such that the hamstrings muscle activation that normally follows gastrocnemius, comes earlier than it, resulting in knee buckling (Nashner et al., 1983).

In dysmetric disequilibrium, there is increased postural sway while standing still. The postural responses are appropriately organized but improperly scaled and often are hypermetric (Horak & Diener, 1994). Postural pertubation often elicits a response that is too large and causes the body to be thrown into another unstable position. Dysmetric, often hypermetric, postural responses are characteristic of cerebellar disorders, the prototype for dysmetric disequilibrium. However, the involuntary movements of chorea can also produce the dysmetric disequilibrium syndrome. High anxiety, fear of falling and suggestibility can also produce hypermetric postural responses. Distraction by another task, such as testing stereognosis, will often reduce sway in patients with anxiety and suggestibility.

Hypokinetic or bradykinetic postural responses are frequent in parkinsonism. The development of force is slow so that the execution of postural responses is slow and may not be sufficiently timely or forceful to maintain upright balance. Recovery from the pull test is noticeably slow, the upper body moving back over the centre of support over a few seconds or longer. Sometimes the patients fall without an apparent effort to resist the perturbation. Despite responses that clinically appear delayed, weak or even absent, the latency of postural responses measured by surface EMG electrodes are not prolonged, but amplitude is reduced (Horak et al., 1992).

Disequilibrium resulting from sensory deprivation is characteristic of vestibular disorders, severe peripheral neuropathies and posterior column disease. Disequilibrium occurs because there is inadequate sensory information to trigger and modify postural responses. These disorders are revealed by situations that deprive the patients of other sensory input such as standing with eyes closed or standing on foam (Horak et al., 1990).

Disequilibrium from sensory disorganization appears to be the cause of falls with thalamic, putaminal, and cortical, particularly parietal and possibly frontal lesions. Primary sensory input is intact but the synthesis of the information into spatial maps is disturbed or there is inattention to the spatial information. Falls are characterized by drifting off balance with no apparent effort to correct balance in thalamic (Masden & Gorelick, 1988) and putaminal astasia (Labadie et al., 1989) progressive supranuclear palsy and advanced parkinsonism. Parietal lesions may be associated with actively pushing the centre of mass toward the lesioned side secondary to a distorted sense of body vertical (Karnath et al., 2000).

Apraxic disequilibrium is the disorganization of arising and standing because the righting and standing synergies are completely inappropriate. The most common example is patients who try to arise from sitting without bringing the feet under the chair but other mechanically impossible strategies for righting and standing may be seen. These types of disequilibrium disorders are commonly associated with frontal lobe dysfunction (Nutt et al., 1993) but may also be seen with advanced parkinsonism.

Gait syndromes

Gait syndromes are based on abnormalities that are apparent while the patient is walking. Waddling and foot drop gait patterns identify weakness. The distance between the feet (base) may be widened or, less commonly, narrowed while standing or walking. Gait speed and stride length are reduced with any gait disorder or perceived risk to upright balance and are therefore of no diagnostic assistance. The cadence or regularity of steps, both length and base, may vary during walking. Deviation or veering from intended direction of travel may be observed. Stiffness or rigidity of the legs or trunk may be apparent by the loss of the normal fluidity of gait. Difficulty initiating or maintaining gait (freezing) is one of the more striking abnormalities of gait. Adaptability may be estimated by the patient's ability to modify walking speed, avoid obstacles, perform precision walking or turn about.

Eight gait patterns are proposed (Table 40.4). The proposed gait patterns are not exclusive; patients may show elements of more than one pattern. Also, gait patterns are not fixed but may change or progress across time in conjunction

Table 40.4. Gait patterns

1. Ataxic: irregular cadence and progression
   a. Cerebellar ataxia
   b. Sensory ataxia
   c. Chorea
2. Stiff/rigid: loss of fluidity, stiffness of legs and trunk
   a. Spasticity
   b. Parkinsonism
   c. Dystonia
   d. Diffuse cortical and subcortical diseases, such as multi-infarct state
3. Weakness: waddling and foot drop
   a. Muscle disorders
   b. Peripheral neuropathies
   c. Corticospinal tract lesions
4. Veering: deviation of gait to one side
   a. Vestibular disorders
   b. Cerebellar disorders
5. Freezing: start and turn hesitation
   a. Parkinsonism
   b. Multi-infarct state
   c. Normal pressure hydrocephalus
6. Wide-based: widened base with standing and walking
   a. Midline cerebellar disorders
   b. Multi-infarct state
   c. In conjunction with ataxic syndromes
7. Cautious: slowing, short steps and *en bloc* turns
   a. Non-specific, multifactorial
8. Psychogenic: bizarre, inconsistent, distractible

with the evolution of the neurological problems. Many gait syndromes begin as a cautious gait and evolve into other syndromes. Finally, gait pattern classification is not to say that the patients have no balance disorders; most do, and the abnormal gait pattern may be a compensatory response to the balance difficulties.

Ataxic gaits are a result of uncertainty when and where the feet will make contact with the support surface with each step. This can be a consequence of dysmetric control of the centre of mass and leg movements as in cerebellar disorders, superimposed involuntary movements as in chorea, impaired proprioception in the feet and legs as in sensory ataxia and a moving support surface as on a ship deck. Ataxic gaits are characterized by irregular, excessive centre of mass motion and disorderly progression (locomotion). Typically, these abnormalities are associated with a widened base and shorter stride. Cadence is also irregular.

Stiff/rigid gaits are gaits in which the usual fluidity of walking is lost. Rotation of trunk is reduced or absent. The range of motion at the knees and hips is reduced, as is arm swing. Base may be abnormally narrow or wide; stride is shortened. Examples are spasticity, parkinsonism, dystonia, multi-infarct states (vascular parkinsonism) and musculoskeletal disorders. The stiffness may be unilateral as in spastic hemiparesis or hemidystonia.

Gaits disturbed by proximal or distal weakness are well recognized. Proximal weakness prevents fixation of the pelvis during single support portions of gait. Myopathies and dystrophies that typically affect proximal muscles commonly produce waddling gaits although occasionally multiple root and peripheral nerve lesions are responsible. Hyperextension of the knee may also occur with proximal weakness. Distal weakness generally affects dorsiflexors of the ankle, requiring the leg to be lifted higher for the toe to clear the ground. Peripheral neuropathies are the common cause of this problem. Corticospinal tract lesions affect the distal leg muscles more than proximal muscles but stiffness and circumduction of the leg differentiate this from weakness caused by peripheral nerve lesions.

Veering gaits are those in which the patient tends to lean, fall or deviate in one direction while walking. Peripheral and central vestibular disorders are the common cause but other brainstem and thalamic lesions may cause similar patterns.

Freezing gaits are those characterized by difficulty initiating (start hesitation and 'slipping clutch' phenomena) and maintaining locomotion while maneuvering in tight quarters, passing through doorways and turning (turn hesitation). There appear to be at least two distinguishable patterns of the freezing gait. Most commonly freezing is associated with a stiff/rigid gait and a narrow base. These patients may have no or reduced lateral sway when trying to initiate walking. Idiopathic parkinsonism, parkinsonism plus syndromes, normal pressure hydrocephalus and vascular parkinsonism are common diagnoses (Giladi et al., 1997). A less common form of freezing is associated with widened base and often exaggerated truncal sway and arm swing to initiate gait. It is this pattern to which 'slipping clutch' is an apt description. It has been associated with multi-infarct state.

Wide based gaits indicate problems with lateral stability. In isolation, that is without dysmetria of the legs and with normal cadence, wide based gaits are seen in midline cerebellar syndromes such as alcoholic cerebellar atrophy and in multi-infarct states.

Cautious gait is marked by mild to moderate slowing, shortening of stride and *en bloc* turns with only minimal widening of the base. Other gait abnormalities are absent. It is termed cautious because it is the gait pattern assumed by a normal person who is concerned about their balance

such as when walking on a slippery surface. Cautious gait is an appropriate response to perceived threats to postural balance. As such, cautious gait is non-specific and may be associated with a variety of problems that impact a person's ability to walk safely. Cautious gait may also be of multifactorial etiology.

A final category is psychogenic gait disorders. Although balance may be disturbed in patients with a psychogenic origin for the problem, most can ambulate as well and therefore are considered as gait disorders. A variety of bizarre patterns that fit none of the above descriptions are possible. Distractibility, inconsistencies and other non-physiological signs are common tip-offs to the diagnosis Keane, 1989; Lampert et al., 1991). Because some of the apraxic disequilibrium syndromes and dystonic gaits may be very bizarre, they can be easily confused with psychogenic gaits.

An 'over cautious' pattern sometimes termed space phobia or fear of falling occurs in some older people with mild, multisystem impairments, generally in response to a fall or some other event arousing their anxiety about falling. Gait is slow, often wide-based, staggering and with prolonged double stance duration. The person must hold on to another person, furniture or the wall to walk (Murphy & Isaacs, 1982). The clinician needs to be 'cautious' about this syndrome and not make the diagnosis without thorough evaluation, including a MRI to look for silent infarcts.

Diagnosis of balance and gait disorders

The remainder of the neurological exam will direct the workup of fall, balance and gait disorders. For unexplained balance and gait disorders, a MRI is indicated and may reveal unexpected infarcts, hydrocephalus, atrophy and particularly subcortical white matter ischemic lesions (Baloh et al., 1995). Vitamin B12 deficiency is another rare cause of unexplained balance and gait disorders.

Treatment of balance and gait disorders

If a treatable lesion is discovered as a cause of imbalance or gait disorders, this is obviously the target of therapy. In many cases there is no single abnormality that is responsible for gait and balance abnormalities and a multifactorial etiology is likely. This is particularly true in the elderly where mild sensory and motor deficits may produce a cautious or pathological gait syndrome. Attempts to improve as many of these factors as possible, even seemingly inconsequential factors, may improve gait and reduce falls (Tinetti et al., 1994). Assessment of home safety to remove hazards, optimize lighting and instal hand-holds is an important method of reducing falls. Strengthening and balance exercises, even in the elderly, reduce risks for falls (Province et al., 1995).

Rehabilitation of balance and gait disorders

The goal of rehabilitation is to eliminate impairments if possible and, if not, to facilitate the most optimal compensatory strategies given the constraints imposed by the impairments. Some impairments, such as weakness and poor range of motion can be readily improved. The extent to which higher level neurological problems affecting balance and gait can be remediated is less clear. However, even if the specific impairments, such as sensory loss, dysmetria, and distorted internal body maps may not be readily improved with exercise and experience, studies have shown that functional balance and gait can be successfully trained (Woollacott & Moore, 1992). Not only can sway area and gait speed improve with training, the use of sensory information for postural orientation can improve and the incidence of falls can be significantly reduced.

The particular therapeutic goal and approach to treatment of balance and gait disorders must be specific to the underlying physiological constraints or impairments. Thus, balance and gait problems due to abnormal timing and scaling of postural synergies would be treated differently from problems due to loss of sensory information and from adaptation and cognitive problems. For example, abnormal synergies for controlling postural sway could be retrained using kinematic biofeedback and functional electrical stimulation during postural sway activities. In contrast, balance and gait in an individual without vestibular information for postural orientation should be retrained by focusing on sensory substitution and increase sensitivity of the remaining visual and somatosensory senses. Patients who compensate poorly for lack of joint coordination by co-contracting the neck or increasing limb spasticity, can be exposed to alternative, less energy inefficient movement patterns, with or without prosthetic or assistive devices. Patients with Parkinson's disease who have difficulty initiating a step, can be shown how to use external cues or imagined cues to trigger a step. In general, rehabilitation of balance and gait should involve exposing subjects to particular tasks and environments that allow the nervous system to discover the most optimal and effective strategies available for their specific functional goals.

In conclusion, this chapter proposes two new classifications that would serve different purposes. The systems

oriented balance and gait disorders classification is intended to provide a logical hierarchy and indicate interrelations of balance and gait disorders. It is partially hypothetical because higher level disorders have received less attention in clinical and laboratory investigations and the proper places for some disorders in the classification are unproven. The pattern or syndrome classification is intended to help the clinician consider the diagnostic possibilities for falls, abnormal postural responses and abnormal gait patterns.

Safe, efficient ambulation is a wonderful attribute of health. Understanding the many ways in which it may be disturbed by neurological disease should lead to better methods to treat or cope with dysfunction.

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Part IV

Disorders of the special senses

41

Smell

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Possibly owing to the fact that, historically, most disorders of smell function have been difficult to diagnose and treat, physicians often downplay this sense in the routine neurological examination. This is unfortunate when one considers that olfactory disorders are relatively common and profoundly effect a patient's quality of life. Along with its sister sense of taste (see Chapter 42), olfaction determines, among other things, the flavour of foods and beverages, and provides an early warning system for detecting leaking natural gas, spoiled food, fire and other adverse environmental situations. Importantly, olfactory disturbances can be an early sign of such serious diseases or anomalies as Alzheimer's disease, idiopathic Parkinson's disease, epilepsy, multiple sclerosis, and schizophrenia. Although some patients initially present with a frank complaint of a smell disturbance, others are unaware of their dysfunction, pointing out the need for routine quantitative olfactory assessment, which is now easily performed in the office.

In this chapter, we (a) summarize key aspects of olfactory anatomy and physiology, (b) present up-to-date practical techniques for the management and quantitative evaluation of the olfactory system, and (c) describe basic olfactory disorders commonly encountered in the neurological setting.

Anatomy and physiology

Olfactory neuroepithelium: a portal to the central nervous system

The olfactory receptors are located within a ~ 2 cm^2 neuroepithelium lining the cribriform plate and regions of the superior turbinate, middle turbinate, and septum. The neurologist should be aware of the fact that, in addition to the main olfactory system (CN I), other specialized neural systems are present in the nose. These include (a) trigeminal (CN V) afferents responsible, for example, for the coolness of menthol vapours (Doty, 1995a), (b) a rudimentary and non-functional vomeronasal organ (VNO) near the base of the septum (Bhatnagar & Meisami, 1998; Smith & Bhatnagar, 2000), and (c) the poorly understood nervus terminalis or terminal nerve (CN O). CN O, a highly conserved neural plexus that ramifies throughout the nasal epithelium, is distinguished by ganglia at nodal points and a high gonadotropin content, and presumably plays no role in human odour perception (Schwanzel-Fukuda & Pfaff, 1995). Throughout life, islands of respiratory-like epithelial metaplasia appear within the epithelium, presumably as a result of cumulative viral, bacterial, and other insults Among the cells within the neuroepithelium (see Fig. 41.1) are (a) the *bipolar sensory receptor neurons* which harbour the seven domain transmembrane odorant receptors on multiple cilia extending from each dendritic knob, (b) the *supporting or sustentacular cells*, which have microvillae and serve structural and metabolic functions, (c) the poorly understood *microvillar cells* located at the surface of the epithelium, (d) the *cells that line the Bowman's glands and ducts*, and (e) the *globose (light)* and *horizontal (dark) basal cells* – cells located near the basement membrane from which most of the other cell types arise (Huard et al., 1998).

Olfactory nerve cells, as well as the proximal extraneural spaces, are well-established conduits for the movement of viruses and exogenous agents from the nasal cavity into the brain. In the case of viruses, transit times occur at rates usually intermediate between slow and fast axonal transport, e.g. around 3 mm/day for rabies virus, 8–16 mm/day for herpes simplex virus, and 14 mm/day for retrovirus (Stroop, 1995). This pathway has been recognized for some time (e.g. Clark, 1929; Hurst, 1936), as has the knowledge that chemical cauterization of the olfactory mucosa protects against viral-related CNS infection (Armstrong & Harrison, 1935; Burnet & Lush, 1938). Such knowledge led to

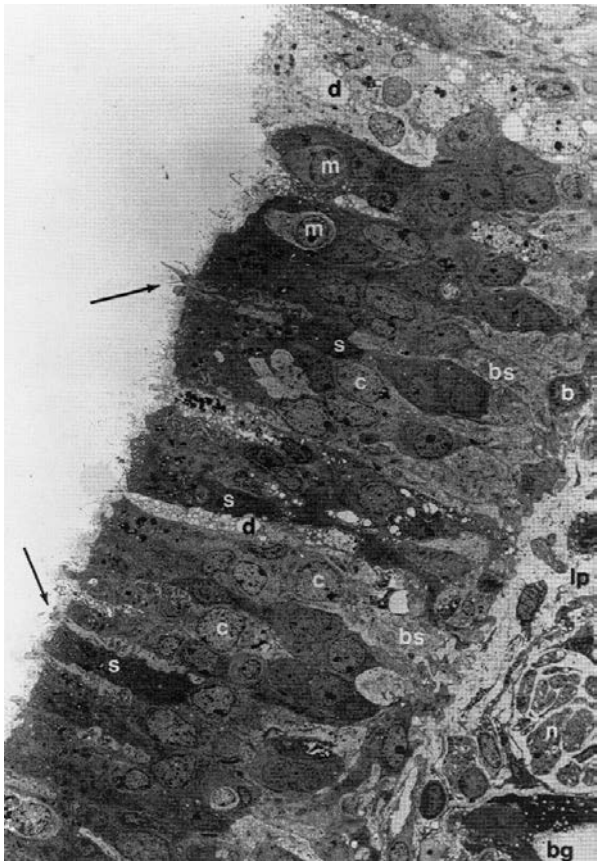

Fig. 41.1. Low-power electron micrograph (×670) of a longitudinal section through a biopsy specimen of human olfactory mucosa taken from the nasal septum. Four cell types are indicated: ciliated olfactory receptors (c), microvillar cells (m), supporting cells (s), and basal cells (b). The arrows point to ciliated olfactory knobs of the bipolar receptor cells. d = degenerating cells; bs = base of the supporting cells; lp = lamina propria; n = nerve bundle; bg = Bowman's gland. (Photo courtesy of David T. Moran.)

a prophylaxis movement in the late 1930s to spray noses of school children with zinc sulfate during poliomyelitis outbreaks (Peet et al., 1937; Schultz & Gebhardt, 1937; Tisdall et al., 1937). More recently, the 'olfactory vector hypothesis' has been proposed to explain both the olfactory loss and the etiology of several common neurodegenerative diseases (Doty, 1991; Doty et al., 1992a; Ferreyra-Moyano & Barragan, 1989; Roberts, 1986; Hawkes et al., 1999).

Olfactory neural transduction

Once odorants traverse the olfactory mucus and reach the cilia, they contact and bind to receptors which initiate the transduction cascades that ultimately result in action potentials. Around 1000 olfactory receptor types are believed to exist, and a given receptor cell contains only one type of receptor (Buck & Axel, 1991). Neurons expressing the same gene seem to be randomly distributed, at least in the mouse, within one of four segregated strip-like 'spatial zones' of the neuroepithelium, and olfactory neurons expressing a given gene seem to project to the same glomeruli within the olfactory bulb (Ngai et al., 1993). A given odorant activates an idiosyncratic pattern of activity across the population of receptors: a pattern that serves as the initial basis for odour perception and discrimination (Shepherd & Firestein, 1991).

Despite the fact that, under normal circumstances, there is continuous neurogenesis within basal segments of the epithelium, many receptor cells are long-lived and become replaced only after damage (Hinds et al., 1984). Both endogenous and exogenous factors promote receptor cell death and replenishment from the basal progenitor stem cells (Mackay-Sim & Kittel, 1990).

The olfactory bulb

The neural components of the olfactory bulb, the first neural processing station in the olfactory pathway, are arranged in six concentric layers: the olfactory nerve layer, the glomerular layer, the external plexiform layer, the mitral cell layer, the internal plexiform layer, and the granule cell layer (Fig. 41.2). The axons of the olfactory nerve cells synapse, within the glomeruli of the glomerular layer, with the dendrites of mitral and tufted cells, the major second order neurons of the olfactory system. The latter cells, in turn, send collaterals that synapse within the periglomerular and external plexiform layers, resulting in 'reverberating' circuits in which negative and positive feedback occur. For example, mitral cells modulate their own output by activating granule cells (which are inhibitory to them). Reciprocal inhibition between neighbouring mitral or tufted cells presumably sharpens the contrast between adjacent channels, perhaps analogous to what occurs among visual receptors within the retina.

The mitral and tufted axons project ipsilaterally to the primary olfactory cortex via the lateral olfactory tract without synapsing in the thalamus. However, some projections from primary to secondary (e.g. orbitofrontal) cortex do relay through the thalamus (see Fig. 41.3). Furthermore, contralateral projections also occur via the anterior commissure, largely from pyramidal cells of the anterior olfactory nucleus (AON).

The primary olfactory cortex

In addition to the AON, the mitral and tufted cells target (from rostral to caudal) (a) the piriform cortex, (b) the

olfactory tubercle, (c) the entorhinal area, (d) the periamygdaloid cortex, and (e) the corticomedial amygdala (Fig. 41.3). Most of the olfactory cortical structures have three distinct layers. The superficial segment of layer 1 contains synapses between (a) the incoming mitral and tufted cell axons and (b) the apical dendrites of the pyramidal cells, the principal olfactory cortical neurons. The deeper segments of layer 1 contain connections among intracortical association areas. Layers 2 and 3 are made up of cell bodies and processes of the pyramidal cells. Small populations of intrinsic short axon cells are present within all three layers. The axons of the pyramidal neurons project reciprocally, via layer 2 and 3 connections, to numerous regions, including the anterior commissure, the mediodorsal thalamus, the posterior hypothalamus, and the medial hypothalamus and hippocampus. Centrifugal fibres richly project from sectors of the olfactory cortex and other central structures to the olfactory bulb, presumably modulating the incoming flow of olfactory sensory signals (Kratskin, 1995) (Fig. 41.4).

Olfactory cortical regions: functional anatomy

While lesions of the olfactory neuroepithelium, the olfactory fila, or the olfactory bulbs and tracts rostral to the olfactory trigone can produce *total anosmia* on the affected side, lesions within olfactory structures more posterior to the olfactory trigone do not typically cause *complete* loss (Gloor, 1997). Orbitofrontal cortex lesions produce difficulties in discriminating or identifying odours, and odour discrimination is reportedly impaired following amygdalotomy (Zatorre and Jones-Gotman, 1991; Jones-Gotman et al., 1997a). In multiple sclerosis, the number of plaques within the inferior medial temporal and inferior frontal lobes correlates strongly ($r = -0.94$) with odour identification test scores (Doty et al., 1997a, 1998). Recent functional imaging studies have reported greater right than left orbitofrontal cortex activation by odorants, suggesting some hemispheric specialization (Malaspina et al., 1998; Yousem et al., 1997a; Zatorre et al., 1992). Olfactory stimulation reliably and significantly activates posterior lateral cerebellar areas, whereas sniffing alone activates mainly anterior central cerebellar regions (Sobel et al., 1998a, b; Yousem et al., 1997).

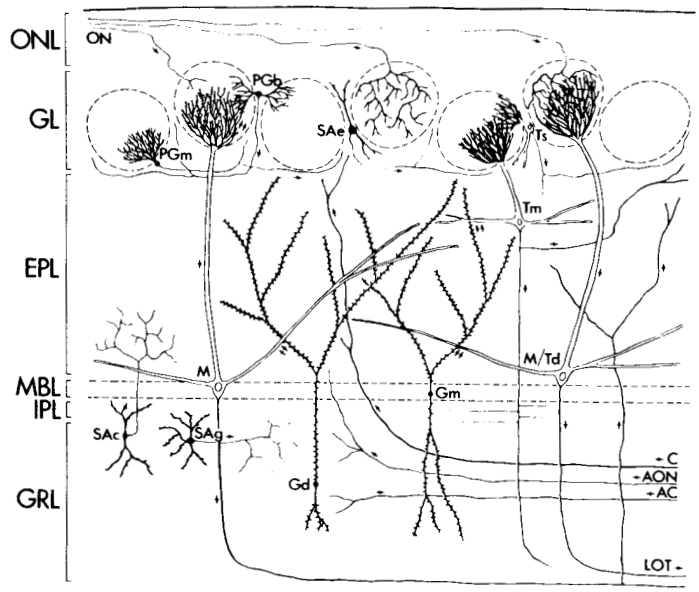

Fig. 41.2. Diagram of major layers and types of neurons in the mammalian olfactory bulb, as based on stained Golgi material. Main layers are indicated on the left as follows: ONL = olfactory nerve layer; GL = glomerular layer; EPL = external plexiform layer; MBL = mitral cell body layer; IPL = internal plexiform layer; GRL = granule cell layer; ON = olfactory nerves; PGb = periglomerular cells with biglomerular dendrites; PGm = periglomerular cell with monoglomerular dendrites; SAe = short-axon cell with extraglomerular dendrites; M = mitral cell; M/Td = displaced mitral or deep tufted cell; Tm = middle tufted cell; Ts = superficial tufted cell; Gm = granule cell with cell body in mitral body layer; Gd = granule cell with cell body in deep layers; SAc = short-axon cell of Cajal; SAg = short-axon cell of Golgi; C = centrifugal fibres; AON = fibres from anterior olfactory nucleus; AC = fibres from anterior commissure; LOT = lateral olfactory tract. (From Shepherd, 1972; Copyright © 1972 American Physiological Society.)

Classification of olfactory disorders

Olfactory disorders can be reliably classified as follows: *anosmia*: inability to detect qualitative olfactory sensations (i.e. absence of smell function); *partial anosmia*: ability to perceive some, but not all, odorants; *hyposmia* or *microsmia*: decreased sensitivity to odorants; hyperosmia: abnormally acute smell function; *dysosmia* (sometimes termed cacosmia or parosmia): distorted or perverted smell perception to odorant stimulation; *phantosmia*: a dysosmic sensation perceived in the absence of an odour stimulus (a.k.a. olfactory hallucination); and *olfactory agnosia*: inability to recognize an odour sensation, even though olfactory processing, language, and general intellectual functions are essentially intact, as in some stroke patients. Presbyosmia is sometimes used to describe smell loss due to ageing, but this term is less specific than those noted above (e.g. it does not distinguish between anosmia and hyposmia) and is laden, by definition, with the notion that it is age per se that is causing the age-related deficit.

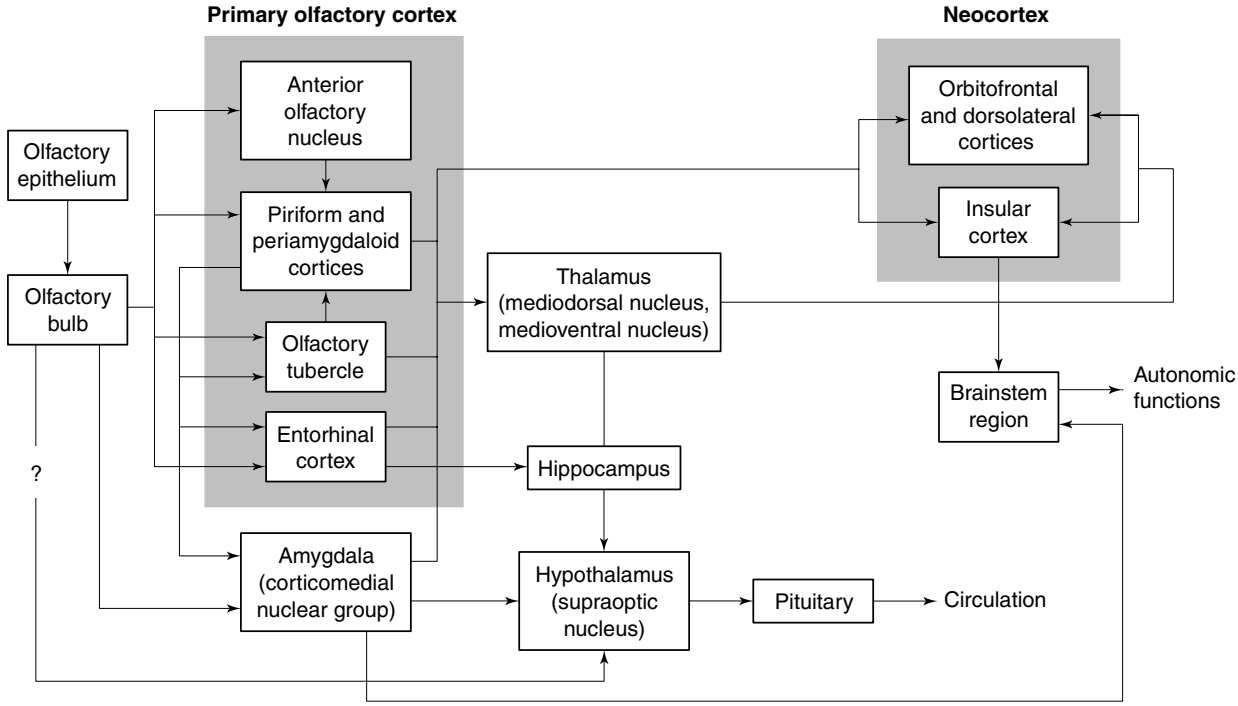

Fig. 41.3. Major afferent neural connections of the olfactory system. Structures common to both the olfactory and limbic systems include the olfactory tubercle, the entorhinal cortex, the amygdala, the hippocampus, and the hypothalamus. Although it is well established that the olfactory fibres project from the amygdala to the 'feeding centre' of the hypothalamus (especially the ventromedial and ventrolateral nuclei), it is unclear whether direct olfactohypothalamic routes exist in humans, as may be the case in some other vertebrates. (Copyright © 2001, Richard L. Doty.)

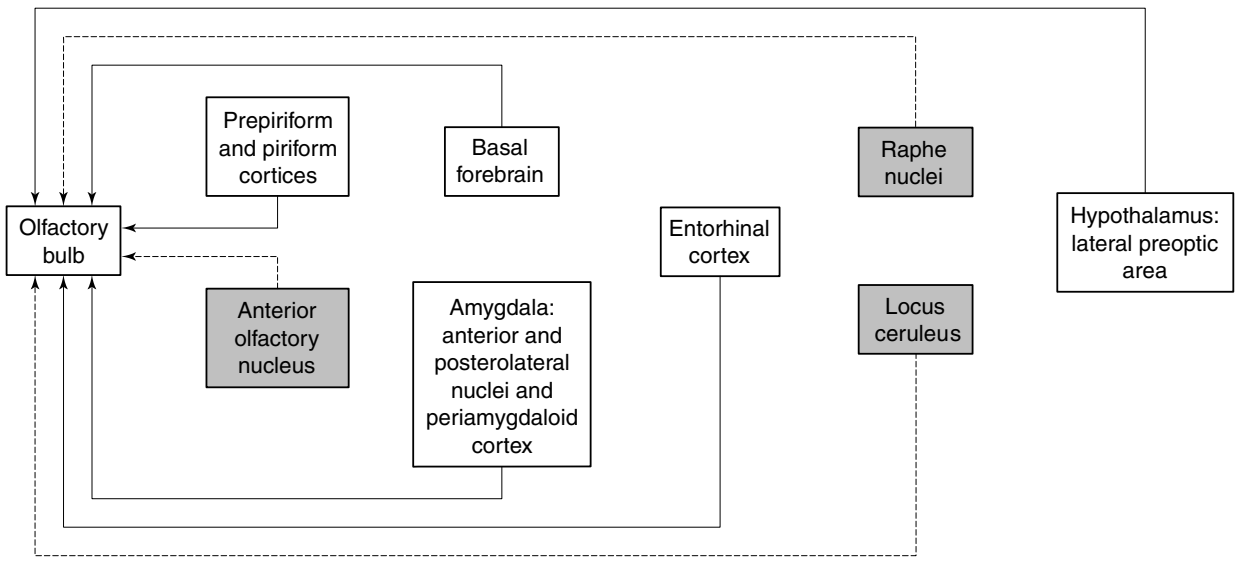

Fig. 41.4. Major neural structures from which centrifugal fibres project to cells within the olfactory bulb. The anterior olfactory nucleus, locus ceruleus, and raphae nuclei are known to have projections to both olfactory bulbs. The other depicted structures are presumed to have primarily, if not solely, ipsilateral projections to the bulbs. (Copyright © 2001, Richard L. Doty.)

Clinical evaluation of olfactory function

History

Details concerning the nature, timing of onset, duration and pattern of fluctuations, if any, of the patient's chemosensory problem are all very important. Discovery of precipitating antecedent events, such as head trauma, viral upper respiratory infections, toxic exposures, and nasal surgeries is critical. A history of allergy should be sought. The use of drugs (e.g. intranasal cocaine), alcohol (e.g. chronic alcoholism in the context of Wernicke and Korsakoff syndromes), and smoking tobacco are also important given the association between smell loss and such factors. A determination of the medications that the patient is or was taking is needed, as some drugs, such as angiotensin-converting enzyme (ACE) inhibitors, often have distinct influences on olfaction. It is critical to be aware that while patients often complain of problems with smell and taste, quantitative testing usually reveals only an olfactory problem, reflecting decreased retronasal stimulation of the olfactory receptors during deglutition (Burdach & Doty, 1987).

The examiner should ascertain whether the patient has any other medical conditions potentially associated with smell impairment (e.g. renal failure, liver disease, hypothyroidism, diabetes, or dementia). Questions regarding epistaxis, discharge (clear, purulent or bloody), nasal obstruction, allergies and somatic symptoms, including headache or irritation may have localizing value. A family history of smell dysfunction may suggest a genetic etiology. Subtle symptoms of central tumours, dementia, parkinsonism, and seizure activity (e.g. automatisms, occurrence of black-outs, auras, and *déjà vu*) should be sought. Delayed puberty in association with anosmia (with or without midline craniofacial abnormalities, deafness, and renal anomalies) suggests the possibility of Kallmann's syndrome or some variant thereof.

Physical examination and laboratory tests

The neurological component of the evaluation should focus on cranial nerve function, with particular attention to possible skull base and intracranial lesions. Visual acuity, visual field, and optic disc examinations aid in the detection of possible intracranial mass lesions and in the detection of the Foster Kennedy syndrome (ipsilateral anosmia, ipsilateral optic atrophy, and contralateral papilledema secondary to raised intracranial pressure) (Watnick & Trobe, 1989). The otolaryngological examination should employ nasal endoscopy, both flexible and rigid, to ensure thorough assessment of the olfactory meatal area. Appropriate medical imaging should be employed to assess sinonasal tract inflammation (e.g. computerized tomography), as well as brain lesions and the integrity of the olfactory bulbs, tracts, and cortical parenchyma (e.g. magnetic resonance imaging). Some laboratory tests (e.g. blood serum tests) may be helpful in detecting underlying medical conditions suggested by history and physical examinations, such as infection, nutritional deficiencies (e.g. B6, B12), allergy, diabetes mellitus, and thyroid, liver, and kidney disease (Bromley, 2000).

Quantitative olfactory testing

A number of practical standardized clinical smell tests are now commercially available (for review, see Doty, 2001a), providing the neurologist with the ability to (a) determine of the validity of patients' complaints (including the detection of malingering), (b) characterize the exact nature of the problem, (c) reliably monitor changes in function over time (including those of iatrogenic etiology), and (d) accurately establish compensation for permanent disability. The most widely used of these tests are self-administered 'scratch and sniff' tests, ranging from the 3-item Pocket Smell Test™ to the 40-item University of Pennsylvania Smell Identification Test (UPSIT; commercially termed the Smell Identification Test™ or SIT) (Doty, 1995b; Doty et al., 1996). Available in English, Spanish, French, and German language versions, the latter test can be self-administered in 10 to 15 minutes by most patients in the waiting room, and scored in less than a minute by non-medical personnel. Results are expressed in terms of a percentile score of a patient's performance relative to age- and sex-matched controls, as well in categories of function: normosmia, mild microsmia, moderate microsmia, severe microsmia, anosmia, and probable malingering. Malingering is inferred from improbable responses in the forced-choice setting.

Although olfactory event-related potentials (OERPs) are available in some specialized medical centers, including our own, their general practicality is limited. They require expensive equipment capable of delivering well-delineated 'square wave' odorant pulses to the olfactory receptors within a background of continuously flowing warmed and humidified air (Doty & Kobal, 1995). Unlike their visual and auditory counterparts, OERPs are unable to discern where in the pathway the anomaly exists.

Causes of olfactory dysfunction

In general, olfactory dysfunction is due to one of three causes: (a) conductive or transport impairments from

obstruction of the nasal passages (e.g. by chronic nasal inflammation, polyposis, etc.); (b) sensorineural impairment from damage to the olfactory neuroepithelium (e.g. by viruses, airborne toxins, etc.); and (c) central olfactory neural impairment from CNS damage (e.g. tumours, masses impacting on olfactory tract, etc.). These categories are not necessarily mutually exclusive. For example, both damage and blockage of airflow to the receptors can occur from chronic rhinosinusitis.

As seen in Table 41.1, there are a number of known etiologies for olfactory disturbance. Nearly two-thirds of cases of chronic anosmia or hyposmia (i.e. those which are presumably permanent) are due to prior upper respiratory infections, head trauma, and nasal and paranasal sinus disease, and most reflect permanent damage to the olfactory neuroepithelium (Deems et al., 1991). Other causes include iatrogenic interventions (e.g. septoplasty, rhinoplasty, turbinectomy, radiation therapy, medications), intranasal neoplasms (e.g. inverting papilloma, hemangioma, and esthesioneuroblastoma), intracranial tumours or lesions (e.g. Foster Kennedy Syndrome, olfactory groove meningiomas, frontal lobe gliomas), neurodegenerative diseases, toxic exposures (which includes smoking), epilepsy, psychiatric disorders, and various endocrine and metabolic disorders. Details regarding some of the more common entities associated with smell loss are discussed below.

Ageing

In later life, decreased smell function is the rule, rather than the exception, and is largely responsible for the well-documented age-related increases in accidental gas poisonings and explosions, as well as weight loss, malnutrition, impaired immunity, and worsening of some medical illnesses (Doty et al., 1984a, Miletic et al., 1996; Mattes & Cowart, 1994). In contrast to the ~ 1% of persons under the age of 65 years with major smell loss, about half of the population between 65 and 80 years of age has such loss (Fig. 41.5). Over the age of 80, this figure rises to nearly 75% (Doty et al., 1984a). Often an accumulation of damage over the years is the culprit and a single event, such as a bad cold, can be the precipitating factor. In some cases, the olfactory loss may reflect, as a result of age-related appositional bone growth, the pinching off of the olfactory fila as they traverse the ethmoid bone (Kalmey et al., 1998). In general, the number olfactory receptors and olfactory bulb glomeruli decrease markedly with age (Smith, 1942; Meisami et al., 1998).

Post-upper respiratory infections

The most common cause of *permanent* smell loss in the adult human is that induced by upper respiratory infections

Table 41.1. Reported agents, diseases, drugs, interventions and other etiologic categories associated in the medical or toxicological literature with olfactory dysfunction. Note that categories are not mutually exclusive

Industrial dusts, metals, volatiles
Acetone
Acids (e.g. sulfuric)
Ashes
Benzene
Benzol
Butyl acetate
Cadmium
Carbon disulfide
Cement
Chalk
Chlorine
Chromium
Coke/coal
Cotton
Cresol
Ethyl acetate
Ethyl & methyl acrylate
Flour
Formaldehyde
Grain
Hydrazine
Hydrogen selenide
Hydrogen sulfide
Iron carboxyl
Lead
Mercury
Nickel
Nitrous gases
Paint solvents
Paper
Pepper
Peppermint oil
Phosphorus oxychloride
Potash
Silicone dioxide
Spices
Trichloroethylene
Drugs
Adrenal steroids (chronic use)
Amino acids (excess)
Cysteine
Histidine
Analgesics
Antipyrine
Anesthetics, local
Cocaine HCl
Procaine HCl
Tetracaine HCl

Table 41.1. (*cont.*)

Anticancer agents (e.g. methotrexate)
Antihistamines (e.g. chlorpheniramine malate) *See also* Table 41.2.
Antimicrobials
  Griseofulvin
  Lincomycin
  Macrolides
  Neomycin
  Penicillins
  Streptomycin
  Tetracyclines
  Tyrothricin
Antirheumatics
  Mercury/gold salts
  D-Penicillamine
Antithyroids
  Methimazole
  Propylthiouracil
  Thiouracil
Antivirals
Cardiovascular/hypertensives
Gastric medications
  Cimetidine
Hyperlipoproteinemia medications
  Artovastatin calcium (Lipitor)
Cholestyramine
Clofibrate
Intranasal saline solutions with:
  Acetylcholine
  Acetyl, β-methylcholine
  Menthol
  Strychnine
  Zinc sulfate
Local vasoconstrictors
Opiates
Codeine
  Hydromorphone HCl
  Morphine
Psychopharmaceuticals (e.g. LSD, psilocybin)
Sympathomimetics
  Amphetamine sulfate
  Fenbutrazate HCl
Phenmetrazine theoclate

Endocrine/metabolic
Addison's disease
Congenital adrenal hyperplasia
Cushing's syndrome
Diabetes mellitus
Froelich's syndrome
Gigantism
Hypergonadotropic hypogonadism
Hypothyroidism
Kallmann's syndrome
Pregnancy

Table 41.1. (*cont.*)

Panhypopituitarism
Pseudohypoparathyroidism
Sjögren's syndrome
Turner's syndrome

Infections – viral/bacterial
Acquired immunodeficiency syndrome (AIDS)
Acute viral rhinitis
Bacterial rhinosinusitis
Bronchiectasis
Fungal
Influenza
Rickettsial
Microfilarial

Lesions of the nose/airway blockage
Adenoid hypertrophy
Allergic rhinitis
  Perennial
  Seasonal
Atrophic rhinitis
Chronic inflammatory rhinitis
Hypertrophic rhinitis
Nasal polyposis
Rhinitis medicamentosa
Structural abnormality
  Deviated septum
  Weakness of alae nasi
Vasomotor rhinitis

Medical interventions
Adrenalectomy
Anesthesia
Anterior craniotomy
Arteriography
Chemotherapy
Frontal lobe resection
Gastrectomy
Hemodialysis
Hypophysectomy
Influenza vaccination
Laryngectomy
Oophorectomy
Paranasal sinus exenteration
Radiation therapy
Rhinoplasty
Temporal lobe resection
Thyroidectomy

Neoplasms – intracranial
Frontal lobe gliomas and other tumours
Midline cranial tumours
  Parasagital meningiomas
  Tumours of the corpus callosum

Table 41.1. (*cont.*)

Olfactory groove/cribriform plate meningiomas
Osteomas
Paraoptic chiasma tumours
Aneurysms
Craniopharyngioma
Pituitary tumours (esp. adenomas)
Suprasellar cholesteatoma
Suprasellar meningioma
Temporal lobe tumours
Neoplasms – Intranasal
Neuro-olfactory tumours
Esthesioepithelioma
Esthesioneuroblastoma
Esthesioneurocytoma
Esthesioneuroepithelioma
Other benign or malignant nasal tumours
Adenocarcinoma
Leukemic infiltration
Nasopharyngeal tumours with extension
Neurofibroma
Paranasal tumours with extension
Schwannoma
Neoplasms – extranasal and extracranial
Breast
Gastrointestinal tract
Laryngeal
Lung
Ovary
Testicular
Neurologic
Amyotrophic lateral sclerosis
Alzheimer's disease
Cerebral abscess (esp. frontal or ethmoidal regions)
Down's syndrome
Familial dysautonomia
Guam ALS/PD/dementia
Head trauma
Huntington's disease
Hydrocephalus
Korsakoff's psychosis
Migraine
Meningitis
Multiple sclerosis
Myesthenia gravis
Paget's disease
Parkinson's disease
Refsum's syndrome
Restless leg syndrome
Syphilis
Syringomyelia

Table 41.1. (*cont.*)

Temporal lobe epilepsy
Hamartomas
Mesial temporal sclerosis
Scars/previous infarcts
Vascular insufficiency/anoxia
Small multiple cerebrovascular accidents
Subclavian steal syndrome
Transient ischemic attacks
Nutritional/metabolic
Abetalipoproteinemia
Chronic alcoholism
Chronic renal failure
Cirrhosis of liver
Gout
Protein calorie malnutition
Total parenteral nutrition w/o adequate replacement
Trace metal deficiencies
Copper
Zinc
Whipple's disease
Vitamin deficiency
Vitamin A
Vitamin B6
Vitamin B12
Pulmonary
Chronic obstructive pulmonary disease
Psychiatric
Anorexia nervosa (severe stage)
Attention deficit disorder
Depressive disorders
Hysteria
Malingering
Olfactory reference syndrome
Schizophrenia
Schizotypy
Seasonal affective disorder

(URIs), such as those associated with the common cold, influenza, and pneumonia. Often the respiratory illness is described as being more severe than usual. Exactly what predisposes someone to viral- or bacterial-induced smell dysfunction or the mechanisms underlying it remains unclear. Direct insult to the olfactory neuroepithelium is likely, but central structures may also be affected. In general, patients with URI-related anosmia have markedly reduced numbers of receptors and when receptors are present, they appear abnormal compared to those patients with hyposmia (Jafek et al., 1990). Although spontaneous recovery in

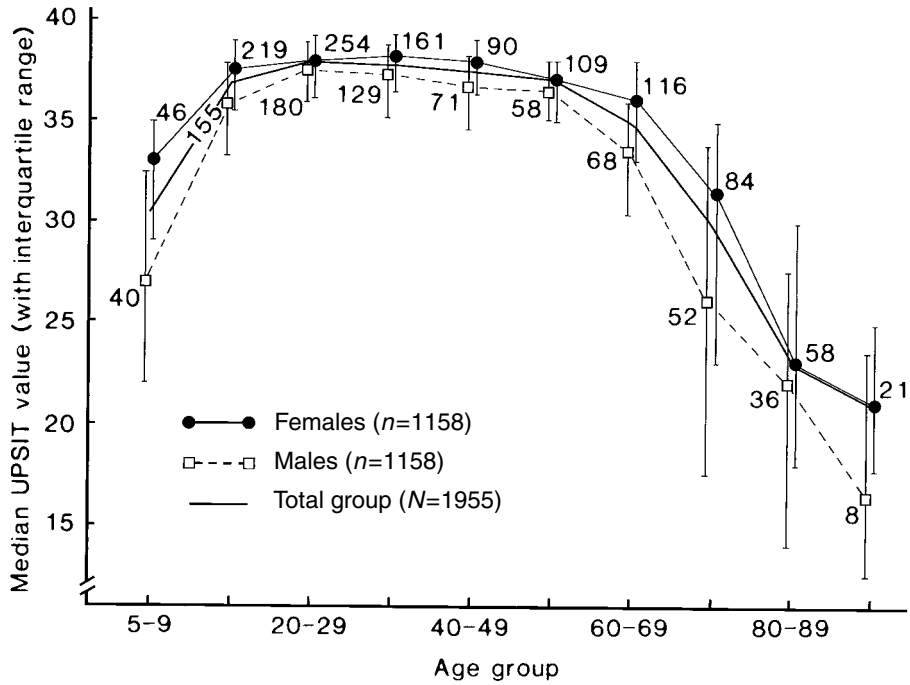

Fig. 41.5. Scores on the University of Pennsylvania Smell Identification Test (UPSIT) as a function of age and gender in a large heterogeneous group of subjects. Numbers by data points indicate sample sizes. (From Doty et al., 1984b; Copyright © 1984, American Association for the Advancement of Science.)

these patients is theoretically possible given the propensity of olfactory neurons to regenerate, meaningful recovery is unlikely when marked loss has been present for a period of time.

Head trauma

Smell disturbance following head trauma is common, particularly where rapid acceleration/deceleration of the brain occurs (i.e. coup contra coup injury). On average, blows to the occiput have been found to produce greater olfactory loss than blows to the front of the head (Doty et al., 1997b). The most common mechanisms include disruption of the sinonasal tract from shearing forces, and direct contusion and ischemia to the olfactory bulb and frontal and temporal poles (Fig. 41.6). The prevalence of olfactory dysfunction in patients with head trauma is typically below 15% (Yousem et al., 1999), and is proportional to the severity of the injury (Doty et al., 1997b). Dysosmia, when present, typically decreases significantly over the post-trauma period (Doty et al., 1997b). In severe cases, MRI images reveal damage to the olfactory bulbs, tracts, and areas of the temporal and frontal lobes (Yousem et al., 1996). Animal studies show that intracranial hemorrhage and ischemia can lead to degeneration of the olfactory epithelium without transection of the olfactory nerves (Nakashima et al., 1983).

Nasal and sinus disease

Unlike the sensorineural dysfunction that can follow a viral syndrome or head trauma, olfactory impairment that accompanies nasal or sinus disease has been traditionally viewed as being solely conductive. However, empirical data suggest that surgical (e.g. excision of polyps) or medical (e.g. administration of topical or systemic steroids) treatment rarely returns function to normal levels, implying that blockage alone cannot explain the olfactory loss (Doty & Mishra, 2001). Recently it has been shown that the severity of histopathological changes within the olfactory mucosa of patients with chronic rhinosinusitis is positively related to the magnitude of olfactory loss (Kern, 2000). Furthermore, biopsies from the neuroepithelial region of patients with nasal disease are less likely to yield olfactory-related tissue than biopsies from controls (Feron et al., 1998). The same is true for anosmic vs. non-anosmic rhinosinusitis patients, the former of whom exhibit a generally more pathological epithelium (e.g. disordered arrangement of cells, more islands of respiratory-like epithelium) (Lee et al., 2000).

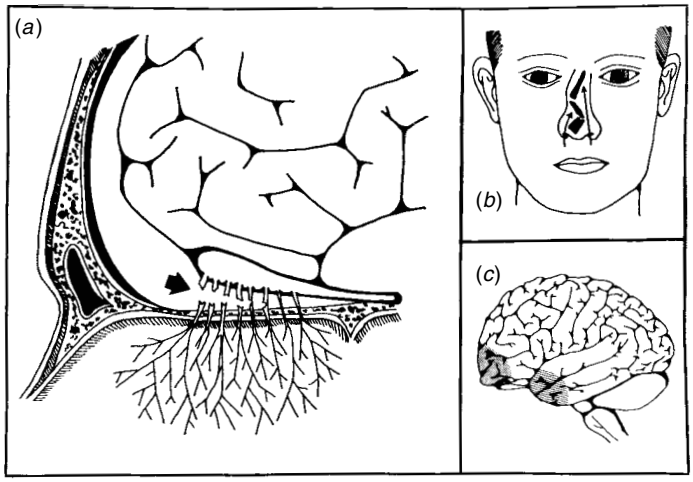

Fig. 41.6. Mechanisms of post-traumatic olfactory dysfunction. (*a*) Shearing or tearing of the olfactory fila. (*b*) Injury to the sinonasal tract (*c*) Cortical contusions and brain hemorrhage. (From Costanzo & Zasler, 1991; Copyright © 1991, Raven Press, Ltd.)

CNS neoplasms

According to Finelli and Mair (1991), the single most egregious error of neurologists is failure to recognize the symptom of anosmia as the principal or sole feature of an olfactory groove neoplasm. Tumours impinging on the olfactory bulbs or tracts, such as olfactory groove meningiomas, frontal lobe gliomas, and suprasellar ridge meningiomas arising from the dura of the cribriform plate, have been associated with olfactory disturbance, as have tumours on the floor of the third ventricle, pituitary tumours that extend above the sella turcica, and tumours in the temporal lobe or uncinate convolution.

Neurodegenerative and other neurological diseases

Olfactory deficits have been described in such neurological disorders as Alzheimer's disease, idiopathic Parkinson's disease, Huntington's disease, alcoholic Korsakoff's syndrome, Pick's disease, the parkinson dementia complex of Guam, amyotrophic lateral sclerosis, schizophrenia, and multiple sclerosis (Mesholam et al., 1998; Doty, 1991; Doty et al., 1998; Moberg et al., 1997a; b). Importantly, olfactory dysfunction may be the first clinical sign of Alzheimer's disease (AD) and idiopathic Parkinson's disease (PD) (Doty et al., 1987, 1988b). Although not classically considered a neurodegenerative disease, schizophrenia also is associated with smell loss that appears to be correlated with disease duration, suggesting a possible progressive or degenerative component to this disorder in olfaction-related pathways (Moberg et al., 1997b). The olfactory bulbs and tracts of patients with schizophrenia are markedly smaller than those of controls (Turetsky et al., 2000).

Two studies have recently demonstrated that smell testing is useful in identifying persons at risk for later significant cognitive decline or AD. Graves et al. (1999) tested 1985 Japanese–American people around the age of 60 with cognitive tests and an abbreviated version of the UPSIT, and then rescreened 1604 of these people after two years. They also genotyped 69% of the follow-up participants for apolipoprotein E (apoE). Overall, olfactory dysfunction in the presence of one or more APOE-e4 alleles was associated with a very high risk of subsequent cognitive decline, and smell testing identified persons who came to exhibit later cognitive decline better than did a global cognitive test. More recently, Devanand et al. (2000) administered the UPSIT to 90 outpatients with mild cognitive impairment at 6-month intervals, along with matched healthy controls. Patients with mild cognitive impairment scored lower on the UPSIT than did the controls. Most importantly, patients with low UPSIT scores ($<$34) were more likely to develop AD than the other patients. Low UPSIT scores, combined with lack of awareness of olfactory deficits on the part of the patients, predicted the time to development of AD. UPSIT scores from 30–35 showed moderate to strong sensitivity and specificity for diagnosis of AD at follow-up.

The underlying physiological basis of the olfactory loss in patients with AD is not yet clear, although this disorder is associated with a profound loss of neurons in the anterior olfactory nucleus, olfactory bulb, and layer II of the entorhinal cortex (Doty, 1991; Gomez-Isla et al., 1996). Limbic brain regions which receive olfactory bulb mitral and tufted cell projections are disproportionately laden with neurofibrillary tangles and neuritic plaques (Delacourte et al., 1999). Deficits in the neurotransmitter acetylcholine may somehow relate to this problem, as it is well established that (a) individuals with no history of cognitive loss that are in the early histopathologic stages of AD exhibit a cholinergic deficit within the inferior temporal lobe and (b) drugs that alter cholinergic function alter the ability to smell. For example, scopolamine, a muscarinic cholinergic antagonist, reportedly decreases olfactory sensitivity (Serby et al., 1990), whereas physostigmine, a cholinesterase inhibitor, improves odour discrimination performance, at least in rats (Doty et al., 1999a).

In idiopathic PD, bilateral olfactory deficits occur before the onset of most of the classical neurological signs and symptoms (Doty et al., 1988b). The PD-related olfactory impairment is unrelated to disease stage, use of anti-parkinson medications, duration of the illness, and severity of the symptoms, such as tremor, rigidity, bradykinesia

or gait disturbance (Doty et al., 1992b). Since olfactory loss is pervasive and marked in PD, as well as in AD, and is absent or not present to the same degree in a number of other neurological disorders, it can be used to distinguish among disorders that share many symptoms and signs with PD (Doty, 1991). For example, while patients with essential tremor, progressive supranuclear palsy, multiple system atrophy and parkinsonism induced by the proneurotoxin 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) share a number of motor symptoms with idiopathic PD, they have little or no olfactory dysfunction (Doty, 1991). Like idiopathic PD, familial PD is also associated with olfactory impairment, and this heritable defect occurs independently of the parkinsonian phenotype (Markopoulou et al., 1997).

In multiple sclerosis, olfactory loss is directly proportional to the number of MS-related plaques in central brain regions associated with olfactory processing (e.g. inferior middle temporal lobe and periorbital frontal cortex) (Doty et al., 1997b, 1998). A 1:1 longitudinal association is present between UPSIT scores and changes in plaque load over time (Doty et al., 1999b), implying that olfactory function increases and decreases as the plaque numbers increase and decrease. In effect, knowledge of a patient's UPSIT score largely predicts the plaque load in the olfaction-related regions.

Other causes

A number of environmental and industrial chemicals have been linked to olfactory dysfunction, including acrylates, cadmium, benzene, formaldehyde, solvents, and nickel dust, although few well-controlled studies exist in this area and most reports are largely anecdotal (Doty & Hastings, 2001). With regard to cigarette smoking, olfactory ability decreases as a function of cumulative smoking dose and cessation of smoking can result in improvement in olfactory function over time (Frye et al., 1990). Medications commonly affect smell function and should be considered early in an evaluation, especially in the context of a new drug therapy (Table 41.2). Olfactory hallucinations occur in mesial temporal lobe seizures and migraine. Hyperosmia is classically associated with pregnancy and hyperemesis gravidarum, although objective evidence of true hypersensitivity, rather than hyperreactivity, is still lacking. Despite the fact that some patients with apparent multiple chemical hypersensitivity syndrome (MCS) report heightened ability to smell, olfactory thresholds are not meaningfully altered (Doty et al., 1988a). Hyperosmia reportedly occurs in some cases of epilepsy during the interictal period, although, as noted above, most patients with long-term epilepsy and intractable seizure activity, such as candidates for temporal lobe resection, are hyposmic.

Treatment of olfactory disorders

As alluded to earlier, meaningful treatments are available for some, but not all, patients whose olfactory dysfunction is conductive; i.e. resulting from blockage of airflow to the olfactory neuroepithelium. Such therapies include allergy management, topical and systemic corticosteroid therapies, and surgical procedures to reduce inflammation or obstructions (e.g. polyps). A brief course of systemic steroid therapy can be useful in distinguishing between conductive and sensorineural olfactory loss, as patients with the former will often respond positively to some extent to the treatment, although longer term systemic steroid therapy is not advised. Topical nasal steroids are often ineffectual in returning smell function because the steroid fails to reach the affected regions in the upper nasal passages. Increased efficacy presumably occurs when the nasal drops or spray are administered in the head-down Moffett position.

Patients with sensorineural causes of olfactory disturbance are difficult to manage, and the prognosis for patients suffering from long-standing total loss due to upper respiratory illness or head trauma is poor. Most patients who recover smell function subsequent to trauma do so within 12 weeks of injury (Costanzo et al., 1995). Although there are no verified treatments for trauma-related olfactory loss, anti-inflammatory agents may minimize post-traumatic sequelae in some cases. Recent rat research suggests that application of nerve growth factor onto the olfactory epithelium may alleviate axotomy-induced degenerative changes in the olfactory receptor neurons, although it is not known whether this has any functional consequence or if such a procedure in humans would be efficacious (Yasuno et al., 2000).

Tobacco smoking by itself rarely causes complete loss of the sense of smell, although patients who quit smoking typically have dose-related improvement in olfactory function and flavour sensation over time (Frye et al., 1990). Central lesions, such as CNS tumours that impinge on olfactory bulbs and tracts and epileptogenic foci within the medial temporal lobe that result in olfactory seizures, can often be resected in a manner that allows for some restoration of olfactory function. Medications that induce distortions of olfaction can often be discontinued and replaced with other types of medications or modes of therapy. Importantly, dopaminergic and cholinergic therapies do not improve the olfactory dysfunction seen in Parkinson's disease, and there is no evidence that neuroleptics alter the

Table 41.2. Selected medications that reportedly alter smell and/or taste. Most of these agents are noted in the Physician's Desk Reference (PDR) as having adverse effects on the olfactory system

Antianxiety agents
Alprazolam (Xanax)
Buspirone (BuSpar)

Antibiotics
Ampicillin
Azithromycin (Zithromax)
Ciprofloxacin (Cipro)
Clarithromycin (Biaxin)
Enalapril (Vaseretic)
Griseofulvin (Grisactin)
Metronidazole (Flagyl)
Ofloxacin (Floxin)
Terbinafine (Lamisil)
Ticarcillan (Timentin)
Tetracycline

Anticonvulsants
Carbamazepine (Tegretol)
Phenytoin (Dilantin)

Antidepressants
Amitriptyline (Elavil)
Clomipramine (Anafranil)
Desipramine (Norpramin)
Doxepin (Sinequan)
Imipramine (Tofranil)
Nortriptyline (Pamelor)

Antihistamines and decongestants
Chlorpheniramine
Loratadine (Claritin)
Pseudoephedrine

Antihypertensives and cardiac medications
Acetazolamide (Diamox)
Amiodarone (Pacerone)
Amiloride (Midamor)
Amiodarone (Cordarone)
Betaxolol (Betoptic)
Captopril (Capoten)
Diltiazem (Cardizem)
Enalapril (Lexxel, Vasotec, Vaseretic)
Hydrochlorothiazide (Esidix)
Nifedipine (Procardia)
Nitroglycerin
Propafenone (Rythmol)
Propranolol (Inderal)
Spironolactone (Aldactone)
Tocainide (Tonocard)

Anti-inflammatory agents
Auranofin (Ridaura)
Beclomethasone (Beclovent, Beconase)
Budesonide (Rhinocort)
Colchicine
Dexamethasone (Decadron)
Flunisolide (Nasalide, Aerobid)
Fluticasone (Flonase)
Gold (Myochrysine)
Hydrocortisone
Penicillamine (Cuprimine)

Antimanic drugs
Lithium

Antimigrane agents
Dihydroergotamine (Migranal)
Naratriptan (Amerge)
Rizatriptan (Maxalt)
Sumatriptan (Imitrex)

Antineoplastics
Cisplatin (Platinol)
Doxorubicin (Adriamycin)
Levamisole (Ergamisol)
Methotrexate (Rheumatrex)
Vincristine (Oncovin)

Antiparkinsonian agents
Levodopa (Larodopa; with carbidopa: Sinemet)

Antipsychotics
Clozapine (Clozaril)
Trifluoperazine (Stelazine)

Antithyroid agents
Methimazole (Tapazole)
Propylthiouracil

Antiviral agents
Ganciclovir (Cytovene)
Interferon (Ruferon-A)
Zalcitabine (HIVID)

Bronchodilators
Biotolterol (Tornalate)
Pirbuterol (Maxair)

Lipid-lowering agents
Atorvastatin (Lipitor)
Fluvastatin (Lescol)
Lovastatin (Mevacor)
Pravastatin (Pravachol)

Muscle relaxants
Baclofen (Lioresal)
Dantrolene (Dantrium)

Pancreatic enzyme preparations
Pancrelipase (Cotazym)

Smoking cessation aids
Nicotine (Nicotrol)

olfactory loss of patients with schizophrenia. Despite the fact there are advocates for zinc and vitamin therapies, there is no compelling evidence that these therapies work except in cases where frank zinc or vitamin deficiencies exist.

Prognosis for recovery seems to be better for patients with not too severe microsmia (e.g. UPSIT scores above 25) than for those with anosmia or severe microsmia. In some etiologies, this reflects the less extensive damage into the basal cell layer of the epithelia and possibly less fibrosis around the foramina of the cribriform plate through which the olfactory nerve axons pass. An important component to therapy for many patients is the quantitative establishment of the true degree of olfactory loss. This places the patient's problem into overall perspective; thus, it can be therapeutic for an older person to learn that, while his or her smell function is not what it used to be, it still falls above the average of his or her peer group.

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42

Taste

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Taste modifies the act of eating, and subsequently has a tremendous impact on one's behaviour and well-being. The physiologic role of the gustatory system is multifold and includes: (a) triggering ingestive and digestive reflex systems that alter the secretion of oral, gastric, pancreatic, and intestinal juices (Schiffman, 1997; Giduck et al., 1987), (b) reinforcing the ingestive process by enhancing the feelings of pleasure and satiety (Warwick et al., 1993), and (c) enabling the individual to determine the quality of sampled foodstuffs and distinguish nutrients (which usually taste 'good') from potential toxins (which usually taste 'bad') (McLaughlin & Margolskee, 1994; Scott & Giza, 1995). Although rarely appreciated, gustatory dysfunction can alter food choices and patterns of consumption, resulting in weight loss, malnutrition, and possibly impaired immunity (Schiffman & Wedral, 1996; Mattes & Cowart, 1994). Increased sensitivity and aversion to bitter-tasting substances on the part of the pregnant mother during the first trimester presumably reflects the need to detect and avoid bitter tasting poisons and teratogens during this critical phase of fetal development. Similarly, increased preferences for salty and bitter tasting substances during the remainder of pregnancy likely encourage the eating of a varied diet and the ingestion of much needed electrolytes to expand fluid volume (Duffy et al., 1998). In someone who is hypertensive or diabetic, taste loss can lead to a dangerous tendency to over-compensate for the loss by adding additional salt or sugar to the food.

In this chapter, we review clinically important aspects of the anatomy and physiology of the gustatory system, describe approaches for quantitatively evaluating this system, and present examples of common types of gustatory dysfunction, along with means for their management or treatment.

Anatomy and physiology

Taste buds, papillae, and initiation of taste transduction

The ~4600 goblet-shaped taste buds are located on the tongue's dorsal surface, the tongue–cheek margin, the base of the tongue, the soft palate, the pharynx, the larynx, the epiglottis, the uvula, and the first third of the esophagus (Miller, 1995). Most are found on the surface of the tongue within the protruding papillae. The fungiform, foliate and vallate (also called circumvallate) papillae harbor most of the taste buds; filiform papillae do not (Fig. 42.1).

Each taste bud contains between 50 and 150 slender epithelial cells arranged in a manner similar to the segments of a grapefruit. The taste pore opens into the centre of the bud, the taste pit, into which microvillae of sensory cells project. Each bud contains not only sensory and supporting cells, but progenitor cells from which the other cell types arise. Light, dark, and intermediate cells can be identified on the basis of their ultrastructural appearance and the presence or lack of dense granules in their apical portion (Farbman, 1980). Taste bud cells have the propensity to replace themselves ('turn over') periodically, with a time course of around two weeks (Beidler & Smallman, 1965).

A tastant initiates gustatory transduction and ultimately action potentials in one of two ways: by directly gating apical ion channels on microvillae of taste bud cells (a process that probably occurs with sour- and salty-tasting substances) or by activating receptors coupled to G-proteins that, in turn, are coupled to various second messenger systems (a process that probably occurs for sweet- and bitter-tasting agents; for review, see Margolskee, 1995). The

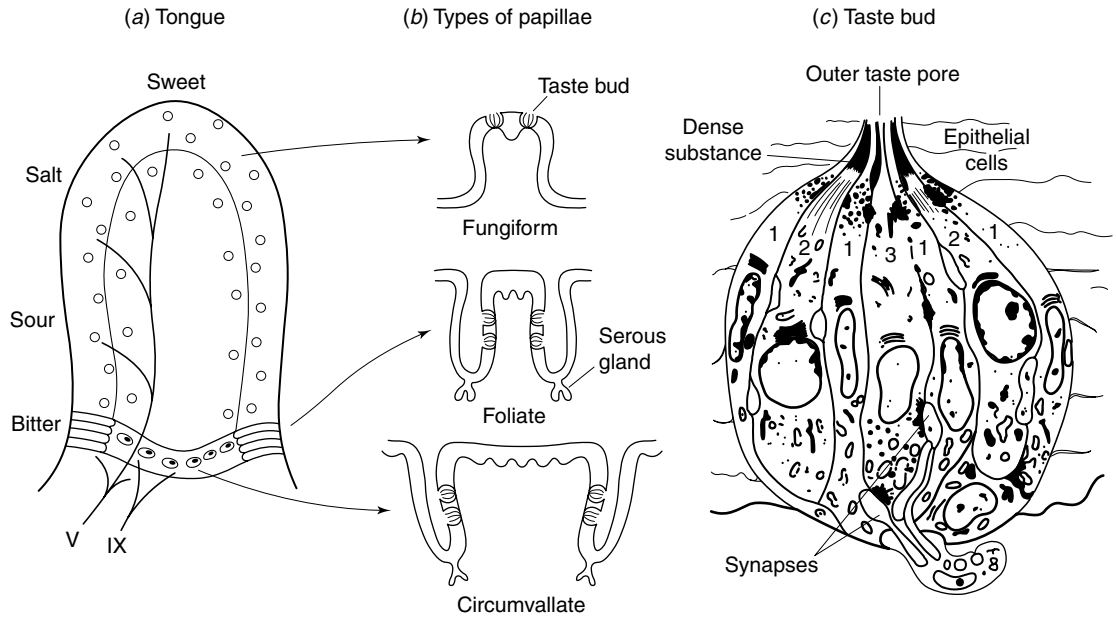

Fig. 42.1. (*a*) Lingual distribution of (*b*) types of papillae that harbour (*c*) taste buds. In (*c*), 1 and 2 are presumably supporting cells, which secrete materials into the lumen of the taste buds; 3 is a sensory receptor cell; and 4 is a basal cell from which the other types of cells arise. (Modified from Shepherd, 1994.)

full range of primary taste sensations may be broader than simply sweet, sour, salty, and bitter, including 'metallic' (iron salts), 'umami' (monosodium glutamate, disodium gluanylate, disodium inosinate), and 'chalky' (calcium salts) (Schiffman, 1997; Kurihara & Kasiwayangi, 2000). The olfactory and trigeminal systems contribute to overall flavour perception by providing aroma, texture, temperature and spiciness.

Saliva and its role in taste function

Saliva contains dozens of different proteins and peptides (Table 42.1) and is secreted into the oral cavity by numerous glands, most importantly the paired parotid, submandibular, and sublingual salivary glands. Saliva is involved in the taste process, *per se*, in at least four ways. First, before tastants can enter the taste buds, they must be solubilized, and tastants dissolve or mix with saliva before entering the taste pore. Secondly, saliva serves as a filter to influence the concentration of tastants that enter the taste buds. For example, when bitter-tasting tannin-containing foods are ingested, there is an increase in the amount of proline-rich salivary proteins that bind tannins (Beidler, 1995). Such binding decreases the amount of tannins available to the taste buds, thereby increasing the taste threshold to the tannins. Third, saliva rinses away tastants and other materials that are introduced into the mouth, decreasing their tendency to linger in the oral cavity. Finally, saliva appears to play a role in taste bud maintenance. For example, taste buds within the fungiform papillae of rats disappear following removal of the submandibular and sublingual salivary glands: disappearance that can be reversed by adding epidermal growth factor to their drinking water (Morris-Witman et al., 2000).

Multiple peripheral pathways to the gustatory nucleus

The taste buds are innervated by branches of several cranial nerves which, unlike CN I, are mixed motor and sensory nerves transmitting multiple forms of information. The facial nerve (CN VII) supplies the taste buds within the fungiform and filiform papillae on the anterior two-thirds of the tongue (via the chorda tympani) and those on the soft palate (via the lesser palatine nerve branch of the greater petrosal nerve). The cell bodies of these afferent gustatory fibres are located in the geniculate ganglion. A short distance of the CN VII taste fibres is shared with the lingual nerve (CN V3) proximal to the tongue. The glossopharyngeal nerve (CN IX) supplies the circumvallate and most foliate taste buds within the posterior third of the tongue via its lingual–tonsillar branch. The

Table 42.1. Proteins and peptides in mammalian whole saliva

N-Acetyl-D-glucosaminidase	IgA
Agglutinagen A	IgG
Agglutinagen B	IgM
Agglutinagen C	Kallikrein
Albumin	Lactoferrin
Aldolase	Lactoperoxidase
Amylase family	Lethal factor
Angiotensin II	Lingual lipase
Anticomplimentary factor	Lipoproteins
Antileukoprotease	Lysozyme
Antitrypsin	Mesodermal growth factor
Aproerytherin	Metalloprotease
Biopterin	Monopterin
Bone marrow colony-stimulating factor	Mucins
	Neopterin
Calmodulin	Nerve growth factor
Carbonic anhydrase	Neural tube growth factor
Cathespin	Parotid glycoprotein family
Collagenase	Peroxidase
Cystatin family	Plasminogen activator
Elastase	Platelet-activating factor
Endothelial growth-stimulating factor	Proline-rich proteins
	Prostaglandins
Esterase	Pterin
Esterase B	Renin
Esteropeptidase	Sialomucin
Ferritin	Sialotonin
Fibronectin	Somatostatin
Fucosyltransferase	Statherin
Gastrin	Tissue plasminogen activator
Glucagon	Tonin
Glutamine-glutamic acid protein family	Transferrin
	VEG protein
Granulocytosis-inducing factor	Vitamin B-binding proteins
	Wound contraction factor
5-Hydroxymethylpterin	Xanthopterin

Notes:
If individual protein family members and isoenzymes are included separately, the total number approaches 200.
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Table 42.2. Relative potency, in terms of taste thresholds, among different chemical compounds that have primarily sweet, sour, salty, or bitter tastes

Salty-tasting substances	*Index*	*Sour-tasting substances*	*Index*
Sodium chloride	1	Hydrochloric acid	1
Ammonium chloride	2.5	Formic acid	1.1
Sodium fluoride	2	Chloracetic acid	0.9
Calcium chloride	1	Lactic acid	0.85
Potassium chloride	0.6	Tartaric acid	0.7
Sodium bromide	0.4	Malic acid	0.6
Lithium chloride	0.4	Acetic acid	0.55
Sodium iodide	0.35	Citric acid	0.46
Sweet-tasting substances	*Index*	*Bitter-tasting substances*	*Index*
Sucrose	1	Quinine	1
Sucrononic acid	200,000	Denatonium	1000
Saccharin	675	Strychnine	3.1
Aspartame	150	Nicotine	1.3
Chloroform	40	Brucine	1.1
Fructose	1.7	Phenylthiourea	0.9
Alanine	1.3	Caffeine	0.4
Glucose	0.8	Morphine	0.02

Notes:
The thresholds can vary as much as several thousand-fold from one compound to another, even within the same class.
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pharyngeal branch of this nerve innervates taste buds in the nasopharynx. The nerve cell bodies of these visceral gustatory afferent fibres are located immediately outside the jugular foramen in the petrosal ganglion. The vagus nerve (CN X) innervates the taste buds on the epiglottis, aryepiglottal folds, and esophagus (via the internal portion of the superior laryngeal branch).

Gustatory cortical regions: functional anatomy

All the peripheral gustatory fibres enter the brainstem and project to the nucleus of the tractus solitarius (NTS), which begins in the rosterolateral medulla and extends caudally along the ventral border of the vestibular nuclei. From this structure, connections are made to higher processing centres described below. The cells of the NTS also make reflexive connections, via the interneurons of the reticular formation, with cranial nuclei that control (a) muscles of facial expression, (b) taste-mediated behaviours such as chewing, licking, salivation and swallowing, and (c) pre-absorptive insulin release (Smith & Shipley, 1992).

In primates, the projections from the NTS to higher centres likely ascend ipsilaterally within the central tegmental tract, to synapse ultimately within the parvicellular division of the ventroposteromedial thalamic nucleus

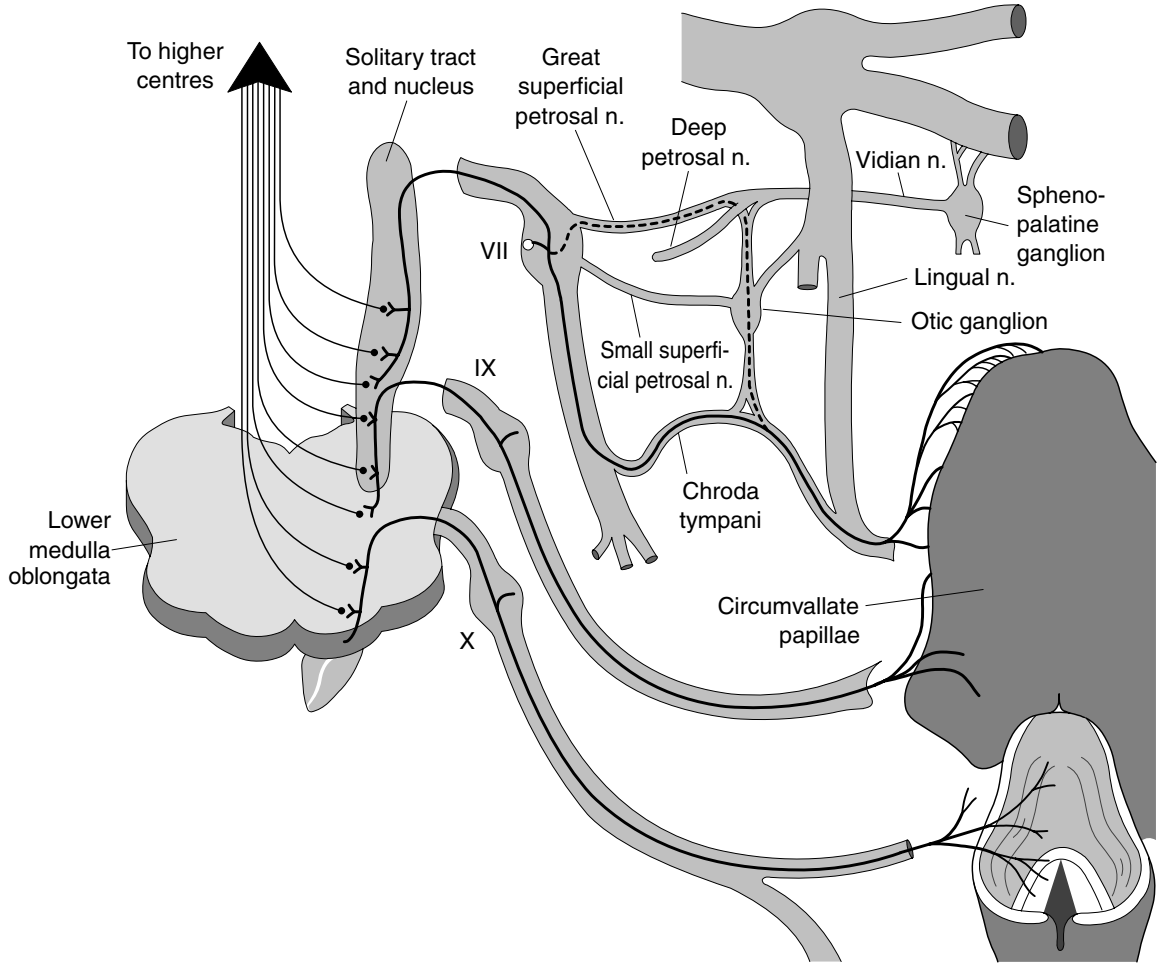

Fig. 42.2. Distribution of cranial nerves to gustatory regions. CN VIII fibres from the geniculate ganglion innervate taste buds on the anterior portion of the tongue and on the soft palate. CN IX fibres from cell bodies within the petrosal ganglion innervate taste buds on foliate and vallate papillae of the tongue, as well as pharyngeal taste buds. CN X fibres from cell bodies in the nodose ganglion innervate taste buds on the epiglottis, larynx and esophagus. (Modified and adapted from Netter, F.H. The CIBA Collection of Medical Illustrations, Vol. 1. Nervous System. Ciba Pharmaceutical Corporation, New York, 1964.)

(termed the thalamic taste nucleus or TTN) (Beckstead et al., 1980; Onoda & Ikeda, 1999). From the TTN, fibres then project to the primary taste cortex, which is located deep in the parietal operculum and adjacent parainsular cortex near somatosensory centres for oral sensation and motor centres for the control of jaw and tongue movement (Pritchard et al., 1986). Functional imaging studies suggest tastants activate insular and perisylvian regions, including the frontal operculum, superior temporal gyrus (opercular part), and inferior parts of the pre- and postcentral gyrus (Gloor, 1997; Faurion et al., 1998). A secondary cortical taste region is located in the caudomedial/caudolateral orbitofrontal cortex, extending several millimetres in front of the primary taste cortex (Rolls, 1995).

Little is known about the role the gustatory cortical regions in the processing of taste information, although none are purely gustatory, as they also contain neurons responsive to touch and temperature (Pritchard, 1991). The orbitofrontal cortex processes information from several sensory pathways (including olfactory, gustatory, and visual), and has been linked to emotion, feeding and social behaviour (Rolls & Baylis, 1994; Rolls et al., 1998). The degree to which taste function is represented on each side of the brain is also poorly understood. In an fMRI study, Cerf et al. (1998) found the superior part of the insula is likely bilaterally innervated; however, significant lateralization of taste function was present in the inferior insula, such that in right-handed subjects there was relatively

more left inferior insula activation, whereas in left-handed subjects the reverse was true.

Classification of gustatory disorders

The classification of gustatory disorders follows a schemata similar to that of olfactory disorders: ageusia: inability to detect qualitative gustatory sensations; i.e. absence of taste; hypogeusia: decreased sensitivity to tastants; dysgeusia: distortion in the perception of a normal taste (e.g. the presence of an unpleasant taste when a normally pleasant tastant is presented); gustatory agnosia: inability to recognize a taste sensation, even though gustatory processing, language, and general intellectual functions are essentially intact.

Clinical evaluation of gustatory function

History

The clinical history for taste dysfunction largely overlaps that described in Chapter 41 for olfactory dysfunction. It is especially important to distinguish alterations in sweet, sour, bitter, and salty perception from changes in the perception of such sensations as chocolate, lemon, chicken, spaghetti, etc., since most 'taste' complaints reflect loss or distortions of the latter sensations which depend upon retronasal stimulation of CN I. Problems with speech articulation, salivation, chewing, swallowing, oral pain or burning, dryness of the mouth, periodontal disease, bruxism and foul breath odour should be noted, along with hearing and balance problems (since previous ear infections and surgery can alter chorda tympani function and produce taste loss or distortions). A determination of recent dental procedures and the patient's history of radiation exposure should also be made. Stomach problems may also be relevant, since acid reflux can damage or irritate taste buds. A careful assessment of medication usage is critical since, as described in detail later in this chapter, a number of drugs, including lipid-lowering agents, antibiotics and antihypertensives, produce significant taste disturbances.

Physical examination and imaging

In the evaluation of the oral cavity, particular attention should be directed towards the teeth and gums, since dysgeusia may result from exudates commonly found in gingivitis or pyorrhea. Inspection of fillings, bridges and other dental work should be made along with inspection of the mucosal surfaces, which may show signs of scarring, inflammation, or atrophy. A whitish lingual plaque can reflect candidiasis, lichen planus, leukoplakia, or food products. Local causes of glossitis include (a) mechanical trauma (e.g. tongue biting, jagged teeth, ill-fitting dentures), (b) irritation (e.g. that due to excessive use of alcohol, tobacco, O_2-liberating mouthwashes or peroxides), and (c) burns. Systemic causes of glossitis include (a) vitamin deficiencies (e.g. B vitamins, C, zinc), (b) anemia (e.g. pernicious, iron-deficiency), and (c) dermatologic syndromes (e.g. Behcet's syndrome, lichen planus, erythema multiforme, aphthous lesions, and pemphigus). Palpation should be performed to detect masses, neoplastic lesions or collections deep in the tongue's musculature. Neurologically, the integrity of CN VII, IX, and X can be evaluated by screening for deficits in non-gustatory functions of these nerves (e.g. facial musculature, swallow, salivation, gag, voice production).

Quantitative gustatory testing

Regional taste testing is needed to establish the function of each of the nerves innervating specific taste bud fields, as whole-mouth tests are insensitive to even complete dysfunction of one or several of the nerves that innervate the tongue. Two general stimulus presentation approaches can be employed. In c*hemical testing*, liquid stimuli are presented to target regions of the tongue or oral cavity via pipettes, Q-tips, or filter paper disks. In e*lectrical testing* (also termed electrogustometry), low levels of electrical current are presented to taste bud fields via small electrodes (Frank & Smith, 1991).

Accurate quantitative taste testing can be quite time consuming, more so for chemical than for electrical testing because of rinsing and stimulus delivery (e.g. intertrial interval) issues. In chemical testing, for example, stimuli representing each of the four basic tastes are typically administered to each side of the anterior (CN VII) and posterior (CN IX) tongue, with rinsing and expectoration following. Thus, a minimum of 16 trials (4 tastants $\times$ 4 tongue regions), as well as 16 rinses and expectorations, are needed to provide a single trial of each taste quality stimulus within the back and front hemilingual surfaces. If a paired blank in a forced-choice trial (e.g. water) is to be presented, then an additional 16 trials are needed. Since multiple stimuli are required to produce reliable responses, a typical taste test requires a considerable number of trials. The regional test used by us employs a micropipette to present 15μl aliquots of suprathreshold tastants (sucrose, citric acid, sodium chloride, and caffeine) that are equated in viscosity to left

and right anterior and posterior tongue regions. A single concentration of each stimulus is presented to each of the four target tongue regions six times, in counterbalanced order, along with a subsequent water rinse. Thus, 96 stimuli and 96 rinses are presented.

Gustatory dysfunction: causes and treatments

Although total loss or markedly diminished whole-mouth gustation exists, such changes are rarely produced by non-metabolic diseases or disorders unassociated with central ischemic or other damage, since regeneration of taste buds can occur and peripheral damage would have to involve multiple pathways to induce taste loss. Thus, while 433 of 585 patients (74%) studied at the University of Pennsylvania with verifiable olfactory loss complained of both smell and taste disturbance, less than 4% had verifiable whole-mouth gustatory dysfunction, and even that dysfunction was limited (Deems et al., 1991).

Regional deficits in taste dysfunction are much more common. For example, in one study sensitivity to three relatively low concentrations of NaCl was measured on the tongue tip and 3 cm posterior to the tongue tip in 12 young (20–29 years of age) and 12 elderly (70–79 years of age) subjects. On average, the young subjects were more sensitive to NaCl on the tongue tip than on the more posterior stimulation site and exhibited, at both tongue loci, an increase in detection performance as the stimulus concentration increased. The elderly subjects, who would be expected to exhibit, at worse, moderate deficits on whole-mouth testing, typically performed at chance level (Matsuda & Doty, 1995).

Most people, including older persons, are unaware of regional taste deficits, despite their wide prevalence. Patients rarely recognize their loss of taste sensation on half of the anterior tongue following unilateral sectioning of the chorda tympani in middle ear surgery. This lack of awareness reflects, in part, the redundancy of the multiple taste nerves, as well as possibly compensatory mechanisms. Anesthetizing or lesioning the chorda tympani (CN VII) unilaterally reportedly enhances taste perception on the rear of the tongue (CN IX), particularly on the side contralateral to that of the anesthesia or lesion (Kveton & Bartoshuk, 1994). The latter phenomenon, which has been interpreted as release of inhibition, probably occurs centrally, since the taste pathways are generally believed not to be crossed until the level of the thalamus.

A wide range of disorders and interventions have been associated with at least some loss of taste function. Mechanisms can include: (a) the release of bad-tasting materials from oral medical conditions (e.g. gingivitis, sialadenitis, oral infections), (b) transport problems of taste chemicals to the taste buds (e.g. caused by excessive chronic dryness of the oral cavity or damage to taste pores from a burn), (c) destruction or loss of taste buds themselves (e.g. from radiotherapy of the oral cavity), (d) damage to one or more neural pathways innervating the taste buds (e.g. Bell's palsy, trauma, dental or surgical procedures), and (e) involvement of central neural structures (e.g. tumour, stroke, multiple sclerosis, epilepsy).

Damage to brainstem structures that subserve taste may produce dysgeusia, although usually not without significant impairment of other cranial nerves or long tracts. Notable brainstem areas involved in taste that are susceptible to injury include the tractus solitarius and its nucleus (where injury produces ipsilateral ageusia) and the pontine tegmentum which involves both gustatory lemnisci (where injury produces bilateral ageusia). Bilateral injury to the thalamus can result in ageusia, although unilateral lesions above the brainstem do not usually cause complete loss of function (likely due to the multiple areas involved in processing taste information). Gustatory disturbance as a result of stroke (either ischemic or hemorrhagic) or demyelination (as seen in multiple sclerosis) (Catalanotto et al., 1984) commonly involve lesions in the gustatory pathway that can be discerned by MRI (Onoda & Ikeda, 1999; Yabe et al., 1995). An example of a stroke-related ischemia in a region of the upper medulla near the right nucleus tractus solitarius that produced altered taste ability is shown in Fig. 42.3 (note that, in this image, the left and right sides are reversed). Taste identification scores and a localized complaint of dysgeusia was greater in the right than in the left CN VII and CN IX lingual fields.

It is noteworthy that gustation may also be affected by injury to cortical association areas outside of the primary gustatory pathways. The concept of left unilateral neglect, typically resulting from contralateral injury to the right hemisphere (e.g. parietal lobe, thalamus, basal ganglia), appears to exist for taste in a manner similar to the visual, auditory, tactile, and olfactory sensory systems (Bellas et al., 1988). A specific syndrome of buccal hemineglect may exist in which patients neglect mouth and food products in the left half of the mouth and are unable to initiate chewing and swallowing when food is in this location (Andre et al., 2000). This syndrome can result in choking or a socially-embarrassing tendency to drool and regurgitate unnoticed food.

Bell's palsy

Although Bell's palsy is frequently associated with ipsilateral loss of taste over the anterior two-thirds of the tongue,

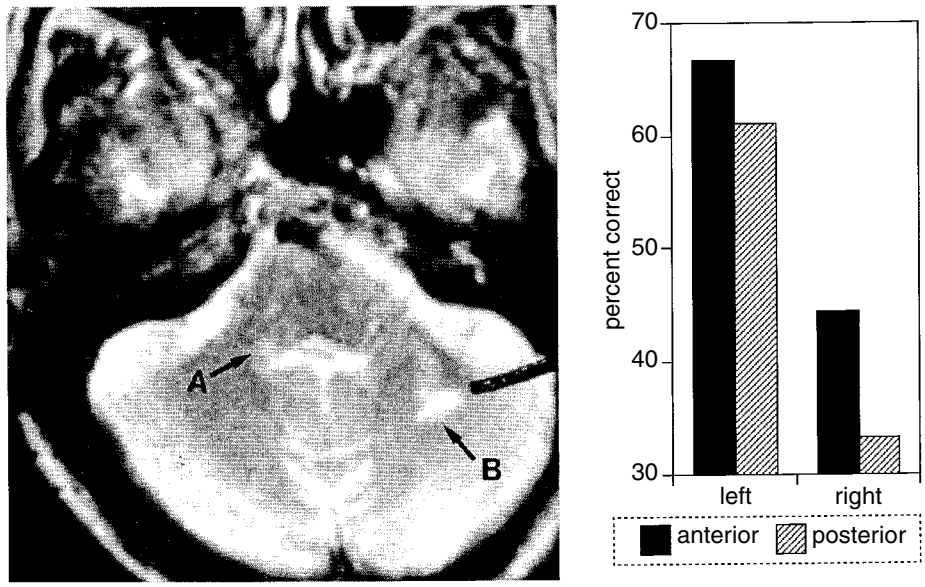

Fig. 42.3. L: Axial T2 (2500/90) MR scan through the upper brain stem reveals a hyperintensive infarct lesion (4×3 mm) in the right medulla (Arrow A). Note also large infarct (15×8 mm) inside the white matter of the left cerebellum (Arrow B). R: Identification scores on the University of Pennsylvania Taste Assessment Test (UPTAT) showing relative decrement on right side of tongue. From a 65-year-old woman with a history of ministrokes who developed a persistent salty/metallic dysgeusia and soreness on the right side of the tongue following a severe 2-day bout of emesis accompanied by marked dehydration and increased blood pressure but unaccompanied by fever. (Copyright © 2001, Richard L. Doty.)

the patient may not recognize this loss. Taste loss in Bell's palsy reflects a lesion somewhere in the neural pathway extending from the pons, along the nervus intermedius portion of the facial nerve (CN VII), through the geniculate ganglion, to the point where the chorda tympani joins the facial nerve in the facial canal. In addition to ipsilateral taste loss and commonly recognized facial weakness, hyperacusis (due to weakness of the stapedius muscle) and impairment of the taste-salivary reflex are present in many cases.

Trauma

Post-traumatic ageusia, as a result of peripheral or central injury, is much less common than post-traumatic anosmia, with solitary ageusia of one or more primary taste modalities occurring in less than 1% of persons with major head injury (Sumner, 1967; Deems et al., 1991). However, the prognosis for post-traumatic ageusia is far better than for post-traumatic anosmia, and recovery from ageusia, when present, usually occurs over a period of a few weeks to months. The etiology of post-traumatic taste dysfunction varies. Head trauma that results in injury to the middle ear, a finding encountered with basilar temporal bone fractures, can potentially result in both ipsilateral impairment of taste and salivary function (by damaging the chorda tympani nerve *and* preganglionic parasympathetic fibres). Trauma to the jaw (e.g. from a punch with a fist) or to the mouth (e.g. from difficult orotracheal intubation, aggressive dental procedures) can result in numbness and taste loss over the anterior two-thirds of the ispilateral tongue, since the chorda tympani-lingual nerve carries both taste and touch information. Compression injury to this nerve may have a greater effect on taste than on fine-touch sensory components, since the chorda tympani fibres of the conjoined nerve are more superficial and posterolateral, and therefore more susceptible to partial transection or pressure on the side of the nerve (Wantanabe et al., 1995). Although presently there are no well-validated treatments for trauma-induced gustatory dysfunction, early steroidal intervention may minimize damage due to inflammatory sequelae in some cases.

Surgical iatrogenesis

A number of surgical procedures have been associated with taste dysfunction. Ear surgery, including tympanoplasty, mastoidectomy, and stapedectomy can damage CN VII (Bull, 1965; Moon & Pullen, 1963; Kveton & Bartoshuk,

1994). The chorda tympani nerve fibres are often stretched or sectioned during surgery for otosclerosis, resulting in taste loss or dygeusia. Such aberrations can last long after the operation (Bull, 1965). Damage to the glossopharyngeal nerve is not uncommon as a result of tonsillectomy, bronchoscopy, or laryngoscopy (Ohtuka et al., 1994; Donati et al., 1991; Arnhold-Schneider & Bernemann, 1987), reflecting the close proximity of the muscle layer of the palatine tonsillar bed to the lingual branch of CN IX (Ohtsuka et al., 1994). Third molar extraction, a very common dental procedure, can damage the lingual nerve and its coexisting chorda tympani fibres, as they lie in close proximity to the mandibular third molars. Such damage is very common; recently the taste function of 17 patients was quantitatively evaluated before third molar extraction, and at 1 month and 6 months thereafter (Shafer et al., 1999). Measurable taste deficits were found in most of these patients that persisted for at least 6 months after surgery, even though complaints of the deficits were rare. Patients with the most deeply impacted teeth exhibited the most severe loss. The chorda tympani nerve may also be injured by the injection of local anesthesia, either by direct contact with the needle or as a result of neurotoxic effects of the anesthetic compound (typically lidocaine and epinephrine) (Shafer et al., 1999; Nickel, 1993). While it is generally assumed that most cases of iatrogenic damage to nerves subserving gustatory function resolve spontaneously over time (reflecting the ability of nerves to regenerate), the limited data available suggest that complete recovery is, in fact, the exception (Bull, 1965; Shafer et al., 1999).

Infections

Local infections have the potential to disturb or impair taste. Important anatomical regions include (a) the teeth and periodontal tissue, (b) the salivary glands, (c) surfaces of the tongue, mouth, and oropharynx, and (d) the middle ear. Importantly, the use of appropriate doses of antibiotic medications may, in and of themselves, have detrimental consequences on taste function (Morris & Kelly, 1993; Schwartz et al., 1996; Adelglass et al., 1998; Magnasco & Magnasco, 1985). Proper oral hygiene and routine dental care should be emphasized to patients as a way of protecting themselves against oral infections.

Medications

Pharmacological agents appear to result in taste disturbances much more frequently than olfactory disturbances. Over 250 medications have been noted in the literature to alter the sense of taste, including antiproliferative drugs, antirheumatic drugs, antibiotic drugs, psychotropic drugs and drugs with sulfhydryl groups, such as penicillamine and captopril (Ackerman & Kasbekar, 1997; Doty et al., 1991; Deems et al., 1991; Bromley, 2000; Schiffman et al., 1998; Schiffman, 1997). Angiotensin-converting enzyme inhibitors are commonly associated with taste disturbance, such as hypogeusia, or excessive metallic, bitter, or sour dysgeusic tastes (Ackerman & Kasbekar, 1997). Such psychotropic medications as amytriptyline, clomipramine, desipramine, imipramine, doxepin, and trifluoperazine as well as protease inhibitors used in the treatment of HIV and AIDS, not only have a taste of their own, but can significantly alter the intensity of other tastants, such as salt and sugar (Schiffman et al., 1998, 1999). Drug-induced taste disorders can, in some instances, be reversed by discontinuance of the offending drug, by employing alternative medications, or by changing drug dosage. However, many pharmacological agents appear to induce long-term alterations in taste that may take months to disappear even after discontinuance of the drug. In situations where xerostomia and excessive dryness occurs as a result of a drug (e.g. an anticholinergic agent), a physician can offer artificial saliva (e.g. Xerolube) to improve comfort, particularly if alternative medications are not available and drug dose cannot be decreased. However, if specific salivary proteins are needed for taste bud maintenance, saliva substitutes may not completely alleviate the chronic effects of lack of saliva on the taste buds.

Although various carcinomas apparently can alter taste function, it is important to recognize that conditioned taste aversions commonly occur among cancer patients undergoing chemo- or radiation therapy. In effect, malaise from the therapy becomes conditioned to the taste of foodstuffs, even if the malaise occurs hours after the intake of the food. In some cases, such conditioned aversions are transient, but in other cases they can be relatively long lasting and can lead to generalized anorexia and cachexia. A strategy for minimizing such aversions is to have the patient consume a novel food immediately before the initiation of therapy. Somehow subsequent conditioned aversions become focused primarily on the novel food, protecting against the formation of conditioned aversions to preferred food items (Chambers & Bernstein, 1995).

Epilepsy

Taste function can be altered by seizure activity, and on occasion gustatory auras appear. Like olfactory auras, gustatory auras usually represent seizure activity predominately within the temporal lobes, although on rare

occasion such activity arises from the orbitofrontal region (Hausser-Hauw & Bancaud, 1987; Acharya et al., 1998; Roper & Gilmore, 1995). Sensations have been reported to include 'peculiar', 'rotten', 'sweet', 'like a cigarette', 'like rotten apples', and 'like vomitus' (for review, see West & Doty, 1995), although many of these 'tastes' likely represent smell sensations miscategorized as tastes by both the patients and their physicians. Usually, taste auras produced by simple partial seizures disappear after the use of antiseizure medications, although this may not be the case with intractable epilepsy. Surgery, e.g. temporal lobe resection, successfully halts most gustatory auras (Acharya et al., 1998).

Other medical causes

There are a number of other causes of gustatory disturbance, including diabetes (where there can be a progressive loss of taste beginning with glucose and extending to other sweeteners, salty stimuli, and then all stimuli), familial dysautonomia (a genetic disorder with lack of taste buds and papillae), hypothyroidism, myasthenia gravis, and Guillain-Barré syndrome. In cases of taste loss secondary to hypothyroidism, thyroxin replacement can normalize taste sensitivity (Mattes & Kare, 1986). In newly diagnosed non-insulin dependent diabetics (based on plasma glucose concentration and glycosolated hemoglobin percentage), quantifiable taste impairment not only exists, but may be somewhat reversible with correction of the hyperglycemia (Perros et al., 1996). Both chronic renal failure and end-stage liver disease have been associated with alterations in taste function, and in some circumstances, transplantation may improve detection thresholds (Bloomfield et al., 1999). It is not clear whether the prodrome or acute headache phase associated with migraine involves definable gustatory phenomena as seen with olfaction. Certain tastes may, however, induce a migraine (Blau and Solomon, 1985). A distinct entity from glossopharyngeal neuralgia, Burning Mouth syndrome (BMS), often referred to as glossalgia or glossodynia, is the subjective sensation of intense burning in the mouth without obvious physical cause that may respond to tricyclic antidepressants (for review, see Tourne & Fricton, 1992). BMS is sometimes associated with dysgeusia.

Fortunately, most cases of idiopathic dysgeusias spontaneously resolve within 2 years (Deems et al., 1996). In some cases, antifungal and antibiotic treatments have been reported to be useful in resolving dysgeusias, although double blind studies of the efficacy of such treatments are lacking. Chlorhexidine, which has a strong positive charge, has been suggested as having possible efficacy for mitigating some salty or bitter dysgeusias when used as mouthwash (Helms et al., 1995).

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43

Disorders of vision

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Vision is the primary sensory input to the brain in terms both of the number of sensory fibres and in the amount of cortical processing area devoted to its analysis. As a consequence there is a protean number of disorders, which range in their pathophysiological mechanisms from disturbed axon conduction, as in optic neuritis, to the abnormal cortical sensory processing apparent in the generation of visual hallucinations. The localization of visual disturbances is often assisted by appropriate analysis and interpretation of visual field defects (Fig 43.1).

Anterior visual pathway

Disorders of the optic nerve

Optic neuritis

Optic neuritis (ON) is a term used to describe an idiopathic optic neuropathy or one resulting from inflammatory, infectious or most commonly demyelinating etiology. In the majority of cases the optic disc is normal on ophthalmoscopy and the term retrobulbar neuritis is used. In those cases in which the optic disc is swollen then the terms papillitis or anterior ON are used.

Clinical features

In typical ON there is usually acute unilateral loss of visual acuity and visual field, which may progress over hours or a few days, reaching its maximal impairment within 1 week. Ninety per cent of cases complain of ocular pain which is noted especially with eye movement, and which may precede the visual impairment by a few days (Lepore, 1991). The visual loss may range from contrast defects with maintained acuity to no light perception. A defect of colour vision is almost universal. Although ON is generally associated with a central scotoma a wide variety of field defects may be found ranging from a central scotoma to altitudinal and nerve fibre layer defects (Keltner et al., 1993). An afferent pupillary defect is present in over 90% of patients with acute ON. The patient is usually aged under 40 years, although ON may occur at any age, and improvement takes place in most patients (90%) to normal or near normal visual acuity over several weeks. There may be persistent subtle residual defects of colour vision, depth perception and contrast sensitivity, which may continue for several months. Subsequent disc pallor may occur but does not correlate closely with the level of visual recovery (McDonald & Barnes, 1992).

ON exemplifies a number of the pathophysiological consequences of axonal demyelination, which may be partial or complete. These include slowed conduction (indicated by the delay in the P100 of the visual evoked potential), and susceptibility of partially demyelinated axons to small increases in local temperature (Uhtoff's phenomenon in which patients with ON become aware of increased visual impairment during exercise), and to mechanical distortion (visual phosphenes on eye movement).

Atypical ON may be unilateral or involve bilateral simultaneous onset of ON in an adult patient. There is often lack of pain and there may be other ocular findings suggestive of an inflammatory process, such as an anterior uveitis. Other features include a worsening of visual function beyond 14 days of onset, in a patient outside the 20–50-year age span. They may also have evidence of other systemic conditions, particularly inflammatory or infectious diseases.

A number of disorders may be associated with typical or atypical ON (Table 43.1).

The evaluation of patients with ON rather depends on whether or not it is a typical or atypical case. Typical ON probably does not necessitate any additional laboratory

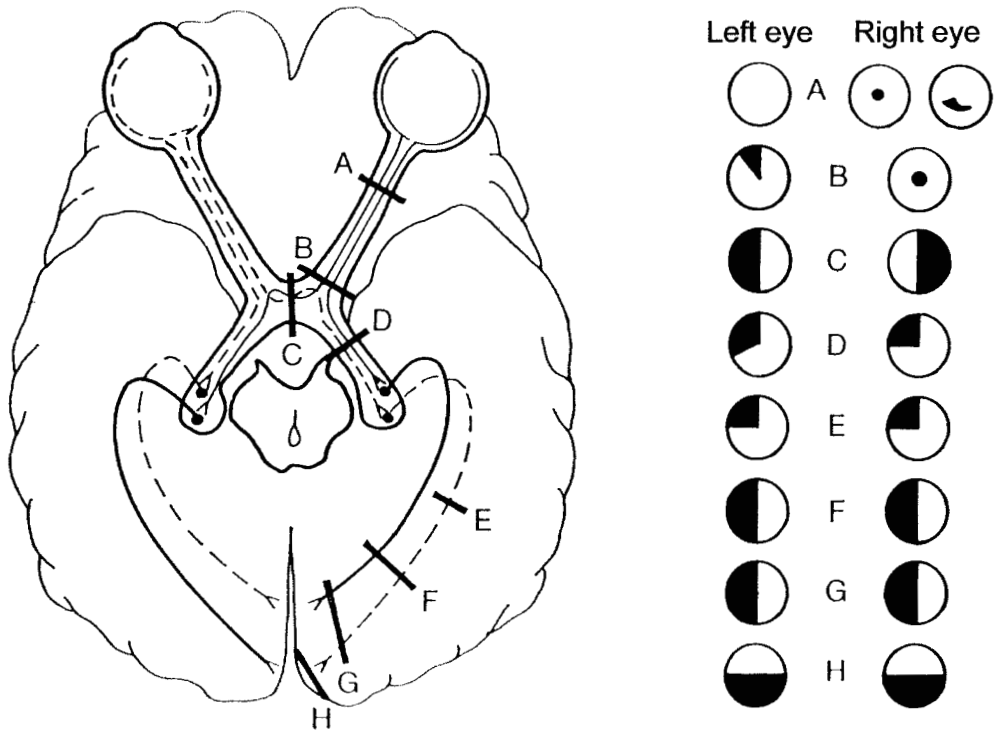

Fig. 43.1. Patterns of visual field loss: (*a*) Optic nerve lesions result in a central scotoma or arcuate defect. (*b*) Optic nerve lesions just prior to the chiasm produce junctional scotoma due to ipsilateral optic nerve involvement with the inferior contralateral crossing fibres (dotted line). (*c*) chiasm lesions produce a bitemporal hemianopia. (*d*) Optic tract lesions result in an incongruous hemianopic field defect. (*e*), (*f*) Lesions of the optic radiation result in either homonymous quadrantanopia or hemianopia depending on the extent and location of the lesion (upper quadrant, temporal lobe; lower quadrant, parietal lobe). (*g*) Lesions of the striate cortex produce a homonymous hemianopia, sometimes with macular sparing, particularly with vascular disturbances. (*h*) Partial lesions of the superior or inferior bank of the striate cortex cause inferior or superior altitudinal field defects, respectively.

investigations, although an abnormal MRI brain scan significantly increases the likelihood of developing multiple sclerosis (Morrisey et al., 1993).

Those patients with atypical ON should have a chest X-ray, laboratory tests including a blood count, biochemistry, and tests for collagen and vascular disease and syphilis serology. Examination of the spinal fluid (CSF) is probably justified in this group of patients.

Management

Although IV methylprednisolone leads to a more rapid visual recovery, at the end of 6 months the visual acuity is no better than without the treatment (Beck et al., 1992). Therefore, steroid treatment of patients with typical ON is unnecessary, unless there is severe ocular pain which cannot be managed with analgesics, or if there is already poor vision in the fellow eye due to some other disease process. The role of beta interferon in preventing the development of multiple sclerosis after a single attack of ON in a patient with an abnormal MRI scan is still unclear.

Ischemic optic neuropathy

Ischaemic optic neuropathy is due to infarction of the optic nerve head, and can be either the more common non-arteritic (idiopathic ischemic neuropathy, anterior ischemic optic neuropathy, AOIN) or arteritic type, when it is usually associated with giant cell arteritis.

Non-arteritic ischemic optic neuropathy

This is characterized by abrupt, painless and generally non-progressive visual loss, associated with an arcuate or altitudinal visual field loss, and tends to occur in patients aged between 45 and 80 years. In nearly all cases, there is optic disc edema, often associated with one or more splinter hemorrhages at the disc margin. Optic atrophy rapidly ensues after the ischemic event. Although previously considered irreversible, as many as 40% of patients may show

Table 43.1. Causes of typical and atypical optic neuritis

Unknown etiology
Multiple sclerosis
Cerebral angiography
CO poisoning
Meningitis
Air embolism
Neoplasm
Tentorial herniation
Cardiac arrest
Systemic lupus erythematosis
Dialysis equilibrium

Table 43.2. Causes of optic atrophy

Deficiency states
Thiamine ('tobacco–alcohol amblyopia')
B12 (pernicious anemia, 'tobacco amblyopia')
Drugs/toxins
Ethambutol
Chlormycetin
Streptomycin
Isoniazid
Chlorpropamide
Digitalis
Chloroquine
Placidyl
Antabuse
Heavy metals
Hereditary optic atrophies
Dominant (juvenile)
Leber's
Associated heredodegenerative neurologic syndromes
Recessive, associated with juvenile diabetes
Demyelination
Grave's disease
Atypical glaucoma
Macular dystrophies

some improvement, and there is a 40% chance of involvement of the fellow eye within 5 years (Ischemic optic neuropathy decompression trial research group, 1995).

The cause of AION remains obscure, although it has been associated with small optic discs (Burde, 1993). The most important aspect of management, since there is no treatment of proven benefit, is to exclude the possibility of the arteritic form, when the fellow eye is particularly vulnerable to similar involvement.

Arteritic ION

The arteritic form of ION usually occurs in giant cell (cranial, temporal) arteritis (GCA), but also rarely occurs in lupus and polyarteritis nodosa. Anyone with AION over the age of 50 should be suspected of having GCA. This often occurs in the context of headache, malaise, weight loss, anorexia, anemia, proximal muscle ache or stiffness, temporal artery tenderness, jaw claudication and fever. These symptoms and signs usually precede the visual loss. The disc infarction is similar to that seen in non-arteritic AION.

A high index of suspicion is required for GCA, and if suspected an urgent erythrocyte sedimentation rate (ESR) and temporal artery biopsy should be arranged. At the same time as the blood for the ESR is taken, the patient should be immediately started on systemic steroids (prednisolone 80 mg daily, plus 200 mg i.v. hydrocortisone immediately). In most patients the ESR is markedly elevated, as is the C-reactive protein. Occasionally the ESR may be normal. A biopsy of the superficial temporal artery should be obtained as soon as possible after the diagnosis has been considered. The biopsy will not be affected by the use of corticosteroids for at least 48 hours. A positive temporal artery biopsy confirms the diagnosis of giant cell arteritis, but in 25% of patients skip areas are found in biopsy specimens, and therefore a negative biopsy may sometimes be obtained.

Steroid treatment should not be tapered or withdrawn too early, since a relapse of symptoms is common. The dose of prednisolone can be gradually tapered after 2–3 weeks to maintain a normal ESR and the patient asymptomatic. Treatment should be continued for at least 6–12 months.

Optic atrophy

Optic atrophy is the final result of a variety of disturbances to the optic nerve or retina. The disc appears pale, which is due to death of the retinal ganglion cells with a dying back of their nerve fibres. This can, therefore, result from diseases which directly involve the ganglion cells themselves or from damage to the axons in the pregeniculate visual pathway, resulting in retrograde atrophy. The development of optic atrophy is usually slow, dependent on its cause. In most instances the optic atrophy is bilateral, the disc appearing chalky-white in colour with clearly defined margins and an absence of disc vasculature and retinal nerve fibres. The differential diagnosis of optic atrophy is considered in Table 43.2.

Heredo-familial optic neuropathies

The hereditary optic neuropathies can either be those which are autosomal dominant or recessive, or those which are due to point mutations in mitochondrial DNA.

The autosomal conditions usually present in childhood with impaired vision and pale optic discs, and due to space restrictions will not be considered further.

Leber's hereditary optic neuropathy (LHON)

This mitochondrial disorder develops primarily in males (approximately 14% women) in the second to third decade of life. It is characterized by an abrupt loss of central vision in one eye usually followed by a loss of vision in the remaining eye which may occur weeks, months or sometimes years later. Occasionally visual loss may occur simultaneously in the two eyes. There is no associated pain on eye movement in contrast to acute ON, and the visual loss is usually permanent with optic atrophy and large absolute central scotomas. However, the fundoscopic picture in the acute phase often shows swelling of the papillary nerve fibre layer, circumpapillary telangiectatic microangiopathy and tortuosity of the retinal vessels (Riorden-Eva et al., 1995).

There is a maternal pattern of inheritance and a number of point mutations in mitochondrial DNA have been identified, particularly at the 11778 location and less frequently at 3460 and 14484 (Mackey, 1994). Patients with the point mutation at 14484 are more likely to show some visual recovery when compared with patients who have a defect at the 11778 (37% as opposed to 4%). It is appropriate, therefore, to carry out genetic testing in those individuals presenting with atypical ON of the appropriate sex and age, even if a positive family history is not available. There is no effective treatment for this condition.

Nutritional and toxic optic neuropathies

Bilateral, slowly progressive central visual loss with centrocaecal scotomas, and usually normal or mild temporally atrophic optic discs characterizes optic nerve failure due to either nutritional deficiency or a toxic cause. Once a family history of one of the hereditary familial diseases has been excluded, this condition should be considered, and is usually due to a combination of alcohol abuse, deficiencies within the B vitamin complex and a frequently high tobacco consumption. With treatment by abstinence of the likely toxic agents and vitamin supplementation, recovery of vision usually occurs, unless the condition is so long standing that optic atrophy has intervened. Recent epidemics of optic neuropathy in Cuba (Sadun et al., 1994), and in West Africa have probably been related to multiple dietary deficiencies.

A wide variety of instances have been cited as causing toxic optic neuropathy which include ethambutol, chloramphenicol, halogenated hyroxyquinolones, lead, isoniazid and vincristine.

Tumours of the optic nerve

Optic nerve sheath meningiomas

Primary optic nerve sheath meningiomas, most frequently found in middle-aged women, are usually unilateral but if bilateral raise the possibility of central neurofibromatosis (NF2). Although most patients will have mild (2–4 mm) proptosis at the time of their initial consultation, patients complain of dimming of vision and decreased colour vision. Visual loss progresses over years with optic disc swelling gradually being supplanted by optic atrophy, with or without the evolution of optociliary venous (retinochoroidal anastamoses) shunt vessels (Dutton, 1992).

The CT picture in patients with these tumours is most often one of diffuse narrow enlargement of the optic nerve, with bulbous swellings of the nerve in the region of the globe and orbital apex. 'Railroad-track' calcification of the optic nerve sheath in the orbit is a characteristic feature. Use of MRI has enabled optic nerve sheath meningiomas to be distinguished from optic nerve gliomas, where the former but not the latter shows that the nerve is readily distinguished from the optic nerve sheath (Lindblom et al., 1992).

Management of patients with optic nerve sheath meningiomas is controversial. While there is general agreement that nerve sheath tumours are most aggressive in children and become progressively more indolent with advancing age, there is no consensus as to the best way to treat these lesions. Clinical resection, particularly when there is intracranial spread, is usually incomplete. These patients rarely die from the meningioma and it is probably best to observe. In some instances radiotherapy has been shown to result in some visual improvement.

Optic nerve gliomas

Optic nerve gliomas, which may also involve the chiasm, are of two distinct types. By far the commonest is the benign glioma of childhood, and the other the malignant glioblastoma in adults (Dutton, 1994). Approximately a quarter of cases occur in the setting of NF-1.

Benign optic nerve gliomas usually present within the first two decades of life, with a peak incidence at 1–6 years of age. The usual presenting manifestations are proptosis and visual loss. The fundus may show either papilledema or optic atrophy. The clinical course of childhood optic nerve gliomas is highly variable. In some tumours enlargement proceeds slowly for a time but then reaches a plateau, while in others the enlargement proceeds unabated (Hoyt & Bagdassarian, 1969). Necropsy has suggested that these tumours are in fact hamartomas rather than true neoplasms. Optic nerve gliomas are generally managed conservatively, although some favour radiation therapy for

lesions with chiasmal involvement and surgery for at least those tumours restricted to the orbit.

Optic nerve gliomas of adulthood are malignant gliomas which usually arise in males aged 40–60 years. These patients often present with a rapid onset of visual failure, which on some occasions may mimic acute ON. The tumour rapidly progresses and the patient usually dies within a short period.

Disorders of the optic chiasm

Approximately 25% of all brain tumours occur in the chiasmal region and since half of these cases initially present with visual loss, an appreciation of the various field abnormalities is important. Although there are a number of other causes for the chiasmal syndrome, eg trauma and demyelination, these are rare. The neuro-ophthalmological signs of a compressive optic chiasm lesion are primarily a field defect and deterioration of visual acuity, which depend on the relationship of the chiasm to the pituitary. The classical field defect of a chiasmal lesion is a bitemporal hemianopia, since pituitary tumours first affect the medial aspect of the chiasm (Holder, 1991). Damage to the lateral aspects of the chiasm due to aneurysm result in nasal field defects. These two observations indicate that the human chiasm is organized in an orderly fashion with medial and lateral aspects of the chiasm comprising fibres originating from the nasal and temporal retinal fibres respectively, which was first anatomically observed by Hoyt and Luis (1963). Hemianopic field defects associated with a compressive optic chiasm lesion may be complete or incomplete and may or may not be symmetrical. Due to the optic nerve being compromised in addition to the chiasm it is unusual to have a bitemporal hemianopia without some reduction in central visual acuity in at least one eye.

The main symptom resulting from the chiasmal syndrome is usually a progressive deterioration of vision, often with associated dimming of the visual field, particularly temporally. A fairly frequent symptom in patients with the chiasmal syndrome is diplopia. This may be a vertical or horizontal separation of images, which usually occurs in the absence of a demonstrable ocular motor paresis. An explanation for this hemifield slide phenomenon is the absence of the temporal field in each eye, which normally acts as a physiological linkage for the two nasal fields. Minor ocular motor imbalance, which does not normally affect binocular fusion, now results in an inability to maintain the two fields in juxtaposition. Some patients will also complain of a disturbance of depth deception, experiencing problems with such tasks as sewing, threading needles or using precision tools. This phenomenon, called chiasmic postfixation blindness, is due to the presence of a blind area beyond the fixation point. The image of objects located in this area falls on the nasal retina which is blind (Kirkham, 1972).

Abnormalities in decussation at the chiasm can also result from congenital disorders. In albinism, in addition to nasal fibres, some temporal fibres also cross at the optic chiasm. The additional crossed fibres result in a systematic shift of the line of decussation into the extra foveal temporal retina. Albinism has many phenotypes and is expressed as a hypopigmentation of the skin, hair and eyes in oculocutaneous albinism (OC) and of the eyes only in ocular albinism (OA). Oculocutaneous albinos can be either tyrosinase positive or negative and further phenotypic subdivisions have been documented (Abadi & Pascal, 1989). There is considerable variability in the visual disorders suffered by albinos. All patients suffer loss of visual acuity, which is invariably associated with foveal hypoplasia. Albinos can also suffer photophobia and nystagmus, the latter contributing to reduced acuity (Abadi & Pascal, 1991). It should be noted, however, that acuity is also reduced in the rare cases where patients are able to fixate, showing that nystagmus alone does not underlie the acuity loss (Abadi & Pascal, 1991). Usually, albinism can be readily diagnosed with fundoscopy and iris transillumination, but some cases can be more difficult to detect. The most reliable measurement that detects the albino aberrant visual projections is the VEP, which has been shown to diagnose patients in 97/98 cases. As nystagmus is often present, however, pattern-onset VEP has revealed the most reliable results in adults (Apkarian, 1992). Appropriate stimulus selection has also proved effective in detecting albino pathway 'misrouting' in infants, so early detection is possible with VEPs (Apkarian et al., 1991). Visual stimulation during fMRI has also proved effective in documenting the albino visual projections (Morland et al., 2001).

Stereopsis was thought to be absent in all patients with congenital chiasmatic abnormalities because fibres representing the central visual field from both eyes project to different hemispheres. There has been one report, however, that documents stereopsis in approximately 10% of albinos, who also had reasonably stable fixation and ocular alignment. This interesting observation implies that adaptive mechanisms involving interhemispheric communication must develop to mediate this aspect of binocular vision (Apkarian, 1996; Zeki & Fries, 1980).

Disorders of the optic tract, radiation and occipital lobe

Optic tract lesions

Lesions of the optic tract, although rare (less than 3% of visual field defects in a series of 100 homonymous hemianopias), often produce specific signs and visual field

abnormalities which allow definitive diagnosis (Newman & Miller, 1983). The optic tract is the first point in the visual pathways where the ipsilateral temporal and contralateral nasal retinal nerve fibres come together, and so the field defect is usually a partial or complete homonymous hemianopia. When partial there is often gross incongruity between the visual field defects found in each eye, which may also be found with lesions of the lateral geniculate nucleus and more rarely the optic radiations. Ophthalmoscopically optic pallor due to retrograde degeneration may be observed. This takes a characteristic form with band or 'bow tie' atrophy in the eye opposite to the lesion due to loss of nasal retinal fibres. Ipsilateral to the lesion, temporal pallor is observed.

Occipital lobe

On reaching the occipital lobe there is a high degree of order in the fibres of the optic radiation and lesions, which are usually due to infarction, trauma or tumour, produce congruent field defects which are homonymous. The only features of the field defect which help localize the lesion to the occipital lobe, rather than the anterior optic radiation, is the presence of macula sparing or a temporal crescent in a homonymous hemianopia.

In macula sparing there is preservation of the visual field within a region of 1–2° up to 10° around the fixation point in the hemianopic field. In the more usual situation the hemianopic field is split along the vertical meridian through the fixation point (macula splitting). Although it has been argued that macula sparing is a result of poor fixation during visual field testing, this would only account for about 1–2° of sparing (Bishoff et al., 1995). Despite the continued controversy concerning the cause of macula sparing there appear to be two main anatomical factors which may explain this phenomenon. Firstly, there is evidence that there is a vertically orientated median strip centred on the fovea in which retinal ganglion cells project either ipsilaterally or contralaterally (Fukuda et al., 1989). The macula, therefore, is bilaterally represented but since this strip is at most responsible for 2° of the central field this is insufficient to explain many cases of macula sparing. The second more probable explanation is the rich anastomotic network between terminal branches of the middle cerebral artery and the posterior cerebral artery which supply the area of the striate cortex containing the macula representation in the occipital pole (Sugishita et al., 1993).

Lesions at the pole of the occipital lobe result in small homonymous central scotomas, which may lead the patient to present with reading difficulties and may be missed if only the peripheral field is examined to confrontation. The central 10° of the primary visual cortex (Horton & Hoyt, 1991). More anterior lesions of the occipital lobe involving the more anterior part of the calcarine fissure, which contains the representation of the unpaired peripheral nasal retina, results in a monocular defect in the peripheral temporal field, called the 'temporal crescent', 60–90° from the fixation point. However, it should be remembered that the most common cause for such unilateral peripheral visual field defects is a retinal lesion rather than an intracranial one. The converse of this defect may be found in which there is sparing of the temporal crescent in a homonymous hemianopia. This usually occurs with a vascular lesion affecting the more posterior striate cortex (Benton et al., 1980).

Bilateral lesions of the occipital lobes may result in varying degrees of homonymous hemianopia, ranging from small bilateral central homonymous scotomas to complete blindness. The extent of the abnormality may vary between the two halves, being partial or complete, hemianopic or quadrantic. Sometimes restricted bilateral lesions of the occipital lobes may result in small bilateral homonymous central scotomas. Altitudinal field defects usually occur as a result of trauma (rarely tumours or vascular events) involving upper or lower occipital poles bilaterally (Holmes, 1918).

fMRI, which can spatially localize brain blood oxygenation accurately, can be used to investigate the effect of lesions of the radiation on cortical activity. It is possible, therefore, to use fMRI during visual stimulation to determine the reason for visual field loss, when damage to the cortical grey matter is absent. Retinotopic mapping fMRI methods, that have become commonplace in the research of normal visual function (DeYoe et al., 1996), may become increasingly useful in investigating visual field defects resulting from occipital damage (Baseler et al., 1999).

Cortical blindness

Cortical blindness usually indicates selective involvement of the occipital visual cortex. The essential features are (i) complete loss of all visual sensation, (ii) loss of reflex lid closure to threat, (iii) normal pupillary light reactions, (iv) normal retina and full extraocular eye movements. The commonest etiology is hypoxia of the striate cortex. Patients with cortical blindness may sometimes be unaware of their visual defect (anosognosia) and vigorously deny it, known as Anton's syndrome. This may occur with lesions elsewhere causing total blindness. There is no satisfactory explanation for this syndrome and the various hypotheses are discussed by Lessell (1975). Several hypotheses have been proposed to explain this syndrome including an alteration in emotional reactivity,

'psychiatric' denial as an accentuation of a common response to illness, a memory disorder for example in Korsokoff's syndrome, and associated lesions elsewhere in areas of the brain responsible for the recognition and interpretation of visual images.

Disorders of higher visual processing

Residual visual function in hemianopias

In his classic work Holmes (1918) showed that the striate cortex damage results in a complete hemianopia. However, incomplete damage to the occipital lobe may result in retention of some aspects of visual perception, the most commonly observed being the ability to perceive small moving objects in the homonymous hemianopia (Riddoch, 1917; Zeki & ffytche, 1998). Riddoch's phenomenon may be the first evidence of recovery of a homonymous hemianopia. This is then usually followed by perception of static targets and finally colour perception returns. Unfortunately, the Riddoch phenomenon is not only found in occipital lesions, but has been reported in patients with lesions in the anterior visual pathways (Safran & Glaser, 1980).

The retention of the ability to localize objects in space and limited pattern discrimination in monkeys in whom both striate cortices had been removed, led to interest in the possible visual functions in the hemianopic field of human patients (Weiskrantz, 1986). Since these patients are unaware of any residual visual capacity and appear blind by standard clinical perimetric methods this visual capacity has been termed 'blindsight' (Weiskrantz et al., 1974; Weiskrantz, 1986). Using forced-choice discrimination methods such patients have revealed their ability to locate stimuli both by saccadic eye movements and by pointing (Cowey & Stoerig, 1991). The extent of the residual visual capacity is varied amongst the patients so far reported, and as yet there is poor correlation with the precise location of lesions in the occipital lobe.

Residual visual function also extends the ability to discriminate between stimuli on the basis of their motion (Barbur et al., 1980; Blythe et al., 1986a, 1987; Morland et al., 1999; Zeki and ffytche, 1998), orientation (Morland et al., 1996; Weiskrantz, 1986), spatial periodicity (Weiskrantz, 1986), and spectral content (Blythe et al., 1987; Morland et al., 1999; Stoerig & Cowey, 1989, 1992). The extent to which different patients have conscious experience of such visual abilities is variable (Weiskrantz, 1986; Weiskrantz et al., 1974) and in individual patients is dependent on the characteristics of the visual stimulus (Morland et al., 1999; Zeki & ffytche, 1998). In one patient with damage to striate cortex, stimulation with visual motion activates extrastriate cortical areas (Barbur et al., 1993; Zeki and ffytche, 1998). However, a general consistency between activity in extrastriate cortex and residual motion processing in hemianopes has yet to be revealed in studies of more than one patient (Barton & Sharpe, 1997).

Reports have documented a reduction in the size of scotomata in patients with cortical lesion following training (Zihl & von Cramon, 1979). Patients were trained to detect targets present within, but near, the boundary of their scotomata. This resulted in an increased visual sensitivity within the trained region that transferred interocularly and to different stimulus attributes such as colour (Zihl & von Cramon, 1979). Further studies also revealed that scotomata could be reduced when patients are trained to saccade to targets in their blind visual fields (Zihl, 1981; Zihl & von Cramon, 1985). Recent work has revealed that hemianopic patients visually scan natural images differently from normal (Pambakian et al., 2000). The degree of abnormality in the scan paths was greatest for patients with the longest period between the lesion onset and time of testing, which suggests development of coping strategies. In addition to the training implemented by Zihl's group (Zihl, 1981; Zihl & von Cramon, 1979, 1985) it may also be possible to train patients to scan scenes so the effects of the visual field defects may be minimized and adaptive strategies may be enhanced (Zihl, 2000; Pambakian et al., 2000).

Functional visual loss in prestriate lesions

There is increasing evidence from electrophysiological studies in primates that once initial processing of visual information has occurred in the striate cortex, segregation of different properties of the visual stimulus occurs in the prestriate cortex (Zeki & Shipp, 1988; Zeki, 1993). This cortical region contains a number of individual representations of the contralateral hemifield, each containing neurons with a particular response characteristic. For example, some areas contain neurons which are selective for colour (V4), and another for motion (V5, middle temporal gyrus, MT). There appears, therefore, to be parallel processing of different aspects of visual information in these various cortical areas before an organized synthesis of the visual scene can be generated. Specific lesions in one or other of these areas might be expected to give rise to an appropriate specific loss of a visual modality. In this section such specific losses are described for colour (achromatopsia), movement (akinetopsia) and faces (prosopagnosia).

Colour

Acquired disorders of colour vision due to lesions of the central nervous system are of two types. In one the colour sense is normal but the naming and recognition of colour is impaired. This can occur as part of an aphasia e.g. Wernicke's or anomic, in the syndrome of alexia without agraphia or as one feature of visual agnosia (see below). In the second type there is an inability to see colours (dyschromatopsia or achromatopsia) (Zeki, 1990).

Patients with lesions in the region of the lingual and fusiform gyri, which lies in the anterior inferior region of the occipital lobe and is considered to be the human homologue of the monkey visual area V4, complain that they cannot see colours and that everything looks grey or in varying shades of black and white (Meadows, 1974a). They are unable to identify the figures on pseudoisochromatic test plates, although able to correctly name the colours of brightly coloured objects. In addition they are unable to perform normally on the Farnsell–Munsworth 100-hue test. Patients with cerebral dyschromatopsia may or may not realize that their colour sense is impaired. Other functions such as visual acuity, object recognition and depth perception are all normal, but there is often an associated visual field defect, usually a bilateral superior homonymous quadrantanopia sometimes also associated with prosopagnosia.

There is good evidence that cortical lesions disrupt selective aspects of colour processing. One patient with reduced colour discrimination appeared to have colour naming responses that were consistent with a lack of colour constancy (Kennard et al., 1995). Colour constancy describes the ability to perceive an object colour as constant when illumination changes to cause a change in the spectral distribution of light reflected from that object. Neurons in the macaque visual area V4 exhibit colour-constant responses, whereas those in V1 do not (Zeki, 1980). This evidence suggests that the lesions of the lingual and fusiform gyri in the patient documented by Kennard et al. (1995) included the human homologue of V4. Functional imaging experiments on normal observers have also implicated the same cortical regions as colour selective (McKeefry & Zeki, 1997; Zeki et al., 1991). Other patients have also been shown to lack colour constancy, some of them with lesions to putative V4 (Clarke et al., 1998), while in other patients lesions appeared exclusive of this cortical area (Ruttiger et al., 1999).

Movement

A case has been reported of a woman who exhibited a selective deficit of movement perception (Zihl et al., 1983). She had no impression of movement in depth and could only discriminate between a stationary and a moving target in the periphery of her otherwise intact visual fields. The patient had bilateral lesions involving the lateral occipito-parieto-temporal junction, which PET has revealed is specifically activated during motion perception and, therefore, appears to be the human homologue of the monkey visual area V5 (Zeki, 1991).

Moving boundaries that are defined by second order features (as opposed to luminance boundaries) are not discriminated normally in patients with lesions in lateral occipital regions (Plant & Nakayama, 1993). A more recent study, however, appears to indicate a considerable overlap in the cortical areas responsible for processing first and second order motion (Greenlee & Smith, 1997).

Visual associated agnosia

The term visual agnosia refers to a rare condition in which there is an inability to recognize and name or demonstrate the use of an object presented visually, in the absence of a language deficit, general intellectual dysfunction or attentional disturbances. The patient is, however, able to name the object when using other sensory modalities such as touch or sound. Teuber (1965) described visual agnosia as a 'percept stripped of its meaning'.

Visual agnosia has been classified in a number of different ways. One classification depends on the specific category of visual material which cannot be recognized, for example a disturbance of recognition of objects (object agnosia), faces (prosopagnosia) and colour (colour agnosia) which may occur in isolation or in various combinations. Lissauer's (1890) classic dichotomous classification of visual agnosia is, however, still relevant today. When a patient is able to copy and match-to-sample objects that he fails to name or recognize visually, his agnosia is termed associative; if he fails on all these tasks or demonstrates perceptual abnormalities his agnosia is termed apperceptive (Tranel & Damasio, 1996).

Apperceptive visual agnosia

Well documented cases of apperceptive visual agnosia are rare (Warrington & James, 1988). They show an inability to copy or match-to-sample drawings which they cannot recognize, and recognition and matching of all other stimuli which demand shape or pattern perception is also affected. Most cases have been associated with cerebral damage due to cardiac arrest, carbon monoxide poisoning or bilateral cerebrovascular infarction. Less severe apperceptive disorders are associated with unilateral and generally right cerebral damage.

Associative visual agnosia

Unlike apperceptive agnosia there is no doubting the existence of associative agnosia as a definite neuropsycholog-

ical syndrome since a number of well-documented cases have been reported (Humphreys & Riddoch, 1993).

These cases exhibit the ability to copy and/or match-to-sample items which they fail to identify visually, without any evidence of primary sensory or sensory motor disturbance. The syndrome is commonly associated with colour agnosia, prosopagnosia and alexia in various combinations. This may reflect task and processing similarities between recognition of faces and objects, resulting in defects of both. Alternatively, lesions giving rise to object agnosia may involve adjacent areas specific for colour or face processing.

Patients with associative visual agnosia show an increasing difficulty in identifying an object when presented as the object itself, as a picture or a line drawing. Auditory and tactile recognition is usually intact. There is no uniformity about the field defects which are often present. A further commonly found feature is the strong tendency these patients have to perseverate either previously viewed objects or, more commonly, the verbal response to them.

A number of hypotheses to explain visual agnosia have been proposed. Geschwind (1965) suggested that agnosia was not a defect of a unitary process of recognition, but rather a special form of a modality-specific naming defect. Using a disconnection explanation similar to that given for dyslexia without dysgraphia and colour agnosia, he suggested that the confabulatory verbal responses are due to a pathological disconnection of the intact speech area from the intact sensory area. Ratcliff and Newcome (1982) have argued, however, that since object recognition, as opposed to naming, is mediated by the semantic system, disconnection must be a visual-semantic one and not merely visual–verbal. However, patients with surgically sectioned cerebral commisures are able to extract meaning from words and pictures when visual input is restricted to the right hemisphere, making it unlikely that this disconnection of an intact right hemisphere would be sufficient to cause agnosia.

A second hypothesis, proposed by Warrington (1975), suggests that the disorder is due to a disturbance of access to visual semantic information itself, since in her patient 'all links of associations were lost, not just verbal' and hence a visual–verbal disconnection was not a sufficient explanation. She regarded preservation of the ability to make same/different judgements with respect to photographs of objects taken from different angles as evidence of preserved 'perceptual classification'. However, other authors have suggested a defect of visual categorization in their patients (Albert et al., 1975). It has to be concluded that both the anatomical basis and clinical criteria for associative visual agnosia are still uncertain, but excellent reviews are available by Farah (1990) and Tranel and Damasio (1996).

Prosopagnosia

Prosopagnosia is a specific inability to recognize familiar faces despite a normal ability to recognize everyday objects, and is therefore, different from visual agnosia (Meadows, 1974b). Although facial recognition is a visual pattern discrimination of great complexity patients with prosopagnosia have no difficulty in discriminating unfamiliar faces and matching faces correctly. Indeed there appears to be no disturbance of visual perception, patients being able to accurately recognize many stimuli which are visually more complex than human faces. It appears that the disorder is not specific to faces but to complex non verbal visual stimuli that belong to a group where individual members are visually similar and yet individually different. For example, prosopagnosics cannot recognize their own car and do not recognize different makes of car; however, they can distinguish different classes of vehicle, e.g. ambulance or fire engine. Similarly a case has been reported of a farmer suddenly becoming unable to distinguish individual animals within his herd and of a bird watcher developing an inability to recognize different species of birds.

Prosopagnosics appear, therefore, to be unable to match a current visual stimulus within a class such as faces, with the memory traces of other members of this specific class which have been built up from past experience (De Renzi, 1997). Pathophysiologically there is disorder of visually triggered contextual memory. Under normal circumstances after multiple exposures to a stimulus, a template of the stimulus is stored, perhaps at several levels, but in prosopagnosics there is a defect in activating this template. Recent brain imaging studies have suggested that these processes involve the inferior temporal lobe and also the ventrolateral frontal cortex (Haxby et al., 1996). Electrophysiological recordings from superior temporal sulcus in monkeys have identified neurones which are specifically responsive to faces, cells which may well be involved in the facial recognition process (Perrett et al., 1984).

Most cases of prosopagnosia are due to infarction, head injury or hypoxia resulting in bilateral lesions in the ventromedial aspects of the occipitotemporal region (Damasio et al., 1982).

Visual illusions

Visual illusions occur when the visually perceived target appears altered in size, shape, colour, position in space and in number of images (Kölmel, 1993). The illusory type of

defects may occur in the entire field of vision, or may effect only the object or the background. The term 'dysmetropsia' indicates the apparent smallness (micropsia), largeness (macropsia) or irregularity of shape (metamorphopsia) of objects. Dysmetropsia usually occurs as a result of retinal disease due to distortion of the relative distance between rods and cones. However, these distortions can also occur as a result of cortical dysfunction, for example in the aura of migraine or epilepsy, chiasmic compression or focal cerebral lesions. Visual allesthesia is a transfer of visual images from one half field to the other (Jacobs, 1980). There may also rarely be an inversion of the visual scene or tilting of the environment in patients with the lateral medullary syndrome (Wallenberg's syndrome) (Hornstein, 1974) . This relates to a disturbance of the vestibular inputs required for normal visual perception.

Visual hallucinations

Visual hallucinations occur under many circumstances, eg drug withdrawal, anoxia, migraine, infection and schizophrenia in addition to those related to focal neurological disease. Those in the latter category may be unformed, consisting of flashes of light (coloured or white), lines, simple shapes or they may be complex highly organized hallucinations of people, objects, etc. (Kölmel, 1993).

Although it is considered that simple visual hallucinations signify involvement of the occipital lobe and complex ones involvement of the temporal lobe this is not always the case, for example complex hallucinations have been observed by patients with hemianopias due to occipital lobe lesions (Kölmel, 1985).

It has long been considered that visual hallucinations could result from irritative foci analogous to epileptic discharges, and certainly electrical stimulation of the occipital and temporal lobes (Penfield and Perot, 1963) supports this suggestion. Other mechanisms in some cases may be a release phenomenon to be found in the context of sensory deprivation (Charles Bonnet syndrome), in which visual cortical areas are deprived of normal visual impulses so releasing cortical activity which normal visual inputs keep suppressed (ffytche et al., 1998) This is the explanation usually given to hallucinations occurring in elderly patients who have impaired vision (Teunisse et al., 1995). However, the term 'peduncular hallucinations' was first described by L'Hermitte (1922) to describe visual hallucinations which appear animated, slow moving, cartoon-like and are usually frightening for the patient. This type of hallucination is usually associated with inversion of the sleep–wake cycle, with diurnal somnolence and nocturnal insomnia, and occurs with lesions in the upper brainstem (McKee et al., 1990).

Palinopsia

Palinopsia is a rare disorder in which there is persistence (perseveration) or recurrence of visual images after the exciting stimulus has been removed (Bender et al., 1968). Although in the literature both perseveration and recurrence of visual images have been lumped together under the term palinopsia it has been argued that they may be distinct (Blythe et al., 1986b). It most commonly occurs during the progressive evolution or resolution of a homonymous hemianopic field defect, usually resulting from a posterior cerebral hemisphere lesion due to neoplasia (Bender et at, 1968), vascular disease or trauma.

Bender et al. (1968) suggested four possible mechanisms for this phenomenon: sensory seizures, psychogenic elaboration or fantasies, visual after-images or hallucinations. Although some patients with palinopsia have had seizures, most have no evidence of seizure activity on the electroencephalogram and the palinopsia does not respond to treatment with anticonvulsants. Patients with palinopsia show no signs of psychopathology and, therefore, it is unlikely that they are due to psychogenic collaborations. Similarly, there is no evidence that visual after-effects in patients with palinopsia are enhanced and such an explanation would not explain the late recurrence of the image (by some several minutes) which occurs in some patients. However, palinopsia may be a type of release phenomenon as described for visual hallucinations. In favour of this possibility is a fact that formed release hallucinations can occur in patients with palinopsia and that in both conditions there is evidence of an interruption of cortical visual processing.

Specific types of palinoptic phenomena are illusory visual spread and polyopia. In illusory visual spread (Critchley, 1951) there is an extension of visual perception over an area greater than that excited by the object presented to the observer. In the time domain visual perseveration of moving objects has also been reported and one patient experienced accelerated movement of a perseverated image.

In instances of usually right-sided occipital lesions patients may experience monocular diplopia or more commonly polyopia (the seeing of multiple images) which persist whichever eye is closed. Rare cases of cerebral induced monocular diplopia emphasize the importance of ensuring that this phenomenon is not present in patients complaining of diplopia. Other causes for monocular diplopia include ocular causes such as corneal irregularities, iris lesions and retinal detachment.

Certain cases of polyopia may be due to epileptic phenomena (Bender & Sobein, 1963) but Bender (1945) in a description of four cases tried to explain the phenomenon as a result of impaired fixation.

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Oculomotor control: normal and abnormal

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An approach to understanding eye movements best begins by considering how they serve vision (Leigh & Zee, 1999). One class of eye movements brings objects of interest onto the fovea and includes saccades and quick phases of nystagmus, which are the fastest of eye movements and allow us to rapidly change our line of sight. A second class of eye movements holds images steady on the fovea and includes pursuit, which allows us to track small objects moving across our visual environment, and vestibular slow phases, which hold images steady on the fovea during head motion. Optokinetic slow phases (OKN, full-field visual following) also help stabilize gaze during head rotation. Vergence eye movements rotate the eyes in opposite directions; they bring the images of an object of interest onto both foveae at once, and then keep them there.

Head motion is of two types: angular (rotations), sensed by the semicircular canals, and linear (translations) sensed by the otoliths. For head rotations, horizontal (yaw), vertical (pitch) and, roll (ear to shoulder), compensatory slow phases in the orbit must be equal and opposite to the angular motion of the head. For head translations, fore–aft, up–down or side-to-side, slow phases must be scaled to the location of the point of regard; the closer the target the greater the amplitude of the compensatory slow-phase for a given amount of translational motion. During natural movements of the head, rotational and translational vestibular reflexes work together with the visual-following reflexes, OKN, pursuit and vergence, so that subjects can maintain their line of sight on the particular location of interest in three-dimensional space.

Oculo-motor control signals

To interpret abnormal ocular motility it is helpful to understand the way the central nervous system controls eye movements under normal circumstances (Leigh & Zee, 1999). Here, we review the normal patterns of innervation for moving the eyes to change gaze accurately, and for holding the eyes steady to maintain gaze on a stationary object of interest. The major hindrance to rotation of the globe is orbital viscosity because the moment of inertia of the globe is relatively small. For rapid eye movements (saccades and quick phases of nystagmus), a powerful contraction of the extraocular muscles is necessary to overcome viscous drag. This is accomplished by a phasic increase in the frequency of neural discharge called the pulse of innervation. Once the eyes are brought to their new position they must be held there against elastic-restoring forces of the orbital tissues, which would return the globe to the primary position. Preventing this centripetal drift requires a sustained contraction of the extraocular muscles. This is produced by a tonic level of neural activity called the step of innervation. The oculomotor control signal for saccadic eye movements is this pulse-step of innervation (Fig. 44.1). This pattern of activity is reflected in the discharge of both ocular motoneurons and the eye muscles themselves.

The immediate premotor command for the saccadic pulse is generated by burst neurons, which for horizontal saccades lie within the pontine paramedian reticular formation (PPRF) and for vertical saccades lie in the prerubral fields of the mesencephalon in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). Burst neurons discharge at high frequencies beginning just before and time locked to the saccade itself. Otherwise they are silent because of inhibitory inputs from omnipause neurons, which are located between the rootlets of the abducens nerve in the nucleus raphe interpositus. Omnipause neurons discharge tonically except during saccades in any direction, when they pause and allow burst neurons to generate a saccade. A separate class of saccade-related neurons, inhibitory burst cells, are located in the

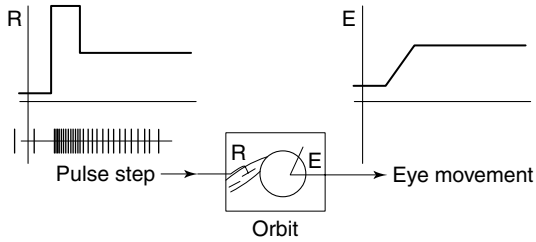

Fig. 44.1. Neural signal for a saccade. (Right) Eye movement; E is eye position in the orbit, and the abscissa scale represents time. (Left) Neural signal sent to the extraocular muscles to produce the saccade. The vertical lines indicate the occurrence of action potentials of an ocular motoneuron. The graph above is a plot of the neuron's discharge rate (*R*) against time. It shows the neurally encoded pulse (velocity command) and step (position command). (From Leigh & Zee, 1999.)

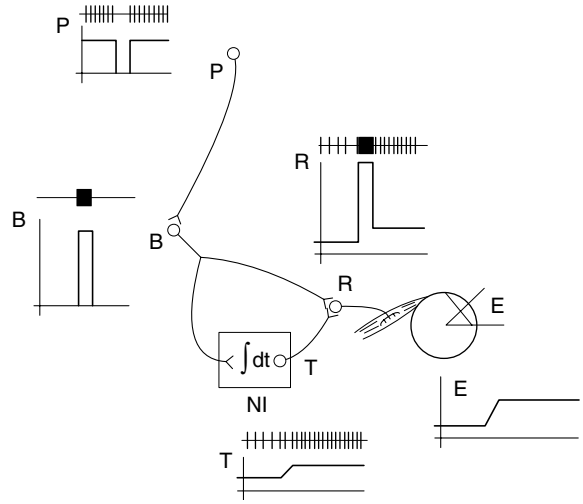

Fig. 44.2. Relationship between pause cells (P) and burst cells (B) during saccades. Pause cells cause discharging just before each saccade, allowing the burst cells to generate the pulse. The pulse is integrated by the neural integrator (NI) to produce the step. The pulse and step combine to produce the innervational change on the ocular motor neurons (OMN) that produces the saccadic eye movement (E). Vertical lines represent individual discharges of neurons. Underneath the schematized neural (spike) discharge is a plot of discharge rate versus time. (From Leigh & Zee, 1999.)

medulla, they act as a brake, and help stop saccades so that they do not overshoot the target.

The step of innervation is created by a neural gaze-holding network or neural integrator that integrates, in the mathematical sense, the saccadic eye velocity command to produce the appropriate position-coded information for the ocular motoneurons. The medial vestibular nucleus and the adjacent nucleus prepositus hypoglossi are important for the neural integration of horizontal oculomotor signals (Arnold et al., 1999). For integration of vertical oculomotor signals the interstitial nucleus of Cajal, coupled with activity in the vestibular and prepositus nuclei (Helmchen et al., 1998) are important. The flocculus of the cerebellum also contributes to the integration of both vertical and horizontal eye movements (Zee et al., 1981); its input is in part from cell groups that lie in the paramedian tracts (PMT) adjacent to the MLF along its extent from the rostral medulla to the caudal midbrain (Büttner-Ennever & Horn, 1996; Nakamagoe et al., 2000). All types of versional eye movements require a step component of innervation to hold gaze at the end of a movement; they share a common neural integrator. Fig. 44.2 shows the relationship between burst neurons, pause neurons, and the neural integrator for the generation of saccadic commands.

Control of horizontal conjugate gaze

The abducens nucleus itself is the site of assembly of the premotor commands for horizontal conjugate eye movements (Büttner-Ennever & Büttner, 1988). The nucleus contains two main types of neurons: abducens motor neurons, with axons that innervate the lateral rectus muscle; and abducens internuclear neurons, with axons that project, via the contralateral medial longitudinal fasciculus (MLF), to the medial rectus subdivision of the contralateral oculomotor nucleus (Fig. 44.3). Lesions of the abducens nucleus, therefore, cause a conjugate gaze palsy, an inability to move the eyes beyond the midline with any type of ipsilaterally-directed versional eye movement (saccadic, pursuit, optokinetic or vestibular). There may also be some horizontal gaze-evoked nystagmus on looking contralateral to the side of the lesion, probably due to involvement of fibres of passage crossing to the contralateral abducens nucleus from the ipsilateral medial vestibular nucleus, or the involvement of the PMT cell group (Müri et al., 1996). Lesions of the MLF, on the other hand, deprive the ipsilateral medial rectus of its innervation during versional eye movements. This leads to paresis of adduction during conjugate gaze but with intact adduction during convergence: internuclear ophthalmoplegia (INO) (Gamlin et al., 1989). There is often a nystagmus in the abducting eye, which may reflect involvement of the PMT cell group adjacent to the MLF, or commissural pathways connecting the two neural integrators on either side of the brain stem. In some cases of INO the abducting nystagmus reflects an adaptive response to the patient habitually fixing with the paretic eye. If a 'conjugate' gaze palsy is not perfectly conjugate, a coexisting abducens nerve lesion

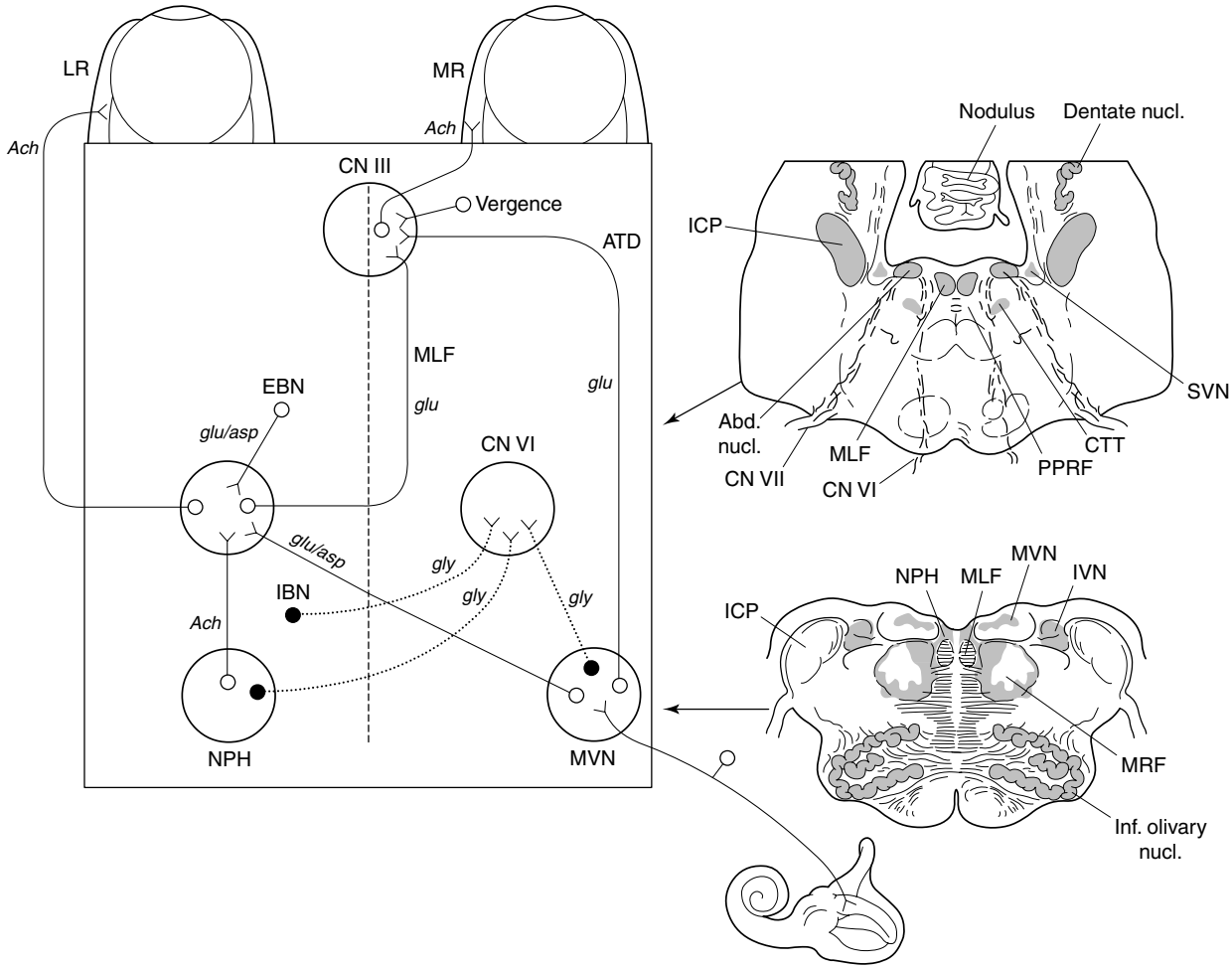

Fig. 44.3. Anatomic scheme for the synthesis of signals for horizontal eye movements. The abducens nucleus (CN VI) contains abducens motoneurons that innervate the ipsilateral lateral rectus muscle (LR) and abducens internuclear neurons that send an ascending projection in the contralateral medial longitudinal fasciculus (MLF) to contact medial rectus (MR) motoneurons in the contralateral third nerve nucleus (CN III). From the horizontal semicircular canal, primary afferents on the vestibular nerve project mainly to the medial vestibular nucleus (MVN), where they synapse and then send an excitatory connection to the contralateral abducens nucleus and an inhibitory projection to the ipsilateral abducens nucleus. Saccadic inputs reach the abducens nucleus from ipsilateral excitatory burst neurons (EBN) and contralateral inhibitory burst neurons (IBN). Eye position information (the output of the neural integrator) reaches the abducens nucleus from neurons within the nucleus prepositus hypoglossi (NPH) and adjacent MVN. The medial rectus motoneurons in CN III also receive a command for vergence eye movements. Putative neurotransmitters for each pathway are shown: Ach, acetylcholine; asp, aspartate; glu, glutamate; gly, glycine. The anatomic sections on the right correspond to the level of the arrowheads on the schematic on the left. Abd. nucl., abducens nucleus; ATD: ascending trait of Deiters; CN VI, abducens nerve; CN VII, facial nerve; CTT, central tegmental tract; ICP, inferior cerebellar peduncle; IVN, inferior vestibular nucleus; Inf. olivary nucl., inferior olivary nucleus; MRF, medullary reticular formation; SVN, superior vestibular nucleus. (From Leigh & Zee, 1999.)

(abduction affected more than adduction) is suggested. A brainstem lesion affecting one abducens nucleus and the adjacent MLF causes paralysis of both ipsilateral conjugate gaze and adduction of the ipsilateral eye. The only remaining movement during attempted conjugate gaze is abduction of the contralateral eye. This is the 'one-and-a-half' syndrome (Wall & Wray, 1983).

How do saccadic, pursuit, and vestibular commands reach the abducens nucleus? The velocity commands for horizontal saccades come from the burst cells located in the pontine paramedian reticular formation (PPRF) adjacent to the abducens nucleus. Lesions here impair ipsilateral saccades, but vestibular slow phases and smooth pursuit may be spared (Johnston & Sharpe, 1989; Kommerell et al., 1987; Horn et al., 1997). This is because vestibular inputs and pursuit commands reach the abducens nucleus by direct projections from the vestibular nuclei; only if these pathways are involved will vestibular or pursuit movements also be affected. The output of the neural integrator (the step (tonic) component for versional eye movements) appears to reach the abducens nucleus via projections from the nucleus prepositus hypoglossi and the medial vestibular nucleus (see Fig. 44.3). Mesencephalic lesions, too, may affect horizontal eye movements, presumably by interrupting descending pathways carrying higher-level commands. A deficit in contralateral saccades and ipsilateral pursuit is the usual finding (Zackon & Sharpe, 1984).

The excitatory command for the horizontal vestibulo-ocular reflex comes from the contralateral vestibular nuclear complex. When the head is still, neurons in the right and left vestibular nuclei discharge tonically at the same rate. During horizontal head rotation the lateral semicircular canal in one labyrinth is stimulated and the lateral canal in the other is inhibited. This creates an imbalance between the discharge rates of the right and left vestibular nuclei; activity increases on one side and decreases on the other. The difference encodes head velocity and provides the command that generates the slow phase of vestibular nystagmus.

Control of vertical conjugate gaze

The midbrain is important for vertical eye movements (Fig. 44.4) (Horn & Büttner-Ennever, 1998; Bhidayasiri et al., 2000). The vertical premotor saccadic command arises in burst cells located in the riMLF. This structure lies ventral to the sylvian aqueduct in the prerubral fields at the junction of the midbrain and thalamus. Each burst neuron projects to motoneurons in a manner such that the eyes are tightly coordinated (yoked) during vertical saccades. Saccadic innervation from riMLF is unilateral to depressor muscles but bilateral to elevator muscles, with axons crossing within the oculomotor nucleus. Thus, riMLF lesions may cause conjugate saccadic palsies that are either complete or selectively downwards (but not upwards). The riMLF on each side of the midbrain contains burst neurons for both up and down saccades, but only for ipsilateral torsional saccades. Therefore, unilateral riMLF lesions can be detected at the bedside if torsional quick phases are absent during ipsidirectional head rotations in roll (ear to shoulder). There also may be a spontaneous torsional nystagmus with quick phases directed with the top poles beating toward the side opposite to the lesion (Helmchen et al., 1996). Bilateral lesions of the riMLF in monkeys and in humans produce a predominantly downward deficit for saccades or paralyse all vertical saccades. Bilateral experimental lesions of the riMLF in monkeys abolish vertical and torsional saccades (Suzuki et al., 1995) but vertical gaze-holding, vestibular eye movements, and pursuit are preserved, as are horizontal saccades.

The interstitial nucleus of Cajal (INC) is important for holding the eye in eccentric gaze after a vertical saccade, and coordinating eye-head movements in roll. Bilateral INC lesions limit the range of vertical gaze, but vertical saccades are not slowed (Helmchen et al., 1998). The posterior commissure (PC) is the route by which INC projects to ocular motoneurons. Inactivation of the PC causes vertical gaze-evoked nystagmus, but destructive lesions cause a more profound defect of vertical gaze, probably due to involvement of the nucleus of the PC.

Unilateral lesions of the INC cause a spontaneous torsional nystagmus with quick phases directed such that the top poles of the eyes beat toward the side of the lesion. There may be a 'see-saw' component to this nystagmus. There also is an ocular tilt reaction (OTR) with contralateral head tilt, skew deviation with hypertropia of the ipsilateral eye, and ocular counterroll with extorsion of the contralateral eye, and intorsion of the ipsilateral eye. This pattern of ocular tilt reaction is similar to that produced by a lesion of the contralateral utricular nerve (Riordan-Eva et al., 1997) and is encountered clinically with a variety of brain stem lesions that involve central otolithic pathways (Brandt & Dieterich, 1994). Lesions in the vestibular periphery or vestibular nuclei (as occurs with Wallenberg's syndrome) usually produce an ipsilateral pattern of ocular tilt reaction, with an ipsilateral head tilt, skew deviation with hypertropia of the contralateral eye, and extorsion of the ipsilateral and intorsion of the contralateral eye. Lesions in the MLF produce a contralateral pattern of ocular tilt reaction similar to that produced with lesions in the INC. Lesions in the MLF also produce an asymmetry in the vertical

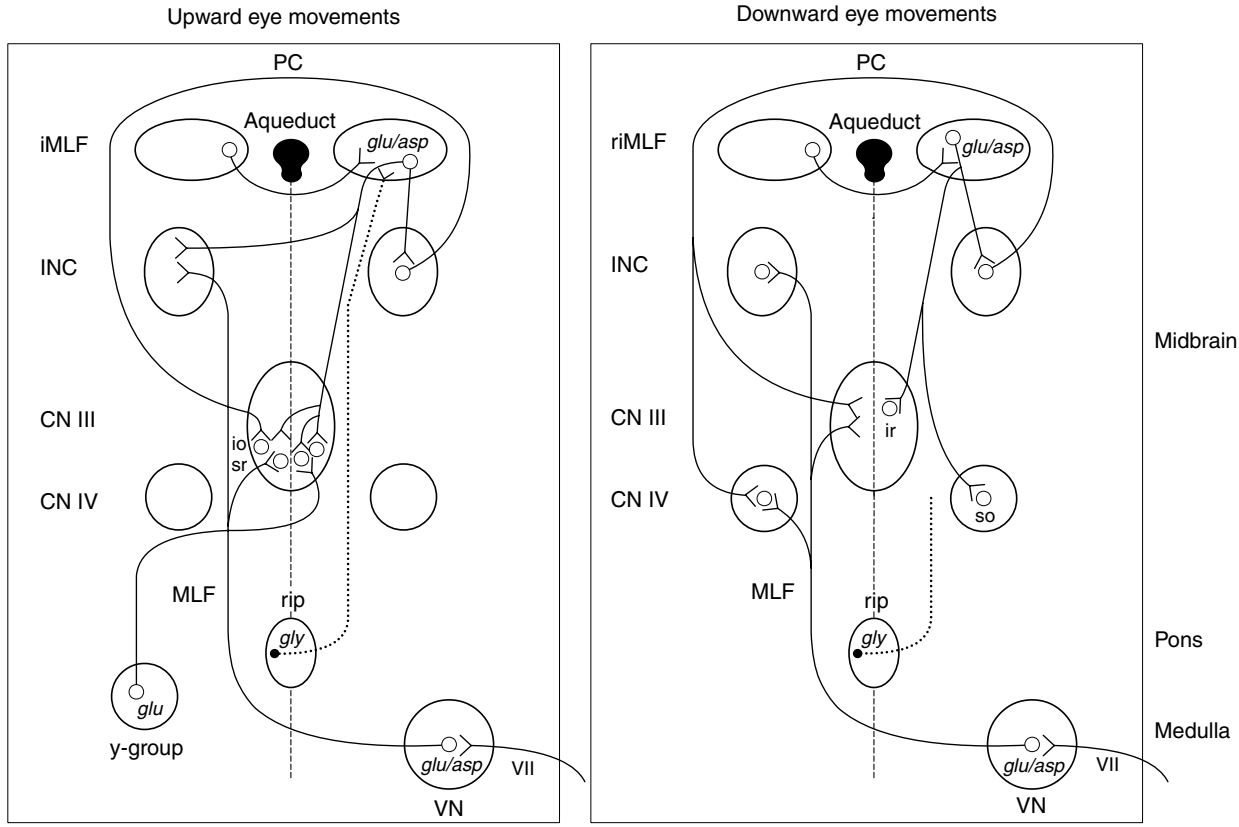

Fig. 44.4. Anatomic schemes for the synthesis of upward, downward, and torsional eye movements. From the vertical semicircular canals, primary afferents on the vestibular nerve (VN) synapse in the vestibular nuclei (VN) and ascend into the medial longitudinal fasciculus (MLF) and brachium conjunctivum (not shown) to contact neurons in the trochlear nucleus (CN IV), oculomotor nucleus (CN III), and the interstitial nucleus of Cajal (INC). (For clarity, only excitatory vestibular projections are shown.) The rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), which lies in the prerubral fields, contains saccadic burst neurons. It receives an inhibitory input from omnipause neurons of the nucleus raphe interpositus (rip), which lie in the pons (for clarity, this projection is only shown for upward movements). Excitatory burst neurons in riMLF project to the motoneurons of CN III and CN IV and send an axon collateral to INC. Each riMLF neuron sends axon collaterals to yoke-pair muscles (Hering's law). Projections to the elevator subnuclei (innervating the superior rectus and inferior oblique muscles) may be bilateral because of axon collaterals crossing at the level of the CN III nucleus. Projections of inhibitory burst neurons are less well understood, and are not shown here. The INC provides a gaze-holding signal, and projects to vertical motoneurons via the posterior commissure. Signals contributing to vertical smooth pursuit and eye-head tracking reach CN III from the y-group via the brachium conjunctivum and a crossing ventral tegmental tract. Neurotransmitters: asp, aspartate; glu, glutamate; gly, glycine. (From Leigh & Zee, 1999.)

vestibulo-ocular reflex (better response with slow phases upwards) due to the sparing of fibres mediating anterior semicircular canal reflexes, which run in part outside the MLF (Cremer et al., 1999).

Higher-level control of saccades

The brainstem circuits that generate the premotor commands for saccades are triggered by inputs both directly from the cerebral hemispheres, and indirectly from the cerebral cortex and the basal ganglia via the superior colliculus (SC). The cerebellum is also an important circuit for generating saccades and receives inputs from the cerebral hemispheres via the pontine relay nuclei. Recent research has emphasized the role of the SC in saccade generation. Although pharmacological inactivation of the SC in experimental animals severely disrupts normal saccadic programming (Lee et al., 1988), destructive lesions in the SC do not permanently abolish voluntary saccades (Albano et

al., 1982). So the cerebral projections to the brainstem, and to the cerebellum via the nucleus reticularis tegmenti pontis (NRTP) also seem important. Lesions restricted to the superior colliculus in humans are rare and are reported to cause relatively minor changes in the triggering of saccades (Pierrot-Deseilligny et al., 1991). A crucial finding is that bilateral lesions of the frontal eye fields and the superior colliculus cause an enduring, severe deficit of voluntary saccades (Schiller et al., 1987). A similar defect occurs with combined bilateral lesions of the frontal and parietal eye fields (Lynch, 1992). Thus, parallel descending pathways are involved in generating voluntary saccades, and it appears that each is capable of triggering saccades.

The frontal lobes contain three major areas that contribute to the control of saccadic eye movements: frontal eye fields (FEF), supplementary eye fields (SEF), and dorsolateral prefrontal cortex. The cingulate cortex and the intralaminar thalamic nuclei, with which the frontal and supplementary eye fields have reciprocal connections, are also important in the control of saccades. Recent studies in normal humans using functional imaging and transcranial magnetic stimulation, combined with studies in patients with focal cerebral lesions, have allowed a more precise understanding of the contribution of the different cerebral areas to the control of saccades (e.g. Gaymard et al., 1998; O'Driscoll et al., 2000; Connolly et al., 2000).

In humans, the FEF is located around the lateral part of the precentral sulcus, involving adjacent areas of the precentral gyrus, the middle frontal gyrus, and the superior frontal gyrus, and corresponding to confluent portions of Brodmann areas 6 and 4, but not area 8 (Blanke et al., 2000). The supplementary eye field (SEF) lies on the dorsomedial surface of the hemisphere, in the posterior–medial portion of the superior frontal gyrus. The dorsolateral prefrontal cortex occupies the middle frontal gyrus and adjacent cortex, corresponding to Brodmann areas 46 and 9.

Acute inactivation of the frontal eye fields in monkey (and presumably in humans), causes an 'ocular motor scotoma', so that all voluntary contralateral saccades with sizes and directions corresponding to the injected site are abolished. Such animals also have a pronounced gaze preference towards the side of the lesion, which is also the case for humans with acute frontal lobe lesions. In humans with chronic frontal eye field lesions there are increases in the reaction time of saccades, especially to remembered target locations, and to imagined targets during the 'antisaccade' task in which patients are required to look in the direction opposite to that of a suddenly-appearing target (Ploner et al., 1999). Other findings include hypometria of saccades made to visual or remembered targets located contralaterally to the side of the lesion, a reduced ability to make saccades in anticipation of predictable stepping movement of a target, when the target moves away from the side of the lesion, and an impaired ability to inhibit inappropriate saccades to a novel visual stimulus. Patients with lesions in the supplementary eye fields have an impaired ability to make a remembered sequence of saccades to an array of visible targets and also have some difficulty with memory-guided saccades. Patients with lesions in the dorsolateral prefrontal cortex show defects in predictive saccades, memory-guided saccades and antisaccades.

The parietal lobe also plays an important role in the control of saccades. Its influence is largely through projections to the superior colliculus, though there are also reciprocal projections between the frontal eye fields and more posterior structures. The parietal eye field (PEF), which in humans lies close to the horizontal portion of the intraparietal sulcus, projects directly to the superior colliculus. The PEF seems important for triggering visually-guided saccades to explore reflexively the visual environment. Patients with unilateral and especially right-sided parietal lesions may show contralateral inattention, ipsilateral gaze deviation or preference, and increased latency for visually- and memory-guided saccades. Bilateral parietal lobe lesions can lead to Balint's syndrome: peripheral visual inattention (simultanagnosia), inaccurate arm pointing ('optic ataxia'), and difficulty in making visually-guided saccades. If all voluntary eye movements are affected, involvement of both frontal and parietal lobes is likely, and the term 'ocular motor apraxia' has been used.

All three frontal areas project to brain stem structures important in saccadic programming via parallel descending pathways. Although direct projections from frontal cortex to the pontine reticular formation do exist, at least in monkeys, the indirect projections via the superior colliculus seem more important.

The frontal eye fields send a direct projection to the superior colliculus but also an indirect projection to the superior colliculus via the caudate nucleus and the pars reticulata of the substantia nigra. The latter, indirect pathway is composed of two serial inhibitory links: a phasically active caudate-nigral inhibition and a tonically active nigrocollicular inhibition (Hikosaka & Wurtz, 1989). If the frontal eye fields cause caudate neurons to discharge, the nigrocollicular inhibition is removed and the superior colliculus is able to activate a saccade. Thus, disease affecting the caudate could impair the ability to make saccades in complex tasks, often related to memory, expectation and reward (Vermersch et al., 1999). Conversely, disease affecting the pars reticulata of the substantia nigra might disinhibit the superior colliculus and so cause excessive, inappropriate saccades. Such a combination of deficits is

encountered in patients with disease of the basal ganglia, such as Huntington's disease (Lasker & Zee, 1997). The subthalamic nucleus, too, has a role for the generation of saccades. Stimulation here in patients with Parkinson's disease leads to an improvement in the generation of memory-guided saccades (Rivaud-Pechoux et al., 2000a).

To summarize, the influence of frontal and parietal cortex on the control of saccades appears to be via two parallel descending pathways. One pathway is via the frontal eye field to the superior colliculus (directly, and indirectly via the basal ganglia). This pathway appears to be more concerned with self-generated changes in gaze, related to remembered, anticipated, or learned behaviour and potential reward. The other pathway is directly from posterior parietal cortex to the superior colliculus. This pathway is more concerned with reorienting gaze to novel visual stimuli and in particular with shifting visual attention to the location of new targets appearing in extrapersonal space. There are, however, strong interconnections between, and common projection sites of, the parietal and the frontal lobes, which precludes a strict separation of function between the two pathways (Chafee & Goldman-Rakic, 2000).

Control of smooth pursuit

In monkeys, a subdivision of the visual system is concerned with the perception of motion. It starts with retinal ganglion cells that project to the magnocellular layers of the lateral geniculate nucleus. Some striate cortex neurons respond to moving visual stimuli, but most information processing occurs in the middle temporal visual area (MT), to which striate cortex projects (Komatsu & Wurtz, 1988). Discrete lesions of the middle temporal area in monkeys produce a scotoma for motion in the affected visual field (Dürsteler & Wurtz, 1988). The consequences are that saccades can still be made accurately to stationary targets in the affected visual field, but moving stimuli cannot be tracked accurately by saccades or smooth pursuit.

The middle temporal visual area projects to the adjacent medial superior temporal visual area (MST); neurons here not only encode moving visual stimuli but also carry an eye movement signal (Newsome et al., 1988). Lesions of the medial superior temporal area cause a deficit of horizontal smooth pursuit for targets moving toward the side of the lesion. Human homologues of the MT and MST are in the occipito-temporo-parietal junction, where Brodmann areas 19, 37, and 39 meet.

Signals about target motion are also passed from posterior structures to frontal areas, which also have neurons that discharge in relation to pursuit and in which areas lesions create abnormalities of pursuit tracking (Shi et al., 1998). Functional imaging studies, too, implicate both posterior and anterior cerebral regions in control of pursuit eye movements (Berman et al., 1999; Petit & Haxby, 1999). Both the frontal and extrastriate visual areas project to the pontine nuclei, especially the dorsolateral pontine nuclei (DLPN) with further relay onto the paraflocculus, flocculus, and dorsal vermis of the cerebellum (Fig. 44.5). The nucleus of the optic tract (NOT) within the midbrain, which receives inputs from areas MT and MST, may be important in the initiation of pursuit by virtue of its projections to the pontine nuclei (Yakushin et al., 2000). The cerebellum plays a critical role in synthesizing the pursuit signal. The dorsal vermis and fastigial nucleus may contribute mainly to the onset of pursuit, whereas the paraflocculus and flocculus mainly sustain the pursuit response. The output of the flocculus and paraflocculus is primarily through the vestibular nuclei and y-group (for vertical responses), but it remains unclear how the fastigial nucleus effects its control of pursuit.

Like the control of saccades there may be a dichotomy between the frontal and parietal contributions to smooth pursuit, the former being associated with more voluntary, internally generated aspects and the latter with more reflexive, externally triggered tracking (Petit & Haxby, 1999; Berman et al., 1999). Similar considerations apply to vergence and changing our line of sight in depth; frontal areas may be more important for generating volitional changes, posterior structures for more reflexive responses (Gamlin & Yoon, 2000).

Cerebellar influences on eye movements

The cerebellum plays an important role in both immediate on-line and long-term adaptive oculomotor control (Walker & Zee, 2000; Dieterich et al., 2000; Demurget et al., 2000). The latter refers to the mechanisms that ensure that eye movements remain appropriate to their stimulus in normal development and aging as well as disease. Three distinct cerebellar syndromes have been identified as the result of studies of discrete lesions.

First, lesions of the flocculus and paraflocculus impair smooth visual tracking – both smooth pursuit with the head still and steady fixation of a target rotating with the head (Zee et al., 1981). The latter, called cancellation of the vestibulo-ocular reflex, is comparable to fixation suppression of caloric nystagmus. Floccular lesions also cause horizontal gaze-evoked nystagmus, which implicates the vestibulocerebellum in the normal function of the neural

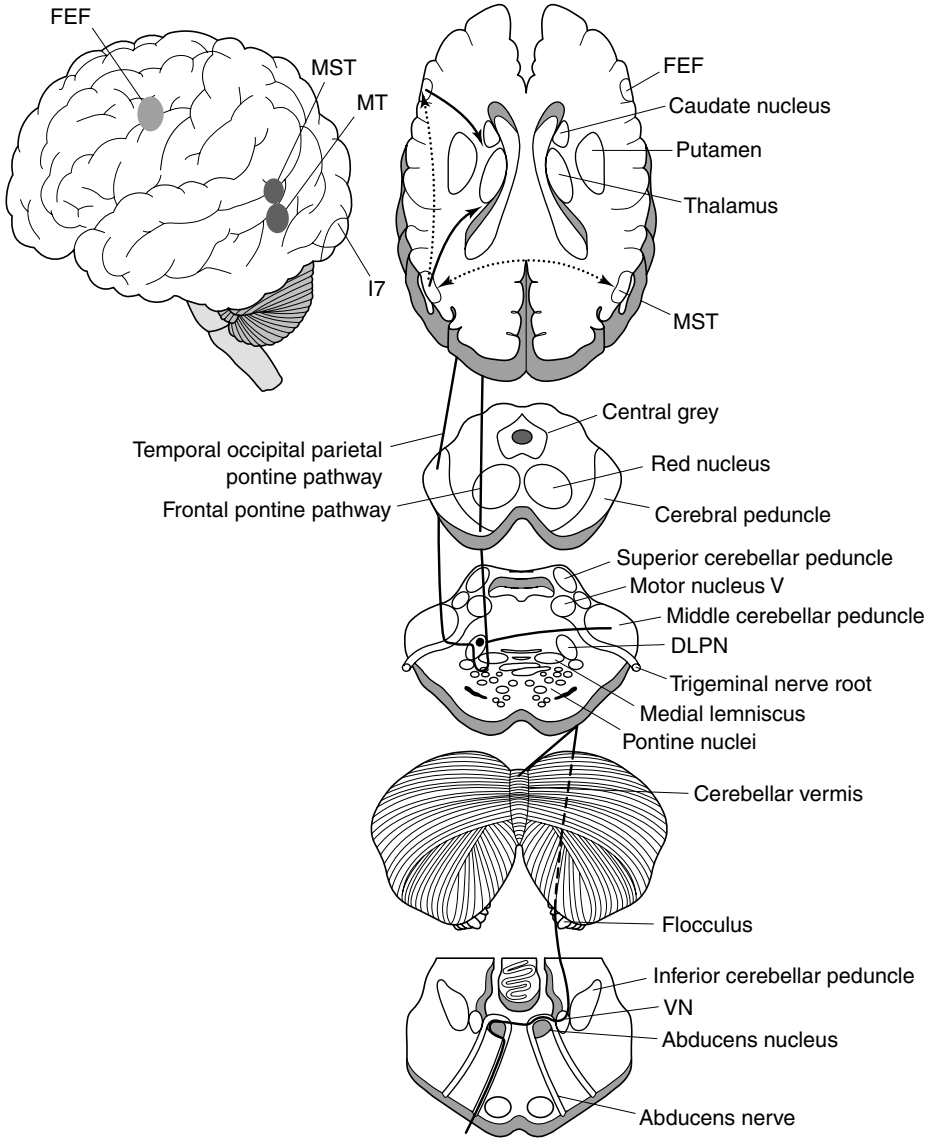

Fig. 44.5. A hypothetical scheme for horizontal smooth pursuit. Primary visual cortex (V1) projects to the homologue of the middle temporal visual area (MT) that in humans lies at the temporal–occipital–parietal junction. MT projects to the homologue of the medial superior temporal visual area (MST) and also to the frontal eye field (FEF). MST also receives inputs from its contralateral counterpart. MST projects through the retrolenticular portion of the internal capsule and the posterior portion of the cerebral peduncle to the dorsolateral pontine nucleus (DLPN). The DLPN also receives inputs important for pursuit from the frontal eye field; these inputs descend in the medial portion of the cerebral peduncle. The DLPN projects, mainly contralaterally, to the flocculus, paraflocculus, and ventral uvula of the cerebellum; projections also pass to the dorsal vermis. The flocculus projects to the ipsilateral vestibular nuclei (VN), which in turn project to the contralateral abducens nucleus. Note that the sections of brain stem are in different planes from those of the cerebral hemispheres. (From Leigh & Zee, 1999.)

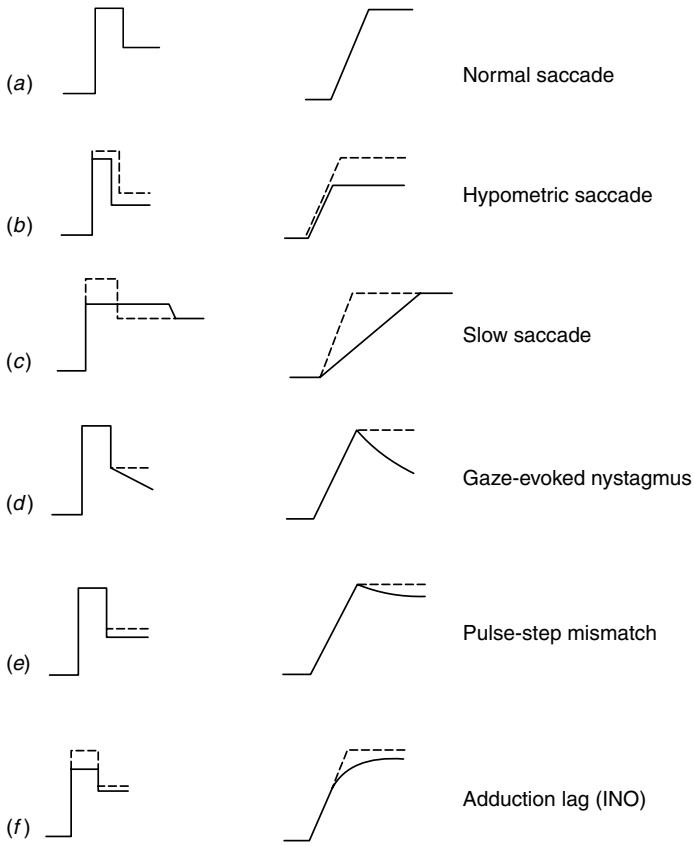

Fig. 44.6. Disorders of the saccadic pulse and step. Innervation patterns are shown on the left, eye movements on the right. Dashed lines indicate the normal response. (*a*) Normal saccade. (*b*) Hypometric saccade: pulse amplitude (width × height) is too small but pulse and step are matched appropriately. (*c*) Slow saccade: decreased pulse height with normal pulse amplitude and normal pulse-step match. (*d*) Gaze-evoked nystagmus: normal pulse, poorly sustained step. (*e*) Pulse-step mismatch (glissade): step is relatively smaller than pulse. (*f*) Pulse-step mismatch due to internuclear ophthalmoplegia (INO): the step is larger than the pulse, and so the eye drifts onward after the initial rapid movement. (From Leigh & Zee, 1999.)

gaze-holding integrator. Other signs of flocculectomy are downbeat nystagmus, rebound nystagmus, and postsaccadic drift or glissades (see under 'Disorders of saccadic eye movements').

Secondly, lesions of the nodulus and adjacent uvula cause a prolongation of vestibular responses as well as periodic alternating nystagmus (Waespe et al., 1985). There also is a failure of tilt-suppression of post-rotary nystagmus (Wiest et al., 1999).

Thirdly, lesions of the dorsal vermis (lobules V–VII) and the underlying fastigial nuclei cause both pursuit abnormalities and saccadic dysmetria. Vermal lesions produce hypometric saccades and impaired pursuit, especially when the eyes initiate their smooth tracking response. Fastigial nuclei lesions produce predominantly hypermetric saccades with relative preservation of pursuit.

The cerebellum also plays an important role in mediating the adaptive capabilities of the oculomotor system. Floccular lesions interfere with the adaptive capability of maintaining the accuracy of vestibular eye movements as well as preventing postsaccadic drift (Yagi et al., 1981; Lisberger et al., 1984; Optican et al., 1986). Lesions in the dorsal vermis produce abnormalities of adaptation for saccades and pursuit (Takagi et al., 1998, 2000).

Disorders of saccadic eye movements

Abnormalities of saccades can be divided into disorders of accuracy, velocity, latency, and stability. Furthermore, they can be analysed as disorders of the saccadic innervational commands: the pulse, the step, and the match between the pulse and the step (Fig. 44.6). For optimal performance the saccadic pulse must be the appropriate amplitude (approximately height × width) to ensure that the saccade is accurate, and of the appropriate height to ensure that the saccade is of high velocity. The saccadic pulse and step must be perfectly matched to prevent drift of the eyes after the saccade. A change in amplitude of the pulse creates saccadic overshoot, saccadic dysmetria. This sign is characteristic of disorders of the dorsal vermis or the fastigial nuclei of the cerebellum, although it appears with lesions in other parts of the nervous system. In Wallenberg's syndrome, for example, a specific pattern of saccadic dysmetria occurs. Saccades overshoot to the side of the lesion and undershoot away from the side of the lesion, and with attempted purely vertical saccades there is an inappropriate horizontal component toward the side of the lesion; this is called 'ipsipulsion' of saccades. With lesions of the superior cerebellar peduncle, the opposite pattern, 'contrapulsion', occurs: saccades overshoot opposite to the side of the lesion (Ranalli & Sharpe, 1986).

A decrease in the height of the saccadic pulse causes slow saccades. Normally, saccades follow a relatively invariant relationship between peak velocity and amplitude, called the 'main sequence'. Slow horizontal saccades usually imply disease affecting the horizontal burst cells in the pons, such as olivopontocerebellar atrophy (e.g. spinocerebellar ataxia types 1 and 2 (SCA1 and 2)). Slow vertical saccades usually imply disease affecting the vertical burst cells of the midbrain, such as progressive supranuclear palsy (Rivaud-Pechoux et al., 2000b) or Neimann–Pick

disease (Rottach et al., 1997). A mismatch in size between the pulse and the step produces brief (several hundred millisecond) postsaccadic drift or glissades. Postsaccadic drift occurs with disease of the vestibulocerebellum. The combination of slow, hypometric saccades and postsaccadic drift also occurs with internuclear ophthalmoplegia (INO), ocular motor nerve palsies, myasthenia gravis and ocular myopathies.

Disorders of saccadic initiation lead to an increase in saccadic latency (the normal saccadic latency is 200 ms). Often an associated head movement or a blink is needed to help initiate the saccade. Impaired saccadic initiation has been reported in patients with a variety of conditions including frontal or parietal lobe lesions, congenital or acquired 'oculomotor apraxia', Huntington's disease, Parkinson's disease and Alzheimer's disease. In patients with Parkinson's disease the saccade initiation deficit is often most obvious when they are instructed to voluntarily make repetitive saccades back and forth between two stationary targets.

Inappropriate saccades disrupt steady fixation, so called saccadic intrusions (Fig. 44.7). They include square-wave jerks, small-amplitude (up to 5°) saccades that take the eyes off target and are followed within 200 ms by a corrective saccade. Square-wave jerks may occur in normal, elderly subjects or in patients with cerebral hemisphere lesions, but they are especially prominent in progressive supranuclear palsy and in cerebellar disease. Square-wave jerks may be an exaggeration of the microsaccades that occur in normal individuals during fixation and can be most easily detected by ophthalmoscopy when the patient is instructed to fixate a target seen with the other eye. Macro-square-wave jerks (10–40° in amplitude) have been observed in multiple sclerosis and olivopontocerebellar atrophy. Macrosaccadic oscillations consist of sequences of markedly hypermetric saccades, separated by a normal intersaccadic interval (several hundred milliseconds), that continually overshoot the target. This causes a prominent back-and-forth oscillation about the point of fixation. Macrosaccadic oscillations reflect an increase in saccadic system gain (the saccade amplitude-target displacement relationship). They are typically found in patients with lesions in the midline deep cerebellar nuclei (Selhorst et al., 1976) but may be found with lesions in the pons (Averbuch-Heller et al., 1996).

Saccadic intrusions should be differentiated from excessive distractibility, in which novel visual targets that are behaviourally irrelevant evoke inappropriate saccades. Excessive distractibility can be demonstrated in the antisaccade task. When instructed to make a saccade in the direction opposite that of a visual stimulus (antisaccade paradigm), patients with Huntington's disease, Alzheimer's disease, schizophrenia, and frontal lobe lesions make an inappropriate saccade to the visual target.

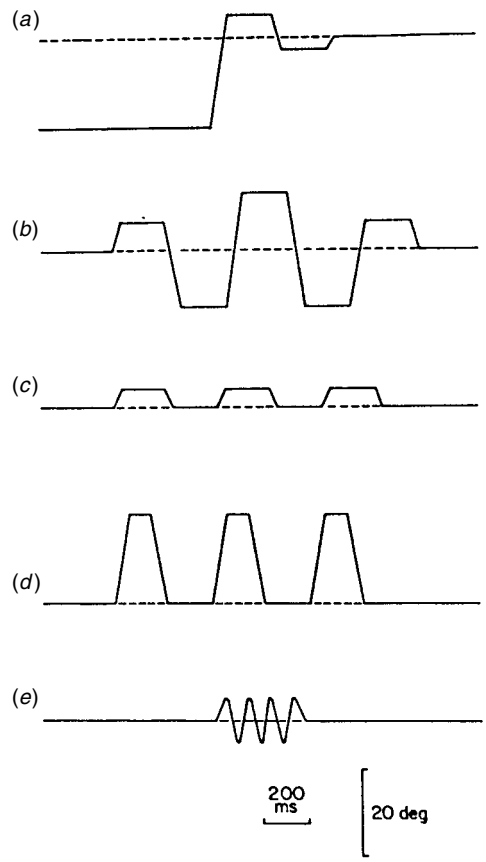

Fig. 44.7. Schematic of saccadic intrusions and oscillations. (*a*) Dysmetria: inaccurate saccades. (*b*) Macrosaccadic oscillations: hypermetric saccades about the position of the target; (*c*) Square-wave jerks: small, uncalled-for saccades away from and back to the position of the target; (*d*) Macrosquare-wave jerks: large, uncalled-for saccades away from and back to the position of the target; (*e*) Ocular flutter: to-and-fro, back-to-back saccades without an intersaccadic interval. (From Leigh & Zee, 1999.)

Saccadic oscillations without an intersaccadic interval (back-to-back, to-and-fro saccades) are called ocular flutter when they are limited to the horizontal plane and opsoclonus when they are multidirectional (horizontal, vertical, and torsional). Either type of oscillation may occur in patients with various types of encephalitis, as a remote effect of neuroblastoma or other tumours, and in association with toxins. An immunological basis is suggested (Connolly et al. 1997). Such oscillations are typically brought out by a change in gaze, eye closure, an associated

blink, or combined saccadic-vergence eye movements (Bhidayasiri et al., 2001). Flutter and opsoclonus may reflect a disorder of saccadic omnipause neurons (Zee & Robinson, 1979), although other explanations are possible (Leigh & Zee, 1999; Ridley et al., 1987). Voluntary nystagmus is another example of saccadic oscillations without an intersaccadic interval.

Disorders of smooth pursuit

Smooth pursuit eye movements that cannot keep up with the moving target, and require 'catch-up' saccades to keep the fovea on target are a common clinical finding. Impaired pursuit is often a side effect of medications such as sedatives and anticonvulsants. It also occurs with disease of the cerebellum or of the brainstem in, for example, progressive supranuclear palsy. Smooth pursuit capability also decreases with age. With lesions of the cerebral hemispheres typically pursuit is impaired for tracking directed toward the side of the lesion.

'Reversal' of smooth pursuit may be seen in some patients with congenital nystagmus: the smooth eye movements are directed opposite to the motion of the target.

Abnormalities of smooth pursuit are usually accompanied by commensurate disturbance of tracking of smoothly moving targets with combined movements of eye and head. This is tested by asking the patient to fixate a target rotating with the head. If cancellation (fixation suppression) of the vestibulo-ocular reflex is intact, no nystagmus is seen and the eyes remain stationary in orbit. When pursuit is defective, cancellation is also impaired and a nystagmus appears. Only when the vestibulo-ocular reflex is abnormal will noticeable discrepancies between smooth pursuit and eye–head tracking be evident.

Mechanisms of nystagmus

Nystagmus is a repetitive, to-and-fro movement of the eyes. When pathologic, it reflects abnormalities in the mechanisms that hold images steady on the retina: visually mediated eye movements (fixation), the vestibulo-ocular reflex, and the neural integrator which makes it possible to hold eccentric gaze (Stahl & Leigh, 2001). A disturbance of any of these mechanisms may cause drifts of the eyes (the slow phases of nystagmus) during attempted steady fixation. Corrective quick phases of saccades then rest the eyes.

Constant-velocity drifts of the eyes (Fig. 44.8(*a*)) with corrective quick phases produce jerk nystagmus, which is usually caused by an imbalance of vestibular or possibly optokinetic or pursuit drives. Lesions of the peripheral vestibular apparatus (labyrinth or nerve VIII) usually cause a mixed horizontal–torsional nystagmus with slow phases directed toward the side of the lesion. Because visually mediated movements are preserved, peripheral vestibular nystagmus is suppressed during fixation. This visual suppression of vestibular nystagmus may be evaluated at the

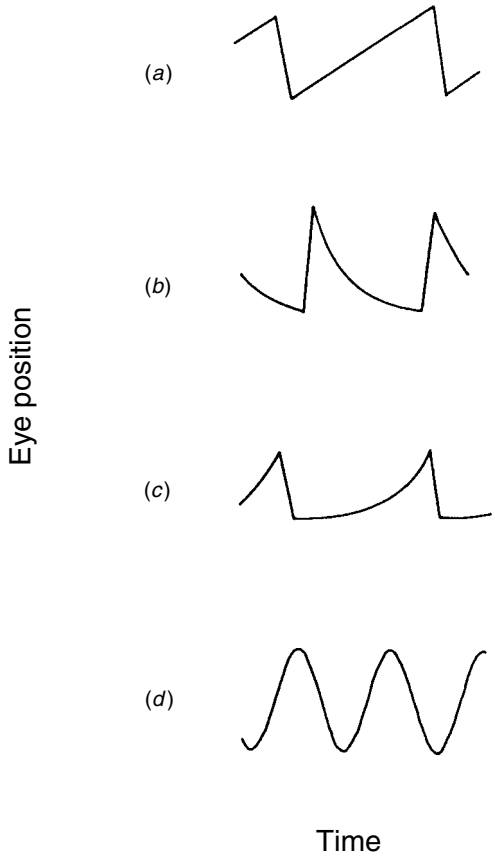

Fig. 44.8. Four common slow-phase waveforms of nystagmus. (*a*) Constant velocity drift of the eyes. This occurs in nystagmus caused by peripheral or central vestibular disease and also with lesions of the cerebral hemispheres. The added quick phases give a 'sawtooth' appearance. (*b*) Drift of the eyes back from an eccentric orbital position toward the midline (gaze-evoked nystagmus). The drift shows a negative exponential time course, with decreasing velocity. This waveform reflects an unsustained eye position signal caused by an impaired neural integrator. (*c*) Drift of the eyes away from the central position with a positive exponential time course (increasing velocity). This waveform suggests an unstable neural integrator and is encountered in the horizontal plane in congenital nystagmus and in the vertical plane in cerebellar disease. (*d*) Pendular nystagmus, which is encountered as a type of congenital nystagmus and with acquired disease. (From Leigh & Zee, 1999.)

bedside by using the ophthalmoscope; when the fixing eye is transiently covered, drifts of the optic disc and retinal vessels may appear or increase in velocity if there is an underlying vestibular imbalance. Frenzel goggles can also be used to remove fixation and bring out nystagmus. Nystagmus induced by a change in head position is frequently due to free-floating otoconia that have become trapped in one of the semicircular canals, benign positional vertigo, but may also be due to central disease. In particular, purely vertical positional nystagmus is suggestive of a posterior fossa lesion.

Nystagmus caused by disease of central vestibular connections may be purely torsional, purely vertical (downbeat or upbeat), or purely horizontal (i.e. without the torsional component that is usually seen with peripheral lesions). Smooth pursuit is usually also affected, so the velocity of slow-phase drift of central vestibular nystagmus does not diminish with fixation. Downbeat nystagmus in primary position usually reflects disease at the craniocervical junction, such as the Arnold–Chiari malformation or degenerative lesions of the cerebellum. Downbeat nystagmus is usually increased by convergence or lateral gaze. Patients with episodic ataxia (EA1) often have interictal downbeat nystagmus; they can be treated with diamox (Brandt & Strupp, 1997). Upbeat nystagmus in primary position occurs with lesions at the pontomedullary or pontomesencephalic junction or in the fourth ventricle. In the medulla it often involves the nucleus intercalatus, one of the perihypoglossal nuclei. Purely torsional nystagmus usually reflects intrinsic brain stem involvement in the vestibular nuclei or lesions in the vestibulocerebellum. Periodic alternating nystagmus (horizontal jerk nystagmus that changes direction every 2 minutes) is a form of central vestibular nystagmus (Leigh et al., 1981) and can be created experimentally by removing the cerebellar nodulus (Waespe et al., 1985). It can be successfully treated with Baclofen (Halmagyi et al., 1980).

Nystagmus on attempted eccentric gaze and with slow phases that show a declining exponential time course (see Fig. 44.8(*b*)) is due to an unsustained eye position command. This is gaze-evoked nystagmus, and it commonly occurs as a side effect of certain medications, especially anticonvulsants, hypnotics, and tranquillizers; with disease of the cerebellar flocculus; or, in the brainstem, with lesions in the paramedian tracts, the nucleus prepositus hypoglossi, and the medial vestibular nuclei. These last structures are frequently involved in Wernicke's encephalopathy and account for the gaze-evoked nystagmus and vestibular paresis in this condition. With prolonged eccentric gaze, gaze-evoked nystagmus may damp and actually change direction, so-called centripetal nystagmus. Following eccentric gaze, a rebound nystagmus occurs when the eyes return to the primary position; slow phases are directed toward the prior position of eccentric gaze. Rebound nystagmus usually coexists with other cerebellar eye signs.

Latent nystagmus also has slow phases with exponentially decreasing velocity (Abadi & Scallan, 2000). Latent nystagmus appears when one eye is occluded; then both eyes drift conjugately with slow phases of the viewing eye directed toward the nose. Latent nystagmus is commonly associated with strabismus (usually an esotropia) and dissociated vertical deviations (DVD) in which the eye under cover is higher. Latent nystagmus is acquired early in life but does not imply any underlying neurologic disease.

Nystagmus with slow phases that show an increasing exponential time course (see Fig. 44.8(*c*)) are typical of congenital nystagmus and may be due to instability of smooth pursuit or gaze-holding mechanisms. Congenital nystagmus is usually horizontal, accentuated by attempted fixation, diminished by convergence or active eyelid closure, associated with a head turn, and sometimes accompanied by 'reversed' smooth pursuit in which slow phases are directed oppositely to that of the target. Occasionally, acquired lesions of the cerebellum produce nystagmus with slow phases that have increasing exponential waveforms; this is usually vertical.

Pendular nystagmus consists of a slow phase that is a sinusoidal oscillation (see Fig. 44. 8(*d*)) rather than a unidirectional drift. Quick phases may be superimposed. Congenital nystagmus often appears pendular, although the slow-phase waveform of the nystagmus is usually not a true sinusoid and the nystagmus becomes jerk at extremes of horizontal gaze. Acquired pendular nystagmus may be a manifestation of multiple sclerosis or a sequel to brainstem infarction with inferior olivary hypertrophy (the syndrome of palatal tremor) (Deuschl et al., 1994). It has recently been proposed that pendular nystagmus in patients with multiple sclerosis may be caused by an instability in the neural integrator that normally guarantees steady gaze (Das et al., 2000). Acquired pendular nystagmus may have both horizontal and vertical components, and the amplitude and phase relationships of the two sine waves determine the trajectory taken by the eyes. For example, the trajectory is oblique if the sine waves are in phase and, more commonly elliptical (or circular) if they are 90° out of phase. Acquired pendular nystagmus is frequently disconjugate and may even be horizontal in one eye and vertical in the other. Gabapentin and memantine often diminish the intensity of acquired pendular nystagmus (Starck et al., 1997; Averbuch-Heller et al., 1997).

Convergence-retraction nystagmus, which occurs with midbrain lesions and usually coexists with upgaze paralysis

Table 44.1. Pulling actions of the extraocular muscles with the eye in primary position

Muscle	Primary action	Secondary action	Tertiary action
Lateral rectus	Abduction	–	–
Medial rectus	Adduction	–	–
Superior rectus	Elevation	Intorsion	Adduction
Inferior rectus	Depression	Extorsion	Adduction
Superior oblique	Intorsion	Depression	Abduction
Inferior oblique	Extorsion	Elevation	Abduction

(Parinaud's syndrome), actually consists of asynchronous adducting saccades (Keane, 1990). Cocontraction may also occur, causing the eyes to retract into the orbit. See–saw nystagmus (one eye goes up, the other down, with variable torsion) may be related to an imbalance in activity in structures that receive projections from the otolith organs (Kanter et al., 1987). The lesions are usually in the midbrain though see–saw nystagmus may accompany lesions in more caudal parts of the brainstem or cerebellum (Pieh and Gottlob, 2000). Humans with developmental disorders of the optic chiasm may have see–saw nystagmus (Dell'Osso et al., 1999a).

Ocular alignment: anatomic and physiologic principles

The primary pulling directions of the six extraocular muscles, when the eye is in primary position, are summarized in Table 44.1. The lateral rectus always abducts and the medial rectus always adducts the eye, but the actions of the vertical muscles depend on the starting position of the eye. The vertical recti and the oblique muscles pull the globe in both vertical and torsional directions. It is important to test the vertical recti and oblique muscles with the eye in a position that will cause the muscle in question to have its greatest vertical action. Thus, to test the vertical recti, bring the eye first into the abducted position; to test the oblique muscle, bring the eye first into the adducted position.

The fibres of the extraocular muscles show histological and histochemical differences from those of limb muscles (Spencer & Porter, 1988; Demer et al., 1995, 1997). As each muscle is traced anteriorly, two parallel layers are formed. The more central or 'global' portion of extraocular muscle contains fibre types that are specialized for developing transient, high tensions, to move the eyes quickly. This global layer of extraocular muscle contains about 60% of total muscle fibre and inserts via a tendon on the sclera of the globe. The more peripheral or 'orbital' layer of extraocular muscle is composed of fibre types that are specialized for sustaining tonic tension. An important recent discovery is that the orbital fibre layer of each muscle does not insert on the globe but, instead, attaches to a pulley of connective tissue (Demer et al., 2000). The pulley for each muscle lies contiguous with the orbital wall or its fascia, between the globe equator and the posterior pole of the eye. Thus, the functional point of origin of the extraocular muscles is not, as previously thought, at the orbital apex, but corresponds to the current position of the pulleys (Clarke et al., 2000). In this sense, all the extraocular muscles are similar to the superior oblique muscle, which has its functional origin at the trochlea (the only pulley that does not move). This scheme is consistent with older electromyographic studies of human extraocular muscles, which demonstrated a 'division of labour' between the global and orbital layers (Scott & Collins, 1973). Furthermore, the geometric rules that govern the axes of rotation of the eyes (such as Listing's law, which limits rotational axes during saccades and pursuit to an approximately frontoparallel plane, and so specifies eye torsion in eccentric gaze positions) may be imposed by the properties of the pulleys.

Extraocular muscle contains pallisade proprioceptors, which lie at the junction of the multiply-innervated extraocular muscle fibres and its tendon of insertion into the globe (Ruskell, 1999). These multiply innervated fibres receive their input from a discrete set of moto neurons, which ring the periphery of the classic borders of the oculomotor, trochlear, and abducens nuclei (Büttner-Ennever, 2000). Thus, it seems possible that the multiply-innervated fibres and pallisade proprioceptors could function similarly to muscle spindles in skeletal muscle though they may also influence dynamic properties of eye movements (Knox et al., 2000; Dell'Osso et al., 1999b). There is, however, no stretch reflex, in the classical sense, associated with the extraocular muscles (Keller & Robinson, 1971). These ocular proprioceptors also seem concerned with localization of objects for limb movements, or long-term adaptation to injury (Lewis et al., 1994, 1999; Ruskell, 1999; Weir et al., 2000).

The courses of the oculomotor nerves

The anatomy of the oculomotor, trochlear, and abducens nerves is reviewed in detail by Leigh and Zee (1999). The oculomotor nucleus sends fibres to extraocular muscles, to the levator palpebrae superioris, pupillary constrictor, and ciliary body. The oculomotor nucleus is a paired structure; its anatomy is summarized in Fig. 44.9. The classic scheme

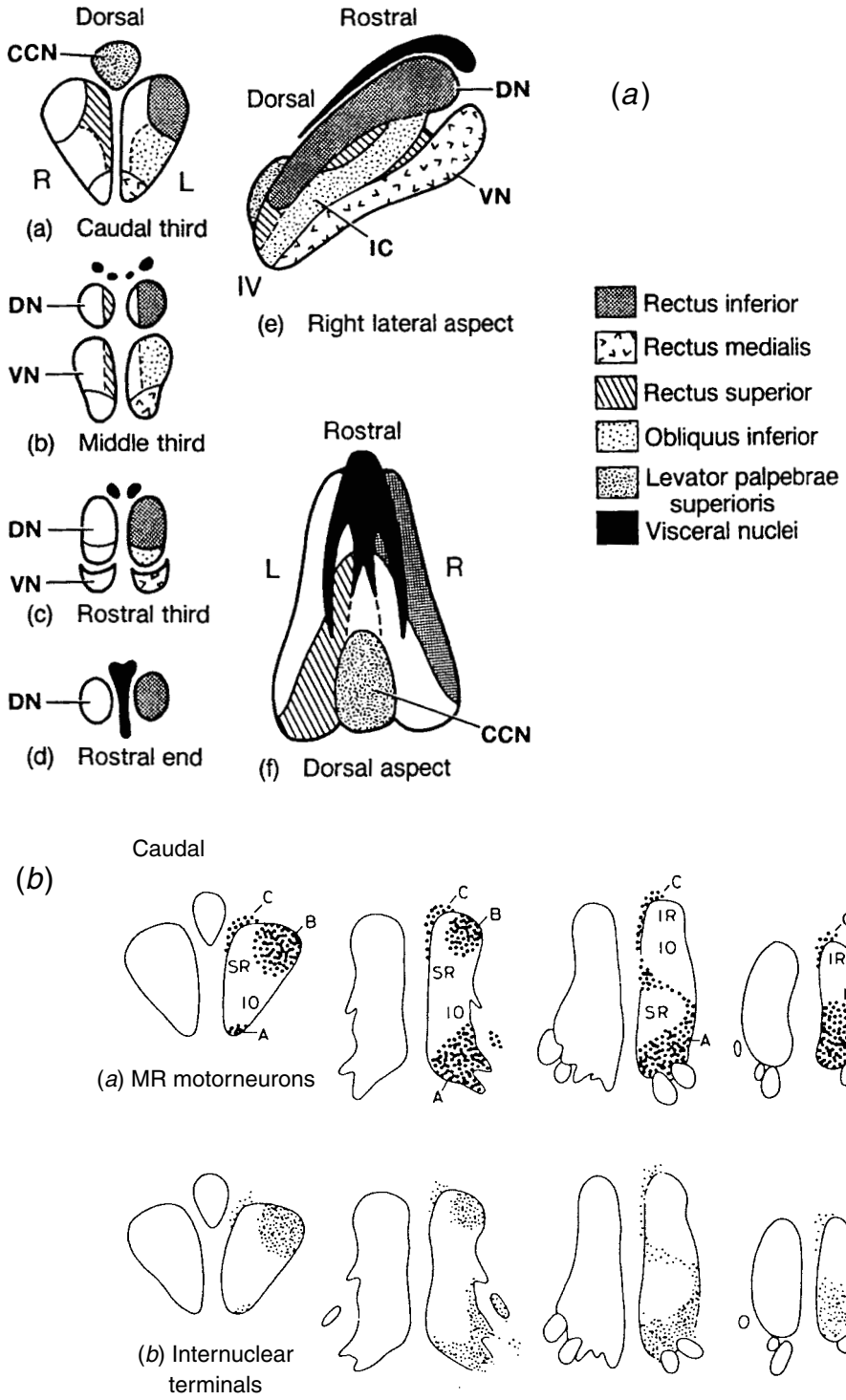

Fig. 44.9. (*a*) Warwick's scheme, based on retrograde denervation studies. CCN, caudal central nucleus; DN, dorsal nucleus; IC, intermediate nucleus; IV, trochlear nucleus; VN, ventral nucleus; R, right; L, left. (*b*) Scheme of Büttner-Ennever and Akert, based on radioactive tracer techniques. Top: The medial rectus (MR) motoneurons, identified by injecting isotope into medial rectus muscle, lie in three groups, A, B, and C. IO, inferior oblique; IR, inferior rectus; SR, superior rectus. Bottom: These same three areas also receive inputs from abducens internuclear neurons as demonstrated by injecting isotope into the contralateral sixth nerve nucleus. (From Leigh & Zee, 1999.)

of Warwick (1953), shown in Fig. 44.9(*a*), has been modified by Büttner-Ennever and Akert (1981) on the basis of studies with tracer techniques. The latter authors demonstrated that the medial rectus neurons (see Fig. 44.9(*b*), top) are distributed in three areas, A, B, and C. Neurons from area C receive pretectal inputs, and their axons mainly innervate the orbital layers of the medial rectus muscle. Neurons in all three locations receive inputs from the internuclear neurons of the contralateral abducens nucleus via the MLF (see Fig. 44.9(*b*), bottom). Projections from the oculomotor nucleus are ipsilateral except those to the superior rectus, which are totally crossed, and those to the levator palpebrae superiors, which are both crossed and uncrossed.

Clinical testing of diplopia: symptoms

Misalignment of the visual axes, strabismus, causes the two images of a seen object to fall on non-corresponding areas of the two retinas. This usually causes diplopia – the sensation of seeing an object at two different locations in space. In addition, the two foveae are simultaneously presented different images, so occasionally two different objects are perceived at the same point in space. This is called visual confusion.

If diplopia is monocular the cause is usually astigmatism or spherical refractive errors, incipient cataract, corneal irregularity, lens dislocation, or eye trauma. Such patients may report that the two images differ in brightness or that there are more than two images. Monocular diplopia caused by lens or corneal abnormality can be overcome by pinhole vision. Rarely, monocular diplopia is due to retinal detachment or to cerebral disorders.

Patients who complain of little or no visual disturbance despite an obvious ocular misalignment usually have had their strabismus from early in life. Thus, it is important to inquire about any history of strabismus, eye patching, eye surgery or abnormal head posture; old photographs may be of help.

Clinical testing of diplopia: physiologic principles

A clinical scheme for diplopia is summarized in Table 44.2. After looking for head tilts or turns, visual acuity, visual fields, pupils, and eyelids should be checked as preliminaries to testing ocular motility. Establishing the range of movement of each eye while the other is covered (ductions) and with both eyes viewing (versions) may reveal limitation of movement caused by extraocular muscle palsy. The direction of any limitation of movement can be correlated with the pulling action of a muscle (see Table 44.1). It is often useful to ask the patient to follow a penlight and to note the relative positions of the two corneal reflections with the eyes in each field of gaze. Subjective tests of diplopia depend on the patient's report of the subjective visual direction of images from one test object for each eye. If both images lie on corresponding retinal elements, for example, both foveae, the object will be reported to lie in the same visual direction. If the two images lie on non-corresponding retinal elements the object may appear to lie in two visual directions and the patient will report diplopia. Two further principles are important in this type of testing: (i) the images are maximally separated when the patient looks into the direction of action of the paretic muscle and (ii) the target seen by the paretic eye is projected more peripherally. The red glass and the Maddox rod (which takes a point source of light and makes it appear as a straight line) help the patient identify which image corresponds to the paretic eye.

Cover tests demand less cooperation by the patient than does the red glass or the Maddox rod. Cover tests depend on the principle that when one eye is required to fix on an object, it preferentially does so with the fovea. (Certain exceptions to this rule, caused by anomalous retinal correspondence, occur in congenital strabismus.) If the principal visual axis is not directed toward the object, an eye movement (saccade) will be necessary to move the image of the object, toward the fovea. The detection and estimated size of this corrective saccade ('movement of

Table 44.2. A summary scheme for diplopia testing

Preliminary examinations
Look for head tilts and turns
Check visual acuity and visual fields
Examine pupils and eyelids
Determine range of movement
First, with one eye viewing (ductions)
Second, with both eyes viewing (versions)
Use objective tests to estimate amount of diplopia in the nine cardinal positions of gaze
Red glass test
Maddox rod
Lancaster red–green test
Use the cover test to examine the tropia in the nine cardinal positions of gaze (prisms can be used to measure the deviation; For vertical deviations, use the Bielschowsky head-tilt test (Fig. 44.11).

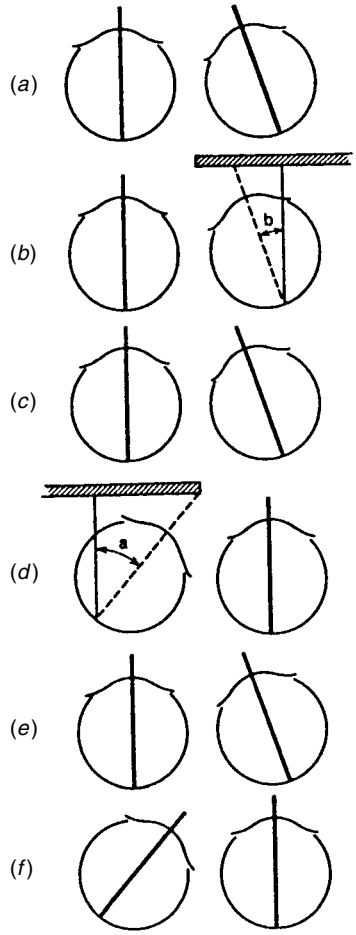

Fig. 44.10. The cover test. (*a*) Initially, with both eyes viewing, there is an esotropia (right eye turned in). (*b*) When the cover is placed before the nonfixating right eye, no movement occurs; nor does it occur when (*c*) the cover is removed. (*d*) When the left eye is covered, the right eye must fixate the target and a movement of redress occurs. Note that the deviation of the sound eye under cover (the secondary deviation-a) is greater than that of the paretic eye under cover (primary deviation-b). When the cover is removed, either (*e*) the left eye again takes up fixation, or (*f*) the paretic eye continues to fixate, if the patient is an 'alternate fixator'. (From Leigh & Zee, 1999.)

redress') provide an indication of misalignment of the visual axes.

The cover test (Fig. 44.10) reveals a tropia, a misalignment of the visual axes when both eyes are viewing. The patient is instructed to fix on a target that requires a visual discrimination (e.g. a letter) and ensures a fixed accommodative state. First, with the eyes in primary position, cover the right eye and look for a movement of the uncovered left eye (movement of redress). If no movement of the left eye is seen when the right eye is covered, remove the cover and then cover the left eye, looking for a movement of redress of the right eye. For horizontal deviations, exotropia (outward deviation) points to medial rectus weakness and esotropia (inward deviation) to lateral rectus weakness. Repeat this test with the eyes brought into the nine cardinal positions of gaze by rotating the head while the eyes fixate on the same target. In this way, the field of gaze in which the deviation is maximal can be determined.

Testing for vertical strabismus with the Bielschowsky head-tilt test

After a paralytic strabismus has been present for some months, changes in the innervation and mechanical properties of the muscles occur so that the deviation may no longer increase when the eyes look into the direction of action of the paretic muscle. This so-called spread of comitance can be particularly troublesome in the diagnosis of vertical muscle palsies. In this situation, noting any change of vertical deviation as the patient tilts the head (ear to shoulder) to the right or to the left can often be helpful (Bielschowsky, 1940). Classically, with a superior oblique palsy, the deviation is increased when the patient's head is tilted to the side of the palsy and reduced with a head tilt to the opposite side (Fig. 44.11). In a patient who has a third nerve palsy and who is unable to adduct the eye, the action of the superior oblique muscle can be best evaluated by looking for intorsion of the abducted eye on attempted downward gaze.

Topologic diagnosis of oculomotor nerve palsies

Causes of palsies of cranial nerves III, IV and VI are summarized in Tables 44.3–44.5.

Etiology of abducens nerve palsy

Disease affecting the abducens nucleus causes an ipsilateral conjugate gaze palsy. This is because the abducens nucleus contains not only abducens motor neurons (bound for the sixth nerve) but also abducens internuclear neurons that pass into the contralateral MLF and so reach the contralateral medial rectus subnucleus (see Fig. 44.3). Hereditary gaze palsies and Möbius' syndrome (horizontal gaze palsy, facial diplegia, and associated developmental anomalies) are probably due to failure of development of the abducens nucleus (Carr et al., 1997). Duane's retraction syndrome is characterized by narrowing of the palpebral fissure on

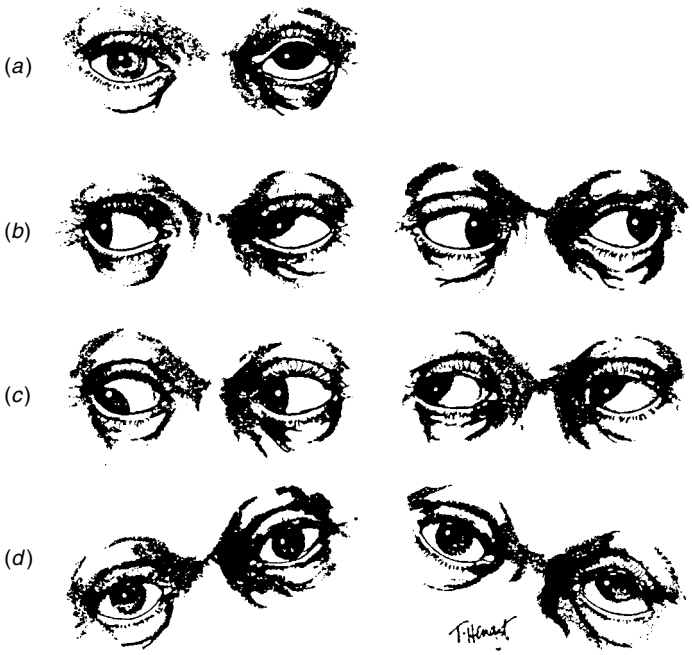

Fig. 44.11. The diagnosis of vertical ocular deviation. The steps in the diagnosis of a left superior oblique palsy are shown. (*a*) In primary position there is a left hypertropia. This could be due to weakness of elevators of the right eye or depressors of the left eye. (*b*) The deviation becomes worse on gaze to the right. This implies weakness of the right superior rectus or the left superior oblique. (*c*) With the eyes in right gaze, the deviation is more marked on looking down. This implies weakness of the left superior oblique muscle. (*d*) The Bielschowsky head-tilt test. With a rightward head tilt, there is no detectable vertical deviation of the eyes. (This would be the patient's preferred head position.) With the head tilted to the left, there is an exaggeration of the left hypertropia. (From Leigh & Zee, 1999.)

adduction (retraction) and (i) limitation of abduction but full adduction (type I), (ii) limitation of adduction but full abduction (type II) or (iii) limitation of both abduction and adduction (type III). Rare cases of Duane's syndrome are acquired, for example, through orbital injury, but in most patients the syndrome is due to abnormal development of the abducens nucleus and aberrant innervation of the lateral rectus muscle by axons from the oculomotor nucleus. Patients with Duane's syndrome seldom complain of diplopia. The syndrome occurs more frequently in females and affects the left eye more than the right.

Lesions of the fascicles of the abducens nerve usually also involve structures through which the nerve passes. For example, sixth nerve palsy may be accompanied by ipsilateral facial weakness and contralateral hemiplegia (Millard–Gubler syndrome). Within its subarachnoid

Table 44.3. Causes of abducens nerve palsy

Nucleus
Congenital gaze palsy and Mobius syndrome
Duane's syndrome (some cases)
Infarction
Tumour
Wernicke's encephalopathy
Fascicular
Infarction
Demyelination
Tumour
Subarachnoid
Meningitis (infectious and neoplastic)
Trauma
Subarachnoid hemorrhage
Cerebellopontine angle and clivus tumour
Aneurysm including an ectatic basilar artery
Petrous
Infection of petrous tip or mastoid
Trauma
Expanding supratentorial lesion
After lumbar puncture
Cavernous sinus and superior orbital fissure
Tumour (e.g. nasopharyngeal carcinoma, pituitary adenoma, meningioma)
Aneurysm
Cavernous sinus thrombosis
Carotid – cavernous sinus thrombosis
Dural arteriovenous fistula
Infectious, including herpes zoster
Localization uncertain
Infarction (often in association with diabetes or hypertension)

Table 44.4. Causes of trochlear nerve palsy

Nuclear and fascicular
Trauma
Hemorrhage or infection
Demyelination
Subarachnoid
Trauma
Tumour
Meningitis
Cavernous sinus and superior orbital fissure
Tumour
Aneurysm
Herpes zoster
Tolosa-Hunt syndrome
Localization uncertain
Infarction (often in association with diabetes or hypertension)

Table 44.5. Causes of oculomotor nerve palsy

Nuclear
Congenital hypoplasia
Infarction
Tumour
Fascicular
Infarction
Tumour
Subarachnoid
Aneurysm of posterior communicating or basilar arteries
Meningitis – infectious or neoplastic
Nerve infarction (often in association with diabetes or hypertension)
Tumour
At the tentorial edge
Uncal herniation
Trauma
Cavernous sinus and superior orbital fissure
Aneurysm
Tumour (pituitary adenoma, meningioma, nasopharyngeal carcinoma)
Pituitary infarction
Cavernous sinus thrombosis
Carotid cavernous fistula
Infections, including herpes zoster
Tolosa–Hunt syndrome
Orbit
Trauma
Tumour
Localizing uncertain
Migraine

course, the sixth nerve may be involved along with other cranial nerves by infective or neoplastic meningitis, chordoma, or enlarged ectatic basilar aneurysm (Table 44.3). Both abnormally increased and decreased intracranial pressure may be associated with abducens nerve palsies (Mokri et al., 1997).

As the abducens nerve rises and passes over the petrous bone, it lies close to the fifth nerve. These adjacent nerves may be involved by infection of the petrous bone causing diplopia and facial pain, Gradenigo's syndrome; deafness commonly coexists.

Within the cavernous sinus the sixth nerve may be involved with carotid aneurysm, carotid-cavernous fistula, dural arteriovenous shunts, or tumours, and may occasionally be recurrent (Blumenthal et al., 1997). Abducens palsy may be accompanied by Horner's syndrome (caused by involvement of adjacent oculosympathetic fibres) or involvement of other cranial nerves in the cavernous sinus.

Abducens nerve palsy should always be differentiated from myasthenia gravis, divergence paresis, convergence spasm (spasm of the near triad) and diseases within the orbit (see Table 44.7).

Etiology of trochlear nerve palsy

Involvement of the trochlear nucleus is rare; when it does occur there is often an associated Horner's syndrome due to involvement of the adjacent descending sympathetic pathways. The most common site of involvement is the subarachnoid course of the nerve. Here the fourth nerves emerge together from the anterior medullary velum. Thus, bilateral fourth nerve palsy after blunt head trauma is most likely due to contrecoup forces transmitted to the emerging nerves by the free edge of the tentorium. It may be associated with cerebellar gait ataxia if the superior vermis is also damaged. The nerves may also be involved in their subarachnoid course by tumour or as a consequence of neurosurgical procedure (Table 44.4).

Within the cavernous sinus, involvement of the trochlear nerve by tumour or aneurysm is usually accompanied by involvement of adjacent cranial nerves. In many cases of trochlear nerve palsy, no cause can be found, although sometimes diabetes or hypertension is associated, and the presumed etiology is ischemic.

Superior oblique palsy should be differentiated from involvement of other vertical extraocular muscles, skew deviation, or restrictive disease of the orbit, especially due to thyroid ophthalmopathy. The Bielschowsky head-tilt test, forced duction tests, and imaging of the orbit, help in making the diagnosis.

Another syndrome peculiar to the superior oblique muscle is superior oblique myokymia. Affected patients typically complain of brief, recurrent episodes of monocular blurring of vision, or tremulous sensations in one eye (Brazis et al., 1994). Some also report vertical or torsional diplopia or oscillopsia. Attacks usually last less than 10 seconds, but they may occur many times per day. The attacks may be brought on by looking downward, by tilting the head toward the side of the affected eye, or by blinking. Most patients with superior oblique myokymia have no underlying disease, though cases have been reported following trochlear nerve palsy, head injury, possible demyelination or brainstem stroke, and with cerebellar tumour. The mechanism for superior oblique myokymia is uncertain but some degree of damage to the trochlear nerve is probably a common predisposing factor.

The eye movements of superior oblique myokymia are often difficult to appreciate on gross examination, but the spasms of torsional–vertical rotations can sometimes be

detected by looking for the movement of a conjunctival vessel as the patient announces the onset of symptoms. They are more easily detected during examination with an ophthalmoscope or slit lamp.

No treatments for superior oblique myokymia are consistently effective, but individual patients may respond to carbamazepine, baclofen, and systemically or topically administered beta blockers. In some patients, superior oblique myokymia spontaneously resolves (Brazis et al., 1994) but in others the symptoms are so troublesome that surgical treatment is considered.

Etiology of oculomotor nerve palsy

Lesions of the nucleus of the third nerve are rare. When they occur, they usually involve structures important for vertical conjugate gaze. Based on current knowledge of the anatomic organization of the oculomotor nucleus it is possible to set certain criteria for diagnosis of nuclear third nerve palsy; unilateral third nerve palsy with contralateral superior rectus paresis and bilateral partial ptosis, and bilateral third nerve palsy associated with spared levator function (internal ophthalmoplegia may be present or absent) almost invariably reflect a lesion in the oculomotor nucleus. However, it is important to recognize that in this small area of the midbrain, the nuclei and fascicles of the oculomotor nerve lie in close proximity, and both may be affected to varying degrees (Umapathi et al., 2000).

Fascicular third nerve lesions usually also involve adjacent structures. Claude's syndrome consists of third nerve palsy, contralateral cerebellar ataxia, and tremor; it is due to involvement of the red nucleus and its cerebellar connections. Weber's syndrome consists of a third nerve palsy and contralateral hemiplegia, the latter caused by involvement of one cerebral peduncle. Benedikt's syndrome combines third nerve palsy, contralateral ataxia, and contralateral hemiplegia; if vertical gaze impairment is also present, it is referred to as Nothnagel's syndrome. Fascicular lesions may lead to a pattern of weakness that mimics effects of more distal lesions.

After its exit from the brainstem, the third nerve runs in the subarachnoid space and is susceptible to meningeal processes (infection, tumour, blood). The third nerve may be compressed by aneurysm, usually from the posterior communicating artery and sometimes from the basilar artery (Table 44.5). In such cases only rarely is the pupil affected alone. A common clinical challenge is to differentiate third nerve compression due to aneurysm from nerve infarction in association with diabetes or hypertension, in which cerebral arteriography is not indicated. The presence of pupillary involvement can be relied on to identify those patients that harbour an aneurysm. Initially, however, the pupil may be spared, so pupil-sparing third nerve palsy requires careful observation for a week before a decision can be made about arteriography. After a week, third nerve palsy with complete pupillary sparing is rarely due to aneurysm. Cases of complete extraocular palsy with normal pupils due to aneurysm are rare. Partial pupillary involvement may be grounds for an arteriogram, although mild involvement of the pupil may occur with noncompressive processes. Spontaneous resolution of an oculomotor paresis does not necessarily mean that aneurysm is excluded. In patients with an acute oculomotor palsy individuals between 20 and 50 years of age are more likely to have an aneurysm (Trobe, 1998) whereas children younger than 11 years almost never do. MRI and angiography often help to differentiate nerve infarction from compressive or brainstem lesions, and gadolinium enhancement of the cisternal portion of the oculomotor nerve is a sensitive index of neoplastic or inflammatory processes, including migraine.

At least some cases of third nerve infarction, usually in association with diabetes, hypertension, or collagen-vascular disease, involve the subarachnoid portion of the nerve. Another site is within the cavernous sinus. Such 'medical third nerve palsies' usually are acute in onset, preceded by facial or orbital pains, and characterized by total or relative sparing of the pupil.

At the tentorial edge the third nerve may be compressed by the uncus of the temporal lobe during cerebral herniation. Pupillary dilatation may be the first warning of such herniation.

Within the cavernous sinus the oculomotor nerve may be compressed by aneurysm or tumour. With carotid aneurysm, about half of all patients suffer pain in the face; abducens and trochlear palsies may coexist. Sparing of the pupils is more common with cavernous sinus than with posterior communicating aneurysms. Tumours in the region of the cavernous sinus often grow slowly and pain is not a usual feature. Often multiple cranial nerves are involved. A relatively common finding with such slowly progressive processes is aberrant regeneration of the oculomotor nerve (Boghen et al., 1979). This is characterized by anomalous synkinetic movements; most commonly the lid elevates during adduction or depression of the eye. Aberrant regeneration of the third nerve also occurs after trauma, intracavernous aneurysms and congenital third nerve palsy. Tumours arising near the cavernous sinus, including meningioma, pituitary adenomas, and lymphomas, may cause third nerve palsy; usually other nerves in the cavernous sinus are also affected. Typically, the tumours grow slowly without producing any pain.

Table 44.6. Causes of multiple oculomotor nerve palsies

Brainstem
Tumour
Infarction
Subarachnoid
Meningitis (infective and neoplastic)
Trauma
Clivus tumour
Aneurysm – ectatic basilar artery
Sarcoidosis
Cavernous sinus and superior orbital fissure
Aneurysm
Tumour (pituitary adenoma, meningioma, nasopharyngeal carcinoma)
Cavernous sinus thrombosis
Pituitary infarction
Carotid-cavernous fistula
Sphenoid sinus mucocele
Infections (herpes zoster)
Tolosa–Hunt syndrome
Orbital
Trauma
Tumour
Mucormycosis
Localization uncertain
Post-inflammatory neuropathy (Guillain–Barré and Miller Fisher syndrome)

Table 44.7. Differential diagnosis of ocular motor nerve palsies

Concomitant strabismus
Disorders of vergence, especially spasm of the near triad
Brainstem disorders causing abnormal prenuclear inputs (e.g. skew deviation)
Myasthenia gravis
Restrictive ophthalmopathy (e.g. Brown's superior oblique tendon sheath syndrome)
Trauma (e.g. blow-out fracture of the orbit)
Ophthalmic Graves' disease
Orbital metastases
Orbital pseudotumour
Orbital infections (e.g. trichinosis)
Disease affecting extraocular muscle
Oculopharyngeal dystrophy
Myotubular myopathy
Myotonic dystrophy
Kearns–Sayre syndrome (mitochondrial cytopathies)

Sometimes, the diagnosis only becomes evident with serial MRI scans. Occasionally, hemorrhage occurs into a pituitary tumour, causing the syndrome of pituitary apoplexy.

As the oculomotor nerve passes through the superior orbital fissure it divides into superior and inferior branches; isolated involvement of either ramus has been reported.

Etiology of multiple oculomotor nerve palsies

The main causes of multiple oculomotor nerve palsies are trauma, basal arachnoiditis and tumour infiltrations, lesions within the cavernous sinus (where the three nerves are adjacent), and generalized neuropathies (Table 44.6).

A low-grade inflammatory disorder of the cavernous sinus produces the Tolosa–Hunt syndrome (Campbell & Okazaki, 1987). It is a disease of middle or later life, and the presenting complaints are retro-orbital pain and diplopia. The third or sixth nerve or combinations of oculomotor nerves may be involved. Sensation over the first two divisions of the trigeminal nerve may be impaired. Slight proptosis and impairment of visual acuity may occur. Diagnosis is by imaging, which demonstrates soft-tissue infiltration in the cavernous sinus, sometimes with extension into the orbit apex, but without erosion of bone (Goto et al., 1990). Corticosteroid medications usually produce a prompt improvement.

The third, fourth, and sixth cranial nerves may be involved as part of a generalized neuropathy associated with toxins or the Guillain–Barré syndrome. The Miller–Fisher variant of the latter condition consists of ophthalmoplegia, areflexia, and ataxia. The pattern of ophthalmoparesis may sometimes suggest central involvement, mimicking gaze palsies or internuclear ophthalmoplegia. Evidence suggests that anti-GQ1b antibodies play a key role in producing the disturbance of eye movements in Miller–Fisher syndrome, Guillain–Barré syndrome, and Bickerstaff's encephalitis (Newsome-Davis, 1997; Ohtsuka et al., 1998). As in Guillain–Barré syndrome, *C. jejuni* may be the responsible trigger, since anti-GQ1b antibodies bind to surface epitopes on this organism (Jacobs et al., 1995). Testing for anti-GQ1b antibodies may be positive in patients presenting with unexplained ophthalmoparesis (Yuki, 1996).

Disorders of ocular alignment not related to disease of the oculomotor nerves

Table 44.7 summarizes the various central and peripheral disorders that may mimic oculomotor palsies. Concomitant strabismus, in which the deviation is constant for all

fields of gaze, is most commonly encountered in children but may occasionally present in adulthood, for example, after one eye has been patched for ophthalmic reasons. Spasm of the near triad (convergence spasm) occurs in hysterical patients and can usually be detected by careful observation of the pupils and by demonstration of a full range of eye movements with one eye viewing or in response to rapid, passive head turns (Griffin et al., 1976). The skew deviation associated with the ocular tilt reaction (OTR) may be difficult to distinguish from peripheral muscle palsies (Donahue et al., 1999).

When diplopia is due to myasthenia gravis, characteristics findings are fatigue brought on by sustained upward or lateral gaze and involvement of extraocular muscles supplied by more than one nerve. Ptosis is common. Such patients may have characteristic 'quiver' eye movements, in which saccades begin at a high speed but fatigue in mid-flight. Intramuscular administration of neostigmine, looking for a change in saccade accuracy, may be useful in documenting a response to anticholinesterase inhibitors in ocular myasthenia gravis. Improvement in eye or lid movements following application of an ice pack or after a brief nap is also diagnostically helpful.

Restrictive ophthalmopathy includes congenital conditions such as Brown's syndrome, in which the adducted eye cannot be elevated (Wilson et al., 1989), sequelae of orbital trauma, and inflammatory conditions. Thyroid ophthalmopathy characteristically causes impaired elevation, and extortion of the eye on abduction (Dresner & Kennerdell, 1985). Thyroid function tests may be abnormal and MRI or computed scanning of the orbit, or orbital ultrasonography may demonstrate enlarged extraocular muscles. Progressive limitation of ocular motility, accompanied by ptosis, is a feature of mitochondrial disorders as well as a number of dystrophic processes. Diplopia is an uncommon complaint in these conditions.

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45

Disorders of the auditory system

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The human auditory system possesses a remarkable ability to evaluate the acoustic environment and to provide the information necessary for normal function and survival. The process of evaluation begins at the periphery, in the ear. In the cochlea, auditory information is frequency analysed, amplified or attenuated, sharply tuned and transformed into electrical neural impulses, which are transmitted and processed in the auditory nerve. In the central auditory system, complex processing of acoustic signals, such as binaural fusion and sound localization, takes place, as well as various perceptual and cognitive processes. The efferent system plays a role in modulation of the auditory information, by balancing the processes of excitation and inhibition. Tonotopic organization, i.e. the anatomical arrangement according to sound frequencies, exists throughout the entire auditory system, and facilitates the maintenance and enhancement of frequency discrimination. The integral parts of the auditory system interact through complex, mainly feedback mechanisms, creating a highly dynamic system, in which abnormal functioning at one level may have functional consequences at other level(s). This functional plasticity in the auditory system is, for instance, reflected in the phenomenon of tonotopic reorganization in the cortex as a result of cochlear damage, and, in the opposite direction, an abnormality in the central auditory system may lead to disinhibition phenomena at the cochlear level. There is a myriad of functional disorders, resulting from pathology in the auditory system, with the loss of hearing sensitivity being the most important. From a neurological point of view, the understanding of auditory dysfunction has considerable importance, as neurological lesions may be associated with damage of auditory pathways. The identification of auditory dysfunction, its relationship to particular anatomical structure(s), and localization of the underlying pathological process, are subjects of continuing interest to both clinicians and scientists. With advances in science and technology, there has been significant progress in gaining better insight into this fascinating system.

Functional anatomy of the auditory system

Outer and middle ear

The outer ear assists in localizing a sound source and serves to reinforce the resonance of the tympanic membrane.

The middle ear (Fig. 45.1) contains the three interarticulated auditory ossicles, which form an elastic spring, the stiffness of which is controlled by the two middle ear muscles, the stapedius and the tensor tympani. Acoustic stimulation leads to contraction, mainly of the stapedius, reducing the middle ear transmission of sound. The neural network of the stapedial reflex is integrated in the lower brainstem and consists of both ipsilateral and contralateral routes, with the efferent pathway in the facial nerve.

The inner ear – cochlea

The inner ear (Fig. 45.1) consists of the organs of balance and the cochlea. The cochlea is divided longitudinally by the basilar and Reissner's membranes into three chambers: the scala vestibuli, tympani and media. The scala vestibuli and tympani contain perilymph. Via the Sylvian aqueduct, the perilymphatic system communicates with the subarachnoid space of the posterior cranial fossa. The scala media is continuous with the vestibular membranous labyrinth, which contains endolymph. The organ of Corti (Fig. 45.2) contains the auditory sensory receptor, located on the basilar membrane and includes both outer (OHC) and

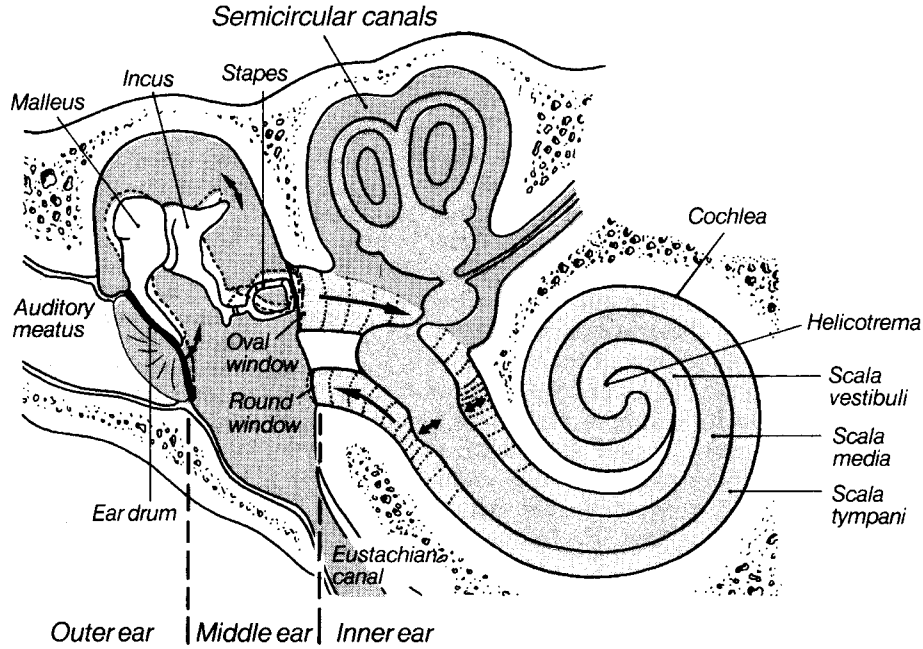

Fig. 45.1. A cross-section of the middle and inner ear. The dotted lines in the middle ear (together with arrows) indicate vibratory movements of the ossicular chain, and the perilymph of the inner ear is driven by sound pressure waves; in the inner ear, longitudinal arrows show the direction of the travelling wave propagation and transverse arrows the site of maximal displacement and vibrations of the scala media. (Adapted from Despopulous & Silbernagl, 1991.)

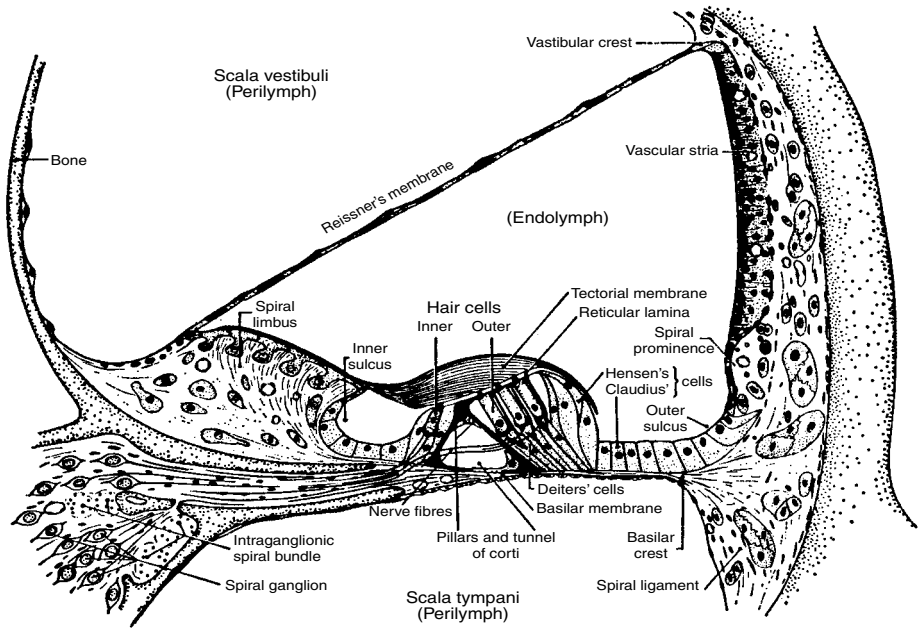

Fig. 45.2. A cross-section of the organ of Corti. (Davis and Associates, 1953.)

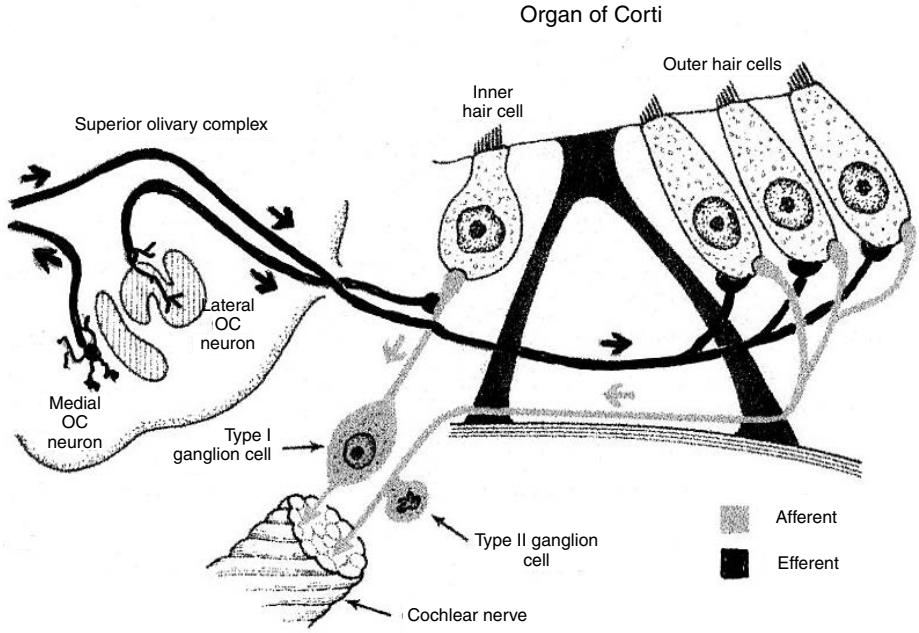

Fig. 45.3. The afferent and efferent innervation of the cochlea. (Schuknecht, 1993.)

inner hair cells (IHC). The OHCs are characterized by the presence of contractile elements, actin–myosin complexes, which are responsible for active mechanical responses in the cochlea.

The vibrations of the stapes footplate in the oval window, induced by sound pressure, cause a passive dynamic displacement of the cochlear partition in the shape of a travelling wave (von Békésy, 1960). As the walls of the endolymphatic duct (scala media) are flexible, the travelling waves are transmitted to the scala tympani, and the wave-like distortion of the endolymphatic duct causes Reissner's membrane and the basilar membrane to swing from one side to the other alternately.

However, the cochlea is not just a passive mechanical signal analyser, but plays an active role in the mechanical processing of sound. The source of active behaviour, as mentioned above, is the OHCs, with their motor capacity for fast oscillating and slow tonic contractions. The fast contractions (Brownell et al., 1985) are phase-locked to the stimulating sound and follow sound-driven passive vibrations of the cochlear partition. They stimulate the actinomyosin network of OHCs, acting to oppose viscous damping in the cochlea and to enhance the oscillations of the cochlear partition. These active oscillations of the OHCs are responsible for the generation of otoacoustic emissions (described below). The slow tonic contractions of OHCs (Zenner, 1986) can alter the stiffness of the cochlear partition in a sharply restricted area, thus modifying the envelope of the travelling wave. These slow contractions result from the activity of the efferent system.

The OHC fast (a.c.) motility, which amplifies sound (by ≈40 dB, near hearing threshold), is linearly correlated to the intensity of sound. However, with an increase in sound pressure level, the cochlea is capable of correcting undesirable (high) shifts of the basilar membrane by the slow OHC (d.c.) movements, leading to reduction of the passive displacement, and non-linear compression of cochlear dynamics (attenuation). Thus, OHCs act as controlled mechano-amplifiers, and feed mechanical oscillations to the IHCs, which are directly involved in the transformation of mechanical energy into neural activity.

Cochlear innervation

The organ of Corti has efferent and afferent innervation (Fig. 45.3). Efferent fibres (see below Efferent system) originate in the superior olivary complex. The lateral olivocochlear (OC) fibres project to afferent fibres of the IHCs, while the medial OC fibres project directly onto the OHCs. About 90–95% (Spoendlin, 1979) of the afferents originate from the IHCs, while approximately 5–10% of them originate from the OHCs. This means that the acoustic information transferred from the cochlea almost exclusively comes from the IHCs.

In contrast, about 95% of all efferent fibres have direct and wide synaptic contact with the OHC bodies, whilst an almost negligible number of the efferent neurons have

indirect postsynaptic contact with IHCs. The afferent fibres form the cochlear nerve, and efferent fibres form the olivocochlear bundle, which travels within the vestibular nerve bundle.

Glutamate is the main neurotransmitter of the afferent fibres. Beside its potent excitatory effect, glutamate also displays a highly neurotoxic effect, observed in various pathological conditions, e.g. acoustic trauma (Puel, 1995).

The efferent olivocochlear innervation to the OHCs provides control of the OHCs via predominantly cholinergic fibres (basal OHCs, for high frequencies) and γ-aminobutyric acid (GABA)-ergic fibres (apical OHCs, for low-frequencies).

The distinctly different innervation pattern of the IHCs and OHCs implies specific physiological roles of the dual sensory system in the cochlea: IHCs as the primary sensory cells that generate action potentials in the auditory nerve, and OHCs as the active mechanoreceptors, which are controlled and modulated by the central nervous system.

Retrocochlear afferent auditory system

The auditory nerve

The auditory nerve, together with the vestibular nerve, passes through the internal acoustic meatus. The high frequency fibres lie on the periphery, while mid–low frequency fibres lie more medially in the nerve. This may explain why the high frequencies are often affected initially by an acoustic neuroma. The auditory nerve enters the brainstem at the cerebellopontine angle, behind the cerebellar peduncle. It branches into three major divisions, to the cochlear nuclei (CN) (Fig. 45.4). These three divisions are located on the posterolateral surface of the pontomedullary junction, so an extra-axial expanding lesion (e.g. from the cerebellopontine angle) may affect the branches or the nuclei causing, respectively, peripheral and central auditory deficits. As the CN receive only ipsilateral input, pathology at this site produces unilateral hearing deficit. The afferents are arranged in the CN according to frequency (tonotopic organization) and various cell types in the CN analyse different aspects of sound. The CN play a fundamental role in the extraction of temporal auditory information (amplitude modulation) from auditory nerve responses and, within these nuclei, lateral inhibition enhances auditory contrast.

The fibres from the CN project ipsi- and contralaterally to the superior olivary complex (SOC), lateral lemniscus (LL) and the nuclei along the LL, and to the reticular formation. Some of the fibres from the CN bypass the SOC and the nuclei of the LL and project directly to the inferior colliculus. Bilateral projections from the CNs to the higher auditory pathways enable the comparison of intensity and travelling time of sound (lateralization).

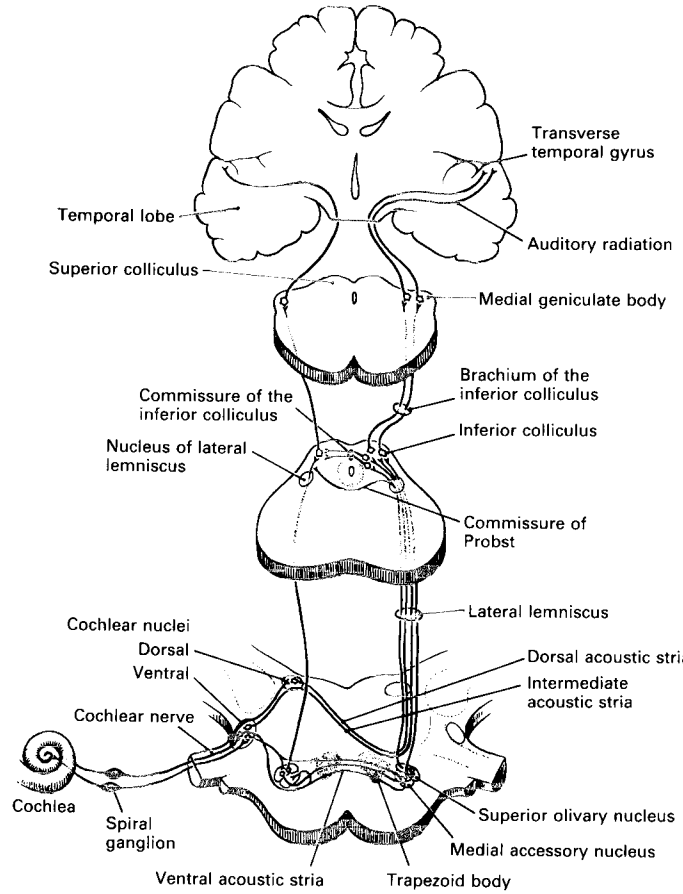

Fig. 45.4. Schematic illustration of the afferent auditory system. (Benjamin & Todd Troust, 1988.)

The superior olivary complex (SOC)

The SOC is composed of several nuclei, including the lateral (LSO) and medial (MSO) nuclei. Both of these structures receive bilateral innervation, and, therefore, provide the anatomical basis for binaural representation and integration of binaurally presented signals (interaural time, phase and intensity difference). A lesion in the SOC may lead to abnormal binaural interaction. However, unilateral disruption of auditory pathways at this level and above, would not lead to a significant hearing loss, due to the crossed, bilateral ascending auditory input.

The lateral lemniscus (LL)

The LL is a major auditory tract containing afferent and efferent fibres. The LL on both sides communicate through

the commissure of Probst, or via the pontine reticular formation.

The inferior colliculus (IC)

The IC receives the auditory fibres predominantly crossing from the opposite side. The IC is highly tonotopically organized and is characterized by extremely sharp tuning curves, suggesting a high degree of frequency resolution. Some of the neurons in the IC are time and spatially sensitive, suggesting a role in temporal and spatial resolution, and ultimately, in sound localization coding.

The medial geniculate body (MGB)

The MGB has ventral, dorsal and medial divisions, of which the ventral contains mainly acoustically responsive cells, while the other divisions are sensitive to both sensory and acoustic stimulation. The MGB is also tonotopically organized and is thought to play a role in the analysis of both binaural stimuli and inter-aural intensity differences. At this level, the processing of natural speech is thought to begin.

From the MGB, there are multiple and complex thalamocortical projections upon the tonotopically organized cortical fields. The major thalamo-cortical pathway, consisting mainly of auditory fibres, originates from the ventral MGB and projects to the primary auditory cortical area in Heschl's gyrus. Another thalamo-cortical pathway, containing in addition to auditory, somatic and, possibly, visual fibres, runs towards the external capsule, and from there to the insula.

The auditory cortical area

The auditory cortical area encompasses the posterior three-quarters of the Sylvian fissure, including the superior temporal lobe, the inferior–posterior frontal lobe and the inferior parietal lobe. Heschl's gyrus is considered the primary auditory cortical area, which receives most of the thalamocortical projections and is tonotopically organized, suggesting that most of the auditory information is processed initially in this area. The secondary auditory cortical areas include the planum temporale, which is significantly longer on the left than on the right side and is located approximately in Wernicke's area, suggesting involvement in receptive language function (left hemisphere is dominant for speech) (Musiek, 1986). Other acoustically responsive areas are the supramarginal gyrus and the insula. The inferior part of the parietal and frontal lobes and the claustrum are also responsive to acoustic stimulation.

The primary auditory area has intra- and interhemispheric connections to different parts of the brain. The auditory cortical areas also have connections to the frontal lobe, including the arcuate fasciculus, which connects Wernicke's and Broca's areas. These connections enable activation of different specialized secondary areas, depending on the complexity of the auditory signals. The secondary, association, areas for hearing are responsible for a variety of complex auditory processing, including the analysis of complex sounds (e.g. noise, music or speech decoding); short-term memory for comparison of tones; inhibition of unwanted motor responses and for intent listening. Lesions of these areas in the dominant hemisphere may lead to a specific loss of function (e.g. sensory aphasia in a lesion of the left hemisphere).

The corpus callosum (CC) contains inter-hemispheric auditory fibres, which connect the cortices of each hemisphere, predominantly homolaterally. The auditory segment of the CC is confined to the posterior half. This is supported by the findings on central auditory tests in patients with section of the posterior part of the CC (Musiek, 1986). The results of animal research indicate the presence of excitatory and inhibitory fibres, suggesting a role of the CC in modulating the activity in both hemispheres, allowing optimal integration of cortical responses. This may be of particular importance for those processes, in which one hemisphere may be dominant, e.g. left hemisphere is dominant for language and sequencing of auditory stimuli, while the right is dominant for spatial auditory perception and the perception of music.

Efferent system

The efferent system runs in parallel to the afferent system, from the cortex to the cochlea, but it is less well defined than the afferent auditory system. It is thought that there is a pathway from the cortex to the MGB and another from the cortex to the various nuclei in the brainstem. The IC receives input from both the cortex and the MGB. From the IC, there are efferent connections to the SOC system and the CN, and to the nuclei of the LL.

The best known part of the efferent system is the olivocochlear (OC) system (Fig. 45.3), arising from the SOC. Fibres from the lateral SO nucleus are arranged in the predominantly uncrossed, lateral olivo-cochlear bundle (LOCB) which projects to afferent fibres of the IHC (see above). The fibres from the medial nucleus are arranged in the mainly crossed, medial olivo-cochlear bundle (MOCB) and project directly onto the OHC. During this course, the MOCB runs in the floor of the fourth ventricle.

The medial efferent olivo-cochlear (MOC) system is considered to be inhibitory (Wiederhold, 1986) and responsible for the control of the OHC motility. It also appears to

be responsible for automatic gain control, adaptation and homeostasis of the cochlea. Anatomical and physiological studies of the IC connections with the SOC system strongly suggest that the IC plays a role in the activity of the OC system.

However, very little is known about the lateral olivocochlear system. It is believed that it modulates sensitivity of the afferent receptors and may have a protective role against excessive noise and/or excitotoxicity (Pujol, 1994; Sahly et al., 1999).

The efferent auditory system with its multisynaptic connections from the cortex to the cochlea suggests the presence of an efficient feedback mechanism, providing a balance between excitatory and inhibitory stimuli. Its assumed role is to facilitate and enhance the targeted acoustic signal and to inhibit unwanted signal, such as noise. It also mediates frequency-selective auditory attention.

Extra-auditory neural connections

The auditory pathways have connections with other parts of the central nervous system.

The reticular formation

A serotoninergic input to the lower brainstem area may provide a basis for modulation of the olivocochlear and middle ear (stapedial and tensor tympani) reflexes (Thompson & Thompson, 1995).

The somatosensory system

The medial division of the MGB (a multisensory thalamic area) probably plays the most important role in the phylogenetically 'old' connection between the auditory and somatosensory systems. Connections with the somatosensory system are also possible via the *extralemniscal system*, which branches off from the classical ascending lemniscal auditory system at the level of the IC and projects to the association cortices (prefrontal area, limbic portions, temporal, parietal and occipital areas) rather than to the primary auditory cortex (Graybiel, 1972). Neurons of the extralemniscal system respond much less specifically to sound stimulation than neurons in the lemniscal system and receive input, not only from the auditory, but also from the somatosensory system. Therefore, somatosensory stimulation, in addition to auditory stimulation, may lead to the perception of sound (e.g. electrical stimulation of the median nerve in some individuals may lead to the perception of tinnitus: Møller et al., 1992).

Another important relay in the polysensory system is the superior colliculus, which includes maps of visual and tactile receptive fields, aligned with the auditory map, and which, in part, therefore, coordinates auditory, visual and somatic information (Huffman & Henson, 1990).

The hypothalamus

The hypothalamus provides input to the auditory pathway via the IC (Adams, 1980).

The limbic system

The limbic system receives projections from the MGB and this link is hypothesized to serve in the attachment of emotional significance to acoustic stimuli (LeDoux et al., 1983).

The cerebellum

The cerebellum is linked to the auditory system probably via the cochlear nuclei (Gacek, 1973), allowing adjustment in the position of the body and the head to the location of sound. The descending acousticomotor system (Huffman & Henson, 1990) involves acousticomotor centres in the cerebellum, the superior colliculus and the medial nucleus of the MGB, which receive projections from the external nucleus (multisensory nucleus) of the inferior colliculus, allowing multisensory integration.

Functional correlates of the pathology in the auditory system

Abnormalities at different levels of the auditory system may have different functional consequences. The most important is hearing loss, which may be associated with other dysfunctions, including loudness recruitment, abnormal auditory adaptation, tinnitus and/or hyperacusis. Other auditory attributes, such as those related to frequency selectivity, temporal resolution (detection of a gap between two stimuli), pitch perception, sound localization, auditory pattern perception, speech perception, or those related to other complex processing of the auditory information are beyond the scope of this brief description.

Hearing loss

Peripheral hearing loss results from abnormalities of the external/ middle ear, cochlea and auditory nerve, up to the entry into the brainstem, beyond which, central hearing impairment occurs. Hearing loss may be divided into two types: conductive and sensorineural. Conductive hearing loss is consequent upon occlusion of the external ear canal, or secondary to pathology of the middle ear and indicates inadequate transmission of sound from the environment to the inner ear. Sensorineural hearing impairment results

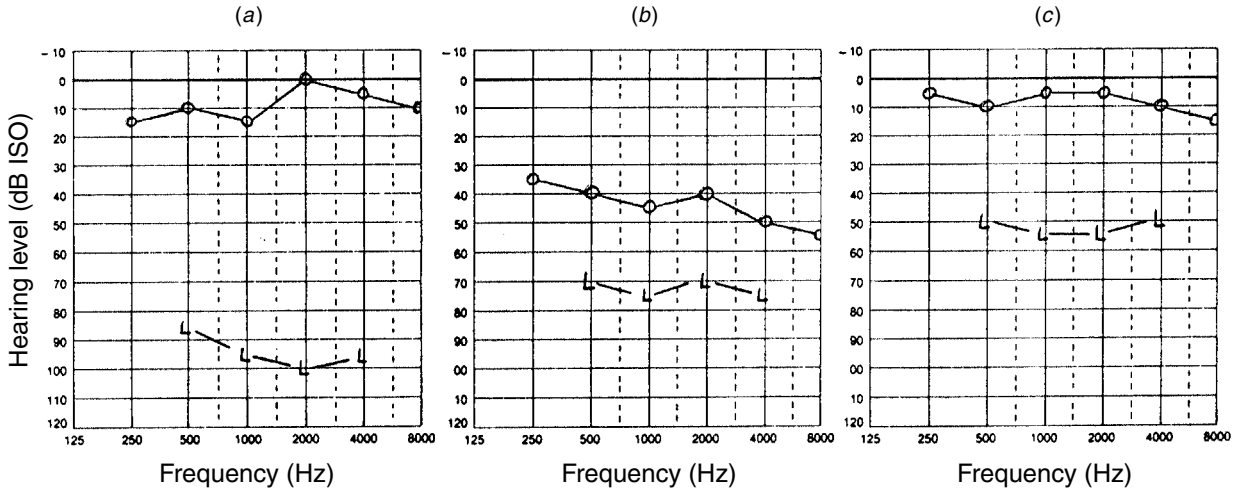

Fig. 45.5. Examples of cochlear dynamic range: in normal subjects (*a*), in cochlear lesion with loudness recruitment (*b*) and narrow dynamic range in hyperacusis (*c*).

most commonly from pathology in the cochlea, less commonly from the auditory nerve, and rarely from a central auditory abnormality.

It is of clinical importance to distinguish conductive from sensorineural hearing loss; sensorineural hearing loss of cochlear origin from that of retrocochlear origin; sensorineural hearing loss resulting from pathology of the VIIIth nerve, from that due to brainstem pathology and higher auditory pathways. The distinction may be extremely difficult if pathology involves both sensory and neural structures.

Loudness recruitment

Loudness recruitment can be defined as an abnormal growth of loudness as a function of suprathreshold sound intensity. This phenomenon is associated with cochlear lesions, in particular OHC damage, although it has been reported in patients with brainstem lesions (Dix & Hood, 1973). One of possible explanations of loudness recruitment is the loss of non-linearity in response to sound as a function of the intensity. In the cochlea, the source of non-linearity are the OHC (as explained in the section on Functional anatomy), which are responsible for the enhancement of sensitivity of signals at low intensity, while responses at high sound levels display saturation. Therefore, patients with extensive OHC lesion, have reduced hearing sensitivity at low sound levels, while with increasing sound intensity, the growth of loudness is passive and linear. An analogous explanation for the presence of loudness recruitment in brainstem lesions could be offered, which may arise due to the damage of neural fibres/nuclei, which are responsible for non-linear intensity coding.

Patients with this type of abnormality complain that loud sounds (e.g. >70 dB) are uncomfortable and even painful. Loudness discomfort levels (LDL) represent the lowest intensity of sound which the individual finds uncomfortably loud, and in normal subjects is in the range 95–115 dB hearing level (Fig. 45.5(a)). In cochlear pathology, the dynamic range is reduced (Fig, 45.5(b)).

Tone decay (or abnormal auditory adaptation)

This phenomenon refers to a very rapid decrease in neuronal responses, while the response to the onset of a sound may be normal or near normal. A reduction of the number of normally functioning auditory nerve fibres has been proposed as one explanation of this phenomenon. It manifests by the loss of sensitivity to a continuous tone (but normal sensitivity to an interrupted tone) in the affected ear, while hearing sensitivity in the unaffected ear persists as long as the stimulation.

Hyperacusis

Hyperacusis can be defined as an abnormal growth in loudness but, unlike loudness recruitment, patients complain of loud perception of ordinary environmental sounds. In the majority of cases it is associated with normal hearing. It is assumed that hyperacusis results from raised spontaneous auditory activity and is considered by some authors to be a condition preceding tinnitus. One of the hypotheses for the

underlying mechanism is disinhibition of efferent feedback auditory control, leading to an increased gain in auditory function. This hypothesis may explain hyperacusis which has been reported in facial/Bell's palsy and in the Ramsay–Hunt syndrome. In these cases, the stapedial reflex, which normally reduces acoustic input, is affected. Hyperacusis is judged clinically by measuring loudness discomfort levels (LDL) which are considerably lower in patients with hyperacusis than in normal subjects (Fig. 45.5(c)).

Tinnitus

Tinnitus is an auditory perception in the absence of external stimulation and it has been assumed that it results from an altered state of excitation and/or inhibition within the auditory system. Aberrant activity, which may be caused by different pathologies and at different levels of the auditory system, may interact with psychological factors, such as stress or depression.

Tinnitus is a subjective phenomenon and so far there has been no convincing objective evidence for tinnitus-related activity. However, the recent emergence of functional imaging techniques has provided new insight into the generation of this symptom. Single-proton emission computed tomography (SPECT), positron-emission tomogaphy (PET) and functional magnetic resonance imaging (fMRI) have demonstrated that more auditory cortical areas are activated in patients with tinnitus than in controls subjects, including the medial temporal lobe and the limbic areas (Shulman et al., 1995; Lockwood et al., 1998, 1999; Levine, 1999). The extent of the neuronal network involved is thought to influence the quality and attributes of tinnitus (e.g. a link to the limbic system may explain the emotional response to tinnitus).

Undoubtedly, functional imaging techniques have pushed forward the frontiers in research on tinnitus, supporting some of the hypotheses and providing new information on spatial aspects of tinnitus-related processing. However, temporal aspects of neural activity which may underlie tinnitus generation remain poorly understood.

Several pathophysiological mechanisms for the generation of tinnitus may be considered:

Abnormal afferent excitation at the cochlear level

- Spontaneous cochlear (OHC) activity, identified by the recording of spontaneous otoacoustic emissions, could be a cause of tinnitus in a small number ($\approx$4%) of patients (for review see Ceranic et al., 1995).
- Glutamate neuro-excito-otoxicity, e.g. in exposure to excessive noise (Pujol, 1994).
- Modulation (enhanced sensitivity) of NMDA and non-NMDA receptors by endogenous opioid peptides dynorphins, released onto the IHC synaptic region by the lateral olivocochlear fibres, as a part of the response to stress (Sahly et al., 1999).

Efferent dysfunction/reduction of GABA effect

Several studies have suggested dysfunction (a reduction in the suppressive effect) of the medial olivocochlear system, and furthermore, a global efferent dysfunction (Attias & Bresloff, 1998), as the underlying mechanisms to tinnitus.

It has also been suggested that general age-related reduction of GABA may contribute to the development of tinnitus in the elderly.

Abnormal auditory activation

- Irritative lesions (e.g. tumours, Espir et al., 1997; Milicic & Alçada, 1999)
- Activation of the auditory system through the activation of other motor/sensory systems, e.g. visual, such as that occurring in a gaze-evoked tinnitus, or tinnitus provoked by jaw clenching (Lockwood et al., 1999); tinnitus evoked by electrical stimulation of the median nerve (Møller et al., 1992). There are also patients who have developed gaze-evoked tinnitus after surgical removal of an acoustic neuroma (Cacace et al., 1994).

Alteration of spontaneous activity due to tonotopic reorganization

Peripheral lesions/dysfunctions, with sound deprivation or overstimulation, result in plastic transformations within the brain (Møller, 2000). The findings from electrophysiological studies and functional imaging (PET, fMRI) of expansion of the brain regions responsive to tones, provide strong evidence for plastic transformation of the brain in these patients. Similar observations have been made in experimental animals after damage to the cochlea (Recanzone et al., 1993). The area in the auditory cortex deprived of its characteristic frequency acquires a new characteristic frequency, which corresponds to that at the edge of the region of cochlear damage, leading to an expansion of cortical representation of a restricted frequency band adjacent to the region of cochlear loss (Robertson & Irvine, 1989). These data suggest that tinnitus may be due to altered spontaneous activity in the CNS due to aberrant neural pathways formed during plastic transformation of the brain.

Stress-related neuro-humoral activity

Circumstantial evidence exists that stress is of relevance in the generation of tinnitus, particularly in individuals with negative psychological conditions, or individuals with psychiatric disturbances. Stress may activate various

biological functions, including the sympathetic adrenal medullary system, with secretion of catecholamines, and the hypothalamic pituitary–adrenocortical system, with the secretion of glucocorticoids (e.g. Cortisol). Failure in homeostasis may lead to abnormal functioning of the auditory system, including the emergence of tinnitus.

Investigation

In addition to the assessment of auditory function, it is important to test vestibular function, in view of the common pathology which may occur at the labyrinthine (Fig. 45.1) and vestibulocochlear nerve levels. There is also the possibility of an abnormality in the acoustico-motor centres in the cerebellum, which reflects in concurrent central auditory and vestibular manifestations (Shulman & Strashun, 1999).

A detailed otoscopic examination is essential in the investigation of hearing disorder and the most relevant tests which serve to define auditory dysfunction are described.

Tuning fork tests

These are simple tests to differentiate conductive from sensorineural hearing loss: the Rinne test identifies a conductive component to hearing loss and the Weber test may detect asymmetrical sensorineural hearing loss, or lateralize a conductive loss.

Pure-tone audiometry

This is a routine clinical technique to determine hearing threshold levels for pure-tone stimuli. In conductive hearing loss the audiogram indicates an air–bone gap, as bone conduction is normal, while cochlear/retrocochlear lesions produce sensorineural hearing impairment, with similar deficits in both air and bone conduction (Fig. 45.6).

Tympanometry

Tympanometry assesses the mechanical properties of the middle ear: the ear drum compliance and the pressure in the middle ear. This test complements the identification of middle ear disorders.

Stapedial reflex

Unilateral acoustic stimulation leads to contraction of the stapedial muscle bilaterally (Fig. 45.7), thus increasing the resistance to the sound transmission through the middle ear, by up to 15 dB.

Acoustic reflex thresholds are measured in response to ipsi- and contralateral tones. They are elevated/absent in conductive and retrocochlear hearing loss. Depending on the site of a lesion and the part of the reflex arc involved, different, characteristic patterns of ipsi- and contra-lateral reflexes can be observed (Fig. 45.8).

Decay of the stapedial reflex reflects abnormal transmission of acoustic signal through the auditory nerve, by the inability to sustain the reflex over a certain period of time. Decay is, therefore, indicative of a neural (e.g. in acoustic neuroma), or a brainstem lesion.

Speech audiometry

The speech discrimination score is affected by the site of a lesion. In the case of cochlear hearing loss, the discrimination score parallels to the hearing loss and can be restored by increasing the intensity of sound. However, in the case of neural hearing loss, there is disproportionally worse speech discrimination than would be expected considering the pure-tone audiometric thresholds.

Otoacoustic emissions

Otoacoustic emissions (OAEs) are weak signals that can be recorded in the sealed ear canal and are considered to reflect cochlear, OHC activity (Kemp, 1978).

All OAEs can be divided in two classes: spontaneous and evoked. Spontaneous otoacoustic emissions are continuous narrow-band signals emitted by the cochlea in the absence of any stimulation. Evoked otoacoustic emissions are recorded following stimulation by different stimuli: transient evoked otoacoustic emissions (TEOAEs), evoked by transient impulses, or distortion product otoacoustic emissions (DPOAEs), evoked by two continuous tones at closely spaced frequencies. TEOAEs can be recorded in almost all normal subjects (Fig. 45.9). DPOAEs have similar characteristics as TEOAEs, however, they provide more frequency specific responses.

OAEs are applied in the evaluation of cochlear function and are particularly valuable in difficult-to-test subjects (e.g. children, or mentally retarded patients). They can also be used in the differential diagnosis of cochlear and retrocochlear lesions: if TEOAEs are recorded in subjects with a moderate or severe sensorineural hearing loss, this would strongly suggest a retrocochlear lesion.

It is important to note that OAE application is limited to those subjects with normal middle ear function, as a middle ear abnormality may alter the transfer of acoustic signals to the cochlea.

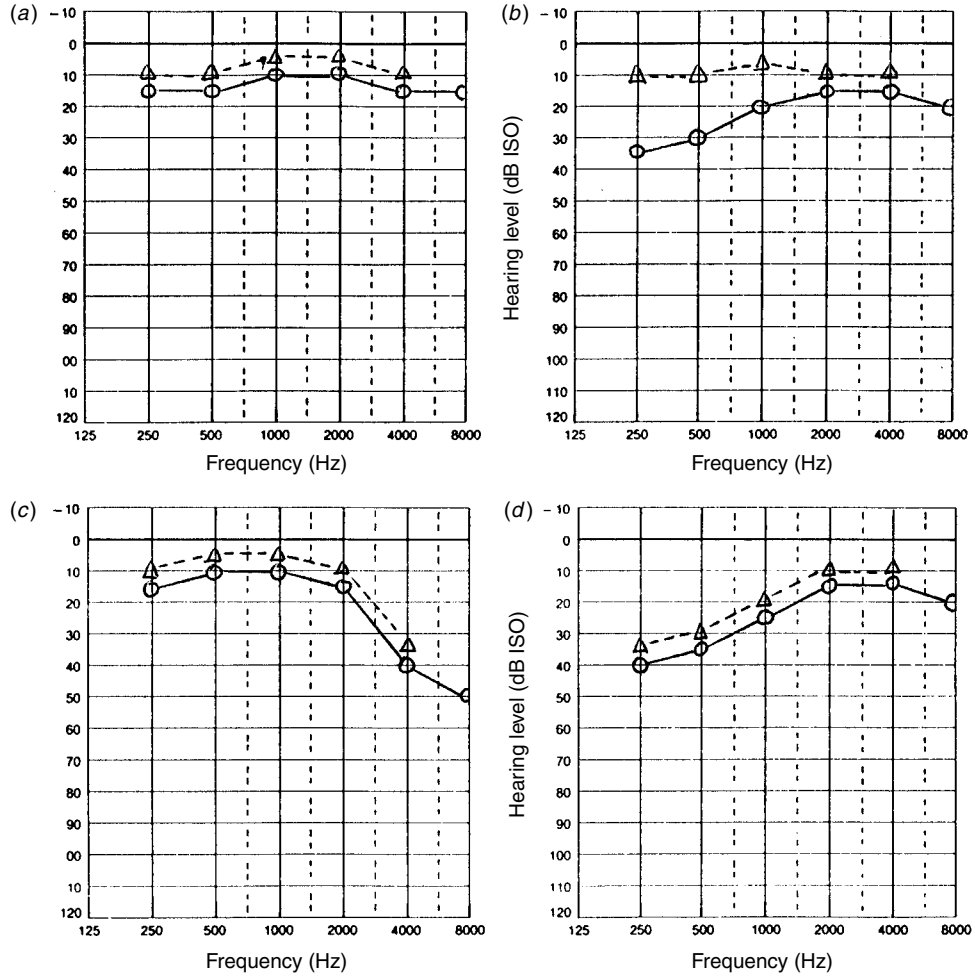

Fig. 45.6. Standard pure-tone audiogram, where the continuous line indicates air-conduction and the interrupted line indicates bone-conduction hearing threshold levels: (*a*) normal, (*b*) conductive, (*c*) sensorineural high-frequency sloping and (d) sensorineural low-frequency hearing loss.

Olivocochlear suppression test

This is an emerging technique for exploring the medial olivo-cochlear system, or so-called phenomenon of 'reciprocal cochlear interaction', in which acoustic stimulation of one ear suppresses TEOAEs in the opposite ear. The MOC suppression test provides general information on the structural integrity of the medial olivo-cochlear reflex arc, and a glimpse into the modulation of cochlear mechanics by efferent stimulation.

Electrophysiological testing

Electrocochleography (ECochG)

Three groups of ECochG potentials can be recorded: the cochlear microphonic, the summating potential, both thought to derive from mainly OHC activity, and the compound action potential, the synchronized activity of the auditory fibres, in response to stimulus onset.

ECochG is mainly used for the evaluation of cochlear function, e.g. in Menière's disease (the pathophysiological rationale is that deflection of the cochlear basilar membrane, consequent upon hydrops, creates an enlarged negative summation potential).

The auditory brainstem response (ABR)

The ABR is thought to be generated within the auditory pathway up to the inferior colliculus (Fig. 45.10). The ABR is particularly useful for the detection of acoustic neurinoma (typically prolonged wave V latency on the affected side) and is very sensitive in intra-axial brainstem lesions. The ABR is also used for objective threshold estimation,

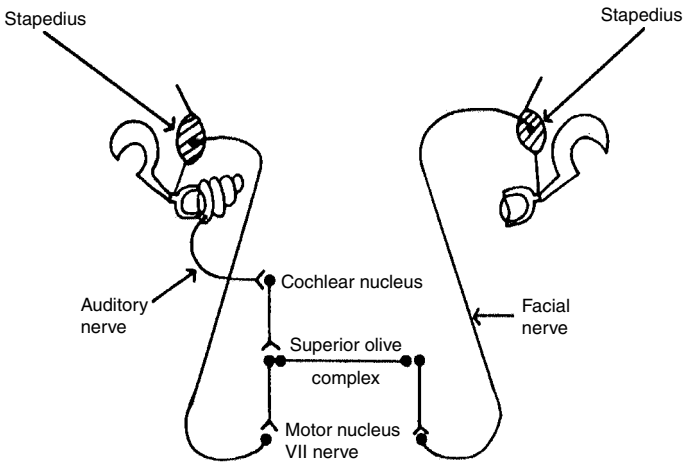

Fig. 45.7. Schematic illustration of main components of the ipsilateral and contralateral acoustic reflex. (Luxon & Cohen, 1997.)

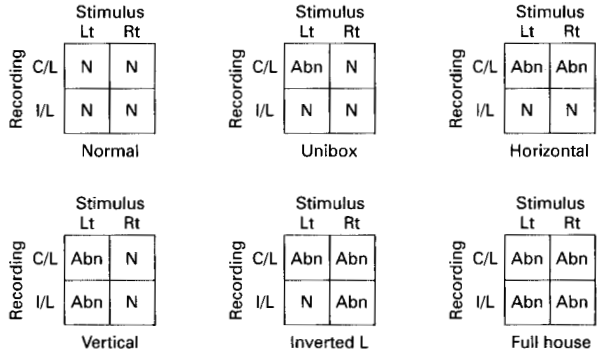

Fig. 45.8. Patterns of acoustic reflex thresholds and common interpretations (Lt-left, Rt-right, C/L-contralateral, I/L-ipsilateral): Unibox = small unilateral brain lesion medial to the cochlear nucleus; Horizontal = midline brainstem lesion; Vertical = left VIIIth nerve lesion; Inverted L = intra-axial brainstem lesion plus extension to the cochlear nucleus or VIIIth nerve on the affected side (a conductive lesion may present in this way); Full house = a midline brainstem lesion with extension to involve the cochlear nuclei and/or VIIIth nerves (N.B. bilateral conductive lesion needs exclusion); Abn = abnormal; N = normal. (Luxon & Cohen, 1997.)

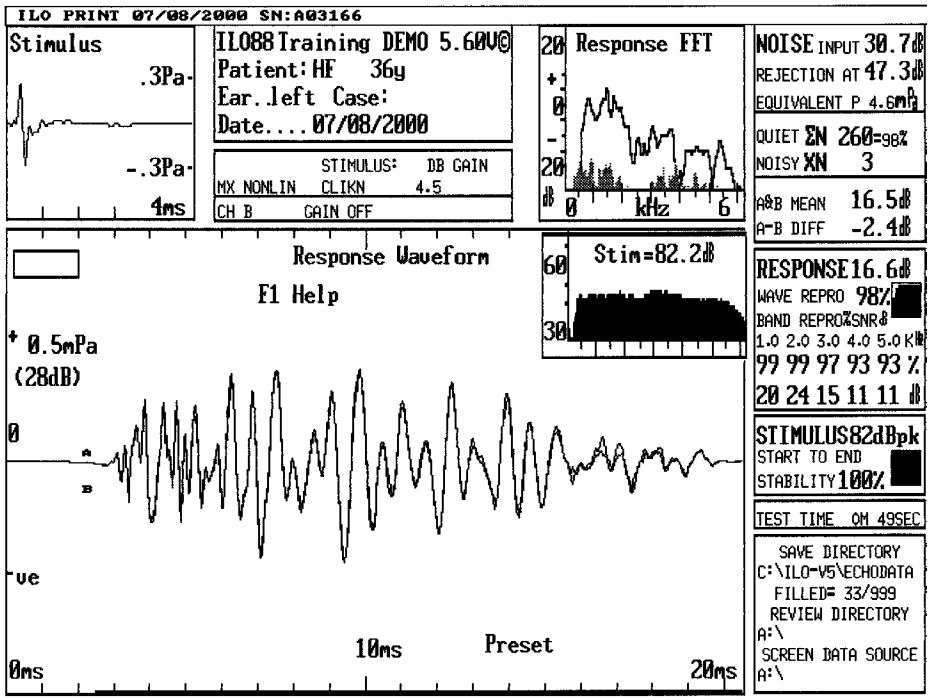

Fig. 45.9. Transient evoked otoacoustic emissions recorded following non-linear click stimulation (82.2 dBSPL) from a normal subject; in the response window (the largest box, denoted as Response Waveform), the waveforms (A and B), resulting from the signals averaged in two separate buffers, show a very high (98%) correlation (A and B almost completely overlap), suggesting a very good cochlear response; response signals are also analysed in frequency domain (Fast Fourier Transforms – FFT), shown above right; the overall response amplitude is automatically displayed, in this case 16.6 dBSPL, shown in the middle right box.

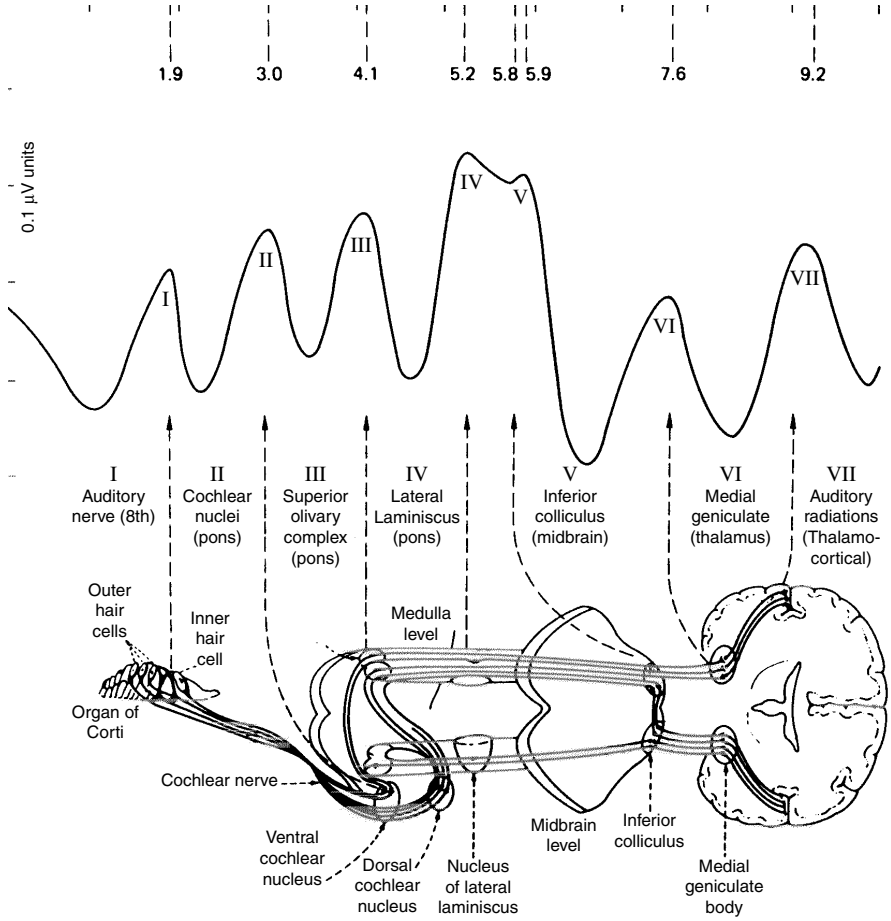

Fig. 45.10. Diagram of the anatomical correlates of the waves observed in the brainstem responses. (Duane, 1977.)

and the resistance to drug effects and general anesthesia make this technique suitable for objective evaluation of hearing thresholds in children.

Middle latency response (MLR)

The temporal lobe or thalamocortical projections are important for generation of the MLR, although it is most likely that multiple generators exist. Evaluation of the MLR is used for assessing the integrity of the central nervous system beyond the brainstem and for threshold estimation of low-frequency hearing sensitivity, as it is less dependent on neural synchrony than ABR. However, it is sensitive to the state of consciousness.

Auditory cortical responses (ACRs)

The ACRs originate mainly from the auditory cortical areas in the temporal lobe. They are generally elicited with a tone burst and, therefore, provide frequency specific responses, which are well correlated with subjective pure-tone thresholds. The ACRs are mainly used for objective threshold estimation, particularly in medico-legal cases, and are only applicable in alert subjects.

Event-related potentials (ERPs)

Unlike other auditory evoked responses, the ERPs are considered to be endogenous potentials, resulting from cognitive processing of sensory information. The temporal lobe and limbic structures, including hippocampus and amygdala, have been implicated as the major sources for the ERP.

The Mismatch negativity (MMN) is a component of the ERPs, generated by a change-discrimination process that mainly occurs in the auditory cortex. The MMN is attention-independent and can be obtained even from uncooperative individuals. In auditory pathology, the MMN might be useful in objective evaluation of cochlear implant function and for objective diagnosis of aphasic patients, dysphasic children and of children with auditory-based learning disabilities (Näätänen, 1995).

Central behavioural testing

Central behavioural tests (CBT) are applied in conjunction with electrophysiological tests and imaging techniques to define and localize an abnormality within the central auditory pathways. One of the limitations of these tests is that the assessment of central structures may be affected by peripheral abnormalities. In addition, due to the parallel organization within the central nervous system and involvement of several structures in a particular function, results may not provide information on the localization of a lesion. Another important consideration in CBT is the availability of adequate normative data.

CBT can be classified according to a common parameter, such as mode of presentation (e.g. monaural or binaural), or type of stimuli used (e.g. tones or speech), as outlined in Table 45.1 (Luxon & Cohen, 1997).

In the construction of the test battery, specific auditory tasks are used to assess specific auditory functions of a particular anatomical structure. For example, in the brainstem, binaural acoustic integration, the extraction of signals from background noise and sound localization occur, and, therefore, assessment of these functions is targeted. Cortical and hemispheric pathology produces subtle auditory dysfunctions which may not be correlated to a specific anatomical location. The classic findings of CBT are functional deficits in the ear contralateral to cortical and hemispheric pathology on dichotic testing.

Table 45.1. Behavioural tests of central auditory processing

A. Monoaural tests
- Degraded speech (filtered speech, interrupted speech, or compressed speech)
- Masked speech (speech-in-noise)
- Synthetic sentence identification with ipsilateral competing message (SSI–ICM)

B. Binaural interaction tests
- Congruent
  - Dichotic digit
  - Dichotic word
  - Dichotic sentence identification
  - Nonsense syllables
- Non-congruent
  - Binaural fusion
  - Rapid alternating speech
  - Interaural intensity difference
  - Masking level difference (MLD)
  - Interaural timing

C. Binaural separation
- Competing sentences
- Threshold of interference

D. Sequencing tasks
- Pitch pattern
- Duration pattern
- Intensity pattern
- Psychoacoustic pattern discrimination

Functional imaging techniques

Functional magnetic resonance imaging (fMRI) of auditory cortical activity

It has been observed that passive and active speech listening generate greater activation of the left than the right hemispheres and this is thought to be related to the left hemisphere specialization for processing spectral changes (Hall et al., 2000) (Fig. 45.11, see colour plate section).

Positron emission tomography (PET)

Studies on functional organization within the auditory cortex support the view of the existence of a hierarchy in functioning of the cortical areas. For example, simple auditory stimuli activate predominantly the contralateral primary cortical area 41, stimuli with interrupted pattern activate bilateral area 42, and stimuli with complex spectral, intensity and temporal structure, such as speech or music, activate more extensive association auditory areas (Mirz et al., 1999).

Etio-pathogenesis of hearing disorders

External/middle ear

The pathology at this level may sometimes affect the more proximal auditory pathway. A severe form of otitis externa (*Pseudomonas aeruginosa*), may spread through the adjacent structures and affect the auditory nerve. The middle ear disease can expand towards the apex of petrous bone (petrositis), affecting the abducens nerve and trigeminal ganglion, with the presentation of Gradenigo's syndrome: otitis media, VIth nerve palsy and trigeminal neuralgia. Involvement of the auditory nerve may lead to hearing loss on that side.

Inner ear (cochlea)

Cochlear lesions can be acquired due to various noxious factors, such as ischemia, hypoxia, trauma, excessive

Table 45.2. Causes of auditory disorders

Congenital and hereditary lesions associated with hearing loss
May be a part of many syndromes (Table 45.3)
– *Failure in normal development*
  Michel defect – complete inner ear aplasia
  Mondini defect – incomplete development of the labyrinth
  Scheibe defect – membranous cochleosaccular dyplasia
– *Secondary degeneration* – isolated auditory defect or in association with other abnormalities (e.g. Arnold–Chiari); Syndromes of inherited spinal degenerations, ataxia and neuropathies (e.g. Friedreich's ataxia)

Trauma and toxicity
– mechanical (transverse fracture of the temporal bone, concussion of the inner ear with secondary degeneration)
– barotrauma
– surgical intervention
– radiotherapy
– ototoxicity (salicylates, aminoglycosides, thalidomide, vincristine)
– acoustic trauma

Infection:
– microbial (syphilis, Lyme disease, meningitis, postchronic suppurative otitis media)
– viral (AIDS, Ramsay–Hunt syndrome)
– mycotic

Ischemia:
– vertebrobasilar ischemia
– arterial occlusion (subclavian steal syndrome)
– aneurysm (anterior inferior cerebellar artery)
– stroke
– vasculitis
– polycythemia (emboli)
– coagulopathies (hereditary coagulation disorders, sickle cells)
Risk factors: cardiovascular disease, hypertension, cardiopulmonary bypass surgery

Neoplasia:
– vestibular schwannoma (syn. acoustic neuroma)
– primary and secondary lesions

Metabolic and endocrine disorders:
– diabetes mellitus
– uremic polyneuropathy
– thyroid dysfunctions

Autoimmune disorders/vasculitis
rheumatoid arthritis, Cogan syndrome, systemic lupus erythematosus, Takayasu disease, Behçet syndrome, polyarteritis nodosa

Table 45.3. Genetic syndromes associated with hearing loss

I. Chromosomal: Down syndrome (trisomy 21), Turner syndrome (X Ch)

II. Autosomal:

Autosomal dominant	*Autosomal recessive*
– Waardenburg	– Usher progressive hearing loss
Type 1 (Ch 2q)	Type 1 (Ch 14q)
Type 2 (Ch 3q)	Type 2 (Ch 1q)
– Neurofibromatosis	Type 3 (Ch 3q)
Type 1 (Ch 17q)	– Pendred (Ch 7q)
Type 2 (Ch 22q)	– Albinism
– BOR syndrome (Ch 8q)	
– Klippel–Feil	
– Wildervanks	
– Treacher-Collins (Ch 5q)	
– Jervell Lange Neilsen syndrome (Ch 7q 11p)	
– Stickler syndrome (Ch 12q)	
– Crouzon syndrome (Ch 10q25–26)	
– Otosclerosis (multifactorial)	

III. X-linked:	*IV. Mitochondrial*
– Alport syndrome (Xq21–22)	– Kearns–Sayre
– Norrie syndrome (Xp11–3)	– Myoclonic epilepsy
– Perilymph gusher syndrome (Xq13)	– Maternally inherited diabetes
– Encephalopathy-hearing loss (Xq22)	– Maternally inherited susceptibility to aminoglycosides
– Large vestibular aqueduct syndrome	– MELAS
– X-linked non-syndromic deafness	

noise, ototoxic drugs (salicylates, aminoglycosides, thalidomide *cis*-platinum, or vincristine), due to age-related degeneration (presbyacusis), autoimmune disorders, or may result from a number congenital/ hereditary abnormalities (Tables 45.2, 45.3 and 45.4).

The molecular and biological mechanisms of ototoxic effects and other forms of cochlear damage, have been the subject of extensive scientific investigation over recent years. Formation of reactive oxygen metabolites (ROM), including free oxygen radicals and other metabolites, are thought to be central to damage of cochlear tissue, as these highly reactive compounds can oxidize a wide variety of targets, such as proteins, mitochondrial DNA (mtDNA), or lipids. Better understanding of these mechanisms has led to a series of experimental studies with coadministration of antioxidants, or ROM scavengers. For example, use of iron chelators was found to reduce gentamicin ototoxicity (Schacht, 1998), and calorie restriction, vitamin C and E

Table 45.4. Causes of hearing loss arising from dysfunctional neurological tissue

Inner ear:	Degeneration of the spiral ganglion cells (inherited – in Roussy–Levy syndrome)
	Neurinoma of the spiral ganglion
Auditory nerve:	Hereditary neuropathies Friedreich's ataxia, Charcot–Marie–Tooth and other hereditary motor-sensory neuropathies, Leber's optic neuropathy
	Auditory neuropathies associated with DIDMOAD, MELAS and other mitochondrial disorders
	Idiopathic auditory neuropathy
	Tumours: Acoustic neurinoma (incl. NF1 and NF2)
	Cerebello-pontine angle lesions
	Metastatic tumours
	Paraneoplastic syndromes
	Infections: Ramsay–Hunt syndrome
	Basal meningitis (bacterial, TB)
	Vascular: Loop, aneurysm
	Malformations: Arnold–Chiari
	Multiple sclerosis (n. root entry zone)
	Trauma (including radiation therapy)
Central nervous system:	
	Tumours: primary and metastatic
	Vascular: Infarct, hemorrhage
	Infections: Encephalitis
	Neurosyphilis
	Lyme disease
	Multiple sclerosis
	Syringo-bulbia
	Neuro-sarcoid
	Neuro-Behçet
	Trauma

supplementation, and melatonin treatment, attenuated age-related hearing loss (Seidman, 2000). These findings herald an exciting future, with potential identification of pharmacological and nutritional strategies for prevention of ototoxicity and different forms of cochlear degeneration.

Cochlear damage is reflected in degeneration and abnormal function of the proximal auditory structures. Loss of hair cells leads to degeneration of the auditory fibres, while efferent fibres remain intact. Neuronal and transneuronal degeneration of auditory axons in the brainstem of an adult mammal, resulting from cochlear damage, has been observed (Morest et al., 1997). Recordings of the spontaneous activity of the auditory nerve have shown a reduction in rate (Liberman & Kiang, 1978) and single fibre recordings have indicated that auditory sensitivity is lost and frequency resolution reduced (Pickles, 1988). However, cochlear lesions lead to an increased excitability of the cochlear nucleus, inferior colliculus (Salvi & Ahroon, 1983) and medial geniculate body (Gerken, 1979). Studies of the auditory cortical neurons have indicated changes in frequency selectivity and a sequence of changes in the relative levels of excitatory and inhibitory inputs to the primary cortical neurons. This leads to an expansion of the receptive field of the cortical neurons (Rajan et al., 1992), which in turn raises the threshold sensitivity and broadens frequency selectivity.

Menière's disease, a condition with both cochlear and vestibular manifestations, deserves special mention. It is considered that endolymphatic hydrops is the underlying pathophysiological abnormality, although it has been suspected that some other mechanisms may be involved, with endolymphatic hydrops being an epiphenomenon. In the absence of known etiology, the diagnosis of Menière's disease is based on the characteristic clinical history, with the classical triad of episodic symptoms of tinnitus, diminished hearing and vertigo, a documented sensorineural shift on pure-tone audiometry and/or reduced speech discrimination score test, as defined by the Committee on Hearing and Equilibrium, American Academy of Ophthalmology and Otolaryngology (1995). Fluctuating sensorineural hearing loss in Menière's disease, typically affects predominantly low frequencies, as in Fig. 45.6(*d*).

Auditory nerve

Different lesions of the auditory nerve, such as trauma, infection (microbial, viral and mycotic), neoplasia (acoustic neuroma, primary and metastatic tumours in the internal acoustic meatus), autoimmune, or congenital/hereditary disorders (Tables 45.2, 45.3 and 45.4), lead to unilateral neural loss. An example of mononeuritis of the eight nerve is the Ramsay–Hunt syndrome (Herpes zoster oticus), with a deep burning pain in the affected ear, followed by a vesicular eruption in the external auditory canal and concha, and subsequent hearing loss and vertigo. The auditory nerve can also be damaged due to pathological processes in the temporal bone, such as otosclerosis, Paget disease, fibrous displasia, or osteopetroses. With regard to congenital abnormalities, in addition to primary abnormalities (i.e. failure in normal development), secondary lesions may occur. Secondary degeneration of the auditory nerve has been reported in association with other defects in many syndromes (e.g. neurofibromatosis, Treacher-Collins, Wildervank, Usher, Kearns-Sayre, Waardenburg, Pendred, Alport) (Yeoh, 1997). In Arnold–Chiari malformation, it is thought that invagination of the brainstem leads to the stretching of the auditory nerve and to auditory symptoms, which could be caused by cochlear anoxia,

while associated increased intracranial pressure may be responsible for pulsatile tinnitus. Degeneration of the auditory nerve is also associated with various inherited spinal degenerations, ataxia and neuropathies (Friedreich's ataxia, hereditary sensory neuropathy) and as an isolated phenomenon (Booth, 1997).

Acoustic neuroma (AN) has been reported to represent 10% of intracranial tumours and over 95% of cerebellopontine lesions (Gonzalez-Revilla, 1948). In addition to the effect on the auditory nerve, AN may cause cochlear degeneration due to chronic partial obstruction of the blood supply by the tumour, biochemical alterations in the inner ear fluids, loss of efferent control of active mechanical tuning and degeneration due to neuronal loss (Prasher et al., 1995). Analysis of 500 patients who underwent AN resection, revealed that unilateral auditory symptoms occur in 83% of patients and that tinnitus was the initial symptom in 11% of patients (Ramsden, 1987), while in a study on 1000 patients, it was found that acoustic disturbances occur in 95% of patients (Matthies & Samii, 1997). The prevalence of tinnitus is higher in patients with a partial hearing loss than in deaf patients, however, postoperative deafness does not mean relief from tinnitus: this symptom may exist in 46% of postoperatively deaf patients (Matthies & Samii, 1997), suggesting that, although the onset of tinnitus may be due to the peripheral effect, its maintenance is mediated through the more proximal, central mechanisms.

Multiple sclerosis may occasionally affect the central auditory system, and even less commonly the auditory nerve. Auditory symptoms have been reported in less than 4% of patients, they are usually unilateral and, in most cases, are of transient character (Booth, 1997).

Auditory neuropathy is a recently recognized clinical entity (Starr et al., 1996) without apparent pathology, with normal cochlear function (normal otoacoustic emissions and cochlear microphonics), but abnormal auditory brainstem evoked responses and poor speech discrimination. Patients present typically with a mild or moderate hearing loss and are characterized by poor response to traditional hearing aids. One of the hypothetical explanations of this disorder is an altered temporal synchrony in firing of the auditory nerve, which could be an early sign of demyelination (Starr et al., 1996), but there is also a possibility of selective damage to the inner hair cells, which may reduce neural input (Salvi et al., 1999).

Central auditory pathways

With the increase in complexity of auditory pathways from the cochlea to the cortex, together with multiple representations of each ear, on each side of the brain, auditory function becomes more complex and multifaceted. Central lesions (Table 45.4) may cause varying degrees of hearing impairment and other auditory dysfunctions, such as disproportionately impaired speech discrimination (relative to hearing sensitivity), tinnitus, hyperacusis, hallucinations, and various abnormalities in sound processing, including derangements of binaural acoustic integration, sound localization, signal sequencing, or auditory pattern recognition.

Lesions of the brainstem can be caused by a variety of lesions, including neoplastic and vascular abnormalities, such as vertebrobasilar disease, mini strokes, vascular spasms, or vascular loops. Intra- and extra-axial lesions of the brainstem may affect auditory function in different ways (Musiek & Baran, 1986). An intra-axial lesion of the brainstem, especially in the pons, is likely to cause a bilateral auditory disorder, as it may disrupt the majority of crossing fibres from the cochlear nuclei and the superior olivary complex. Intra-axial lesions, for example, secondary to central pontine haemorrhage, have given rise to bilateral low-frequency hearing loss, reflecting the tonotopic organisation of the auditory pathways, with the lowest frequencies being encoded centrally (Cohen et al., 1996). An extra-axial lesion of the mid to low lateral pons may directly affect the cochlear nuclei, the only superficially located auditory structure, leading to ipsilateral deficits. An extra-axial or intra-axial lesion at the level of the inferior colliculus (midbrain) and MGB (thalamus) is more likely to cause a contralateral deficit on behavioural central tests. In general, lesions of the brainstem appear to affect dichotic integration tasks rather than dichotic separation tasks. Large space-occupying lesions in the brainstem or cerebellum may cause multiple deficits, with additional secondary effects due to compression, displacement, vascular disruption, or hydrocephalus.

Subcortical and cortical auditory pathways

The pathology of the auditory cortex (grey matter) and hemispheres (grey and white matter) results mainly from ischemic, neoplastic or demyelinating lesions. Hearing deficit at this level is very rare and is most likely to be caused by vascular disease of both temporal lobes.

Management

Hearing loss

It is important to ensure all preventive measures are undertaken to avoid permanent hearing loss, e.g. regulations regarding occupational noise exposure and serum monitoring of known ototoxic drugs, e.g. gentamicin. In the majority of cases, hearing loss is permanent, but in some

patients hearing loss can be treated surgically or pharmacologically. In those with irreversible hearing loss, the management is directed towards reduction of the effect of any auditory disability or handicap, by the application of different types of amplification devices and implants.

Surgical treatment

In a small proportion of cases, limited to those with middle ear disorders, surgical intervention may improve or restore hearing, for example, following myringotomy, with or without grommet insertion, in otitis media with effusion, stapedectomy for otosclerosis, or in osteogenesis imperfecta. Surgical procedures for acoustic neuroma, may preserve hearing, but usually lead to an increased, if not total, hearing loss. Surgical treatment is also used in Menière's disease, primarily for management of vestibular symptoms, although the evidence for conservative procedures, such as endolymphatic sac decompression, remain controversial. Destructive procedures, e.g. labyrinthectomy and vestibular nerve section, should be undertaken with great care in the light of the significant prevalence of bilateral Menière's disease.

Pharmacological treatment

This form of treatment is more orientated towards preservation, rather than towards an improvement of hearing, and is determined by the etiology of hearing loss. In hearing loss, such as Menière's disease, treatment is directed towards the assumed underlying pathophysiological mechanism (endolymphatic hydrops), and consists of diuretic treatment and/or dietary restriction of sodium intake, which has been reported to improve symptoms in 60–70% of patient (Gates, 1999). Autoimmune hearing disorders are treated with steroids (glucocorticoids), and their application in some cases of idiopathic hearing loss has also been recommended, although with questionable effect, as spontaneous remission may occur (McKee, 1997).

Rehabilitation

This is the management option for most patients with hearing loss (Stephens, 1997).

I. Instrumentational rehabilitation consists of the application of personal and environmental devices.

Personal instrumentation is the most important component of rehabilitation and includes:

1. Hearing aid systems (hearing aid and ear mould). There is a wide range of devices, from low- to high-powered, from simple linear to sophisticated programmable digital hearing aids, whose application depends on many factors, including configuration and severity of hearing loss.
2. Bone anchored hearing aids, are applied in patients with significant conductive hearing loss and consist of a surgically implanted (mastoid) titanium base to which is attached an electronic amplification system, allowing bone-transmission of sound.
3. Vibrotactile hearing aids are applied in individuals with profound hearing impairment in whom is not possible to deliver acoustic signal above the threshold. Vibrotactile information is delivered via a vibration transducer, often worn on the forearm.
4. Cochlear implants bypass the transduction mechanisms of the cochlea by electrically stimulating the auditory nerve directly, and they are used in profoundly hearing-impaired individuals.
5. Brainstem implants are applied in patients who have no remaining auditory nerve, e.g. subsequent to surgical removal of vestibular neuroma. The cochlear nucleus, as the termination site for all auditory fibres, and therefore, most peripheral of the central structures, is the target of stimulation.

II. Non-instrumental rehabilitation includes the application of environmental aids, those using sound to enhance loudness and clarity (e.g. additional speaker/receiver, or induction coil systems), or those using visual information (e.g. text telephones, subtitle TV/videos, or video telephones) and alerting and warning systems (e.g. flashing doorbell or the telephone bell, also include use of trained dogs).

Tinnitus

There are several lines in the management of this complex symptom.

Treatment of underlying disorders

Medical evaluation may indicate conditions which could be of relevance for the emergence of tinnitus (cardiovascular, renal, metabolic and autoimmune disease, or the effects of medications and drugs). Auditory assessment may identify the presence and site of a lesion, which could be treatable.

Pharmacological treatment

There have been attempts, with varying success, to base pharmacological treatment on hypothetical underlying mechanisms, as highlighted above in the section on tinnitus. Ca^{2+}-antagonists (nimodipine), $GABA_A$ and $GABA_B$ agonists (benzodiazepines and baclofen, respectively), and drugs for depression of neuronal response to excitatory stimuli and hyperpolarization of neuronal membranes (phenytoin, carbamazepine) have all been tried.

In patients with significant associated anxiety, or depression, treatment with tranquillizers and antidepressants (e.g. tricyclic nortriptyline) may be of value. More recently, selective serotonin reuptake inhibitors, as modulators of tonic inhibition of auditory pathways, were found to be effective in some patients with tinnitus, particularly in those with associated depression.

The quality of evidence for the efficacy of pharmacological treatment of tinnitus is poor. This is largely due to the difficulty in undertaking adequate studies, as tinnitus is a symptom of different pathologies and different underlying mechanisms may be involved. Therefore, it is of importance to identify any audiological, or relevant abnormality in order to provide 'tailored' treatment for each individual.

Tinnitus retraining therapy (TRT)

TRT includes counselling and sound therapy (see below Instrumentation), based on neurophysiological model of tinnitus (Jastreboff & Hazell, 1993). Directive counselling is aimed at providing the patient with clear information about the possible mechanism(s) of tinnitus and how it can be influenced adversely or beneficially; person-centred counselling deals with the stress and needs and ways of dealing with problems; cognitive counselling is aimed at identifying and dispelling patients' false beliefs, attitudes, or fears.

Instrumentation

Hearing aids are the first line in management for patients with associated hearing loss, as they reduce awareness of tinnitus by amplification of external sounds. Tinnitus maskers and low-level noise generators may mask or at least reduce the effect of tinnitus. Other devices, as a part of a masking strategy, include pillow speakers or a tape recorder, which may alleviate tinnitus at night, while walkmans can be used during the day.

Surgical treatment

In addition to evidence-based surgical treatment of specific underlying lesions, other surgical procedures, for the treatment of tinnitus *per se*, such as auditory nerve section, or cochlear destruction, have provided little evidence of effectiveness and may even make tinnitus worse.

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46

Vertigo and vestibular disorders

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Vertigo is an unpleasant distortion of static gravitational orientation, or an erroneous perception of motion of either the sufferer or the environment. It is not a disease entity, but rather the outcome of many pathological or physiological processes. Vertigo is best described as a multisensory and sensorimotor syndrome with perceptual, postural, ocular motor and autonomic manifestations induced by either

– unusual and therefore unadapted (motion) stimulation of the intact sensory systems, or
– pathological (lesional) dysfunction.

Vertigo, dizziness, and disequilibrium are common complaints of patients of all ages, particularly the elderly. As presenting symptoms, they occur in 5–10% of all patients seen by general practitioners and 10–20% of all patients seen by neurologists and otolaryngologists. The clinical spectrum of vertigo is broad, extending from vestibular rotatory vertigo with nausea and vomiting to presyncope light-headedness, from drug intoxication to hypoglycemic dizziness, from visual vertigo to phobias and panic attacks, and from motion sickness to height vertigo. Appropriate preventions and treatments differ for different types of dizziness and vertigo; they include drug therapy, physical therapy, psychotherapy and surgery.

The 'vestibular' vertigo syndromes

Vertigo usually implies a mismatch between the vestibular, visual, and somatosensory systems. These three sensory systems subserve both static and dynamic spatial orientation, locomotion, and control of posture by constantly providing reafferent cues. The sensory information is partially redundant in that two or three senses may simultaneously provide similar information about the same action. Thanks to this overlapping of their functional ranges, it is possible for one sense to substitute, at least in part, for deficiencies in the others. When information from two sensory sources conflicts, the intensity of the vertigo is a function of the degree of mismatch; it is increased if information from an intact sensory system is lost, as for example in a patient with pathological vestibular vertigo who closes his eyes. The distressing sensorimotor consequences of the mismatch are frequently based on our earlier experiences with orientation, balance, and locomotion, i.e. there is a mismatch between the expected and the actually perceived pattern of multisensory input.

Vertigo may thus be induced by physiological stimulation of the intact sensorimotor systems (height vertigo; motion sickness) or by pathological dysfunction of any of the stabilizing sensory systems, especially the vestibular system (Table 46.1). The symptoms of vertigo include sensory qualities identified as arising from vestibular, visual, and somatosensory sources. As distinct from one's perception of self-motion during natural locomotion, the experience of vertigo is linked to impaired perception of a stationary environment; this perception is mediated by central nervous system processes known as 'space constancy mechanisms'. Loss of the external stationary reference system required for orientation and postural regulation contributes to the distressing mixture of self-motion and surround motion (Brandt & Daroff, 1980b).

Signs and symptoms

Physiological and clinical vertigo syndromes (Table 46.2) are commonly characterized by a combination of phenomena involving perceptual, ocular motor, postural and autonomic manifestations: vertigo, nystagmus, ataxia, and nausea (Fig. 46.1; Brandt & Daroff 1980b). These four manifestations correlate with different aspects of vestibular function and emanate from different sites within the central nervous system.

Table 46.1. Physiological or pathological vertigo

Physiological stimulation	Height vertigo
	Motion sickness
Pathological dysfunction	Labyrinthine and vestibular nerve disorders
	Central vestibular disorders

Table 46.2. Syndromal manifestations of vertigo

Syndrome	Manifestation
Perceptual	Vertigo, disorientation
Ocular motor	Nystagmus, ocular deviation
Postural	Ataxia, falls
Autonomic	Nausea, vomiting, anxiety

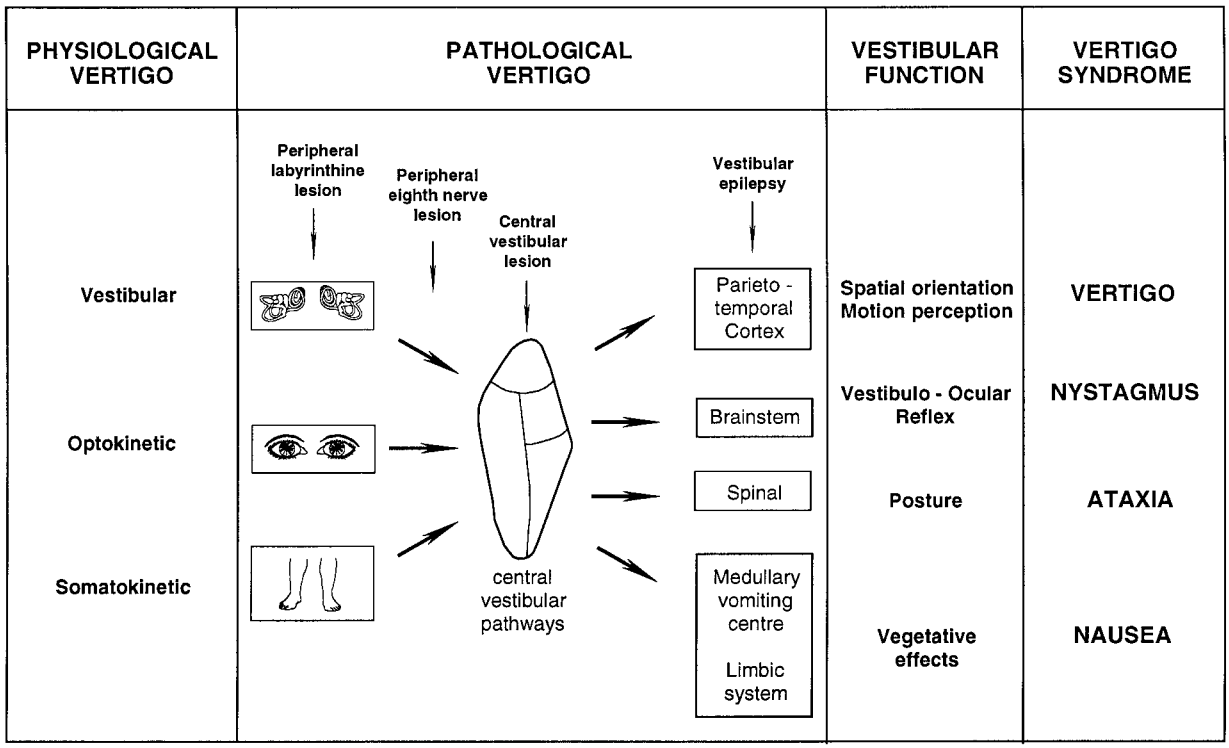

Fig. 46.1. Classification of physiological vertigo and vestibular disorders with their origin at different sites within peripheral or central vestibular structures. Vestibular disorders are not clinical entities but different sensorimotor syndromes arising from unusual stimulation or lesional dysfunction. (From Brandt & Daroff, 1980b.)

1. The vertigo itself results from a disturbance of cortical spatial orientation.
2. Nystagmus is secondary to a direction-specific imbalance in the vestibulo-ocular reflex, which activates brainstem neuronal circuitry.
3. Vestibular ataxia and postural imbalance are caused by inappropriate or abnormal activation of monosynaptic and polysynaptic vestibulospinal pathways.
4. The unpleasant autonomic responses with nausea, vomiting, and anxiety travel along ascending and descending vestibulo-autonomic pathways to activate the medullary vomiting center.

Under certain conditions, distressing symptoms and malaise may be preceded by a pleasurable autonomic sensation, which is presumably mediated through the limbic system and accounts for the popularity of amusement park rides and the like.

The mismatch concept

Physiological vertigo (motion sickness) and pathological vertigo (peripheral or central vestibular dysfunction) are thought to be generated by an acute sensorimotor conflict (mismatch) between the converging sensory inputs and

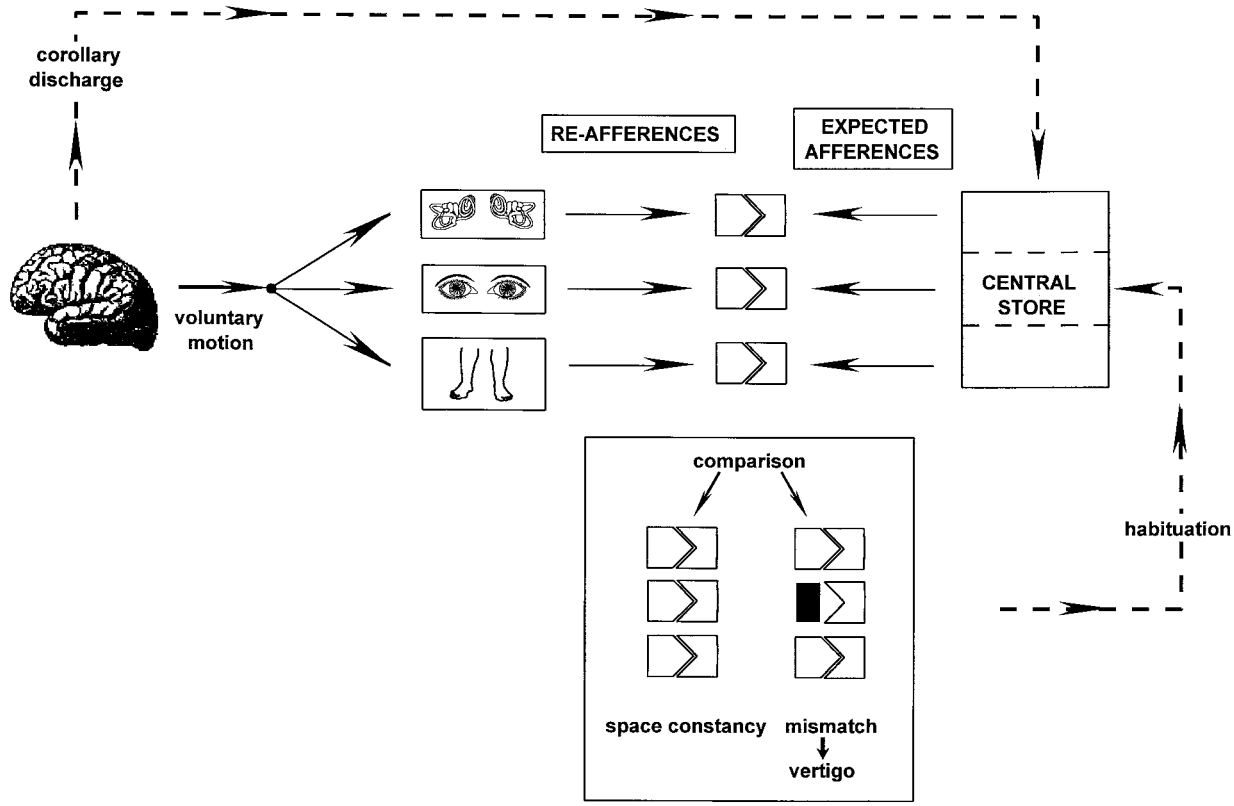

Fig. 46.2. Schematic diagram of the sensory conflict or the neural mismatch concept of vertigo and motion sickness. An active movement leads to stimulation of the sensory organs whose messages are compared with a multisensory pattern of expectation calibrated by earlier experience of motions (central store). The pattern of expectation is prepared either by the efference copy signal which is emitted parallel to and simultaneously with the motion impulse, or by vestibular excitation during passive transportation in vehicles. If concurrent sensory stimulation and the pattern of expectation are in agreement, self-motion is perceived while 'space constancy' is maintained. If, for example, there is no appropriate visual report of motion, as a result of the field of view being filled with stationary environmental contrasts (reading in the car), a sensory mismatch occurs. With repeated stimulation, motion sickness is induced through summation; the repeated stimulation leads to a rearrangement of the stored pattern of expectation, however, so that a habituation to the initially challenging stimulation is attained within a few days. An acute unilateral labyrinthine loss causes vertigo, because the self-motion sensation induced by the vestibular tone imbalance is contradicted by vision and the somatosensors.

the expected sensory patterns (Fig. 46.2) or a vestibular tone imbalance. A mismatch arises, for example, when the multisensory consequences of being a passenger in a moving vehicle or of moving actively do not match the expected patterns which have been calibrated by prior experience of active locomotion. Thus, it is the sensory mismatch (e.g. visual–vestibular or between right and left vestibular input) rather than the sensory loss which causes vertigo. The absence of one channel of the redundant sensory input, important as it is for demanding balancing tasks in sports, rarely manifests as vertigo. Inappropriate information from one or multiple sensory systems produces an illusion of body motion and causes vertigo. An acute unilateral labyrinthine dysfunction (see vestibular neuritis) causes vertigo because the sensation of self-motion induced by the vestibular tone imbalance is contradicted by vision and the somatosensors.

Approaching the patient

Dizziness is a vexing symptom, difficult to assess because of its purely subjective character and its variety of sensations. The sensation of spinning or rotatory vertigo is much more specific; if it persists, it undoubtedly indicates acute pathology of the labyrinth, the vestibular nerve, or the caudal brainstem, which contains the vestibular nuclei.

History taking allows the early differentiation of vertigo

and disequilibrium disorders into seven categories that serve as a practical guide for differential diagnosis:

(i) dizziness and light-headedness (e.g. hyperventilation, intoxication)
(ii) single or recurrent attacks of (rotatory) vertigo (e.g. Menière's disease, basilar migraine)
(iii) sustained (rotatory) vertigo (e.g. Wallenberg's syndrome)
(iv) positional/positioning vertigo (e.g. benign paroxysmal positional vertigo, central positional vertigo)
(v) oscillopsia, the apparent motion of the visual scene (e.g. bilateral vestibular failure, downbeat nystagmus)
(vi) vertigo associated with auditory dysfunction (e.g. Menière's disease, Cogan's syndrome)
(vii) dizziness or to-and-fro vertigo with postural imbalance (e.g. somatoform phobic postural vertigo, central vestibular disorders, episodic ataxia)

Management of vestibular disorders

The prevailing good prognosis of vertigo should be emphasized, because

– many forms of vertigo have a benign cause and are characterized by spontaneous recovery of vestibular function or central compensation of a peripheral vestibular tone imbalance, and
– most forms of vertigo can be effectively relieved by pharmacological treatment (Table 46.3), physical therapy (Table 46.4), surgery (Table 46.5), or psychotherapy [7].

There is, however, no common treatment, and vestibular suppressants (Table 46.6) provide only symptomatic relief of vertigo and nausea. A specific therapeutic approach thus requires recognition of the numerous particular pathomechanisms involved (Baloh & Halmagyi, 1996; Brandt, 1999; Bronstein et al., 1996). Such therapy can include causative, symptomatic, or preventive approaches.

Antivertiginous and antiemetic drugs

A variety of drugs used for symptomatic relief of vertigo and nausea (Table 46.4) have the major side effect of general sedation (Foster & Baloh, 1996). Vestibular suppressants, including anticholinergics, antihistamines, and benzodiazepines, provide symptomatic relief of distressing symptoms by down-regulating vestibular excitability. Antiemetics preferably control nausea and vomiting by acting on the medullary vomiting center, the chemoreceptor trigger zone, or the gastrointestinal tract itself. Vestibular suppressants are often acetylcholine and histamine antagonists, which act as acetylcholine antagonists by competitive inhibition at muscarinic receptors in the vestibular nuclei, their most likely site of action. Vestibular suppression by benzodiazepines is best explained by their $GABA_A$ agonistic effect, because GABA is the major neuroinhibitory transmitter for vestibular neurons. Antiemetics are effective mainly due to their dopamine (D_2) antagonist

Table 46.3. Pharmacologic therapies for vertigo

Therapy	Vertigo
Vestibular suppressants	Symptomatic relief of nausea (in acute peripheral and vestibular nuclei lesions), prevention of motion sickness
Antiepileptic drugs	Vestibular epilepsy, vestibular paroxysmia (disabling positional vertigo), paroxysmal dysarthria and ataxia in MS, other central vestibular paroxysms, superior oblique myokymia
Beta-receptor blockers	Basilar migraine (vestibular migraine; benign recurrent vertigo)
Betahistine	Menière's disease
Antibiotics	Infections of the ear and temporal bone
Ototoxic antibiotics	Menière's disease (Menière's drop attacks)
Corticosteroids	Vestibular neuritis, autoimmune inner ear disease
Baclofen	Downbeat or upbeat nystagmus or vertigo
Acetazolamide	Familial periodic ataxia or vertigo

Source: From Brandt (1999).

Table 46.4. Physical therapies for vertigo

Therapy	Vertigo
Deliberate manoeuvres	Benign paroxysmal positioning vertigo
Vestibular exercises	Vestibular rehabilitation, central compensation of acute vestibular loss, habituation for prevention of motion sickness, improvement of balance skills (e.g. in the elderly)
Physical therapy (neck collar)	Cervical vertigo (fiction or reality?)

Source: From Brandt (1999).

Table 46.5. Surgical interventions for vertigo

Surgery	Vertigo
Surgical decompression of eighth nerve	Tumour (acoustic neurinoma) or cyst
Surgical decompression of vertebral artery	Rotational vertebral artery occlusion
Ampullary nerve section or canal plugging	Benign paroxysmal positioning vertigo
Endolymphatic shunt	Menière's disease
Vestibular nerve section or labyrinthectomy	Intractable Menière's disease
Surgical patching	Perilymph fistula

Source: From Brandt (1999).

properties, but some antiemetics also have muscarinergic or antihistaminic (H_1) properties that may assist in vestibular suppression as well. Primary vestibular suppressants such as scopolamine also effectively suppress vomiting by virtue of their muscarinergic action. Antiemetics are more selective in action. They are primarily used to control nausea and vomiting; for treatment of severe vertigo with nausea, they are often combined with antivertiginous drugs (Foster & Baloh, 1996).

There are only four clear indications for the use of antivertiginous (vestibular suppressants) and antiemetic drugs to control vertigo, nausea, and vomiting (Brandt, 1999):

(i) to prevent nausea due to acute peripheral vestibulopathy (for the first 1–3 days or as long as nausea lasts),
(ii) to prevent severe vertigo and nausea due to acute brainstem or archicerebellar lesions near the vestibular nuclei,
(iii) to prevent severe vertigo attacks that frequently recur, and
(iv) to prevent motion sickness.

For conditions 1 and 2, fast-acting compounds with vestibular and general sedation should be preferably administered, e.g. diazepam or promethazine combined with dimenhydrinate if nausea and vomiting are exceptionally severe. These drugs should not be given after nausea has disappeared, because they prolong the time course of central compensation of an acute vestibular tone imbalance.

Mobility and vestibular excitability are major requirements for recovery and vestibular rehabilitation. Antivertiginous and antiemetic drugs are not indicated for patients suffering from chronic dizziness. A prophylactic treatment with vestibular suppressants, e.g. scopolamine or dimenhydrinate, is justified only in exceptional situations of rare patients who have frequent and severe vertigo attacks. In severe cases of benign paroxysmal positioning vertigo it may become necessary to control nausea and vomiting when performing physical liberatory manoeuvres. It is our own experience that severe central positioning vomiting is best controlled by benzodiazepines rather than antiemetics or typical vestibular suppressants (Arbusow et al., 1998). Scopolamine administered transdermally as Transderm Scop provides a continuous blood level over a 3-day period and effectively prevents motion sickness. The selection of vestibular suppressants and antiemetic drugs should take into account that those that reach a peak effect 7–9 hours after ingestion (Manning et al., 1992) are ineffective for treating short vertigo attacks.

Vestibular compensation

Central compensation of a unilateral peripheral vestibular loss is considered the prototype of brain plasticity. Readjustment of the vestibular reflexes, which act on eye and body muscles, requires sensory feedback from the sensory mismatch elicited by voluntary movements. Therefore, on the basis of our current knowledge of vestibular physiology, continued management should consist of vestibular exercises that promote central compensation (Strupp et al., 1998).

Postural normalization in frogs after a complete unilateral labyrinthectomy occurs within about 60 days (Flohr et al., 1981). Recovery from vestibular lesions is neither a simple nor a single process; multiple processes are involved. Analysis of the mechanisms of recovery requires a careful comparison of normalization between parallel phenomena at the behavioural level, on the one hand, and the neuronal level, on the other. Incongruences in the time course and the magnitude of the changes in behaviour and neuronal activity clearly indicate that multiple processes of compensation occur in distributed neuronal networks for vestibulo-ocular, vestibulo-spinal and perceptual disturbances at different locations and at different times (Dieringer, 1995; Curthoys & Halmagyi, 1994).

Substitution of vestibular function

Vestibular compensation is less perfect than generally believed. For instance, after acute unilateral vestibular

Table 46.6. Commonly used antivertiginous and antiemetic drugs

Drug	Dosage	Action
Anticholinergics		Muscarine antagonist
Scopolamine (Transderm Scop)	0.6 mg po q 4–6 h or Transdermal patch: 1 q 3 days	
Antihistamines		
Dimenhydrinate (Dramamine)	50 mg po q 4–6 h or im q 4–6 h or 100 mg suppository q 8–10 h	Histamine (H_1) antagonist Muscarine antagonist
Meclizine (Antivert, Bonine)	25 mg po q 4–6 h	Histamine (H_1) antagonist Muscarine antagonist
Promethazine (Phenergan)	15 or 50 mg po q 4–6 h or im q 4–6 h or suppository q 4–6 h	Histamine (H_1) antagonist Muscarine antagonist Dopamine (D_2) antagonist
Phenothiazine		
Prochlorperazine (Compazine)	5 or 10 mg po q 4–6 h or im q 6 h or 25 mg suppository q 12 h	Muscarine antagonist Dopamine (D_2) antagonist
Butyrophenone		
Droperidol (Inapsine)	2.5 or 5 mg im q 12 h	Muscarine antagonist Dopamine (D_2) antagonist
Benzodiazepines		
Diazepam (Valium)	5 or 10 mg po bid–qid im q 4–6 h or iv q 4–6 h	$GABA_A$ agonist
Clonazepam (Klonopin)	0.5 mg po tid	$GABA_A$ agonist

Source: From Brandt 1999.

deafferentation, which occurs in vestibular neuritis, the process of normalization is impressive for *static* conditions in the absence of head motion: the initial rotatory vertigo, spontaneous nystagmus, and postural imbalance subside. Compensation is, however, less impressive for *dynamic* conditions, especially when the vestibular system is exposed to high-frequency head accelerations (Curthoys & Halmagyi, 1994). The dynamic disequilibrium, i.e. VOR asymmetry, causes oscillopsia, the illusory movement of the environment due to excessive slip of images upon the retina during fast head movements or walking, because after uni- and bilateral peripheral vestibular lesions the VOR cannot generate fast compensatory eye rotations during high-frequency head rotations. The dynamic vestibular tone imbalance can be detected clinically by provoking a directional head-shaking nystagmus (Hain et al., 1987) or by bedside testing of the VOR with rapid head rotation (Halmagyi & Curthoys, 1988).

Vestibular compensation is usually considered a central 'repair mechanism' for a vestibular tone imbalance secondary to a peripheral vestibular loss. However, central compensation is also possible for central vestibular tone imbalances, which is best demonstrated by the cessation of nystagmus and lateropulsion in Wallenberg's syndrome. It is still poorly understood which central vestibular syndromes can be compensated and which cannot. Upbeat and downbeat nystagmus may serve as an example. Acquired upbeat nystagmus is rarely permanent, whereas acquired downbeat nystagmus may be permanent.

Three types of vestibular dysfunction

Basically there are three types of vestibular dysfunction.

Congenital or acquired bilateral vestibular failure = vestibular loss

Key symptoms are oscillopsia associated with head movements (due to the defective vestibulo-ocular reflex) and unsteadiness of gait, particularly in the dark or on unlevel ground (when visual and somatosensory input cannot substitute for the missing vestibulo-spinal control).

These patients have no complaints when standing still without head movement.

Diagnosis is made by a bedside test for defective vestibulo-ocular reflex and the absence of nystagmic reaction to both caloric and rotatory pendular testing.

Acute unilateral lesions of the labyrinth, vestibular nerve, or central vestibular pathways = vestibular tone imbalance

Key symptoms are rotatory vertigo or perceived body tilt with spontaneous nystagmus, ocular torsion, or skew deviation associated with a direction-specific deviation of gait and body falls (due to the lesion-induced vestibular tone imbalance).

Typically a lesion-induced vestibular tone imbalance manifests as an acute syndrome with slow gradual restitution within days to weeks by either central compensation, sensory substitution, or resolution of the lesion.

Diagnosis is made by the combination of perceptual, ocular motor, and postural signs and symptoms. The direction of nystagmus or deviation of posture and gait allows one to determine the particular tone imbalance in one of the three major planes of action of the vestibular system (yaw, pitch, or roll).

Inadequate paroxysmal stimulation of the vestibular system = vestibular attacks

Key symptoms are attacks of vertigo, ocular motor dysfunction, and postural imbalance which may occur spontaneously (basilar migraine, paroxysmal vertigo of childhood, episodic ataxia type I or II, vestibular epilepsy) or may be elicited by changes in head position (benign paroxysmal positional vertigo, vestibular paroxysmia).

Diagnosis of the different etiologies for these attacks is based on careful taking of patient history, clinical examination, and testing of the vestibular function.

Table 46.7 shows the frequency of vertigo syndromes diagnosed in our Neurological Dizziness Unit and gives relevant examples that will be described in the following.

Table 46.7. Frequency of different vertigo syndromes in 3038 patients seen in a neurological dizziness unit (1989–1999)

	Frequency	
Diagnosis	*n*	%
1. Benign paroxysmal positional vertigo	533	17.6
2. Somatoform phobic postural vertigo	434	14.3
3. Central vestibular syndromes with vertigo	364	12.0
4. Peripheral vestibulopathy (vestibular neuritis)	263	8.7
5. Basilar migraine, vestibular migraine	241	7.9
6. Menière's disease	200	6.6
7. Bilateral vestibular failure	89	2.9
8. Psychogenic vertigo (without 2)	89	2.9
9. Vestibular paroxysmia (neurovascular cross-compression)	63	2.1
10. Perilymph fistula	7	0.3
Various rare vertigo syndromes	112	3.7
Unknown etiology	132	4.3
Other central vestibular syndromes (without vertigo)	396	13.0
Other disorders	115	3.8

Bilateral vestibular failure

Bilateral vestibular failure (BVF) is a disorder of the peripheral labyrinth or the eighth nerve which has various etiologies. It is either acquired or congenital, or familial or sporadic. BVF occurs simultaneously or sequentially in both ears, and takes either an abrupt or slowly progressive course. A chronic bilateral loss of vestibular function is surprisingly well tolerated. Moreover, there is no continuing distressing vertigo, spontaneous nystagmus, or postural falls, which are typical signs of a vestibular tone imbalance caused by acute unilateral lesions. The key symptoms are oscillopsia during locomotion or head movements and unsteadiness, particularly in the dark. The entity was first described by Dandy (1941) in patients who had undergone bilateral vestibular neurectomies. Generally patients with BVF are first referred not only for assessment of dizziness and dysequilibrium, but also for examination of ocular motor disorders, ataxia, or hearing loss, conditions in which BVF is often not suspected prior to investigation (Rinne et al., 1995).

The diagnosis is made with the simple bedside test for defective vestibulo-ocular reflex during rapid, passive head turns (Halmagyi & Curthoys, 1988). It is confirmed by the absence of nystagmic reaction to both caloric and rotatory pendular testing while the patient sits in a rotary chair. The most frequent etiologies include ototoxicity, autoimmune disorders, meningitis, neuropathies, sequential vestibular neuritis, cerebellar degeneration, tumours, and miscellaneous otological diseases. So-called idiopathic BVF is found in more than 20% of patients (Baloh et al., 1989; Vibert et al., 1995; Rinne et al., 1995). Subjective symptoms in the acute stage tend to improve with time by processes of somatosensory and visual 'substitution' of vestibular function. Vestibular rehabilitation is supportive of this improvement, but the efficacy of physical therapy is limited. The spontaneous recovery of patients with BVF is relatively rare and incomplete. A permanent loss of vestibular function is the more frequent result; however, the thus-afflicted patient remains largely asymptomatic until

confronted with high-frequency motion conditions or situations where proprioceptors or vision cannot replace the deficient vestibular system.

Vestibular neuritis

Acute unilateral (idiopathic) vestibular paralysis, also known as vestibular neuritis (VN), is a common cause of peripheral vestibular vertigo. It accounts for about 8% of the patients referred to a neurological dizziness unit (Table 46.7).

The chief symptom is the acute onset of prolonged severe rotatory vertigo, associated with spontaneous horizontal–rotatory nystagmus, postural imbalance, and nausea without concomitant auditory dysfunction. Caloric testing invariably shows ipsilateral hypo- or non-responsiveness (as a sign of horizontal semicircular canal paresis). Epidemic occurrence of the condition, the frequency of preceding upper respiratory tract infections, a small number of postmortem studies that found cell degeneration of one or more vestibular nerve trunks, and the demonstration of latent herpes simplex virus type I in human vestibular ganglia, all suggest that the cause may be a viral infection (or reactivation) of the vestibular nerve (Schuknecht & Kitamura, 1981; Arbusow et al., 1999), similar to those producing Bell's palsy and sudden sensorineural hearing loss.

VN is most likely a partial rather than a complete vestibular paresis, with predominant involvement of the horizontal and anterior semicircular canals (sparing the posterior semicircular canal). The condition mainly affects adults, ages 30 to 60, and has a natural history of gradual recovery within 1 to 6 weeks. Recovery is a product of combined (i) peripheral restoration of labyrinthine function (frequently incomplete); (ii) substitution for the unilateral vestibular deficit by contralateral vestibular input and the somatosensory and the visual systems; and (iii) central compensation of the vestibular tone imbalance (aided by physical exercise).

Diagnosis of VN is based on the simple assessment of an acute vestibular tone imbalance associated with a unilateral peripheral vestibular loss (bedside testing of high-frequency VOR; caloric testing) after clinical exclusion of a central neurological disorder. As this diagnostic procedure lacks selectivity, pathological processes other than VN which also cause an acute unilateral loss of peripheral labyrinthine function may be wrongly labelled. Thus, the term VN does not describe a well-defined clinical entity, but rather a syndrome in which peripheral vestibular paralysis can have a number of possible causes (usually viral or vascular). Some authors have proposed other sites for the lesion: peripheral labyrinth, vestibular nerve, or the insertion site of the root of the eighth nerve into the pontomedullary brainstem (here an MS plaque can mimic VN). Differential diagnosis includes all other causes of acute loss of peripheral labyrinthine function.

Benign paroxysmal positional vertigo

Benign paroxysmal positioning vertigo (BPPV; also known as positioning vertigo) was initially defined by Bárány in 1921. BPPV is the most common cause of vertigo, particularly in the elderly. By age 70, about 30% of all elderly subjects have experienced BPPV at least once. This condition is characterized by brief attacks of rotatory vertigo and concomitant positioning rotatory–linear nystagmus which are elicited by rapid changes in head position relative to gravity. BPPV is a mechanical disorder of the inner ear in which the precipitating positioning of the head causes an abnormal stimulation, usually of the posterior semicircular canal (p-BPPV) of the undermost ear, less frequently of the horizontal (h-BPPV) or anterior (a-BPPV) semicircular canal.

Schuknecht (1969) hypothesized that heavy debris settle on the cupula (cupulolithiasis) of the canal, transforming it from a transducer of angular acceleration into a transducer of linear acceleration. It is now generally accepted that in the typical case the debris float freely within the endolymph of the canal ('canalolithiasis') (Parnes & McClure, 1991; Epley, 1992; Brandt & Steddin, 1993). The debris, possibly particles detached from the otoliths, congeal to form a free-floating clot (plug). Since the clot is heavier than the endolymph, it will always gravitate to the most dependent part of the canal during changes in head position which alter the angle of the cupular plane relative to gravity. Analogous to a plunger, the clot induces bidirectional (push or pull) forces on the cupula, thereby triggering the BPPV attack. Canalolithiasis explains all the features of BPPV: latency, short duration, fatigability (diminution with repeated positioning), changes in direction of nystagmus with changes in head position, and the efficacy of physical therapy (Brandt & Steddin, 1993).

In 1980 Brandt and Daroff proposed the first effective physical therapy (positioning exercises) for BPPV. Based on the assumption that cupulolithiasis was the underlying mechanism, the exercises were a sequence of rapid lateral head/trunk tilts, repeated serially to promote loosening and, ultimately, dispersion of the debris toward the utricular cavity. In 1988 Semont and coworkers introduced a single liberatory manoeuvre, and Epley promoted a variation in

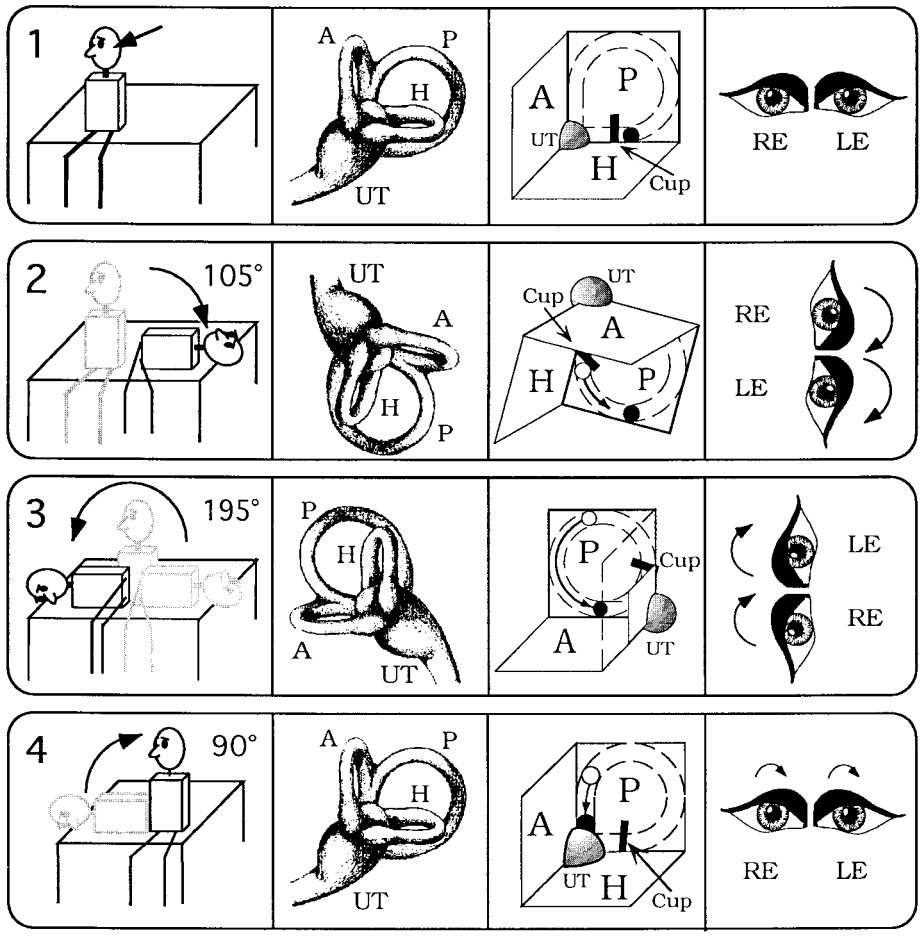

Fig. 46.3. Schematic drawing of the liberatory manoeuvre in a patient with typical BPPV of the left ear. Boxes from left to right: position of body and head, position of labyrinth in space, position and movement of the clot in the posterior canal and resulting cupula deflection, and direction of the rotatory nystagmus. The clot is depicted as an open circle within the canal; a black circle represents the final resting position of the clot. (i) In the sitting position, the head is turned horizontally 45° to the unaffected ear. The clot, which is heavier than endolymph, settles at the base of the left posterior semicircular canal. (ii) The patient is tilted approximately 105° toward the left (affected) ear. The change in head position, relative to gravity, causes the clot to gravitate to the lowermost part of the canal and the cupula to deflect downward, inducing BPPV with rotatory nystagmus beating toward the undermost ear. The patient maintains this position for 3 minutes. (iii) The patient is turned approximately 195° with the nose down, causing the clot to move toward the exit of the canal. The endolymphatic flow again deflects the cupula such that the nystagmus beats toward the left ear, now uppermost. The patient remains in this position for 3 minutes. (iv) The patient is slowly moved to the sitting position; this causes the clot to enter the utricular cavity. Abbreviations: A, P, and H = anterior, posterior, horizontal semicircular canals. Cup = cupula, UT = utricular cavity, RE = right eye, and LE = left eye. (From Brandt et al., 1994.)

1992. If performed properly, all three forms of therapy (Brandt–Daroff exercises and Semont and Epley's liberatory manoeuvre) are effective in BPPV patients (Herdman et al., 1993). The efficacy of physical therapy (Fig. 46.3) makes selective surgical destructions such as transsection of the posterior nerve (Gacek, 1984) or non-ampullary plugging of the posterior semicircular canal (Pace-Balzan & Rutka, 1991) largely unnecessary.

About 5–10% of BPPV patients suffer from horizontal canalolithiasis (h-BPPV; McClure, 1985). h-BPPV is elicited when the head of the supine patient is turned from side to side, around the longitudinal z-axis. Combinations are possible, and transitions from p-BPPV to h-BPPV occur, if the clot moves from one to the other semicircular canal. Transitions from canalolithiasis to cupulolithiasis in h-BPPV patients have been described (Steddin & Brandt,

1996). Most of the cases appear to be idiopathic (degenerative?), their incidence increasing with advancing age. Prolonged bedrest also facilitates their occurrence. Other cases arise due to trauma, vestibular neuritis, or inner ear infections.

The diagnosis of typical BPPV is simple and safe: the patient must have the usual history and exhibit positioning nystagmus toward the causative, undermost ear. Diagnosis is less easy in rare cases, for example, in patients with horizontal semicircular canal cupulolithiasis who exhibit positional nystagmus beating toward the uppermost ear for several minutes. Differential diagnosis includes different forms of central vestibular vertigo or nystagmus, vestibular paroxysmia, perilymph fistula, drug or alcohol intoxication, vertebrobasilar ischemia, Menière's disease and psychogenic vertigo.

Vestibular paroxysmia

Episodic vertigo and other vestibular syndromes can result from pathological excitation of various vestibular structures: the labyrinthine receptors, the vestibular nerve, the vestibular nuclei, and their ascending pathways to the thalamus and the cortex. There is evidence that neurovascular cross-compression of the eighth nerve is the probable cause of vestibular paroxysmia (also termed disabling positional vertigo), including both paroxysmal hyperactivity and progressive functional loss. Analogously to trigeminal neuralgia, vestibular paroxysmia is diagnosed by the occurrence of short attacks and series of rotational or to-and-fro vertigo, which are precipitated or modulated by changing head position and frequently associated with hypacusis and tinnitus (Brandt & Dieterich, 1994b).

This variable syndrome was first described by Jannetta (1975) and later labeled 'disabling positional vertigo' by the same authors (Jannetta et al., 1984; Møller et al., 1986).

Lacking a well-defined syndrome and a diagnostic test, the non-surgical clinician finds it difficult to believe in this disease. The increasing number of reports on vestibular paroxysmia prompt us to share our own preliminary experience with episodic vertigo, a treatable condition that has long escaped notice. The conservative therapeutic approach to the typical clinical syndrome of neurovascular compression of the eighth nerve is mainly based on the efficacy of treatment with carbamazepine, the recurrence of attacks following drug washout phases, and the exclusion of a central (particularly a demyelinating) disease. There is still no pathognomonic sign of the condition, and to date the current imaging techniques for identifying causative nerve-vessel contacts leave much to be desired, since vessel contacts can also be imaged (even at root entry zones) in asymptomatic patients.

According to our findings, the diagnosis can be established on the basis of six characteristic features (Brandt & Dieterich, 1994b):

(i) short attacks of rotational or to-and-fro vertigo lasting for seconds to minutes,
(ii) attacks frequently provoked by particular head positions and whose duration is modified by changing head position,
(iii) hypacusis or tinnitus permanently or during the attack,
(iv) auditory or vestibular deficits measurable by neurophysiological methods,
(v) efficacy of carbamazepine, and
(vi) a central cause excluded by clinical, neurophysiological, and imaging investigations.

As distinct from typical trigeminal neuralgia – in which there is no significant sensory loss, vestibular paroxysmia is characterized by paroxysmal hyperactivity combined with some functional deficit in the attack-free interval.

Central vestibular disorders

Topographic diagnosis in neurology is frequently based on lesions along the course of long motor or sensory pathways. This is well established for the pyramidal tract and the visual pathways. Likewise, clinical studies of the differential effects of central vestibular pathway lesions have increasingly shown vestibular syndromes to be accurate indicators for a topographic diagnosis. Vestibular pathways run from the eighth nerve and the vestibular nuclei through ascending fibres, such as the ipsilateral or contralateral medial longitudinal fasciculus, the brachium conjunctivum, or the ventral tegmental tract to the oculomotor nuclei, the supranuclear integration centres in the rostral midbrain, and the vestibular thalamic subnuclei. From there they reach several cortex areas through the thalamic projection. Another relevant ascending projection reaches the cortex from vestibular nuclei via vestibular cerebellum structures, in particular the fastigial nucleus.

In the majority of cases, central vestibular vertigo syndromes are caused by dysfunction or a deficit of sensory input induced by a lesion. In a small proportion of cases they are due to pathological excitation of various structures, extending from the peripheral vestibular organ to the vestibular cortex. Since peripheral vestibular disorders are always characterized by a combination of perceptual, ocular motor, and postural signs and symptoms, central

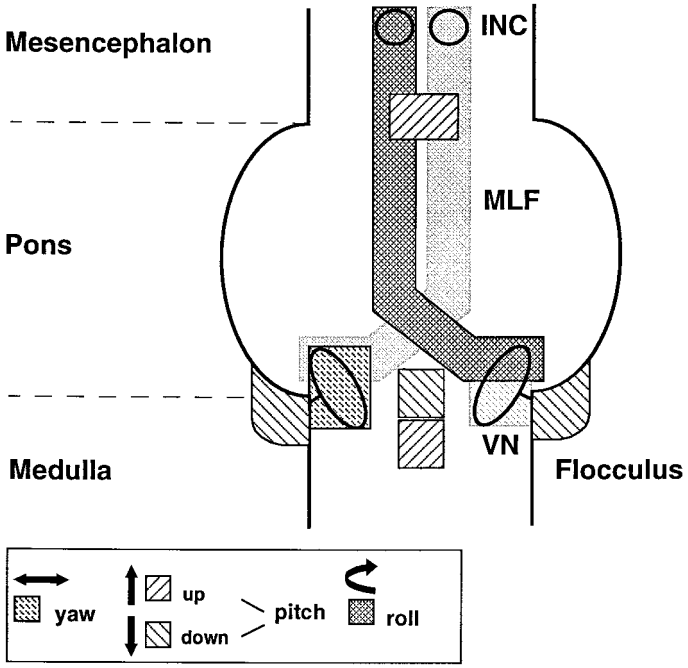

Fig. 46.4. Vestibular syndromes in roll, pitch, and yaw planes: critical areas are schematically represented based on our current knowledge of vestibular and ocular motor structures and pathways, a lesion of which causes a vestibular tone imbalance in one of the three major planes of action. The mere clinical sign of a vertical, torsional, or horizontal nystagmus, if central vestibular, allows a topographic diagnosis of the lesion, although the particular vestibular structures involved are still under discussion. Whereas a vestibular tone imbalance in the roll plane indicates unilateral brainstem lesions (a crossing in the pons), vertical nystagmus indicates bilateral lesions. Two separate causative loci are known for upbeat nystagmus: medullary or pontomesencephalic. Downbeat nystagmus indicates a bilateral paramedian lesion of the commissural fibres between the vestibular nuclei or a bilateral flocculus lesion. Horizontal nystagmus indicates unilateral pontomedullary lesions involving the vestibular nuclei. The differentiation of vestibular ocular motor signs according to the three major planes of action of the VOR and their mapping to distinct and separate areas in the brainstem are helpful for topographic diagnosis and for avoiding incorrect assignment of clinical signs to brainstem lesions identified with imaging techniques (INC = interstitial nucleus of Cajal, MLF = medial longitudinal fasciculus, VN = vestibular nucleus). (From Brandt & Dieterich, 1994.)

vestibular disorders may manifest as 'a complete syndrome' or with only single components. The ocular motor aspect, for example, predominates in the syndromes of upbeat or downbeat nystagmus. Lateral falls may occur without vertigo in vestibular thalamic lesions (thalamic astasia) or as lateropulsion in Wallenberg's syndrome.

Clinical classification (Fig. 46.4)

The 'elementary' neuronal network of the vestibular system is the di- or trisynaptic VOR. VOR properties are routinely tested in all patients who complain of dizziness (Leigh & Brandt, 1993) and are a part of the examination of the unconscious patient. There is evidence for a useful clinical classification of central vestibular syndromes according to the three major planes of action of the VOR: yaw, roll, and pitch (Brandt, 1991, Brandt & Dieterich 1994a).

Vestibular disorders in (horizontal) yaw plane

Yaw plane signs are horizontal nystagmus, past pointing, rotational and lateral body falls, deviation of perceived straight ahead.

Vestibular disorders in (frontal) roll plane

Roll plane signs are torsional nystagmus, skew deviation, ocular torsion, tilts of head, body, and perceived vertical.

Vestibular disorders in (sagittal) pitch plane

Pitch plane signs are upbeat/downbeat nystagmus, forward/backward tilts and falls, deviations of perceived horizontal.

The thus defined VOR syndromes allow for a precise topographic diagnosis of brainstem lesions as to their level and side (Brandt & Dieterich, 1994a).

- *A tone imbalance in yaw* indicates lesions of the lateral medulla including the root entry zone of the eighth nerve and/or the vestibular nuclei.
- *A tone imbalance in roll* indicates unilateral lesions (ipsiversive at pontomedullary level, contraversive at pontomesencephalic level).
- *A tone imbalance in pitch* indicates bilateral (paramedian) lesions or bilateral dysfunction of the flocculus.

It is hypothesized that signal processing of the VOR in roll and pitch is conveyed by the same rather than separate ascending pathways in the medial longitudinal fasciculus and the brachium conjunctivum. A unilateral lesion (or stimulation) of these 'graviceptive' pathways (which transduce input from vertical semicircular canals and otoliths) affects function in roll, whereas bilateral lesions (or stimulation) affects function in pitch. Thus, the vestibular system is able to change its functional plane of action from roll to pitch by switching from a unilateral to a bilateral mode of operation.

Pure syndromes in yaw are rare, since the small causative area covering the medial and superior vestibular nucleus is not only adjacent to but overlapped by the structures also subserving roll and pitch function. A lesion frequently

Table 46.8. Central vestibular syndromes

Site	Syndrome	Mechanism/Etiology
Vestibular cortex (multisensory)	Vestibular epilepsy	Vestibular seizures are auras (simple or complex partial multisensory seizures)
	Volvular epilepsy	Sensorimotor 'vestibular' rotatory seizures with walking in small circles
	Non-epileptic cortical vertigo	Rare rotatory vertigo in acute lesions of the parieto-insular vestibular cortex
	Spatial hemineglect (contraversive)	Multisensory horizontal deviation of spatial attention with (right) parietal or frontal cortex lesions
	Transient room-tilt illusions	Paroxysmal or transient mismatch of visual- and vestibular 3D spatial coordinate maps in vestibular brainstem, parietal, or frontal cortex lesions
	Tilt of perceived vertical with body lateropulsion (mostly contraversive)	Vestibular tone imbalance in roll with acute lesions of the parieto-insular vestibular cortex
Thalamus	Thalamic astasia	Dorsolateral vestibular thalamic lesions
	Tilt of perceived vertical (ipsiversive or contraversive) with body lateropulsion	Vestibular tone imbalance in roll
Mesodiencephalic brainstem	Ocular tilt reaction (contraversive; ipsiversive if paroxysmal)	Vestibular tone imbalance in roll (integrator-ocular tilt reaction with lesions of the interstitial nucleus of Cajal)
	Torsional nystagmus (ipsiversive or contraversive)	Ipsiversive in lesions of the interstitial nucleus of Cajal Contraversive in rostral lesions of the medial longitudinal fascicle
Mesencephalic brainstem	Skew torsion (contraversive)	Vestibular tone imbalance in roll with lesions of medial longitudinal fascicle
	Upbeat nystagmus	Vestibular tone imbalance in pitch in bilateral brachium conjunctivum lesions
Ponto-medullary brainstem	Tilt of perceived vertical, lateropulsion, ocular tilt reaction	Vestibular tone imbalance in roll with medial and/or superior vestibular nuclei lesions
	Pseudo 'vestibular neuritis'	Lacunar infarction or MS plaque at the root entry zone of the eighth nerve
	Downbeat nystagmus	Vestibular tone imbalance in pitch
	Transient room-tilt illusion	Acute severe vestibular tone imbalance in roll or pitch
	Paroxysmal room-tilt illusion in MS	Transversally spreading ephaptic axonal activity
	Paroxysmal dysarthria/ataxia in MS	Transversally spreading ephaptic axonal activation
	Paroxysmal vertigo evoked by lateral gaze	Vestibular nuclei lesion?
Medulla	Upbeat nystagmus	Vestibular tone imbalance in pitch? (nucleus prepositus hypoglossi)
Vestibular cerebellum	Downbeat nystagmus	Vestibular tone imbalance in pitch caused by bilateral flocculus lesions (disinhibition)
	Positional downbeat nystagmus	Disinhibited otolith–canal interaction in nodulus lesions?
	Familial episodic ataxia (EA1 with myokymia and EA2 with vertigo)	EA1 = autosomally dominant inherited potassium channelopathy EA2 = autosomally dominant inherited calcium channelopathy
	Encephalitis with predominant vertigo	Viral infection of cerebellum
	Epidemic vertigo	Viral infection of cerebellum

results in mixed (e.g. torsional and horizontal) nystagmus. The lesional sites of yaw syndromes are restricted to the pontomedullary level because of the short distance between the vestibular nuclei and the integration centre for horizontal eye movements in the paramedian pontine reticular formation. Syndromes in roll and pitch, however, may arise from brainstem lesions located in an area extending from the medulla to the mesencephalon, an area corresponding to the large distance between the vestibular nuclei and the integration centres for vertical and torsional eye movements in the rostral midbrain. Whereas vestibular tone imbalances in pitch, which involve bilateral pathways, may occur with various intoxications or metabolic disorders, this is an unusual etiology for tone imbalances in yaw or roll, which involve vestibular pathways unilaterally.

Some vestibular disorders are characterized by a simultaneously peripheral and central vestibular involvement. Examples are large acoustic neurinomas, infarctions of the anterior inferior cerebellar artery, head trauma, and syndromes induced by alcohol intoxication. Others may affect the vestibular nerve root in the brainstem (lacunar infarction, focal demyelination in MS).

Cortical vestibular syndromes include vestibular seizures (vestibular epilepsy) and lesional dysfunction with tilt of the perceived vertical, lateropulsion, rarely rotational vertigo. There is no primary vestibular cortex, but cortical vestibular function is embedded in a network of multisensory visual–vestibular–somatosensory functions and distributed over several separate and distinct areas in the temporo-parietal region.

The parieto-insular vestibular cortex (Guldin & Grüsser, 1996) seems to act as a kind of main integration centre. Dysfunction of this multisensory and sensorimotor cortex for spatial orientation and self-motion perception may be involved in spatial hemineglect and rare paroxysmal room-tilt illusions. Visual–vestibular interaction in self-motion perception is obviously based on reciprocal inhibitory interaction, a mechanism that makes perception of self-motion more robust and largely insensitive to visual–vestibular mismatches.

Most central vertigo syndromes have a specific locus (Table 46.8) but not a specific etiology.

Acknowledgment

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Part V

Disorders of spine and spinal cord

47

Spinal cord injury and repair

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Many victims of spinal cord injury are young and will live a near-normal lifespan (Fig. 47.1). Therefore, the toll to individuals and society is high. The average lifetime cost of treating a person with traumatic spinal cord injury in the United States runs between $500 000 and $2 million, depending on factors such as the extent of injury and where the cord is injured (higher levels correspond to greater disability and greater costs). Total direct costs of caring for Americans with spinal cord injury exceed $8 billion per year (DeVivo, 1997).

Current state of acute pharmacological treatment

This enormous human and economic toll calls for effective therapies. It was not until the 1990s, however, that the first proven therapy for spinal cord injury was introduced. A multicentre clinical study (National Acute Spinal Cord Injury Study, NASCIS 2) revealed that a high dose of the steroid methylprednisolone reduced disability when administered within 8 hours of the trauma (Bracken et al., 1990). Although the effectiveness of this drug was modest, the availability of any treatment for spinal cord injury was heartening. Subsequently, the multicentre NASCIS 3 trial compared treatment with methylprednisolone for 24 h (same treatment as in NASCIS 2) vs. treatment for 48 h. All patients treated with methylprednisolone within 3 hours of injury showed essentially identical rates of motor recovery. When treatment was initiated between 3 h and 8 h of injury, patients receiving the 48-hour protocol showed significantly more improvement in motor function. Therefore, the US standard of care is administration of methylprednisolone (bolus 30 mg/kg) within the first 8 h after injury. Treatment initiated within the first 3 h is continued (5.4 mg/kg/h) for 24 h, whereas treatment initiated between 3 h and 8 h is continued for 48 h.

Despite these studies, methylprednisolone remains controversial in other countries (Short et al., 2000). Additional experimental drugs, including SYGEN (GM-1 ganglioside), naloxone, and trilizad, have been tested in multicentre clinical trials, but primary endpoints were never achieved.

More recently, cellular and molecular advances in neurobiology have provided powerful insights into the nature of spinal cord injury and opened up new horizons for neural repair and restoration of function. In this chapter we describe how this rapidly burgeoning knowledge might be harnessed to help individuals with spinal cord unjury regain lost functions.

The working cord

The spinal cord is the primary pathway of communication between the brain and the body (Fig. 47.2, see colour plate section), and excellent reviews of its anatomy and physiology are available elsewhere (Byrne et al., 2000).

Millions of axons carry impulses up and down the spinal cord. Axons from neurons in the brain's motor cortex travel up to 1 metre to reach target neurons at each segmental level of the cord; the target neurons connect to relevant muscle cells in the body. Sensations from the skin and other organs travel as electrical signals in the reverse direction, relayed to the appropriate segment of the spinal cord and then up through axons within the cord to locations in the brain and cerebellum. These ascending sensory pathways allow you to feel the soft fur of a kitten, to sense pain when stung by a bee, to locate the position of your arm in the dark, and to know when to empty your bladder. The motor and sensory pathways are organized in a well-understood somatotopic manner, with sacral fibres tending to be more peripheral and cervical fibres more central. This discrete

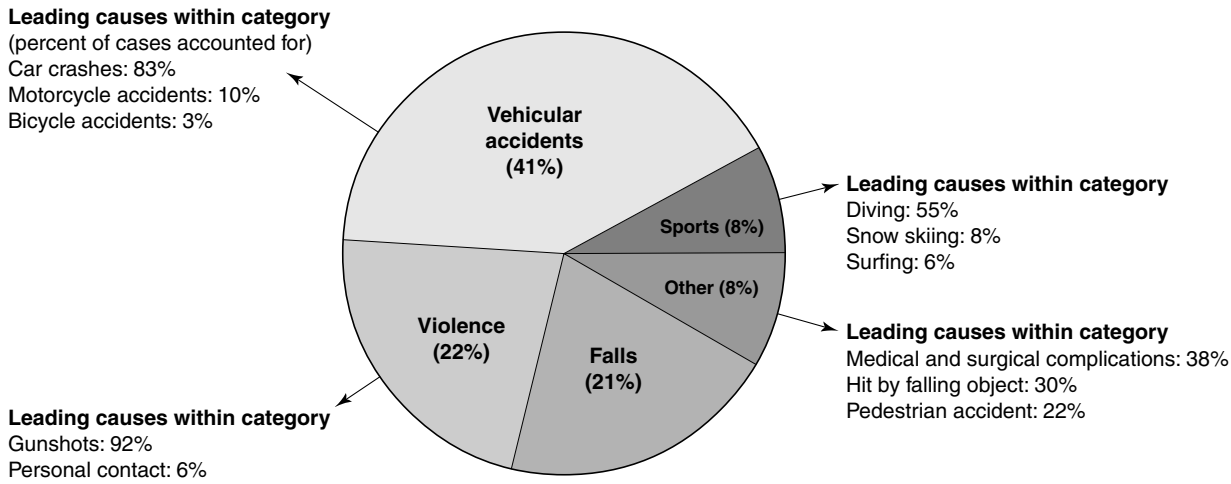

Fig. 47.1. Spinal cord injuries result from traumatic and non-traumatic causes (1994–1998), in roughly equal numbers. The following numbers and pie chart refer to traumatic cases in the United States. Incidence: 10 000 new cases per year. Prevalence: about 230 000. Men account for about 80% of cases. Most (43%) patients are injured between ages 16 and 30, whereas 28% are injured between ages 31 and 45. (Data were obtained from the National Spinal Cord Injury Statistical Center, University of Alabama, Birmingham.)

anatomical and physiological organization provides an ideal venue for research.

When injury strikes

Traumatic injury directly damages the delicate spinal cord with mechanical force, which typically is generated when broken fragments of vertebrae or soft tissue (ligament, herniated disc) impinge on the cord. Within minutes, small-blood vessels hemorrhage, and the spinal cord swells. These events obstruct the normal delivery of nutrients and oxygen to the injured part of the cord, causing many local neurons and glia to starve to death. This immediate damage is not the end of the destruction. A cascade of events triggered by the initial injury leads to secondary injury that progressively enlarges the damaged region during subsequent minutes, hours, and days (Fig. 47.3, see colour plate section). As a result of both initial and secondary injury, the cord can be left in disarray, with neuronal synaptic connections disrupted and many untraumatized axons rendered inactive by demyelination. With the exception of high velocity gunshot injuries and knife wounds, however, it is not common for trauma to completely severe the spinal cord. In postmortem studies, more than 60% of cases show some continuity of CNS tissue across the lesion (Bunge et al., 1993). Typically, a doughnut-shaped rim of white matter remains at the injury level (Bunge et al., 1993; Kakulas et al., 1998; Kakulas, 1999a,b) (Fig. 47.4). However, scarring and the formation of a fluid-filled cavity (a syrinx) can occur, providing physical barriers to axon regeneration. Unlike many of the rodent contusion spinal cord injury models that reproducibly produce a central syrinx at the lesion site, only 20% to 30% of persons surviving traumatic spinal cord injury have a syrinx (Bunge et al., 1993).

What can be done about these barriers to functional recovery? Most laboratories are trying to accomplish two main therapeutic goals: limiting tissue damage, primarily by blocking important steps in the secondary injury cascade, and enhancing recovery, primarily by promoting the regeneration and reconnection of nerve cells. Accomplishing these goals in an optimal manner will require multiple interventions, administered in an orderly sequence, and involving a delicate balance between enhancing favourable (e.g. growth-promoting) factors and neutralizing unfavourable (e.g. growth-inhibiting) ones (Fig. 47.5, see colour plate section).

Terminology, classification and evolution of clinical approaches

To establish a foundation for understanding human spinal cord injury, we will provide clinical terminology and discuss outcomes. To convey severity, medical caregivers use the simple but accurate American Spinal Injury Association (ASIA) Impairment Scale (Table 47.1), a 5-category (A to E) system (ASIA, 1996). Although this classification scale has

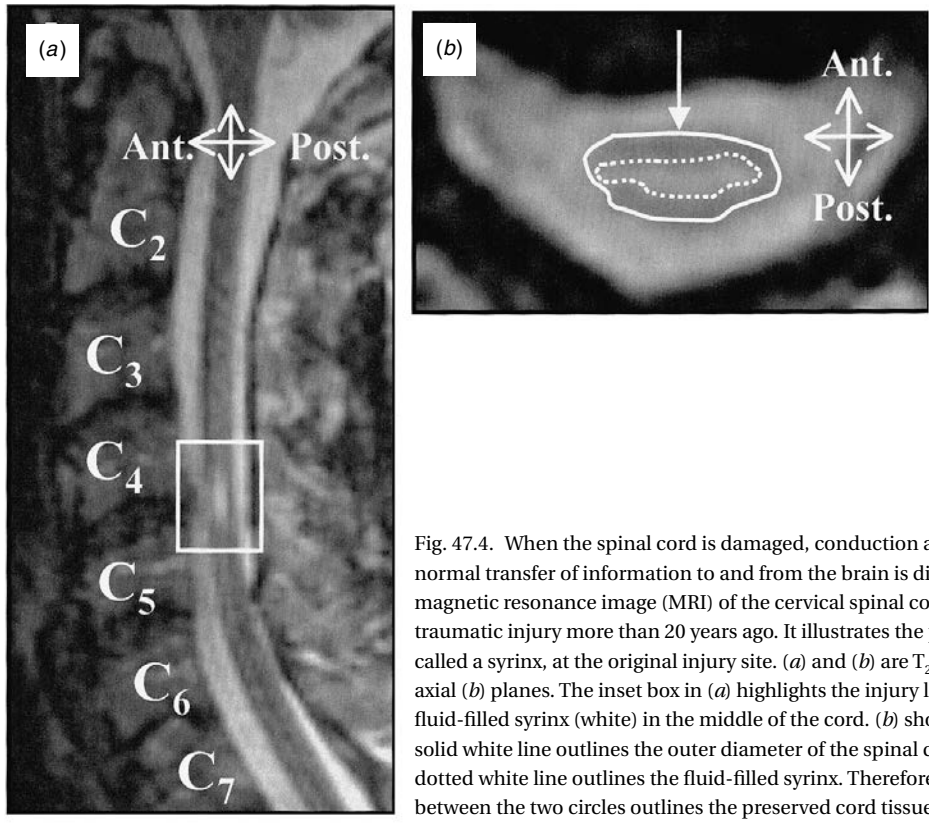

Fig. 47.4. When the spinal cord is damaged, conduction along axons is blocked, and the normal transfer of information to and from the brain is disrupted. (*a*) and (*b*) show a magnetic resonance image (MRI) of the cervical spinal cord of a patient who experienced a traumatic injury more than 20 years ago. It illustrates the presence of a fluid-filled cavity, called a syrinx, at the original injury site. (*a*) and (*b*) are T_2-weighted MRIs in sagittal (*a*) and axial (*b*) planes. The inset box in (*a*) highlights the injury level at C4/5 and demonstrates a fluid-filled syrinx (white) in the middle of the cord. (*b*) shows the syrinx more closely. The solid white line outlines the outer diameter of the spinal cord at the C4/5 level. The inner dotted white line outlines the fluid-filled syrinx. Therefore, the doughnut-shaped area between the two circles outlines the preserved cord tissue.

traditionally used the terms 'complete' and 'incomplete', there is no benefit to retaining such confusing, redundant, and outdated terminology. The terms mean little to individuals with spinal cord injury and, in most cases, are mistakenly believed to indicate the degree of anatomical connection (e.g. incomplete) or disconnection (severed cord; e.g. complete) of the spinal cord. Dimitrijevic and colleagues (Dimitrijevic, 1988; Dimitrijevic et al., 1983) introduced the term 'discomplete' to explain their finding of electrophysiological transmission of signals across a lesion in individuals with ASIA class A injuries (e.g. clinically complete, having lost all sensation and voluntary motor functions below the level of the lesion). Such a term is also not very useful because most injuries that do not physically separate the cord leave residual axonal connections across the lesion (Bunge et al., 1993; Kakulas, 1999a,b).

Our ability to accurately predict clinical outcomes based on early examination is very limited. The most important predictor of better outcomes is retention of sacral sensation (S4–5), particularly pinprick, 72 h to 1 week after injury (Waters et al., 1995; Marino et al., 1999). The most relevant generalities that can be drawn from the many years of outcome studies in the field are summarized in Table 47.2. About 10% to 15% of individuals with ASIA A-grade lesions convert to ASIA B–D; however, only about 3% regain functional strength below the lesion level (ASIA D). Approximately 54% of individuals with initial sacral sensory sparing (ASIA B grade) gain substantial functional strength below the lesion (e.g. will convert to ASIA C–D).

Eighty-six per cent of those classified as ASIA C–D at 72 h regain useful motor function. Age is also a prognostic factor: in central cord syndromes, 91% of patients under age 50 recover ambulation, whereas only 41% over age 50 recover similar capabilities. Recovery of function is the most relevant endpoint for individuals with spinal cord injury and their caregivers. Table 47.3 outlines predicted functional recovery based on injury level for the more severe (A–C) ASIA grades.

When spinal cord damage results from trauma, most initial ER examinations reveal no function below the level of injury, primarily because of spinal shock. Spinal shock is an interesting but poorly understood phenomenon (Bach-y-Rita & Illis, 1993) and this initial lack of function does not necessarily predict a poor outcome, and it should not influence medical and surgical decisions. The usefulness of tests such as motor and sensory evoked potentials,

Table 47.1. ASIA impairment scale

Scale grade	ASIA impairment scale
A	Complete: no motor or sensory function is preserved in the sacral segments S4–S5
B	Incomplete: sensory but not motor function is preserved below the neurologic level and includes the sacral segments S4–S5
C	Incomplete: motor function is preserved below the neurologic level, and more than half of key muscles below the neurologic level have a muscle strength grade <3
D	Incomplete: motor function is preserved below the neurologic level, and at least half of key muscles below the neurologic level have a grade of 3 or above
E	Normal: motor and sensory functions are normal.

Table 47.2. Summary of recovery in ASIA A–D patients

ASIA A

1. Most (60% to 90%) regain one motor level (Stauffer, 1984).
2. 0% to 11% will improve one or more ASIA grades (Frankel et al., 1969; Maynard et al., 1979; Wu et al., 1992; Bedbrook & Sakae, 1982; Stover & Fine, 1986; Ditunno et al., 1995).
3. 4% to 10% may undergo late conversion (after 30 days) to ASIA B or better (Waters et al., 1991, 1993). This can occur up to 2.5 yrs after injury.
4. Most motor recovery occurs during the first 6 months after injury, with the greatest rate of change during the initial 3 months. Motor strength can continue to improve during second year.
5. Muscles graded 1–3 in the zone of partial preservation (ZPP) will recover useful motor function.

ASIA B–D

6. Of ASIA B patients, sacral preservation of pinprick denotes better prognosis for recovery of functional ambulation than ability to sense light touch: 66% to 89% pinprick vs. 11% to 14% light touch (Foo et al., 1981; Folman & el Masri, 1989; Crozier et al., 1991; Waters et al., 1994; Katoh & el Masry, 1995).
7. Of ASIA C patients, 52% to 76% recover to ASIA D or E, compared with 20% to 28.3% of all ASIA B patients (Frankel et al., 1969; Ditunno et al., 1995; Bedbrook & Sakae, 1982; Stauffer, 1983).
8. Central cord syndromes (CCS): generally favourable prognosis (Merriam et al., 1986; Foo, 1986; Penrod et al., 1990; Roth et al., 1990), but age is a key determinant, with patients <50 yr having a better prognosis for ambulation than patients over 50 yr (97% vs. 41%). (Foo, 1986; Merriam et al., 1986; Penrod et al., 1990).
9. In general, Brown–Sequard syndrome (BSS) lesions recover more than central cord syndromes, which recover more than anterior cord syndromes (Stauffer, 1984).

cranial magnetic stimulation, and functional imaging is being examined, but these are still early days.

The recent rush of scientific advances in aspects of regeneration has changed the way we interact with individuals with spinal cord injury. We used to tell newly injured individuals that recovery was unlikely and that they should adapt to life in a wheelchair. This approach is no longer considered productive. Although the clinician's armamentarium for treating spinal cord injury remains limited by the lag between laboratory observations and clinical trials, we can now offer hope, because regeneration and some restoration of function are becoming achievable targets. The old view of limiting rehabilitation to ergonomics, adaptation, and strengthening is giving way to the idea that therapies that promote regeneration can restore additional function. Thus, studies of how environmental factors affect recovery from CNS injury are attracting attention (Ivanco & Greenough, 2000). The constraint-induced, forced-use studies in stroke rehabilitation (for review see Taub et al., 1999) and all the developmental data indicating the importance of patterned neural activity in preserving and (re-)generating the CNS, support the theory that modifying the environment to optimize neural activity is an important therapeutic goal.

Limiting secondary injury

As in conditions such as stroke (see 'Cellular mechanisms of neurological damage', 'Principles of neuroprotection', and 'Principles of ischemic stroke management', Chapters 5, 14, 81, this volume and Volume 2), trauma to the spinal cord appears to induce additional neural cell death through a process called excitotoxicity (for review see Schwab & Bartholdi, 1996; Lee et al., 1999; McDonald et al., 1999). Glutamate, an amino acid neurotransmitter normally released in minute amounts from nerve terminals for signalling, is discharged excessively after neuronal injury (McAdoo et al., 1997). Building up in the extracellular space, it overactivates receptors on the membranes of neighbouring neurons and glial cells. These glutamate receptors open ion channels, admitting large amounts of

Table 47.3. Expected functional outcome based on injury level

Level (ASIA)	Breathing	Mobility	Driving	Transfers	Bowel	Bladder	Eating & grooming	Dressing upper extremities	Dressing lower extremities
C1–3	D	Power chair	N/A	D	D	D	D	D	D
C4	I	Power chair	N/A	D	D	D	D	D	D
C5	I	Power chair	Modified van	D	D	D	Partially D	Partially D	D
C6	I	Power and manual chair	Modified van	Perhaps I	I	I–O D–O	Partially D	Partially D	D
C7–8	I	Manual chair	Hand controls	I	I	I	I	I	Perhaps I
T1–12	I	Manual chair; bipedal ambulation with extensive bracing	Hand controls	I	I	I	I	I	I
L–S	I	Manual chair; bipedal ambulation with/ without bracing	With/without hand controls	I	I	I	I	I	I

Notes:
D = dependent.
I = independent.
O = orthosis.

calcium and sodium into the cells. The resulting sustained elevation in intracellular calcium triggers a series of destructive events: protein-destroying enzymes are switched on, and bursts of oxygen free radicals damage cell membranes and intracellular organelles. Unable to withstand these insults, nerve cells die, compounding the direct damage from the initial mechanical injury.

As well as protecting neurons from excitotoxic injury, it is vital to protect spinal cord white matter, the outer ring of tissue that carries ascending and descending axons. It is not uncommon for a lesion to be confined to the central tissue, which contains nerve cell bodies (grey matter), while the surrounding white matter is spared. Such a central cord lesion confines motor and sensory disturbances to areas innervated at that level (for example, a C6 lesion affects the upper limbs) without much affecting function below that level, such as gait, bowel or bladder function. In contrast, destruction of white matter at the same segment, even if the injury spares grey matter, renders a person tetraplegic and incontinent.

Several studies of animal models of spinal cord injury suggest that anti-excitotoxic treatments can be beneficial (Faden & Simon, 1988; Wrathall et el., 1994). However, initial work that focused on the role of NMDA-type glutamate receptors documented preferential protection of grey matter, which did not bode well for functional improvements that depend on white matter preservation (most animal models involve thoracic spinal cord injury). More recent work has focused attention on the benefits of blocking a subclass of glutamate receptors called AMPA receptors (Wrathall et al., 1994, 1996). Such treatment protects white matter and improves locomotor function, but understanding of the cellular mechanism awaits later studies.

Although excitotoxicity has traditionally been thought to kill only neurons, recent studies suggest that it may also kill oligodendrocytes, which myelinate CNS axons. Thus, excitotoxic damage to oligodendrocytes contributes to white matter injury (Matute et al., 1997; McDonald et al., 1998a, 1998b, 1999; Li et al., 1999b; Li & Stys, 2000) and to demyelination and axonal conduction block often found in the injured spinal cord (Gledhill et al., 1973; Bresnahan, 1978; Bunge et al., 1993; Waxman, 1989, 1992).

In the past 5 years, recognition that a second form of cell death, programmed cell death or apoptosis, also occurs in the injured spinal cord, has opened new doors to protective strategies (Kerr et al., 1972; Wyllie et al., 1980). Apoptosis is essential to normal CNS development, when it removes unneeded cells, and it may be triggered inappropriately later in life when certain key structures, such as DNA, sustain damage (Johnson et al., 1996; Lee et al., 1999), leading to the unfortunate loss of nerve cells. Many of the neuroprotective effects of neurotrophins observed in animal and in vitro models of CNS injury prevent such apoptotic death of neurons and glia. Thus, NT-3 and BDNF have well-described injury-limiting effects in addition to prominent regenerative actions (see below).

Recent animal (Crowe et al., 1997; Liu et al., 1997; Shuman et al., 1997; Li et al., 1999a; Springer et al., 1999) and human (Emery et al., 1998) studies have revealed that a prominent wave of oligodendrocyte apoptosis may occur days to weeks after spinal cord injury, at quite remote sites. This delayed reaction may be triggered by a combination of early excitotoxic injury and a later loss of vital surface or trophic factor interactions as truncated axons slowly degenerate (for review see Beattie et al., 2000; Zipfel et al., 2000). Furthermore, administration of drugs or creation of dominant negative mutations that inhibit apoptosis permits rats and mice subjected to traumatic spinal cord injury to regain a better level of ambulation (Liu et al., 1997; Li et al., 2000).

Ultimately, treatments aimed at reducing secondary damage in the injured spinal cord will likely encompass multiple drugs delivered at different intervals and targeted at specific mechanisms of cell death in distinct cell populations. Almost certainly, the strategy of blocking excitotoxic and apoptotic death pathways will be augmented by delivery of trophic factors capable of promoting neuronal and glial cell survival. A great deal has been learned recently about the identities of these factors, their effects, and their mechanisms of action. Factors that regulate the production of neurotrophins and their receptors in oligodendrocytes, astrocytes, and microglia also have been discovered, and these may be useful for enhancing production of selected neurotrophins in the injured spinal cord.

Once interventions can limit secondary tissue injury as much as possible, the therapeutic focus will shift to promoting nerve cell regeneration and reconnection. The reminder of this article will summarize emerging concepts and potential strategies in this area. To obtain meaningful recovery of function, we will not need to completely shield the damaged spinal cord from secondary injury or entirely rebuild it. Preserving or re-establishing a fraction of the lost connections may enhance important functions, such as control of the bladder, bowel, and respiration. Studies from as early as the 1950s have indicated that preservation of less than 10% of the normal axon complement in the cat spinal cord can support walking (Blight, 1983), though this should not be viewed as the optimal requirement for restoring function. Moreover, detailed anatomical postmortem studies of chronic human spinal cord injury reveal that small residual connections across the lesion can preserve some function (Kakulas, 1999a,b). In one individual with ASIA C spinal cord injury, only 1.17 mm^2 of white matter remained at the level of the lesion. One individual with some preserved motor function below the level of cervical injury had only 3175 corticospinal axons, less than 8% of the number (41 472) of similar axons in normal controls.

Injuries that are lower by just a single segment, at cervical level C6 instead of C5, for example (a difference of about 1.7 cm) also have fewer effects. Whereas a person with a C5 injury level has no upper extremity function other than limited motion at the shoulders, a person with a C6 injury can move shoulder and elbow joints, and surgical transfer of muscle tendons may restore partial hand function. Therefore, small anatomical gains can result in disproportionately higher functional gains Therapeutic implications of this observation are that small additive and stepwise treatments can be expected to produce large gains in function.

The critical balance

A complex constellation of signals is required for successful regeneration of spinal cord cells and for axons to reach their correct targets during development and regeneration. The fate of disconnected axons is determined by the balance between growth-promoting (chemoattractant) and growth-inhibiting (chemorepulsant) molecules in the local environment. The growth cone on the tip of a regenerating axon makes directional choices based on the multitude of guidance molecules it encounters.

Large families of guidance molecules have been discovered. They can be: (i) presented on the surface of a cell, (ii) fixed to the extracellular matrix, or (iii) secreted into extracellular fluid. Moreover, interactions can be simple or intricate. Some molecules act by altering the electrical charge of the local environment. Others work in a lock-and-key fashion, docking at specific receptors on target axons. These interactions can trigger a complex chemical cascade within the growth cone that makes the cone retreat, advance, or both, depending on the nature of the effectors. Soluble growth factors are being evaluated for their ability to stimulate regeneration after spinal cord injury, but the manipulation of substrate-bound guidance molecules lies largely in the future. Tipping the balance in favour of growth enhancement vs. growth inhibition will be the cornerstone of success.

Regrowth of nerve fibres: overcoming inhibition

Unlike developing neurons, mature peripheral nerves or certain networks in the CNS of invertebrates, fish, amphibians, and reptiles, mammals regenerate poorly after their axons are severed. This does not appear to be an intrinsic limitation of the adult neuron itself, however. In the 1980s,

Albert J. Aguayo and colleagues showed that adult rat neurons can regenerate when provided with a permissive environment. Using a piece of peripheral nerve from the leg as a graft, they constructed a bridge across the injured region of the spinal cord and redirected the cut axons across the graft. After many weeks, they observed robust axonal regeneration from the spinal cord into the graft, in some cases up to 30 to 40 mm (Richardson et al., 1980; David & Aguayo, 1981). But the credit for the first demonstration of the capacity of CNS neurons to regenerate predates these studies by 70 years (Tello, 1911); pieces of peripheral nerve were transplanted into the cortex of young rabbits, and several weeks later bundles of fibres entered the graft. These observations suggest that mammalian central neurons are reluctant to regrow after injury because of shortcomings in their immediate environment.

One promising approach to this problem is to study systems that can regenerate so factors that promote or inhibit regeneration can be identified. A particularly attractive system is the immature mammalian CNS. For example, spinal cord axons from the South American opossum, *Monodelphis domestica*, can regenerate after injury before, but not after, postnatal day 11 (for review see Nicholls & Saunders, 1996). The abrupt loss of regenerative capability appears in several cases to correlate with onset of myelination. Thus, motor axons in the hatchling chick regenerate if the spinal cord is cut before oligodendrocytes myelinate them (Steeves et al., 1994). Also, experimentally delaying myelination extends the period during which injured axons can regenerate (Keirstead et al., 1992). These studies suggest that myelin formation may be a key barrier to axon regeneration in the mature mammalian spinal cord.

More than a decade of work has focused on identifying specific nerve growth-preventing proteins in myelin (for review see Schwab et al., 1993; Schwab & Bartholdi, 1996), and the gene for one of these was recently cloned (Nogo A & B; Chen et al., 2000). Called myelin-associated neurite growth inhibitors, these proteins can prevent axonal outgrowth from cultured neurons (for review see Huber & Schwab, 2000). Applying a neutralizing antibody (termed IN–1, for inhibitor neutralizing antibody) induced axon growth from neurons cultured on the inhibitory molecules. Furthermore, infusing IN-1 into the injured rat spinal cord promoted long-distance regeneration in a small percentage of interrupted axons and improved the rats' ability to use their forepaws (Schnell & Schwab, 1990; von Meyenburg et al., 1998). In preparation for clinical trials, the active part of IN-1 has been cloned and re-engineered to be more acceptable to the human immune system. These recombinant humanized antibody fragments have recently been tested for their safety and regenerative properties in animal models of spinal cord injury (Brosamle et al., 2000).

Research has expanded the list of isolated inhibitory molecules to many families (Fitch & Silver, 1997; Kapfhammer, 1997), including the proteoglycans (for review, see Davies & Silver, 1998). In recent studies, regenerating axons from adult neurons stopped growing when confronted with a chondroitin sulfate proteoglycan-rich boundary, though they were able to cross the lesion and extend for long distances in the boundary's absence (Davies et al., 1997). Given the apparent multiplicity of molecules capable of inhibiting nerve fibre regeneration, a cocktail of drugs may be necessary to fully unmask the natural capacity of adult spinal cord neurons to regenerate after injury. As well as blocking inhibitory proteins (e.g. with antibody), it also might be possible to reduce inhibition by down-regulating production of these proteins. As the genes for key inhibitor molecules are cloned, researchers will be able to study their regulatory sites. This knowledge could be used to determine how expression of an inhibitory protein changes after injury and to devise methods for turning off the relevant gene.

Promoting outgrowth

As well as removing the inhibition of axonal regeneration, it might be possible to increase the availability of growth-promoting molecules. Major insights have come from studying axonal outgrowth during normal embryonic development. More than four decades ago, Rita Levi-Montalcini and Viktor Hamburger identified and isolated nerve growth factor (NGF), a small, soluble protein that supports the survival and development of sensory and sympathetic neurons. This pioneering work precipitated a successful search for additional neurotrophic factors, and NGF is now known to be one of a family of related neurotrophins that promote neuronal cell survival and axonal outgrowth during embryogenesis; several other families of trophic factors also have been identified (for review see Lindsay et al., 1994). However, synthesis of the messenger RNA needed to produce neurotrophic factors and their receptors can be depressed for weeks following spinal cord injury. Also, responses to neurotrophic factors can be selective for specific cell types and individual cell functions, depending on the location and expression of the receptors that are activated. For example, NT-3 selectively stimulates regrowth of injured corticospinal tract axons (Schnell et al., 1994; Grill et al., 1997; Houweling et al., 1998; von Meyenburg et al., 1998). It also can enhance cell survival and promote remyelination

(McTigue et al., 1998). In contrast, the fibroblast growth factor (FGF) family has more widespread effects, both in promoting growth and stimulating the formation of new cells from progenitors (see below). They also affect non-neural cell function. Growth-related factors such as platelet-derived growth factor (PDGF) can stimulate the replication of oligodendrocyte progenitors (for review, see Grinspan et al., 1994).

Considerable evidence suggests that endogenous production of growth factors in the injured cord falls short and that boosting the supply might improve cell survival and regeneration. This might be achieved by exogenous administration, endogenous delivery via gene transfer (see below), or modulating cellular production. Manipulating factors that regulate neurotrophin production might selectively enhance production of certain neurotrophins in the injured spinal cord and therefore promote regeneration. Promising results with many of the neurotrophic factors have been achieved in models of spinal cord injury (Schnell et al., 1994; Grill et al.;, 1997; Blesch et al., 1998; Houweling et al., 1998; von Meyenburg et al., 1998; McTigue et al., 1998; Zhang et al., 1998; Liu et al., 1999; Blits et al., 2000).

These efforts will need to be wary of unintended consequences, such as enhancing pain, already a common long-term complication of spinal cord injury (excellent reviews of this area are available: Beric, 1997; Christensen & Hulsebosch, 1997). Pain might increase because of aberrant axon sprouting within the CNS or by peripheral mechanisms such as growth factor-mediated sensitization of skin nociceptors (Mendell, 1999; Shu & Mendell, 1999). A paradoxical injury-enhancing effect of neurotrophins has also been recognized, in both culture and in vivo models of spinal cord injury (Koh et al., 1995; Gwag et al., 1995; McDonald et al., 2002).

Establishing correct functional connections

Promoting nerve outgrowth will be useful only if strategies to link regenerated axons with their suitable synaptic targets also can be developed. Powerful insights into axon guidance have come from studies of the developing nervous system, where a complex set of temporally and spatially regulated events coordinates the precise formation of intricate neural circuits. In the embryo, molecular signals that act directly on the leading tip (growth cone) of the lengthening axon choreograph outgrowth. Fortunately, the last several years have produced unprecedented advances in identifying many new families of targeting, guidance, and adhesion molecules that are expressed during development (for review see Leutwyler, 1995; Tessier-Lavigne & Goodman, 1996; Guthrie & Varela-Echavarria, 1997; Walsh & Doherty, 1997; Terman & Kolodkin, 1999; Joosten & Bar, 1999; Quinn et al., 1999; Raper, 2000 (see also Chapter 97 by Compston in Volume 2)). Some are diffusible molecules released from cells. Their concentration gradients attract the growth cone, guiding it to another neuron or developing muscle fibre. Other signals are contained in the extracellular matrix (the material outside cells). For instance, a family of factors called netrins helps guide axons in the mammalian spinal cord by calling axons in one direction and repelling them from others (Serafini et al., 1994). By displaying netrins and other guidance molecules as if they were highway signs, the extracellular matrix acts as scaffolding that tells axons precisely where to go. Like highway signs, these signals must appear in the correct sequence; otherwise, an axon would lose its way. Unfortunately, we do not yet know how to reconstitute this sequence after injury. However, our present level of understanding may permit the design of interventions aimed at modulating the presentation of some of these guidance molecules, perhaps well enough to aid regeneration. Moreover, recent experiences with grafted fetal neurons have suggested that some axons can find appropriate targets even without additional chemical signals.

Building bridges

Since the demonstration that peripheral nerves can support the regrowth of CNS axons (Richardson et al., 1980; David & Aguayo, 1981) and, in one case, lead to the formation of functional synaptic connections, many research groups have explored the value of bridging the gap created by cord damage (Fig 47.5, see colour plate section). In one study, Schwann cells (the myelinating glia of the peripheral nervous system) transplanted into the spinal cord promoted axonal regeneration after a section of the spinal cord was completely removed (Xu et al., 1995). The Schwann cell produces a variety of growth factors and extracellular matrix molecules known to promote axon regeneration. Grown in culture and packed into a plastic-like tube, they have been used to connect the two ends of transected spinal cord. In combination with growth factor or methylprednisolone treatments, these grafts have allowed neurons to grow axons (Menei et al., 1998).

Knowledge of bridges and inhibitory factors has been combined to enhance behavioural recovery in spinal cord-injured rats. Peripheral nerves were grafted between the two ends of a severed spinal cord, and glue made of fibrin kept the nerves in place and released acidic fibroblast

growth factor (aFGF) into the injured area (Cheng et al., 1996, 1997). The peripheral nerves were directed from white matter to the less inhibitory grey matter so regenerating axons would grow in that direction. Six months after this procedure, the corticospinal tract had partly regenerated. The rats also had regained some ability to walk. These studies have been difficult to replicate in other laboratories perhaps because of the complexity of the surgery.

Lessons learned from the Schwann cell have provided insights into what makes a good cellular candidate for supporting axonal regrowth (Bunge, 1993). An exciting example is the recent transplantation of olfactory ensheathing glial cells. These cells are found only in the olfactory nerve and bulb, and they reside in a unique area that permits axons to grow continually throughout adult life (for review, see Ramon-Cueto & Avila, 1998). In an early study, olfactory ensheathing glial cells were transplanted into the rat spinal cord where the corticospinal tract had been cut. After several months, there was partial regrowth of corticospinal axons and some improvement in the limb functions these nerves normally control (Li et al., 1997). In another study, transplanting ensheathing glia into cut cord stumps next to Schwann cell grafts led to long-distance axonal regeneration. It also improved growth of regenerated axons from graft into contiguous cord (Ramon-Cueto et al., 1998). Additional studies add to the intriguing concept that transplanted olfactory ensheathing glial cells might be competent escorts for regenerating axons in the damaged spinal cord (Ramon-Cueto & Nieto-Samparedo, 1994; Ramon-Cueto et al., 1994, 1998, 2000; Li et al., 1997, 1998; Perez et al., 1998; Navarro et al., 1999). Some work even suggests that these cells might be capable of myelinating single axons akin to Schwann cells (Li et al., 1997; Imaizumi et al., 1998, 2000; Barnett et al., 2000), but this finding remains controversial because these cells normally wrap groups of axons and their isolation is susceptible to contamination by Schwann cells. Understanding their regeneration-aiding properties is a next step for scientists. Armed with the why and how, researchers may be able to create or engineer cells that exhibit combinations of growth-promoting properties.

Replacing lost cells: cell transplants and genetic vectors

Cell transplants can serve three important functions (for review see Bjorklund & Lindvall, 2000). First, they can generate a local supply of key molecules, such as growth factors or guidance molecules, to promote cellular survival or regeneration. Secondly, they can provide mechanical stability and serve as a bridge (see above), supporting the regrowth of injured CNS axons. Third, they can replace lost neuronal or glial cells, restoring cellular functions such as signalling and axon myelination.

Adult neurons are unsuitable for transplantation because they neither divide nor survive isolation and relocation. Several different types of cells have been successfully transplanted into the injured spinal cord, however. They include fetal spinal cord tissue, immortalized neural cell lines, genetically engineered fibroblasts, CNS stem cells, and embryonic stem (ES) cells.

For several decades, pioneering groups have explored the transplantation of fetal CNS tissue into animal models of spinal cord injury. This tissue survives and partially integrates into the injured host cord, leading to limited segmental forms of functional recovery (Nygren et al., 1977; Buchanan & Nornes, 1986; Reier et al., 1986; Bernstein & Goldberg, 1987; Yakovleff et al., 1989; Jakeman & Reier, 1991; Bregman et al., 1993). Host fibres grow into the transplants, and transplanted neurons extend axons into host tissue. This valuable experience has emphasized the therapeutic potential of immature neuronal cells, but ethical dilemmas and the availability of suitable tissue limit the usefulness of this approach in humans. Another source of transplantable material is cell lines derived from central neurons that have been transformed by retroviral vectors. The cells are immature and capable of indefinite replication. They survive and respond to local environmental cues after transplantation; moreover, the adult CNS retains the capacity to direct their differentiation into more mature neurons (Park et al., 1999; Vescovi & Snyder, 1999; Whittemore, 1999). There is concern that such immortalized cells might undergo malignant transformation and become cancerous, however.

Other laboratories have used genetically engineered non-neuronal cells to obtain neurotrophic molecules and extracellular matrix molecules known to promote regeneration. This approach was recently applied to the injured spinal cord (Grill et al., 1997; McTigue et al., 1998). Fibroblasts were engineered to produce the neurotrophic molecule NT-3. After the cells were transplanted into the cut spinal cord, there was substantial regrowth of the corticospinal tract and improved stepping across the graft (Grill et al., 1997). Later work demonstrated enhanced myelination of regenerated axons in the graft (McTigue et el., 1998). The ability of this approach to provide effective bridges that support the regrowth of host axons is a particular strength that may well drive its incorporation into future therapies.

Another approach to cellular replacement is to take advantage of stem cells still present in the adult CNS. These retain the fetal capacity to survive isolation, replicate, and

differentiate into mature cells. For many years, it was believed that the number of neurons in the mammalian brain and spinal cord is fixed at birth and that neurons cannot be replaced, unlike cells in organs such as skin or liver. As early as the 1960s, however, pioneering studies demonstrated that some cells in the adult hippocampal dentate gyrus divide, differentiating into neurons (Altman & Das, 1965). Such progenitor cells can be isolated from the mature brain, cultured, and transplanted back into adult brain, where they can turn into neurons. Recently, this approach has been expanded to cells isolated from the mature spinal cord (Shihabuddin et al., 1997; Horner et al., 2000).

Exciting recent work has demonstrated that formation of new neurons is a more universal and dynamic process that occurs even in adult humans (Eriksson et al., 1998; Del Bigio, 1999). The process appears to be influenced by the local physical and chemical environment (Kempermann et al., 1998; Kempermann and Gage, 1999; Gould et al., 1999a,b; Nilsson et al., 1999). However, we are just beginning to understand how to regulate progenitor cell birth and survival of subsequent differentiated neural cells, and endogenous production of sufficient numbers of cells to replace those lost from spinal cord injury is not feasible at present. The potential consequences of disturbing these neurotransmitter systems with the polypharmacy typically used to treat spinal cord injury should be carefully weighed against putative benefits.

How might stem cells be used for spinal cord repair? As we begin to understand the signals that determine when stem cells divide and how they commit to a particular cell fate (oligodendrocyte, astrocyte, or neuron), we may be able to isolate adult stem cells from a biopsy of the injured spinal cord, propagate them to gain adequate numbers, induce them to form the required cell types, and transplant them back into the same person's injured cord. Moreover, stem cells can be genetically engineered as easily as fibroblasts, so they could be made to function as biological timed-release capsules, delivering growth factors or guidance molecules at key stages of regeneration. Unlike fibroblasts, stem cells are capable of migrating and integrating into host tissue. Thus stem cells delivered to a single site might repopulate remote locations.

Other researchers are beginning to examine even more primordial stem cells, called embryonic stem cells, which are pluripotent (capable of forming any cell in the body) and immortal (living and dividing forever). Such cells have been isolated from rats, fish, chickens, Rhesus monkeys, and most recently from humans (Shamblott et al., 1998; Thomson et al., 1998; Itskovitz-Eldor et al., 2000; for review, see McDonald, 2002). When embryonic stem cells that were induced by retinoic acid to become neural precursors were transplanted into the contusion injury site of rat spinal cord 9 days after injury, they migrated long distances, differentiated into neurons, astrocytes, and oligodendrocytes, and promoted some recovery of locomotion (McDonald et al., 1999). That was an important result because no previous studies had demonstrated improved walking when transplantation was delayed for more than 24 hours. Subsequently, embryonic stem cells have been successfully coaxed to produce oligodendrocyte precursors that can myelinate axons in culture and when transplanted into the immature CNS (Brustle et al., 1999) and the injured adult spinal cord (Liu et al., 2000).

Neural xenotransplantation is another approach. It has been attempted in individuals with Huntington's disease (Philpott et al., 1997; Bachoud-Levi et al., 2000), Parkinson's disease (Kordower et al., 1995, 1998; Freeman et al., 1999), stroke (http://www.laytonbio.com; http://www.diacrin.com), epilepsy (http://www.diacrin.com), and spinal cord injury (Reier et al., 1994; Thompson et al., 1998; Wirth et al., 1999; http://www.diacrin.com). Xenotransplantation is favoured for use in human studies now since the greatest safety data is available. The major disadvantage of this approach is the possibility of rejection of the foreign tissue.

As an alternative to cell transplantation, replication-deficient viral vectors could transfer genes coding for desirable growth factors, blocking antibodies, or guidance molecules directly into surviving spinal cord cells. Virus-mediated gene transfer is most easily achieved into dividing cell types, but adenoviruses and lentiviruses have been used experimentally to transfer genes into non-dividing adult neurons (Suhr & Gage, 1999; Kafri et al., 2000). Maintaining high levels of foreign gene expression over time and limiting destruction by the host's immune system remain significant technical hurdles to clinical use. The recent development of 'gutless' adenoviruses, which lack the genes for immunoreactive coat molecules, and the design of strategies to protect infected cells by selectively repelling or killing invading immune cells are producing headway.

Finally, not all CNS diseases are equally amenable to cell replacement therapy. The best chance for success may lie in applications whose clinical efficacy is determined by a single defined biological mechanism, such as myelination to restore long-tract neurotransmission in spinal cord injury. We will do well, however, not to promise too much too early and to focus on therapies that would seem likely to work, such as those that have shown benefits in animal models. At present, achievable neuronal transplantation is limited to re-establishing local, short-distance connections (such as interneurons). Long-tract connections

across a spinal cord lesion have not been seen in any animal model.

Perhaps the most success in animal models has been achieved by transplanting oligodendrocytes and their progenitors. Both the biology of the oligodendrocyte lineage and myelination are well understood, and this glial system is relatively simple compared with the neuronal system, which involves dozens of types of neurons and tens of thousands of interconnections. Therefore, the inherent risks associated with glial cells are limited compared with those associated with neurons.

Restoration of function: limited rebuilding, not cure

Fortunately, all available evidence indicates that the damaged spinal cord will not have to be completely rebuilt to obtain meaningful recovery. Animal studies suggest that less than 10% of functional long-tract connections are required to support locomotion (Blight, 1983). As previously mentioned, the preserved rim of white matter that carries long tracts between the brain and periphery of the body might be sufficient to restore meaningful function. Animal studies indicate that axons in this rim commonly remain anatomically intact but are non-functional because of focal demyelination or faulty myelination. Therefore, remyelinating intact connections seems like a reasonable approach to restoring function (Gledhill et al., 1973; Waxman, 1992; Bunge et al., 1993). Although such limited restoration may not enable people with spinal cord injury to walk, it might restore control over the bowel and bladder or improve limb mobility. Such gains facilitate independence.

Several research groups have suggested that some functional recovery may be possible without remyelination if conduction along existing dysfunctional axons can be improved. They used a potassium-channel blocker called 4-aminopyridine to enhance the flow of nerve impulses, allowing axons to transmit electrical information past demyelinated zones (Blight, 1989; Waxman, 1993). Some patients treated with 4-aminopyridine had encouraging improvement in aspects of sensory or motor function (Hansebout et al., 1993; Hayes et al., 1993, 1994).

Also, rats that sustained a lesion of the left corticospinal tract at the level of the brainstem were treated with IN-1. This antibody treatment improved movements of the forepaw (movements requiring corticospinal function) even though only a small fraction of the transected fibres regenerated. Recovery was probably attained by compensatory sprouting and reinnervation of denervated targets by unharmed fibre systems, a phenomenon not observed in untreated rats (Z'Graggen et al., 1998; Raineteau et al., 1999). Many other functions, such as gait or breathing, are partially controlled at the level of the spinal cord via central pattern generators. Recovery of limited supraspinal input is required to improve complex functions such as gait.

Rehabilitative strategies for rebuilding function

In addition to the new directions in pharmacologic, genetic, and transplantation research, there is important progress in clinical rehabilitation (for review see Sadowsky et al., 2002). For example, surgical reconstruction can provide important gains in function. Procedures include functional tendon transfers, peripheral nerve transplantation, and nerve splitting to reactive previously paralysed muscles. Functional electrical stimulation (FES) also has achieved considerable success and received FDA approval. It uses sophisticated electronics to activate intact but distant nerves, which then can regain control of muscles rendered useless by spinal cord injury. For example, FES can harness shoulder movements to move a paralysed hand (Fig. 47.6) (Freehand System; http://www.neurocontrol.com) or regain bowel and bladder control (Vocare System; http://www.neurocontrol.com; for review see Sadowsky et al., 2002). An FES system similar to the Freehand system can restore some simple functions to the legs, such as initiating standing to assist in transfers. Simpler FES systems restore diaphragmatic breathing by pacing the phrenic nerve, and they can aid coughing in patients whose respiration is impaired.

Additional research is altering the scope of rehabilitation by modifying neuronal circuitry. Several groups have shown that a distal region of the spinal cord that has been disconnected from the brain by injury is capable of learning and that early gait training may help promote walking abilities in a subset of individuals with spinal cord injury (Lovely et al., 1986; Barbeau & Rossignol, 1987; Wernig & Muller, 1992; for review see Barbeau et al., 1999). The central pattern generators can produce rhythmic, oscillating activity of limb flexor and extensor muscle groups without supraspinal or afferent input, and the molecular mechanisms that contribute to this phenomenon are being unravelled (Grillner et al., 1998; Barbeau et al., 1999). Gait patterns can be elicited by tapping into the central pattern generators via descending input and by sensory feedback. Such rehabilitative treatments may accomplish more than simple training; they may enhance regeneration. Taken together, studies of CNS development and regeneration suggest that optimal levels of patterned

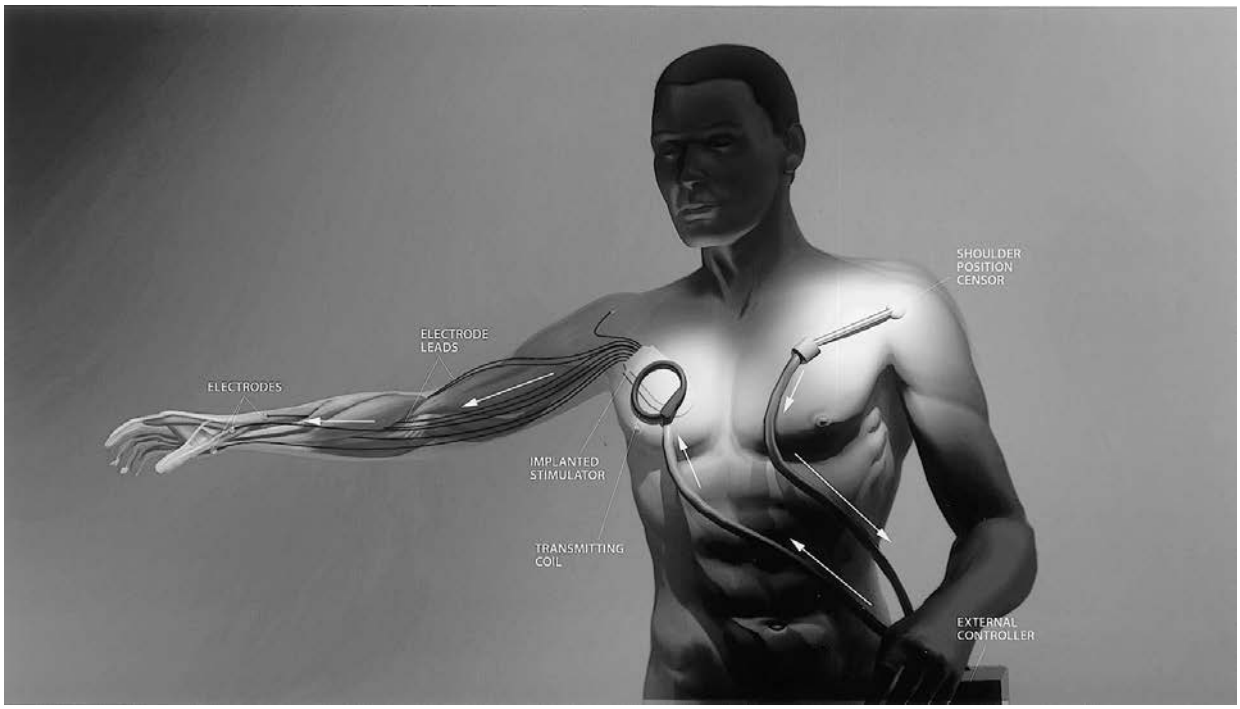

Fig. 47.6. The Freehand System is approved by the FDA for restoration of hand function in spinal cord injury. Particular movements by the opposite shoulder activate a detector that sends signals to an external control unit. That unit, in turn, relays the signals to an implanted transmitting coil connected to wires that terminate on selected arm and hand muscles. Shoulder movements then provide two types of hand function important for grasping a fork or a cup. (Reproduced with permission from *Scientific American* (McDonald et al., 1999).)

neural activity are important for many aspects of regeneration, including remyelination, new synapse formation, and the birth and survival of new progenitor cells. The enhanced functional recovery observed in the recent constraint-induced, forced-use stroke studies may represent such activity-dependent regeneration (Wolf et al., 1989; Miltner et al., 1999; van der Lee et al., 1999).

Development of systems that reduce environmental barriers to mobility and environmental control also is making major headway. For example, Johnson and Johnson recently developed a multicomputer-controlled wheelchair capable of ascending and descending stairs; it may be introduced as early as 2001. Continued progress in clinical rehabilitation will help maximize the benefits attained through advances in protective and regenerative drug therapies.

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48

Myelopathies

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An etiological classification of myelopathies yields an extensive list of diverse conditions (Table 48.1). In clinical practice, myelopathies are classified into spinal cord syndromes, based on patterns of neurological symptoms and signs, which identify the anatomical location and distribution of spinal cord pathology. The time course of symptoms is useful in distinguishing between different etiologies. Vascular lesions generally present with acute onset or rapid progression of symptoms. Inflammatory disease evolves in a subacute manner and may fluctuate over days or weeks. Compressive lesions also may present with a subacute onset and generally have a progressive course. Degenerative myelopathies are usually slowly progressive over months or years. The evolution and type of spinal cord syndrome suggest certain diagnostic possibilities and guide appropriate investigation.

Symptoms and signs of spinal cord disease

Motor symptoms and signs

The clinical presentation of an evolving myelopathy often is precipitated by limb weakness and spasticity due to corticospinal tract involvement. Arm and leg weakness suggests a cervical cord lesion. A paraparesis, with leg weakness or walking difficulty alone, suggests a lesion of the thoracic spinal cord or below. Progressive cervical cord lesions may evolve in a sequence, beginning with weakness of the arm ipsilateral to the lesion, followed by weakness of the ipsilateral then contralateral leg, and finally the contralateral arm.

Exacerbation of symptoms by exercise, or during increases in body temperature (hot weather or a hot bath) suggests demyelination, but may also occur in dural arteriovenous malformations of the spinal cord.

Motor signs of spinal cord disease reflect involvement of the long tracts of the spinal cord with increased muscle tone, brisk tendon reflexes, extensor plantar responses and weakness of hip and knee flexion and ankle dorsiflexion. Involvement of the anterior horn cells or anterior (motor) spinal nerve roots produces additional lower motor neuron signs of segmental wasting and weakness (Table 48.2).

Sensory symptoms and signs

Back pain

Back pain is often an early complaint of a myelopathy, preceding any motor symptoms. The site of pain may localize the level of a focal structural lesion such as a spinal epidural abscess, vertebral body collapse or intervertebral disc prolapse. Dull, poorly localized backache is common in intrinsic spinal lesions but is of little localizing or diagnostic value. An increase in pain when coughing and straining or exacerbation of pain with movement suggests an extramedullary (extradural) compressive lesion. Nocturnal back pain when recumbent occurs in extradural spinal lesions such as a thoracic meningioma or a benign spinal nerve root sheath tumour (schwannoma/neurofibroma). Severe thoracic or interscapular pain may be the presenting feature of inflammatory transverse myelitis.

Radicular symptoms and signs

Compression of posterior spinal roots by extrinsic spinal cord lesions or infiltration of the posterior root entry zone by intrinsic cord lesions, causes radicular pains which radiate along the affected dermatome, localizing the level of spinal pathology (Fig. 48.1). Radicular pains are typically sharp or knife-like and accompanied by cutaneous burning dysesthesia or hyperesthesia over the affected skin. Thoracic sensory root involvement can produce constricting chest or

Table 48.1. Etiological classification of myelopathies

Trauma
Vascular
Anterior spinal artery thrombosis
Spinal arteriovenous malformation
Dural arteriovenous malformation
Epidural hematoma
Hematomyelia
Arteritis (polyarteritis nodosa, systemic lupus erythematosus)
Inflammatory
Idiopathic transverse myelitis
Multiple sclerosis, Devic's disease
Postinfectious encephalomyelitis
Idiopathic necrotic myelopathy
Infectious
Neurotropic viruses
Herpes zoster, Herpes simplex, Polio
Coxsackie, echovirus, cytomegalovirus, Epstein–Barr
Retrovirus myelopathies
Human immunodeficiency virus (HIV) vacuolar myelopathy
Human T-lymphotrophic virus type I (HTLV I) tropical myelopathies
Mycoplasma myelopathy
Spinal epidural abscess
Syphilitic meningomyelitis
Tuberculosis
Osteitis (Pott's disease)
Radiculomyelitis
Schistosoma myelopathy
Granulomatous
Sarcoidosis
Neoplastic
Primary
Intramedullary – astrocytoma, ependymoma
Extramedullary – neurofibroma, meningioma
Secondary
Intramedullary metastasis (rare)
Extradural metastasis
Contiguous spread – paravertebral neuroblastoma, lymphoma
Paraneoplastic
Necrotic myelopathy
Myeloradiculoneuropathy
Degenerative
Motor neuron disease
Vertebral disease with myelopathy
Cervical spondylotic myelopathy
Intervertebral disc prolapse
Rheumatoid arthritis (atlantoaxial subluxation)
Psoriatic arthropathy
Achondroplasia
Mucopolysaccharidoses
Paget's disease
Congenital
Spinal dysraphism:
Spina bifida
Diastematomyelia
Syringomyelia
Hereditary
Hereditary spastic paraplegia
Friedreich's ataxia
Spinal muscular atrophy
Nutritional
Malabsorption syndromes with myelopathy
Vitamin B12 deficiency (subacute combined degeneration)
Vitamin E deficiency (Bassen–Kornzweig disease)
Toxins
Tropical spastic paraparesis (such as cassava)
Lathyrism (chick pea – *Lathyrus sativa*)
Miscellaneous
Caisson disease (decompression myelopathy in divers)
Myelopathy of systemic disease (liver failure)
Radiation myelopathy

Table 48.3. Segmental innervation of muscles

C3, 4	Trapezius
C4, 5	Rhomboids
C5	Deltoid
C5, 6	Supraspinatus, Infraspinatus, Biceps
C6	Brachioradialis
C7	Triceps, Extensor digitorum
C8	Flexor digitorum superficialis and profundus
T1	Intrinsic hand muscles
T7–10	Upper rectus abdominis
T10–12	Lower rectus abdominis
L1	Iliopsoas
L2	Adductor magnus
L3, L4	Quadriceps femoris
L4	Tibialis anterior
L5	Extensor hallucis longus
L5, S1	Hamstrings
S1	Extensor digitorum brevis
S1, S2	Soleus, gastrocnemius

abdominal pain, severe enough to suggest myocardial infarction, aortic dissection or an acute abdomen. Extradural spinal lesions (metastatic carcinoma, abscess) produce radicular pain, local tenderness and restriction of movement at the affected level before spinal cord compression develops and long tract signs appear. Intramedullary spinal lesions such as primary spinal tumours produce long

Table 48.3. Segmental sensory and motor innervation of tendon and cutaneous reflexes

Biceps reflex	C5, 6
Brachioradialis reflex	C6
Triceps reflex	C7
Finger reflexes	C8
Abdominal reflexes	
upper	T8–12
lower	T10–12
Knee (patellar) reflex	L3, 4
Adductor reflex	L2
Cremasteric reflex	L1, 2
Plantar reflex	L5
Ankle reflex	S1
Anal reflex	S4, 5

tract symptoms and signs early in the illness while root involvement is unusual and occurs late. In contrast to the severity of radicular pain, examination may reveal only subtle sensory loss in radicular lesions. Depression or absence of a tendon or cutaneous reflex may also be a valuable sign of a radicular sensory lesion (Table 48.3).

Sensory tract symptoms and signs

Paresthesiae (tingling, 'pins and needles') and loss of sensation are common in diseases of the long spinal sensory tracts. The distribution and extent of sensory tract symptoms depend on the site and size of the lesion. The trunk is frequently involved and is an important clinical clue to a sensory tract lesion. In progressive myelopathies, a sensory tract disturbance may evolve, ascending from the legs onto the trunk, or decending down the trunk to the legs. The pattern of spread occurs as the lesion enlarges and encroaches on adjacent laminated sensory fibres in the sensory tracts (Fig. 48.2). The combination of trunkal, upper and lower limb sensory symptoms indicates cervical cord involvement. Leg and trunk symptoms alone point towards thoracic or lumbar cord involvement.

Spinothalamic tract symptoms and signs

Cutaneous dysesthesia (burning, prickling, itching), abnormal warm or cold sensations, hyperesthesia (enhanced sensitivity to minor or trivial sensory stimuli) and hyperpathia are characteristic of a spinothalamic tract sensory disturbance. Spontaneous deep, poorly localized pain may be felt in areas of sensory loss (anaesthesia dolorosa). The patient may be unaware of the sensory deficit and sustain burns, accidental soft tissue injury or bony damage (Charcot's

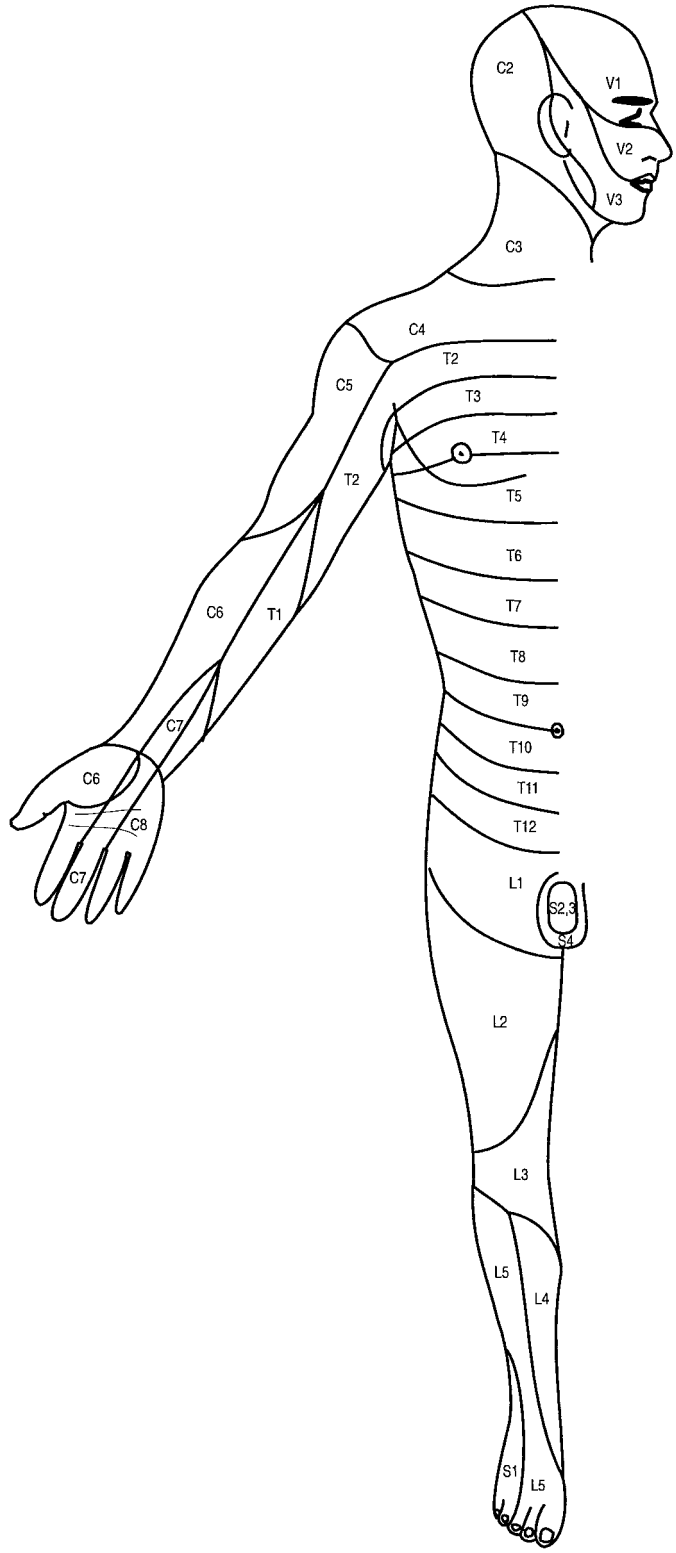


Fig. 48.1. Distribution of dermatomes on the anterior surface of the body.

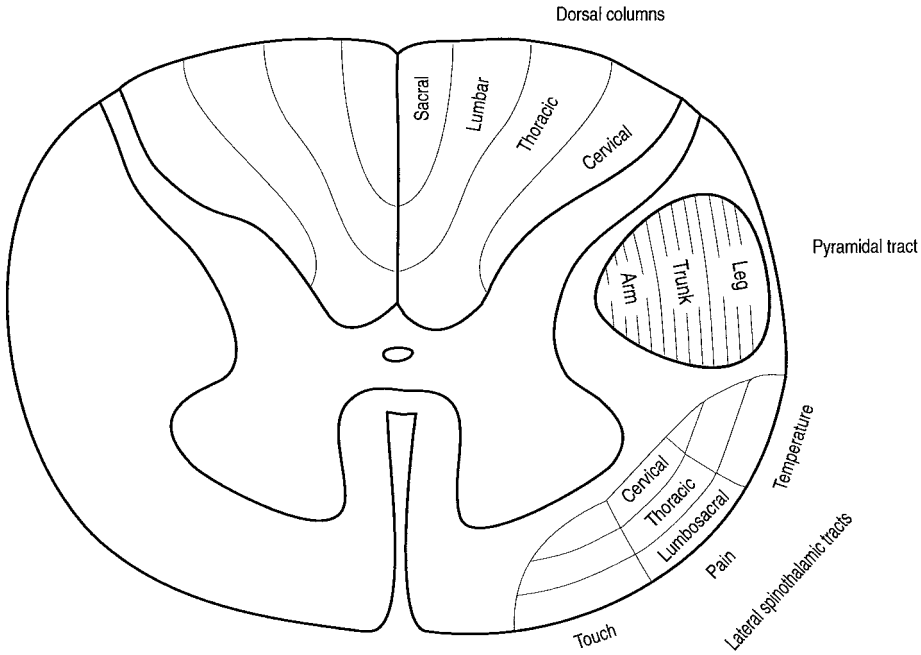


Fig. 48.2. Cross section of the cervical spinal cord demonstrating the lamination of the long sensory and motor tracts.

joints) in areas of impaired pain and temperature perception.

A lateral spinothalamic tract lesion results in contralateral pain and temperature loss (dissociated), sensory loss beginning two or three segments below the lesion. The upper limit of a spinothalamic sensory loss is often marked by a rim of hyperesthesia (Fig. 48.3). Pain and temperature fibres decussate shortly after entry into the spinal cord and ascend in the spinothalamic tract. A discrete central cord lesion may therefore only interrupt sensation from a few adjacent segments, producing a suspended, dissociated cape or breastplate sensory loss (Fig. 48.3). Lamination of the spinothalamic tract fibres leads to sparing of sacral sensation in intramedullary lesions (sacral sparing) and sensory levels that can be well below the actual lesion (Fig. 48.2). Accordingly, a spinothalamic sensory level can be misleading in assessing the site of a spinal lesion. The pattern of sensory loss also does not distinguish between intramedullary and extramedullary lesions. The precise lesion level is best obtained from magnetic resonance imaging of the whole spinal cord.

Posterior column symptoms and signs

Posterior column lesions give rise to paresthesiae and numbness often accompanied by sensations of limb swelling, constricting bands around the limbs and trunk or a sensation that a limb is 'encased in plaster'. Discrete lesions of the laminated dorsal column fibres may affect sensation in isolated body segments at the level of the lesion or several segments distal to the level of the lesion (Fig. 48.2). For example, dorsal column lesions in the cervical cord can lead to bilateral symmetrical loss of discriminatory sensation in the hands or tight bands around a leg or the trunk. Loss of proprioception (deafferentation) results in clumsiness of hand or foot movement (sensory ataxia), that may be misinterpreted as weakness. A characteristic symptom of dorsal column lesions is 'electric' paresthesiae radiating down the back, induced by neck flexion (L'hermitte's phenomenon).

Sphincters

Urinary retention and constipation may precede the onset of overt paralysis in a spinal cord syndrome, particularly when the conus medullaris or cauda equina are involved. Sphincter involvement is an early feature in intrinsic or intramedullary spinal lesions and a late feature in extrinsic compression of the spinal cord, after the appearance of motor symptoms.

Patterns of spinal cord syndromes

In lesions of the thoracic and cervical spinal cord, certain patterns of abnormality are well recognized (Fig. 48.3).

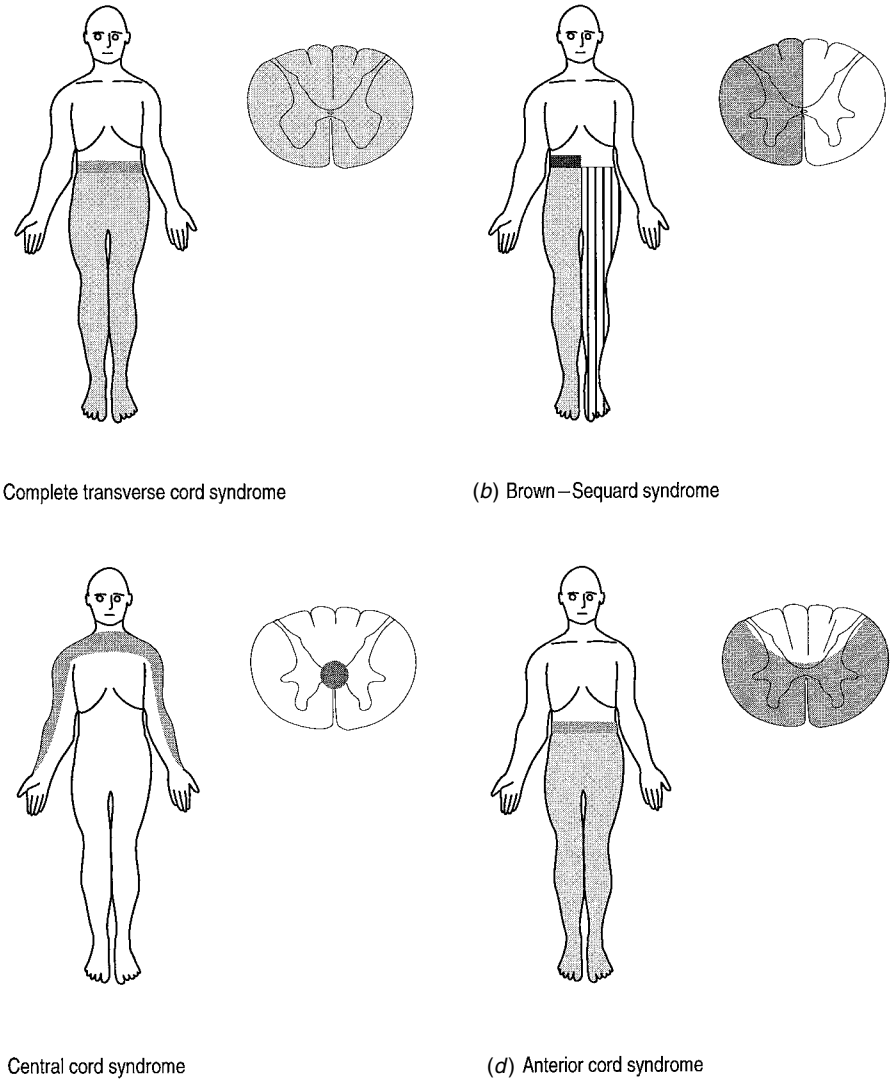


Fig. 48.3. Patterns of spinal cord disease. (*a*) Complete transection of the spinal cord produces paralysis and anesthesia below the level of the lesion. There is often a rim of hyperesthesia at the upper level of the sensory loss. (*b*) In a Brown–Sequard or hemicord syndrome, upper motor neurone signs including weakness and dorsal column signs are found below the lesion on the same side, and there is a contralateral loss of spinothalamic sensory modalities (vertical stripes). Again, there may be a rim of hyperesthesia on the side of the spinal lesion. (*c*) A central cord syndrome interrupts decussating spinothalamic fibres over a few spinal segments and produces a suspended dissociated sensory loss. In this example, C4, 5, 6 dermatomes are affected. (*d*) An anterior cord syndrome produces upper motor neurone signs below the level of the lesion with impaired spinothalamic sensation. A rim of hyperesthesia at the upper level of the spinothalamic sensory level is also shown. Dorsal column function is spared. Lower motor neuron signs may also be present if the cervical or lumbar cord is affected.

Hemicord (Brown–Séquard) syndrome

A unilateral lesion of the spinal cord results in a contralateral loss of spinothalamic sensation (pain and temperature), ipsilateral weakness with upper motor neuron signs, and ipsilateral dorsal column (proprioception) sensory loss (Brown–Séquard syndrome). Light touch is preserved. The syndrome may be partial or complete. Demyelination, knife or bullet injuries, and cord compression are common causes.

Anterior cord syndromes

The anterior cord syndrome consists of paralysis with upper and lower motor neuron signs, a bilateral spinothalamic (pain and temperature) sensory loss and sphincter paralysis. Posterior column sensory modalities are spared. Ischemia in the territory of the anterior spinal artery is the commonest cause.

Central (cervical) cord syndromes

A central cervical cord syndrome produces a combination of lower motor neuron signs of muscle wasting and weakness and depressed or absent tendon reflexes in the arms, a paraparesis and a suspended dissociated sensory loss over the arms and trunk. Acute central cervical cord lesions produce bilateral arm weakness, pain and hyperpathia. Rarely, central cord lesions may result in segmental muscle rigidity and spasms. Central cord lesions are caused by flexion–extension spinal trauma, neoplasms, watershed (hypotensive) cord ischemia and syringomyelia.

Radiculomyelopathy syndromes

Radiculomyelopathies present two broad clinical scenarios. The first comprises a sensory or motor radicular lesion at the upper level of an extrinsic compressive or intrinsic infiltrative myelopathy. Segmental amyotrophy or sensory radiculopathy are evident at the level of the lesion and upper motor neuron and sensory tract signs are found below. In the second, multiple spinal levels are involved and a combination of upper and lower motor neuron signs and sensory root and tract signs are evident. The common causes of radiculomyelopathies are listed in Table 48.4.

Spinal shock

Segmental reflex activity is abolished below the level of an acute spinal lesion (spinal shock) for 1 to 6 weeks after the injury. Areflexic quadriplegia in cervical cord lesions or paraplegia in thoracic cord lesions is accompanied by abnormal autonomic control below the lesion, with loss of vasomotor tone, profuse sweating and piloerection. Return of spinal reflex activity is marked by the appearance of upper motor neuron signs, exaggerated tendon reflexes and enhanced cutaneous flexor reflexes, which become the dominant physical signs of a chronic spinal cord lesion. Minor cutaneous stimuli may elicit flexor spasms, reflex defecation or micturition and profuse sweating.

Table 48.4. Causes of radiculomyelopathy classified according to whether one or multiple spinal levels are involved

Single level	
Acute transverse myelitis	
Vascular	Spinal cord infarction (anterior spinal artery thrombosis)
	Spinal arteriovenous malformation
Neoplastic	Primary spinal tumour
	Extradural metastatic carcinoma
	Carcinomatous meningitis
Infective	Spinal epidural abscess
Multiple levels	
Cervical and lumbar spondylosis	
Necrotic myelopathy	
Chronic meningitis (infectious or granulomatous)	
Spinal arachnoiditis	
Neoplastic	Carcinomatous or lymphomatous meningitis
Paraneoplastic	Carcinomatous neuromyopathy

Specific spinal cord syndromes

Foramen magnum lesions

A slowly evolving asymmetric quadriparesis, lower cranial nerve (accesssory and hypoglossal) palsies, neck stiffness, abnormal posturing of the neck, a Horner's syndrome and subtle sensory changes occur in foramen magnum lesions and may escape detection in the early stages. Compression of the upper cervical sensory roots and distortion of the spinal cord produce neck and occipital pain in the C2–4 dermatomes, sensory impairment in the first division of the trigeminal nerve and contralateral spinothalamic sensory loss. Downbeat nystagmus is characteristic of lesions at this site. In addition to an asymmetric quadriparesis, high cervical lesions may produce lower motor neuron signs of wasting and weakness in intrinsic hand muscles, due to venous stasis with ischemia in the distal

C8–T1 spinal segments (Stark et al., 1981). Phrenic nerve involvement may interfere with diaphragm function and ventilation. Causes include a benign nerve root sheath tumour (schwannoma/neurofibroma), anterior atlantoaxial subluxation in rheumatoid arthritis and psoriatic arthropathy, achondroplasia and the mucopolysaccharidoses.

Cervical spinal cord lesions

Lesions of the cervical spinal cord produce a myeloradiculopathy with a combination of upper and lower motor neuron signs in the arms, a spastic paraparesis, sensory loss in the arms and sensory tract signs over the trunk and lower limbs. Clinical guides to the level of the lesion include the highest motor and sensory segments affected and lower motor neuron signs (muscle wasting, weakness, and fasciculation) (Table 48.2). The pattern of muscle tone and tendon reflex change in the arms (Table 48.3) is determined by the level of the lesion. Lower motor neuron signs (muscle wasting, weakness), depression or absence of tendon reflexes and sensory loss will be evident at the level of the lesion while upper motor neurone signs (increased muscle tone, brisk tendon reflexes) will be evident below the lesion.

Sensory loss in cervical lesions may be radicular and limited to a dermatome with loss of light touch, or extend over several segments in a spinothalamic or posterior column tract distribution, with preservation of light touch.

Thoracic spinal cord lesions

The upper border of a thoracic spinothalamic sensory level lies two or three segments below the approximate level of the thoracic lesion. Radicular pain provides a more accurate thoracic level, but radicular sensory loss may be difficult to elicit. In addition to paraplegia, thoracic cord lesions may produce trunkal weakness due to either upper or lower motor neuron involvement. Signs of abdominal weakness include loss of abdominal muscle tone with paradoxical protrusion of the abdominal wall during coughing, exhalation and attempted trunkal flexion (when sitting up). Thoracic cord lesions below T10 produce differential weakness of lower abdominal muscles so that on sitting up or lifting the head when supine, contraction of the upper recti (innervated by T7–T10) will be unopposed by the paralysed lower recti (T10–T12) resulting in an upward movement of the umbilicus (Beevor's sign). Superficial abdominal reflexes are abolished below the level of the spinal lesion.

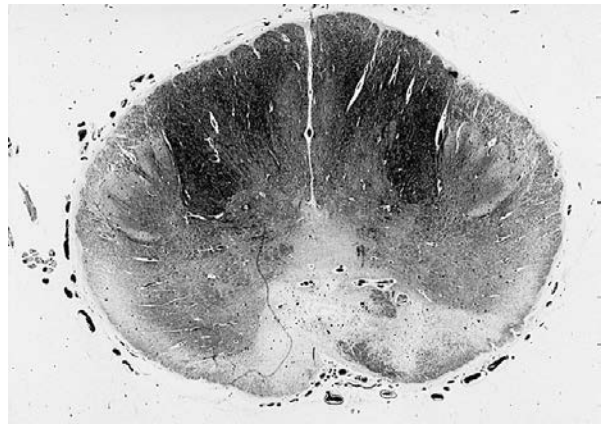


Fig. 48.4. Old cystic ischemic necrosis C4 cord in the territory of the anterior spinal artery (Weil stain for myelin ×7 magnification).

Conus medullaris and cauda equina lesions

Conus lesions result in early and prominent sphincter impairment (urinary retention and constipation), sacral sensory loss affecting lower perineal segments (S3–S5) more than leg segments (L5–S2) and impotence. Leg muscle weakness is variable in conus lesions and may be mild unless the lesion extends higher in the lumbar cord. An extensor plantar response implies the lesion affects the spinal cord above the L5 segment (innervating the extensor digitorum longus muscle). Reflex change will be determined by the level of the lesion.

An asymmetric, flaccid, areflexic paralysis with radicular sensory loss, urinary or fecal incontinence and loss of anal tone points towards predominant involvement of the cauda equina. Muscle wasting with fasciculation indicates a chronic lesion.

Causes of myelopathy

Vascular myelopathies

Spinal cord infarction

Anterior spinal artery occlusion

Infarction of the spinal cord typically involves the territory of the anterior spinal artery, which supplies the anterior two-thirds of the spinal cord and results in an anterior cord syndrome with paraplegia, a mid-thoracic spinothalamic sensory level and sphincter paralysis (Fig. 48.4). A mid-thoracic level (T4–T6) is most common, as it lies in

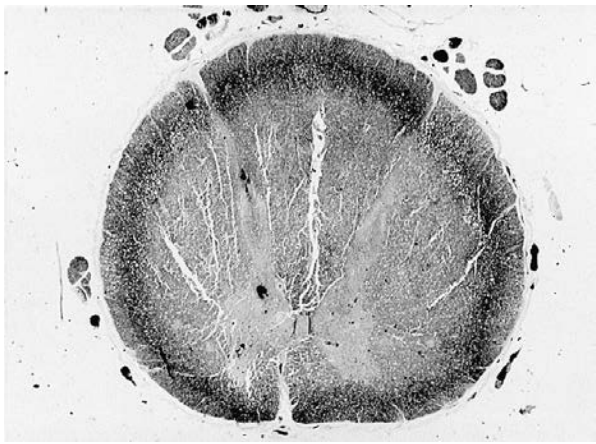


Fig. 48.5. Recent ischemic necrosis of central cord affecting central grey matter and surrounding white matter of T5 spinal cord secondary to prolonged hypotension. Only a peripheral rim of myelin is preserved (Weil stain for myelin ×8 magnification).

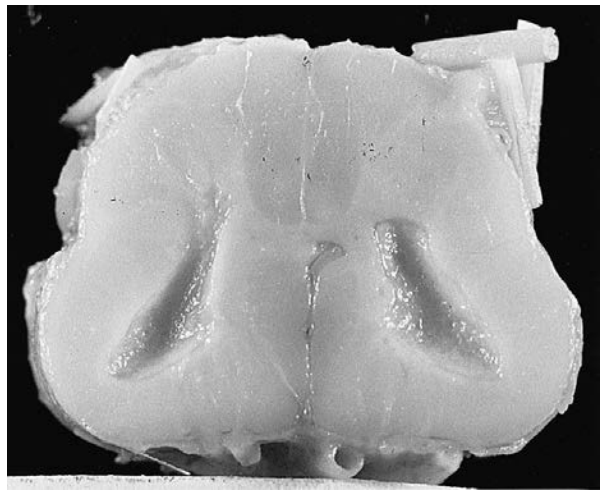


Fig. 48.6. Old central spinal cord infarction with cystic necrosis of anterior grey matter (×8 magnification).

the critical rostrocaudal watershed zone of the spinal circulation which is derived from segmental arteries between T10 and L3 (the artery of Adamkiewicz) and descending branches from the vertebral and ascending cervical arteries. The vascular pathology is usually thromboembolic occlusion of spinal segmental arteries, such as the artery of Adamkiewicz, or aortic disease (dissection, clamping in surgery, severe atheroma). Primary atheromatous occlusion of the anterior spinal artery itself is uncommon, but the vessel may be occluded by vasculitis or systemic embolism.

Segmental artery occlusion

Occlusion of cervical segmental arteries causing infarction of the cervical cord and quadriplegia is rare. Lumbosacral radicular artery thromboembolism (Anderson & Willoughby, 1987) and compression of lumbosacral radicular arteries by a prolapsed intervertebral disc (Lazorthes, 1972) may cause infarction of the conus medullaris.

Central cord infarction

Profound hypotension, aortic dissection or surgical clamping of the aorta may lead to painless watershed infarction of the central grey matter of the low thoracic and lumbosacral spinal cord (Blumbergs & Byrne, 1980) (Fig. 48.5). This selective damage produces paraparesis, patchy upper and lower motor neuron signs in the legs, dissociated sensory loss, and sphincter paralysis. Central cord ischemia may involve the interneurons in spinal grey matter (Fig. 48.6) leading to rigidity and myoclonus of

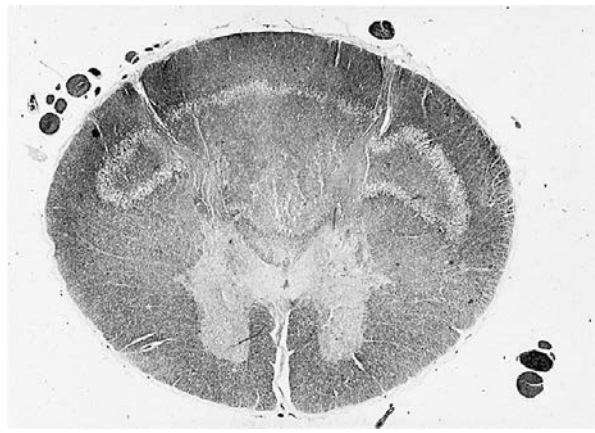


Fig. 48.7. Watershed ischemic necrosis of T3 spinal cord secondary to prolonged hypotension from a dissecting aortic aneurysm (Weil stain for myelin ×8 magnification).

spinal origin. Rarely, watershed infarction occurs at the boundary of the intrinsic anterior and posterior vascular territories of the mid thoracic spinal cord (Fig. 48.7).

Spinal vascular malformations

Intradural (especially intramedullary) spinal arteriovenous malformations present with the sudden onset of neck pain, limb weakness, radicular or tract sensory loss and sphincter disturbance due to spinal subarachnoid hemorrhage or hematomyelia. These malformations involve the cervical and thoracic spinal cord. Symptoms appear in the first and second decades (Rosenblum et al., 1987). In contrast, dural

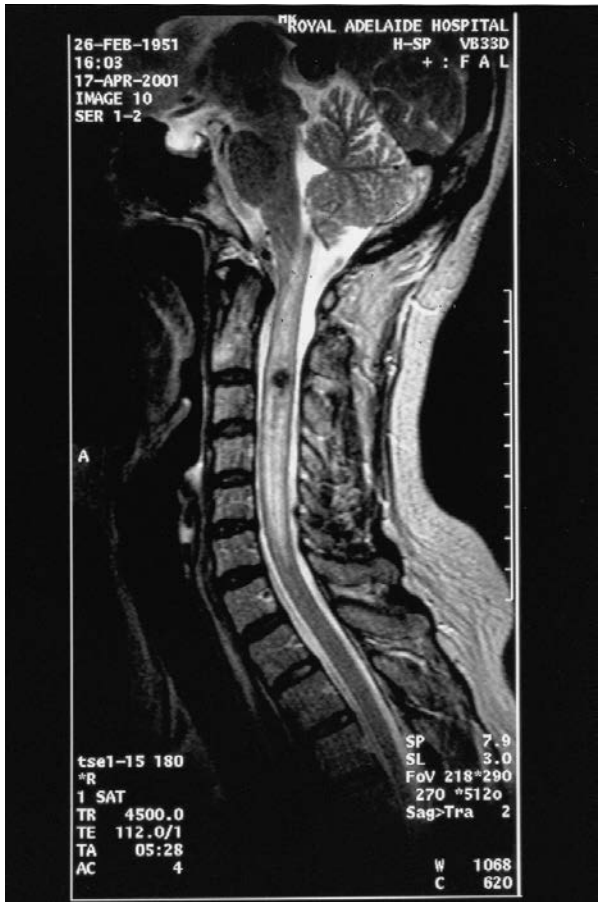


Fig. 48.8. Magnetic resonance image of the cervical spinal cord in a 50-year-old woman who presented with an acute hematomyelia resulting in transient quadriplegia with a sensory level at C4 showing a cavernous angioma (cavernoma).

arteriovenous fistulae occur in the low thoracic and lumbar cord, most commonly in elderly men. A slowly progressive paraparesis with upper and lower motor neuron signs, sensory symptoms including pain and sphincter disturbances evolve slowly over months to years (Logue, 1979). These deficits are caused by prolonged venous hypertension (Kendall & Logue, 1977). Symptoms may be exacerbated by exercise. A spinal cavernous angioma may present with an acute cord syndrome due to hemorrhage and hematomyelia (Fig. 48.8) or a slowly progressive myelopathy secondary to the intraspinal mass lesion (Fig. 48.9) (Deutsch et al., 2000). Neurocutaneous manifestations, such as vertebral anomalies, scoliosis, cutaneous angiomata and spinal dysraphism may accompany spinal vascular malformations (Aminoff & Logue, 1974).

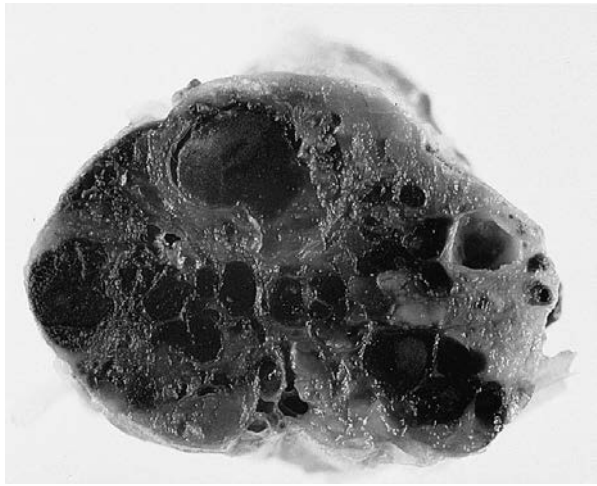
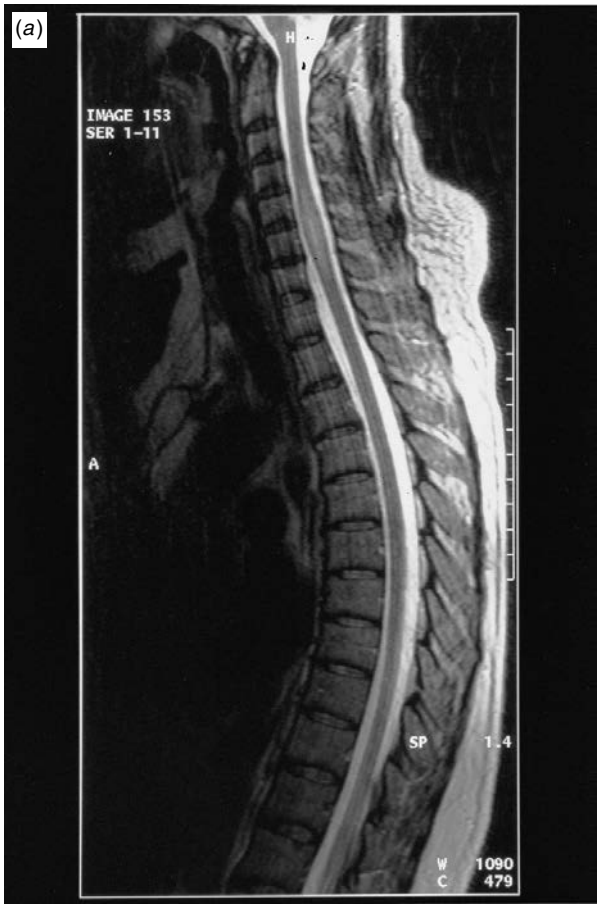


Fig. 48.9. Cavernous angioma of T5 spinal cord.

Inflammatory myelopathies – acute transverse myelitis

Acute or subacute transverse myelitis due to inflammatory demyelination may occur in multiple sclerosis or in a monophasic postinfectious encephalomyelitis. Symptoms include paresthesiae ascending from the legs onto the trunk and a thoracic sensory level (both cervical and thoracic cord can be affected), paraparesis or quadriparesis and sphincter disturbance. Ropper and Poskanzer (1978) identified three groups of acute transverse myelitis. In the first, ascending sensory symptoms evolve over 1–14 days, followed by good recovery. The second, characterized by an acute onset and rapid progression with back pain and paraplegia, had a poor outcome. A third group present with the gradual onset and stuttering progression of symptoms over weeks and have a similar outcome to the first group. This syndrome appears to represent a distinct entity. Cerebrospinal fluid may show a lymphocytic pleocytosis with raised protein but not oligoclonal bands. Magnetic resonance imaging of the spinal cord reveals extensive or confluent high signal lesions extending over several segments (Fig. 48.10). Less than 10% of cases progress to develop multiple sclerosis. This number may be even lower if cases with cerebrospinal fluid oligoclonal bands and cerebral white matter lesions on imaging, both of which favour a diagnosis of multiple sclerosis, are excluded. Acute myelopathies in multiple sclerosis tend to be of gradual evolution with partial, asymmetric spinal cord syndromes (Miller et al., 1987).



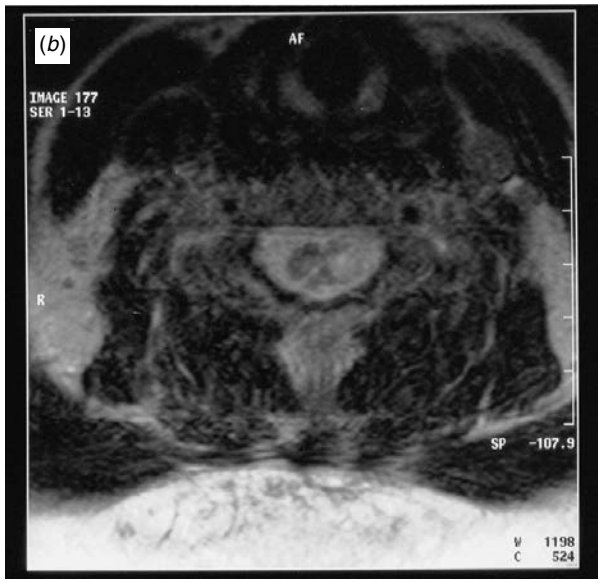


Fig. 48.10. Magnetic resonance image of the cervical spinal cord in a 53-year-old woman presenting with a left Brown–Sequard syndrome and an elongated area of high signal in the central and right side of the cervical spinal cord. The transverse view was taken at the level of C5.

Infectious myelopathies

A wide range of infections are associated with acute myelopathy, either by direct invasion, postinfectious demyelination or abscess formation. Systemic bacterial infections may be complicated by an epidural or extradural abscess. These present with back and root pain, fever and local tenderness which precedes the development of spinal cord compression by a few days. Tuberculous osteitis destroys thoracic vertebral bodies and intervertebral discs over a period of months leading to a progressive kyphosis, spinal cord compression and paraplegia (Pott's paraplegia). Schistosoma myelopathy involving the conus medullaris progresses to paraplegia over days to weeks (Scrimgeour & Gajdusek, 1985). Mycoplasma infections may be complicated by meningoencephalitis and transverse myelopathy.

Several viruses (coxsackie, echovirus, cytomegalovirus, Epstein–Barr) have also been reported to produce transverse myelitis. Neurotropic viruses (herpes zoster, poliomyelitis, herpes simplex) affect predominantly the grey matter of the spinal cord with anterior horn cell loss, resulting in segmental lower motor neuron signs of muscle fasciculation, wasting and weakness. A vacuolar myelopathy, affecting white matter tracts of the thoracic cord, particularly the posterior columns and corticospinal tract, occurs in up to 20% of patients with the acquired immune deficiency syndrome (AIDS) and HIV (human immunodeficiency virus) infection (Petito et al., 1985). Pathological changes of myelin vacuolation sparing axons is found in 50% of cases of AIDS (Shepherd et al., 1999). Asymmetric limb weakness develops over several weeks followed by sensory signs and sphincter involvement. Tropical spastic paraparesis, or myelopathy associated with human T-lymphotropic virus type I (HTLV I) infection (Johnson, 1987) (HAM), is a common cause of paraparesis in tropical regions such as the Caribbean, and also Japan. Paraparesis evolves in a slow but progressive manner with upper motor neuron signs and prominent sphincter involvement. Upper limb reflexes are brisk but arm weakness is uncommon. Loss of vibration sense, peripheral sensory

impairment and depressed or absent ankle jerks suggesting a neuropathy are common. A thoracic sensory level may be observed in some cases and sensory symptoms may herald the onset of HAM. Pathologically, the spinal lesions are characterized by degeneration of myelin and axons in the anterolateral and posterior columns and an inflammatory process presumably directed against HTLV-1 infected T-lymphocytes (Izumo et al., 2000).

Myelopathy in neoplasia

Secondary extradural metastases from lung, breast or prostate carcinoma in vertebral bodies extend into the extradural space causing focal back pain, radicular pain and subsequently spinal cord compression, evolving over weeks to months. The thoracic cord is most commonly involved. Once spinal compression begins, paraplegia evolves over days with sphincter disturbances. Neoplastic destruction of vertebral bodies may lead to vertebral collapse, dislocation and increasing angular deformity further compromising cord function. A similar progressive myelopathy may accompany intramedullary spinal metastases, which are rarer than extradural metastases and not accompanied by vertebral body destruction.

Carcinomatous meningitis due to neoplastic infiltration of the leptomeninges presents with a subacute onset of lower motor neuron signs, absent tendon reflexes, extensor plantar responses, and a peripheral sensory loss (Olson et al., 1974). Pain and multifocal involvement of the central nervous system are additional clues to the diagnosis.

Primary spinal tumours, intramedullary ependymoma and astrocytoma, or extramedullary neurofibroma and meningioma evolve slowly over months and years. Symptoms are produced by internal disruption of the long tracts of the spinal cord or the development of syringomyelia in intramedullary tumours and spinal nerve root or spinal cord compression in extramedullary tumours.

Necrotizing myelopathies

A subacute necrotic myelopathy developing over weeks occurs as a rare paraneoplastic event (Mancall & Rosales, 1964), but also may appear as an isolated myelopathy in the absence of other systemic disease (Katz & Ropper, 2000). Sensory symptoms, including pain, are prominent early and may ascend from the lower limbs or descend down the trunk. Progression may occur in a stepwise manner. Upper and lower motor neuron signs are common. Imaging studies reveal cord swelling and cavitation. Spinal cord necrosis is evident on pathological examination (Fig. 48.11).

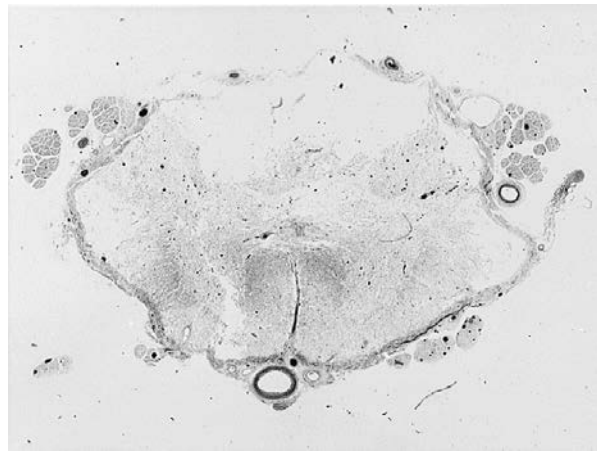


Fig. 48.11. T10 necrotic paraneoplastic myelopathy associated with renal cell carcinoma (Trichrome ×8 magnification).

Cervical spondyslosis and myelopathy

Degenerative cervical spondylosis with myelopathy is a common cause of cervical cord disease. The most frequently affected levels, in descending order of frequency are C5–C6, C6–C7, and C4–C5. The clinical picture is of a myeloradiculopathy. Wasting of intrinsic hand muscles rarely occurs in cervical spondylosis, since the levels commonly involved (C5–6, C6–7) are above the T1 spinal segment. Prominent hand wasting in association with a cervical cord syndrome suggests intrinsic spinal disease such as motor neuron disease or syringomyelia rather than cervical spondylosis. Sensory symptoms are often not prominent in cervical spondylosis and myelopathy. Pain and radicular sensory loss in the distribution of (C5, 6 or 7) dermatomes suggests a lateral cervical disc protrusion, though objective sensory loss may be subtle and less dramatic than symptoms. Reduced vibration and joint position sense in the feet reflect dorsal column involvement. Dorsal column involvement occasionally leads to loss of joint position sense and clumsy deafferented hands (Fig. 48.12). Spinothalamic involvement may manifest as a painful central cord syndrome or occasionally a distal symmetrical loss of pain and temperature mimicking a small fibre peripheral neuropathy.

Syringomyelia

The classical clinical presentation of syringomyelia is a progressive dissociated sensory loss involving pain and temperature, accompanied by loss of tendon reflexes, muscle wasting and weakness in one or both upper limbs,

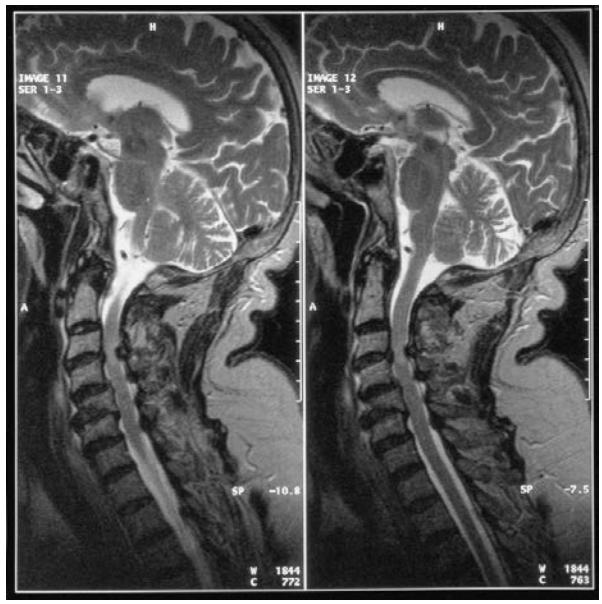


Fig. 48.12. Magnetic resonance image of the cervical spinal cord in an 83-year-old woman with progressive sensory ataxia of the hands and a paraparesis showing multiple levels of spondylosis and marked canal stenosis at C3, 4, C4, 5 and C5, 6 with cord compression and distortion at these levels.

particularly the hands. Sensory loss over the limbs and trunk is 'suspended' in a cape, hemicape or breastplate distribution reflecting interruption of decussating spinothalamic fibres over a series of adjacent segments (Fig. 48.3). Deep aching neck and radicular pain are common. There may be a spastic paraparesis. Considerable variation occurs in the extent of these signs, depending on the diameter and length of the syrinx (Fig. 48.13). The advent of MRI has greatly improved the diagnosis of syringomyelia and increased recognition of variants (Fig. 48.14). Other features include soft tissue and bony damage secondary to loss of pain and temperature sensation with painless burns, thickening and discoloration of the skin, hyperhidrosis, arthropathy (Charcot's joints) and scoliosis. Occasionally, propioceptive loss is evident if the cavity encroaches on the posterior columns.

The cervical spinal cord is the commonest site for development of a syrinx. In many cases a craniocervical junction developmental defect, such as an Arnold Chiari malformation is present. A syrinx may develop in association with intraspinal tumours or follow significant spinal trauma. Post-traumatic syringomyelia may develop many years after spinal trauma, presenting with a painless deterioration in motor function and an ascending sensory level (Rossier et al., 1985).

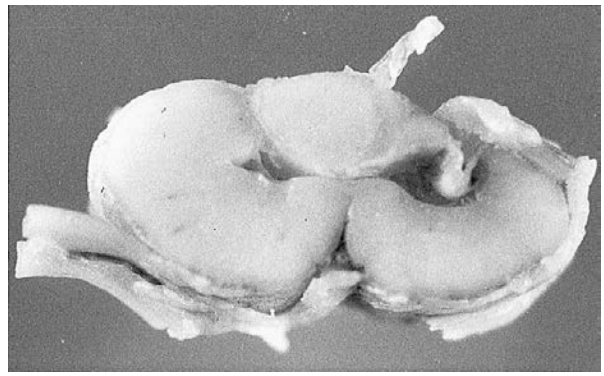


Fig. 48.13. Syringomyelia with the syrinx at C4 level involving the right lateral and dorsal white matter columns, right posterior horn of the central grey matter, base of the left dorsal white matter and adjacent left dorsal horn.

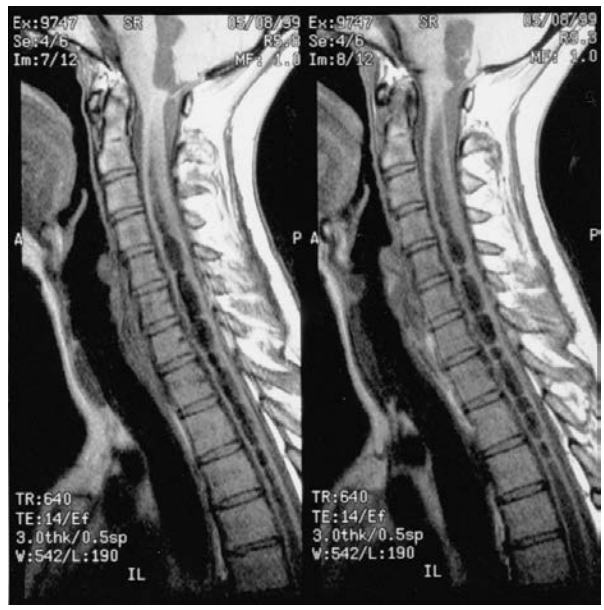


Fig. 48.14. Magnetic resonance image of the cervical spinal cord and craniocervical junction in a 32-year-old woman with loss of pain and temperature sensation and a deep burning discomfort in the C4–8 dermatomes of both arms and a mild spastic paraparesis, showing an extensive syrinx throughout the cervical spinal cord, extending into the brainstem above and the thoracic cord below.

Connective tissue disease

Myelopathy is a rare complication of connective tissue disease. Systemic lupus erythematosus may present with myelopathy. Sjogren's syndrome and mixed connective tissue disease also may be complicated by myelopathy. The presentation of myelopathy may take the form of acute transverse myelitis or evolve in a chronic progressive manner affecting predominantly the corticospinal tracts. MRI of the spinal cord may show patchy areas of increased signal or no abnormality. Pathological examination reveals microscopic perivascular inflammation, fibrinoid necrosis of arterioles and degeneration of white matter tracts. Necrotizing vasculitis affecting the anterior spinal artery and spinal subarachnoid hemorrhage have also been described.

Toxic myelopathies

Lathyrism, caused by a toxin derived from *Lathyrus sativa*, the chickling pea produces a spastic paraparesis in southern India and other tropical countries (Ludolph et al., 1987).

Nutritional deficiencies and myelopathy

Vitamin B12 deficiency and subacute combined degeneration of the cord

The myelopathy of subacute combined degeneration affects the posterior and lateral columns of the spinal cord. Neuropathy may also develop leading to a combination of upper motor neuron signs, depressed or absent ankle jerks and distal sensory impairment with prominent dorsal column sensory loss. Symptoms may begin in the upper limbs and include L'Hermitte's sign, indicating a predilection for cervical spinal cord involvement.

Increasingly recognized is the myeloneuropathy similar to subacute combined degeneration that results from prolonged exposure to nitrous oxide. Posterior and lateral columns are affected and accompanied by an axonal neuropathy and megaloblastic anemia. Nitrous oxide inhibits methionine synthetase mimicking the effect of vitamin B12 deficiency.

Radiation myelopathy

Inclusion of the spinal cord in the radiotherapy field when treatment involves radiation doses greater than 3, 500 rads predisposes to the development of radiation myelopathy. Myelopathy develops after an interval of 6 months or even years and progresses slowly over weeks to months. Initial symptoms may be sensory or a progressive quadriparesis culminating in a complete transverse cord syndrome (Fig. 48.15).

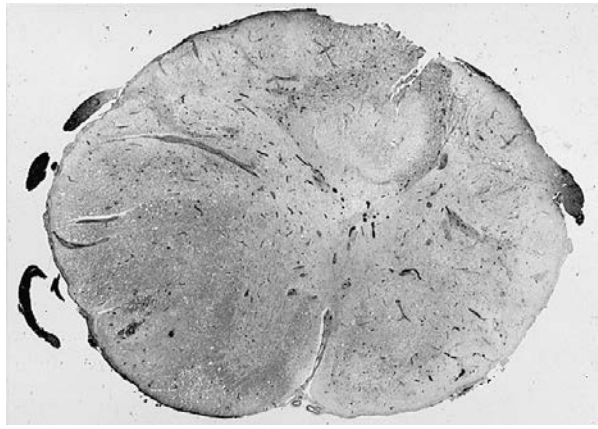


Fig. 48.15. Radiation necrosis of the C1 cord with swelling of the cord and loss of myelin (Weil stain for myelin ×5 magnification).

Decompression myelopathy

Myelopathy, presenting with predominantly sensory symptoms beginning within 6 hours of the last dive, is common in decompression sickness (Caisson disease).

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49

Diseases of the vertebral column

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Abnormalities of the vertebral column

Embryology of the spine

Interpretation of congenital and acquired anomalies of the vertebral column is aided by an understanding of normal development. In early fetal life the ectodermal germ layer gives rise to the primitive neural tube. This normally closes by the end of the fourth intrauterine week; failure of this primary neurulation results in fusion defects such as anencephaly or spina bifida. By this time the primary brain vesicles are present, representing forebrain, midbrain and hindbrain. Mesoderm lies around the neural tube and by the end of the fifth intrauterine week will have completed segmentation into 42–44 recognizable somite pairs (occipital to coccygeal). Once established, the epithelioid cells of these somites rapidly transform and migrate towards the notochord where they differentiate into three distinct cell lines: sclerotomes (from which connective tissue, cartilage and bone are derived), myotomes (providing segmental muscle) and dermatomes (providing segmental skin). Chondrification of the sclerotomes leads to the development of ossification centres, with an anterior and posterior centre for each vertebral body and a pair for each arch. The process is largely complete by the end of the third month of fetal development. Disruption during these early stages accounts for many of the vertebral and craniocervical anomalies. There is increasing interest in the possible role of abnormal notochord signalling and Pax-1 gene expression in these segmentation defects (see for example, David et al., 1997). After the third month of gestation the vertebral column and dura lengthen more rapidly than the spinal cord resulting in regression of the cord tip, leaving the filum terminale below. By term the cord tip typically lies at the L2–3 interspace. Failure of normal cord ascent may lead to tethering of the spinal cord.

Idiopathic scoliosis

Scoliosis refers to a lateral deviation of the spine and is always abnormal. It may be classified on the basis of clinical examination into structural and non-structural forms. In a structural scoliosis there is a rotational component to the curve which is best seen on forward flexion when prominence of rib or loin musculature becomes apparent. This is not the case in non-structural scoliosis, where there is no rotational element. Non-structural scoliosis may be a marker of other pathology such as leg length discrepancy or muscle spasm but is rarely of clinical significance in itself. If associated with underlying neurological disease it may progress to a structural deformity.

Once a structural scoliosis is diagnosed, the severity and potential for progression must be assessed. Erect posteroanterior and lateral X-rays should be taken in a standardized manner so that serial films can be compared. The severity of the curve is given by the Cobb angle, which describes the angle created by the intersection of lines drawn across the end plates of the upper and lowermost vertebrae delineating the curve i.e those with the greatest opposing tilt as illustrated in Fig. 49.1. Angles $>20°$ in skeletally immature children demand particular vigilance; it is during periods of rapid growth that scoliosis may progress significantly, thus scoliosis presenting in younger children has a greater risk of progression. Progression in adults is less common, although underlying neuromuscular disease, pregnancy and osteoporosis pose increased risks.

The major causes of structural scoliosis are given in Table 49.1. The commonest type is idiopathic scoliosis which accounts for around 70% of all cases. The child is otherwise healthy and no underlying pathology is found. The prevalence of adolescent scoliosis, the commonest form, is approximately 4% of the population if mild cases are included (Dickens, 1997). The majority are right sided,

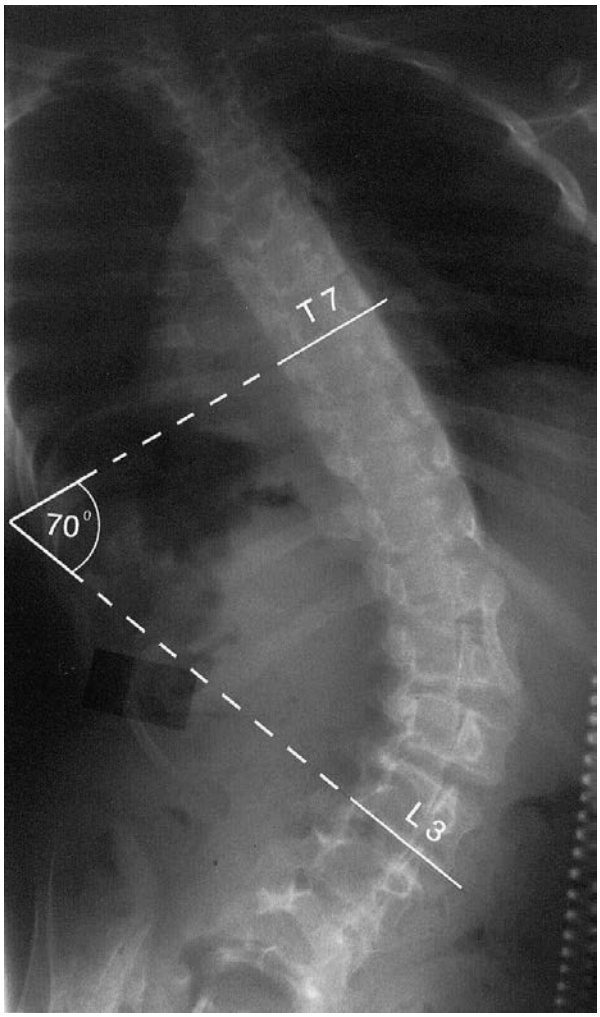

Fig. 49.1. Plain antero-posterior spine X-ray showing thoracolumbar scoliosis in an adolescent with a spino-cerebellar syndrome. The Cobb angle drawn between the apices of the curve measures 70 degrees.

Table 49.1. Causes of structural scoliosis

Idiopathic scoliosis
Infantile <3 years
Juvenile 3–10 years
Adolescent >10 years
Congenital scoliosis
Failure of vertebral segmentation and/or formation
Neuromuscular scoliosis
Neuropathic
Upper motoneuron, e.g. Cerebral palsy
Lower motoneuron, e.g. Spinomuscular atrophy, Poliomyelitis
Mixed, e.g. Myelomeningocoele and spinal dysraphism
Myopathic
Hereditary neuropathies and dysautonomias
Congential myopathies
Muscular dystrophies, e.g. Duchenne
Miscellaneous causes
Skeletal dysplasias
Marfan syndrome
Neurofibromatosis
Spinocerebellar degenerations including Freidrich's ataxia
Arthrogryposis
Rett's syndrome
Metabolic bone disease
Dystonia
Parkinson's disease and parkinsonian syndromes
Craniocervical junction anomalies especially if associated with syringomyelia
Spinal tumours/trauma/irradiation

thoracic and painless. An MRI scan is advised if features are atypical or neurological signs are present, for example a left-sided lumbar curve or absent abdominal reflexes, as these features may indicate underlying pathology such as spinal cord tumours or Chiari malformation. The infantile and juvenile forms of idiopathic scoliosis are uncommon.

The cause of idiopathic scoliosis is multifactorial and the development and progression of the scoliosis may have different mechanisms. There is often a positive family history of scoliosis, with girls eight times more likely than boys to require treatment (Dickens, 1997). The inheritance can be described by a dominant major gene diallele model (the gene is as yet unidentified) with incomplete penetrance (Axenovich et al., 1999). Progression of the curve is more common in thoracic or large curves (>35°) with skeletal maturity another important consideration. The consequences of severe idiopathic scoliosis are cosmetic deformity, cardiopulmonary compromise and back pain.

Congenital scoliosis

In congenital scoliosis the vertebrae are anomalous due either to a failure of natural segmentation, leading to asymmetric fusion, or to failure of formation, in which only part of the vertebra is formed. Often there is a combination of both pathologies. In congenital scoliosis there is a high incidence of associated anomalies. These include neuraxis anomalies in up to 40% of patients, renal and gastrointestinal tract abnormalities in around 20% and congenital heart defects in approximately 10% (McMaster & Ohtsukak, 1982). Sometimes the scoliosis is part of a syn-

dromic diagnosis such as in the Klippel–Feil and Noonan syndromes. Clinically the scoliosis may vary from a mild non-progressive deformity to a severe and rapidly progressive curve that compromises the spinal cord. There is often an associated kyphosis.

Neuromuscular scoliosis

Spinal deformity is common in many of the neuromuscular disorders. In the developed world cerebral palsy, spina bifida and Duchenne muscular dystrophy are the most common causes of neuromuscular scoliosis, although poliomyelitis is still an important cause in developing countries. Because of the underlying condition, the spinal curvature, in contrast to idiopathic scoliosis, generally presents earlier, is more extensive and is more likely to deteriorate through childhood and into adult life. Other systems are often already compromised; for example, there may be muscle imbalance, cardiopulmonary insufficiency, poor nutrition, insensate skin and osteoporosis. These problems may be further exacerbated by the physical and functional effects of the scoliosis itself. In addition, the scoliosis may adversely affect walking and seating and cause pain as the ribs abut the iliac crest. This is often compounded by coexisting pelvic obliquity, particularly in the non-ambulant patient.

Kyphosis and lordosis

The spine naturally shows some curvature in the anteroposterior plane, seen as a kyphosis in the thoracic region and lordosis at the lumbar spine. A normal lumbar lordosis shows full correction on forward flexion. Excessive lordosis may occur postlaminectomy, in the neuromuscular conditions, or when there is fixed flexion deformity at the hip.

A kyphosis $>40°$ is abnormal. It may be congenital, due to a lack of fusion of the vertebral bodies anteriorly or a lack of formation of one or more anterior bodies. Although less common than congenital scoliosis, it carries a more severe prognosis as a higher proportion of patients will develop progressive deformity and myelopathy particularly during the adolescent growth spurt (McMaster & Singh, 1999). Patients with anterior failure of vertebral body formation, who present with a sharp angle kyphosis, are at particular risk of rapid progression and spinal cord compression. Early arthrodesis is indicated in these cases. Schuermann's kyphosis is the most common form of acquired kyphosis, presenting in adolescents it is generally benign. Kyphosis only occasionally progresses once skeletal maturity is reached.

Miscellaneous causes of spinal deformity

A number of primary diseases of bone and connective tissue produce pathology of the spine and craniocervical junction. Those that present neurological problems are classified into four broad categories:

Osteopenic disorders

In these bone mineralization is reduced. These include endocrine diseases such as hyperparathyroidism, Cushing's disease, osteomalacia, primary osteoporosis and osteogenesis imperfecta.

Osteogenesis imperfecta (OI) is a heritable disorder of collagen that results in osteopenia and increased bone fragility. In the majority of patients mutations are found in the genes encoding the $\alpha 1$ and $\alpha 2$ collagen chains. These result in reduced amounts of collagen which is often structurally abnormal. To date, over 200 mutations have been described (Dalgleish, 1997); however, there is no close correlation between the molecular abnormalities and the clinical manifestations which are highly variable. Prenatal diagnosis is available for some forms of the disease. The Sillence classification delineates four major phenotypes on the basis of bone fragility, growth and the presence or absence of additional features such as blue sclerae, dentinogenesis imperfecta and presenile hearing loss (Sillence, 1981). Progressive skeletal deformity is a particular feature of OI type III and often requires orthopedic intervention. Basilar invagination is a rare but important complication of OI. This may be associated with ventral brainstem compression, hydromyelia and hydrocephalus. It generally presents in early adult life with progressive neurological symptoms and signs, the commonest being headache and lower cranial nerve dysfunction, particularly atypical trigeminal neuralgia. Other features include quadriparesis, ataxia and nystagmus (Sawin & Menezes, 1997). Trigeminal pain, if intractable, may require stereotactic surgery. The treatment of myelopathy involves ventral decompression and occipito-cervical fusion, with or without decompression of the foramen magnum (Lynch & Crockard, 1999).

Currently, there is much interest in the role of bisphosphonates in the management of OI. There is evidence that these drugs reduce bone pain, improve both bone density and vertebral height (Glorieux et al., 1998). However, long-term benefits on disease progression, function and quality of life have yet to be demonstrated.

Skeletal dysplasias

Menezes has classified these into 5 categories, the largest being the osteochondrodysplasias and the dysostoses (Menezes & Ryken, 1992). Osteochondrodysplasias are

defined as abnormalities of cartilage or bone growth and development. They generally present as short-limbed dwarfism, with achondroplasia the commonest form. Around 50% of children with achondroplasia have a thoracolumbar kyphosis in infancy and there is a risk of spinal cord stenosis. Patients characteristically have macrocephaly but a small mid face and small foramen magnum. These abnormalities place them at risk of symptomatic stenosis and hydrocephalus. Sleep apnea is seen in the majority of patients, which may have a central or respiratory cause. Cervicomedullary decompression with resection of the foramen magnum may be necessary. Atlantoaxial instability has been increasingly recognized in the skeletal dysplasias.

The dysostoses are defined as malformations of individual bones singly or in combination. These include the craniosynostoses (Crouzon and Apert syndromes) in which vertebral anomalies are commonly recognized and Klippel–Feil syndrome which is discussed later.

The metabolic storage disorders

These include the mucopolysaccharidoses, the glycoprotein storage disorders, the gangliosidoses and the mucolipidoses. These neurodegenerative diseases vary in their severity but show characteristic skeletal dysplasias, such as 'hooked' vertebrae, broad ribs and flared pelvis. Thoracolumbar kyphosis is common, with a risk of spinal cord compression. Other neurological complications include cognitive deterioration, carpal tunnel syndrome and deafness. In Morquio's syndrome (mucopolysaccharidosis IV) the os odontium is dysplastic or absent. These patients also have striking ligamentous laxity which gives a particularly high risk of atlantoaxial instablity and spinal cord compression.

Mesenchymal and connective tissue disorders

Neurofibromatosis is considered in detail in Chapter 128. Around 30% of patients will develop scoliosis, of which 40% will have associated cervical spine abnormalities. The scoliosis often manifests as an acute-angled short segment kyphoscoliosis which will inevitably progress unless fusion is performed (Winter et al., 1979). Approximately 50% of patients with Marfan's syndrome will develop significant scoliosis.

Management of spinal deformity

Patient management varies from case to case and will be influenced by the underlying diagnosis, current levels of function especially ambulatory abilities, life expectancy and concomitant medical problems.

In kyphosis bracing is advocated for skeletally immature patients with progressive curves $<60°$. Surgery is often required if the curve exceeds 60°.

In patients with idiopathic scoliosis bracing may delay or arrest scoliosis progression in the skeletally immature child. Indications for bracing are curves $>30°$ or earlier if there is radiological progression. Bracing is rarely effective once the curve exceeds 45°. It may improve pain in adults with scoliosis. A thoracolumbar spinal orthosis is generally used, with an added cervical extension (as in the Milwaukee brace) if the apex of the curve is above T8. If bracing is not appropriate, or fails to control the scoliosis, surgical stabilization is necessary, although this may be at the cost of spinal growth.

In congenital or neuromuscular scoliosis there may be a role for bracing but given the relentless progression of the scoliosis in many of these conditions, early surgery is often indicated. In non-ambulant patients the spinal fusion should involve the pelvis. Surgical risk, particularly of hemostasis and postoperative chest infection, is high in this patient group.

A solid arthrodesis is the primary goal of surgery, often requiring joint excision, decortication and bone grafts. Instrumentation is added to achieve and maintain correction as well as providing stability to the fusion mass. Surgical procedures will vary but are largely determined by the underlying pathology. The reader is referred to standard orthopedic texts (see Moe's textbook of scoliosis, 1994). Good results are dependent on meticulous patient selection at all stages, with multidisciplinary preoperative assessment, intraoperative neurophysiological spinal cord monitoring and intensive care support postoperatively. Complications include immediate perioperative problems such as hemorrhage and pneumothorax. Infection occurs in up to 2% of patients. Paraplegia occurs in $<1\%$ of patients and postoperative paraparesis warrants urgent removal of any instrumentation. Up to 5% of patients experience failure of graft implantation usually due to pseudarthrosis.

Craniovertebral junction anomalies

The pathophysiology of the craniocervical junction anomalies is complex. A useful classification is proposed by Menezes (1999), reproduced in Table 49.2, subdivides the anomalies into congenital, developmental and acquired causes.

Clinical features of craniocervical junction anomaly

Symptoms and signs may be insidious or of rapid onset. Clinical presentation is diverse as dysfunction may occur

Table 49.2. Causes of craniovertebral anomalies

1. Congenital anomalies and malformations
   A. Occipital sclerotome malformations – atlas assimilation, proatlas remnants
   B. Atlas malformations – bifid atlas, assimilation, fusion, absent arches
   C. Axis malformations – segmentation defects, odontoid dysplasias
2. Developmental and acquired anomalies
   A. Foramen magnum abnormalities
      (i) foramen stenosis, e.g. Achondroplasia
      (ii) secondary invagination, e.g. Ostoeogenesis Impefecta, Paget's

B. Atlantoaxial instability
   (i) Down's syndrome
   (ii) metabolic disorders, e.g. Morquio, Hurler syndromes
   (iii) Infections, e.g. Grisel's syndrome, Tuberculosis
   (iv) Trauma
   (v) Inflammation, e.g. rheumatoid arthritis, Reiter's syndrome
   (vi) Tumour, e.g. osteoblastoma, neurofibromatosis
   (vii) Miscellaneous, e.g. syringomyelia

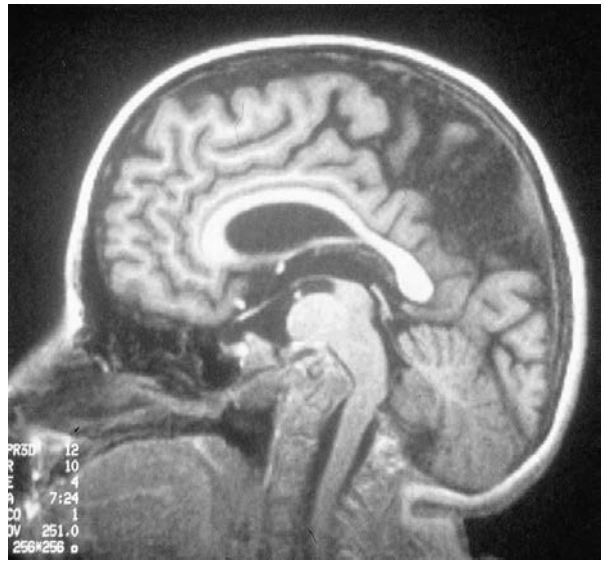

Fig. 49.2. Sagittal MRI brain demonstrating basilar impression in an adolescent with severe (type III) osteogenesis imperfecta (OI).

at many levels: the lower brainstem, cranial nerves, cervical roots and upper cervical cord may be compromised by pressure from bone or soft tissue, there also may be indirect compromise of the blood supply. Congenital anomalies of the craniocervical junction are often associated with dysmorphic features and obvious skeletal anomalies. Patients most commonly complain of headache and neck pain worsened by movement and coughing. Pain characteristically originates in the suboccipital region and radiates to the vertex, in a C2 distribution. Head tilt and 'torticollis' are common. In children with craniocervical junction anomalies hearing loss is the most common cranial nerve symptom. In adults, trigeminal distribution pain and neuralgia may result from direct compression of the V nerve or compression of the V nerve nuclei in the upper cervical cord. Lesions of other cranial nerves particularly IX, X, XI and XII are also seen. Spinal cord compression produces a myelopathic picture with upper motor neuron features, often progressing to loss of bladder and bowel control. Occasionally, the myelopathy is confined to the upper limbs. Sometimes there is a predilection for the dorsal columns, producing marked joint position sense loss. Brainstem involvement may produce dysphagia, dysarthria, internuclear ophthalmoplegia and nystagmus (most commonly horizontal but more classically down beating). Central apnea, drop attacks and syncope are important additional features. The intimate relationship of the vertebral arteries to the upper cervical spine and foramen magnum may increase the risk of basilar migraine and vertebro-basilar ischemia.

There are three principal mechanisms by which the craniocervical junction anomalies lead to neurological signs. Frequently, more than one mechanism coexists.

Direct compression

This may result from developmental abnormalities of the odontoid process. Of particular importance is the condition os odontoidium where the odontoid and the body of the axis are not fused. Atlas assimilation, where there is failure of segmentation between the fourth occipital and first spinal sclerotomes, is relatively common and is particularly associated with the Chiari malformations. Direct compression may also result from abnormal articulation around cervical vertebral blocks as is seen in the Klippel–Feil syndrome.

Structural

Basilar invagination describes deformity of the osseous structures of the skull base which leads to upward displacement of the edge of the foramen magnum (see Fig. 49.2). In its primary congenital form it is often associated with platybasia where the clivus and anterior skull base are abnormally flattened. It may be associated with more subtle developmental bony anomalies and associated neurodysgeneses such as hindbrain herniation (particularly Chiari malformations) and syringohydromyelia. The

foramen magnum itself may be narrow, usually as a feature of underlying skeletal dysplasia, as in achondroplasia. Acquired forms of basilar invagination are more common and result from any bone softening condition. The most important causes are osteogenesis imperfecta (see Fig. 49.2) and Paget's disease. Diagnosis of basilar invagination on cervical spine X-ray involves measuring the position of the odontoid tip with respect to either the foramen magnum itself (McRae's line) or from lines drawn between the roof of the hard palate and either the posterior lip of the foramen magnum (Chamberlain's line) or the caudal part of the occipital bone (McGregor's line).

Atlantoaxial instability

Atlantoaxial dislocation results from incompetence of the transverse ligaments or abnormalities of the dens itself (Stevens et al., 1994). Instability is defined by an atlanto-dens interval >5 mm, and is demonstrated by flexion/extension X-rays of cervical spine or 3D CT reconstruction, the latter also allows assessment of any rotational component. Instability may occur spontaneously or develop secondarily due to inflammation or trauma. It is a recognized feature of the complex developmental craniofacial and cranio-vertebral anomalies, particularly if there is atlas assimilation and segmentation failure as in the Klippel–Feil syndrome. Syndromes which are also associated with ligamentous laxity carry a particular risk of dislocation; such as the mucopolysaccharidoses and Down's syndrome (Fig. 49.3).

The surgical treatment of craniocervical junction anomaly is complex and beyond the scope of this chapter (see Robertson & Coakham, 1999). If neurological symptoms and signs of brain stem compression occur surgery is usually indicated. Treatment of basilar invagination, for example, due to osteogenesis imperfecta involves ventral decompression and dorsal occipitocervical fusion.

Down's syndrome

Trisomy 21 occurs in around one in 650 live births and is the single most common cause of severe learning difficulties. It initially presents with characteristic dysmorphic features and hypotonia, often with associated cardiac and gastrointestinal anomalies. It is estimated that up to 25% of patients with Down's syndrome have asymptomatic atlantoaxial instability. Only around 1% are symptomatic (Pueschal & Scola, 1987). Recognized presentations include mild pyramidal tract signs with gait disturbance or the precipitous onset of cord compression. In the absence of signs or symptoms, screening of the atlanto-dens interval is no longer routine, however sports such as trampolining and somersaults should be avoided. Once symptoms are present, surgical stabilization is recommended.

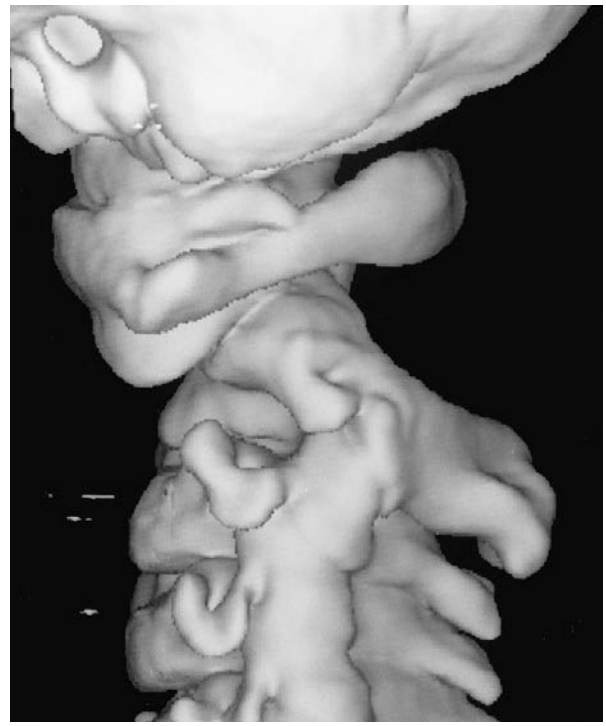

Fig. 49.3. Three dimensional CT reconstruction showing atlanto-axial subluxation in an 8-year-old child with Down's syndrome.

Chiari malformations

Chiari described four types of hindbrain malformation. The Chiari I malformation is demonstrated on neuroimaging by the dorsal extension of the cerebellar tonsils below the level of the foramen magnum (Fig. 49.4). Some studies report the prevalence of tonsillar descent (3–5 mm below the foramen magnum) on sagittal MRI in asymptomatic individuals to be as high as 20%. However, more definitive volumetric reconstruction of coronal MRI demonstrates that the complex shape of the rostral cerebellum may lead to sagittal MRI overestimating tonsillar descent (Savy et al., 1994). The true prevalence of Chiari I in asymptomatic individuals is probably less than 1%, although it rises if tonsillar descent on sagittal MRI is associated with appropriate symptoms or other hind brain anomalies and in around 50% of cases of true cerebellar ectopia there is elongation of the medulla. Approximately 50% of Chiari I malformations are associated with craniocervical anomalies and

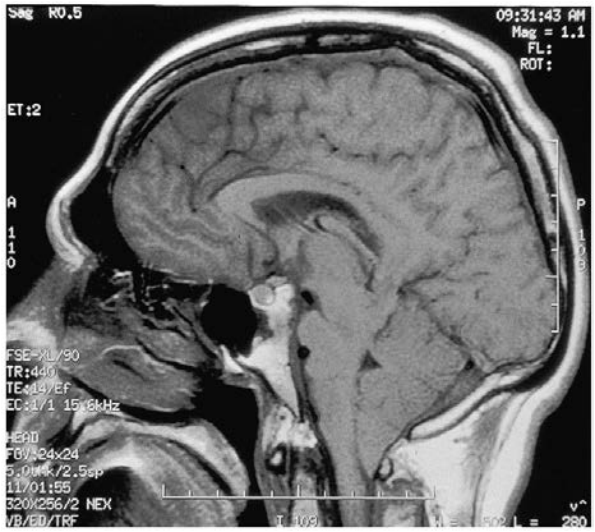

Fig. 49.4. Sagittal MRI brain showing Chiari I malformation.

syringomyelia (Milhorat et al., 1999). The development of Chiari I is likely to be multifactorial. It has been postulated on the basis of familial aggregation that Chiari I is a disorder of para-axial mesoderm (Milhorat et al., 1999). However, unlike Chiari II–IV there are clear examples of acquired Chiari I in which serial MRI has demonstrated postnatal development of the anomaly (Huang & Constantine, 1994). Furthermore, lowering of CSF pressure following lumbar puncture or lumbar peritoneal shunting may be a risk factor for cerebellar tonsil descent (Chumas et al., 1993; Payner et al., 1994). There are well-documented examples of 'Chiari' or 'pseudo-Chiari' malformations improving following treatment of abnormally low CSF pressure due to CSF leakage (Samii et al., 1999).

The symptoms and signs resulting from Chiari I overlap with those associated with other craniocervical anomalies (see above). These include headache especially cough headache, nystagmus and quadriplegia. Additional symptoms and signs may result from associated hydrocephalus or syringomyelia. The condition is rarely symptomatic in childhood. Unusual presentations of Chiari I have been described. These include sudden death, syncope, ventricular fibrillation due to head movement, lingual myoclonus, pulsatile tinnitus, Menière's-type symptoms, acquired esotropia, central apnea and paroxysmal rage. Surgical treatment involves decompression of the foramen magnum and should be offered on the basis of significant and relevant symptoms, e.g. severe cough headache, or the presence of physical signs indicating neurological compromise.

Chiari II malformation is a congenital anomaly which is associated with myelomeningocele and hydrocephalus in >90% of cases and generally manifests in the neonatal period. It consists of caudal displacement of the medulla and cerebellum (particularly vermis) into the cervical canal overriding the spinal cord often accompanied by partial herniation of the fourth ventricle and distortion of midbrain tectum. Associated abnormalities of supratentorial and midbrain structures are common. Chiari III is analogous to type II but describes downward displacement of the cerebellum into a posterior encephalocele, again with elongation and herniation of the fourth ventricle. Clinical features are severe and often life threatening, particularly where there is cranial nerve dysfunction.

The Chiari IV malformation describes cerebellar hypoplasia and on current understanding is not part of the Chiari spectrum.

Spinal dysraphism

Spinal dysraphic states are caused by localized failure of neural tube closure during fetal development. Myelomeningocele is the most common form, with an incidence of 0.8/1000 live births. There are marked regional variations in its incidence and the condition is heterogeneous. There are strong genetic components and recurrence risks rise from 1–2% after one affected child to 10% with two affected children (Todorov, 1982). The process of neuralation may be disrupted by teratogenic agents and in particular by maternal and/or fetal folate deficiency. Early folic acid supplementation reduces the incidence of neural tube defects, so that all women are recommended to take supplemental folate prior to conception and during the first trimester. This advice is especially important for women with a previously affected pregnancy or those taking anticonvulsants in whom the incidence of neural tube defects is around 1% of pregnancies, larger amounts of folic acid are recommended for these women. Routine antenatal screening provides a prenatal diagnosis in many cases; raised maternal serum α fetoprotein is associated with open neural tube defects and fetal ultrasonography allows cranial and vertebral structures to be visualized directly. Prenatal counselling and termination can then be offered.

Myelomeningocele and myeloscisis comprise 95% of cases of spinal dysraphism, with exposed neural tissue a common feature (Fig. 49.5). In a meningocele and in spina bifida occulta neural elements are covered by skin. The clinical features are determined by the extent of the myelocele and the presence of associated abnormalities, which may include both neural and extraneural anomalies.

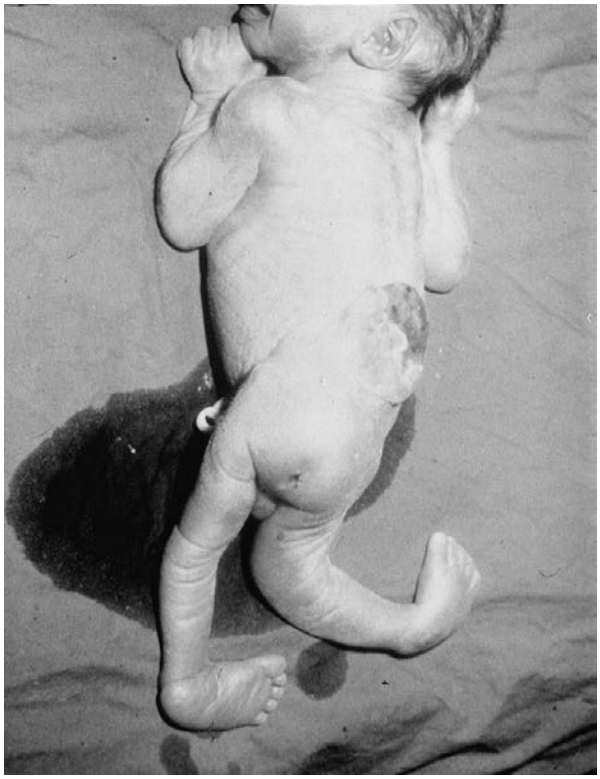

Fig. 49.5. A new born infant with thoroco-lumbar myelomeningocele. He has a neuropathic bladder, patulous anus and flaccid lower limbs with bilateral talipes.

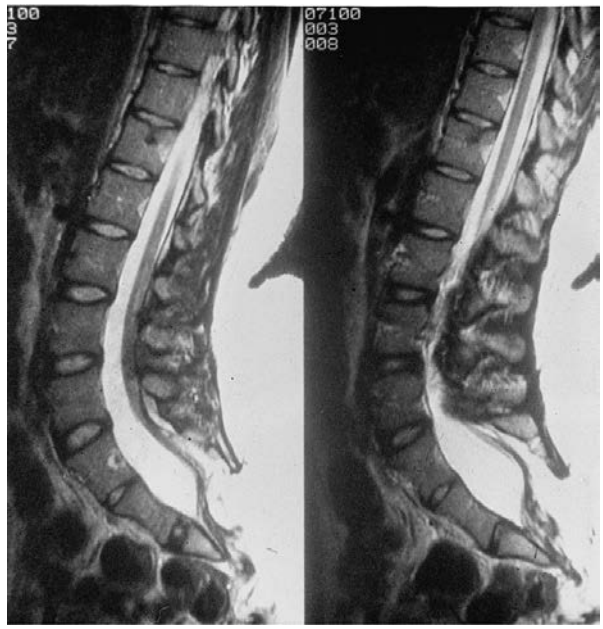

Fig. 49.6. Sagittal MRI of lumbar–sacral spine showing a lipomyelomeningocele.

Progressive hydrocephalus requiring surgical treatment is present in 90% of cases and around 70% have a Chiari II malformation. Learning difficulties are common, one-third have an IQ < 80. Syringomyelia is present in up to 75% of cases and is often associated with severe scoliosis. Approximately a third of patients have diastematomyelia.

Approximately 80% of open spina bifida defects are located in the lumbosacral area. The sensory level indicates the upper level of the lesion. Lesions above L3 result in complete paraplegia, but motor deficits may otherwise be patchy with a mixed pattern of upper and lower motoneuron signs. Sphincter and detrusor function is always compromised and careful urological assessment is required. Surgical closure is undertaken within 48–72 hours of delivery to reduce the risk of ascending infection and protect viable neural tissue within the placode. Following closure delayed hydrocephalus is likely. Patients generally require ongoing medical care by a multidisciplinary team.

Spina bifida occulta describes occult dysraphism, where neural structures have not herniated through the mesenchymal defect. It includes diastematomyelia, terminal myelocystocele and tight filum terminale. Lipomyelomeningocele and dermal sinuses are often included in this classification as they also result from abnormal neurulation. Spina bifida occulta is often neurologically asymptomatic. The majority of patients have associated cutaneous abnormalities such as a tuft of hair or a dimple over the region, and plain X-rays show underlying vertebral anomalies. MRI scan then confirms the diagnosis (Fig. 49.6). Two neurological presentations are recognized. First, a congenital asymmetric weakness and atrophy of the lower limbs and second the 'tethered cord syndrome' with progressive and sometimes precipitous onset of weakness and spasticity. The latter often presents in childhood or during the adolescent growth spurt and is an important cause of toe walking in childhood. Both presentations may be associated with sphincter disturbance. Treatment is primarily neurosurgical, with release of the spinal cord from the tethering lesion, with full preoperative neurological and urological assessment. Orthopedic, orthotic and physiotherapy management of lower limb deformity is also important.

Klippel–Feil syndrome

Described in 1912, the disorder is characterized by a short neck, impaired neck mobility and a low hairline (Klippel & Feil, 1912). The incidence is approximately 1: 40 000 births. The skeletal abnormalities include fusion of two or more

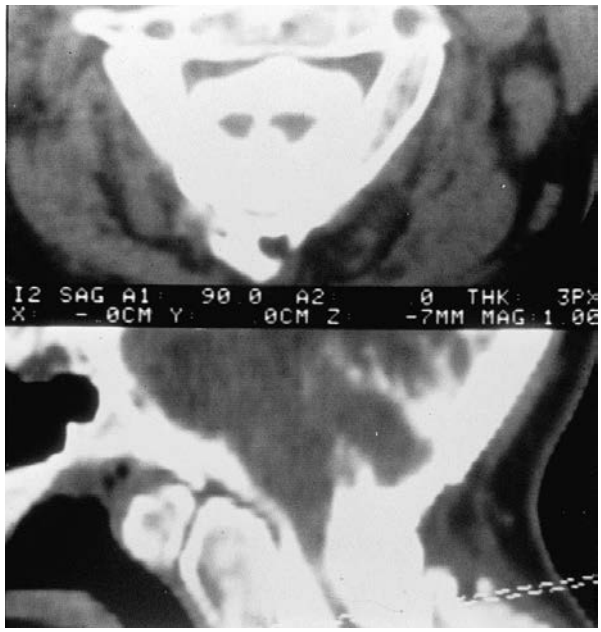

Fig. 49.7. Axial CT myelogram with sagittal reconstruction showing split cervical spinal cord in a patient with Klippel–Feil syndrome.

cervical or cervicothoracic vertebrae. The syndrome is heterogeneous; differing numbers and positions of fused vertebrae are described and the associated anomalies are highly variable (Clarke et al., 1998). The condition may be familial: dominant, recessive and X-linked inheritance patterns have been proposed. A dominant form in which there is chromosome 8 inversion is described (Clarke et al., 1995). Despite the sometimes dramatic spinal abnormalities, a follow-up study over a 10-year period has indicated that only 20% of patients experienced significant cervical spine symptoms and only 6% required surgical intervention (Theiss et al., 1997).

Extravertebral anomalies associated with Klippel–Feil syndrome affect multiple systems. Skeletal and systemic abnormalities include: scoliosis, scapula elevation, rib anomalies, cranio-facial dysmorphology, pulmonary, cardiac, gastrointestinal and urogenital anomalies. Neurological problems include syringomyelia, cranial nerve abnormalities, Duane's retraction syndrome, deafness, acquired myelopathy due to the spinal abnormality, thin corpus callosum, split cervical spinal cord (see Fig. 49.7) and failure of pyramidal tract decussation (Gunderson & Solitaire, 1968; Schott & Wyke, 1981; David et al., 1996). The latter anomaly is particularly interesting as it may underlie the intense congenital mirror movements which affect a number of these patients.

Congenital mirror movements

These are intense involuntary movements, primarily of distal upper limb muscles, which mirror the voluntary unilateral movement. They cannot be suppressed and typically do not occur during passive movement. Mirror movements occur normally during a child's motor development, however, they are rarely intense and disappear by the age of 6 years. Pathological mirror movements are rarely disabling and patients learn adaptive proximal movements so as to avoid inappropriate finger movements, for example wrong key strikes whilst typing. Neurophysiological study of mirror movements has provided new insights into central motor control and plasticity.

A single subject with Klippel–Feil syndrome and mirror movements has been studied in detail (Farmer et al., 1990). Similar neurophysiological findings have been reported in patients with congenital mirror movements and mirror movements in association with X-linked Kallman syndrome (Cohen et al., 1991; Mayston et al., 1997). Unilateral focal electrical or magnetic brain stimulation of either left or right primary motor cortex at threshold in non-mirroring subjects evokes contralateral short latency EMG responses due to rapid conduction through pyramidal tract pathways (see Fig. 49.8). In contrast, mirroring individuals show simultaneous bilateral short latency EMG responses following unilateral motor cortex stimulation. Abnormal bilateral EMG responses indicate that in subjects with mirror movements the corticospinal tract is aberrant and bilaterally represented. In mirroring subjects the short latency (N20) component of the somatosensory evoked potential is confined to the contralateral sensory cortex. Spinal (short) latency cutaneomuscular (CMR) and stretch reflexes are confined, as in normal subjects, to the stimulated side. However, in mirroring subjects the long-latency components of the CMR and stretch reflexes are simultaneously present in both the stimulated and non-stimulated limbs (Farmer et al., 1990; Matthews et al., 1990; Capaday et al., 1991). This abnormal crossing of the long-latency CMR and stretch reflexes in mirroring subjects has provided strong evidence in support of the view that in human hand muscles long-latency reflexes are transmitted via a transcortical loop (see Fig. 49.8). Cross-correlation analysis of EMG activity recorded simultaneously from homologous muscles of left and right hands, reveals, in contrast to healthy subjects, the presence of a short duration peak at time zero, indicating that during normal muscle contraction both hands receive abnormal common presynaptic drive (see Fig. 49.8). This abnormal drive can be shown to be highly muscle specific, indicating that abnormal bilateral corticospinal axons innervate the

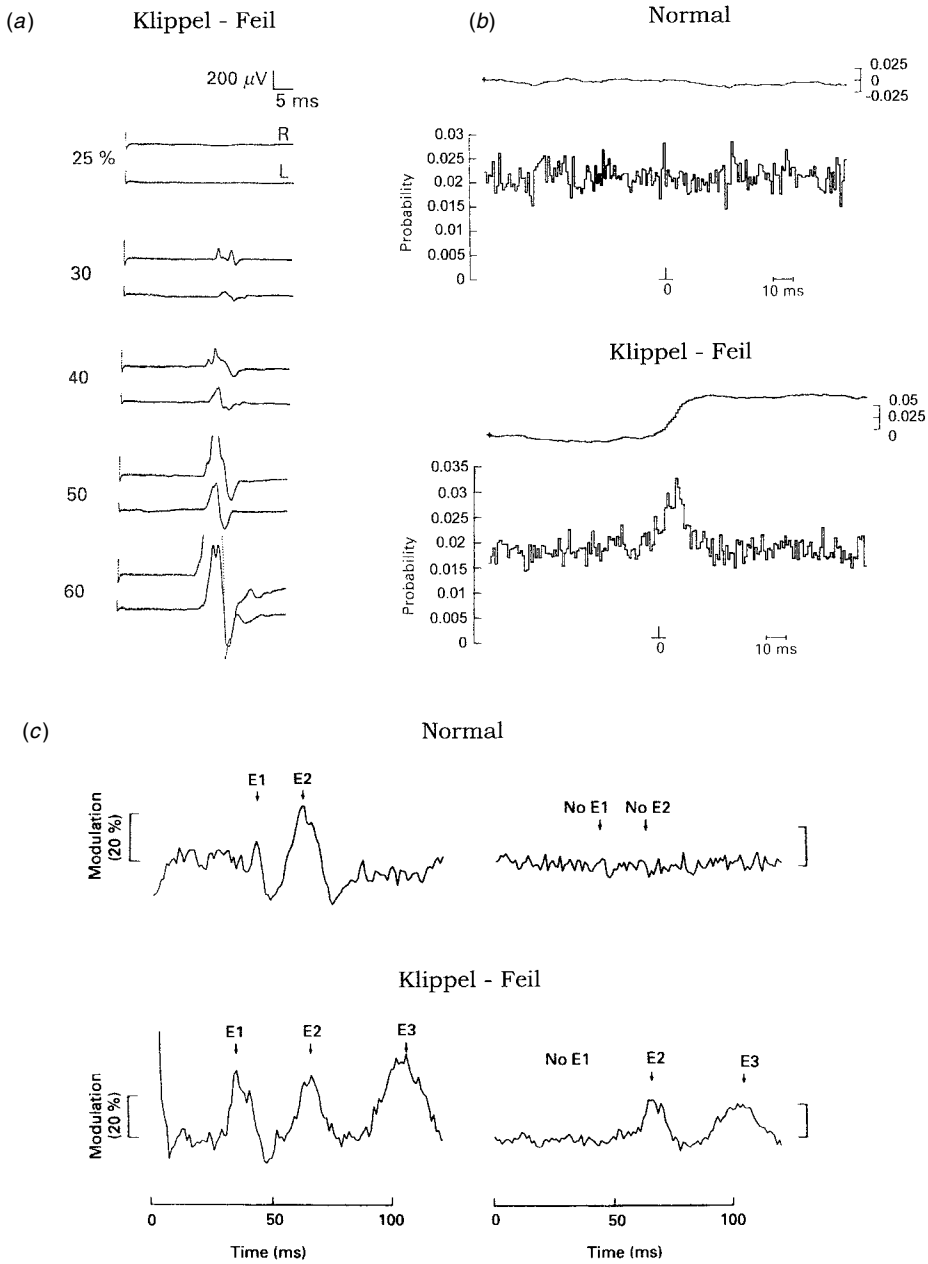

Fig. 49.8. Neurophysiological data from a normal subject and a subject with Klippel–Feil syndrome and mirror movements. (*a*) Abnormal bilateral short-latency muscle responses to focal transcutaneous electrical stimulation of the left motor cortex in the Klippel–Feil subject. (*b*) Cross-correlation histograms and CUSUM constructed between simultaneous left and right hand muscle EMGs in the normal subject and the Klippel–Feil subject. The abnormal peak in the Klippel–Feil subject data reflects abnormal common presynaptic drive to left and right spinal motoneurons. (*c*) Cutaneomuscular reflexes in the normal subject and Klippel–Feil subject. In contrast to normal subjects, those with mirror movements show crossing of long-latency reflex activity (E2 and E3 components), similar results are found for the long-latency stretch reflex, indicating that late reflex components are generated by a transcortical loop.

equivalent motoneuron pools, e.g. those of first dorsal interosseous muscle on left and right sides of the spinal cord. These findings indicate that voluntary and long-loop reflex activity in abnormal central motor pathways produces the mirror movements of Klippel–Feil syndrome.

Mirror movements in childhood hemiplegia

Neurophysiological studies of mirror movements have been extended to include childhood hemiplegia. Intense mirror movements are a recognized feature of childhood hemiplegia and have been proposed to represent a physical sign of corticospinal tract re-wiring following early brain damage (Woods & Teuber, 1978). Children with hemiplegia and mirror movements have been studied using the approach outlined above for Klippel–Feil syndrome. The findings are similar except that the corticospinal axons reach both sides of the spinal cord from the undamaged motor cortex (Farmer et al., 1991; Carr et al., 1993). The presence of mirror movements with characteristic neurophysiological findings is associated with MRI scans in which there is no gliosis in response to the cerebral injury, suggesting that antenatal insults before gestational age 28 weeks causing hemiplegia are associated with pyramidal tract plasticity and mirror movements. This remarkable central nervous reorganization may help to sustain function of the child's hemiplegic hand albeit at the expense of mirror movements (Carr et al., 1993).

Paget's disease

The disorder is rare before the age of 40 but becomes increasingly common with time, affecting 10% of 90-year-olds. The clinical features are those of bone pain, local deformity, bone enlargement, pathological fracture and a predisposition to sarcomatous change. The disorder often affects the skull and spine and as a result neurological involvement is common. Diagnosis is made by typical radiological appearances and the finding of an elevated serum alkaline phosphatase. The disease is one of excessive bone resorption with excessive osteoblastic and osteolytic activity. A genetic predisposition is described and some familial cases have been linked to chromosome 18q (Cody et al., 1997). Pagetic osteoclasts contain nuclear inclusions and osteoclastic infection with paramyxoviruses is one postulated cause of the disease (Singer, 1999).

There are a numerous potential neurological sequelae of Paget's disease. Direct compression by Pagetic bone may lead to the following: headache, dementia, brainstem and cerebellar dysfunction, cranial neuropathies, myelopathy, cauda equina syndrome, and radiculopathies. The most common cranial neuropathy is sensorineural deafness; optic atrophy, trigeminal neuralgia and hemifacial spasm are also described. Pagetic softening of the skull may lead to basilar invagination resulting in brain stem and high cervical compression syndromes and occasionally hydrocephalus. The brain and spinal cord can become acutely compressed due to epidural hematoma. The vascularity of Pagetic bone may lead to cerebral ischemia as part of a steal syndrome (compared to normal bone, blood flow in Pagetic bone is increased threefold). Neurological syndromes may also develop due to compression of blood vessels.

Paget's disease generally responds to treatment with bisphosphonates although a relative resistance to these drugs is described (Gutteridge et al., 1999). First-line treatment is with potent oral bisphosphonates. Second-line treatment regimes include calcitonin, etidronate and intravenous bisphonsphonates (Poncelet, 1999). Bone pain in particular can resolve within 1–2 weeks of commencement of treatment, treatment efficacy may be monitored by serum alkaline phosphatase levels and a therapeutic response may be expected in approximately 80% of patients treated. Neurological syndromes often improve with medical treatment. Rapidly progressive neurological syndromes require high dose intravenous bisphosphonate therapy and/or treatment with calcitonin. However, hydrocephalus generally requires shunting. Surgical decompression for basilar invagination, cranial nerve lesions, spinal cord and root compression is indicated if neurological symptoms and signs progress rapidly or despite best medical treatment (Poncelet, 1999). Medical treatment prior to surgical intervention may reduce bone vascularity and thus the risk of perioperative hemorrhage.

Rheumatoid arthritis

Rheumatoid arthritis is a chronic, inflammatory, immune-mediated symmetrical polyarthritis with a predilication for the distal joints. Females are affected twice a commonly as males and the prevalance ranges from 0.2–2 % of the population. The inflamed synovium is termed the pannus; it is characterized by T and B cell activation, cytokine release, immune complex deposition, angiogenesis, and cellular proliferation. This inflammatory process leads to damage and destruction of bone, cartilage and ligaments. Aggressive immunosuppressive therapy with disease modifying drugs (in particular sulfasalazine and methotrexate) improves the prognosis of rheumatoid arthritis (Madhok et al., 2000), it is not yet known whether this approach

reduces the incidence of neurological complications of the disease.

Neurological manifestations of rheumatoid arthritis include entrapment neuropathy, vasculitic neuropathy, myopathy and ischemic syndromes due to vasculitis, these are discussed further in Chapter 94 on the vasculitides. The spinal cord manifestations result from ligamentous disruption, bone destruction and secondary osteoporosis. A rare syndrome of diffuse dural infiltration with inflammatory cells producing a pachymeningitis has been described.

Patients with rheumatoid arthritis of the cervical spine frequently experience headache and neck pain. The most feared neurological complication of rheumatoid arthritis is upper cervical cord and brainstem compression. Involvement of the atlanto-axial ligament often combined with local pannus formation and bone destruction produces subluxation. Atlanto-axial subluxation affects 25% of rheumatoid patients of whom 25% have neurological signs. Atlanto-axial subluxation may occur in lateral, rotational, anterior, posterior and vertical directions; the latter three directions being the most neurologically significant. Rheumatoid arthritis may affect the spinal cord caudal to the C1/C2 level independently or in association with a high cord lesion. Postmortem studies of myelopathy show necrosis, gliosis and Wallerian degeneration within ascending and descending white matter (Fujiwara et al., 1999). The degree of atlanto-axial subluxation is well characterized by plain flexion–extension radiography; however, because a large part of the compression is due to inflammatory soft tissue proper assessment requires magnetic resonance imaging (Rogers et al., 1994).

In a series of 235 rheumatoid patients referred for neurosurgical assessment of craniocervical junction instability 60% had myelopathy, the majority of these either had motor or mixed motor and sensory long-tract signs; in approximately 10% the predominant deficits were loss of joint position and Rombergism, indicating a mainly posterior compression. Cranial nerve signs and nystagmus were rare and in this series were associated with other pathologies especially Chiari malformation (Rogers et al., 1994). The combination of mild neurological impairment and rheumatological/orthopedic problems puts rheumatoid patients at increased risk of falls and even minor cervical injury can produce catastrophic neurological deterioration. Atlanto-axial subluxation increases the anesthetic risk due to neck extension during artificial ventilation. Surgical treatment of these patients requires posterior stablization. However, in patients with irreducible subluxation and anterior neuroaxis compression, transoral decompression is undertaken first.

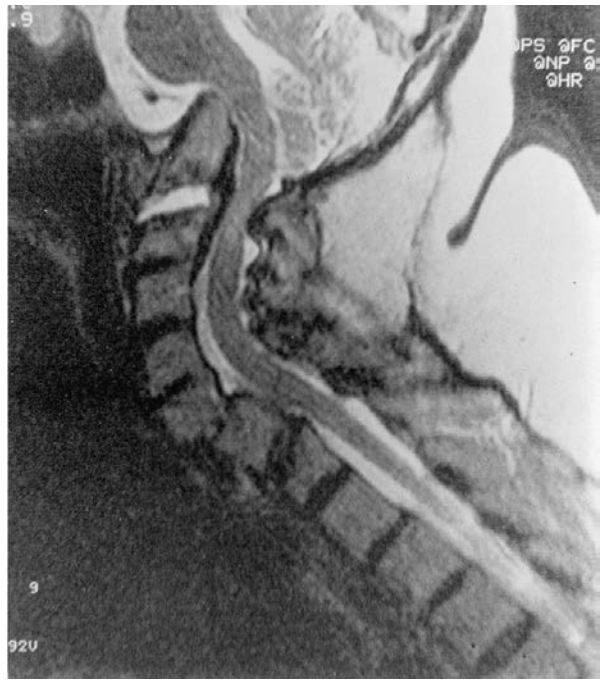

Fig. 49.9. Sagittal MRI of a patient with rheumatoid arthritis showing hind-brain compression from atlanto-axial involvement and multilevel degenerative disease of the cervical spine.

Selection of appropriate patients for surgical intervention presents a major clinical problem. The policy of waiting until rheumatoid patients with atlanto-axial subluxation develop signs of serious myelopathy has been strongly challenged on the basis that once spinal cord damage has been sustained it is rarely reversible (Fig. 49.9). In a prospective trial it has been shown that, following surgical stabilization with or without transoral anterior decompression, approximately 60% of ambulant patients will show stabilization or improvement of their functional status, in contrast only 20% of non-ambulant patients will show any recovery (Casey et al., 1996). Furthermore, surgical morbidity and mortality were found to be significantly higher in the non-ambulant (12.7%) compared to the ambulant group (8.9%).

Spondyloarthropathies

The inflammatory spondyloarthropathies include ankylosing spondylitis, psoriatic arthritis, arthritis associated with inflammatory bowel disease and reactive arthritis, e.g. Reiter's disease. Low back pain is common to all conditions. The primary neurological manifestations are best

represented through consideration of ankylosing spondylitis, although they may also occur in association with the other spondyloarthritides.

Ankylosing spondylitis usually presents with gradual onset low back pain and stiffness of the large joints. The condition can affect other organ systems. Men are affected more than women. Disease onset is typically before age 40. HLA B27 is strongly associated with in excess of 90% of patients expressing the antigen. The pathological hallmark is the development of enthesopathy, that is inflammation around sites of tendonous insertion. In the spine syndesmophytes form at the point where spinal ligaments attach to the vertebral bodies.

The neurological manifestations of ankylosing spondylitis are usually a late stage complication. Loss of spinal movement is associated with vertebral body squaring and extensive loss of ligamentous laxity due to syndesmophyte formation. This process produces a rigid spine with kyphosis. Spinal involvement may produce atlanto-axial subluxation, pathological vertebral fracture, discovertebral destruction, spinal canal especially lumbar canal stenosis and a cauda equina syndrome. Atlanto-axial subluxation is rarer than in rheumatoid arthritis; the management issues, however, are similar. Spinal rigidity and disco-vertebral problems predispose to cord compression. Acute spinal cord compression due to epidural hematoma is a recognized problem.

Cauda equina syndrome is a rare late stage complication of ankylosing spondylitis. It presents gradually with leg pain, leg weakness, sensory disturbance and sphinteric dysfunction. On imaging studies posterior lumbar–sacral diverticulae are present. An arachnoiditis may also contribute to the development of the cauda equina syndrome, the presence of the diverticulae, however, indicates that ankylosing spondylitis is the likely cause rather than some other form of arachnoiditis. It is important to remember that spinal irradiation was used to treat ankylosing spondylitis and late radiation neurological damage and bone sarcoma may result.

Superficial siderosis

This is a condition in which there is abnormal subarachnoid hemosiderin deposition. The condition affects many neurological systems and when taken together the symptoms and signs form a coherent and recognizable clinical picture. A recent literature review of 87 cases (Fearnley et al., 1995) revealed the following clinical features: sensorineural deafness (95%), cerebellar ataxia (88%), pyramidal signs (76%), dementia (24%), bladder disturbance (24%), anosmia (at least 17%), aniscoria (at least 10%) and sensory signs (13%). Less frequent features included extraocular motor palsies, and lower motor neuron signs (5–10% each). Neck pain, low back pains and sciatic type pain were well-recognized clinical features. T2-weighted MRI studies of these patients reveal a dark rim, representing the paramagnetic affects of iron deposition, particularly around posterior fossa structures, the spinal cord and occasionally the cerebral hemispheres (Fig. 49.10).

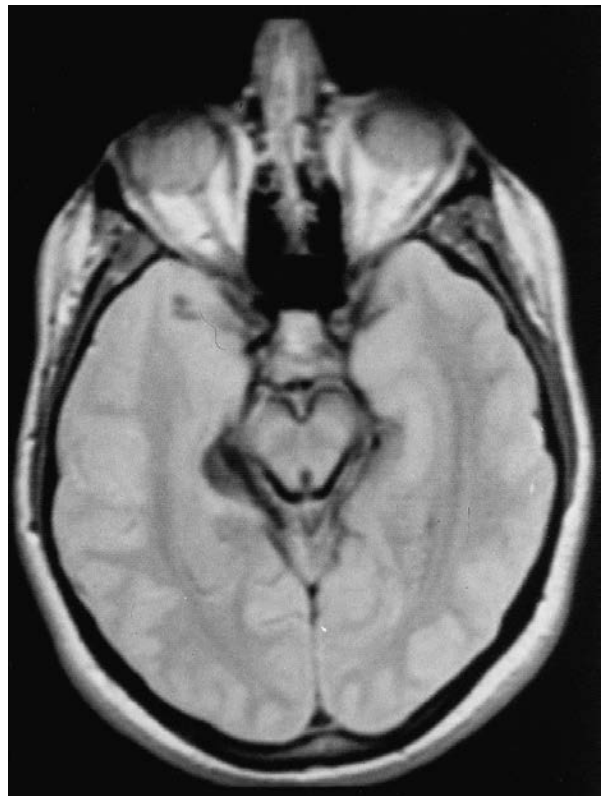

Fig. 49.10. Axial MRI of the brain in a patient with superficial siderosis showing a dark rim around dorsal and ventral mid-brain structures due to iron deposition.

Previous spinal surgery is a recognized cause of superficial siderosis with chronic subarachnoid bleeding due to small blood vessel anomaly. Local spinal pathology affecting the dura such as a root lesion or vascular anomaly is a recognized cause of the condition. The remainder of cases in which a cause may be identified result from subarachnoid hemorrhage or the consequences of hemispherectomy. The serious long-term prognosis of the disorder means an exhaustive search for a bleeding source should be undertaken. This may involve exploratory surgery of a region from which chronic bleeding may occur, for example the site of previous surgery. Successful surgical

ablation of a bleeding source has, in anecdotal accounts, produced arrest of the condition. The role of medical treatment with chelation therapy (trientene) is not established although again anecdotal accounts suggest such treatment may have a role in slowing disease progression.

In conclusion, diseases of the vertebral column are relatively common. However, the neurologist or neurosurgeon will tend to see only those cases at the severe end of the spectrum. A good understanding of these conditions is necessary for diagnosis both of the condition, its neurological sequelae and optimal medical and surgical management.

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50

Cervical pain

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Several terms apply to pain of cervical origin. These include radiculopathy, radicular pain or brachialgia, neck pain, and somatic referred pain. In the past and to some extent still, these terms have been confused, and sometimes used wrongly as equivalent and referring to the same phenomenon. The conditions or symptoms to which these terms refer differ in mechanism and cause; they differ with respect to the investigations required and the treatment that is appropriate. It is important, therefore, not just for taxonomic purposes (Merskey & Bogduk, 1994) but also for clinical purposes, to define how the terms should correctly be used.

Radiculopathy is a condition in which conduction along peripheral nerves is blocked at the level of the spinal nerve or its roots (Merskey & Bogduk, 1994). It is manifest clinically as numbness and/or weakness in a segmental distribution. Reflexes may be impaired according to whether conduction is blocked in Ia afferents or motor efferents or both. Paresthesiae may be another feature, and are indicative of the spinal nerve or its roots becoming ischemic. In essence, radiculopathy is a classical neurological disorder, manifest by objective neurological signs in a segmental distribution. Although pain may be an accompanying feature, it is not a necessary criterion. The diagnosis of radiculopathy is based on the objective neurological signs.

Radicular pain is pain arising from a disorder of a spinal nerve or nerve root (Merskey & Bogduk, 1994). It is perceived in the distribution of that nerve. Accordingly, cervical radicular pain is perceived in the upper limb. For that reason cervical radicular pain is not neck pain. Although neck pain may be a small component of radicular pain, radicular pain is never perceived exclusively in the neck. Its cardinal distribution is in the arm and forearm. Radicular pain may occur in association with radiculopathy, and for that reason it has been customary to group the two into one entity. Doing so, however, creates misconceptions, for not all pain that is associated with radiculopathy is necessarily radicular pain; radicular pain can occur without features of radiculopathy; and radiculopathy can occur without pain.

Neck pain is pain perceived in the cervical region of the spine, i.e. anywhere in the region bounded superiorly by the superior nuchal line, inferiorly by an imaginary transverse line through the T1 spinous process, and laterally by the margins of the posterior cervical muscles (Merskey & Bogduk, 1994). In this regard, it is clearly distinguished from radicular pain for, by definition, it is not perceived in the upper limb. Moreover, neck pain and radicular pain differ in mechanism. Neck pain is nociceptive, i.e. it arises as a result of stimulation of nerve endings in the structure that is the source of pain. In contrast, radicular pain is produced by the generation of ectopic impulses in the affected nerve.

Somatic referred pain is pain perceived in a region innervated by nerves, or branches of nerves, other than those that innervate the actual source of pain (Merskey & Bogduk, 1994). It does not involve the stimulation of nerve roots. Its mechanism involves convergence within the central nervous system between afferents from the two disparate sites. In that regard it is an extension of nociceptive pain. Its causes are the same as those of neck pain.

From the cervical spine, somatic pain can be referred to the head, to the anterior chest wall, to the upper limb girdle, and into the upper limb itself. In this latter distribution it can be confused with, and may be difficult to distinguish from, cervical radicular pain. It is that confusion, in the past, that has perhaps caused disappointment to physicians and their patients. Failure to recognize the difference between somatic referred pain and cervical radicular pain can result in investigations being pursued and treatments being applied for radicular pain when the patient has somatic referred pain; the result being either negative results, or false positive results and failed treatment.

Table 50.1. Less common causes of cervical radiculopathy, listed by structure and pathology

Structure	Pathology
Zygapophysial joint	Ganglion
	Tumour
	Inflammation
	Rheumatoid arthritis
	Gout
	Ankylosing spondylitis
	Fracture
Vertebral body	Primary tumour
	Secondary tumour
	Paget's disease
	Fracture
	Osteomyelitis
	Hydatid
	Hyperparathyroidism
Meninges	Cysts
	Meningioma
	Dermoid cyst
	Epidermoid cyst
Blood vessels	Angioma
	Arteritis
Nerve sheath	Neurofibroma
	Schwannoma
Nerve	Neuroblastoma
	Ganglioneuroma

Source: From Bogduk, 1999.

Radiculopathy

Pathology

There is a large number of possible causes of cervical radiculopathy. In essence, any space-occupying lesion that compromises a cervical spinal nerve or its roots can cause radiculopathy (Bogduk, 1999), (Table 50.1). Rare causes of cervical radiculopathy include conditions that affect the nerve intrinsically or do not involve the anatomic relations of the nerve. These include: giant-cell arteritis (Sanchez et al., 1983), sarcoidosis (Atkinson et al., 1982), Pancoast tumour (Vargo & Flood, 1990), and even intracranial tumour (Clar & Cianca, 1998). However, by far the most common causes of cervical radiculopathy are disc protrusions and cervical spondylosis.

Disc protrusions are described as 'soft' or 'hard'. Soft protrusions consist of nuclear material that is extruded into the vertebral canal in a fairly focal manner. Hard protrusions are masses of disc material, usually in the form of a transverse bar or ridge, and which consist of fibrocartilage or are otherwise rendered hard by being ossified or encased by osteophytes from the vertebral margins.

Disc protrusions are also classified as medial or lateral, according to their principal location and the structures that they affect. Medial protrusions narrow the vertebral canal and affect the spinal cord. They typically cause myelopathy and so, are manifest by long tract signs. Lateral protrusions narrow the intervertebral foramen, and cause radiculopathy. They occur most commonly at the C5–6 and C6–7 levels, less commonly at C4–5, and all but rarely at C3–4 and C7–T1 (Odom et al., 1958; Yamano, 1985; Yoss et al, 1957; Henderson et al., 1983).

Cervical spondylosis is characterized by hard disc protrusions and osteophytes from the uncovertebral region or the zygapophysial joints. These can cause radiculopathy if and when they compromise the spinal nerve in the intervertebral foramen.

Mechanism

There are no experimental data that explicitly reveal the mechanism of radiculopathy. The prevailing view is that conduction block in the affected nerve is produced by compression of the nerve. Either the axons are compressed directly or their blood supply is compromised by the compression. Post-inflammatory scarring is another possibility, but its incidence has not been explicitly determined.

It is probably important not to extrapolate to the cervical spine data from experimental and clinical studies in the lumbar spine. In the lumbar spine, the evidence points to inflammatory processes being cardinal amongst the mechanisms of lumbar radiculopathy (Bogduk & Govind, 1999), but this may not pertain to the cervical spine. Lumbar disc prolapse is an acute event that involves an inflammatory response to the prolapsed material. Whereas this may be analogous to soft protrusions in the neck, it is not analogous to hard protrusions or spinal nerve compression by osteophytes, for which there is no evidence of an inflammatory process.

Clinical features

The characteristic features of cervical radiculopathy are numbness, weakness, paresthesiae, and hyporeflexia, in some combination. Different studies attest to a different relative incidence of these features in patients with surgically proven radiculopathy (Table 50.2), but this may reflect differences in the criteria used by surgeons to justify operation, rather than real differences in incidence.

Table 50.2. Proportion of patients with radiculopathy presenting with the neurological features listed

Ref	N	Numbness	Weakness	Paresthesiae	Hyporeflexia
Gregorius et al., 1976	41	0.60	0.70	–	–
Lunsford et al., 1980	295	0.50	0.35	0.26	0.55
Yoss et al., 1957	100	0.24	0.10	0.65	0.65
Honet and Puri, 1976	82	0.59	0.51	–	0.52
Henderson et al., 1983	841	0.85	0.68	0.99	0.71

Clinical diagnosis

The presence of numbness, weakness, or paresthesiae allows the diagnosis of radiculopathy to be made clinically. Testing for numbness is a reasonably reliable procedure, carrying a kappa score of between 0.45 and 0.64 (Viikari-Juntura, 1987). The validity of clinical examination is also reasonable, but differs according to the criterion standard used (Bogduk, 1999). If the criterion standard is evidence of nerve root compression on CT myelography, neurological signs have high sensitivity, but only moderate to good specificity (Viikari-Juntura et al., 1989), resulting in positive likelihood ratios of only between 2 and 4 (Bogduk, 1999). Better figures arise when surgical findings are used as the criterion standard, and in the context of determining the segmental level.

For correctly detecting a C6 radiculopathy, the likelihood ratio of numbness in the C6 dermatome is 2.7, and that of biceps weakness is 3.4. For a decreased biceps jerk the likelihood ratio is 4.8, and that of paresthesiae in the C6 dermatome is 3.2 (Bogduk, 1999). For correctly detecting C7 radiculopathy, the likelihood ratio of C7 numbness is 4.4; that of triceps weakness is only 2.0; but that of a decreased triceps reflex is 3.8 (Bogduk, 1999). Paresthesiae in the C7 dermatome has a likelihood ratio of 7.7, and is therefore the strongest indicator of C7 radiculopathy (Bogduk, 1999).

The axial compression test (An, 1996; Spurling & Scoville, 1944) has good reliability (Viikari-Juntura, 1987). Adding the compression test to the neurological examination increases diagnostic confidence considerably, by increasing specificity (Viikari-Juntura et al., 1989), and raising the likelihood ratio to more than 8.0 (Bogduk, 1999). Other tests, such as the arm abduction test (Beatty et al., 1987; Davidson et al., 1981; Fast et al., 1989), and manual traction on the neck (Viikari-Juntura et al., 1989) are highly specific but poorly sensitive (Viikari-Juntura et al., 1989); and when added to the examination do not improve diagnostic confidence (Bogduk, 1999).

In essence, radiculopathy can be strongly suspected when the patient presents with some combination of numbness, weakness, paresthesiae, and hyporeflexia, in a segmental distribution. Diagnostic confidence is increased if a compression test is added, but other clinical tests are not contributory and are superfluous. The affected segment can be determined quite well from a good clinical examination alone.

Investigations

Nerve conduction tests do not aid in establishing the diagnosis of cervical radiculopathy (Bogduk, 1999). Clinical examination provides sufficient diagnostic confidence to make 'confirmation' by nerve conduction tests superfluous. Nor does electromyography help in pinpointing the affected segment (Bogduk, 1999). Nerve conduction tests are required only when the clinical picture is not distinctly one of radiculopathy, and the possibility arises of a peripheral neuropathy being the cause of the symptoms and signs.

Nor is medical imaging required to make the diagnosis of radiculopathy, in the first instance. Its role, rather, is to identify the actual cause of the radiculopathy. For this purpose, MRI has a greater sensitivity and specificity than CT or CT myelography, for it can better resolve soft-tissue lesions, and detect them sooner (Bogduk, 1999). Any deficiency of MRI in resolving small bony lesions can be overcome by supplementing MRI with a plain film (Kaiser & Holland, 1998).

Treatment

In considering treatment, it is important to distinguish radiculopathy from radicular pain. If radiculopathy is due to compression of nerve roots, there is no reason, *a priori*, to believe or to expect that physical therapy, drug therapy, or exercise will somehow relieve that compression. Indeed, there are no data from descriptive studies, let alone from controlled trials, to indicate that any form of conservative therapy is of benefit expressly for cervical radiculopathy. Surgical decompression is the only definitive form of management.

Radicular pain

Causes

No literature explicitly lists the causes of cervical radicular pain. Instead, because radicular pain has usually been considered in conjunction with radiculopathy, radicular pain has conventionally been attributed to the same conditions as cause radiculopathy. Accordingly, the most common causes of cervical radicular pain are cervical disc protrusions and cervical spondylosis.

Mechanisms

There are also no data on the mechanisms explicitly of cervical radicular pain. Such experiments as have been conducted, both in animals (Howe, 1979; Howe et al., 1977) and in human subjects (MacNab, 1972; Smyth & Wright, 1959), pertain to lumbar radicular pain. Those experiments show that compression or traction of normal nerve roots evokes paresthesiae or numbness, but does not cause pain. For a nerve root to produce pain it has to be inflamed. However, compression of a dorsal root ganglion does evoke activity in nociceptive afferents. Therefore, it would seem that for compression to be a mechanism of cervical radicular pain, the dorsal root ganglion of the affected nerve has to be compressed. The specific pathophysiological mechanism would appear to be the generation of ectopic impulses from the ganglion, although this has yet to be explicitly demonstrated experimentally.

Clinical features

Rules that maintain that radicular pain follows a dermatomal pattern (Ahlgren & Garfin, 1996) are wrong. Experimental studies, in which cervical nerves have been stimulated mechanically with a needle, show that radicular pain is perceived widely over areas not encompassed by any single dermatome (Slipman et al., 1998). Moreover, regardless of the segment involved, cervical radicular pain is perceived proximally over the scapular region and shoulder girdle, where the corresponding dermatome is not represented. Furthermore, it is perceived deeply and, indeed, more so than in areas of skin.

This should not be surprising, even though it may seem contrary to popular wisdom. If a dorsal root ganglion is compressed and causes pain, all afferents subtended by that ganglion are likely to be affected, not just those from the corresponding dermatome. That includes afferents from deep tissues such as muscles, ligaments and joints. This would seem to be the basis of the deep, gnawing pain that accompanies stimulation of a cervical spinal nerve.

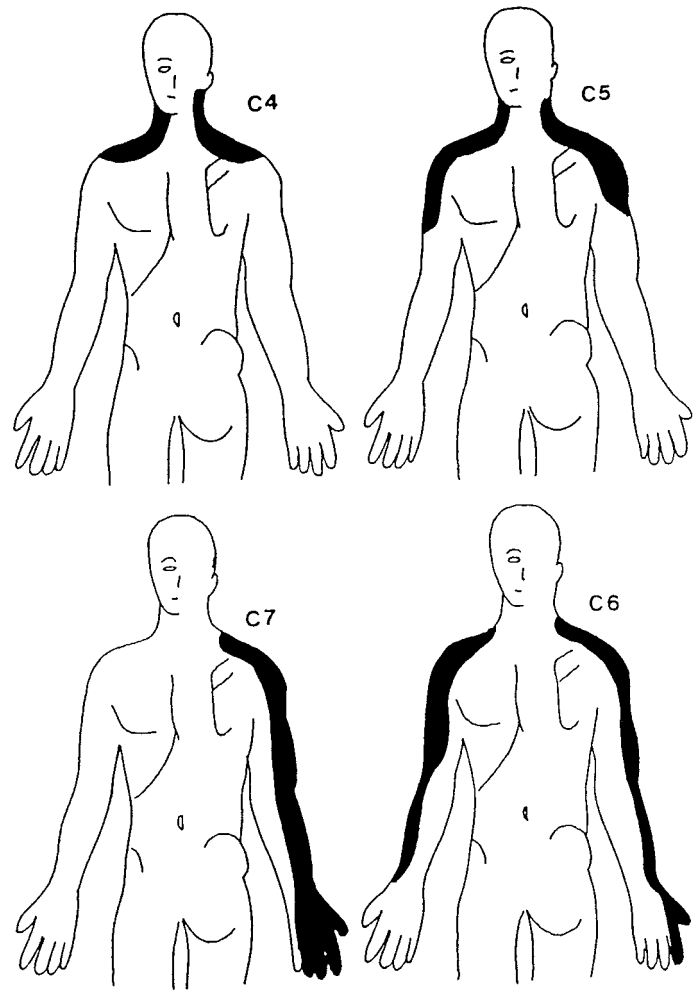

Fig. 50.1. Maps of the most common and consistent distributions of pain evoked by mechanical stimulation of the C4, C5, C6, and C7 spinal nerves. (Based on Slipman et al., 1998. Reproduced, with permission, from Bogduk, 1999.)

Although cervical radicular pain is not dermatomal, it can be portrayed as following a nevertheless segmental pattern, referred to as dynatomal (Slipman et al., 1998). Although the pain may extend to other areas, and although particular dynatomes differ from individual to individual, the areas in which radicular pain is most often and most consistently perceived are illustrated in Fig. 50.1. Quite clearly, the areas are not dermatomes, even though some do overlap the corresponding dermatome, although only in part. Conspicuously, the dynatomes for C6 and for C7 radiate from over the shoulder into the distal upper limb. They are not restricted to the forearm

and hand. The dynatomes for C4 and C5 are not distinguishable from one another clinically; but those of C6 and C7 are distinguished from C5 by their distal extent. However, although the C7 dynatome extends somewhat more posteriorly over the forearm than does the C6 dynatome, C7 radicular pain cannot be reliably distinguished from C6 pain.

Diagnosis

An important realization is that not all pain in the upper limb is necessarily radicular pain. Radicular pain needs to be distinguished from somatic referred pain (q.v.). This becomes particularly pertinent when pain is the only clinical feature, i.e. neurological signs are absent.

If features of radiculopathy are present, any accompanying pain in the upper limb is likely to be radicular in origin, particularly if it extends distally into the forearm. In that event, however, the pain and its distribution do not bear on the diagnosis. The diagnosis rests on the features of the radiculopathy. It is the segmental distribution of numbness, weakness, paresthesiae, and hyporeflexia that implicate a radiculopathy and its segmental level. It is only the association with radiculopathy that permits the assumption that the pain is radicular.

Investigations

No investigations confirm or help in the diagnosis of cervical radicular pain. Nerve conduction tests and medical imaging may be applied in the pursuit of radiculopathy, but they demonstrate nothing about pain. If medical imaging demonstrates nerve root compression, it explains the radiculopathy. Any relationship with pain is only inferential. Medical imaging does not show pain. Indeed, cervical radicular pain bears only a weak relationship with radiological signs of nerve root compression (Viikari-Juntura et al., 1989). Neither is dependably predictive of the other. Therefore, whereas it may be appropriate to undertake medical imaging for radiculopathy, it is not appropriate for the investigation of pain.

Natural history

There are few data on the natural history of cervical radicular pain. On the basis of anecdotal reports, cervical radicular pain seems to have a favourable natural history (Dillin et al., 1986; Persson et al., 1997). In studies of conservative therapy, some 70% of patients treated with placebo improve, and 20% lose all symptoms (British Association of Physical Medicine, 1966). In one survey of 561 patients, 90% were considered normal or only mildly incapacitated at 5 years (Radhakrishan et al., 1994).

Treatment

It has been traditional to treat cervical radicular pain conservatively. However, the literature is quite vague about what constitutes conservative therapy. By default, it is any therapy that occurs before surgery. The literature that provides information embraces various combinations of drug therapy, physical therapy, traction, collars, bed rest, exercise and transcutaneous electrical nerve stimulation (Bogduk, 1999).

The few controlled trials available paint a sobering picture of the efficacy of conservative therapy for cervical radicular pain. One study found no difference in outcome for patients treated with traction, sham traction, collar, heat, or placebo (British Association of Physical Medicine, 1966). Another study compared neck exercises, traction, and no treatment (Goldie & Landquist, 1970). According to the patients, a greater proportion of those receiving no treatment failed to improve. According to the physician's assessment, there was no difference between the three groups. In a rigorous study of patients with chronic radicular pain due to cervical spondylosis, weighted traction proved no better than placebo traction, in terms of pain scores, sleep disturbance, social dysfunction, and activities of daily living (Klaber-Moffett et al., 1990).

Some studies in the pain literature promote the use of epidural injections of steroids for cervical radicular pain. No controlled studies validate this therapy, and the descriptive studies are far from compelling. Collectively, they attest to between 0% and 30% of patients obtaining complete relief, and a similar proportion of patients obtaining 75% relief (Bogduk, 1999). One descriptive study has promoted fluroscopically-guided, transforaminal injection of steroids, but provides incomplete data on efficacy (Bush & Hillier, 1996).

Surgery is ultimately the mainstay of treatment for cervical radicular pain. According to descriptive studies it offers a high yield of successful results, irrespective of the technique used (Bogduk, 1999). There has been only one controlled study of surgery for cervical radicular pain (Persson et al., 1997). Patients were randomly allocated to treatment by physiotherapy, a collar, or surgery. At 4 months follow-up, all groups had improved, and the surgery group had less pain; but this difference was extinguished by 12 months. However, fewer than 10% of patients in each group were free of pain at 12 months. This low success rate is inconsistent with the reputed efficacy of surgery for cervical radicular pain.

Somatic referred pain

The early clinical experiments on somatic referred pain determined the distribution of pain when noxious stimuli were administered to interspinous muscles in normal volunteers (Kellgren, 1939; Feinstein et al., 1954). The patterns of distribution observed were segmental, but did not correspond to dermatomes (Fig. 50.2). The significance of these studies was that they showed that pain referred into the upper limb could be produced by means other than the stimulation of spinal nerves or nerve roots. For clinical purposes, these studies established that not all pain referred to the upper limb was necessarily radicular.

More recent studies have examined the patterns of distribution of pain in normal volunteers from particular structures in the cervical spine other than the interspinous muscles. These include the atlanto-axial and atlanto-occipital joints (Dreyfuss et al., 1994), and the cervical zygohypophyseal joints (Dwyer et al., 1990). The patterns observed are quasi-segmental but unrelated to dermatomes (Fig. 50.3). Similar patterns of pain have been noted in patients with neck pain undergoing cervical disc stimulation (Grubb & Kelly, 2000). This similarity indicates that patterns of referred pain do not reflect the structure that is the source of pain, but they do relate to its innervation. Structures with the same segmental innervation will produce referred pain in similar areas.

Somatic referred pain is not a separate diagnostic entity. It is just a physiological phenomenon. Since it can arise from virtually any structure in the neck its sources and causes are the same as those of neck pain.

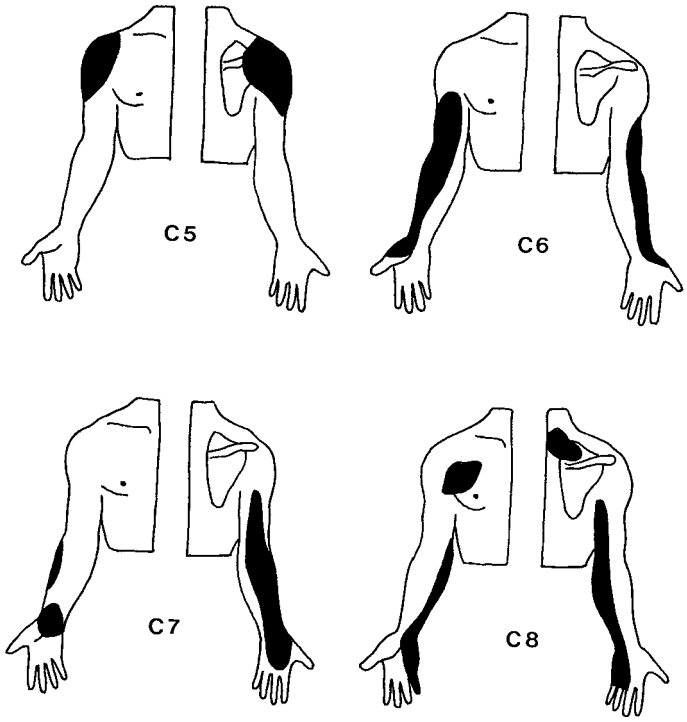

Fig. 50.2. Maps of the distribution of somatic referred pain elicited in normal volunteers by noxious stimulation of the interspinous ligaments. (Based on Kellgren, 1939.)

Neck pain

Epidemiology

Neck pain is common. Acute neck pain affects some 10% of the community, and the prevalence of chronic neck pain is about 14% (Bovim et al., 1994; Makela et al., 1991; van der Donk et al., 1991; Lawrence, 1969). It is more common among manual workers, office workers, secretaries and sewing machine operators (Vasseljen & Westgaard, 1995; Kamwendo et al., 1991; Westgaard & Jansen, 1992).

Etiology

The possible causes of neck pain can be classified as serious or non-threatening conditions, and as common or uncommon conditions (Table 50.3). Known causes involving demonstrable pathology are uncommon.

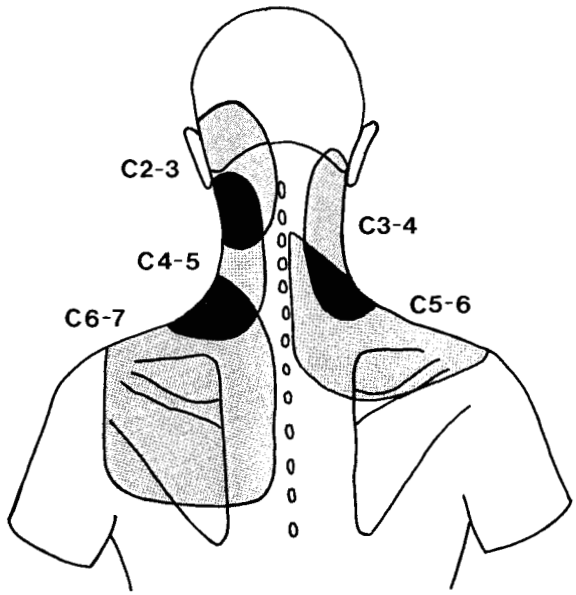

Fig. 50.3. Maps of the distribution of referred pain elicited in normal volunteers by noxious distension of the cervical zygapophysical joints. (Based on Dwyer et al., 1990.)

Table 50.3. The causes of neck pain grouped according to whether they are common and serious

	Non-threatening	Serious
Uncommon	Rheumatoid arthritis Ankylosing spondylitis Reiter's syndrome Psoriatic arthritis Crystal arthropathies	Fractures Tumours Spinal infections Dissecting aneurysms Spinal hematomas Metabolic disorders
Common	Cervical spinal pain of unknown origin Acceleration-deceleration Injuries of the neck Zygapophysial joint pain Discogenic pain	

Neck pain can occur in patients with rheumatoid arthritis, but it is unlikely to be the sole presenting feature. Fewer than 2% of patients with rheumatoid arthritis have neck pain as their only feature (Sharp et al., 1958). Rheumatoid arthritis becomes potentially serious if it affects the C1–2 joints, but even then the prognosis is favourable (Isdale & Conlon, 1971). Some 10% of patients with ankylosing spondylitis may present with neck pain (Hochberg et al., 1978), but the rarity of ankylosing spondylitis renders it an uncommon cause of neck pain.

Tumours, infections and metabolic disorders are very uncommon causes of neck pain. Although their prevalence has not been explicitly established, the failure of large radiological surveys to detect such conditions (Heller et al., 1983; Johnson & Lucas, 1997) implies that their prevalence is less than 0.4% in primary care.

Headache is the most common presenting feature of internal carotid artery dissection, but neck pain has been the sole presenting feature in some 6% of cases (Silbert et al., 1995; Biousse et al., 1994). In 17% of patients headache may occur in combination with neck pain (Biousse et al., 1994). Neck pain has been the initial presenting feature in 50% to 90% of patients with vertebral artery dissection, but is usually also accompanied by headache, typically in the occipital region although not exclusively so (Silbert et al., 1995; Sturzenegger, 1994). Although the typical features of dissecting aneurysms of the aorta are chest pain and cardiovascular distress, neck pain has been reported as the presenting feature in some 6% of cases (Garrard & Barnes, 1996; Hirst et al., 1958).

Although considered common, and feared as a cause of neck pain (for medicolegal reasons), fractures of the neck are actually not common. In accident and emergency settings, only about 3% of patients suspected of having a fracture prove to have fractures upon cervical radiography (MacNamara, 1988; Bachuklis et al., 1987; Roberge et al., 1988; Kreipke et al., 1989; Hoffman et al., 1992; Gerrelts et al., 1991).

Missing from Table 50.3 are cervical spondylosis and cervical osteoarthrosis. Although hallowed by tradition, these entities defy legitimate diagnosis. Clinically, they are indistinguishable from any other cause of neck pain. The only available diagnostic criterion are the radiological features of these conditions, but these features are only age-changes. They correlate poorly with neck pain (Heller et al., 1983). Indeed, cervical osteoarthrosis is more common in patients with no neck pain (Fridenberg & Miller, 1963).

For patients with neck pain whose cause is not apparent, the International Association for the Study of Pain recommends the rubric: cervical spinal pain of unknown origin, as an honest diagnosis (Merskey & Bogduk, 1994). Acceleration– deceleration injury, or whiplash, is perhaps the most common traumatic basis for neck pain. However, it does not constitute a diagnosis in a patho-anatomic sense. It is a label that simply recognizes the reported circumstances of onset of neck pain. Zygapophysial joint pain and discogenic pain are specific subsets of what otherwise might be known as 'mechanical' neck pain but their diagnosis requires invasive procedures such as zygapophysial joint blocks and disc stimulation (q.v.).

Although favoured by many, there is no evidence that trigger points are a cause of neck pain. Even in the hands of experts, the diagnosis is unreliable (Wolfe et al., 1992); and the absence of a criterion standard means that its validity cannot be tested. Furthermore, trigger points in the neck do not satisfy the prescribed criteria for a trigger point. They are characterized solely by tenderness and reproduction of pain, in which regard they cannot be distinguished from tenderness of underlying zygapophysial joints (Bogduk & Simons, 1993).

Whiplash

Neck pain due to whiplash is distinguished by an onset attributed to a motor vehicle accident. In western societies the incidence of reported whiplash accidents is about 1 per 1000 population per year (Barnsley et al., 1994a, 1998). However, that is not to say that all cases develop neck pain. The natural history of neck pain attributed to whiplash is quite benign. Within 12 months some 75% of victims are asymptomatic, with the figure rising to 82% by 2 years. This leaves some 20% of patients still with symptoms, but only 4% are severely disabled (Radanov et al., 1995). The prevalence, in the general community, of chronic neck pain due

to whiplash has been calculated as about 1% or less, making it only a fraction of the causes of chronic neck pain (Barnsley et al., 1994a, 1998).

Given the natural history of neck pain after whiplash, the majority of patients must sustain no substantive injury to their neck. Perhaps they suffer a minor muscle sprain, or simply jarring of their neck. However, a minority of patients suffer definite injuries.

Rare injuries include disruption of the alar ligaments, prevertebral hematoma, perforation of the oesophagus, tears of the sympathetic trunk, damage to the recurrent laryngeal nerve, spinal cord injury, periplymph fistula, thrombosis or traumatic aneurysms of the vertebral or internal carotid arteries, retinal angiopathy, and anterior spinal artery syndrome (Barnsley et al., 1994a, 1998). Fractures after whiplash are so uncommon as to be rare. Such fractures as have been attributed to whiplash have been reported only in case studies or small, descriptive series. These fractures may be difficult to detect on conventional investigations, and special attention needs to be paid to their possibility if they are to be detected. The majority involve the upper cervical spine, and include fractures of the odontoid process (Seletz, 1958; Signoret et al., 1986), the laminae and articular processes of C2 (Seletz, 1958; Signoret et al., 1986; Craig & Hodgson, 1991), and the occipital condyles (Stroobants et al., 1994). In one study of 283 patients with acute neck pain after whiplash, however, no fractures were found on plain radiography (Hoffman et al., 1992). This result implies a prevalence of less than 1.3%.

The most likely lesions that underlie chronic neck pain after whiplash are injuries to the intervertebral discs and zygapophysial joints. Cineradiography studies in normal volunteers undergoing simulated whiplash collisions reveal that at some 100 msec after impact, the cervical spine undergoes a sigmoid deformation, during which the lower cervical vertebrae undergo extension about an abnormal axis of rotation (Kaneoka et al., 1999). The movement is such that the anterior edges of the vertebral bodies separate and the zygapophysial joints impact. These movements indicate that the anterior anulus fibrosus can be sprained while the zygapophysial joints can suffer impaction fractures or contusions to their meniscoids (Kaneoka et al., 1999). These are the very lesions that have been demonstrated in postmortem studies of victims of motor vehicle accidents (Jonsson et al., 1994; Taylor & Twomey, 1993; Taylor & Taylor, 1996).

Clinical diagnosis

Critical to the clinical assessment of neck pain is a thorough and careful history. A history of substantial trauma warns of the possibility of fracture, or of vascular injury. Past medical history, current general health, and associated features provide clues to possible serious causes of neck pain. A past history of cancer, weight loss, and ill health, warn of tumour. Transient ischemic episodes warn of vertebral or carotid aneurysms. Arthropathy elsewhere in the body warns of inflammatory joint disease. Neck pain in the elderly warrants consideration of myeloma and Paget's disease. Hyperparathyroidism is a possible cause of spinal pain that is easily overlooked because of its rarity. Neurological symptoms, however, convert the presentation from one of neck pain to one of a neurological disorder. In most cases, however, history reveals no medical disorder; the presentation is simply one of neck pain.

Physical examination offers little towards the diagnosis of neck pain. Typically, the patient will be tender in the cervical spine, and will exhibit restriction of neck movements because of pain. Neither of these features, however, is a valid indicator of any particular source or cause of pain.

In this context, neurological examination is immaterial in the assessment of neck pain, for it is not a neurological disorder. Neurological examination is pertinent if the patient has neurological symptoms, but not if pain is the only presenting feature. In that event, a screening neurological examination, looking for weakness or numbness, is all that is warranted.

Special techniques of examination, such the detection of cervical intersegmental motion, have either not been shown to be valid, or have been found to lack reliability, validity or both. For the detection of tenderness over the zygapophysial joints, inter-observer agreement is good, with a kappa score of 0.68 (Hubka & Phelan, 1994). For other signs, particularly those espoused by chiropractors, observer agreement is poor (Gross et al., 1996; Levoska et al., 1991; Sandmark & Nisell, 1995; De Boer et al., 1985; Nansel et al., 1989; Mior et al., 1985; Smedmark et al., 2000).

Plain radiography

Plain radiography for neck pain is indicated only if the physician has grounds to suspect a fracture or some other serious condition. In the absence of such clinical indicators, different guidelines apply. In two large studies, each involving over 1000 patients with neck pain, no instances of unexpected malignancy or infection were found (Heller et al., 1983; Johnson & Lucas, 1997). The British study concluded that 'the request for X-ray films of the cervical spine "just in case" such a finding is present is probably unjustified.' (Heller et al., 1983). The US study found that upon 5-year follow-up 'no medically dangerous diagnoses would

have been missed if the cervical spine series had not been done'. (Johnson & Lucas, 1997).

What plain radiography is likely to reveal in a patient with neck pain is either a normal cervical spine or cervical spondylosis. The features of cervical spondylosis, however, are simply age-related changes. In some studies cervical spondylosis occurs somewhat more commonly in symptomatic individuals than in asymptomatic individuals (van der Donk et al., 1991; Heller et al., 1983), but the odds ratios for disc degeneration or osteoarthritis as predictors of neck pain are only 1.1 and 0.97, respectively, for women, and 1.7 and 1.8 for men (van der Donk et al., 1991). In other studies, the prevalence of disc degeneration, at individual segments of the neck, is not significantly different between symptomatic patients and asymptomatic controls (Fridenberg & Miller, 1963). Non-covertebral osteophytes and osteoarthrosis are less prevalent in symptomatic individuals (Fridenburg & Miller, 1963).

Loss of lordosis is a feature sometimes reported in cervical spine films, but this phenomenon is a normal variant, and carries no diagnostic implication. It is equally prevalent amongst patients with acute neck pain, chronic neck pain and no neck pain (Helliwell et al., 1994). It is independent of age and symptoms but is more common in females (Helliwell et al., 1994).

CT scanning

No data, and no studies, justify the use of CT as a screening test for undiagnosed neck pain. CT may be of use in better defining known or suspected pathology, such as fractures or tumours; it may be of value in defining the cause of radicular pain; but it offers no value in the pursuit of uncomplicated neck pain. Nothing that might be evident on CT has been shown to correlate with any known cause of neck pain.

MRI

In the context of neck pain, magnetic resonance imaging offers little prospect of a positive diagnosis. Nevertheless, because of its high sensitivity for unusual disorders it is the premier screening tool for chronic, undiagnosed neck pain. In that context, however, its utility lies in ruling out undetected disorders rather than in pinpointing the cause of pain. For finding the cause of pain, MRI is as useless as CT. Moreover, it is confounded by the high incidence of so-called abnormalities in totally asymptomatic individuals.

Disc degeneration, disc bulges, spinal stenosis, and even spinal cord impingement occur in asymptomatic individuals, and with increasing frequency with age (Boden et al., 1990; Teresi et al., 1987). Finding such abnormalities does not provide a diagnosis. In the context of whiplash, multiple studies have failed to detect any diagnostic abnormality in patients with uncomplicated neck pain (Ellertsson et al., 1978; Pettersson et al., 1994; Fagerlund et al., 1995; Borchgrevink et al., 1995; Ronnen et al., 1996; Voyvodic et al., 1997).

SPECT scanning

A small study has provided encouraging news concerning the possible utility of single-positron emission tomography (Seitz et al., 1995). It found that, in patients with acute neck pain after whiplash, SPECT could reveal small fractures undetected by plain radiography or obscured by osteoarthrosis of the joint affected. The fractures consisted of small articular fractures and avulsions of the vertebral rims. The optimum time for using SPECT would seem to be at about four to six weeks after injury. However, the utility of SPECT needs to be determined by larger studies before its wholesale application can be justified.

In the context of chronic neck pain, the one study published on SPECT scanning reported no correlation between whether a zygapophysial joint appeared active or not and whether or not it was painful (Barnsley et al., 1992). Thus, there is no proven utility of SPECT in chronic neck pain.

Invasive techniques

It is not surprising that medical imaging lacks utility for the vast majority of patients with neck pain. Pain is a symptom. It cannot be seen on morphological tests. It requires physiological tests. In this regard, two such tests have been advocated.

Disc stimulation

Disc stimulation is a test designed to determine if an intervertebral disc is painful or not. It involves introducing a needle into the centre of the suspected disc, through which contrast medium is injected in order to stress the disc by distending it from within (Bogduk et al., 1995). The recommended criteria for a diagnosis of discogenic pain are that stressing a particular disc reproduces the patient's pain but provided that stressing adjacent discs does not (Merskey & Bogduk, 1994; Bogduk et al., 1995).

Although championed in some quarters, cervical disc stimulation is fraught with persisting problems. Cervical discs are painful even in asymptomatic individuals.

However, they are not particularly painful. Therefore, it is recommended that the criteria for discogenic pain include reproduction of pain to a level of at least 7 on a 10-point visual analogue scale (Schellhas et al., 1996).

Even so, cervical disc stimulation is compromised by false-positive responses. Disc stimulation can be positive in patients in whom the zygapophysial joints of the same segment are actually the source of pain (Bogduk & Aprill, 1993). Consequently, discogenic pain cannot be diagnosed unless it is shown that other joints in the same segment are not painful.

Furthermore, a recent study has shown that cervical discs are infrequently symptomatic at single levels (Grubb & Kelly, 2000). Positive responses are commonly encountered at two, three, and even four levels or more. The assessment of the patient is, therefore, not complete unless and until all levels are studied; which makes cervical disc stimulation a demanding procedure. If disc stimulation is undertaken at only one, two, or three, preferred or habitual levels, the likelihood of a false-positive result is high.

The one virtue of cervical disc stimulation is that, if multiple discs are found to be symptomatic, surgery is not indicated. Disc stimulation, therefore, plays an important role in reducing unnecessary and futile cervical surgery (Grubb & Kelly, 2000).

Zygohypophyseal joint blocks

Zygohypophyseal (Z joint) blocks can be used to test if a zygohypophyseal joint is the source of a patient's neck pain. They involve anesthetizing, under fluoroscopic control, the small nerves that innervate the target joint, each with not more than 0.3 ml of local anesthetic (Bogduk & Lord, 1998). Z joint blocks have face-validity, in that they selectively anesthetize the target nerves, and do not anesthetize any nearby structures that realistically might be the source of pain (Barnsley & Bogduk, 1993). Single diagnostic blocks, however, are not valid. They carry a false-positive rate of some 27% (Barnsley et al., 1993a). Controls are, therefore, required in each and every patient. When performed under controlled conditions, Z joint blocks have proven construct validity (Barnsley et al., 1993b).

Depending on the circumstances, either placebo controls or comparative diagnostic blocks can be used (Bogduk & Lord, 1998). Comparative blocks involve the administration, on separate occasions, of local anesthetic agents with differing durations of action (Barnsley et al., 1993a). A valid response is one in which the patient obtains a duration of relief concordant with the expected duration of action of the agent administered, i.e. long-lasting relief when a long-acting agent is used, and short-lasting relief when a short-acting agent is used. Controlled studies have shown that diagnostic decisions based on this paradigm are robust (Lord et al., 1995).

Epidemiological studies, using double-blind, controlled, diagnostic blocks, have shown that zygapophysial joint pain is the single most common basis of chronic neck pain after whiplash. On worst-case figures, it accounts for at least 49% of patients (Barnsley et al., 1995; Lord et al., 1996a). In patients with neck pain after severe motor vehicle accidents, the prevalence of Z joint pain is as high as 80% (Gibson et al., 2000). The joints most commonly involved are C5–6 and C6–7 in patients with neck pain and somatic referred pain to the shoulder girdle, and C2–3 in patients with neck pains and headache (Lord & Bogduk, 1996). In patients in whom headache is the dominant symptom, the source of pain can be traced to the C2–3 joint in some 53% of cases (Lord et al., 1994).

Of all the possible diagnostic tests that might be applied to a patient with neck pain, Z joint blocks are the only validated test. Of all the possible causes of chronic neck pain, Z joint pain is the only proven entity, and is the most common cause after whiplash.

Conservative therapy

Many treatments have been used and recommended for neck pain (Bisbee & Hartsell, 1993; Greenman, 1993; Tessell et al., 1993). These include, rest, collars, exercises, posture control, physical therapy, traction, manual therapy, analgesics, trigger point injection, epidural steroids, craniosacral manipulation, and manipulation under general anesthesia. Compelling evidence of efficacy is lacking for most of these interventions. For others the evidence indicates lack of efficacy.

A systematic review of physical and manual therapies (Aker et al., 1996) detailed the positive and negative studies and, where possible, calculated effect sizes of various therapies. Some therapies were reported as having no effect above comparison therapies; others were found to have a positive effect. However, the review did not address the duration of positive effects or their clinical significance; nor did it address outcome measures such as the proportion of patients obtaining complete relief. The only outcome measure used to identify positive effects was improvement of pain, in terms of the mean or median scores on a visual analogue scale. The review was satisfied with statistically significant improvement beyond control as the cardinal, if not only, measure of successful therapy.

Despite its graciousness in this regard, the review nonetheless concluded that:

> there is early evidence to support the use of manual treatments in combination with other treatments for short term pain relief, but in general, conservative interventions have not been studied in enough detail to assess efficacy or effectiveness adequately (Aker et al., 1996).

A less gracious appraisal of the literature (Bogduk, 1998) provides a more alarming view. For acute neck pain not due to whiplash, spray and stretch therapy (Snow et al., 1992) and laser acupuncture (Thorsen et al., 1992) are no more effective than placebo. Traction is not discernibly more effective than isometric exercises (Goldie & Landquist, 1970), and when combined with other interventions, traction offers no advantage over traction alone (Caldwell & Krusen, 1962). Neck school is no better than no treatment (Kamwendo & Linton, 1991). One study reported that, immediately after treatment, manipulation combined with azopropazone afforded greater relief of pain than treatment with azopropazone alone, but the difference was extinguished one and three weeks later (Howe et al., 1983). In another study, there was no significant difference at 3 weeks between patients receiving one to three manipulations and those treated with a muscle relaxant (Sloop et al., 1982).

For chronic neck pain not due to whiplash, there are no studies of the efficacy of exercise, collars, TENS, neck school, spray and stretch, or traction. Wearing magnetic necklaces is no more efficacious than placebo (Hong et al., 1982). Laser acupuncture is no more effective than sham transcutaneous electrical nerve stimulation (TENS) (Lewith & Machin, 1981); and needle acupuncture is no more effective than sham acupuncture or an injection of diazepam (Thomas et al., 1991), or sham TENS (Petrie & Langley, 1983; Petrie & Hazelman, 1986). Compared to no treatment, a programme of gymnastics was found to offer no therapeutic benefit (Takala et al., 1994).

In a study that focused on manipulation for back pain, 64 patients with neck pain were treated (Koes et al., 1992). Separate data on these patients were not reported in the original publication, but subsequent analysis found no statistically significant differences in response between those patients receiving manual therapy and those receiving physiotherapy and general practice care (Hurwitz et al., 1996). Another study compared manipulation, physiotherapy, and being treated with salicylate (Brodin, 1984, 1985). It reported a statistically significant benefit from manipulation. Analysis of the data, however, reveals that the difference arose because of poorer outcomes in the patients treated with physiotherapy. Between the outcomes of patients treated with manipulation and those treated with salicylate, there was no statistically significant difference.

In a methodologically strong study (Foley-Nolan et al., 1990) pulsed electromagnetic therapy delivered through a collar was found to have a significantly greater effect on pain than a collar alone. The difference arose, however, because of a greater proportion of patients in the active treatment group reporting 'moderately better' as opposed to 'no change' in the control group. The number of patients 'completely well' or 'much better' was not significantly different in the two groups. The study did not report the duration of effect for any period after cessation of treatment.

For acute neck pain after whiplash, the Quebec Task Force on Whiplash Associated Disorders attempted a major synthesis of the literature available up to September 1993, but was unable to compose a systematic review or meta-analysis (Spitzer et al., 1995). Out of 10382 potentially relevant articles, only 62 were accepted as both relevant and scientifically meritorious. The Task Force concluded that: 'the evidence was found to be sparse and generally of unacceptable quality' (Spitzer et al., 1995).

Rest and analgesia (McKinney et al., 1989), combinations of TENS, ultrasound and pulsed electromagnetic therapy (Provinciali et al., 1996), and soft collars (McKinney et al., 1989; Foley-Nolan et al., 1992; Mealy et al., 1986), have each been used in controlled studies as reference treatments, and each has been found to be inferior to other interventions. Traction offers no additional benefit when added to instruction, moist heat and exercise (Zylbergold & Piper, 1985), and is no better than rest in a collar (Pennie & Agambar, 1990). Receiving pulsed electromagnetic therapy delivered from a device implanted in a collar affords greater improvement in pain than wearing the same collar with a dummy device (Foley-Nolan et al., 1992); but the difference is apparent only for the first four weeks of treatment; by 12 weeks electromagnetic therapy affords no advantage.

The application of ice for the first 24 hours after injury, followed by mobilization, local heat, exercises and analgesia is superior to rest, analgesia and a soft collar (Mealy et al., 1986), at 4 weeks and 8 weeks after treatment, but no long-term data are available. Active out-patient physiotherapy (consisting of a tailored programme of hot and cold applications, short-wave diathermy, hydrotherapy, traction, and mobilization), and a home-exercise programme both achieve greater improvements than rest and analgesia, at one month and two months after treatment, but active physiotherapy is not superior to home exercises alone (Provinciali et al., 1996). In a long-term follow-up,

however, home exercises achieved a greater proportion of patients free of pain (McKinney, 1989).

So-called 'multimodal therapy', consisting of relaxation training, reduction of cervical lordosis, psychological support, eye fixation exercises, and massage and mobilization, is superior to applications of TENS, pulsed electromagnetic therapy, ultrasound, and calcic iontophoresis, at 2 weeks and 4 weeks after therapy (Provinciali et al., 1996); but in the long term, results are no better than those achieved by other and simpler means, including rest and analgesia and wearing a collar.

In essence, the combined data on physical and manual therapy, do show that intervention is superior to rest and analgesia, but the impact pertains to a decrease in average pain score, and is evident only at 4 to 8 weeks after onset of pain. Thereafter, either there are no data or the suggestion that patients not treated actively eventually achieve the same degree of recovery. The impact of physical and manual therapy is to achieve not resolution in a greater proportion of patients but a more rapid resolution in the early weeks after onset of pain. The only long-term data indicate that a greater proportion of patients achieve complete recovery when treated with home exercise.

A challenging observation has been a study in which an index treatment was compared with rest, analgesia and a collar. At 6 months and at 1 year after treatment, there were few differences, but the results favoured the index treatment. That treatment was reassurance, a direction to resume normal activities, and denial of sick-leave (Borchgrevink et al., 1998).

For chronic neck pain after whiplash, there is no evidence of the efficacy of any conservative therapy. Even the Quebec Task Force (Spitzer et al., 1995), in its consensus approach, recommended no specific therapy. For patients still unresolved by 12 weeks, it recommended only evaluation by a multidisciplinary team, without venturing what sort of management this might result in, and without offering any evidence of the efficacy of multidisciplinary pain management.

Medical therapy

There are no data explicitly demonstrating the efficacy of analgesics, non-steroidal anti-inflammatory agents, or other drugs, for neck pain of any nature (Spitzer et al., 1995). If such agents are used, it is on the basis of presumed efficacy, but should be in the full knowledge that, for neck pain, they may be no more effective than placebo.

No studies have demonstrated the efficacy for neck pain of any form of injection into the neck, be that using local anesthetic, sclerosing agents, or corticosteroids. For chronic neck pain stemming from the zygapophysial joints, intra-articular injections of corticosteroids are no more effective than injections of local anesthetic, and both treatments fail to achieve sustained relief in more than a minority of patients (Barnsley et al., 1994b).

Surgical therapy

There is no compelling evidence of the efficacy of cervical fusion for neck pain. Such studies as have reported on this therapy claim success (Kikuchi et al., 1981; Whitecloud & Seago, 1987) but outcome measures are few and lacking in rigour. Some studies report disheartening results (De Palma et al., 1972), particularly for surgical therapy of neck pain after whiplash (Algers et al., 1993).

The one surgical procedure that has withstood scientific scrutiny is percutaneous, radiofrequency, medial branch neurotomy. In this procedure, the nerves that innervate the cervical zygapophysial joints are coagulated in an effort to relieve pain stemming from these joints (Lord et al., 1998). Under double-blind, controlled conditions, the procedure has proven not to be a placebo (Lord et al., 1996b). Moreover, it is the only treatment for neck pain that has been shown to achieve complete relief of pain, and restoration of activities of daily living (Lord et al., 1996b; 1998). Furthermore, relief of pain is attended by complete resolution of psychological distress (Wallis et al., 1997). A limitation of the procedure, however, is that pain recurs as the nerves regenerate. However, in that event, the procedure can be repeated and the pain once again completely relieved. Long-term studies have shown that continued, repeated relief can be sustained for up to 2000 days (McDonald et al., 1999).

Recommendations

In the light of the available evidence, the best recommendations that might be offered are:

For acute neck pain,

- Simple analgesics or non-steroidal anti-inflammatory agents might be used to provide analgesia while patients undergo natural recovery, but in the knowledge that the efficacy of these agents may be no greater than placebo.
- There is no evidence to justify the use of major tranquillizers or tricyclic antidepressants.

For neck pain after whiplash, during the first 8 weeks after injury,

- Patients could be treated with rest and analgesia, but
- A more rapid resolution of pain might be achieved by the use of ice, and passive mobilization, although
- A home-exercise programme offers just as much chance

of rapid resolution and a greater chance of being pain-free at 2 years; however,
- Firm reassurance, and insistence to resume normal activities, may be as effective as any other measure.

In the face of refuting data, and given the availability of a proven alternative,
- Traction, electromagnetic therapy, collars, TENS, ultrasound, neck school, spray and stretch, laser therapy, or traction, should not be used in the treatment of acute neck pain.

For chronic neck pain,
- No physical therapy is justified on the basis of available evidence.
- The use of analgesics might be justified on humanitarian grounds but not on the basis of evidence of efficacy.
- If NSAIDs are used their efficacy should be determined, and patients carefully monitored for side effects.
- Intra-articular injections of corticosteroids into the cervical zygapophysial joints should not be used unless it can be shown that the patient can achieve lasting and worthwhile relief that is cost-effective.
- Disc excision and fusion for neck pain without neurological signs might be entertained on the basis of uncontrolled clinical trials of this procedure, but this form of therapy would best be reserved for the context of clinical trials approved by an ethics committee or an institutional review board, and designed to determine its efficacy and safety.
- Radiofrequency neurotomy can be used to provide complete relief of pain in patients diagnosed rigorously as suffering from cervical zygapophysial joint pain, but the use of this procedure should be restricted to trained and accredited providers.

Resolving a dilemma

Quite clearly, neck pain is not radicular pain. Neck pain is perceived in the cervical region, not in the upper limb. Neck pain, however, can be associated with referred pain; and it is this somatic referred pain that can be difficult to distinguish from radicular pain.

The patterns observed for referred pain from cervical joints in normal volunteers (Fig. 50.3) were more restricted than those reported for interspinous ligaments (Fig. 50.2). The pain was restricted to the immediate vicinity of the neck and shoulder girdle, and did not extend distally into the upper limb. One reason for this difference is perhaps that the stimuli used were more restrained and less intense. Whereas the interspinous ligaments were stimulated with injections of hypertonic saline, the cervical joints were stimulated with injections of contrast medium to distend the joint. In order not to disrupt the joint, injections were terminated immediately once pain was elicited. In essence, the stimulus was minimal. It may be, therefore, wider areas of referral could occur from cervical joints or discs if stronger noxious stimuli were applied to these structures. However, this has not been tested experimentally; nor has it been borne out clinically.

No clinical studies have reported relief of somatic referred pain in the distal upper limb. Patients in whom somatic referred pain has been relieved by injections of local anesthetic into the neck have had referred pain no further than the shoulder girdle (Barnsley et al., 1995; Lord et al., 1996a). It seems, therefore, in practice, that somatic referred pain from the neck does not commonly extend beyond the region of the shoulder girdle. This empirical fact bears on the distinction between somatic referred pain and cervical radicular pain.

Since somatic referred pain from C6 or C7 does not commonly extend into the forearm, yet C6 and C7 radicular pain does, it is reasonable to deduce that referred pain that extends into the forearm is more likely to be radicular in origin than to be somatic referred pain. In contrast, C5 radicular pain typically extends only over the shoulder girdle (Fig. 50.1), and in that regard cannot be distinguished from somatic referred pain stemming from C5,6 structures (Fig. 50.3). However, epidemiologically, C5 radicular pain is not common (Merskey & Bogduk, 1994) but C5,6 somatic referred pain is (Barnsley et al., 1995; Lord et al., 1996a; Lord & Bogduk, 1996). Therefore, the pre-test probability of pain over the shoulder girdle favours somatic referred pain. Consequently, physicians should be guarded in diagnosing pain over the shoulder girdle as radicular pain.

The cardinal distinction between cervical radicular pain and somatic referred pain is that somatic referred pain is not associated with neurological signs; yet radicular pain usually is. Therefore, the presence of neurological signs favours a diagnosis of radicular pain, and in the case of pain extending into the forearm, neurological signs all but confirm the diagnosis of radicular pain.

These guidelines, however, are not absolute. Physicians need to heed that a patient's pain may not necessarily be entirely radicular; they may have components both of radicular pain and of somatic referred pain. It may be that a patient suffers a condition that by different, and parallel, mechanisms produces different clinical features. The condition may produce nociceptive pain, which if severe may radiate as somatic referred pain. Meanwhile, the same condition may also mechanically compromise a spinal nerve and produce both radicular pain and radiculopathy. For example, an arthritic C6–7 zygapophysial joint may be

locally painful and produce neck pain; it may produce somatic referred pain to the shoulder region; but its osteophytes may also compress the C6 spinal nerve to produce C6 radicular pain and C6 radiculopathy. In that event, the neurological signs and the forearm pain can be attributed to the radicular component of the diathesis; the neck pain stems from the joint itself, and not from nerve root irritation; but the pain across the shoulder is a mixture of somatic referred pain and the proximal component of the radicular pain.

Such combinations may underlie treatment failures. If all of the patient's symptoms are summarily attributed to radiculopathy and are treated as such, the radicular components may well be relieved; but the somatic components may not; and the patient will be left with neck pain and somatic referred pain. It is for such reasons that each of the patient's symptoms and signs should be analysed separately, and if necessary investigated and treated separately.

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Diagnosis and management of low back pain

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Low back pain (with or without sciatica) is one of the most common complaints of patients in all developed countries (Ackerman et al., 1997a; BenDebba et al., 1997; Deyo & Tsui-Wu, 1987; Fredrickson et al., 1984; Long, 1989; Long et al., 1979). In the USA, it is the second most common reason to see a physician (Carey et al., 1995), and the most common reason for Workmen's Compensation claims (Long et al., 1996). Surgery on the spine now ranks third among procedures in the Medicare population (Zeidman & Long, 1996).

Thus, it is surprising to discover that there is no complete classification system for low back pain with or without sciatica, and standards for diagnosis, treatment, and assessment of outcomes of therapy have not been established (BenDebba et al., 1997; Merskey & Bogduk, 1994).

One of the principal reasons why this situation exists is that for most patients, the causes of low back pain remain unknown, and the value of therapy is uncertain (Bigos et al., 1994; Waddell et al., 1984). The magnitude of the problem and the huge expenditures required for low back pain make it particularly important to understand what is currently known and not known about back pain, so that treatment is rational and based upon the most up-to-date information and guidelines.

Classification of low back pain

Classifications may be etiologic, based upon anatomical descriptions, or may use surrogate descriptors when anatomical and pathological details are not well understood. The most common classification system for low back pain is temporal and relates to descriptions of patients, rather than to pathological processes (BenDebba, 1997; Bigos et al., 1994; Long et al., 1996). This practical system is of real value in managing patients, although it does not provide the desired etiologic accuracy that is available with anatomical and pathological classifications (Bogduk, 1997; Main et al., 1992).

Transient low back pain

Transient low back pain is that which occurs so briefly that the patient does not seek medical attention. The etiologies of these brief periods of low back pain remain unknown, but will be discussed in greater detail later in the chapter.

Acute low back pain

Acute low back pain lasts for a longer period of time, usually a few days, and often brings the patient to medical attention. These patients have been addressed in guidelines promulgated by the consensus method from the National Institute for Health Policy Research (Bigos et al., 1994). Such patients require a careful history with the intent to determine if there are danger signals suggesting that this episode of back pain is a symptom of a serious underlying disease or the result of major trauma. It is unlikely that the history will be important otherwise, but in the acute phase, the primary concern is that an important intercurrent disease such as trauma with resultant fracture or instability, infection, or neoplasm may be missed. The physician needs to ensure that the back pain is not referred from gastrointestinal or renal disease and is not a symptom of vascular disease such as aortic aneurysm. Back pain as a part of an arthritic syndrome, such as ankylosing spondylitis or rheumatoid arthritis is possible, but generally such a diagnosis is less critical in the acute phase.

The physical examination requires inspection of the back, palpation for assessment of muscle spasm and local tenderness, assessment of range of motion, and/or a neurological evaluation that examines reflexes, strength,

and sensation in the lower extremities. Any acute neurological loss is important, but only severe deficits are likely to precipitate immediate therapy. Patients usually know about bowel or bladder dysfunction, but it is important to ask even though definitive testing is not required in the absence of complaints. A key issue in the neurological examination is the differential diagnosis, which should separate lumbar radicular abnormalities from other neurological deficits (Deyo et al., 1992; Dreyfuss et al., 1996; Mooney, 1987).

Management of acute low back pain

If there are no indications of intercurrent disease and no evidence of significant neurological loss, consensus guidelines indicate that no further evaluation is required (Bigos et al., 1994). Specifically, imaging studies need not be done. Indications for imaging of any kind are: a history of significant trauma, the presence of known or suspected intercurrent disease, and the presence of a significant neurological deficit. Without them, treatment is expectant. Patients should be prescribed rest or limited activity for a few days until improvement begins. Adequate analgesia is important (Long et al., 1979; Solomon et al., 1980). No other treatment is required because spontaneous recovery will occur in most patients within a few days. In fact, patients should be returned to full function as soon as possible (Turner, 1996). There is good evidence that recovery is hastened by increased activity as tolerated (van den Hoogen et al., 1998). Most patients will recover substantially within the first month. If they do not, or if any new important neurological or other symptomatic changes occur, imaging is then reasonable (Bigos et al., 1994; Liang & Komaroff, 1982). Plain films with flexion/extension and MRI give the most information. CT is a reasonable substitute, but will provide less information about soft tissue changes than MRI. The purpose of imaging is not necessarily to make a diagnosis, but rather to determine if a surgically remediable abnormality or otherwise treatable disease is present (Ackerman et al., 1997b,c; Lindstrom et al., 1992). There is little evidence to support the use of physical therapy, manipulation therapy, or any alternative medicine treatments at any time in the management of acute low back pain. The cost is substantial and the benefit marginal even in the most favourable studies (American Academy of Orthopedic Surgeons and North American Spine Society, 1996; Anderson et al., 1999; Bigos et al., 1994; Cherkin et al., 1996b, 1998; Koes et al., 1991a,b, 1994; Koes & van den Hoogen, 1994; Linton & Kamwendo, 1987).

Many experienced practitioners use a short course of oral steroids when an acute radicular syndrome is present without neurological deficit (Sonne et al., 1985). There is no definitive study supporting this practice, but many practitioners find that a short course of oral steroids will rapidly relieve radicular pain. Some clinicians use epidural steroids for the same purpose. It has always been our contention that the evidence for substantial improvement is meagre and that the procedure is not without risk. We use oral steroids for acute radicular syndromes, but have discouraged the use of epidural steroids because we believe that their limited benefits do not clearly justify the cost and risks associated with them. Since most patients recover spontaneously, the least intervention possible in acute syndromes is best (American Academy of Orthopedic Surgeons and North American Spine Society, 1996; Bigos et al., 1994; Carey et al., 1995; Indahl, 1995; Long & Watts, 1996; Long & Zeidman, 1994; van Tulder et al., 1997).

The persistent low back pain syndrome

Not all patients recover spontaneously (Lindstrom et al., 1995). Recently, we identified a subgroup in which symptoms persist after 3 months and apparently become permanent (Ackerman et al., 1997c; Long et al., 1996; Long & Watts, 1996; Long & Zeidman, 1994). For these patients who still complain of substantial pain and disability after 3 months, it is appropriate to carry out an immediate investigation to identify the cause of the pain. Although there are specific constellations of signs that denote specific root involvement, they occur rarely and the neurological examination is seldom diagnostic. The most important sign is the positive straight leg-raising test. When present, this strongly suggests root compression, but does not suggest the cause (Long et al., 1996).

The imaging evaluation begins with flexion and extension plain films and MRI (Ackerman et al., 1997c; American Academy of Orthopedic Surgeons, 1995). CT of the lumbar spine is indicated when the disease is thought to have a significant bony involvement. CT myelogram, which was the major diagnostic test until fairly recently, is now rarely indicated. It is used principally when intradural pathology is suspected or when a patient cannot tolerate MRI and plain CT does not provide adequate information (Fullenlove & Williams, 1957; Loisel et al., 1997; Scavone et al., 1981).

Of interest is that in an extensive prospective review of nearly 4,000 patients, we found no clinically significant psychological dysfunction in patients with persistent low back pain complaints (BenDebba et al., 1997; Long et al., 1996).

The chronic pain syndrome

The group described above is quite different from a group of patients identified well over 30 years ago in whom pain

complaints with clinically significant psychological dysfunction produce a completely disabling syndrome (Morley et al., 1999; Waddell et al., 1984). These patients, who have high levels of psychological distress and are disabled by pain without evidence of physical impairment, differ from patients with the persistent pain syndrome (Bigos et al., 1991; Main et al., 1992). Their evaluation and treatment has been studied intensively in multidisciplinary pain treatment centres (Long et al., 1981, 1988; Long, 1992). At Johns Hopkins, we evaluate this group by using a medical model that comprises an exhaustive investigation of possible causes of the pain, assessment of physical impairment, and careful assessment of psychological dysfunction. Treatment consists of a multidisciplinary approach that involves eliminating the cause of the pain, improving physical functioning, and attending to psychological needs (Loisel et al., 1997; Long 1991a,b; Phillips & Grant, 1991a; Zeidman & Long, 1996).

Etiologies of low back pain

The major problem in classifying low back pain is that it is a symptom of many diseases for which correlations are excellent, but the underlying causative factors are not understood (Bogduk & Long, 1979). Obviously, the pain is generated through the activation of nociceptors serving the abnormal areas (Ackerman et al., 1997c; Long, 1989; Merskey & Bogduk, 1994). What activates these nociceptors, however, is unclear (Mooney, 1987). Most experts agree that compression of individual lumbar nerve roots will produce pain, both localized in the spine and with a radicular character (Smyth & Wright, 1959). Relief of the compression usually improves the pain. Severe degrees of dislocation with movement also produce pain (Fredrickson et al., 1984). Nevertheless, there is no consensus about what minimal degree of subluxation is required to be either pathological or painful. Some believe that small movements that are not discernible on imaging studies may be sufficient to cause chronic pain (Mooney & Robertson, 1976; Morley et al., 1999); others suggest that the mediators are the chemical components of the inflammatory cascade that may occur acutely or may be a part of the spondylotic process (Mooney, 1987). Definitive data do not exist to prove or disprove these hypotheses. Although, there is a strong association of back pain with spondylotic disease in the majority of sufferers, this correlation is clearly not absolute. Moreover, several authors have demonstrated that patients with significant spondylotic disease may be asymptomatic (Ackerman et al., 1997b; Fullenlove & Williams, 1957; Splinthoff, 1953).

In the absence of definitive data, it is necessary to define clinical hypotheses for the origins of back pain and direct treatments empirically. The fundamental hypothesis that leads to surgery is that some patients have back and leg pain associated with nerve root compression, instability of the spine, or both, and that these are the only conditions currently known that surgery can ameliorate (Long, 1978, 1985, 1987; Long et al., 1988). Only a small minority of patients with back pain have either of these conditions demonstrated. So, for the majority of patients, the cause of their complaint remains unknown and assumptions about primary or secondary painful phenomena remain descriptive (Bogduk & Long, 1979; Dreyfuss et al., 1996; Hirschberg et al., 1979; Ingpen & Burry, 1970; Johnson, 1989).

Specific conditions associated with back pain

Back pain as a consequence of systemic disease

Back pain may occur as a consequence of a number of organ-specific diseases that manifest themselves in or near the lumbar spine, particularly in the retroperitoneal space. These include aortic aneurysm, metastatic or locally invasive neoplasm, inflammatory disease of the bowel, kidney diseases of many kinds, pelvic neoplasia and inflammatory disease, and endometriosis. Hip disease, lower extremity occlusive vascular disease, and sensory motor neuropathies can mimic lumbar radiculopathy. In a study of nearly 4000 patients, however, only 3% had back pain as a symptom of intercurrent disease and almost all of these were previously undetected metastatic cancer (Long et al., 1996; Magora & Schwartz, 1976). Intradural spinal cord tumours are occasionally present with back pain. In all these instances, the history usually reveals that this pain differs from the usual back pain of unknown etiology (Ackerman et al., 1997c; Deyo et al., 1992; Deyo & Tsui-Wu, 1987; Phillips & Grant, 1991b; van den Hoogen et al., 1998; von Korff, 1994).

Infections

Lumbar diskitis, with or without paravertebral abscess, is an unusual and extremely serious cause of back pain (Waldvogel & Vasey, 1980; Zeidman & Long, 1996). The most common infective agents are tuberculosis and infections spread from other sources, such as dental or kidney infections. Most patients have a history suggestive of infection, including malaise, chills, and fever, but sometimes pain is the only or predominant symptom and fever does not occur. Imaging studies based upon symptoms indicative of infection will invariably make the diagnosis, except in the most acute cases.

Arthritis and spondylitis

Severe back pain is the defining symptom in a number of spondylitic and arthritic diseases, the most common of which is rheumatoid arthritis. Ankylosing spondylitis in males is another well-known disease. Arthropathy of zygapophyseal joints occurs in psoriasis, and in both gout and pseudo-gout. Inadequately treated acromegaly is often complicated by intractable back pain. Most of the less frequently encountered arthritides can also present with back pain. Back pain and spinal stenosis are common early midlife complications in achondroplasia. Imaging studies and an appropriate diagnosis of the underlying arthritic condition usually establish the cause of the pain (Long, 1978, 1991a).

Back strain and fibromyalgia

The most common cause of acute back pain is generally assumed to be muscular strain and/or muscular-ligamentous inflammation (Ingpen & Burry, 1970; Johnson, 1989). The assumption is made because of the presence of focal tender points and spasm in muscles. Since no clearly defined structural abnormalities are found, back strain, myositis, fibromyalgia, or any of several other descriptive diagnoses are commonly made (Johnson, 1989). There is no definitive evidence that these are real entities; they are inferred because of local nonspecific findings. Clearly, all of these local changes exist in patients, but whether they are primary causes of the problem or simply secondary to the, as yet, undefined abnormalities of the lumbar spine is not known. Still, patients improve with treatment of these local abnormalities, whether they are primary or epiphenomena (Anderson et al., 1999; Cherkin et al., 1998; Fordyce et al., 1986; Indahl et al., 1995). Treatment consists of analgesic and anti-inflammatory agents, and passive measures such as heat, massage, ultrasound, electrical stimulation, and local analgesic and/or steroid injection. Bed rest is often helpful for a few days, as well as some restriction of activities that aggravate the pain (Bigos et al., 1994; Deyo, 1996; Long, 1989).

The argument over the reality of a primary diagnosis of fibromyalgia persists. Those who believe in a unifying diagnosis have not yet demonstrated diagnostic features that reliably define a disease process. In practical terms, it makes little difference, because the treatments are all symptomatic (Wheeler & Hanley, 1995).

Surgery is indicated for very specific diagnoses and all other treatments for spinal problems are either expectant, awaiting spontaneous resolution, or symptomatic (American Academy of Orthopedic Surgeons, 1995). For this reason, the most important issues for patients with persistent or chronic low back pain are to be certain that there is no treatable underlying pathology, that there is no evidence of serious intercurrent disease, and to determine if surgical therapy can change the structural abnormalities found in the spine. When all three issues are addressed and nothing treatable is found, use of symptomatic therapies is routine. The evidence that these symptomatic therapies are valuable is marginal. The best published data suggest that weight loss, general conditioning, and a specific exercise program aimed at strengthening lumbar and abdominal muscles will be beneficial (Forssell, 1981; Indahl et al., 1998; Jackson & Brown, 1983; Lindstrom et al., 1992; Moffett et al., 1999). Our data strongly suggest that most of the currently used symptomatic therapies will not result in significant improvement (Cherkin et al., 1996a; Frymoyer & Cats-Baril, 1987; Koes et al., 1991a,b, 1994).

Degenerative disc disease and spondylosis

The majority of patients with persistent low back pain have general spondylotic changes that are characterized by loss of disc hydration, inflammatory and hypertrophic changes in bones and ligaments, fissures and tears in the annulus, fibrosis, loss of disc height, facet arthropathy including synovial cyst formation, and changes in spinal alignment including spondylolisthesis, retrolisthesis, and many variations of scoliosis. The simplest expression is lumbar disc herniation.

The herniated lumbar disc

Disc herniations are usually heralded by back pain and radicular pain in the distribution of the nerves affected, with or without neurological changes related to those same nerves. Herniation may be traumatic or spontaneous. It may be preceded by a long history of lesser back problems or may occur as a first-time event. Herniation occurs most commonly at L4–L5 and L5–S1 with higher levels being involved only about 15% of the time. Typical herniations are midline, lateral within the spinal canal, or far lateral in the foramen or beyond. The most important feature is the history of radicular pain. Massive disc herniations may also compromise bowel, bladder, and sexual functions, but the typical disc affects one or two nerve roots only.

Herniations at L5–S1 may affect either nerve root or both. Involvement of the S1 nerve root produces sciatica with pain reaching the lateral side of the foot and sole. The ankle reflex is diminished or absent. Sensory loss occurs in the lateral two toes, lateral foot, and sole. Motor loss produces weakness of extension of the foot. Involvement of the L5 nerve root produces sciatica that reaches the top of

the foot, the medial foot, and first three toes, in particular the great toe. There is no associated reflex change. Sensory loss occurs in the top of the foot and specifically in the web space between the first and second toes. Weakness is manifested by impaired ability to flex foot and toes. Straight leg-raising is a strong confirmatory sign. With a patient lying flat, the painful leg is raised slowly while extended. Sciatic pain must be reproduced for the test to be positive. When the non-painful leg is raised and contralateral pain occurs, this is called positive crossed straight leg-raising and is a very reliable sign of nerve root compression. In all patients with disc herniation, there may be associated non-specific findings of muscle spasm, paravertebral muscle tenderness, sciatic notch and sciatic nerve tenderness, but these do not aid in the diagnosis.

Involvement of the L4 nerve root causes absence or diminution of the knee reflex, sensory loss in the anterior thigh and lateral leg, and weakness of leg extension. Sciatic stretch by straight leg-raising may be positive. The femoral stretch, which is assessed by passively moving the leg posteriorly, may also be positive.

Higher disc herniations affecting the upper lumbar roots have no associated reflex changes. Sensory and motor changes are those appropriate for the roots involved. Femoral stretch will be positive, but straight leg-raising will be negative.

Far lateral disc herniations may have a special characteristic. Because the dorsal root ganglion is affected, the pain is perceived as burning and particularly unpleasant. Such a sign is suggestive only.

Most acute disc herniations relent with time and do not require surgery. Indications for urgent operation are intractable pain that cannot be relieved with reasonable analgesics; a lower extremity neurological loss that would be undesirable if permanent; and significant change in bowel, bladder or sexual function. Otherwise, most patients can be treated expectantly with adequate analgesia, bed rest, and then restriction of activities until recovery occurs. Most patients begin to improve within a few days and many show signs of recovery within the first week. Substantial improvement is probable within the first month. Most patients recover completely within 3 months. In the acute situation, imaging studies are not required immediately unless pain or neurological deficits are severe. If a patient fails to follow the expected course of spontaneous improvement, MRI is the imaging study of choice. Surgical therapy should proceed when it is clear the patient's symptoms warrant intervention and spontaneous recovery is not likely to occur. There is no evidence that interposing physical therapy, manipulation, or any form of alternative medicine will alter the natural history of the disc herniation. For many years, the standard practice has been to interpose physical therapy as a requirement for surgery. The evidence that this is beneficial is marginal (Long, 1987; Long et al., 1996).

New treatments for the herniated lumbar disc are introduced continually (Solomon et al., 1980; van Tulder et al., 1997). Intradiscal therapies have included the injection of steroids, agents that dissolve the nucleus pulposus, and sclerosing agents to strengthen ligaments. Percutaneous removal of disc material has been attempted with lasers, nucleotones, and more typical surgical instruments controlled by endoscopes. A recent addition to this percutaneous armamentarium has been the concept of intradiscal heat coagulation, which is thought to strengthen the internal structure of the disc and which some postulate may destroy sensory nociceptors. Most of these techniques come and go without being subjected to rigorous clinical trials. Because the natural history of acute back pain and sciatica is one of spontaneous improvement, it is easy for practitioners and patients to believe that the prescribed treatments have produced the observed improvement (Wheeler & Hanley, 1995).

Spinal stenosis

Another common spondylitic syndrome is spinal stenosis. The disease usually appears in patients who begin with congenitally short pedicles and then have further compromise of the central spinal canal and neural foramina by age-related spondylotic changes. The typical syndrome combines back pain with a leg pain complex known as claudication. With activity, leg pain generally worsens and a transient neurological deficit may occur. The syndrome is very similar to vascular claudication, but examination of the vascular system usually reveals no significant abnormality. Neurological findings are variable and the history is more important because the neurological abnormalities are often transient and related to exercise or position. In severe cases simply standing is enough to precipitate symptoms. Diagnosis is obvious on MRI. In severely incapacitated patients, surgical decompression with restoration of an adequate canal and/or foraminal capacity is, typically, highly efficacious (Long & Watts, 1996).

Spinal instability

There is much debate about what constitutes spinal instability. Pain associated with obvious subluxation of spinal elements with movement is well-documented (Schneiderman et al., 1995), but how to define the degree of movement required to diagnose instability is uncertain (Bogduk, 1997; Bogduk & Long, 1979, 1980). So-called glacial instability that changes perceptibly over months or

years is also generally thought to be painful, but definitive supportive clinical data are lacking (Phillips & Grant, 1991b). All spinal fusions are based upon the elimination of instability or correction of biomechanical deformity (Indahl et al., 1998). Correction of significant and/or progressive scoliosis in all its forms and stabilization of obvious subluxation are well accepted. The value of fusion procedures in less obvious instability situations is less well demonstrated (Moreton, 1966).

Degenerative disc and spondylotic abnormalities without instability or root compression

Degenerative changes have been observed on imaging studies in many people. Loss of disc hydration begins in late youth to early middle age in a large percentage of the population. This so-called degenerative disc disease continues to progress to late middle age and then usually stabilizes. In some people progressive changes continue to occur. Nevertheless, many people with substantial degenerative changes have no symptoms, and many people with significant symptoms have few, if any, degenerative changes. It is generally accepted that these degenerative disc changes are causally related to pain, but the cause of the pain is unknown. Because of the poor correlation between clinical syndrome and imaging findings, a large variety of treatment modalities have been used without strong evidence of their efficacy. Therapy is usually symptomatic, of limited value, so it is not surprising that there are many treatment schemes touted to be the answer for low back pain (Moffett et al., 1999). The appearance of new explanations and new treatments has been a cyclical event.

The national low back pain study (NLBPS)

Our concepts of treatment are based on the results of an eight-centre nationwide study of patients with significant persisting back and/or leg pain, known as the NLBPS. The study began more than 10 years ago and is still ongoing. Our goal was to study those patients who were seriously incapacitated by low back pain uncomplicated by multiple interventional treatments or previous surgery. As already stated, most acute back and leg pain is self-limited and does not require significant treatment. Therefore, we identified a group of patients with pain persisting for 3 months or longer, who were referred to orthopedic or neurological surgeons for evaluation and possible surgical treatment. Complete history and a thorough physical examination, as well as imaging studies, were used to establish the diagnosis thought most likely to account for each patient's pain and functional impairment. The outcome of therapy was monitored over a 2-year period with a battery of tests that assess all the characteristics of the complaint: pain severity, function disability, psychological status, symptoms other than pain, and healthcare utilization. This was an effectiveness study that examined the value of all therapies employed, but did not allow comparisons between therapies.

The demographic make-up of the patient population proved to mimic that of the general population. Of the more than 2300 patients enrolled in the study, 1441 were prescribed conservative care, 332 were prescribed no treatment, and 331 were prescribed immediate surgical care. Another 254 patients went to surgery after failure of conservative care.

All the patients in the study were significantly disabled by their problem, such that they had been referred to an orthopedic or neurological surgeon for possible surgery. Over 80% had a final diagnosis implicating spondylotic disease as the cause of their symptoms, and 60% had a diagnosis of nerve root compression syndrome. Nevertheless, only 25% of the entire study population were selected for surgery.

Instability was infrequently diagnosed, occurring in only 10% of the patients. It was surprising to discover that the physical examination was irrelevant to the diagnosis. The history was the most important diagnostic determinant, and as expected, sciatica was the predominant symptom leading to surgery. The only physical finding consistently predictive of nerve root compression was a positive straight leg-raising test. Most patients had no neurological abnormalities. Reflex, motor, or sensory changes occurred in about one third of the patients, and the classic triad taught to be diagnostic of lumbar disc disease was observed in less than 1% of patients. Whereas significant neurological deficits are certainly indications for surgery, we found such cases to be rare even in patients with significant disc protrusion (Long et al., 1996).

The patients' psychological profile was consistent with that of a typical ill patient population. There was no evidence for psychopathology in the genesis of the complaint of low back pain (BenDebba et al., 1997; Phillips Grant, 1991a).

The first important finding from the follow-up studies was that there was no significant spontaneous improvement with time. The entire cohort was followed for 2 years and a subset was followed for 5 years. Spontaneous improvement was observed in neither. Thus, we believe we have identified a group of patients who comprise a consistent syndrome. These are patients who do not improve spontaneously; but usually have episodic pain for years. We have referred to them as persistent back pain patients

to differentiate them from acute and chronic low back pain patients. No conservative care modality, whether recommended by the study physicians, other physicians, or chosen independently by patients, had any significant effect on the complaint of back pain and sciatica. Since none were of significant value, there is little evidence to suggest that using any of the so-called conservative care measures could prevent surgery (Long et al., 1996).

It is important not to misunderstand these statements. They apply only to persistent back pain patients. Most patients with acute low back pain and sciatica, even with demonstrated disc herniation, will improve spontaneously with no more than symptomatic treatment (Bigos et al., 1994). Surgery is rarely required, unless pain is intolerable or a significant neurological deficit is present. Our data indicate that when spontaneous recovery does not occur, it is unlikely that any of the conservative care measures will change the natural history of the disease, or give the patient symptomatic relief. This is a radical departure from the usual treatment approach and will require long-term validation.

The outcome of surgery was quite different and very satisfactory. However, the experts in spinal surgery involved in our study chose only a small number of the referred patients for surgical treatment. The most common indication for surgery was unrelieved radicular pain (BenDebba et al., 2000). For most patients, the severity of pain led to the surgical decision, and most of the surgeries were complex procedures. The goal was to relieve nerve root compression, and/or eliminate instability. Twenty per cent of the surgically treated patients has a fusion.

Outcomes for the surgically treated patients were excellent, with over 90% of patients being satisfactorily relieved of pain without mortality and without significant morbidity. Only 2% of patients were unchanged or worse, and only 5% required reoperation. These outcomes persisted throughout the follow-up period. Thus, it appears that patients with sciatica secondary to disc herniation, spinal stenosis, or spondylolisthesis, whose pain is severe enough to warrant surgery, can be predictably relieved with little or no risk. Nevertheless, these patients constitute a small minority, even among those who are referred to orthopedic and neurological surgeons who are knowledgeable about spinal problems (Long et al., 1996).

Diagnostic blocks in decision-making in low back pain

Diagnostic blockade is widely used in patients with low back and leg pain as an adjunct in the decision-making process (Bogduk & Long, 1979, 1980). The rationale is sound, but clinical correlations are as tenuous as those between radiological findings and clinical syndromes. The concept is that if a specific structure in the spine is anesthetized with a local anesthetic, the pain originating in or mediated by that structure should be relieved. In an effort to make the blocks more helpful, a second parameter, the provocation of the patient's own pain syndrome, has been added to the interpretation. Thus, with provocative diagnostic blockade, the patient is queried about the reproduction of their usual pain syndrome during needle placement and during injection. Relief of pain is assessed after injection. The most significant block is the one that both provokes and relieves pain. Blocks in common usage include lumbar zygapophyseal joints, individual nerve roots, and intradiscal blocks. Although these applications are rational and intuitively correct, there are two problems with their utilization: first, selectivity and specificity are weak; second, clinical correlations between the results of blocks and treatment outcomes are lacking. Bogduk has studied specificity and selectivity of cervical blocks in great detail. The most reliable blocks include placebo controls. Uncontrolled blocks, and blocks of adjacent nerves or major nerve trunks made up of overlapping root origins are less specific. Currently, in our clinic, provocative blocks are used as adjuncts to strengthen clinical decisions already made on other grounds. They are never used alone to guide surgery. Much more data will be required before these provocative blocks can be considered more than adjunctive in the diagnostic and decision-making process.

Impairment, disability, litigation, and the compensation process

The problem of low back pain in the United States and in most developed nations is complicated by its intimate relationship with disability and litigation (Bigos et al., 1991; Frank et al., 1998; Mayer et al., 1987; Scheer et al., 1995). The impairment guides of The American Medical Association are used 94% of the time for the spine. It is clear to most experts that patients involved in litigation and disability claims do not recover as well as those without such claims. In our own national low back pain study, all patients employed at the time of surgery returned to work at the same job without restrictions; virtually none of the patients involved in disability returned to work. Those involved in litigation complained much more, used more medical resources, and were much less likely to return to work when compared with similar patients without litigation, although no significant differences between the two

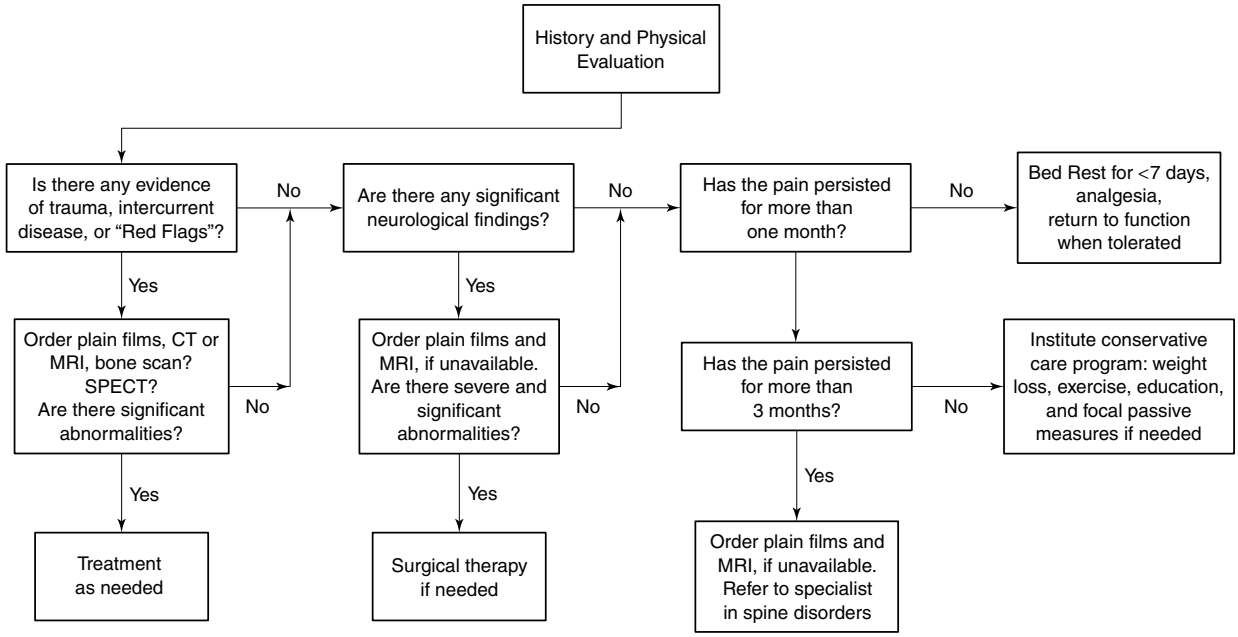

Fig. 51.1. A paradigm for the management of low back pain complaints.

groups in terms of diagnoses or therapies could be discerned. Nevertheless, physicians complicate the social issues through diagnoses and choice of treatments. The social and political issues surrounding the disability question are complex and well beyond the scope of this chapter. There is no doubt, however, that the presence of claimed disability increases complaints, leads to greater medical utilization, and greatly reduces the vocational capabilities of patients after apparently successful surgery. Patients with disability claims should not be deprived of surgical treatments for diseases known to respond well to surgery, nor should the indications for surgery be expanded for them.

A management paradigm for low back pain

Our current paradigm, illustrated in Fig. 51.1, follows the rules for management of acute low back pain with or without leg pain promulgated by the Agency for Health Policy and Research. This means no evaluation for the majority of patients acutely, but adequate symptomatic relief. Rapid return to function is important. Patients are restricted from aggressive practitioners who use any form of surgical or conservative care, and spontaneous healing is allowed to occur. When patients do not improve spontaneously within 1 month, or if symptoms remain incapacitating for more than a short period of time, evaluation proceeds. Surgery is performed immediately for those with sufficient symptoms and clear-cut root compression or instability. There is no reason to implement any conservative care program since none will be of value. When surgery is contemplated it should proceed only after 3 months of waiting, unless symptoms preclude such a wait. The majority of patients will not be candidates for surgery. The best evidence suggests that most patients do not respond to conventional conservative programs, but can benefit by an intensive program that includes weight control, local measures for relief of muscular and ligamentous pain, and a vigorous functional exercise program that restores them to their maximum capabilities.

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Part VI

Disorders of body functions

52

Autonomic function and dysfunction

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The autonomic nervous system is a dynamic system intimately involved with the function of every organ in the body. In addition, it plays a key role in integrative function, such as control of the circulation and regulation of body temperature. Its motor (efferent) components, consist of the parasympathetic nervous system with a cranial and sacral spinal outflow, and the sympathetic nervous system with a thoraco-lumbar spinal outflow (Fig. 52.1). However, there is interaction at various levels of the neural axis. Thus, virtually every afferent in the body, through relays at a cerebral or spinal level, influences function of the autonomic nervous system. Centres in the brain can activate autonomic pathways directly or by stimulating spinal autonomic centres. There are multiple neurotransmitters at different synapses and ganglia that are better defined in the periphery than centrally (Fig. 52.2). Complex processes at parasympathetic and sympathetic nerve terminals influence the synthesis, release and re-uptake of various transmitters (Figs 52.3 and 52.4). The autonomic supply to the gut and pelvic viscera (enteric nervous system) additionally is richly endowed with peptides, amines and purines involved in neurotransmission and neuromodulation; they also have direct effects, especially upon the gastrointestinal tract and splanchnic circulation.

Classification of autonomic disorders

An outline classification is provided (Table 52.1). There are primary disorders where the etiology is not known; examples are pure autonomic failure (PAF) and multiple system atrophy (MSA). A large number of secondary autonomic disorders may be hereditary, associated with disease (such as diabetes mellitus), due to a specific deficit (dopamine beta-hydroxylase deficiency) or the result of trauma. A variety of drugs, poisons and toxins cause autonomic dysfunction by directly influencing sympathetic or parasympathetic activity, or by causing an autonomic neuropathy. In neurally mediated syncope, autonomic function is intermittently abnormal with either overactivity (such as increased vagal tone causing bradycardia) or underactivity (sympathetic withdrawal causing hypotension); the most common is vasovagal syncope. A recently described disorder is postural tachycardia syndrome (PoTS).

In many of these autonomic disorders there is involvement of different organs or systems. Some are localized, predominantly affecting one organ, area or system, such as the pupil in the Holmes–Adie syndrome, the face in Horner's syndrome and sweat glands in essential hyperhidrosis.

Clinical manifestations

Characteristic features follow dysfunction affecting the sympathetic and parasympathetic nervous systems. Sympathetic adrenergic failure results in orthostatic (postural) hypotension and ejaculatory failure, while sympathetic cholinergic failure causes anhidrosis. The reverse, sympathetic overactivity, may result in hypertension, tachycardia and hyperhidrosis. Parasympathetic failure causes a fixed heart rate, an atonic urinary bladder, a sluggish large bowel and erectile failure; overactivity can result in bradycardia and even cardiac arrest. Thus, a wide spectrum of manifestations can occur in autonomic dysfunction (Table 52.2), with various combinations depending upon the extent of the lesion, the associated disorder and the ensuing functional deficit. In disorders such as multiple system atrophy, there may be difficulties in diagnosis, as non-automic disorders may result in similar symptoms.

In the Riley–Day syndrome (familial dysautonomia), there usually is a history of consanguinity and an Ashkenazi

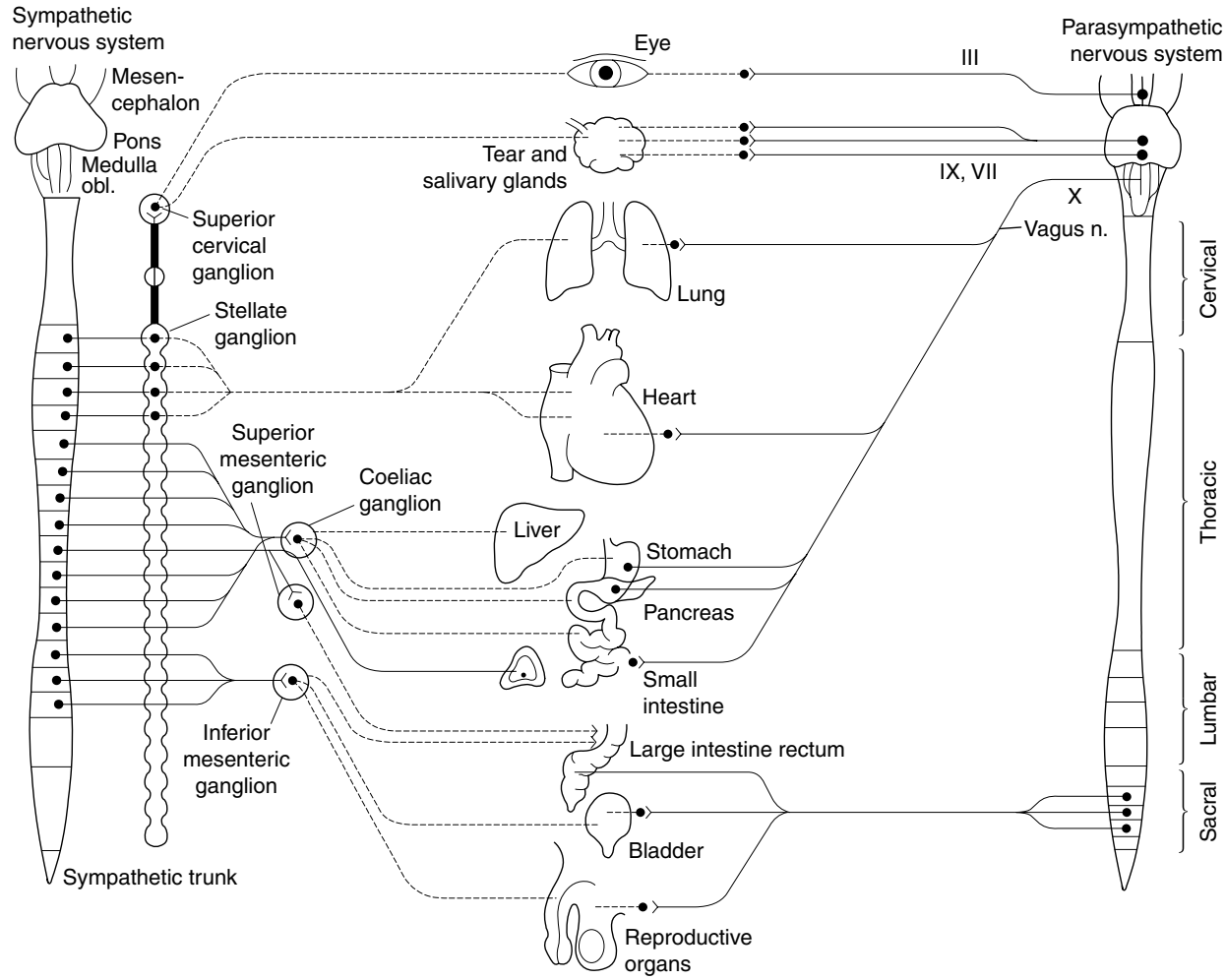

Fig. 52.1. Parasympathetic and sympathetic innervation of major organs. (From Janig, 1987.)

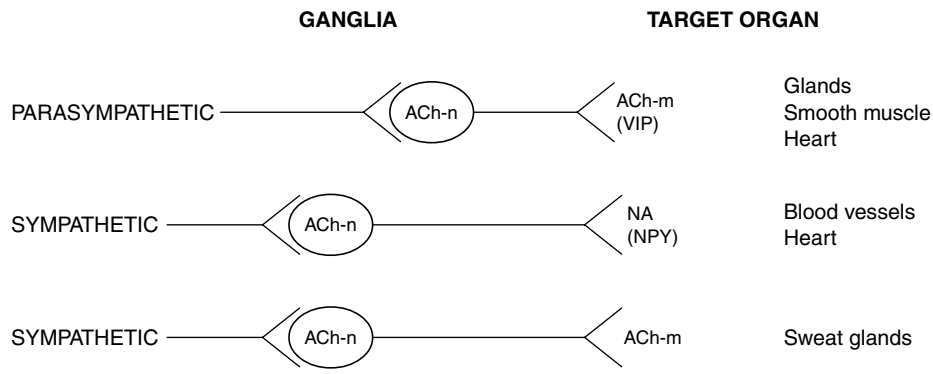

Fig. 52.2. Outline of the major transmitters at autonomic ganglia and postganglionic sites on target organs supplied by the sympathetic and parasympathetic efferent pathways. The acetylcholine receptor at all ganglia is of the nicotinic subtype (ACh-n). Ganglionic blockers such as hexamethonium thus prevent both parasympathetic and sympathetic activation. Atropine, however, acts only on the muscarinic (ACH-m) receptor at postganglionic parasympathetic and sympathetic cholinergic sites. The cotransmitters along with the primary transmitters are also indicated (NA = noradrenaline; VIP = vasoactive intestinal polypeptide; NPY = neuropeptide Y). (From Mathias, 2000a.)

Table 52.1. Outline classification of autonomic disorders

Primary
- Acute/subacute autonomic neuropathy
- Chronic autonomic failure
  - – pure autonomic failure
  - – multiple system atrophy

Secondary
- Hereditary
  - – Riley–Day syndrome
  - – familial amyloid polyneuropathy
- Metabolic
  - – diabetes mellitus
- Enzyme deficiency
  - – dopamine beta-hydroxylase deficiency
- Inflammatory
  - – Guillain–Barré syndrome
- Infectious
  - – Chagas disease
- Trauma
  - – spinal cord transection

Drugs, poisons and toxins
- Direct effects
- Autonomic neuropathy
  - – alcohol

Neurally-mediated syncope
- Vasovagal syncope
- Carotid sinus hypersensitivity
- Miscellaneous causes
  - – micturition syncope

Postural tachycardia syndrome

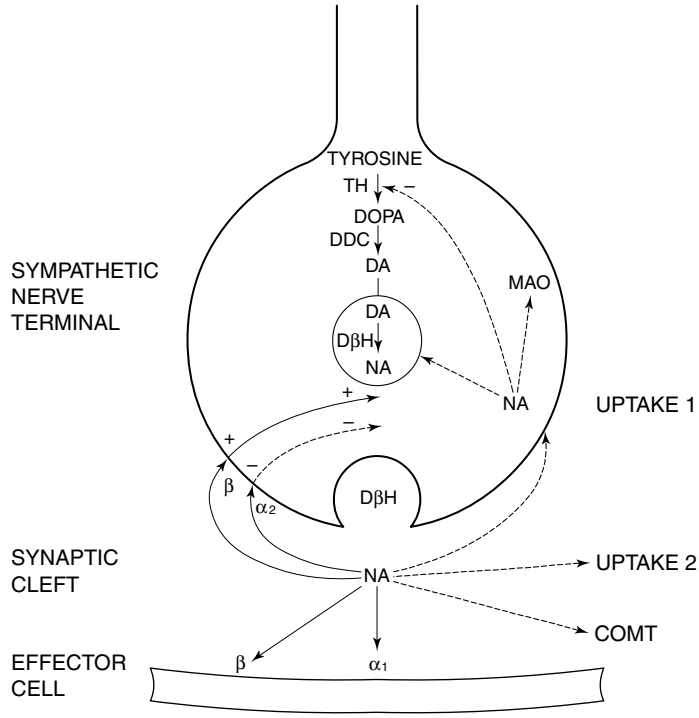

Fig. 52.3. Schema of some pathways in the formation, release and metabolism of noradrenaline from sympathetic nerve terminals. Tyrosine is converted into dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase (TH). DOPA is converted into dopamine (DA) by dopadecarboxylase. In the vesicles DA is converted into noradrenaline (NA) by dopamine beta-hydroxylase (DβH). Nerve impulses release both DβH and NA into the synaptic cleft by exocytosis. NA acts predominantly on alpha$_1$-adrenoceptors but has actions on beta-adrenoceptors on the effector cell of target organs. It also has presynaptic adrenoceptor effects. Those acting on alpha$_2$ adrenoceptors inhibit NA release; those on beta-adrenoceptors stimulate NA release. NA may be taken up by a neuronal (uptake 1) process into the cytosol, where it may inhibit further formation of DOPA through the rate-limiting enzyme TH. NA may be taken into vesicles or metabolized by monoamine oxidase (MAO) in the mitochondria. NA may be taken up by a higher capacity but lower affinity extraneuronal process (uptake 2) in peripheral tissues, such as vascular and cardiac muscle and certain glands. NA is also metabolized by catechol-o-methyl transferase (COMT). NA measured in plasma is the overspill not affected by these numerous processes. (From Mathias, 2000a.)

Jewish origin; the disorder often is recognized at birth. Vasovagal syncope presents commonly in the teenage years, while familial amyloid polyneuropathy begins in early adulthood and middle age. Neurodegenerative disorders such as multiple system atrophy present in the mid- to late 50s. There may be a gender preponderance; vasovagal syncope is more common in females. A detailed history is essential and must include drug medication intake and previous exposure to chemical substances.

In secondary autonomic disorders and those caused by drugs, the features of the underlying or associated disorder need consideration as these may exacerbate autonomic manifestations. Individual assessments are necessary, especially of psyche, in conditions such as vasovagal syncope, also know as emotional syncope.

The clinical findings may be confined to an area, organ or involve a system. In essential hyperhidrosis only the palms and soles may be affected, while in the Holmer – Adie pupil there is impairment of parasympathetic function of the iris musculature. In generalized disorders a cardinal feature is orthostatic (postural) hypotension (Fig. 52.5). This is defined as a decrease in systolic blood pressure of more than 20 mm Hg, or a fall in diastolic blood pressure of more than 10 mm Hg, while either standing or during head-up tilt to 60° for at least 3 minutes (Schatz et al., 1996). A variety of

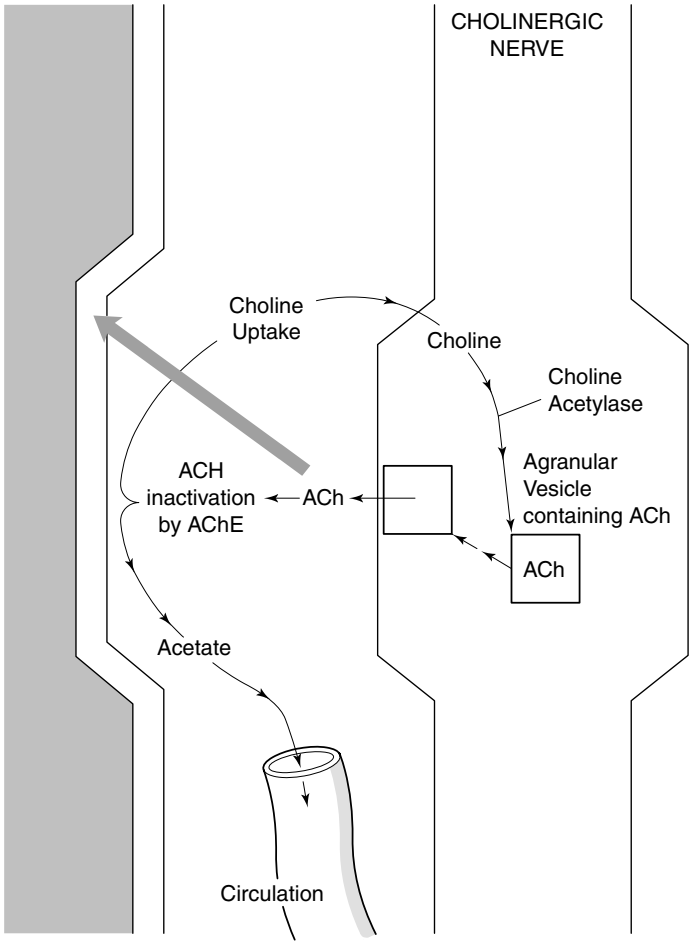

Fig. 52.4. Schema of pathway in the formation of acetylcholine (AChL) from choline and its inactivation by acetylcholine esterases (from Appenzeller & Oribe, 1997).

Table 52.2. Some clinical manifestations of autonomic dysfunction

Cardiovascular	
Postural hypotension	Supine hypertension
Lability of blood pressure	Paroxysmal hypertension
Tachycardia	Bradycardia
Sudomotor	
Hypohidrosis or anhidrosis	Hyperhidrosis
Gustatory sweating	
Hyperpyrexia	Heat intolerance
Alimentary	
Xerostomia	Dysphagia
Gastroparesis	Dumping syndrome
Constipation	Diarrhea
Urinary	
Nocturia	Frequency
Urgency	
Retention	Incontinence
Sexual	
Erectile failure	Ejaculatory failure
Retrograde ejaculation	
Eye	
Pupillary abnormalities	Partial ptosis
Alacrima	Lachrymation with food ingestion

symptoms accompany the fall in blood pressure (Mathias et al., 1999) (Table 52.3). These depend upon the rapidity and degree of fall in blood pressure, the extent to which compensatory factors come into play and the underlying disorder; additionally many factors influence orthostatic hypotension (Table 52.4). These range from stimuli in daily life such as food ingestion and mild exercise (Figs. 52.6 and 52.7) that can accentuate or exaggerate orthostatic hypotension. Determination of the mechanisms contributing to orthostatic hypotension is of importance in management.

Investigation of autonomic function and dysfunction

Activity may be measured directly or indirectly; sympathetic neural activity is measured electrophysiologically (using microneurography) or biochemically (by measuring plasma levels of noradrenaline and adrenaline or using spillover techniques) (Wallin et al., 1996). Each has its limitations, especially as measurements in a particular territory may not reflect activity either in the whole body or in other regions. In clinical practice, functional effects are measured with investigation directed to systems and organs (Mathias & Bannister, 1999a, b) (Table 52.5). Screening tests have been developed for evaluating cardiovascular autonomic function. They utilize safe and mainly non-invasive techniques and in combination with the clinical history and examination determine if further or detailed investigation is needed. The main objectives of investigation are:

(i) to assess if autonomic function is normal or abnormal;
(ii) if the latter, to ascertain the degree of autonomic dysfunction with an emphasis on the site of lesion and functional deficit;
(iii) to determine the underlying or associated disease as this will need concurrent treatment with management of autonomic dysfunction.

Non-autonomic tests may be needed to diagnose or delineate the underlying disorder. These include MRI scans of

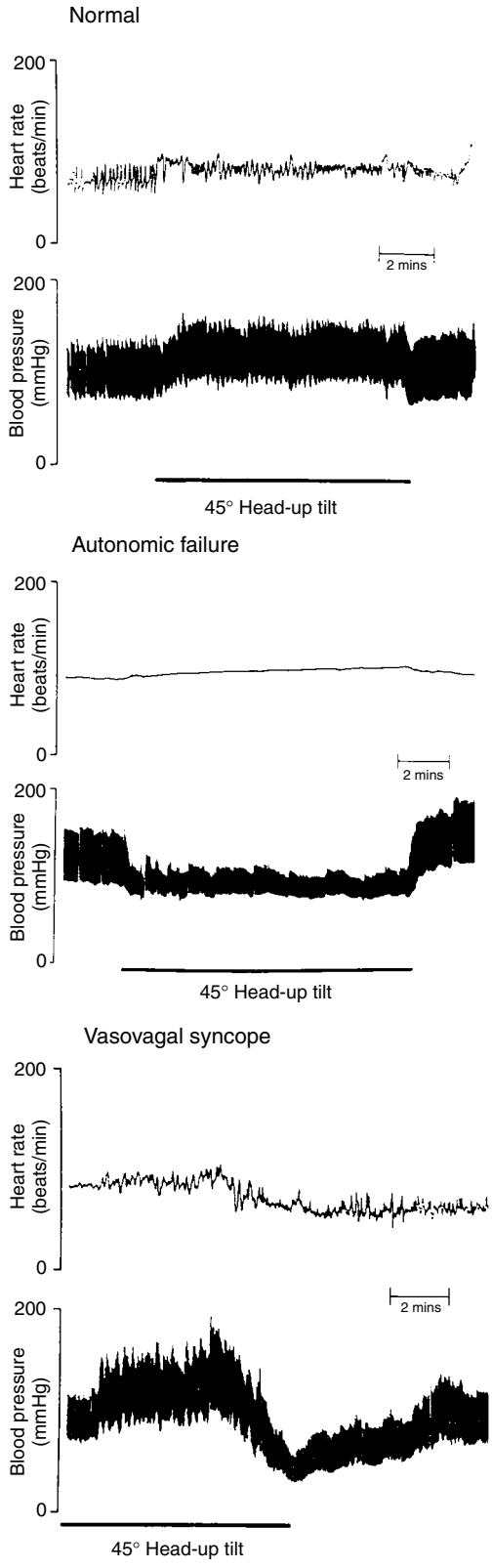

Table 52.3. Some of the various symptoms resulting from orthostatic hypotension and impaired perfusion of various organs

Cerebral hypoperfusion
- Dizziness
- Visual disturbances
  - Blurred
  - Tunnel
  - Scotoma
  - Greying out
  - Blacking out
  - Colour defects
- Loss of consciousness
- Impaired cognition

Muscle hypoperfusion
- Paracervical and suboccipital ('coathanger') ache
- Lower back/buttock ache
- Calf claudication

Cardiac hypoperfusion
- Angina pectoris

Spinal cord hypoperfusion

Renal hypoperfusion
- Oliguria

Non-specific
- Weakness, lethargy, fatigue
- Falls

Source: Adapted from Mathias (2000a).

Fig. 52.5. Blood pressure and heart rate before, during and after head-up tilt in a normal subject (uppermost panel), a patient with pure autonomic failure (middle panel), and a patient with vazovagal syncope (lowermost panel). In the normal subject there is no fall in blood pressure during head-up tilt, unlike the patient with autonomic failure in whom blood pressure falls promptly and remains low with a blood pressure overshoot on return to the horizontal. In the patient with autonomic failure there is only a minimal change in heart rate despite the marked blood pressure fall. In the patient with vazovagal syncope there was initially no fall in blood pressure during head-up tilt; in the latter part of tilt, as indicated inthe record, blood pressure initially rose and then markedly fell, to extremely low levels, so that the patient had to be returned to the horizontal. Heart rate also fell. In each case continuous blood pressure and heart rate were recorded with the Portapress II. (From Mathias & Bannister, 1999a).

Table 52.4. Factors influencing postural (orthostatic) hypotension

Speed of positional change
Time of day (worse in the morning)
Prolonged recumbency
Warm environment (hot weather, central heating, hot bath)
Raising intrathoracic pressure – micturition, defecation or coughing
Food and alcohol ingestion
Water ingestion[a]
Physical exertion
Manoeuvres and positions[b] (bending forward, abdominal compression, leg crossing, squatting, activating calf muscle pump)
Drugs with vasoactive properties (including dopaminergic agents)

Notes:
[a] May raise blood pressure, unlike food and alcohol.
[b] Usually reduce the postural fall in blood pressure.
Source: Adapted from Mathias and Bannister (1999).

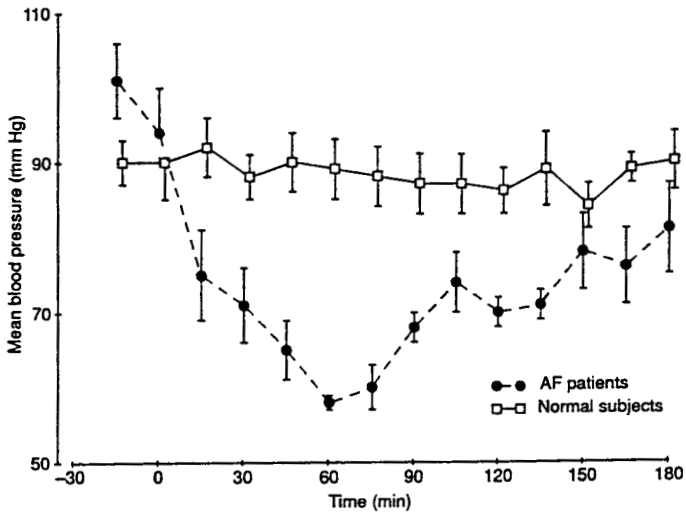

Fig. 52.6. Percentage change in mean blood pressure in a group of patients with chronic autonomic failure (dashed line, filled circles) and normal subjects (continuous line, open square) before and after food ingestion at time 0. The indicate mean ± SEM. (From Mathias et al., 1989.)

Table 52.5. Outline of investigations in autonomic failure

Cardiovascular	
Physiological	Head-up tilt (45°)[a]; standing[a]; Valsalva[a] manoeuvre[a]
	Pressor stimuli – isometric exercise[a], cold pressor[a], mental arithmetic[a]
	Heart rate responses – deep breathing[a], hyperventilation[a], standing[a], head-up tilt[a], 30: 15 ratio
	Liquid meal challenge
	Exercise testing
	Carotid sinus massage
Biochemical	Plasma noradrenaline – supine and head-up tilt or standing; urinary catecholamines; plasma renin activity and aldosterone
Pharmacological	Noradrenaline – α-adrenoceptors – vascular
	Isoprenaline – β-adrenoceptors – vascular and cardiac
	Tyramine – pressor and noradrenaline response
	Edrophonium – noradrenaline response
	Atropine – parasympathetic cardiac blockade
Sudomotor	Central regulation – thermoregulatory sweat test
	Sweat gland response – intradermal acetylcholine, quantitative sudomotor axon reflex test (Q-SART), localized sweat test
	Sympathetic skin response
Gastrointestinal	Barium studies, video-cine-fluoroscopy, endoscopy, gastric emptying studies
Renal function and urinary tract	Day and night urine volumes and sodium/potassium excretion
	Urodynamic studies, intravenous urography, ultrasound examination, sphincter electromyography
Sexual function	Penile plethysmography
	Intracavernosal papaverine
Respiratory	Laryngoscopy
	Sleep studies to assess apnea/oxygen desaturation
Eye	Lachrymal function – Schirmer's test
	Pupil function – pharmacological and physiological

Notes:
[a] Indicates screening tests used in our Units.
Source: From Mathias and Bannister (1999a).

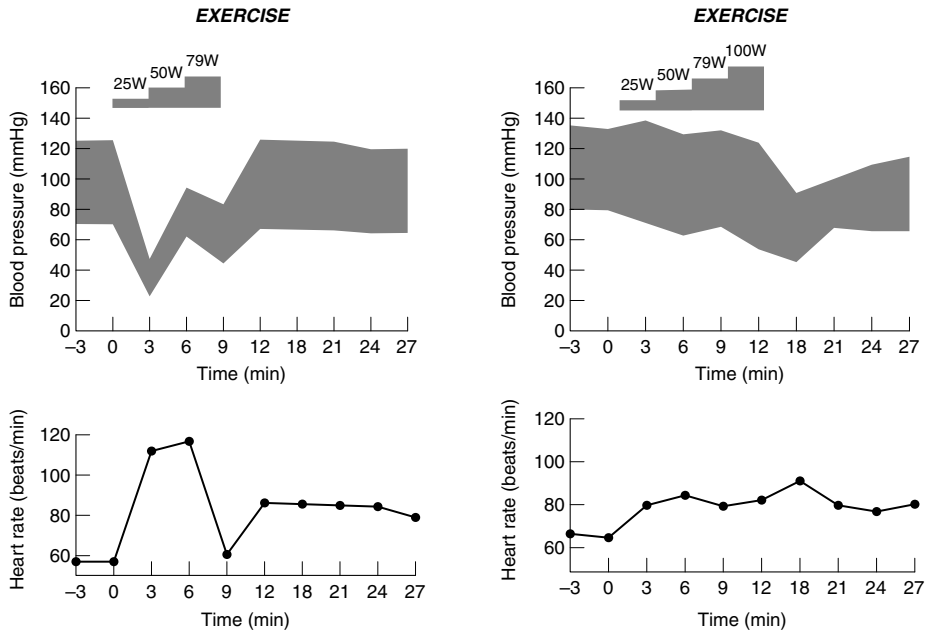

Fig. 52.7. Systolic and diastolic blood pressure (top) and heart rate (bottom) in two patients with autonomic failure before, during and after bicycle exercise performed with the patients in the supine position at different workloads, ranging from 25 to 100 watts. In the patient on the left there is a marked fall in blood pressure on initiating exercise; she had to crawl upstairs because of severe exercise induced hypotension. In the patient on the right, there are minor changes in blood pressure during exercise, but a marked decrease soon after stopping exercise. This patient was usually asymptomatic while walking, but developed postural symptoms when he stopped walking and stood still. It is likely that the decrease in blood pressure postexercise was due to vasodilatation in exercising skeletal muscle, not opposed by the calf muscle pump. (From Mathias & Williams, 1994.)

the brain in neurodegenerative disorders, sural nerve or cutaneous nerve biopsy in peripheral nerve disorders, genetic testing in familial amyloid polyneuropathies, and a range of non-neurological investigations, from HIV testing to defining the site of the primary in paraneoplastic autonomic neuropathy.

Management of autonomic disorders

A comprehensive approach is needed, especially in autonomic disorders that involve multiple systems and organs. The principles outlined for the management of orthostatic hypotension involve a combination of non-pharmacological and pharmacological measures (Table 52.6), that are based on pathophysiological mechanisms (Mathias & Kimber, 1999). In neurogenic orthostatic hypotension cure usually is not possible, and management in the individual patient should be directed to reducing disability, enabling independence and ensuring a reasonable quality of life whilst providing advice that is practical, and drugs that are safe. A similar approach should be used for impairment of sudomotor, gastrointestinal, urinary bladder and sexual function (Table 52.7) and modified accordingly.

Surgical intervention may be needed, such as tracheostomy in MSA with laryngeal abductor paresis or insertion of a percutaneous enterogastrotomy tube for severe dysphagia. Complex procedures, such as hepatic transplantation reduce levels of variant transthyretin in familial amyloid polyneuropathy and halt deposition of amyloid in nerves, while pancreatic (usually in combination with renal) transplantation improves certain features in diabetic autonomic neuropathy. In essential hyperhidrosis there is a role for percutaneous endoscopic sympathectomy; botulism toxin has been proved useful (Naumann et al., 1997).

In addition to autonomic deficits, attention should be paid to associated features, such as depression in the parkinsonian syndromes, or anxiety and phobia in vasovagal syncope. Education of the patient is of importance as increased knowledge of the disorder and its mechanisms improves patient compliance and management. In disorders such as MSA, education of the spouse, carers and medical therapists is important.

Table 52.6. Management of orthostatic hypotension

Non-pharmacological measures
To be avoided
– Sudden head-up postural change (especially on waking)
– Prolonged recumbency
– Straining during micturition and defecation
– High environmental temperature (including hot baths)
– 'Severe' exertion
– Large meals (especially with refined carbohydrate)
– Alcohol
– Drugs with vasodepressor properties
To be introduced
– Head-up tilt during sleep
– Small, frequent meals
– High salt intake
– Judicious exercise (including swimming)
– Body positions and manoeuvres
To be considered
– Elastic stockings
– Abdominal binders
– Water ingestion
Pharmacological measures
Starter drug:
– fludrocortisone
Sympathomimetics
– ephedrine, midodrine, l-dihydroxyphenylserine
Specific Targeting
– desmopressin for nocturnal polyuria
– octreotide for postprandial hypotension
– erythopoietin for anemia

Sources: Adapted from Mathias and Kimber (1999).

Primary autonomic failure syndromes

These include the acute/sub-acute dysautonomias and chronic autonomic failure syndromes (Table 52.8).

Acute/subacute dysautonomia

These are relatively rare disorders. In pure pandysautonomia, there are features of both sympathetic and parasympathetic failure. Orthostatic hypotension often is a major problem. The peripheral nerves may be affected in pure dysautonomia with other neurological features. The prognosis in pandysautonomia is variable, with complete recovery in some. The response to immunoglobulin therapy (Heafield et al., 1996; Smit et al., 1997) suggests an immunological etiology.

Table 52.7. Outline of management strategies in autonomic failure when different systems are involved, as in MSA

Specific	for orthostatic hypotension and bladder, bowel and sexual dysfunction: non-pharmacological and pharmacological therapy
	for respiratory abnormalities: to consider tracheotomy
	for oropharyngeal dysphagia: to consider percutaneous endoscopic gastrotomy
General	for depression etc.
Education	of patient, partners, relatives, carers, practitioners (medical and supportive therapists, to include physiotherapists, occupational therapists, speech therapists, dietitians)
Patient support groups	
	to disseminate information and increase awareness. They include:
	Shy–Drager Association in USA
	Autonomic disorders Association Sarah Matheson Trust in UK
Integrative approaches	
	Autonomic nurse specialist or autonomic liaison nurse to co-ordinate and promote seamless management

Pure cholinergic dysautonomia is an even rarer condition mainly affecting children and young adults. There are symptoms of parasympathetic failure (blurred vision, dry eyes, xerostomia, dysphagia involving mainly the lower esophagus, constipation and urinary retention), and sympathetic cholinergic failure (anhidrosis and a tendency to hyperthermia). The signs include dilated pupils, raised heart rate, dry and hot skin, a distended abdomen and a palpable urinary bladder. Orthostatic hypotension is absent as sympathetic vasoconstrictor function is not impaired. Recovery from the defect is unlikely. Therapy should include maintenance of fluid balance and body temperature. A barium meal examination must be avoided as it will be retained in the colon. The differential diagnosis includes anticholinergic drugs that may cause similar features, but with recovery in a few days. A variant of botulinum (botulism B) affects cholinergic pathways alone with sparing of the motor pathways; substantial recovery often occurs within a few months.

Chronic autonomic failure syndromes

The main disorders, along with diseases with overlapping features, are schematically outlined in Fig. 52.8.

Table 52.8. Primary autonomic failure syndromes

Acute/subacute autonomic neuropathy
– Pure pandysautonomia
– Pandysautonomia with additional neurological features
– Pure cholinergic dysautonomia
Chronic autonomic failure
– Pure autonomic failure
– Multiple system atrophy
– Parkinson's disease with autonomic failure
– Diffuse Lewy Body Disease

Table 52.9. Clinical manifestations and possible presenting features of syndromes of primary chronic autonomic failure

System affected	Clinical features
Cardiovascular	Orthostatic hypotension
Sudomotor	Anhidrosis, heat intolerance
Gastrointestinal[a]	Constipation, occasionally diarrhea, dysphagia
Renal and urinary bladder	Nocturia, frequency, urgency, incontinence, retention of urine
Reproductive	Erectile and ejaculatory failure
Ocular	Anisocoria, Horner's syndrome
Respiratory[a]	Stridor, inspiratory gasps, apneic episodes
Neurologic	Parkinsonian, cerebellar and pyramidal

Notes:

[a] Certain features, such as oropharyngeal dysphagia and respiratory abnormalities (including those resulting from laryngeal-abductor paresis), occur in multiple system atrophy rather than in pure autonomic failure.

Source: From Mathias (1997).

Pure autonomic failure

These patients often are over the age of 50 at presentation. In the majority the diagnosis usually is considered when orthostatic hypotension is detected. The onset may be insidious as a number of compensatory mechanisms, often unwittingly used, help reduce the symptoms of orthostatic hypotension. Alternative diagnoses, ranging from epilepsy to a psychiatric disorder, may be considered erroneously. In males, impotence is common. Nocturia (rather than the urinary symptoms listed in Table 52.6) is frequent, along with constipation. Impairment of sweating may not be recognized in temperate climates. Heat intolerance and collapse may occur in tropical areas. The clinical and laboratory features include widespread sympathetic failure, usually with parasympathetic deficits. The physiological and biochemical tests indicate a peripheral autonomic lesion which is consistent with the neuropathological data available (Matthews, 1999). Lewy bodies have been reported in autonomic ganglia.

In PAF, management of orthostatic hypotension is of importance as it contributes to morbidity and may result in injury. Control of bowel and bladder function, and in males sexual function, may need to be addressed. The overall prognosis in PAF is good, with a life expectancy not dissimilar to healthy individuals of an equivalent age.

Multiple system atrophy

This probably is the most common neurodegenerative condition affecting the autonomic nervous system in humans. It is synonymous with the Shy–Drager syndrome and is a sporadic non-familial disorder with autonomic, parkinsonian, cerebellar and pyramidal features that occur in any combination over a varying time scale (Mathias & Williams, 1994; Wenning et al., 1994; Gilman et al., 1998) (Table 52.9). It is a progressive disorder but with an unpredictable rate of progression; this adds to difficulties in diagnosis. The majority with MSA have parkinsonian features at some stage of the disease. When parkinsonism is a presenting feature there are difficulties in distinguishing MSA from Parkinson's disease (PD). This accounts for why up to 25% of patients diagnosed in vivo as IPD were found at postmortem to have the characteristic neuropathological features of MSA. In the early stages, depending on the presentation, patients may consult a range of specialists, from neurologists and cardiologists to urologists and psychiatrists.

There are three major subgroups in MSA based on their neurological features; the parkinsonian form (MSA-P; where the neuropathological findings include striatonigral degeneration), the cerebellar form (MSA-C; with olivopontocerebellar degeneration) and the mixed form, with a combination of neurological features (MSA-M); with striatonigral and olivopontocerebellar degeneration (Daniel, 1999). A key neuropathological feature is the presence of intracytoplasmic argyrophyllic inclusions in oligodendrocytes, within defined areas of the brain and spinal cord. Programmed cell death (apoptosis) appears to be specific for oligodendrocytes in MSA (Probst-Cousin et al., 1998). Cell loss in various brainstem nuclei (including the vagus), the intermediolateral cell mass in the thoracic and lumbar spinal cord, and Onuf's nucleus in the sacral spinal cord account for various abnormalities. The paravertebral ganglia and visceral (enteric) plexuses are not affected.

In MSA, the additional neurological features do not necessarily help distinction from overlapping syndromes. In

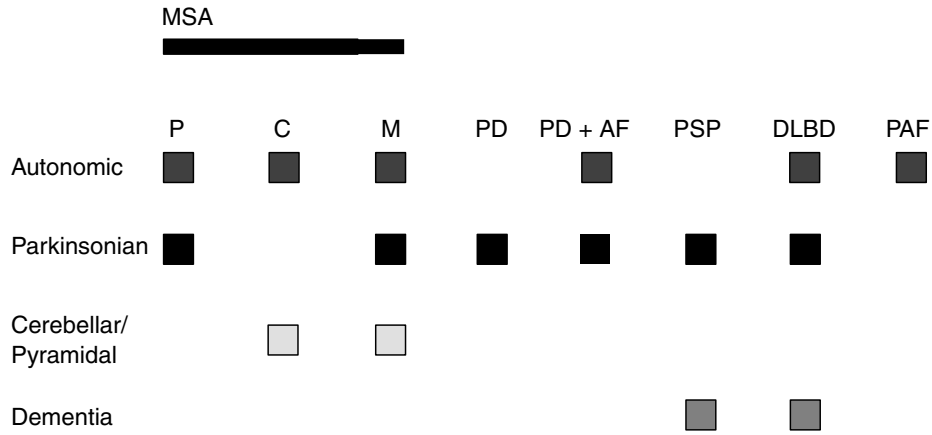

Fig. 52.8. The major clinical features in parkinsonian syndromes and allied disorders with autonomic failure. These include the three major neurologic forms of multiple system atrophy – the parkinsonian form (MSA-P, also called striatonigral degeneration), the cerebellar form (MSA-C, also olivoponocerebellar atrophy) and the multiple or mixed form (MSA-M, which has features of both other forms); idiopathic Parkinson's disease (PD), Parkinson's disease + autonomic failure (PD + AF); progressive supranuclear palsy (PSP), diffuse Lewy body disease (DLBD) and pure autonomic failure (PAF). (Adapted from Mathias, 1997.)

the parkinsonian forms, the onset of bradkinesia and rigidity is often bilateral, with minimal or no tremor, unlike PD. Lack of a motor response to dopaminergic drugs alone is not helpful, as two-thirds of MSA patients respond favourably initially, although side effects and refractoriness to the motor benefits with time lowers this to a third or less. The presence of autonomic failure (especially cardiovascular and genitourinary) in a patient with parkinsonism should alert one to the possibility of MSA. Respiratory abnormalities and oropharyngeal dysphagia favour MSA, and often occur as the disease advances.

Investigation aids diagnosis and management (Table 52.10). Neuroimaging (especially positron emission tomography, MR scanning of the brain and proton magnetic resonance spectroscopy of the basal ganglia), may help distinguish MSA from other parkinsonian syndromes. The presence of orthostatic hypotension does not necessarily indicate autonomic failure (Table 52.11), although its recording is of importance for management. Cardiac sympathetic denervation is not observed in MSA, and this is consistent with a central, preganglionic lesion. The sympathetic skin response often is abnormal in the mixed form, but up to a third of either MSA-P or MSA-C have a preserved SSR, excluding it as a diagnostic test in the early stages. The combined neuropharmacological–neuroendocrine approach using clonidine-growth hormone (GH) testing separates central from peripheral autonomic failure (Thomaides et al., 1992). The centrally acting alpha-2 adrenoceptor agonist clonidine stimulates hypothalamic GH releasing hormone that acts on the anterior pituitary to release GH (Fig. 52.9(a),(b)). After clonidine, levels of GH rise in PAF, where there is no central autonomic abnormality. In the different forms of MSA there is no GH response to clonidine. However, another GH secretagogue, L-dopa, raises GHRH and GH levels in MSA (Kimber et al., 1999) while apomorphine raises GH in MSA with a greater response in PD (Friess et al., 2001), indicating that the abnormal response is not the result of widespread and hypothalamic neuronal fall-out, and probably indicates a specific alpha-2 adrenoceptor-hypothalamic deficit. Early reports indicate preservation of the clonidine-GH response in non-drug treated PD (Kimber et al., 1997a); this may not apply to drug-treated PD. Whether the clonidine-GH test will distinguish MSA from other parkinsonian and peripheral autonomic syndromes at an early stage remains to be determined. In MSA, the urethral or anal sphincter electromyograph is usually abnormal, characteristically indicating denervation and reinnervation (Palace et al., 1997). False positives include prostatic surgery in the male and multiparous females; it also may be abnormal in progressive supranuclear palsy (PSP). The combination of orthostatic hypotension and an abnormal urethral/anal sphincter electromyograph, in conjunction with the characteristic clinical features, are virtually confirmatory of MSA.

The prognosis in MSA is poor compared with PD and PAF, as the motor and autonomic deficits progressively worsen. There is a refractoriness to anti-parkinsonian agents; orthostatic hypotension may further impair mobility. Communication becomes increasingly difficult. In the cerebellar form, worsening truncal ataxia may cause falls

Table 52.10. Some of the investigations used in parkinsonism to evaluate autonomic function and separate MSA from IPD

Neuroimaging studies
- Magnetic resonance imaging
- Magnetic resonance spectroscopy
- Positron emission tomography – with various ligands

Autonomic screening tests
- to determine if orthostatic hypotension is present
- to assess sympathetic vasoconstrictor responses
- to evaluate parasympathetic cardiac responses

Additional autonomic tests
- food and exercise challenge
- 24-hour ambulatory blood pressure and heart rate profile

Cardiac sympathetic evaluation
- meta-iodo-benzyl-guanidine and gamma scintiscanning
- 6-Fluorodopamine and positron emission tomography scanning

Sympathetic skin response

Clonidine-growth hormone stimulation test

Urethral or anal sphincter electromyography

Table 52.11. Some of the possible causes of orthostatic hypotension in a patient with parkinsonian features

Side effects of anti-parkinsonian therapy
L-DOPA, bromocriptine, pergolide
the combination of L-DOPA and COMT inhibitors (tolcapone)
the MAO 'b' inhibitor, selegiline

Coincidental disease causing autonomic dysfunction
e.g. diabetes mellitus

Coincidental administration of drugs for an allied condition
Antihypertensives
α-adrenoceptor blockers (for benign prostatic hypertrophy)
Vasodilators (for ischemic heart disease)
Diuretics (for cardiac failure)

Multiple system atrophy (Shy–Drager syndrome)

Parkinson's disease with autonomic failure

Diffuse Lewy body disease

Source: Adapted from Mathias and Kimber (1999).

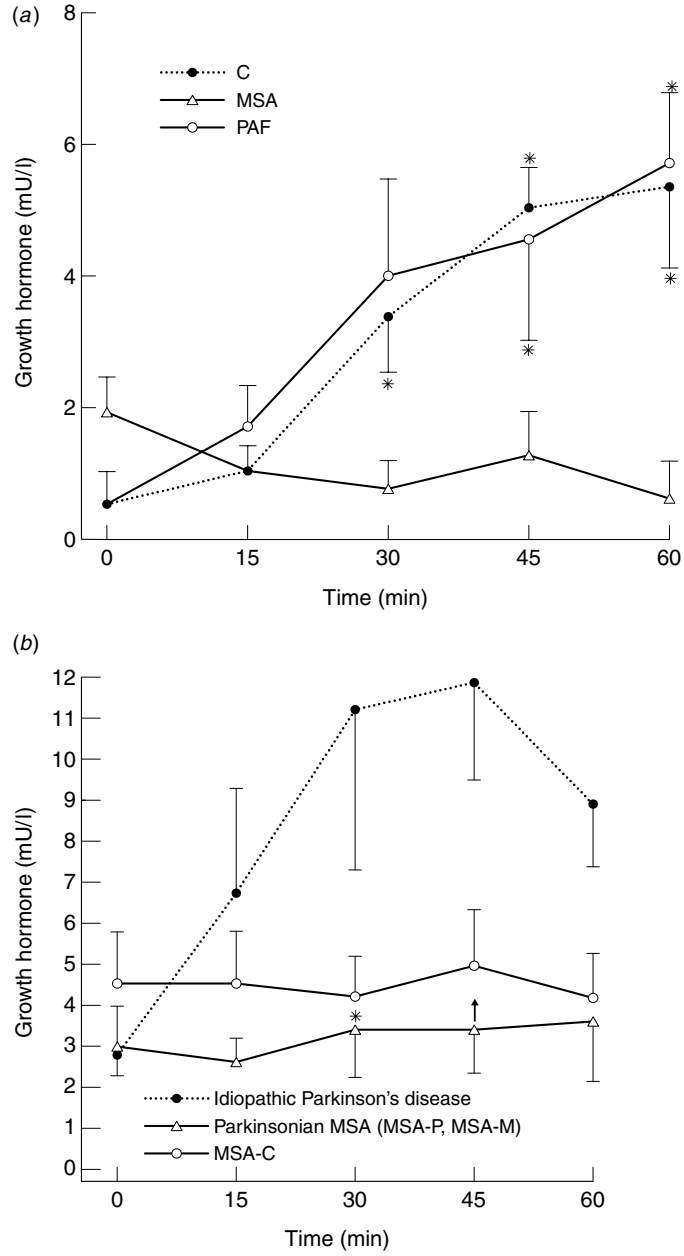

Fig. 52.9. (*a*) Serum growth hormone (GH) concentrations before (0) and at 15 min intervals for 60 min after clonidine (2 μg/kg/min) in normal subjects (C, controls) and in patients who have multiple system atrophy (MSA) and pure autonomic failure (PAF). GH concentrations rise in controls and in patients who have PAF with a peripheral lesion; there is no rise in patients with MSA with a central lesion. (From Thomaides et al., 1992.)

(*b*) Lack of serum GH response to clonidine in the two forms of MSA (the cerebellar form, MSA-C and the parkinsonian forms, MSA-P and MSA-M) in contrast to patients with idiopathic Parkinson's disease with no autonomic deficit, in whom there is a significant rise in GH levels. (From Kimber et al., 1997a.)

and an inability to stand upright; incoordination in the upper limbs, speech deficits and nystagmus add to the disability. Oropharyngeal dysphagia enhances the risk of aspiration, especially as many have vocal cord abnormalities; a percutaneous feeding gastrostomy may be needed. Respiratory abnormalities that include obstructive (due to laryngeal abductor cord paresis) and central apnea, may necessitate a tracheostomy.

In MSA there currently is no means of reversing the neurological decline. Supportive therapy is an essential component in management and should incorporate the family, therapists and community. Many autonomic features can be helped, and this includes orthostatic hypotension, bowel, bladder and sexual dysfunction.

Idiopathic Parkinson's disease and other parkinsonian disorders

In PD, autonomic features usually are not prominent, especially in the early stages. Orthostatic hypotension if present, may be related to increased duration of disease, age and multiple drug therapy. A varying prevalence has been described, from rare to high (58% with 38.5% symptomatic) (Mathias, 1998a,b). Meta-iodo-benzylguanidine with gamma scintiscanning, and fluorodopamine with positron emission tomographic scanning, of the heart indicate that cardiac sympathetic denervation may occur early in the disorder, often without other detectable autonomic features (Goldstein et al., 1997, Orima et al., 1999). The implications of this observation are unclear and have relevance to cardiac arrhythmias and drug therapy in PD. Whether the urinary and gastrointestinal features are due to autonomic or other mechanisms is unclear. In PD Lewy bodies are present in the esophageal and colonic myenteric plexuses with reduction of dopaminergic neurons in the latter.

There is a smaller group, often of older patients with apparently classic PD, who have been successfully treated with l-dopa for many years and then develop features of autonomic failure, usually with severe postural hypotension. They thus differ from the majority of patients with PD in whom autonomic deficits, if present, are relatively mild. Cardiac scanning techniques indicate sympathetic denervation, favouring a peripheral lesion similar to PAF (Goldstein et al., 1997). These patients also have low basal plasma noradrenaline levels and their orthostatic hypotension does not respond to yohimbine (whose actions are dependent on intact sympathetic nerves). The etiology of PD with AF is unknown. It may be a coincidental association of a common condition with an uncommon disorder (PAF), or an indication of vulnerability to autonomic degeneration in a sub-group of PD, that may be linked to increasing age, chronic anti-parkinsonian drug therapy, an inherent metabolic susceptibility, or to a combination of these factors. These patients do not appear to suffer from the many complications of MSA and clinically appear to differ from them.

Dizziness and orthostatic hypotension is more common in diffuse Lewy body disease(DLBD), than previously recognized. Some patients may be mistakenly diagnosed as PAF or MSA. In PAF, Lewy bodies are also present in the peripheral autonomic nervous system, raising the possibility that it may be a forme fruste, or an early stage, of DLBD. In PSP, unlike previous reports, more recent studies indicate lack of orthostatic hypotension and cardiovascular autonomic features, which has now been proposed as an exclusionary feature in the diagnosis of this disorder (Kimber et al., 2000). Urinary abnormalities and an abnormal sphincter electromyograph may be present; there is evidence of degeneration of Onuf's nucleus in the sacral cord. In Huntingdon's disease, defects in vasoregulation have been described and attributed to involvement of suprabulbar structures including caudate nuclei, but there is no significant cardiovascular abnormality; however, hyperhidrosis, diarrhea and sphincter disturbances may occur. In Guamanian parkinsonism and parkinsonian–dementia complex, there are autonomic abnormalities affecting the cardiovascular system that are greater than usually observed in PD and less than MSA but may be confounded by diabetes and antihypertensive drug therapy. Whether there are autonomic abnormalities of significance in other parkinsonian syndromes remains to be determined.

Secondary autonomic failure

There is a wide range of secondary disorders (Table 52.12). Some are described briefly below.

Hereditary

Riley–Day syndrome; familial dysautonomia

This occurs in children of Ashkenazi–Jewish extraction (Axelrod, 1999). They have absent fungiform papillae, lack of corneal reflexes, decreased deep tendon reflexes and a diminished response to pain. This is often observed at birth. An abnormal intradermal histamine skin test (with an absent flare response) and pupillary hypersensitivity to cholinomimetics, confirms the diagnosis. The defective gene has been mapped to the long arm of chromosome 9 (q31).

Table 52.12. Secondary autonomic failure

Congenital
- Nerve growth factor deficiency

Hereditary

Autosomal dominant
- Familial amyloid neuropathy
- Porphyria

Autosomal recessive
- Familial dysautonomia (Riley–Day syndrome)
- Dopamine beta-hydroxylase deficiency
- Aromatic L-amino acid decarboxylase deficiency

X-linked recessive
- Fabry's disease

Metabolic diseases
- Diabetes mellitus
- Chronic renal failure
- Chronic liver disease
- Vitamin B_{12} deficiency
- Alcohol-induced

Inflammatory
- Guillain–Barré syndrome
- Transverse myelitis

Infections
- Bacterial – tetanus, leprosy
- Viral – human immuno-deficiency virus infection
- Parasitic – Chagas' disease
- Prion – fatal familial insomnia

Neoplasia
- Brain tumours – especially of third ventricle or posterior fossa
- Paraneoplastic, to include adenocarcinomas – lung, pancreas and Lambert–Eaton syndrome

Connective tissue disorders
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Mixed connective tissue disease

Surgery
- Regional sympathectomy – upper limb, splanchnic
- Vagotomy and drainage procedures – 'dumping syndrome'
- Organ transplantation – heart, kidney

Trauma
- Spinal cord transection

A variety of symptoms, resulting from both autonomic underactivity and overactivity may occur. These include a labile blood pressure (with hypertension and postural hypotension), parasympathetic abnormalities (with periodic vomiting, dysphagia, constipation and diarrhea) and urinary bladder disturbances. Neurological abnormalities, associated skeletal problems (scoliosis) and renal failure previously contributed to a poor prognosis. The ability to anticipate complications and provide adequate support and therapy has resulted in a number of children now reaching adulthood.

Amyloid polyneuropathy

Both light chain (AL) and familial amyloid polyneuropathy (FAP) result in autonomic dysfunction (Reilly & Thomas, 1999). In the AL form, amyloid is derived from monoclonal light chains, secondary to multiple myeloma, malignant lymphoma or Waldenstrom's macroglobulinemia. The features vary with an overall poor prognosis. In FAP, symptoms usually occur in adulthood. Sensory, motor and autonomic abnormalities result from deposition in peripheral nerves of mutated amyloid protein, mainly produced in the liver. Motor and sensory neuropathy often begins in the lower limbs. Classification of FAP is now based on the chemical and molecular nature of the constituent proteins and not on clinical presentation. There are various forms; transthyretin (TTR) FAP; FAP Ala 60 (Irish/ Appalachian) and FAP Ser 84 and His 58. The cardiovascular system, gut and urinary bladder can be affected at any stage. The disease relentlessly progresses but at a variable rate. There may be dissociation of autonomic symptoms from functional deficits; this is of importance, as evaluation and treatment of cardiovascular autonomic abnormalities is essential in reducing morbidity and mortality especially during hepatic transplantation. Currently, this is the only way to reduce levels of variant transthyretin and its deposition in nerves; it prevents progression of, and may reverse some, neuropathic features. It may be of greater value if performed before nerve damage occurs.

Dopamine beta-hydroxylase deficiency

This rare disorder, recognized in the mid-1980s, has been described in seven patients, two of whom are siblings (Mathias & Bannister, 1999c). Symptoms began in childhood, although an autonomic disorder was not considered until they became teenagers, when orthostatic hypotension was first recognised. Whether the symptoms become more prominent, or are easier to detect at this time, is unclear. The clinical features indicate sympathetic adrenergic failure with sparing of sympathetic cholinergic and parasympathetic function. Sweating is preserved and

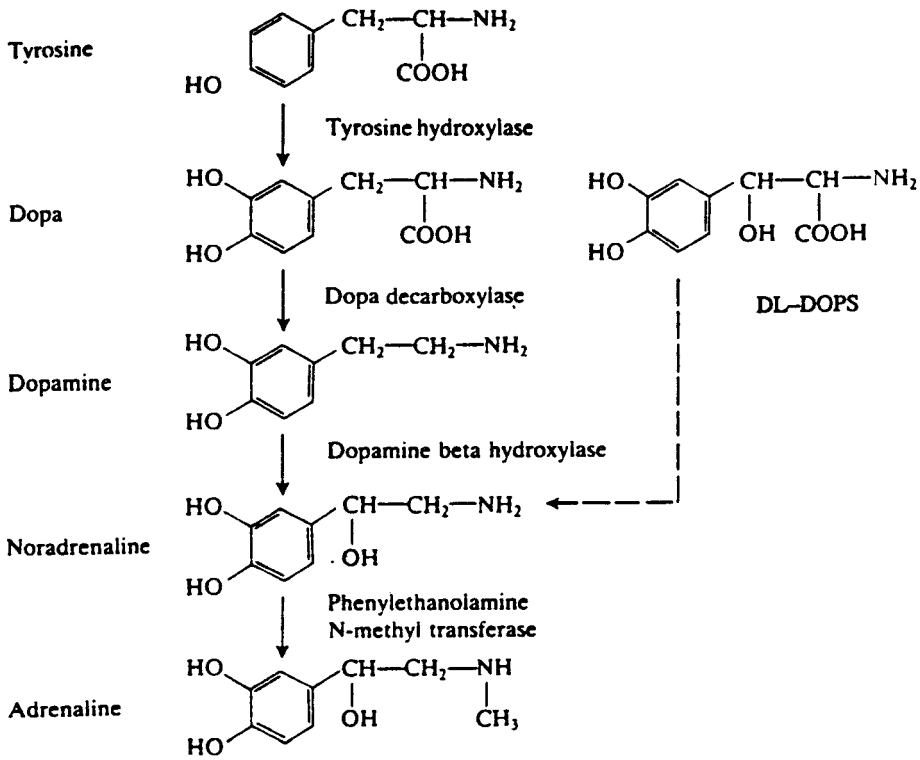

Fig. 52.10. Biosynthetic pathway in the formation of noradrenaline and adrenaline. The structure of DL-DOPS is indicated on the right. It is converted directly to noradrenaline by dopa decarboxylase, thus bypassing dopamine β-hydroxylase.

urinary bladder and bowel function is normal; in one of the males erection was possible but ejaculation was difficult to achieve. The diagnosis may be made from basal levels of plasma catecholamines, as noradrenaline and adrenaline levels are undetectable while dopamine levels are elevated. The enzymatic defect is highly specific, with the sympathetic nerve pathways and terminals otherwise intact, as has been demonstrated by both electron microscopy and preservation of muscle sympathetic nerve activity using microneurography. These subjects, therefore, are a unique model of superselective sympathetic adrenergic failure. Treatment is with the pro-drug L-dihydroxyphenylserine (Fig. 52.10), which has a structure similar to noradrenaline except for a carboxyl group that is acted upon by the enzyme dopadecarboxylase (abundantly present in extraneuronal tissues such as the liver and kidneys), thus transforming it into noradrenaline. This reduces orthostatic hypotension and has resulted in remarkable improvements in their ability to lead active lives.

Diabetes mellitus

There is a high incidence of both peripheral and autonomic neuropathy, especially in older, long-standing diabetics on insulin therapy (Watkins, 1998). Their morbidity and mortality is considerably higher than in those without a neuropathy. It initially often involves the vagus, with characteristic features of cardiac vagal denervation. This may occur in conjunction with partial preservation of the cardiac sympathetic and may predispose diabetics, many of whom have ischemic heart disease, to sudden death from cardiac dysrhythmias. In some, sympathetic failure may cause orthostatic hypotension, that may be enhanced by insulin (Fig. 52.11). Awareness of hypoglycemia, that depends on autonomic activation, is diminished. There may be involvement of the gastro-intestinal tract (gastroparesis diabeticorum and diabetic diarrhea), the urinary bladder (diabetic cystopathy) and in the male, impotence. Sudomotor abnormalities include gustatory sweating. Damage to other organs may occur through non-neuropathic factors and compounds the problems caused by the neuropathy. Diabetic foot problems may result from a combination of neuropathy and ischemia. Other than maintaining normoglycemia, there is no known means to prevent and reverse the neuropathy except possibly by pancreatic transplantation.

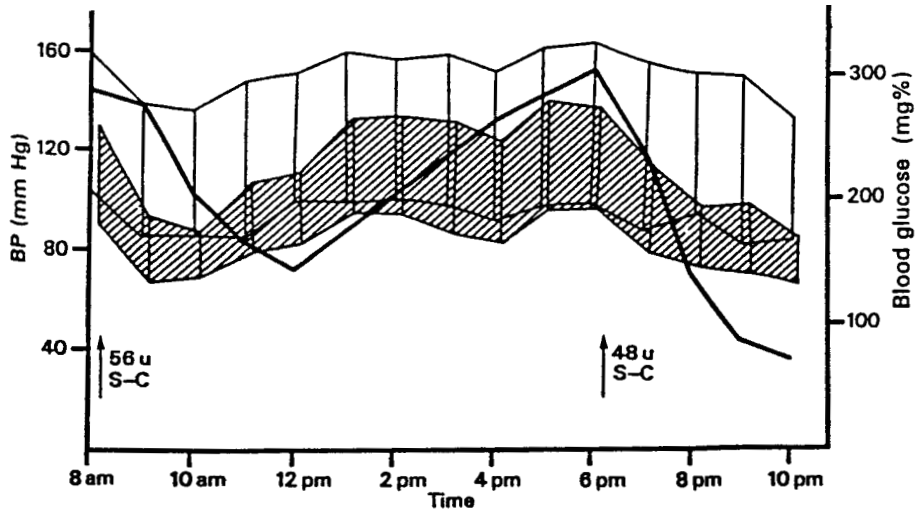

Fig. 52.11. Diurnal variation of lying and standing blood pressure in a 48-year-old man with severe diabetic autonomic neuropathy. Insulin was given subcutaneously (S-C) at times shown by the vertical arrows. The unhatched area shows supine blood pressure, the hatched area the standing blood pressure, and the continuous line the blood glucose. (From Watkins & Edmonds, 1999.)

Spinal cord diseases

Autonomic dysfunction affecting various systems occurs in spinal cord disease, as the entire sympathetic and the sacral sympathetic outflow is from the spinal cord (Mathias & Frankel, 1999). The level of completeness of lesion determines the degree of dysfunction.

Cardiovascular autonomic dysfunction can contribute to morbidity and mortality, especially in cervical and high thoracic spinal cord lesions. Orthostatic hypotension results from the inability of the brain to activate efferent sympathetic pathways, despite preservation of baroreceptor afferent and central connections. In these subjects the reverse, paroxysmal hypertension, may occur following large bowel and urinary bladder contraction as part of the mass reflex, in the syndrome of autonomic dysreflexia (Fig. 52.12). This is due to isolated spinal cord reflex activity (without the restraint of cerebral control) and can be induced by a variety of stimuli, from cutaneous, skeletal muscle or visceral sources, below the level of the lesion. In the acute phase after injury, such patients may have a different set of clinical problems, because of 'spinal shock' and the absence of even isolated spinal sympathetic activity; some of these result also from excessive cardiac vagal activity causing bradycardia or even cardiac arrest.

A combination of autonomic underactivity and overactivity may occur in non-spinal disorders. In the Guillain–Barré syndrome both autonomic hyperactivity and underactivity may occur (Asahina et at., 2001); tachycardia and hypotension may alternate with bradycardia and hypertension. The precise mechanisms are unclear and the possibilities should be anticipated as appropriate drugs may be needed. Cardiovascular disturbances of a similar nature may occur in tetanus, especially in those who suffer muscle paralysis and are on assisted respiration.

Drugs, chemicals, toxins

Drugs may cause autonomic dysfunction through their recognized pharmacological effects, such as sympatholytic agents (Table 52.13). A side effect of a drug may cause clinical problems when used in high dosage or over a prolonged period (such as the anticholinergic effects of antidepressants), or when autonomic deficits are unmasked or induced in susceptible individuals. Examples of the latter include L-dopa worsening orthostatic hypotension in MSA (Fig. 52.13), the ability of pressor agents to cause severe hypertension in autonomic failure because of denervation supersensitivity (Fig. 52.6), and the antiarrhythmic disopyramide inducing urinary retention in subjects with benign prostatic hypertrophy. Drugs such as perhexeline maleate, vincristine and alcohol may induce autonomic dysfunction independently of their pharmacological properties, by causing an autonomic neuropathy.

Neurally mediated syncope

These disorders are characterized by an intermittent cardiovascular autonomic abnormality resulting in syncope (loss of consciousness synonymous with fainting, blackouts) (Kapoor, 2000; Mathias et al., 2001) (Table 52.14). An

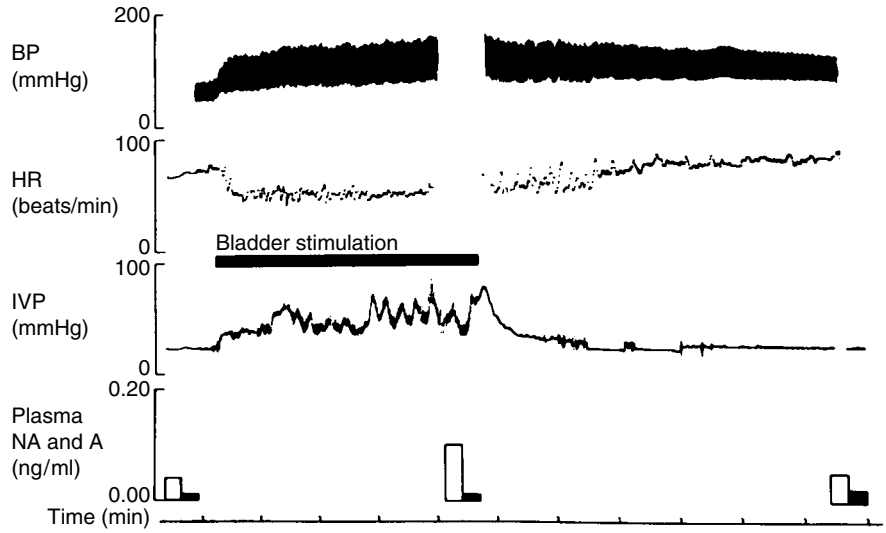

Fig. 52.12. Blood pressure (BP), heart rate (HR), intravesical pressure (IVP), and plasma noradrenaline (NA; open histogram) and adrenaline (A; filled histogram) levels in a tetraplegic patient before, during and after bladder stimulation induced by suprapubic percussion of the anterior abdominal wall. The rist in BP is accompanied by a fall in heart rate as a result of increased vagal activity in response to the rise in blood pressure. Levels of plasma NA, but not A rise, suggesting an increase in sympathetic neural activity independently of adrenomedullary activation. (From Mathias & Frankel, 1999.)

increase in cardiac parasympathetic activity causes severe bradycardia or cardiac arrest (cardio-inhibitory form) and withdrawal of sympathetic nerve activity results in hypotension (vasodepressor form). The two may occur separately, or together as the mixed form (Fig. 52.14). Between episodes there may be no abnormalities detected on routine autonomic testing.

In the young, the more common condition is vasovagal syncope. There is often a family history of a similar disorder (Mathias et al., 1998). It is more common in women. It may be induced by various stimuli, from fear and the sight of blood, to venepuncture and at times even discussion of venepuncture. Standing still, a warm environmental temperature and other factors that promote vasodilation, including gravitational pooling, can induce syncope. Modified testing, which includes prolonged tilt-table testing and, in some, application of a provocative stimulus (including venepuncture or pseudo-venepuncture), may induce an episode. Cardiac conduction disorders and other causes of syncope need to be excluded. Some advocate supraphysiological (head-up tilt and lower body negative pressure) and pharmacological (head-up tilt and isoprenaline infusion) testing; these stimuli however, may provoke an attack in subjects who have never fainted (El-Bedawi & Hainsworth, 1994; Morillo et al., 1995). Management includes reducing or preventing exposure to precipitating causes although these may be unclear; in some behavioural therapy (especially in those with phobias), is needed. A high salt diet, exercise and various drugs such as fludrocortisone, vasopressor agents, and antidepressants (including the serotonin-uptake release inhibitors), have been used with varying success. In some with the cardio-inhibitory form, a cardiac demand pacemaker is of value. The long-term prognosis is favourable and in many, attacks do not occur after the third decade.

In the elderly, carotid sinus hypersensitivity may be more common than previously thought; it may be a major cause of unexplained falls (McIntosh et al., 1993). There may be a classical history of syncope induced by head movements or collar tightening; in many the precipitating factors are unclear. Investigation should include carotid sinus massage performed with requisite precautions in the laboratory with adequate resuscitation facilities, ideally using beat-by-beat blood pressure and heart rate recording. Carotid massage also should be performed with the subject tilted head-up, as hypotension is more likely to occur in situations when sympathetic nerve activity is needed. In the cardio-inhibitory form a cardiac demand pacemaker is used. The vasodepressor forms are more difficult to manage and pressor agents have been used. Denervation of the carotid sinus may be used especially in unilateral hypersensitivity.

Table 52.13. Drugs/chemicals/poisons/toxins

DECREASING SYMPATHETIC ACTIVITY

Centrally acting

- Clonidine
- Methyldopa
- Reserpine
- Barbiturates
- Anesthetics

Peripherally acting

- Sympathetic nerve ending (guanethidine, bethanadine)
- Alpha-adrenoceptor blockade (phenoxybenzamine)
- Beta-adrenoceptor blockade (propranolol)

INCREASING SYMPATHETIC ACTIVITY

- Amphetamines
- Releasing noradrenaline (tyramine)
- Uptake blockers (imipramine)
- Monoamine oxidase inhibitors (tranylcypromine)
- Beta-adrenoceptor stimulants (isoprenaline)
- Following drug withdrawal (clonidine, alcohol, opiates)

DECREASING PARASYMPATHETIC ACTIVITY

- Antidepressants (imipramine)
- Tranquillizers (phenothiazines)
- Antidysrhythmics (disopyramide)
- Anticholinergics (atropine, probanthine, benztropine)
- Toxins (botulinum)

INCREASING PARASYMPATHETIC ACTIVITY

- Cholinomimetics (carbachol, bethanechol, pilocarpine, mushroom poisoning)
- Anticholinesterases
- Reversible carbamate inhibitors (pyridostigmine, neostigmine)
- Organophosphorus inhibitors (parathion)

Miscellaneous

- Alcohol, thiamine (vitamin B_1 deficiency)
- Vincristine, perhexiline maleate
- Thallium and arsenic
- Mercury poisoning (Pink disease)
- Cyclosporin
- CNS serotonergic syndrome
- Ciguatera (reef fish) toxicity
- Jelly fish and marine animal venoms

Table 52.14. Neurally mediated syncope

Vasovagal syncope

Carotid sinus hypersensitivity

Variants of reflexly induced syncope

- Tracheal stimulation in spinal shock
- Swallow syncope
- Glossopharyngeal vagal irritation
- Pelvic examination/instrumentation
- Defecation syncope
- Micturition syncope
- Cough syncope
- Laughter-induced syncope
- Fainting lark (Mess trick)

Associations with

- Children (vagotonia)
- Athletes (postexercise)
- Weight lifters
- Oarsmen

Drug-induced (Bezold–Jarisch reflex)

- First dose effect of angiotensin-1 converting enzyme inhibitors and prazosin

A variety of stimuli and circumstances may induce neurally mediated syncope. In some, reflexly induced exaggeration of vagal activity is responsible, as in cardiac arrest caused by tracheal stimulation in tetraplegics on artificial respiration, where increased vagal tone is not opposed by sympathetic activity or the pulmonary inflation reflex (Fig. 52.15). Syncope induced by swallowing (in some in association glossopharyngeal neuralgia) (Deguchi & Mathias, 1999) and, caused by pelvic and rectal examinations or instrumentation, are other examples. Malignancies in the pharynx and thorax may increase the tendency to reflexly induced syncope. In micturition and defecation syncope changes in intrathoracic pressure may contribute as in cough and laughter-induced, trumpet blowing and voluntary syncope ('fainting lark'). In extremely fit subjects, such as sportsmen, increased vagal tone, as occurs in children, also may contribute to syncope. The first-dose hypotensive effect of certain drugs may be neurally mediated, via the Bezold–Jarisch reflex.

Postural tachycardia syndrome (PoTS)

The postural tachycardia syndrome (PoTS) is a disorder mainly affecting women between the ages of 20 and 50, with symptoms of orthostatic intolerance (light headedness and other manifestations of cerebral hypoperfusion), often with palpitations (Low et al., 1995). The symptoms disappear on sitting or lying down. Investigations exclude orthostatic hypotension and autonomic failure. During postural challenge heart rate increases by 30 beats per minute or over. There are similarities with the syndromes initially described by Da Costa & Lewis (also known as

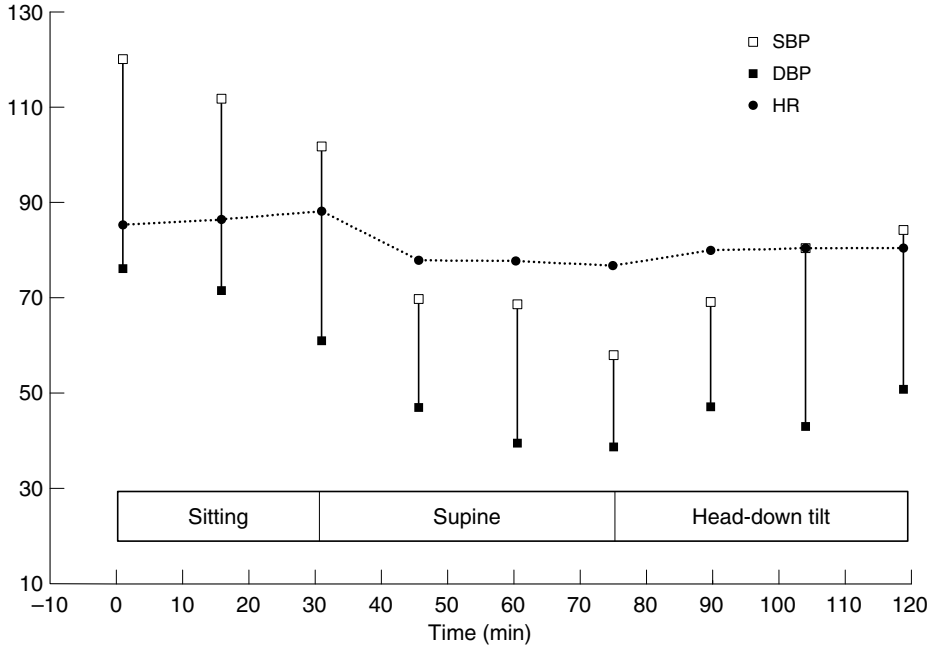

Fig. 52.13. The effect of a single standard oral dose of L-dopa (250 mg) and a dopa-decarboxylase inhibitor carbidopa (25 mg) given at time zero, on the blood pressure of a patient with parkinsonian features. There was a marked fall in blood pressure after 30 mins, resulting in the patient first being placed supine and then head-down. On investigation the patient had autonomic failure, with orthostatic hypotension unmasked by L-dopa; the final diagnosis was the parkinsonian form of multiple system atrophy. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. (From Mathias, 2000b.)

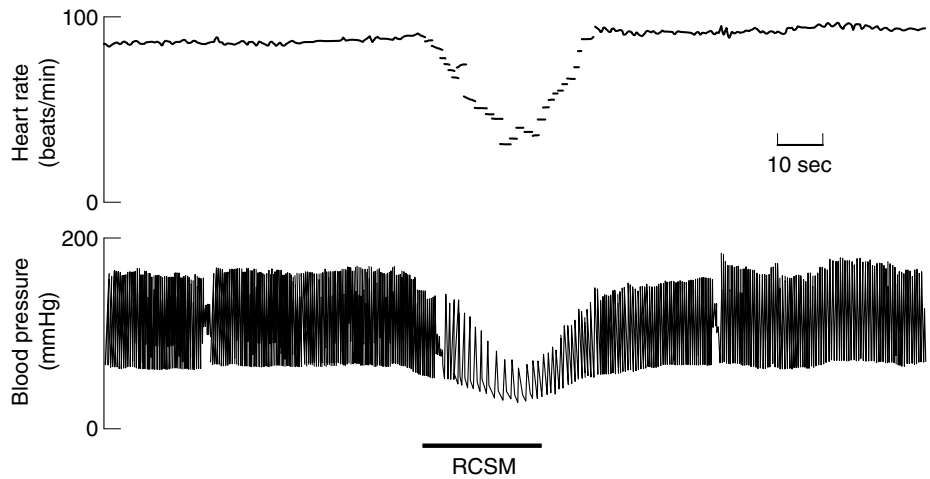

Fig. 52.14. Heart rate and blood pressure before, during and after right carotid sinus massage (RCSM) in a patient with syncopal episodes. There is a fall in both heart rate and blood pressure during carotid sinus massage, typical of the mixed (cardioinhibitory and vasodepressor) form of this disorder. The breaks in the record indicate calibration at intervals by the Finapres machine. (From Mathias, 2000a.)

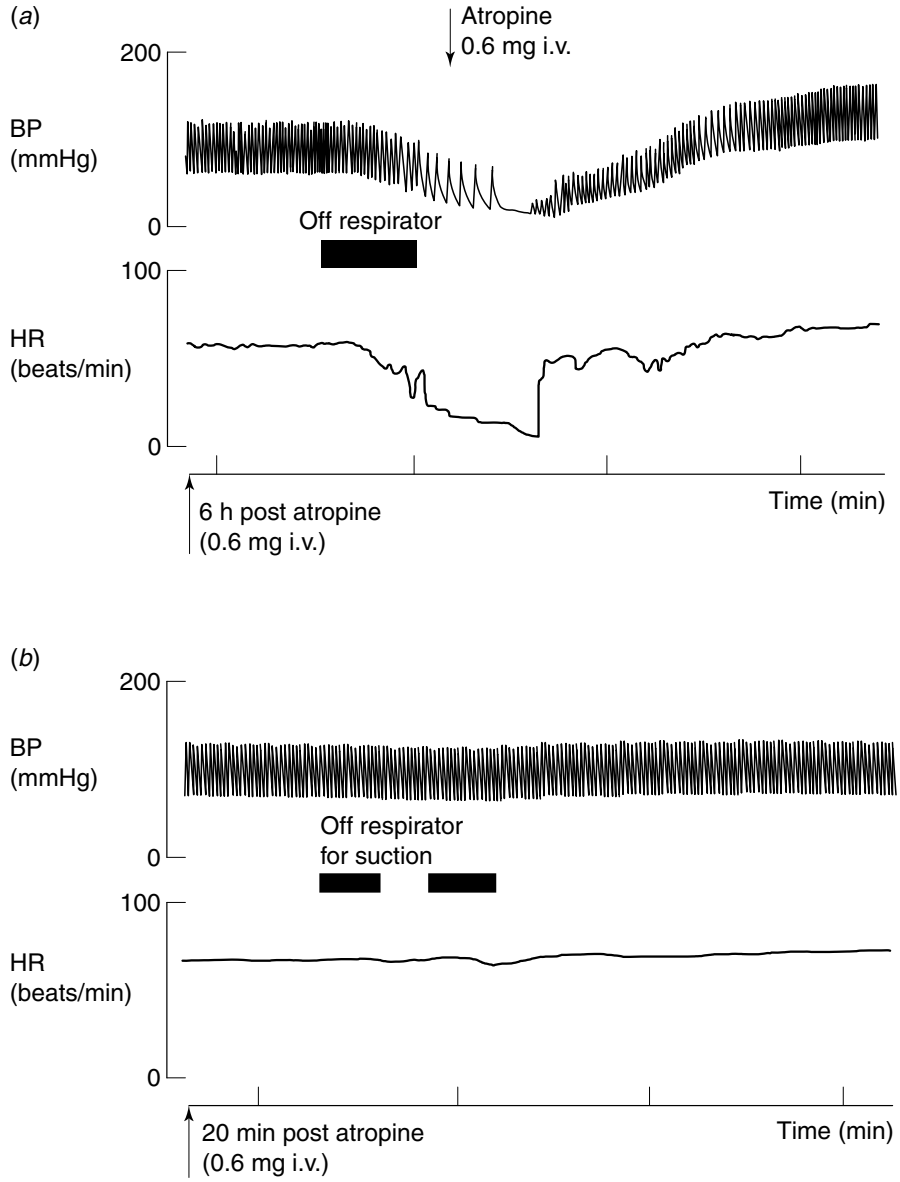

Fig. 52.15. (*a*) The effect of disconnecting the respirator (as required for aspirating the airways) on the blood pressure (BP) and heart rate (HR) of a recently injured tetraplegic patient (C4/5 lesion) in spinal shock, 6 hours after the last dose of intravenous atropine. Sinus bradycardia and cardiac arrest (also observed on the electrocardiograph) were reversed by reconnection, intravenous atropine and external cardiac massage. (From Frankel et al., 1975.)

(*b*) The effect of tracheal suction, 20 minutes after atropine. Disconnection from the respirator and tracheal suction did not lower either heart rate or blood pressure. (From Mathias, 1976.)

soldier's heart syndrome or neurocirculatory esthenia), mitral valve prolapse syndrome, chronic fatigue syndrome (Schondorf & Freeman, 1999) and deconditioning following prolonged bed rest and microgravity during spaceflight. The condition appears heterogenous (Khurana, 1995). In some the disorder appears to follow a viral infection. There may be features of a partial autonomic neuropathy, with lower limb denervation (Schondorf & Low, 1993; Jacob et al., 2000). In a family with affected twins, a genetic basis, with a defect in the noradrenaline transporter system, has been described which accounted for the raised basal noradrenaline levels. A mutation of the gene encoding the noradrenaline transporter was thought responsible for the hyperadrenergic state (Shannon et al., 2000). Hypovolemia may contribute.

The prognosis is variable, and some patients may recover with time. A variety of drugs, including beta blockers and drugs used in the treatment of orthostatic hypotension need to be considered; methods to increase volume expansion appear beneficial.

Localized autonomic disorders

Examples of these are listed in Table 52.15 with a brief description of a few.

The Holmes–Adie pupil is characteristically dilated and sluggishly responsive to light but responds to near vision, hence the descriptive term 'near-light dissociation'. It results from parasympathetic denervation, probably of the ciliary ganglia, with supersensitivity of the iris musculature to locally applied cholinomimetics. The term Holmes–Adie syndrome is used when associated with absent tendon reflexes; this probably is due to involvement of dorsal root ganglia, accounting for the absent H reflex on electrophysiological testing. Some patients have areas of anhidrosis, although they often complain of hyperhidrosis that is likely to be compensatory in nature (Ross syndrome). Others may have cardiovascular autonomic deficits, a chronic dry cough and diarrhea (Kimber et al., 1998). Although considered benign, in some the disorder may be progressive, with baroreceptor reflex dysfunction causing labile hypertension and also orthostatic hypotension.

In Horner's syndrome, there is partial ptosis and a small pupil as the sympathetic fibres to the face are affected. It may result from a lesion along the course of the facial sympathetic supply, in the brain, spinal cord, the upper thoracic ganglia or post-ganglionic efferents that follow the vasculature. Although it causes few, if any, symptoms it may be a harbinger of a serious underlying disorder.

Table 52.15. Examples of localized autonomic disorders

Holmes – Adie pupil
Horner's syndrome
Crocodile tears (Bogorad's syndrome)
Gustatory sweating (Frey's syndrome)
Essential (primary) hyperhidrosis
Reflex sympathetic dystrophy
Hirchsprung's disease (congenital megacolon)
Chagas' disease (*Trypanosomiasis cruzii*)
Surgical procedures[a]
– Sympathectomy – regional
– Vagotomy and gastric drainage procedures in 'dumping syndrome'
– Organ transplantation – heart, lungs

Notes:

[a] Surgery may cause some of the disorders listed above (such as Frey's syndrome following parotid surgery).

The lachrymal glands have a rich autonomic innervation. Alachryma may occur as part of a generalized autonomic disorder. 'Crocodile' tears may result from aberrant reinnervation of the lachrymal gland with fibres from the salivary glands. The mechanisms are similar to gustatory sweating, due to aberrant reinnervation between salivary and facial sweat glands; in both acetylcholine is the neurotransmitter. In essential (primary) hyperhidrosis there is no peripheral neural abnormality; whether hypothalamic dysfunction or altered behavioural responses are the trigger to hyperhidrosis is unclear. The treatment of hyperhidrosis, especially of the palms and face includes percutaneous endoscopic transthoracic sympathectomy, with bilateral ablation of ganglia between T2 and T4; compensatory hyperhidrosis affecting the trunk and lower limbs may occur postsurgery and in some may be worse than the original complaint. Injection of botulinum toxin especially into small areas such as the palm, face and axillae has been successfully used, but needs to be repeated and long-term benefits are unknown (Naumann et al., 1997). In reflex sympathetic dystrophy (chronic regional pain syndrome; CRPS type 2), there is debate about whether features such as sweating and vascular changes have an autonomic basis (Kimber et al., 1997b; in some these abnormalities are relieved by sympatholytic (guanethidine) blockade.

Localized disorders of the gut include Hirschsprung's disease. In Chagas' disease (after infection with *Trypanosoma cruzii*) the intrinsic autonomic ganglia in the esophagus, colon and heart are specifically targeted, probably by an immunological process. Various surgical procedures may be complicated by autonomic dysfunction, an

example being the dumping syndrome complicating vagotomy and gastric drainage procedures. Denervation of transplanted organs such as heart or kidneys also may result in dysfunction; reinnervation may occur in due course.

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53

Human brain–gut interactions: mechanisms of swallowing, visceral perception, and anal continence in health and disease

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It is now increasingly recognized that the brain plays an important role in modulating gut function. For example, alterations in emotional state can lead to disturbed gastrointestinal symptoms such as diarrhea, dyspepsia and even abdominal pain. Furthermore, alterations in gastrointestinal motility have been described after lesions to the central nervous system, for instance symptoms such as dysphagia after stroke, anal incontinence in cerebrovascular disease and multiple sclerosis and even alterations in small bowel motility following brainstem damage.

In this chapter I will describe current knowledge of human brain–gut interactions both in health and disease in relation to three specific areas: mechanisms of swallowing, mechanisms of anal continence and mechanisms of visceral perception. Particularly, I aim to bring the reader up to date with some newer concepts in relation to the neurophysiology of human cortical swallowing and anal motor function as well as touching on the newer areas of visceral sensitivity and functional bowel disorders. Finally, I will look at future directions specifically looking at potential therapies which may help in disease states that disrupt the human brain–gut axis.

Basic anatomy and physiology of the brain–gut axis

The enteric nervous system

The human brain–gut axis is a complex sensory motor system which has both extrinsic and intrinsic neural elements. At the intrinsic level the enteric nervous system represents an integrative system of neurons and interneurons with structural complexity and functional heterogenicity similar to that of the brain and spinal cord (Gershon, 1981). The principal role of the enteric nervous system (ENS) is to control and coordinate gut functions, including motility, secretion, mucosal transport and blood flow as necessary for normal digestive processes. These functions are mediated by the ENS via motor neurons located within enteric ganglia which form the final common pathway to the effector cells of the GI tract. The ENS houses a matrix of differing cell populations, which each play a role in maintaining intrinsic gastrointestinal sensory motor activity and include mast cells, smooth muscle cells, interstitial cells of Cajal, enteric enteroenteric cells and motor neurons. These also are subject to the release of various neurotransmitters, growth factors and cytokines which result in an enteric micro-environment that controls GI motility in an autonomous manner.

Vagal and spinal innervation

Whilst the enteric nervous system is almost autonomous it does receive input from extrinsic pathways via the central nervous system (CNS) via both vagal and spinal pathways linking it with the brain and spinal cord (Fig. 53.1). As a result this has led to the concept of the brain–gut axis revolving around both the 'big brain' and the 'little brain' representing the CNS and the ENS, respectively (Aziz & Thompson, 1998). The connecting pathways intervening can be conveniently divided into vagal (para-sympathetic) pathways and spinal (sympathetic) pathways.

Vagal pathways

The vagus nerve conveys a large amount of information between viscera and the brainstem, and contains both afferent and efferent fibres which in man innervate the entire gut as far as the distal third of the colon (Roman & Gonella, 1987). Approximately 90% of fibres within the vagal trunks are unmyelinated afferent neurons with cell bodies located in the nodose ganglion which lies just below

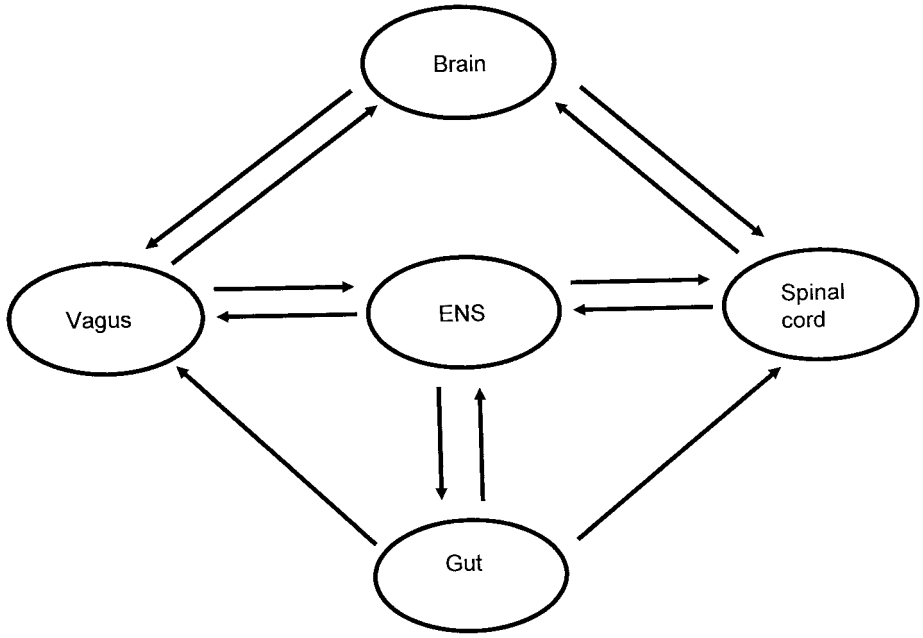

Fig. 53.1. Schematic representation of the intrinsic and extrinsic innervation of the gut.

the jugular foramen. There resides within the nodose ganglia a crude viscerotopic organization corresponding to sensory neurons projecting to soft palate and pharynx located superiorly and those projecting to the stomach, small bowel and lower GI tract which are located more caudally (Altschuler et al., 1989). Afferent fibres from the nodose ganglia then terminate in the brainstem within the medial division of the nucleus tractus solitarius (NTS), where a further viscerotopic organization within distinct subnuclei is displayed. Vagal afferents are believed to mediate non-noxious physiological sensation, such as anxiety and nausea and have a relatively low threshold of response to mechanical and electrical stimulation. There is also increasing evidence that vagal afferents may play a role in the modulation, at least, of nociceptive input from the bowel (Randich & Gebhart, 1992).

The other 10% of the vagal fibres are efferents that project from both the nucleus ambiguous and the dorsal motor nucleus representing the vagal motor nuclei complex. The nucleus ambiguous (NA) is located in the ventrolateral medulla and tends to innervate the striated musculature of the upper GI tract including the pharynx, larynx and upper esophagus and thus plays an important role in the complex motor act of swallowing. By comparison, the dorsal motor nucleus (DMN) of the vagus provides efferents to smooth muscle regions of the gut in association with myenteric plexus neurons. DMN motor neurons display extensive dendritic arborizations allowing some degree of coordination of efferent activity. These dendrites not only innervate specific viscera but also have linkages with NTS resulting in organ specific monosynaptic interactions between the NTS and the DMN and functionally provide the circuitry for 'the vasovagal' reflexes, such as the gastro-gastric reflex, the enterogastric reflex, the hepatopancreatic reflex and the gastrocolic reflex (Gillis et al., 1989). In both the DMN and NA there is some topographic subnuclei organization both in terms of the striated muscle of the gut in the nucleus ambiguous and in abdominal viscera in the dorsal motor nucleus.

In addition to the vagus there is a second 'parasympathetic' innervation of the GI tract which will be further described in this chapter as sacral pathways. These are projections from pre-ganglionic neurons located in the intermediate grey matter of the sacral cord segments (S1 to S5) and innervate the distal colon, rectum and internal anal sphincter via pelvic ganglia from where postganglionic pelvic nerve fibres innervate the enteric ganglia. As with the vagus, there are both afferent and efferent pathways with the afferent fibres from the colon going via the pelvic nerve afferents to the dorsal root ganglia of the sacral segments. Some of these fibres then send projections to preganglionic neurons to the ENS of the lower colon and result in spinal reflexes that regulate colonic motility and defecation. A somatic component of this innervation is the pudendal nerve which has motor neurons located in the ventral horn of S1 and S2 segments and innervates the

external anal sphincter while pudendal afferents relay sensory information from the anal sphincter margin and canal back to the spinal cord.

Spinal pathways

In addition to the vagal pathways innervating the gastrointestinal tract, there are also spinal visceral afferents which have been wrongly termed 'sympathetic' pathways as they pass via prevertebral and paravertebral ganglia of the sympathetic system to the spinal cord but importantly have their cell bodies in the dorsal root ganglia of the cervical, thoracic, and upper lumbar spinal segments. These spinal afferents are predominately unmyelinated C and A-delta fibres and relay predominantly mechanoreceptive and chemical stimuli to a noxious level (Sengupta & Gebhart, 1994). It is important to recognize that considerable segmental overlap exists in the spinal cord in relation to the spinal afferents which partially explains the poor viscerotopic localization of sensation from the GI tract. Furthermore, because there is convergence of such spinal afferents with somatic afferents, the result is some degree of referred pain from a particular organ to a corresponding cutaneous area on the body surface. As with other spinal afferents, visceral spinal afferents are then transmitted proximally within the spinal cord via a number of tracts of which the spinothalamic and the dorsal column pathways are most important. Thus the role of visceral spinal afferents is one predominantly of transmission of nociceptive information; however, it is likely that these afferents have stimulus response functions that cover both physiological and nociceptive ranges of stimulation so that they play the major role in visceral perception and sensitivity.

In addition to spinal afferents there are also associated sympathetic efferent pathways from the cervical, thoracic and lumbar segments of the spinal cord. These have preganglionic and postganglionic synaptic connections the latter of which most prominently represent the celiac and superior mesenteric ganglia and the inferior mesenteric ganglion which innervate the proximal bowel and the distal bowel respectively. It is likely that these sympathetic efferent connections result in an inhibition of GI function and consequently a reduction in motility via the release of acetylcholine.

Supra spinal and higher centre influences on intrinsic and extrinsic neural pathways to the gut

Both the vagal and spinal pathways and consequently the enteric nervous system are under the influence of higher centre regulatory processing. The vagus nerve carries afferent projections via the NTS to higher brain regions via a relay in the pons and medulla, from where there appear to be at least four levels of input. The first are direct projections to autonomic motor nuclei involving both parasympathetic and sympathetic preganglionic neurons in the dorsal motor nucleus and the nucleus ambiguous of the vagus as well as the intermediolateral cell column of the spinal cord. These projections provide the anatomical substrate for short autonomic reflex loops. Secondly, the NTS sends relays to the motor components for ingestion found in the trigeminal, facial, and hypoglossal nuclei and also in the nucleus ambiguous. Thirdly, visceral information is relayed to more rostral regions of the brainstem such as the parabrachial nuclei, which are in turn connected to higher centres. Fourthly, long projections terminate in the thalamus, hypothalamus and limbic and insular cortical regions that mediate autonomic neuroendocrine and behavioural functions. These regions all have reciprocal connections with other brain regions such as the area prostrema, the parabrachial nucleus, hypothalamus, amygdala and the orbitofrontal, insular and inferior limbic and cingulate cortex (Sawchenko, 1983). These connections integrate sensory input arriving from the nucleus of the tractus solitarius with descending influences from higher brain centres and provide the circuitry for visceral reflex loops. This integration presumably results in the orchestration of autonomic reflexes involving GI, cardiovascular and respiratory activities such as that which occur in vomiting. Visceral spinal afferents also project to higher centres via relays in the brainstem and thalamus. From the thalamus, sensory information passes to the insular cortex, the primary somatosensory cortex and the prelimbic, limbic and infra-limbic areas of the medial pre-frontal cortex. It is likely that these pathways are responsible for the integration of somatic and visceral input from wide areas of the body.

Vagal motor pathways also receive direct connections from anterolateral motor strip, premotor cortex, insula and probably a number of other areas including the supplementary motor cortex, all of which have been associated with the motor control of swallowing and other GI functions. In a similar manner, sacral motor pathways appear to have direct connections via cortical spinal tracts from more medial aspects of the motor strip as well as areas similar to that which have already been mentioned to the vagus nerve. Finally, sympathetic efferents are recognized to have connections via projections from the hypothalamus, medial forebrain, anterior sigmoid and orbital and cingulate gyri of the cerebral cortex, which when stimulated can result in inhibition of colonic motility (Rostad, 1973).

Mechanisms of swallowing

The process of swallowing is a complex neuromuscular activity which allows the safe transport of material from the mouth to the stomach for digestion without compromising the airway. This is a fairly simplistic description as the act of swallowing requires a sophisticated integration of both central control and anatomical structures to produce the sensory motor output that we call the swallow. In addition to transporting food, swallowing is also concerned with the protection of the airway, ejection of noxious ingested substances and the preparation of food material. Therefore, when considering swallowing it is important to consider both the anatomy, physiology and the neurophysiology behind this exquisitely complex function.

Anatomy of the swallowing tract

The anatomy of the swallowing tract encompasses the oral cavity, the pharynx which is functionally linked with the larynx and the esophagus. In total, there are at least 32 pairs of muscles which act synergistically to produce the swallow, thereby making it one of the most superior 'reflexes' in the human body. The oral cavity is surrounded by supportive structures including the mandible, maxilla, hard palate and alveolar ridges which house dentition. The mouth itself is enclosed by various muscles including those of mastication and facial expression as well as the intrinsic and extrinsic muscles of the tongue and soft palate. The pharynx supported by pharyngo-basilar fascia comprises three sequentially placed constrictor muscles with the cricopharyngeus distally and stylopharyngeus proximally. Anterior to this, on the anterior wall of the hypopharynx is a cartilaginous box known as the larynx which is surrounded and connected to the hyoid bone and thyroid fascia by the strap muscles of the neck. Intrinsically, the larynx contains eight pairs of muscles of which only two pairs (the aryepiglottic muscles or 'false vocal cords' and the lateral cricoarytenoid muscles or 'true vocal cords') are responsible predominantly for airway protection during swallowing. Extending posteriorly and rostrally is the epiglottis, which forms the base of the tongue and is at its apex connected with the larynx. Beyond the pharynx and the high pressure zone of the upper esophageal sphincter is a 20 cm long muscular tube known as the esophagus. The esophagus consists of predominately striated muscle fibres in its proximal one-third, mixed smooth muscle and striated muscle fibres in its middle third, and predominantly smooth muscle fibres in its distal third which merge with the cardia of the stomach at the level of the lower esophageal sphincter.

The physiological events of swallowing

Swallowing is commonly described as having three distinct phases or stages which comprise the oral phase, the pharyngeal phase and the esophageal phase (Kennedy & Kent, 1988). It was generally thought that the oral phase is voluntary, whereas the pharyngeal and esophageal phases are involuntary; however, it is now accepted that higher inputs can influence both these latter two phases, probably more in a modulatory capacity. Humans swallow on average once every minute which is supplemented by the production of saliva which when absent or reduced inhibits the ability to swallow. Swallowing almost completely tails off during deep (stage 4) sleep but does occur during REM sleep, indicating that a level of arousal is necessary for swallowing to take place (Lichter & Muir, 1975). The oral phase is sometimes described as being preceded by the preparatory phase, particularly when solid or semisolid foods are ingested. Mastication and mixing with saliva occurs at this point and the bolus is then cupped in the anterior portion of the tongue before being propelled by an upward and compressing force initiated by the tongue against the hard palate to 'squeeze' the bolus into the pharynx. During this phase, the soft palate rises to seal off the naso-pharynx and thus completes the oral phase which lasts 0.6 to 1.2 seconds.

The pharyngeal phase typically begins as the bolus reaches the faucial pillars of the hypopharynx. Simultaneously, the larynx and hyoid bone are lifted upwards and forwards by contraction of the strap muscles of the neck and in so doing enlarges the space available for the pharynx to receive the incoming bolus. The bolus is then propelled aborally by sequential contractions of the constrictor muscles of the pharynx and this is associated with a reflex relaxation of the normally high toned upper esophageal sphincter to allow passage of the bolus into the esophagus. During transport through the pharynx, respiration is momentarily halted, the swallow usually occurring whilst in expiration. Concurrently, a protective mechanism of aryepiglottic fold closure and approximation of the arytenoid and epiglottic cartilage by contraction of the intrinsic muscles of the larynx then occurs. The whole pharyngeal phase usually takes less than 0.6 seconds.

Thus commences the esophageal phase of swallowing which comprises a propagated peristaltic wave which propels the bolus at approximately 2 to 4 cm per second. As the bolus passes through the esophageal body, the lower esophageal sphincter relaxes and the bolus enters the stomach, the esophageal phase lasts between 6 and 10 seconds, and the whole process of swallowing usually 12 seconds in total.

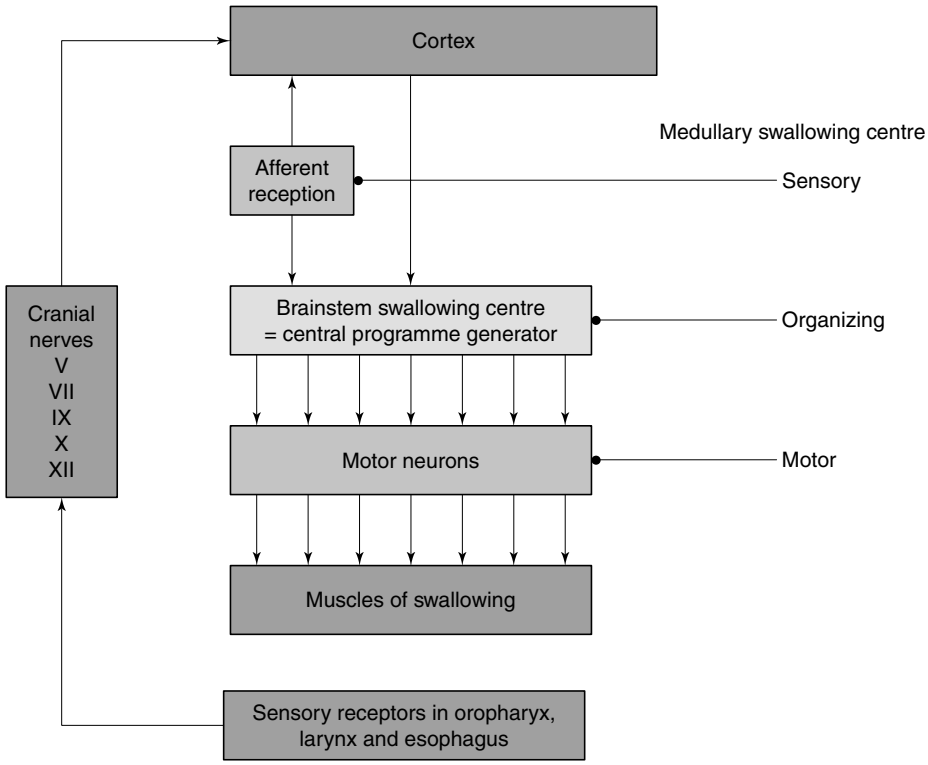

Fig. 53.2. The hierarchical organization of the central regulation of swallowing. Input from the periphery and higher centres converge onto interneurons in the brainstem swallowing centre, which generates the sequenced pattern of swallowing via the bulbar motor nuclei.

The neurophysiology of swallowing

The central neural control of swallowing can be divided into essentially three basic components: an afferent system, a central processor and regulating system and an efferent system (Fig. 53.2). At this point it is important to emphasize that the central processing system has at least three levels including the brainstem swallowing centre, subcortical structures and the cortex itself.

The afferent system

Afferent input comes from three cranial nerves innervating the muscles of the swallowing tract and includes the trigeminal nerve, the glossopharyngeal nerve and the vagus nerve, of which its superior laryngeal branch appears to have most importance. Stimulation of any of these nerves can initiate or modulate a swallow (Miller, 1982). These afferent fibres terminate centrally at the level of the brainstem in the tractus solitarius and in the nucleus of the spinal trigeminal system before converging in the NTS. There is however, a second projection which ascends via a pontine relay to the level of the cortex without transgressing the NTS (Car et al., 1975). The most potent trigger for swallowing is the superior laryngeal nerve which is only matched by direct stimulation of the nucleus of the tractus solitarius, suggesting that the solitary system is a major contributor of swallowing afferent input (Jean, 1984). Importantly, anesthesia of areas innervated by these cranial nerve afferents will disrupt but will not necessarily completely abolish the ability to swallow (Mansson & Sandberg, 1974). Sensation from the oral, pharyngeal and laryngeal regions includes a broad range of modalities including two point discrimination, vibrotactile detection, somesthetic sensitivity, proprioception, nociception, chemical sensitivity and thermal sensitivity (Miller, 1999). The oral, pharyngeal and laryngeal mucosae possess an epithelium innervated by both free nerve endings and within deeper layers more organised sensory receptors. Of interest there appear to be chemosensitive receptors that are specifically water responsive which will not trigger at isotonic levels. There also appear to be different groups of cold responsive sensory fibres which discharge at around 25 to 30 °C. Mechanical stimuli appear to be the most effective stimuli for exciting NTS neurons within receptive fields

of the oral cavity and epiglottis, a moving mechanical stimulus excites more neurons than a static stimulus. When comparing the receptive field responsiveness within the oral cavity, it appears that mechanical stimulation is more potent than chemical stimulation which in turn is greater than thermal stimulation (Miller, 1999).

The efferent system

The efferent system comprises motor neuron pools, consisting of the facial motor nucleus, the hypoglossal motor nucleus, the trigeminal motor nucleus, and the vagal motor nuclei. Inputs from the brainstem central pattern generator and from supra-bulbar regions impinge on these motor nuclei in a manner which synergistically produces the swallow. The cranial motor nuclei mentioned above have subdivisions based on the motor neurons innervating specific muscles. The facial motor nucleus is involved with the labial muscles for which there are several functions both in swallowing and speech as well as chewing. The hypoglossal nucleus contains the motor neurons innervating the intrinsic and extrinsic muscles of the tongue, which are involved in numerous motor functions including speech, respiration, licking, mastication as well as swallowing. The trigeminal motor nucleus contains the motor neuron pools that innervate the mandibular muscles and can be divided into four nuclei which appear to develop at different times during development in the fetus (Miller, 1999). The nucleus ambiguous is also subdivided into at least four layers including the compact layer, semi-compact layer, the loose layer and the external formation. These motor neurons innervate the palatal, pharyngeal, laryngeal and esophageal muscles. Finally the dorsal motor nucleus of the vagus contains neurons that innervate the esophagus and portions of the proximal gastrointestinal tract. It appears that the earliest motor neuron to develop during swallowing in the fetus is probably the hypoglossal nerve (Miller, 1999) as tongue activities are present in the fetus at about the same time as the jaw opening reflex. Indeed by the eleventh week of development of the human fetus, the first pharyngeal motor responses can also be detected.

Whilst lesions to the facial motor nucleus do not implicitly result in dysphagia, lesions to the nucleus ambiguous and to a lesser extent the hypoglossal and trigeminal motor nuclei result in more significant dysphagic symptoms (Miller, 1999). Thus, as a result of input from the NTS and higher centres to the dorsal region of the medulla and the brainstem swallowing centre, motoneurons in this region will provide the patterned sequential discharge activating the oral pharyngeal and esophageal phases of swallowing.

Central and supra-bulbar regulatory systems

Brainstem swallowing centre

Much of the research pertaining to the central regulation of human swallowing has focused on the issue of the brainstem swallowing centre. This important swallowing region is central to the regulation of human swallowing and is distributed within the reticular formation just dorsal to the inferior olive either side of the midline in the medulla (Jean, 1990). It is believed that this network of neurons and interneurons integrates incoming information from other levels, both central and peripheral, before activating a preprogrammed sequence of responses which then dictate the pattern of swallowing. The concept of a central pattern generator within the brainstem is supported by the fact that even after disruption of both afferent and efferent fibres to this region, the pattern of swallowing remains essentially unchanged when studied in animals (Jean, 1990).

It appears that the circuitry of the central pattern generator has different populations of interneurons responsible for the different temporal stages of swallowing and termed 'early' 'late' and 'very late' neurons which closely correspond to their muscular counterparts within the oropharynx, lower pharynx and striated muscle portion of the esophagus, and the smooth muscle esophagus respectively (Jean, 1984). Functionally, it appears that the brainstem swallowing centre can be divided into two, the dorsal medullary region and the ventral medullary region. The dorsal medullary region provides the neurons that initiate the sequential activity of swallowing and can be defined as generating neurons. The ventral medullary region which includes an area around the nucleus ambiguous appears to play a switching role in modifying and activating the motor neuron pools controlling swallowing output. In between these two regions there is a short interneuronal network that has both excitatory and inhibitory components and which relays information from the dorsal region to the ventral region.

Within both regions of the medulla there are a number of neurotransmitter substances which appear to have relevant roles (Bieger, 1993); for example, the injection of glutamate into the dorsal region of the brainstem evokes pharyngeal swallowing suggesting that it is excitatory. By comparison, injection of dopamine or noradrenalin appears to inhibit the elicitation of pharyngeal swallowing. It also appears likely that gamma-aminobutyric acid, acetylcholine, n-methyl D-aspartate and nitric oxide probably play an important role in the inhibitory and excitatory regulation of swallowing.

In addition to the medullary brainstem swallowing centre, there appears to be a separate area within the

pontine reticular formation which will also when stimulated evoke swallowing. This region, when stimulated at low intensity will evoke both swallowing and rhythmic jaw movements but at high intensity results in more inhibitory effects. It is likely that pathways from the afferent innervation of swallowing project to this region as well as the medullary area on their way to the antero-lateral cortex. Activation of the pontine region may in fact result in a transcortical reflex to evoke the swallow rather than the pontine area being directly involved in the initiation of swallowing.

Supra-bulbar regions influencing swallowing

There is extensive experimental evidence to support the role of subcortical structures in the control and modulation of swallowing (Bieger & Hochman, 1976). These regions can be anatomically divided into the hindbrain, comprising the cerebellum, the midbrain, comprising the substantia nigra and the ventral tegmentum and basal forebrain, comprising the hypothalamus, amygdala and basal ganglia. In animals, activation of all these sites has been shown to facilitate the swallow response when combined with either superior laryngeal nerve stimulation or cortical stimulation. Evidence from human studies also suggests an important contribution from subcortical areas, such as the basal ganglia, where dysphagia is a common consequence of Parkinson's disease (Bernheimer et al., 1973). In a recent functional imaging study of human swallowing it was demonstrated that areas including the left amygdala and the left cerebellum as well as the dorsal brainstem show increased regional cerebral blood flow during volitional swallowing (Hamdy et al., 1999). The lateralized nature of these activations was of interest and supported the possibility that swallowing displays significant interhemispheric asymmetry in its motor control.

The cerebral cortex has been strongly implicated in the control of swallowing where numerous investigators have observed a stimulation of the cerebral cortex both in animals and humans can elicit the full swallow sequence (Martin & Sessle, 1993; Penfield & Boldery, 1937). The areas implicated in these studies seem to be the dorsolateral and antero-lateral frontal cortex as well as the premotor cortex, the frontal operculum and also the insula. Much of the information regarding the cerebral localization of human swallowing has relied on inference from studies of swallowing abnormalities following cerebral injury (Veis & Logemann, 1985; Gordon et al., 1987; Horner & Massey, 1988). From these reports a rather diffuse picture has emerged of those areas of the brain considered important, for example, lesions located in the thalamus, pyramidal tracts, frontal operculum and the insula have all been associated with dysphagia. More recently, functional imaging has also established a clear role for the lateral sensorimotor cortex and, in particular, the right insula during the process of swallowing (Hamdy et al., 1999). More information has come from the studies of transcranial magnetic stimulation of the human precentral gyrus in understanding the cortical control of swallowing (Hamdy et al., 1996, 1997b, 1998a). Transcranial magnetic stimulation uses a very short rapidly changing magnetic field to induce electric current in the brain beneath the stimulator. These studies usually employ single shocks given several seconds apart and, following stimulation, the cortical evoked motor response can be recorded as electromyographic activity from electrodes housed within an intraluminal catheter inserted into pharynx and esophagus. Following cortical stimulation, the type of response observed is usually a simple EMG potential which has a latency of about 8 to 10 milliseconds, compatible with a fairly direct and rapidly conducting pathway from cortex to the muscle (Fig. 53.3). During these magnetic stimulation mapping studies the projections to the various swallowing muscles were demonstrated to be somatotopically arranged in the motor strip with the oral muscles most lateral and the pharynx and esophagus more medial. A more interesting finding from a large group of healthy subjects studied was that in the majority of individuals, the projection from one hemisphere tended to be larger than the other suggesting an asymmetric representation for swallowing between the two hemispheres, independent of handedness. These findings have also been validated with functional imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) where cerebral lateralization has been also observed (Hamdy et al., 1996, 1999). These functional imaging studies have, however, identified a number of other cortical areas associated with swallowing including anterior cingulate cortex, premotor cortex (including the supplementary motor cortex), the insular cortex, frontal opercular cortex and the temporal cortex. Taken together these observations suggest that swallow-related cortical activity is multidimensional, recruiting brain areas implicated in the processing of motor, sensory and presumably attention/affective aspects of the task.

Swallowing dysfunction after injury to the central nervous system

Difficulty in swallowing can occur as a consequence of disease to either the anatomical structures involved in swallowing or more commonly to the central nervous system controlling swallowing (neurogenic dysphagia).

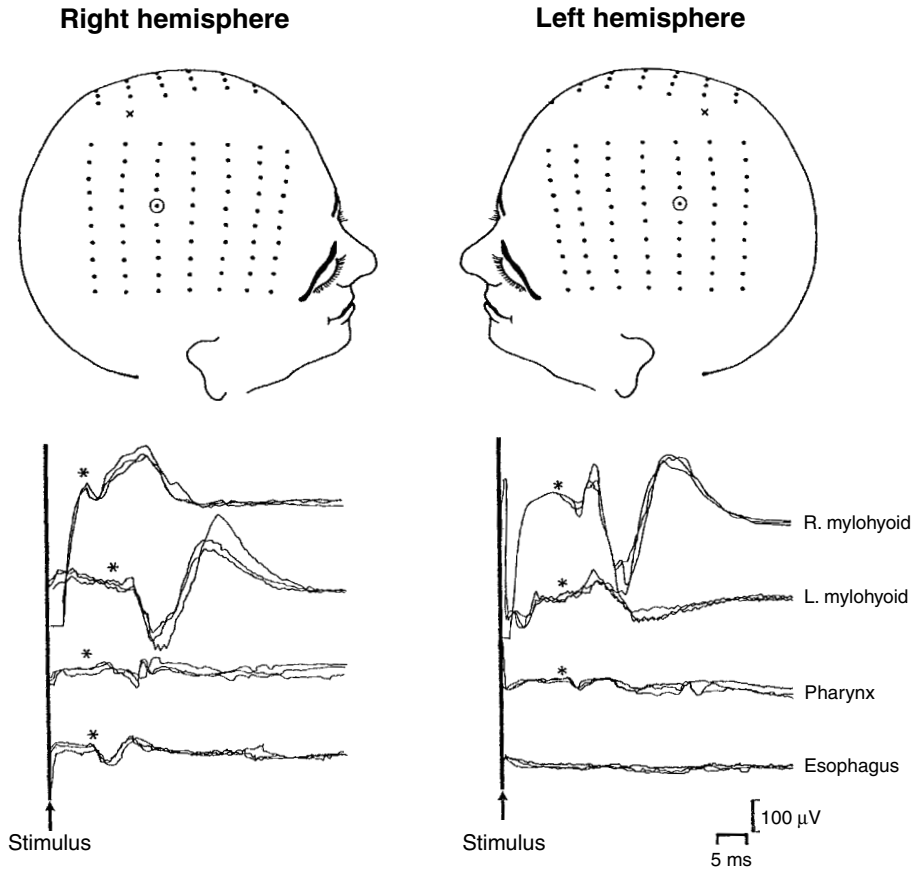

Fig. 53.3. Schematic representations of the sites of stimulation on a scalp grid in relation to the head surface are shown above. The cranial vertex is marked by X. The cortically evoked EMG responses recorded in one normal subject from: right mylohyoid muscle, left mylohyoid muscle, pharynx, and esophagus, following transcranial magnetic stimulation of the right and left hemispheres are shown below. The sites of stimulation on the grid from which these responses were obtained are indicated by the open circle. Responses to three stimuli have been superimposed to show reproducibility. It is evident, however, that the pharyngeal and esophageal responses obtained from the right hemisphere are larger than those from the left hemisphere. (* indicates onset of EMG response.)

The anatomical problems which disrupt swallowing are myriad and include almost any gastrointestinal disease process which affects the oral cavity through to the duodenum. It is therefore important to exclude any intrinsic disease to the gut before making a diagnosis of neurogenic dysphagia in someone presenting with symptoms of swallowing difficulty.

There are many neurological conditions that can disrupt swallowing including diseases of the muscle or neuro muscular junction, e.g. polymyositis, myasthenia gravis and the muscular dystrophies; diseases of the peripheral nerves, e.g. Guillain–Barré syndrome, polio and diptheria; and disease affecting the central swallowing centres, e.g. stroke, head injuries, motor neuron disease, Parkinson's disease, multiple sclerosis and other neurologic diseases. In addition, it is important to recognise that any pharmacological agent which alters neuromuscular function can produce dysphagia. It is beyond the scope of this chapter to go into detail of the many neurological conditions which can affect swallowing and for the rest of this section I will discuss the clinical consequences and underlining mechanisms related to dysphagia following cerebrovascular disease, specifically stroke.

Injury to swallowing areas of motor cortex and/or their connections to the brainstem will usually result in problems with swallowing (dysphagia). The commonest reason for dysphagia is now stroke. Traditionally, it had been assumed that only strokes producing brainstem or bilateral cortical damage are associated with dysphagia; however, since the 1970s it has been increasingly recognized that unilateral cerebral lesions can also cause dysphagia (Barer, 1989; Meadows, 1973; Daniels & Foundas,

1997). Up to half of all stroke patients experience dysphagia, which is associated with the life-threatening complications of pulmonary aspiration and malnutrition. Dysphagia leads to increased lengths of stay in hospital and greater demands on health service resources.

Diagnosing dysphagia following cerebral injury can be difficult and therefore requires a high level of clinical suspicion. The pattern of disordered swallowing after stroke is usually a combination of oral and pharyngeal abnormalities, typically delayed swallow reflex with pooling or stasis of residue in the hypopharynx associated with reduced pharyngeal peristalsis and weak tongue control but occasionally esophageal abnormalities may be apparent. Clinical suspicion of swallowing difficulty should be followed up by thorough bedside swallowing assessment and where appropriate imaging of the swallowing process such as videofluoroscopy. The bedside examination incorporates a number of clinical measures including assessment of the patient's feeding status, posture, breathing and cooperation levels before examining the patients oral musculature, oral reflexes, pharyngeal swallow and usually a trial feed with 5 to 10 ml of water given either by spoon or in a beaker. The bedside assessment is cheap and relatively easy to perform and has the advantage of involving no radiation exposure. However, it lacks sensitivity and does not give detailed information of the pharyngeal stage of swallowing making it prone to missing significant aspiration, especially silent aspiration. When the diagnosis is in doubt, videofluoroscopy can give a detailed anatomical assessment of the pharyngeal swallow and has the advantage of detecting silent aspiration and other abnormalities of the swallow anatomy. However it is expensive, involves radiation and uses a non-physiological medium i.e. barium, which may not give a true picture of the patients swallowing performance. A recent advance is the introduction of flexible endoscopic evaluation of swallowing (FEES). FEES involves the passing of a nasoendoscope into the oropharynx while a small volume of a coloured physiological meal or liquid is ingested. This allows the anatomy of the pharyngeal swallow to be directly visualized and the swallowing mechanism assessed.

The management of dysphagia after stroke is therefore critical. With severe dysphagia the risk of aspiration is high and the patient is therefore kept nil by mouth with early commencement of parenteral fluids. With less severe dysphagia, based upon videofluoroscopic and bedside swallowing assessment outcomes, there are a number of therapeutic interventions which can be tried. These interventions include changing diet, posture and food placement adjustment as well as methods for sensitizing or de-sensitizing the oropharynx to alter the swallow reflex. Unfortunately, the efficacy of these therapeutic manoeuvres is a matter of some controversy: at present there are no randomized controlled trials of these interventions to show proven efficacy in improving the swallow after stroke. Consequently, patients often require nasogastric tube or gastrostomy feeding until swallowing improves spontaneously.

Mechanism for dysphagia following stroke

Whilst it is relatively easy to appreciate the mechanisms behind dysphagia following bilateral cortical stroke or brainstem disease the mechanism underlying dysphagia after unilateral cerebral injury particularly after hemispheric injury has remained unclear. Speculated suggestions include occult disease in the unaffected hemisphere, cerebral edema leading to pressure on the adjacent hemisphere or brainstem, and the possibility that swallowing, like speech, may show significant cerebral lateralization. Indeed, in a transcranial magnetic stimulation study of the projections from both hemispheres to the swallowing musculature in a large series of pure unilateral hemispheric stroke patients, of which half had dysphagia, it was observed that whilst stimulation of the damaged hemisphere produced little or no response in either dysphagic or non-dysphagic patients, stimulation of the undamaged hemisphere evoked much larger responses in the non-dysphagic than in the dysphagic subjects (Hamdy et al., 1997a). The conclusion from this study was that the size of the hemispheric projection of the undamaged side to swallowing muscles determined the presence or absence of dysphagia with the implication that dysphagia would occur if damage had affected the side of the brain with the largest or dominant projection. This observation supported the concept that swallowing is lateralized within the cerebral cortex.

Mechanisms of recovery of swallowing after cerebral injury

Given sufficient time, a large proportion of dysphagic stroke patients eventually recover the ability to swallow again (Barer, 1989). The mechanism for this recovery, seen in as many as 90% of the initially dysphagic stroke patients has, however, remained controversial. In a recent study of stroke using transcranial magnetic stimulation both dysphagic and non-dysphagic patients were serially mapped over several months while swallowing recovered (Hamdy et al., 1998a). The findings of this study showed that the area of pharyngeal representation in the undamaged hemisphere increased markedly in patients who recovered

whilst there was no change in patients who had persistent dysphagia or in patients who were non-dysphagic. Furthermore no changes were seen in the damaged hemisphere in any of the groups of patients. These observations imply that over a period of weeks, the recovery of swallowing after stroke depends on compensatory reorganization in the undamaged hemisphere. The situation appears to differ from that in the limb muscles where some magnetic stimulation studies have indicated that limb recovery after hemiparesis is more likely to result from an increase in the activity of the remaining viable cortex in the damaged hemisphere (Turton et al., 1996). In such cases, scope for expansion of a normal connection from the undamaged part of the brain may be a limiting factor in recovery.

Mechanisms of anal continence

The anal sphincter is a midline muscular structure at the terminus of the gastrointestinal tract that functions to maintain fecal continence. It has two components, the internal sphincter and the external sphincter. Whereas the internal anal sphincter consists of circular smooth muscle and is innervated predominately by autonomic fibres from the pelvic plexus and sacral spinal cord, the external sphincter is of striated muscle and is innervated by the somatic fibres of the second, third and fourth sacral segments via the pudendal nerve. The neural control of anal continence therefore has sensorimotor contributions from both intrinsic and extrinsic reflexes, the former predominately via myenteric interaction within the internal anal sphincter, and the latter via strong descending volitional interactions with the motor neurons innervating the external anal sphincter (Christensen, 1983).

The neurophysiology of anal continence

Anal continence represents an important physiological and socially essential gastrointestinal function which is regulated by sensorimotor interactions within the anal sphincter and pelvic floor. In particular, contraction of the external anal sphincter serves to increase anal canal pressure both voluntarily, when the urge to defecate becomes strong and via more involuntary reflexes, for instance during coughing when intra abdominal pressure suddenly rises. In either case, the cerebral cortex is able to modulate this activity via powerful descending inputs to the pelvic plexus and sacral nerves so defecation can be resisted until a socially convenient opportunity arises. The importance of cortical influences in the control of the external anal sphincter is well recognized, direct stimulation of the most medial motor cortex adjacent to the interhemispheric fissure will induce anal sphincter contractions (Leyton & Sherrington, 1917). More recent experiments in humans have shown that the corticofugal pathways to the external anal sphincter can be studied non-invasively by recording the electro-myographic and manometric responses evoked by transcranial electric and magnetic stimulation of the motor cortex (Merton et al., 1982; Turnbull et al., 1999). These studies have suggested that the motor cortical representation of anal sphincter function is bilateral and may display, as with swallowing, an interhemispheric asymmetry.

The peripheral innervation of the external anal sphincter comes from the pudendal nerve. Anatomical and electrical physiological studies of the innervation of the external anal sphincter in animals has shown that most of the pudendal projections to and from the external anal sphincter are centrally organized to spinal segments L6 to S3 with the majority with the S1, S2 segments (Thor et al., 1989). Furthermore the motor neurons innervating the external anal sphincter, are particularly located in the dorsomedial and ventromedial divisions of Onuf's nucleus in the ventral horn of the spinal cord while the afferent axonal projections appear to cluster within the marginal zone, intermediate grey and dorsal grey surrounding the nucleus gracile of the dorsal column and laminal 1, around the dorsal horn of the spinal cord. Of interest is the observation that, while there is clear unilateral spinal predominance of these projections during retrograde tracing studies of a single nerve, in both the efferent and afferent pathways, there is contralateral axonal connectivity across the midline, suggesting degrees of bilateral convergence. In a recent study of pudendal nerve function it was found in a number of healthy volunteers that the evoked muscle potential to pudendal nerve stimulation can be quite asymmetric between the two sides (Hamdy et al., 1999). Furthermore, when pudendal or even lumbar sacral stimulation was used to condition the peripheral pathway, cortical stimulation of the anal region of the motor strip induced much greater responses in the anal sphincter compared to no conditioning (Hamdy et al., 1998b). Importantly, stimulation of the pudendal nerve with the larger response induced significantly more facilitation of the cortico-anal pathway than stimulation of the pudendal with the smaller response. This suggested that there may indeed be some functional asymmetry in the pudendal pathways to the anal sphincter possibly in conjunction with asymmetry at higher levels.

Anal incontinence

Anal incontinence represents a distressing complication of disease to the central nervous system, for example injury to

the pelvic nerves, as in instrumental deliveries at child birth, will result in significant anal sphincter dysfunction, as well as disruption of the brain–gut axis from cortex to sphincter seen in conditions such as stroke, multiple sclerosis and spinal injury. In the case of the former, anal incontinence has been attributed to pudendal nerve damage where a number of studies have shown clear abnormalities in pudendal nerve function (as determined by prolonged nerve conduction terminal latency) in incontinent female patients following vaginal delivery both with and without instrumental intervention (Snooks et al., 1984). It is important to mention at this stage that more detailed evaluation of these patients, however, often reveals underlying anatomical defects of the anal sphincter as a consequence of the delivery and which also explains the incontinence in many cases (Sultan et al., 1993). Nonetheless electrophysiologic assessment of pudendal nerve function remains of some importance as this parameter may be clinically relevant in differentiating patients with fecal leakage from solid stool incontinence and there exist patients without external anal sphincter defects who have significant continence problems and whose only demonstrable abnormality is that of pudendal neuropathy.

Fecal incontinence can present in the setting of central nervous system damage such as in patients with stroke or frontal lobe damage, for example it has been demonstrated that the fecal incontinence is strongly associated with larger strokes and particularly when the cerebral cortex is involved (Nakayama et al., 1997). Fecal incontinence is also frequently encountered in patients with multiple sclerosis and one survey of anorectal function in subjects with multiple sclerosis has suggested that there may be central motor mechanisms involved (Jameson et al., 1994).

Functional bowel disorders

An increasingly common condition seen by both general practitioners and hospital doctors is that of functional bowel disorder, of which the most important is irritable bowel syndrome. This and its associated conditions including non-ulcer dyspepsia, non-cardiac chest pain and proctalgia are likely to have some degree of commonality in both their physiological mechanisms and treatment approaches. Irritable bowel syndrome (IBS) has often been characterized into a syndrome consisting of abdominal pain or discomfort for at least 12 weeks in the preceding 12 months and two of the following: pain relief with defecation; onset associated with change in frequency of stool; onset associated with change in form (appearance of) stool. As many as 15% of all people experience a mild version of irritable bowel syndrome although only a small minority seek medical care. The speculated underlying mechanisms behind irritable bowel include a disturbance of colonic motility, visceral hyper-algesia and an abnormality of processing sensory information from the gut within the cerebral cortex (Mayer & Raybould, 1990). Whilst the pathophysiology of IBS remains a matter of controversy it is likely that the condition is multifactorial involving all three potential mechanisms as well as other factors including genetics, environment, psychological factors including life stress, psychological state, coping mechanisms and social support. Therefore, the treatment of functional bowel disorders such as IBS revolves around both psychologic and pharmacological treatments. These include education and reassurance, potential lifestyle and dietary modifications and then pharmacological agents, which may act on gut motility and sensation, such as either laxatives or antidiarrheal agents and for more severe cases, psychological treatment including antidepressants.

Future directions in human brain–gut interactions

With the advent of functional non-invasive brain imaging techniques it is likely that future understanding of the mechanisms underlying visceral sensitivity, functional bowel disorders and indeed understanding mechanisms behind dysphagia after cerebral injury and incontinence after central nervous system injury will be further elucidated. For example, it has been recently demonstrated that sensory stimulation of the pharynx can induce reorganizational changes in swallowing areas of the motor cortex which outlast the period of stimulation by several minutes (Hamdy et al., 1998a,b,c). The changes recorded to pharyngeal stimulation appear reminiscent of the spontaneous changes associated with swallowing recovery after stroke. It is possible therefore that sensory stimulation techniques may hold an attractive therapeutic approach for treating dysphagia after stroke. Furthermore, lumbo-sacral stimulation which normally induces sphincter contraction in the external anal sphincter, may in future play a role in conditioning anal sphincter muscles in a way which aids anal function in patients with fecal incontinence. Finally functional imaging techniques such as fMRI and PET as well as magnetoencephalography may also allow the dissection of mechanisms underlying functional bowel disorders including influences such as emotion, attention and other psychological constructs. The ability of PET studies to provide ligand information on the neuropharmacology of the brain processing of visceral sensation as well as the

motor control of swallowing and anal continence may well allow future drug treatment to be developed which may be able to target abnormal processing of visceral areas with a view to either enhancing function or blocking aberrant function within the human brain–gut axis.

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54

Eating disorders: neurobiology and symptomatology

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The 1990s have witnessed a remarkable upsurge in research on neurochemical pathways in the central nervous system (CNS) that contribute to the regulation of food intake and body weight homeostasis. These investigations have been driven in part by increasing recognition that obesity, anorexia nervosa and bulimia nervosa represent major public health concerns. Moreover, advances in molecular neurobiology have accelerated the identification of new peptides, proteins and their receptors in the hypothalamus and other brain regions critical to the regulation of ingestive behaviour. This chapter begins with a clinical overview of anorexia nervosa and bulimia nervosa, including brief summaries of diagnostic criteria and therapeutic considerations. Subsequent sections highlight promising areas of research on the clinical neurobiology of these disorders. Findings to date suggest that alterations in regulatory systems involving serotonin, cholecystokinin (CCK) and leptin may contribute to the initial onset or perpetuation of eating disorder symptoms.

Anorexia nervosa

Symptom patterns and diagnostic criteria

Descriptions of anorexia nervosa as a disorder of unexplained weight loss first appeared in the medical literature more than a century ago. The central psychological symptom of the disorder is 'refusal to maintain body weight at or above a minimally normal weight for age and height' (Table 54.1) (American Psychiatric Association, 2000). Patients demonstrate a persistent preoccupation with body shape and weight, with an underlying pervasive fear of becoming fat. Clinical observations and laboratory studies have shown that patients with anorexia nervosa do not suffer from loss of appetite, however (Sunday & Halmi, 1996). The characteristic amenorrhea appearing in postmenarcheal women is generally thought to be a consequence of malnutrition, although in some cases the loss of menstrual cycles can precede the onset of significant weight loss.

In most survey data, the prevalence of anorexia nervosa is approximately 0.5% among adolescent girls and young women. The typical age of onset is 18 years, and the prevalence in boys and young men is estimated to be 10% of that in females (Lucas et al., 1991; Whitaker et al., 1990). Episodes of recurrent dieting typically precede the onset of an eating disorder, and psychological and cultural factors contributing to increased preoccupation with body weight and appearance are thought to play a role in the etiology of anorexia nervosa. Behavioural risk factors include perfectionism and negative self-esteem (Fairburn et al., 1999). Based on family and twin studies, heritability estimates for the disorder are approximately 60% (Wade et al., 2000).

Anorexia nervosa is often a chronic illness, with multiple episodes of weight recovery and relapse. Studies of the natural course of the disorder have shown that 50% or more of patients recover after 10 years. Up to 20% or more of patients are likely to have a poor outcome (Eckert et al., 1995; Hsu, 1996; Strober et al., 1997b), with an aggregate mortality rate of approximately 6% per decade (Sullivan, 1995). There are few predictors of clinical outcome, although very early onset and very low weight at initial assessment may be associated with less favourable outcomes.

Clinical assessment and therapeutic approaches

In the clinical evaluation of patients with an eating disorder, it is useful to obtain detailed information about the individual's daily eating patterns, quantity of foods consumed, eating-related rituals and perceptions, and associated feelings of anxiety. Although the prototypical

Table 54.1. Diagnostic criteria for anorexia nervosa[a]

A. Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g. weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected).
B. Intense fear of gaining weight or becoming fat, even though underweight.
C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body shape and weight on self-evaluation, or denial of the seriousness of current low body weight.
D. In postmenarcheal females, amenorrhea, i.e. the absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g. estrogen, administration.)

Specify type:

Restricting type: during the episode of anorexia nervosa, the person has not regularly engaged in binge-eating or purging behaviour (i.e. self-induced vomiting or the misuse of laxatives, diuretics or enemas)

Binge-eating/Purging type: during the current episode of anorexia nervosa, the person has regularly engaged in binge-eating or purging behaviour (i.e. self-induced vomiting or the misuse of laxatives, diuretics or enemas)

Notes:

[a] Diagnostic criteria in Tables 54.1 and 54.2 are reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 4th edn, Text Revision. © 2000 American Psychiatric Association.

Table 54.2. Diagnostic criteria for bulimia nervosa[a]

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
(1) eating, in a discrete period of time (e.g. within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances
(2) a sense of lack of control over eating during the episode (e.g. a feeling that one cannot stop eating or control what or how much one is eating)
B. Recurrent inappropriate compensatory behaviour in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas or other medications; fasting; or excessive exercise.
C. The binge eating and inappropriate compensatory behaviours both occur, on average, at least twice a week for 3 months.
D. Self-evaluation is unduly influenced by body shape and weight.
E. The disturbance does not occur exclusively during episodes of anorexia nervosa.

Specify type:

Purging type: during the current episode of bulimia nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics or enemas.

Non-purging type: during the current episode of bulimia nervosa, the person has used other inappropriate compensatory behaviours, such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics or enemas

patient is often described as food avoidant, approximately half of women with anorexia nervosa develop recurrent binge eating episodes, often after about a year of the disorder. To facilitate increased understanding of clinical and biological correlates of these patterns, diagnostic criteria include designations for patients with 'restricting' and 'binge-eating/purging' types (Table 54.1).

A detailed psychiatric history is important for evaluation of comorbid major psychiatric disorders. Major depression occurs in more than half of patients with anorexia nervosa, although depressed mood can also be a consequence of weight loss *per se* and may resolve spontaneously with weight gain. Attention should be given to the evaluation of suicidality, anxiety disorders (including obsessive–compulsive disorder) and substance use disorders. The clinician also needs to be alert to the possibility of other neuropsychiatric syndromes (e.g. psychotic disorders) which can in rare instances present with unexplained weight loss. Assessment of psychosocial stressors, family history and, for younger patients, family relationships can be important in planning therapeutic interventions.

The initial assessment of a patient with anorexia nervosa includes a careful medical history and physical examination, with particular attention to possible medical or neurological causes for altered eating patterns and malnutrition. Physical examination commonly reveals signs of cachexia, e.g. bradycardia and hypotension. Basic laboratory tests include complete blood count, urinalysis, evaluation of serum electrolyte, blood urea nitrogen, and creatinine levels, and thyroid function tests (American Psychiatric Association Workgroup on Eating Disorders, 2000). An electrocardiogram is often part of the initial evaluation. Inclusion of additional laboratory tests, as well as evaluation for osteopenia and osteoporosis, is related to the extent and duration of malnutrition. Endocrine abnormalities are commonly present, including elevated serum cortisol, decreased thyroid hormone levels, and decreases in gonadal hormone levels (Stoving et al., 1999). Neurological

complications include myopathy (McLoughlin et al., 1998), or central pontine myelinolysis (Copeland, 1989).

Neuroimaging studies may be included in the clinical assessment for the evaluation of neurological or atypical behavioural symptoms (American Psychiatric Association Workgroup on Eating Disorders, 2000). Brain imaging studies have shown that low weight anorexic patients have decreased cortical size reflected in enlargement of cerebral ventricles and cortical sulci (Jimerson et al., 1998). These patterns usually normalize with weight restoration, although there is some evidence for persistent changes (Lambe et al., 1997). Studies of cerebral blood flow with single-photon emission computed tomography (SPECT) and cerebral metabolic rate with positron emission tomography (PET) have reported unilateral decreases in temporal lobe blood flow (Gordon et al., 1997), and trends toward alterations in frontal and parietal cortical metabolic rates that persist following weight restoration (Delvenne et al., 1996).

Treatment planning for anorexia nervosa generally includes the collaborative efforts of a primary care physician and a mental health professional. Interventions commonly involve individual psychotherapy, family therapy (particularly for the younger patient) and nutritional consultation. Hospitalization may be necessitated for medical stabilization or for monitoring of severe psychiatric symptomatology such as suicidal ideation. Although the recent trend has been toward relatively brief inpatient stays, specialized inpatient programmes based on behavioural and cognitive–behavioural interventions can be of significant benefit to the severely underweight patient. Participation in a day treatment programme can facilitate the transition from hospitalization to outpatient treatment.

In controlled trials, pharmacological treatments including antidepressants and neuroleptic medications have generally demonstrated very limited benefit as an adjunct to inpatient-based weight restoration programmes (Jimerson et al., 1996). Similarly, recent studies have failed to demonstrate a significant benefit for selective serotonin reuptake inhibitor (SSRI) antidepressant medications in weight restoration programmes (Attia et al., 1998; Ferguson et al., 1999; Strober et al., 1999). Preliminary studies have provided mixed evidence regarding the possible efficacy of an SSRI in the prevention of relapse following weight restoration (Kaye et al., 1998a; Strober et al., 1997a).

Bulimia nervosa

Symptom patterns and diagnostic criteria

In the 1970s, clinicians recognized a syndrome in normal weight individuals characterized by recurrent episodes of binge eating accompanied by compensatory weight-control measures. Initially conceptualized as a variant of anorexia nervosa, bulimia was included in the psychiatric diagnostic criteria in 1980. Current diagnostic criteria specify that binge eating episodes occur on average twice per week, and that abnormal eating patterns are accompanied by psychological symptoms involving preoccupation with body shape and weight (Table 54.2) (American Psychiatric Association, 2000). Survey studies have suggested that important clinical characteristics of bulimia nervosa may be manifested by individuals with subclinical forms of the disorder (e.g. individuals who meet all criteria except that their average frequency of binge eating is only once per week).

Bulimia nervosa has a prevalence of approximately 2–3% among adolescent girls and young women (Kendler et al., 1991), and resembles anorexia nervosa in the average age of onset (approximately 18 years) and in the ten-fold increased prevalence in girls and young women in comparison to boys and young men. Psychological and cultural factors resulting in increased preoccupation with slimness, as well as a history of obesity, are thought to play a role in the onset of bulimia nervosa (Fairburn et al., 1997). There is an increased risk of eating disorders in family members of bulimic patients (Kassett et al., 1989), and twin studies have shown heritability of approximately 55% (Kendler et al., 1991). Naturalistic follow-up studies indicate that approximately three-quarters of patients have recovered by seven years following initial assessment (Herzog et al., 1999).

Provisional criteria for 'binge eating disorder' have been included in an appendix listing in DSM-IV-TR (American Psychiatric Association, 2000). As recently reviewed, this disorder is characterized by recurrent binge eating in the absence of compensatory weight control behaviours, resulting in patients who tend to be overweight (Devlin, 1996).

Clinical assessment and therapeutic approaches

During the initial clinical assessment, it is valuable for the clinician to inquire specifically regarding eating patterns, frequency and type of purging behaviours, and body weight fluctuations. Clinical observations and laboratory studies have demonstrated that patients with bulimia nervosa have impaired postingestive satiety, possibly contributing to the large size of binge meals (Kissileff et al., 1996). Although 'objectively' large binge eating episodes are required by the diagnostic criteria (Table 54.2), some patients may describe 'subjective' binge episodes which have similar psychological characteristics but are smaller in size. A detailed psychiatric history is important to identify comorbid major psychiatric disorders, including major depression, which occurs in more than half of patients with bulimia nervosa, suicidal ideation, substance use disorders and anxiety disorders. As with ano-

rexia nervosa, review of family history and psychosocial stressors is important in planning therapeutic interventions.

The scope of the medical assessment is based on the patient's symptoms and the clinical setting. In reviewing the clinical history, the clinician should be alert to atypical symptoms suggestive of an underlying medical or neurological disorder (e.g. Kleine–Levin syndrome). The physical examination may reveal findings such as bradycardia and hypotension associated with nutritional abnormalities, or erosion of the dental enamel or parotid gland swelling associated with binge eating and purging behaviours. Based on symptom patterns, initial laboratory tests may include serum electrolytes, blood urea nitrogen levels, creatinine levels, thyroid function tests, complete blood count, urinalysis, and electrocardiogram (American Psychiatric Association Workgroup on Eating Disorders, 2000). Although abnormal results are less common than for anorexia nervosa, bulimia nervosa is associated with hypokalemia (Wolfe et al., 2001), which could contribute to life-threatening cardiac arrhythmias. Atypical behavioural symptoms or abnormal findings on neurological examination may necessitate neuroimaging studies.

Since 1990 there have been extensive studies of psychotherapeutic and psychopharmacological interventions for bulimia nervosa (Jimerson et al., 1996; Mitchell et al., 1997). For many patients, the initial intervention is a trial of short-term psychotherapy, with recent studies of cognitive–behavioural therapy or interpersonal therapy showing an approximately two-thirds decrease in frequency of binge eating. Efficacy of antidepressant medications has also been demonstrated in double-blind, controlled trials, the largest of which showed significant therapeutic response to an SSRI medication (fluoxetine). Relatively early intervention with antidepressant medications is often considered for patients who do not respond during the initial phases of psychotherapy (Agras et al., 2000), and for patients who have comorbid psychiatric disorders such as major depression. In spite of the effectiveness of current treatment approaches, only a minority of patients achieve full abstinence from binge eating and purging during short-term treatments. In planning medication treatment for an individual patient, consultation with a specialist may assist in considering choice and dose of medication, and special side effects issues in this patient group.

Neurobiology of the eating disorders

Serotonin

Hypotheses linking abnormal regulation of CNS serotonin with the eating disorders resulted from preclinical observations showing that this neurotransmitter, as well as the catecholamines, play an important role in the regulation of ingestive behaviour (Blundell, 1986; Samanin & Garattini, 1996). Activation of serotonergic pathways in the medial basal hypothalamus was shown to limit meal size by enhancing postingestive satiety (Leibowitz & Alexander, 1998). Conversely, activation of inhibitory serotonin-1A somato-dendritic autoreceptors on cell bodies in the raphe nuclei decreases hypothalamic serotonin release and enhances food intake. Serotonin-2C receptors are thought to play an important role in the satiety response, given that mutant mice deficient in serotonin-2C receptors have significantly increased food intake, with resulting obesity (Tecott et al., 1995). Studies in healthy volunteers have shown that serotonin receptor agonist drugs such as *m*-chlorophenylpiperazine (*m*CPP) decrease food intake (Brewerton et al., 1994). The indirect serotonin agonist dexfenfluramine, which was used in the treatment of obesity prior to its withdrawal from the market because of cardiac side effects, was thought to decrease food intake through facilitation of CNS serotonergic transmission.

Based on these observations, clinical investigators hypothesized that increased serotonin function could contribute to small meal size and weight loss in anorexia nervosa (Jimerson et al., 1990). Cerebrospinal fluid (CSF) concentrations of the major serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA) were abnormally low in anorexia nervosa, however (Kaye et al., 1984). Responsiveness of CNS serotonin pathways, assessed by measuring the release of prolactin and cortisol following the administration of serotonin agonist drugs, was also diminished in low weight anorexic patients. As patients gained weight, CSF metabolite and neuroendocrine response measures returned towards normal, suggesting that abnormalities in the low weight patients could be a result of malnutrition (Brewerton & Jimerson, 1996; Hadigan et al., 1995; Monteleone et al., 1998; O'Dwyer et al., 1996). Studies showing elevated CSF 5-HIAA levels and abnormal test meal responses in patients who have achieved stable weight restoration suggest that anorexia nervosa may be associated with abnormalities of serotonin regulation independent of nutritional status (Kaye et al., 1991; Ward et al., 1998). There has also been considerable interest in genetic linkage studies in anorexia nervosa (Gorwood et al., 1998), with preliminary findings suggesting a possible association with an altered serotonin-2A receptor gene promoter polymorphism (Collier et al., 1997).

Diminished serotonergic responsiveness in bulimia nervosa is thought to contribute to impaired satiety and binge eating, and to the efficacy of antidepressant medications. Thus, patients with severe symptoms of bulimia

nervosa have low CSF 5-HIAA concentrations (Jimerson et al., 1992), and diminished neuroendocrine responses following single dose administration of serotonin agonist drugs (Brewerton et al., 1992; Jimerson et al., 1997; Levitan et al., 1997; Monteleone et al., 1998). Differences were observed following careful matching of controls for such clinical parameters as height-adjusted body weight, age, and menstrual cycle phase. Patients who have recovered from bulimia nervosa also demonstrate abnormal serotonin-related behavioural responses, although neuroendocrine hormone release appears to be normal (Kaye et al., 1998b; Smith et al., 1999; Wolfe et al., 2000). Recent studies have begun to explore whether recurrent dieting episodes may promote the onset of bulimia nervosa by decreasing CNS serotonin synthesis (Cowen et al., 1996).

Cholecystokinin

Normal regulation of body weight is dependent on a homeostatic balance between energy expenditure and food intake. While initial investigations of the CNS control of eating behaviour focused on the role of the monoamine neurotransmitters, studies of peripheral influences on eating behaviour revealed that the gut-related peptide CCK is involved in limiting meal size (Gibbs et al., 1973). In humans, exogenous CCK administration decreased meal size through augmentation of postingestive satiety (Kissileff et al., 1981). These effects are thought to be mediated in part through inhibition of gastric emptying, with resultant satiety-related signalling relayed to the CNS via vagal afferent pathways. Additionally, CCK released into the circulation may act at selective receptors in brain regions where the blood–brain barrier is relatively permeable to peptides (Moran et al., 1986).

It has been postulated than an increase in postingestive CCK release might contribute to small meal size in anorexia nervosa. However, CCK response to a test meal does not appear to be abnormal in patients with anorexia nervosa (Geracioti, Jr. et al., 1992; Pirke et al., 1994). Variability in responses across studies has been noted, possibly a result of differences in patient characteristics and peptide assay methodology. Other related studies in anorexia nervosa have shown normal CCK-like immunoreactivity in CSF (Gerner & Yamada, 1982), and low T-lymphocyte concentrations of cholecystokinin octapeptide (Brambilla et al., 1996).

Studies in bulimia nervosa indicate that diminished CCK responsiveness may contribute to attenuated postingestive satiety. Thus, in comparison to healthy controls, patients with bulimia nervosa have shown significantly attenuated responses in plasma CCK concentrations and in satiety ratings (Geracioti, Jr. & Liddle, 1988; Pirke et al., 1994; Devlin et al., 1997). Further studies are needed to evaluate the extent to which these changes may be a consequence of abnormal eating patterns and related changes in gastric physiology (Geliebter et al., 1992). Other findings in bulimia nervosa include decreased concentrations of CCK octapeptide in CSF (Lydiard et al., 1993) and in T-lymphocytes (Brambilla et al., 1996). Thus, current studies indicate that changes in CCK function may help to perpetuate recurrent binge eating in bulimia nervosa.

Leptin

An important new chapter in research on the regulation of food intake and body weight opened with the discovery of the adipose tissue hormone leptin (Zhang et al., 1994). Leptin acts in the CNS to decrease food intake, and in the periphery to increase energy metabolism (Friedman & Halaas, 1998; Schwartz et al., 1999; Tang-Christensen et al., 1999). Leptin administration decreases meal size in rodents (Kahler et al., 1998; Flynn et al., 1998), suggesting a role in mechanisms related to satiety. Leptin may be particularly involved in the longer-term regulation of body weight, acting as a feedback signal to the CNS conveying information related to adipose stores (Woods et al., 2000).

The effects of leptin on eating behaviour are likely to be mediated in the medial hypothalamus, where there are relatively high concentrations of the signalling, long-form of the leptin receptor. Activation of leptin receptors in the arcuate nucleus is thought to inhibit the release of the orexigenic peptide NPY in the paraventricular nucleus of the hypothalamus (Schwartz et al., 1996). On-going studies have delineated complex interactions between a number of other CNS neuropeptides, such as the melanocortins and their antagonists, in the regulation of feeding (Elmquist et al., 1999). There is also recent evidence that hypothalamic regulation of food intake may be influenced by alterations in fatty acid synthesis. Thus, inhibition of fatty acid synthase in mice through peripheral administration of C75, a synthetic derivative of cerulenin, resulted in marked weight loss which was not dependent on leptin (Loftus et al., 2000). This observation may reflect a novel mechanism for body weight homeostatis, and a possible future direction for therapeutic intervention research in obesity.

While a role for leptin deficiency has been demonstrated in animal models of obesity, the role of abnormal leptin regulation in human obesity is uncertain. In healthy volunteers and overweight individuals, there is a high correlation of leptin with body mass index or percentage body fat (Considine et al., 1996). In general, obese patients do not have decreased leptin levels, so it has been proposed that obesity may involve postreceptor forms of leptin resis-

tance. Preliminary clinical trials in obese patients have shown a modest effect of leptin in decreasing body weight (Heymsfield et al., 1999).

In anorexia nervosa, leptin levels are markedly reduced and increase to normal levels following weight restoration (Hebebrand et al., 1995; Grinspoon et al., 1996; Mantzoros et al., 1997; Eckert et al., 1998). A disproportionate rise in leptin levels during treatment could contribute to the commonly observed resistance to weight restoration (Mantzoros et al., 1997). Leptin may play a role in some of the neuroendocrine alterations (e.g. decreased gonadal hormones and decreased thyroid hormone levels) observed in low weight anorexic patients (Flier, 1998).

In comparison to controls matched for age, gender and body weight, patients with bulimia nervosa have significantly decreased leptin levels (Brewerton et al., 2000; Jimerson et al., 2000; Monteleone et al., 2000). Moreover, there appears to be a persistent decrease in leptin levels in patients who have achieved stable remission from bulimia nervosa, suggesting a trait-related characteristic (Jimerson et al., 2000). Follow-up studies are needed to assess whether diminished leptin function contributes to impaired satiety, decreased thyroid hormone levels, and decreased resting metabolic rate in this disorder (Obarzanek et al., 1991), possibly reflecting a biological risk factor for the onset of bulimia nervosa.

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Sleep and its disorders

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Sleep is a necessary behaviour

Our lives are dominated by daily cycles of sleep and wake. The origin of these cycles begins with the earliest life on this planet. Life requires energy and the only available source of energy for the earliest life was the sun. Because of the cyclic availability of solar energy, prokaryotes evolved adaptations to use energy during the solar day, and to carry out other functions at night. With the evolution of nervous systems in primitive animals, this pattern of adaptation was maintained as rest–activity cycles. Recent studies indicate that, even in an invertebrate such as the fruit fly, *Drosophila*, the rest–activity cycles bear a striking resemblance to sleep–wake cycles in mammals. Sleep has long been recognized to have a restorative function and sleep is required to maintain life. Total deprivation of sleep results in death and even relatively brief periods of sleep deprivation, when repeated over several days, produce profound decrements in vigilance, psychomotor performance and mood. One of the commonest, transient forms of sleep disruption, that occurring with jet lag, can produce cognitive impairment and structural brain changes when it is chronic. Thus, sleep is necessary for life and successful adaptive, waking behaviour.

Sleep disorders are common and important

Loss of sleep is a major problem in our industrialized society, with an immense impact on health and productivity. This occurs as a conseqeunce of economic pressures and the pace of modern life but also results from environmental constraints that alter the normal pattern of the rest–activity cycle; shift work is an important example. Further, common medical and psychiatric illnesses impair sleep resulting in insomnia and chronic sleep deprivation. Finally, we now recognize that there are many primary sleep disorders that have a significant impact on health and normal function. In this chapter, we will review the neurobiology of sleep and important sleep disorders.

Neurobiology of sleep

Behaviour is divided into three states, waking, REM sleep and non-REM (NREM) sleep

With the development of electroencephalography (EEG) in the first half of the twentieth centry, it became possible to record brain activity continuously and to correlate the activity obtained from surface scalp electrodes with behavioural state. With this it was quickly recognized that the waking state is associated with desynchronized, low voltage EEG dominated by high frequency activity, predominantly in the 8–12 Hz range. As sleep supervenes, the EEG activity increases in voltage but decreases in frequency progressively over time with increasing synchrony until, with deep sleep, the very high voltage, slow activity of non-REM (NREM), or slow wave, sleep is evident. In a normal, young individual, sleep is initiated with a gradual slowing of EEG activity accompanied by a loss of responsiveness. Sleep is initiated with NREM sleep which is typically described to have four stages, designated stages 1–4, which are characterized by increasing unresponsiveness and slowing of the EEG. After 60–75 minutes of NREM sleep, REM sleep, a state characterized by an activated EEG, irregular, rapid eye movements (REM), muscular atonia, and unresponsiveness to sensory stimuli replaces it (Fig. 55.1). Work by several investigators, particularly Nathaniel Kleitman and his associates, demonstrated that the activated EEG of REM sleep is essentially equivalent to that of waking and that dreaming is the behavioural concomitant of the activated cortex of REM sleep.

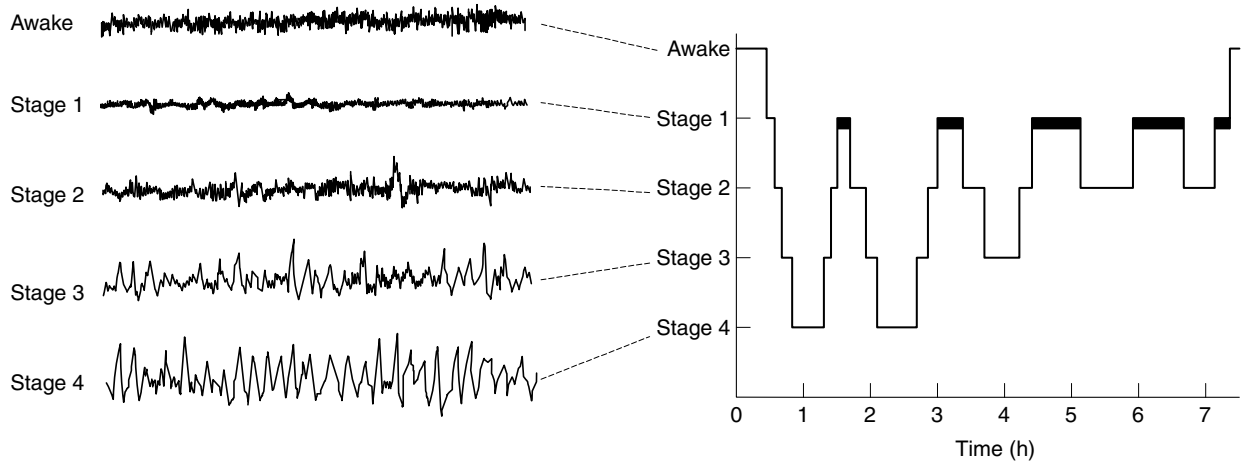

Fig. 55.1. NREM sleep stages and distribution of NREM and REM sleep through a single night. The EEG patterns of the stages (stages 1–4) of NREM sleep are shown on the left. On the right is the transition from NREM to REM sleep over the course of the sleep period. REM sleep epochs are designated by the dark bars above NREM stage 1 (▬).

Waking is an active state with behavioural adaptation

The waking state is associated with a conscious perception of environmental events and ongoing integrative activities of learning, problem solving, cognition and emotion and a motor output which includes speech, writing and a panoply of simple and complex motor acts. The essential feature of human adaptive waking behaviour is its complexity. It was assumed early in the twentieth century that waking was maintained by sensory information transmitted through the well-known lemniscal sensory pathways. This view was revised in the late 1940s when Giuseppi Moruzzi and Horace Magoun showed that the rostral brainstem reticular formation is critical to maintaining the waking state. Animals with lesions destroying the midbrain reticular formation, but preserving lemniscal sensory pathways, particularly visual and olfactory input, remained in a constant, unresponsive state with a high voltage, low frequency EEG. The same state is observed in humans with similar lesions. These observations led to the concept of an 'ascending reticular activating system', which has been extended and amplified over the last 50 years. The components of this system and the pathways through which it activates the cerebral cortex are shown in Fig. 55.2. Activity in the reticular activating system is driven, at least in part, by sensory input from all primary modalities. The reticular activating system provides input to activating-arousal systems in brainstem (locus ceruleus, midbrain raphe nuclei, pontine cholinergic nuclei), hypothalamus (posterior and lateral hypothalamus), thalamus and basal forebrain. These systems provide input to the cerebral cortex to maintain it in an activated state which permits the elaboration of the varieties of adaptive, and sometimes maladaptive, behaviours that characterize the waking state. The contribution of each of these systems to arousal and the waking state is different, and not yet thoroughly understood. Recent work, which will be described in greater detail in a discussion of narcolepsy, has emphasized the role of the hypothalamus. This was first appreciated by Constantine von Economo in the pathology of encephalitis lethargica and demonstrated experimentally by Walle Nauta who showed prolonged and profound deficits in arousal in animals with posterior hypothalamic lesions. The important role of the hypothalamus in sleep–wake regulation was neglected for many years but is now more fully appreciated. The hypothalamus contains both arousal/wake-promoting areas and sleep-promoting areas (for review, see Jones, 2000). Lesions involving the anterior hypothalamus result in diminished arousal. Recent work has shown a small group of ventrolateral preoptic neurons that are activated during NREM sleep and, as we will see in sections to follow, the posterior hypothalamus contains several areas which appear to function in waking and arousal.

In the 1960s, the noradrenaline neurons of the locus ceruleus and the serotonin neurons of the midbrain raphe were shown to project widely over the forebrain, including to the entire cerebral cortex, a pattern of projection that indicates a role in behavioural state regulation. Neurons of the locus ceruleus fire continuously during waking. They respond particulary to stimuli that produce behavioural vigilance and may have a special function in producing the heightened capacity for adaptive behaviour that accompanies

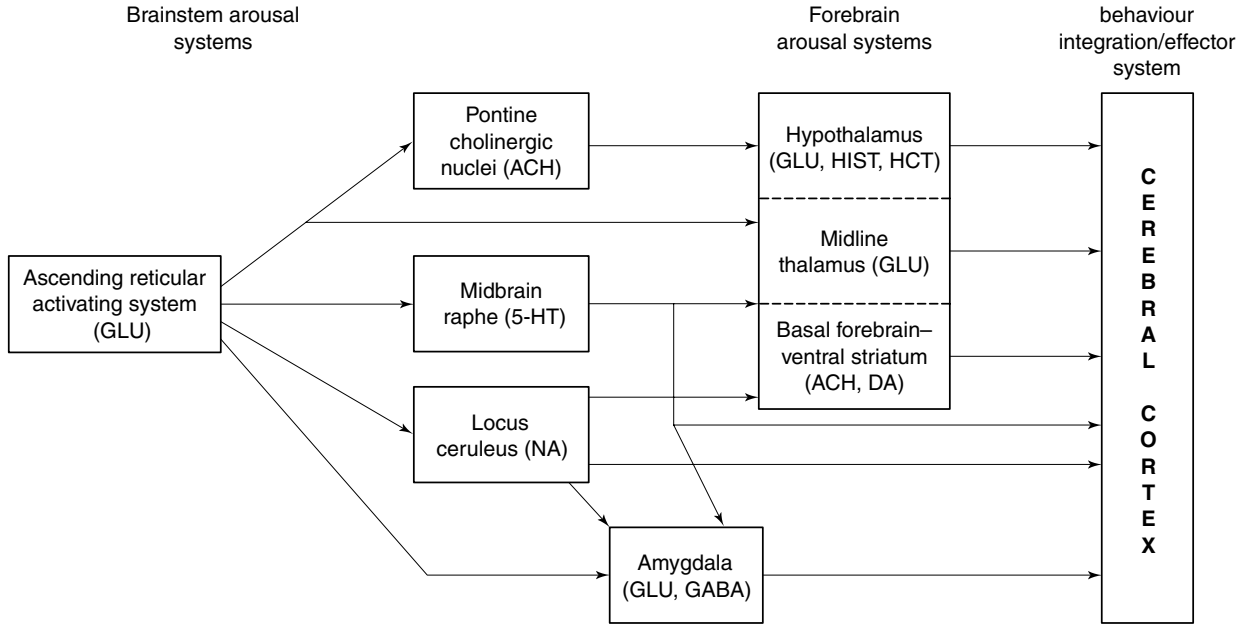

Fig. 55.2. Arousal systems in the human brain (see text for description). The transmitters associated with each system are abbreviated: ACH, acetylcholine; DA, dopamine; GABA, gamma aminobutyric acid; GLU, glutamate; HIST, histamine; HYP, hypocretin; NA, noradrenaline; 5HT, serotonin.

vigilance. During NREM sleep, the firing of locus ceruleus neurons diminishes compared to waking and they cease firing in REM sleep. The firing of midbrain raphe neurons projecting to forebrain has a similar pattern except that they typically do not respond to sensory input. Both of these systems, the noradrenaline neurons of the locus ceruleus and the serotonin neurons of the midbrain raphe nuclei, have widespread projections to diencephalon, basal forebrain and cerebral cortex. The action of norepinephrine and serotonin at synapses is predominantly modulatory and its seems likely that the action of these systems is to alter the responsiveness of forebrain neurons to other inputs and to contribute to induction of arousal and the maintenance of the waking state in this manner. In contrast, the cholinergic input from basal forebrain and the glutamatergic inputs from thalamus and hypothalamus play a more direct role in arousal and maintaining the waking state.

Sleep–wake regulation requires circadian and homeostatic factors

Circadian timing is crucial to sleep–wake regulation

The solar cycle of light and dark is the most pervasive, cyclic stimulus in the environment. Animals have evolved rest–activity cycles, sleep–wake cycles in higher vertebrates, to maximize adaptation to their environment. These cycles have two predominant features: (i) in a normal solar cycle, they are exactly 24 hours in length and exhibit a precise phase relationship to the solar cycle, a phenomenon termed 'entrainment'; (ii) in the absence of a light–dark cycle, they are maintained by endogenous timing mechanisms, or clocks. These features predict the fundamental organization of a circadian timing system, a set of related neural structures which functions to provide a precise temporal organization of physiological processes and behaviour. The circadian timing system has three components: (i) photoreceptors that transduce photic information into neural information that is conveyed to circadian pacemakers by entrainment pathways; (ii) pacemakers which receive entrainment information and contain genetically determined molecular timing mechanisms that generate a cellular circadian output; (iii) efferent pathways from the pacemakers to effector systems that are under circadian control. The components of the circadian timing system are shown in Fig. 55.3. Photic information appears to be transduced by a unique set of photoreceptors which appear to be neither rods nor cones. These photoreceptors are connected by as yet unknown retinal elements to a subset of retinal ganglion cells distributed over the entire retina that project only to the circadian timing system through the retinohypotha-

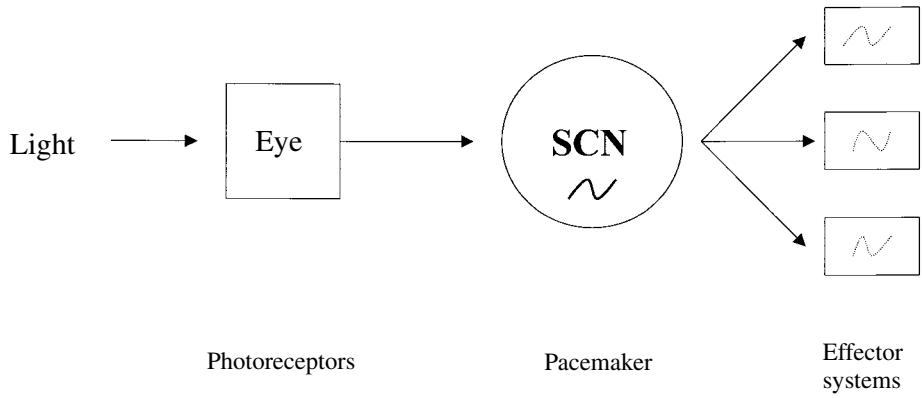

Fig. 55.3. Components of the circadian timing system. See text for description.

lamic tract. Destruction of the retinohypothalamic tract eliminates circadian rhythm entrainment without affecting other aspects of visual function, providing the basis for a disorder of entrainment as a specific sleep disorder (see below).

The circadian pacemaker in mammals that controls most circadian rhythms, particularly the sleep–wake rhythm, is the suprachiasmatic nucleus (SCN) of the hypothalamus. Lesions of the SCN eliminate most circadian rhythms, including the rhythm in sleep–wake behaviour. Neurons of the SCN exhibit a circadian rhythm in firing rate, both in vivo and in vitro and transplantation of fetal SCN into the brains of animals rendered arrhythmic by SCN lesions restores circadian control of sleep–wake behaviour. The output of the SCN is predominantly to hypothalamus and different pathways provide circadian control of separate functions. For example, SCN projections to paraventricular hypothalamic nucleus neurons which, in turn, project to the upper thoracic intermediolateral cell column provide circadian control of melatonin secretion through superior cervical ganglion sympathetic innervation of the pineal gland. Similarly, a separate set of SCN projections to parvocellular corticotropin releasing hormone (CRH) neurons of the paraventricular hypothalamic nucleus controls the production and secretion of CRH at the median eminence with downstream control of pituitary corticotropins and cortisol producing cells of the adrenal cortex. Until recently, the pathways involved in sleep–wake regulation were not well understood. It now seems clear that SCN projections to neuron groups in the posterior and lateral hypothalamus promoting arousal and wakefulness (Fig. 55.2) mediate this function. The function of the SCN in controlling the sleep–wake cycle is one of maintaining arousal against homeostatic drive for sleep. Thus, the circadian system, particularly the SCN, could be viewed as the component of the hypothalamic arousal/waking system depicted in Fig. 55.2.

Homeostatic drive for sleep interacts with circadian control of waking

It is apparent to all humans that a need for sleep, termed homeostatic drive, increases as a function of the waking time since the last period of sleep. Early in the study of sleep control, it was assumed that this was the principal mechanism controlling sleep onset and duration. The role of the circadian system was first recognized to interact with homeostatic mechanisms in a systematic way by Alexander Borbély and Sergei Daan and their associates (Borbély et al., 1989). The homeostatic mechanisms can be conceptualized as a simple, time-dependent accumulation of a sleep-promoting substance, S, which continues to accumulate until it is dissipated by sleep. The extent to which S is lost is a function of the duration of the sleep period.

The nature of S, of whether it is a simple mechanism or multiple factors, is not known. For many years, there have been proposals that the homeostatic propensity for sleep reflects the build-up of sleep-promoting substances in brain. A number of studies have implicated a variety of neuroactive peptides and cytokines as sleep promoting. Perhaps the most intriguing molecule is adenosine. The effects of caffeine and related adenosine-receptor blockers are well known. Adenosine has been shown to accumulate in brain with sleep deprivation, including in areas important for the maintenance of arousal, further supporting this compound as a sleep-promoting substance.

NREM sleep facilitates adaptive, waking behaviour

NREM, or slow wave, sleep is a behavioural state characterized by a lack of response to environmental stimuli, minimal movements and a reduction of brain activity. The

majority of total sleep time, which averages 7.5–8.5 hours a day in normal young adults, is spent in NREM sleep. Sleep is typically consolidated with approximately 95% of the night spent asleep in normal young individuals. NREM sleep occupies 75 to 80% and REM 20 to 25% of the total sleep period. NREM and REM sleep alternate in approximately 90-minute epochs with NREM periods becoming shorter and REM periods longer over the night. The proportion of total sleep time in NREM sleep gradually increases over the lifespan as REM sleep diminishes and aging is typically associated with less stage 3 and 4 NREM sleep and more sleep interruptions. Although dreaming is associated primarily with REM sleep, it is well established that dreams can occur in NREM sleep. In general, dreams in NREM sleep are much less frequent, briefer and less complex than those occurring with REM sleep. Although there continues to be speculation about the function of REM sleep (see below), it is generally accepted that NREM sleep has a restorative function that promotes successful adaptive waking behaviour. This includes both a permissive role in restoring a variety of somatic functions and one in restoring brain function. There is substantial support for a hypothesis that NREM sleep works to restore effective brain energy metabolism. Recent data indicate that memory consolidation is an important concomitant of NREM sleep.

Brain activity is reduced in NREM sleep

Consonant with the view that NREM sleep is restorative, the onset of NREM sleep is heralded by increased voltage, slow activity that reflects a synchronous discharge of populations of thalamocortical neurons. And, with positron emission tomography (PET), global cerebral blood flow (CBF) and glucose utilization are shown to be reduced indicating a decrease in information processing as that is reflected in the energy requirements of synaptic activity. CBF decreases by approximately 25% in stages 3–4 NREM sleep in comparison to waking. With analysis of regional blood flow (rCBF), decreases are found in cerebellum, brainstem, thalamus, basal ganglia, basal forebrain and over much of the cortex with only primary sensory areas maintaining waking levels of rCBF (Braun et al., 1997). Extensive electrophysiological analysis since 1985, particularly by Mircea Steriade and David McCormick and their collaborators (for review, see McCormick & Bal, 1997), has shown that NREM sleep represents an interaction between the neurons of thalamic relay nuclei which each project to cerebral cortex with collaterals to thalamic reticular nucleus, cortical neurons projecting to thalamic reticular nucleus and thalamic relay nuclei and the inhibitory projections of thalamic reticular nucleus to relay nuclei. With the sleep-promoting effects of the sleep homeostatic control mechanisms, there is a gradual hyperpolarization of the components of the thalamocortical system that results in synchronous firing with consequent EEG changes of sleep spindle formation and slow waves which result in the NREM state.

REM sleep reflects an activated forebrain

The typical pattern of sleep is onset with NREM sleep followed by REM sleep in epochs of 90–100 minutes. Through the night the NREM component decreases while the REM component increases and awakening typically occurs from REM sleep. In REM sleep, individuals are unresponsive but the EEG is essentially indistinguishable from waking with low voltage, desynchronized activity. REM sleep is also associated with muscular hypotonia and with saccadic eye movements, the 'REM' of REM sleep. The behaviour of REM sleep is dreaming. When individuals are awakened from REM sleep, approximately 80% report having a dream. There is an extensive literature, beginning particularly with the Freudian psychoanalytic era in psychiatry, reporting analysis of the content of dreams. More recently, attempts have been made to provide a formal, scientific analysis of dream content (for review see Hobson et al., 1998). The content of dreams typically includes visual and motor material which, since sensory input and motor output are inhibited in REM, represent hallucinations. Dream imagery is often bizarre and it is typical to have abrupt transitions in content. There is increased and intensified emotion associated with dream content, particularly fear–anxiety. Dream content proceeds without volitional control. This changing, vivid material of dreams is consonant with an activated cerebral cortex, as is indicated by the nature of REM sleep EEG activity and the fact that glucose utilization in the cortex in REM sleep is equivalent to that in waking. It seems likely that dream content reflects an activated state, and the fact that the cortex is isolated from sensory input and motor output. The other constant feature of dreams is that they are forgotten, lost to conscious recall, unless the individual awakens from a dream and immediately recounts the dream content in the waking state. Since dreams appear to represent a process of cortical activation superimposed on the relatively quiescent state of NREM sleep, the content of the dream can only reflect an ensemble activity of cortical neuronal populations. The mental content of that activity, in turn, must be founded in the experience of that individual and the specific patterns of brain activation occurring in the REM state.

Recent PET studies have provided new insight into the neurobiology of REM sleep. Although there are some small differences among the studies, all show that REM sleep, in comparison to waking, is associated with increased activity in the pons and midbrain, the basal ganglia, hypothalamus and a set of limbic–paralimbic structures including the anterior cingulate and subgenual cortex, orbitofrontal cortex, parahippocampal cortex, and amygdala either as increased cerebral blood flow or as increased glucose utilization. This pattern of increased regional activity in REM is strikingly different from the regional pattern in waking, and that in NREM sleep.

The mechanisms that initiate the onset of REM sleep are unknown, but also probably reflect a combination of homeostatic and circadian factors. The onset of REM sleep occurs with the coincidence of two sets of events, firing from a group of cholinergic REM-on neurons in the pontine reticular formation and diminished firing of the aminergic neurons of the locus ceruleus and raphe nuclei. The firing of the pontine cholinergic neurons generates the forebrain activation of REM sleep and this appears to occur as a consequence of the removal of a tonic inhibition of these neurons by the locus and raphe.

Sleep disorders

Disturbances of sleep are among the most frequent complaints brought to physicians. Sleep disorders are both common and have an extensive morbidity, interfering with performance on the job and in social and family interactions and leading to accidents at work and while driving. And sleep disorders exacerbate medical and psychiatric illnesses. Patients with sleep disorders typically complain of one or more of three types of problems, insomnia, excessive daytime sleepiness or abnormal movements, sensations and behaviours during sleep or at nocturnal awakenings. The approach to these complaints requires a detailed history, physical and neurological examination including an assessment of mental status and the appropriate laboratory tests. Sleep disorders medicine has evolved into a subspeciality with a board examination. There is an International Classification of Sleep Disorders: Diagnostic and Coding Manual (1997) which has four categories of disorders: (i) dyssomnias, disorders of initiating and maintaining sleep and disorders of excessive daytime sleepiness; (ii) parasomnias, disorders which do not present with insomnia or excessive daytime sleepiness; (iii) disorders associated with medical or psychiatric illnesses; (iv) proposed sleep disorders, ones for which there is insufficient current evidence to definitively establish them as sleep disorders. Major examples of the first three categories will be presented below.

Dyssomnias

Sleep apnea syndrome

Sleep apnea syndrome refers to episodes of transient cessation of breathing during sleep ($\geqslant$10 seconds) that disrupt sleep and thereby lead to excessive daytime sleepiness. In most cases, this is related to occlusion of the pharyngeal airway and is referred to as an obstructive sleep apnea syndrome. In other cases, there is reduced ventilatory effort during sleep in the absence of any discrete airway obstruction, and this is referred to as a central sleep apnea syndrome. A third condition, the upper airway resistance syndrome (UARS), consists of increased respiratory effort in the absence of discrete apneic events. This increased effort leads to non-restorative sleep which, in turn, produces daytime sleepiness.

These syndromes occur most commonly in obese, aging men but are not restricted to these Pickwickian types. Epidemiological studies suggest that roughly 4% of men and 2% of women ages 30 to 60 will meet minimal diagnostic criteria for obstructive sleep apnea syndrome. The most common clinical symptoms reported are daytime sleepiness in the presence of sleep-related snoring with occasional pauses in breathing or 'gasping' for breath during sleep. Other daytime symptoms include fatigue, morning headaches, and cognitive changes such as reduced concentration and attention. The sleepiness of sleep apnea is differentiated from the sleepiness of narcolepsy by the constant, unrelenting nature of the sleepiness, whereas, in narcolepsy, the sleepiness is qualitatively more sudden in onset and offset. The constant sleepiness and fatigue need to be differentiated from similar sleep symptoms in psychiatric patients by the concurrent changes in mood or personality found in psychiatric disorders that are not found in the isolated apneic patient.

The pathophysiology of obstructive sleep apnea syndrome is related to the anatomic factors that maintain airway patency during sleep. The site of airway obstruction in obstructive sleep apnea syndrome is in the pharynx. Whether this airway will close during sleep reflects the balance between forces that narrow the airway, such as intrapharyngeal suction during inspiration, and forces that dilate the airway, such as the tone of pharyngeal airway muscles. Anatomical abnormalities found in apneic patients in this area include the manifestations of obesity, enlarged tonsils, and facial bony abnormalities. Additionally, sleep itself is associated with a loss of tone in

pharyngeal muscles that maintain the outward pressure necessary for airway patency. Alcohol may contribute to symptoms by acting as an extrinsic suppressant of pharyngeal muscle tone that exacerbates apnea by reducing the outward pressure on the pharyngeal airway.

Central sleep apnea syndrome refers to the periodic loss of ventilatory effort with associated cessation of breathing during sleep. This is differentiated from obstructive type apneas in which there is a loss of breathing despite persistent attempts at ventilation. These patients constitute less than 10% of apneic patients. The pathogenesis of central sleep apnea is likely to be diverse, given the broad conditions that produce this type of breathing during sleep such as central alveolar hypoventilation, congestive heart failure, nasal obstruction and dysautonomias. In general, a final common pathway appears to be some disturbance in the respiratory control system that includes sensors for hypoxia and hypercapnia and brainstem and forebrain centres that influence respiratory function in response to metabolic and behavioural demands. Clinically, patients with alveolar hypoventilation present with signs of respiratory failure, whereas non-hypercapnic patients may present with insomnia, normal body habitus and awakenings with gasping for breath. Diagnosis is definitively made in the research setting by the use of an esophageal balloon. Treatment for the hypercapnic patient with hypoventilation during waking requires ventilation at night using a nasal mask and a pressure-cycled ventilator. For the non-hypercapnic patient, treatment consists of correcting the underlying problem (e.g. nasal obstruction, congestive heart failure) or watchful waiting as approximately 20% may resolve spontaneously. Nasal CPAP can be tried if the patient is obese, snores and has heart failure. Oxygen administration may be helpful if the apneic events are associated with hypoxemia. If symptoms are persistent, a carbonic anhydrase inhibitor can be useful.

Primary insomnia

Insomnia is the experience of inadequate or poor quality of sleep and is characterized by one or more of the following: difficulty falling asleep, difficulty maintaining sleep and/or awakening earlier than one would prefer. Additionally, patients have daytime dysfunction that may include fatigue, altered mood and difficulty with cognitive functions that require attention and concentration. Roughly 10% of the adult population suffers from chronic insomnia and 30 to 50% will experience transient insomnia at some point in their life. Females appear to be more affected across the lifespan and the elderly are particularly vulnerable. Consequences of insomnia may include poor daytime performance, an increased likelihood of subsequent development of a mental disorder such as depression or anxiety, and increased medical morbidity and mortality. Insomnias may be classified as either short term (transient) or long term (chronic) and as either primary or secondary to another general medical or mental disorder.

Transient insomnias occur in otherwise healthy individuals and are usually related to sleeping in an unfamiliar environment, an environment that is temporarily disrupted by noises, sounds or temperature changes, a recent life stressor, a change in the timing of bedtime related to travel across time zones or shift work, or to acute administration or withdrawal of a medication that affects the sleep/wake cycle. In each case, identification of the etiology is important. Short-term (1 to 4 weeks) sedative hypnotic use may be indicated. Care should be taken to taper and discontinue this medication following resolution of the acute event to avoid the development of psychological or physiological dependence on the hypnotic.

Chronic primary insomnias are by definition primary and not secondary to other medical or mental disorders. Other terms that have been used to define this population include pyschophysiological insomnia, sleep state misperception and idiopathic insomnia. The term psychophysiological insomnia stems from a literature which suggests that insomnia patients suffer from psychophysiological 'hyperarousal'. A vicious cycle of precipitating event, increased arousal, difficulty sleeping, preoccupation with inability to sleep leading to even more arousal and inability to sleep defines the pathophysiology of these patients. The neurobiology of the concept of 'hyperarousal' however, remains poorly defined. In part, the presence of an excessive amount of high frequency EEG activity within the sleep period is used in support of the concept of hyperarousal. Sleep state misperception refers to the subjective perception of being awake throughout the night, despite the presence of polysomnographically determined sleep. In general, primary insomnia patients tend to underestimate the actual amount of sleep they are getting in a night. These observations raise the likelihood that the sleep that insomniac patients experience may not represent the restorative sleep that non-insomniac patients receive each night. The presence of high frequency EEG activity within polysomnographically determined sleep may represent a less differentiated behavioural state that includes components of both sleep and wakefulness in the same individual. Treatment of insomnia is multifaceted and includes behavioural and pharmacological approaches. Historically, there should be no evidence that the insomnia is secondary, and if so, the underlying disorder should be evaluated and treated. Several behavioural strategies are available. Relaxation techniques include progressive

muscle relaxation, EMG biofeedback, meditation, and guided imagery. Stimulus control therapy follows from a learning model of insomnia. In this model, insomniacs develop negative associations to the bedroom, and the sleeping environment that when exposed to, produce increased arousal and subsequent insomnia. Stimulus control instructions include: 'lie down only when you feel sleepy', 'use the bed and bedroom for sleep and sex only', and 'get out of bed and go to another room if you are not sleeping'. Along with these instructions include prescriptions to maintain the same clock times for going to bed and getting out of bed the next day as well as to avoid daytime napping, irrespective of how much sleep had been obtained on the preceding night. Sleep restriction therapy refers to restricting the amount of time in bed to the time that a person believes he/she is actually sleeping. For example, a schedule for someone who believes he/she is sleeping for 6 hours might be set for midnight to 6 am; for 4 hours from 1 am to 5 am; or for 8 hours from 10 pm to 6 am. These individuals should also be instructed to avoid daytime napping. This counters the natural tendency of insomniac patients to nap or prolong their times in bed in an effort to obtain more sleep. This is often counterproductive as it lightens the sleep that they do get, increasing the likelihood of middle of the night and early morning awakenings. Cognitive therapy for insomnia includes questioning erroneous beliefs that an insomniac patient may have regarding the catastrophic consequences of insomnia and beliefs regarding the inadequacy of sleep that they are having.

Narcolepsy

Narcolepsy is a sleep disorder, recognized as a distinct entity for more than a century, characterized by excessive daytime sleepiness and the intrusion of REM sleep phenomena, particularly cataplexy (muscle atonia induced by emotion-provoking stimuli), into waking. Individuals with narcolepsy may fall asleep at any time during the day, often very abruptly. These uncontrollable episodes of daytime sleeping are the necessary and predominant manifestation of narcolepsy in most affected individuals and this symptom, particularly when associated with cataplexy, produces severe impairment of function in social interactions and work performance and a very diminished quality of life. Despite the occurrence of daytime sleep episodes, total daily sleep time is unaltered because night sleep is reduced proportionately to that occurring during the day. The diagnosis of narcolepsy is often difficult because there are many causes of excessive daytime sleepiness, and this problem is accentuated because a lack of understanding of the pathophysiology of the disease has prevented development of a simple and reliable diagnostic test. It appears, however, that this situation will change in the near future. A series of recent studies indicates that narcolepsy will be a model for the application of molecular genetics and molecular biology to the understanding of disease.

Unfolding the basis for narcolepsy began in 1998 with the discovery of a new gene, expressed in the hypothalamus, that codes for new peptides termed hypocretins, or orexins. The term 'orexin' appears inappropriate as it was applied with the view that the peptides function primarily in the control of feeding and this clearly is not the case. 'Hypocretin' was applied to signify that the gene is expressed in the hypothalamus and that the peptide product belongs to the secretin family of peptides. Following discovery of the hypocretin gene, and characterization of the peptide, immunohistochemical studies showed that hypocretin neurons are located exclusively in the posterior and lateral hypothalamus with axonal projections distributed widely over the neuraxis, particularly to areas involved in arousal and to the entire neocortex in rodents and the human. Transgenic mice with deletion of the hypocretin gene exhibit a behavioural phenotype consistent with narcolepsy, and a well-characterized canine model of narcolepsy was found to carry a mutation in the gene for a hypocretin receptor. Analysis of CSF from narcoleptic patients demonstrated a marked reduction in hypocretin content in comparison to controls. Finally, immunohistochemical analysis of narcoleptic brains shows a striking loss of hypocretin neurons and their axonal plexuses in the hypothalamus. Thus, in less than 2 years we progressed from almost no understanding of the pathophysiology of narcolepsy to a detailed account of a very selective neuropathology. The principal issues remaining are to determine the basis for the hypocretin neuron pathology and how this results in the manifestations of the disease. Although there are instances of familial cases, narcolepsy is predominantly a sporadic disease. Until the recent work on the hypocretin neuron pathology, the only known biological association was the finding that over 90% of narcoleptics have the histocompatibility marker HLA-DQB1 0602. This suggests that the hypocretin neuron pathology may occur on an autoimmune basis; that is, the fundamental basis of the pathophysiology is a genetically determined immune system status that results in a predilection to autoimmune responses in which individuals produce antibodies against hypocretin. This is an attractive hypothesis but it remains to be established.

There are two independent clusters of symptoms that may require treatment in narcoleptic patients. The first is daytime sleepiness. Given the severity of the sleepiness, it

would be unusual for behavioural interventions to be completely effective. Some patients find that adding periodic, brief daytime naps reduces some of the sleep attacks. Allowing for adequate sleep at night is advised, and occasionally, these patients will demonstrate insomnia, or nightmares, that require the use of a sedative hypnotic medication. The primary treatment for sleepiness, however, consists of the use of either a stimulant medication or a medication that promotes wakefulness. The commonly used stimulants include methylphenidate, dextroamphetamine, and pemoline, in descending order of stimulant potency. Short-acting preparations last around 4 hours and longer-acting preparations extend this effect a few hours. Consequently, these medications are often prescribed at least at morning and around lunchtime. Occasionally, a patient may need a late afternoon dose if he/she anticipates being involved in activities during the evening that require full attention. Often, the development of tolerance to low doses forces escalation to effective levels. Side effects such as nervousness, affective symptoms and nocturnal insomnia require monitoring. An alternate medication is modafinil. This medication often reduces daytime sleep and benefits most patients. Some patients, however, do not obtain full relief of their sleepiness with modafinil and require addition of a stimulant. Modafinil is an interesting addition to the treatment of narcolepsy in that it does not appear to act via the dopamine systems, has very limited potential for abuse and does not appear to induce tolerance.

The second cluster of symptoms that require treatment includes cataplexy, hypnagogic hallucinations and sleep onset paralysis. Of these, the cataplexy is the most significant symptom clinically, as it is associated with considerable limitation in psychosocial function and potential danger to the individual as a result of personal injury from falls. These symptoms are generally effectively managed with the use of antidepressant agents such as clomipramine, the selective serotonin reuptake inhibitors, or venlafaxine. Dosages that relieve cataplexy are generally lower than those used to treat depression. Tolerance to these agents can develop which may require switching to an alternative agent.

Disorders of circadian function

The function of the CTS is to provide a temporal organization of physiological processes and behaviour to promote effective adaptation to the environment. At the behavioural level, this is expressed in regular cycles of sleep and waking and disorders of circadian function are typically characterized by disturbances of sleep and waking and by other behavioural symptoms that reflect both the sleep disturbances and alterations of circadian regulation of waking adaptive behaviour. From the organization of the CTS, we would expect three types of circadian disorder: abnormalities of entrainment, pacemaker function and pacemaker coupling to effector systems (for recent review, see Moore, 1998).

Disorders of entrainment

Blindness (non-24 hour sleep–wake syndrome)

Congenital and acquired blindness provide instances of pure disorders of entrainment. Individuals who are blind typically attempt to adapt their behaviour to that of their community. For a number of years it was believed that the blind accomplished this by entraining their circadian system to the social cues of the environment, but it now appears that many are not able to do so. Blind subjects fall into two categories. The first is composed of individuals with a free-running melatonin rhythm indicating that they were not entrained to the environmental light–dark cycle. These individuals typically maintain 24-hour sleep–wake cycles, however, and when their melatonin rhythm peaks during sleep, they report sleeping well and feeling well. When their melatonin and sleep periods are out of phase, they experience sleep disturbances and other symptoms indicative of disturbed circadian regulation. The second blind group has entrained melatonin rhythms and sleep–wake cycles and reports no symptoms of sleep disturbance or those related to circadian disruption. Some of these individuals show a normal suppression of peak melatonin levels by light even though they are totally blind. The nocturnal suppression of peak melatonin levels is a function of the retinohypothalamic projections so that we must conclude that, in these individuals, the retinal phototransduction mechanisms are intact through those pathways even though all other retinal mechanisms are non-functional. The mirror image of this is individuals who are not blind but exhibit the free-running rhythms and symptoms of the non-24-hour sleep–wake syndrome. Although this remains to be established, we would presume that these individuals lack the specific circadian phototransduction process. There are also blind individuals who are normally entrained but lack light suppression of melatonin. It is assumed that these individuals employ a non-photic entrainment process.

Rapid time zone change syndrome (jet lag)

The jet lag syndrome is a disorder of modern life. Symptoms of rapid time zone change occur in some indi-

viduals with changes of as little as 3 hours but at least a 5-hour change is required for most. The typical symptoms of jet lag include sleep disruption, fatigue, difficulty concentrating, gastrointestinal distress, impaired psychomotor coordination, reduced cognitive skills and alterations of mood. The symptoms remit spontaneously over days with their duration determined by the direction of travel, west to east produces more impairment than east to west, and the number of time zones crossed. Numerous measures have been reported to ameliorate jet lag but the evidence is usually anecdotal. Recent studies done with a placebo control indicate that melatonin is an effective treatment, presumably by acting on the SCN pacemaker. An interesting recent study has reported both cognitive changes and temporal lobe atrophy in individuals with chronic jet lag (Cho, 2001).

Work shift syndrome

Many workers in industrialized countries perform their occupation at unusual hours. This is particularly true of health care workers, police and security guards, truck drivers and some workers in heavy industry. The factors involved in adjusting to shift work are complex and disruption of circadian mechanisms is only one of those involved. The major symptom of work shift disorder is impaired sleep and attendant impairment of function. There have been recent descriptions of the use of bright light and melatonin to treat the circadian abnormalities associated with shift work.

Delayed sleep phase syndrome

This is a syndrome characterized by a persistent inability to fall asleep and arise at conventional clock times. This reflects a delay in the phase of the sleep–wake cycle. Sleep onset is usually delayed to early morning hours with a consequent delay in arising. If individuals attempt to go to bed earlier, they are unable to go to sleep until their usual time and, if they attempt to maintain a normal schedule, they suffer insomnia and daytime fatigue. This syndrome has customarily been viewed as a consequence of choice, or lifestyle, so-called 'night' people. It often begins in the teenage years which, with the other behavioural manifestations of this difficult period, has tended to reinforce this view. While the symptoms clearly represent lifestyle in some individuals, it is also clearly a disorder of entrainment in others in which there appears to be an alteration of normal pacemaker sensitivity to entraining stimuli.

Advanced sleep phase syndrome

This is the mirror image of the delayed sleep phase syndrome. Individuals with the advanced sleep phase syndrome have persistent early onset of sleep, usually around 7–9 pm with a consequent awakening at 3–5 am. Attempts to delay sleep onset are usually met with failure and complaints of an inability to stay awake for social events in the evening, and being alone without companionship in the early morning, are typical. If they try to maintain a normal bedtime, they have difficulty with severe evening fatigue. This syndrome is most often reported in the elderly.

Disorders of pacemaker function and pacemaker–effector coupling

There are two types of disorders associated with pacemaker dysfunction. The first is a loss of circadian function; arrhythmicity similar to that seen in animals with destruction of the pacemaker. The second is an alteration of normal pacemaker output. A diminution of the amplitude of circadian rhythms is characteristic of aging. In this circumstance, however, it is unclear whether the problem is at the level of the pacemaker or reflects a partial inability of effector systems to respond to a normal pacemaker input.

Irregular sleep–wake pattern syndrome

This is a relatively uncommon syndrome in which affected individuals have an irregular distribution of sleep and wake with numerous interruptions. These individuals complain both of their difficult schedule and insomnia and of daytime fatigue, and appear to be arrhythmic. In some instances in which 24-hour recordings have been made, there is no discernible rhythm in core body temperature. This may occur in two situations, with evident hypothalamic pathology such as a tumour compressing the anterior hypothalamus, and spontaneously without evident neuropathology.

Syndrome associated with decreased amplitude

In many elderly individuals, there is increased fragmentation of sleep and less sleep in the deeper stages of slow wave sleep, decreased amplitude of the body temperature rhythm and decreased amplitude of the cortisol and melatonin rhythms as well as the advance in phase described above. These observations suggest that there is a decrease in pacemaker output in aging and that the symptomatic expression of this abnormality is insomnia. It has been reported recently that melatonin therapy, which should improve pacemaker coupling, is significantly better than placebo in treating sleep disturbances in the elderly. It is not possible to state, however, that the sleep disturbances of the elderly do not include problems of pacemaker coupling to output systems. It seems likely that a complex

interaction of decreased pacemaker output and decreased responsiveness of effector systems to pacemaker output are operative in many of the circadian disturbances of the elderly.

Parasomnias

Restless legs syndrome/periodic limb movement disorder

The restless legs syndrome (RLS) and periodic limb movement disorder are related sleep disorders. Restless legs refers to a waking complaint that interferes with sleep onset, whereas periodic limb movements are found during sleep and may interfere with restorative sleep. The restless legs complaint is a dysesthesia described as an uncomfortable restless, or creeping and crawling sensation in the lower legs. This sensation is only relieved with vigorous movement of the legs, often requiring the patient to get out of bed. The disorder affects between 5 and 10% of the population, beginning generally in mid-life. Periodic limb movements during sleep often occur with restless legs syndrome, but may be found in isolation. In this disorder, stereotypic periodic (every 20–40 seconds) limb movements (0.5 to 5 second extensions of the big toe and dorsiflexion of the foot at the ankle are often associated with signs of arousal from sleep, such as K complexes followed by alpha EEG waves. The degree to which PLMS is a disorder that either impairs sleep or that requires any intervention remains unclear, however, since roughly 11% of the normal population without sleep complaints, especially the aged, will demonstrate PLMS on polysomnographic assessment.

The pathophysiology of RLS and PLMS has not been well defined. The effectiveness of dopamine agonists and levodopa in the treatment of RLS-PLMS suggests that abnormal dopaminergic function in the CNS may play a role. The efficacy of opiates in the treatment of the disorder suggests a role for the endogenous opiate system. Associated medical conditions for RLS include uremia, iron deficiency anemia, peripheral neuropathy, fibromyalgia, magnesium deficiency, rheumatoid arthritis and post-traumatic stress disorder. Medications that exacerbate RLS or PLMS include lithium, tricyclic and SSRI medications as well as withdrawal from anticonvulsants, benzodiazepines and barbiturates. Bupropion is one antidepressant that has been associated with a reduction in periodic limb movements, perhaps related to its dopaminergic activity.

The treatment of RLS and PLMS is primarily dopaminergic agonists, or levodopa/carbidopa, administered at bedtime. The relatively short duration of action of these drugs often requires a second dose during the night unless the sustained release preparation is used. Benzodiazepines and traditional sedative/hypnotics consolidate sleep and may reduce arousal secondary to the PLMS. Opiate medications are useful in the treatment of these disorders but, given their abuse potential, they should be employed as a last measure. Less information is available to support the use of other agents such as carbamazepine, clonidine and gabapentin.

NREM parasomnias

Three related sleep disorders, or sleep syndromes, fall into a category of NREM parasomnias: confusional arousals, sleep terrors and sleepwalking. Each is thought to represent a 'disorder or arousal'. As a group, these disorders tend to occur normally in children below the age of 5 when behavioural state regulation is not yet well differentiated. There appears to be a genetic tendency for these disorders as a group. Persistence into adulthood is not the norm, but when they do, they can interfere with psychosocial functioning. They each tend to occur out of a deeper NREM sleep stage (slow wave sleep) early in the night and each is associated with amnesia for the event.

Confusional arousals refer to periods of partial sleep and partial waking behaviour with amnesia for the events on full awakening. The individual will have the appearance of being confused, disoriented with incomplete responsiveness to their surroundings. These episodes may last from a few seconds to a few minutes with return to sleep.

Sleep terrors refer to periods in which the individual seems to be in the midst of a panic-like state with crying out, sitting erect in bed with acute autonomic arousal such as increases in heart rate, respiration and sweating. No recall of the event is noted.

Sleep walking refers to the appearance of motor behaviour during sleep that can lead to an individual getting out of bed and walking around his/her environment. Occasionally the motor behaviour is isolated to the bed, with uncomplicated, brief, automatic behaviours. At other times, the behaviour can be very complex, including walking around the bedroom performing some stereotypic act, or leaving the bedroom and walking around the house. Sleep-related eating episodes are not uncommon. On rare occasions, a sleepwalker may leave his/her immediate home, walk around the neighbourhood or even drive a car. In general, the individual returns to bed voluntarily, either on completion of the episode, or after full awakening from the episode. The individual is often somewhat difficult to arouse and only partially responsive to environmental stimuli. Complete amnesia for the events is most common.

The pathophysiology for all of the confusional arousals is unclear. A strong genetic component is recognized for both sleep terrors and sleepwalking. Aside from this, factors which are associated with increasing the depth of sleep, such as sleep deprivation, or dissociating sleep, such as acute toxic/metabolic changes, or stressing an individual may increase the likelihood that these episodes will occur in genetically predisposed individuals. Presumably, these episodes occur when there is dissociation between the brain mechanisms that regulate cortical activation or behavioural arousal and those that regulate motor behaviour. It remains unclear whether there is an association between these events and psychopathology. Any association may simply be related to the observations that mental disorders are themselves associated with disruptions in sleep continuity, factors that would be expected to increase the frequency of such events in susceptible individuals.

The diagnosis of each of these disorders is generally a clinical one. Reports of parasomnias in the first third of the night with specific features as described above support the diagnoses. Polysomnography can be performed, although it is infrequently helpful given the difficulty of 'capturing' one of the episodes in the sleep laboratory. Attempts to precipitate an episode in the lab by forced arousals from delta sleep may aid in diagnosis. In cases where a seizure disorder may be suspected, one or several daytime diagnostic EEGs and an EEG during sleep may be performed to detect epileptiform activity.

Treatment of these disorders is largely conservative and educational in nature, informing the patient and his/her family about sleep and the generally benign longitudinal course of parasomnic behaviours. At the time of occurrence, the individuals should not be disturbed, but rather the parasomnic events should be allowed to self-terminate. Occasionally, forced arousals during an event can precipitate an unconscious aggressive attack. Minimizing sleep deprivation, stressors and medications or dietary factors that may interfere with sleep integrity (e.g. alcohol, caffeine, antidepressant medications) are recommended. If there is reason to suspect that the behaviours may be interfering with either sleep integrity or with daytime functioning, occasional use of sleep consolidating medications such as the benzodiazepines may be effective in preventing the escalation of these partial arousals into more complex behaviours during sleep. If an underlying mental disorder is present that appears to be interfering with sleep continuity, this can be referred for appropriate intervention, either psychotherapy or pharmacotherapy with non-alerting antidepressant medications. If there is a history of either self- or other- injury during the events, steps should be taken to 'sleepwalker-proof' the bedroom and surrounding environment. This may include the removal of potentially dangerous objects, locking doors and separating bed-partners from the sleepwalker.

Nightmares

The term 'nightmare' implies a vivid dream in which something catastrophic or frightening is happening either to the dreamer or to someone else. Often, this term also implies an awakening from the frightening dream in a fearful state. There is no clear distinction, however, between a nightmare and a dream. Nearly everyone has experienced a nightmare suggesting that this is a normal phenomenon of sleep. In general, the causal occurrence of nightmares does not come to the attention of the medical community and no interventions are required. Nightmares are more common in childhood than in adulthood and more common in girls than in boys. The prevalence of a nightmare disorder is difficult to define, however, given the difficulty in defining a separate disorder from the more common occurrence of having bad dreams.

The pathophysiology of nightmares is unknown. Human brain imaging studies performed during REM sleep consistently reveal selective activation of anterior limbic and paralimbic structures, regions thought to play a significant role in emotional behaviour, although no comparative studies have been performed to differentiate regional cerebral function during REM sleep in healthy subjects vs. nightmare disorder subjects. Elevations in autonomic arousal prior to awakening with a nightmare have been observed. Behavioural studies suggest that individuals with 'thin' interpersonal boundaries, defined as more open, sensitive and vulnerable to intrusions, are more susceptible to suffering from nightmares. Numerous drugs that affect sleep, and REM sleep specifically, such as many antidepressant medications, are known to precipitate nightmares. Alcohol withdrawal is particularly associated with bizarre vivid dreaming. Subjects with post-traumatic stress disorder have recurrent intrusive nightmares related to their traumatic life experience as part of their diagnostic criteria.

Given the diverse etiologies of nightmares, there is no uniform therapy. Identification and removal of precipitating factors including toxic/metabolic or drug induced is often the simplest treatment. There have been no empirical medication trials to determine the efficacy of any medication treatment for nightmare sufferers and clinical experience would suggest that response is highly individual. Psychotherapy may be of some benefit in cases where the nightmare appears to reflect an unsuccessful attempt at some type of emotionally adaptive behaviour to a stressful life situation.

REM sleep behaviour disorder

Clinically, REM sleep behaviour disorder (RBD) refers to a parasomnia in which there are sleep-related behaviours associated with elaborate dream mentation. Depending on the elaborateness of the behaviour and the aggressiveness of the dream, these behaviours can result in accidental self- or other injury. In general, the nature of the dream enactments is out of character for the person's waking behaviour. Often, the presenting complaint comes from the bed-partner who is concerned about the behaviours rather than the actual patient who often is unaware that anything unusual has happened during sleep. The disorder most often occurs in men and is more common in aging.

The pathophysiology of the disorder can best be understood, based on an understanding of the normal physiology of REM sleep. REM sleep occurs periodically throughout the night, alternating with NREM sleep in roughly 90-minute cycles. During REM sleep the brain is in an active behavioural state in which cerebral metabolism and other signs of cortical activation are comparable to those of waking. Two exceptions include the absence of conscious awareness and the near complete immobilization of skeletal musculature via an active inhibition of motor activity by pontine centres in the locus ceruleus region. These exert an excitatory influence on the magnocellular reticular nucleus of the medulla. This nucleus in turn, hyperpolarizes spinal motor neurons. It is inferred that a defect in some aspect of this REM sleep atonia system is disturbed in patients suffering from REM sleep behaviour disorder.

Acute toxic/metabolic RBD has been associated with alcohol and benzodiazepine Withdrawal, or an adverse effect associated with administration of tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors and clomipramine. Chronic RBD is either idiopathic (estimated to be around 40%) or associated with some form of neurologic insult. These can be from a variety of etiologies including vascular, malignant, infectious and degenerative. The specific pathology in each case, although presumed to have a final common pathway on the REM sleep atonia system is not known.

Diagnosis is suspected based on a clinical report of potentially harmful sleep-related behaviours in which there appears to be an acting out of some dream sequence. Diagnosis is confirmed in a polysomnographic study that shows increased tone, or increased twitching in the chin EMG channel. Videotaping sleep-related behaviours is helpful diagnostically when increased movements are seen during a polysomnographically identified REM sleep period.

The most widely supported treatment for RBD is administration of clonazepam at bedtime beginning with small doses and titrating upwards to achieve clinical benefit. In general, tolerance is not seen and this medication is reported to be helpful in over 90% of cases.

Medical–psychiatric sleep disorders

Sleep disorders associated with psychiatric illness

We turn now to characterizing the sleep disturbances in the major mental disorders, where the vast majority of research has been in the areas of depression and schizophrenia.

Depression

The majority of patients with mood disorders describe difficulty falling asleep, difficulty staying asleep, and difficulty returning to sleep after early morning awakenings. Clinically, they report a paradoxical state of physical daytime fatigue, yet with persistent mental activity that makes it difficult for them to fall asleep at night. Whereas insomnia characterizes the melancholia of middle age and elderly unipolar depression, younger patients and bipolar depressed patients will often describe difficulty getting up in the morning and hypersomnia during the daytime.

An extensive literature describes the changes in electroencephalographic (EEG) sleep in patients with depression. Measures derived from the EEG sleep recordings that have been found to differ between healthy and depressed subjects include measures of sleep continuity, measures of visually scored EEG sleep stages, and automated measures of characteristics of the EEG waveform across the sleep period such as period amplitude or EEG spectral power measures.

The changes in subjective sleep complaints are paralleled by EEG measures of sleep. These include increases in sleep latency and decreases in sleep continuity. In terms of EEG sleep stages or 'sleep architecture', depressed patients often show reduced state 3 and 4 NREM sleep. Several changes in REM sleep have also been noted. These include an increase in the amount of REM sleep, a shortening of the time to onset of the first REM period of the night, a shortened REM latency, and an increase in the frequency of eye movements within a rapid eye movement period. Depressed women appear to have relative preservation of stages 3 and 4 slow wave sleep in relation to depressed men.

Other studies have correlated the severity of psychopathology with sleep abnormalities in depression. Patients

with psychotic depression have particularly severe EEG sleep disturbances and very short REM sleep latencies. Patients with recurrent depression have more severe REM sleep disturbances than patients in their first episode and sleep continuity and REM sleep disturbances are more prominent early in a recurrent depressive episode. EEG sleep findings help to inform our understanding of the neurobiology of longitudinal course and treatment outcome in depression. Although severely reduced REM latencies, phasic REM measures and sleep continuity disturbances generally move toward control values after remission of depression, most sleep measures show high correlations with clinical manifestations across the course of an episode. Reduced REM latency is associated with increased response rates to pharmacotherapy, but not to psychotherapy. Depressed patients with abnormal sleep profiles (reduced REM latency, increased REM density and poor sleep continuity) are significantly less likely to respond to cognitive behaviour therapy and interpersonal therapy than patients with a 'normal' profile. Reduced REM latency and decreased delta EEG activity in the first episode appear to be associated with increased likelihood, or decreased time until recurrence, of depression in patients treated with medications or psychotherapy.

Each of the major neurotransmitter systems which has been shown to modulate the ascending activation of the cortex, i.e. the cholinergic, noradrenergic and serotonergic systems, have been implicated in the pathophysiology of mood disorders. Nearly all effective antidepressant medications show a pronounced inhibition of REM sleep including a prolongation of the first REM cycle and a reduction in the overall percentage of REM sleep except for nefazadone and bupropion which do not suppress REM sleep. Enhanced cholinergic function concurrent with reduced monoaminergic tone in the central nervous system has been proposed as a pharmacologic model for depression. In an exaggerated sense, the state of REM sleep mimics the formulation. REM can be viewed as a cholinergically driven state with reduced firing of noradrenergic and serotonergic neurons. Cholinergic agents such as the muscarinic agonist, arecoline, physostigmine and scopolamine produce exaggerated REM sleep effects in depressed patients in comparison to patients with eating disorders, personality disorders, anxiety disorders, and healthy controls. These studies suggest that there may be a supersensitivity of the cholinergic system driving REM sleep in depressed patients, although an alternative plausible hypothesis is that there may be reduced monoaminergic (5-HT and/or NA) inhibition of the brainstem cholinergic nuclei. Selective serotonin reuptake inhibitors (SSRIs) are known to have prominent REM suppressing activity, most notably early in the night when alterations in REM sleep are most common in depression. A tryptophan-free diet, which depletes central serotonin activity, is noted to decrease REM latency in healthy controls and in depressed patients and ipsaparone, a 5-HT1a agonist, is noted to prolong REM latency in both normal controls and in depressed patients. Anatomically, 5-HT1a receptors have been conceptualized as the limbic receptors given their high densities in the hippocampus, the septum, the amygdala, and cortical paralimbic structures. The action of serotonin in these structures is largely inhibitory. Given the importance of limbic and paralimbic structures in REM sleep modulation, the influence of SSRIs may be mediated by these limbic receptors. Importantly, in the brainstem laterodorsal tegmental nucleus, a cholinergic cell group involved in the generation of REM sleep, bursting cholinergic neurons are inhibited by the action of serotonin on 5-HT1a receptors. The 5-HT1a antagonist pindolol reduces REM sleep in healthy subjects. This has been interpreted to be a consequence of a reduction in midbrain raphe serotonin neuron autoregulation resulting in increased serotonergic input to pontine cholinergic centres which inhibits REM sleep.

Given the selective activation of limbic and paralimbic structures during REM sleep in healthy subjects, the study of the functional neuroanatomy during REM sleep in depressed patients may provide insight into the pathophysiology of depression. In contrast to healthy controls, depressed patients fail to activate anterior paralimbic structures (anterior cingulate and medial prefrontal cortices) from waking to REM sleep and show large activations in the dorsal tectum and activations in the sensorimotor cortex, inferior temporal cortex, uncus, amygdala, and subicular complex during REM sleep. These findings indicate that depressed patients have patterns of brain activation from waking to REM sleep that differ markedly from healthy controls. In the context of models relating forebrain function during REM sleep to attention, motivation, emotion and memory, these results suggest that REM sleep abnormalities in depressed patients are associated with alterations in limbic and paralimbic forebrain function which reflect the basic pathophysiology of depression (Fig. 55.4, see colour plate section).

Functional neuroimaging of sleep in depressed subjects would be expected to provide insight into homeostatic regulation of sleep in mood disorders patients since this is a time in which the build-up of a sleep-dependent process, process S, is discharged and during which growth hormone secretion occurs. Whole brain and regional cerebral glucose metabolism are elevated during the first NREM period of the night for depressed men in relation to

healthy men suggesting a reduction of homeostatic mechanisms secondary to cortical hyperarousal. Other studies have shown that reductions in delta sleep in depressed patients are associated with reductions in afternoon waking relative and global blood flow. This suggests that the elevations in glucose metabolism during NREM sleep in depressed patients are not related to a waking hypermetabolic state. Studies across waking and NREM sleep are needed in order to clarify this notion. Depression symptoms respond to acute sleep deprivation and imaging studies have shown that depressed patients who have high pre-treatment relative glucose metabolic rates in the medial prefrontal cortex are more likely to respond to sleep deprivation. Further, a reduction in relative metabolism in this region was found following sleep deprivation.

Schizophrenia

The predominant current view in biological psychiatry is that schizophrenia is a developmental brain disorder with many of its manifestations the consequence of selective, early onset neuronal degeneration. Early sleep studies sought to test the intriguing hypothesis that aspects of the thought disorder in schizophrenia are a spillover of the dream state into wakefulness. No evidence has accrued to support this view, but subtle alterations in architecture of REM sleep have been reported. These are difficult to interpret, however, as studies examining treatment of naïve schizophrenia patients show no increases in REM sleep and the increases in REM sleep observed in previously treated subjects probably reflect effects of medication withdrawal, and/or changes related to the acute psychotic state.

Slow wave sleep is of particular interest to schizophrenia because of the implication of the prefrontal cortex in this disorder and in the generation of NREM sleep. Several studies have shown a reduction of NREM sleep in schizophrenic patients. NREM sleep deficits have been seen in acute, chronic, and remitted states and in never-medicated, neuroleptic-treated and unmedicated patients. Research since 1990 has focused increasingly on both the positive and negative syndromes of schizophrenia, a conceptual distinction of particular importance to understanding its pathophysiology. In a longitudinal study, alterations of NREM sleep appeared to be stable when polysomnographic studies were repeated at 1 year, but the REM sleep parameters appeared to change. These observations suggest that NREM sleep deficits in schizophrenia might be trait related. Consistent with this view, delta sleep abnormalities have been found to correlate with negative symptoms and with impaired outcome at one and at two years.

In general, it has been difficult to determine a clear abnormality in sleep–wake regulation in schizophrenia.

Alzheimer's disease

Disturbances in sleep commonly accompany Alzheimer's disease. These disturbances are a significant cause of distress for caregivers often leading to institutionalization of these patients. The changes in sleep often parallel the changes in cognitive function in demented patients. Also, daytime agitation has been associated with sleep quality at night. A large-scale community-based study of Alzheimer's disease patients reported that sleeping more than usual and early morning awakenings were the most common sleep disturbances in non-institutionalized patients. Night-time awakenings, however, were more disturbing to caregivers. Night-time awakenings were associated with male gender, and greater memory and functional declines. Three groups of subjects were identified in association with nocturnal awakenings: (i) patients with only daytime inactivity; (ii) patients with fearfulness, fidgeting and occasional sadness; and (iii) patients with multiple behavioural problems including frequent episodes of sadness, fearfulness, inactivity, fidgeting and hallucinations.

In terms of sleep laboratory-based evaluations, sleep continuity disturbances in these patients include decreased sleep efficiencies, increased lighter stage 1 NREM sleep, and an increased frequency of arousals and awakenings. Sleep architecture abnormalities include decreases in stages 3 and 4 NREM sleep and some reports of decreases in REM sleep. Loss of sleep spindling and K complexes have also been noted in dementia. Sleep apnea has been observed in 33 to 53% of patients with probable Alzheimer's disease. It is unclear if there is an increased prevalence of sleep apnea, however, in Alzheimer's patients in relation to age- and gender-matched controls. Nocturnal behavioural disruptions, or 'sun-downing' are reported commonly in the clinical management of Alzheimer's patients, although specific diagnostic criteria for a 'sun-downing' episode have been difficult to define. Despite extensive clinical research in this area, the pathophysiology of sun-downing, including its relationship with brain mechanisms that control sleep/wake and circadian regulation remain unclear. Overall, the literature on sleep in Alzheimer's disease suggests that the primary defect in this disease is the more general neurodegenerative changes that lead to the profound cognitive and functional declines of this disease and that the sleep changes are secondary manifestations of the disorder. If sleep is viewed as generated by core sleep systems that then require a relatively intact neural cortex and subcortical areas for expression of behavioural states, then the sleep changes in Alzheimer's disease are most likely related to end-organ failure, in the cortex, as opposed to pathology in key sleep or circadian systems themselves.

Parkinson's disease

Light, fragmented sleep occurs frequently in Parkinson's disease patients. Sleep problems have been reported in as high as 74–96% of patients. Complaints included frequent awakenings, early awakening, nocturnal cramps, pains, nightmares, vivid dreams, visual hallucinations, vocalizations, somnambulisms, impaired motor function during sleep, myoclonic jerks, excessive daytime sleepiness, REM sleep behaviour disorder, sleep-related violence leading to injury. These changes may result from the disease itself, or to complications from treatment with dopaminergic agents. Additionally, depression is common in Parkinson's disease and the sleep disruption may in part be related to this comorbid disorder.

Sleep architecture abnormalities include increased awakenings, reductions in stages 3 and 4 sleep, REM sleep and sleep spindles. Reductions in REM latency have been observed. Increased muscular activity, contractions and periodic limb movements may prevent slow-wave sleep and foster light fragmented sleep. Disorganized respiration is also found. Recent studies have raised concern about abrupt onset daytime sleep episodes in Parkinson's disease in association with treatment with newer dopamine agonists. Although this requires further analysis, it is unclear whether the sleep episodes are more frequent with dopamine agonist therapy than in the Parkinson's disease population.

In conclusion, sleep disorders are common and carry a substantial morbidity and cost to society. They occur as primary disorders, responses to the environmental demands of modern society, major manifestations of psychiatric diseases and important complications of medical illnesses, including neurological diseases. Understanding the neurobiology of sleep and sleep disorders is critical to the practice of neurology.

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Bladder and sexual dysfunction

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Control of bladder function

The bladder performs only two functions, storage and voiding of urine. Control of these two mutually exclusive activities requires intact central and peripheral neural pathways. Neural programmes for each exist in the dorsal tegmentum of the pons, and suprapontine influences act to switch from one state to the other. The decision as to when to initiate voiding is determined by the perceived state of bladder filling and an assessment of the social circumstances.

As an individual may micturate once every 4 or so hours, and take only one or two minutes to void, the bladder is in storage mode for most of the time. During the storage phase, contraction of the detrusor smooth muscle in the bladder is prevented by inhibiting parasympathetic outflow. Closure of the bladder outlet is maintained by sympathetic influences on the detrusor smooth muscle in the bladder neck region and by contraction of the striated muscle of the urethral sphincter and pelvic floor innervated by the pudendal nerve. Voiding is initiated by a complete relaxation of the urethral sphincter and the reciprocal action of a sustained detrusor contraction, so that urine is effectively expelled.

To effect both storage and voiding, connections between the pons and the sacral spinal cord must be intact as well as the peripheral innervation which arises from the most caudal segments of the sacral cord (reviewed in Chapter 53). From there the peripheral innervation passes through the cauda equina to the sacral plexus and via the pelvic and pudendal nerves to innervate the bladder and sphincter. Thus the innervation needed for control of the bladder is extensive, requiring suprapontine inputs, intact spinal connections between the pons and the sacral cord, as well as intact peripheral nerves. Urinary continence is thus a severe test of neurological integrity.

An excellent review on the control of bladder function is available (de Groat, 1999).

Bladder dysfunction in neurological disease

Cortical lesions

Anterior regions of the frontal cortex are crucial for bladder control. This was shown by a series of patients with disturbed bladder control who had had various frontal lobe disturbances, including intracranial tumours, intracranial aneurysm rupture, penetrating brain injuries or prefrontal lobotomy (Andrew & Nathan, 1964). The typical clinical picture of frontal lobe incontinence is of a patient with normally coordinated micturition who has severe urgency, urge incontinence and frequency, or loss of sensation of impending micturition but who is not demented such that they are aware of and embarrassed by the incontinence. Micturition is normally coordinated, indicating that the disturbance is in the higher control of these processes.

Six cases were described with disturbances of micturition due to aneurysms of anterior communicating or anterior cerebral arteries (Andrew et al., 1966). The authors hypothesize that the disconnection of the frontal or anterior cingulate regions from the septal and hypothalamic areas allows micturition to proceed automatically and involuntarily following brain damage. In an earlier paper Ueki analysed the urinary symptoms of 462 patients being operated upon for brain tumours, 34 cases of frontal lobectomy and 16 cases of bilateral anterior cingulectomy. He concluded that there was a strong positive influence on micturition by an area in the pons and an inhibitory input from the frontal lobe and bilateral paracentral lobules (Ueki, 1960).

Positron emission tomography (PET) studies of male and females voiding have shown that there is significant activity in the right inferior frontal gyrus during voiding that is not present during the withholding phase (Blok et. al., 1997).

It should be noted that, as well as urinary incontinence, urinary retention has also been described in patients with right frontal lobe pathology, with restoration of normal voiding after successful treatment of the lesions.

Head injuries

There are a few reports of bladder dysfunction occurring after minor head injuries. However, serious traumatic head injury is typically followed by a period of detrusor areflexia, followed by detrusor hyperreflexia (McGuire, 1984). In 17 patients in a vegetative state 1–6 months after injury, urodynamics revealed that all patients had detrusor hyperreflexia (Krimchansky et al., 1999).

Cerebrovascular disease

The effects of a stroke on bladder function depend upon the size and site of the disruption caused to cerebral tissue and pathways. During the early stages of injury, a period of detrusor areflexia may occur, resulting in acute urinary retention, but after this initial period most commonly detrusor hyperreflexia develops (Khan et al., 1990; Wein & Barrett, 1988). Urodynamic studies show that voiding is mostly normally coordinated, with the most common cystometric finding being detrusor hyperreflexia. The patient complains of frequency and urgency, and may also have urge incontinence. The presence of urinary incontinence within seven days of a stroke is actually a stronger prognostic indicator of poor survival than a depressed level of consciousness (Wade & Langton-Hewer, 1985).

Epilepsy

Urinary incontinence is a common feature of generalized tonic clonic seizures, and occurs due to relaxation of the external sphincter (Gastaut et al., 1974). However, urinary incontinence and ictal urination are rare during focal seizures (Freeman & Schachter, 1995; Liporace & Sperling, 1997). Symptoms of detrusor overactivity may occur with seizures, manifested by urgency and urge incontinence. Urinary urgency may be seen during typical absence seizures, and urodynamics have revealed detrusor hyperreflexia during such seizures (Gastaut et al., 1964). 'Ictal urinary urge' is a rare symptom during temporal lobe seizures (Baumgartner et al., 2000).

Basal ganglia

Bladder dysfunction may occur for a number of different reasons in patients with parkinsonism.

In idiopathic Parkinson's disease (IPD), bladder symptoms usually occur later, and thus in elderly men bladder overflow obstruction caused by benign prostatic hyperplasia is usually the cause of urinary symptoms. Patients with IPD typically complain of frequency and urgency. They may also suffer from urge incontinence because with poor mobility they may not have time to reach a toilet. The most common urodynamic finding is detrusor hyperreflexia (DH), because in health the basal ganglia have an inhibitory effect on the micturition reflex. Animal studies have supported this, concluding that the D1 receptor is the main inhibitory influence (Yoshimura et al., 1992).

In patients with mild parkinsonism but disproportionately severe urinary symptoms, or where urinary symptoms precede the development of neurological involvement, a diagnosis of multiple system atrophy (MSA) must be considered. A retrospective study of 62 patients diagnosed with MSA showed that bladder symptoms and erectile dysfunction preceded the diagnosis of MSA by 4–5 years, and the onset of neurological symptoms by 2 years. Almost half the male patients had had a transurethral prostatectomy (TURP), from which few benefited (Beck et al., 1994).

That urinary complaints are so severe early on in patients with MSA may be explained by the fact that the disease affects several locations in the central nervous system which are important for bladder control. Both DH and incomplete bladder emptying may be seen in these patients, the former tending to present first, followed by increasing post micturition residuals over time. DH may be explained by neuronal loss in the pontine region, and incomplete bladder emptying by degeneration of the parasympathetic input to the detrusor following neuronal loss in the intermediate grey matter of the sacral cord segments (S_1–S_5). In addition to the hyperreflexia and increasing residuals, these patients also develop sphincteric weakness due to anterior horn cell loss in Onuf's nucleus, exacerbating their incontinence (Kirby et al., 1986).

The reports of poor outcome of patients with Parkinson's disease from prostatic surgery may well have been due to the inclusion of some patients with MSA, and a TURP should be considered only if there is convincing evidence of bladder outflow obstruction in a man with a definite diagnosis of IPD.

Spinal cord

Interruption of the spinal pathways which connect the pontine micturition centre (PMC) with the sacral cord has

severe consequences for micturition, and spinal cord pathology is the most common cause of neurogenic bladder dysfunction. As the innervation of the bladder arises more caudally than that of the lower limbs, unless the lesion is entirely confined to the conus, patients with bladder dysfunction due to spinal cord disease will almost always have neurological signs in their lower limbs.

Patients develop detrusor hyperreflexia due to the emergence of new spinal segmental reflexes, and experimental work in cats suggests C fibres become the major afferents (de Groat, 1998). Patients complain of frequency and urgency due to their small bladder capacity and may also suffer from urge incontinence if DH is severe and/or they have poor mobility. Decreased sacral neural input to the detrusor in these patients can lead to decreased bladder emptying. Residual urine can exacerbate the symptoms due to detrusor hyperreflexia.

Reciprocal activity of the detrusor and external urethral sphincter, which is required for normal voiding, needs intact connections between the sacral spinal cord and the PMC. When these are lost, uncoordinated activity results, with the sphincter contracting during detrusor contraction, a condition known as detrusor sphincter dyssynergia (DSD) (Betts, 1999). Although the voiding process may have been as severely disrupted as the storage process, it is usually symptoms related to the latter that the patient complains of. Symptoms of hesitancy and an interrupted stream may only be elicited on direct questioning. Approximately 75% of patients with MS have bladder dysfunction, a similar percentage to those who have been shown to have spinal cord involvement. Patients most commonly complain of urgency, and several series of urodynamic studies have shown that this is due to DH.

Patients with MS rarely develop upper tract problems, in contrast to patients with spinal cord injury (SCI). The reason for this is unknown, but treatment of these patients must therefore be directed towards symptomatic relief. This can be hard to achieve, as with disease progression DH worsens as does the inability to effect bladder emptying. The deterioration in bladder function occurs against a background of decreasing mobility and possibly cognitive decline, making symptomatic relief and the avoidance of urge incontinence a difficult goal (Fowler, 1997).

Bladder dysfunction also occurs in other non-traumatic forms of spinal cord disease. In transverse myelitis bladder dysfunction may typically be the only remaining neurological remnant of a condition that, during the acute illness, may have required artificial ventilation and caused a quadraparesis (Sakakibara et al., 1996). The reason for this is unknown. Patients with tropical spastic paraparesis, a progressive myelopathy caused by infection with HTLV-1, may have DH as a presenting symptom.

Management of patients with traumatic spinal cord injury (SCI) necessarily has a different focus as, in this group, upper tract damage can occur (Arnold, 1999). Renal failure arises secondary to DH and loss of compliance which causes ureteric reflux, hydonephrosis and subsequent upper tract damage. Thus these patients, who are often young and otherwise fit, need to have their bladder problems managed aggressively. They often have surgical rather than solely medical management.

Spina bifida

Open and closed spina bifida are the commonest causes of neurogenic bladder dysfunction in childhood, and can also cause significant problems in adults (Borzyskowski, 1999).

Patients may develop similar complications from bladder dysfunction to those patients with spinal cord injury, namely DH, ureteric reflux, and subsequent renal failure. However the advent of CISC, anticholinergic medication and newer surgical techniques has decreased the morbidity from urological problems. Even so, the most common reason for hospital admission in these patients remains urological problems. Three types of bladder dysfunction, detailed below, have been identified, and these are classified according to detrusor behaviour (Rickwood et al., 1982). Urethral dysfunction is almost universal across the three groups, being dyssynergic in the first group and static in the other two groups.

The first type is ‘contractile’, where patients exhibit DH with a normal bladder. DSD is commonly seen. The majority of patients have decreased capacity and incomplete bladder emptying and incontinence. The risk of upper tract damage is significant if vesicoureteric reflux is present.

‘Intermediate’ is the commonest type of dysfunction, and also has the highest risk of upper tract damage. Intravesical pressure is continuously raised as bladder wall compliance is reduced. The distal sphincter mechanism is defective, both incompetent and obstructive, and this, combined with poor detrusor function leads to incomplete bladder emptying and incontinence. Surgery is frequently required to protect the upper tracts.

The final type of dysfunction is ‘acontractile’, where the detrusor is atonic. This, together with the incompetent bladder neck and dysfunctional sphincter mechanism leads to overflow and stress incontinence. The upper tracts are relatively safe in this group of patients.

Cauda equina

Sacral sympathetic outflow and somatic efferent and afferent fibres travel in the cauda equina, with damage to it therefore resulting in loss of sensation in the perineal saddle area as well as parasympathetic loss to the bladder, bowel and sexual organs.

Bladder dysfunction is unpredictable. Many patients report a reduced flow, incomplete bladder emptying, and in severe cases retention with overflow incontinence due to urodynamically confirmed detrusor areflexia. However, some have symptoms related to DH which has also been reported on urodynamics. Bladder neck incompetence may make stress incontinence an added problem for these patients.

Urodynamics in patients with tethered spinal cord reveals DH together with incomplete bladder emptying. Surgery to release the cord has been claimed to improve bladder dysfunction, but the operation is usually performed to treat pain or prevent neurological progression.

Peripheral innervation

Diabetic neuropathy

Bladder involvement is common as evidenced by cystometry, but is often asymptomatic. Both bladder afferents and detrusor efferents may be involved, and patients symptoms result from a decreased sensation of bladder filling and increasingly ineffective emptying, resulting in overflow incontinence and chronic low-pressure urinary retention. These patients mostly have signs and symptoms of generalized neuropathy, especially affecting the feet. This is because the peripheral small fibres are affected in a length-dependent manner, such that when the bladder is affected, the longer fibres subserving sensation to the lower limbs have also been affected. Urodynamics confirms decreased sensation of bladder filling, impaired detrusor contractility and incomplete emptying.

Amyloid neuropathy

Urogenital dysfunction may result in patients with both inherited familial polyneuropathy and amyloidosis secondary to benign plasma cell dyscrasia or myeloma. Amyloid deposition in the pelvic autonomic nerves can lead to similar symptoms as seen in patients with urogenital dysfunction secondary to diabetes. By the time pelvic autonomic dysfunction results however, there will typically be symptoms or signs related to somatic sensory involvement.

Immune mediated neuropathies

In severe cases of Guillain–Barré syndrome bladder dysfunction may result, and cystometry has shown delay in the initial sensations of bladder filling and detrusor areflexia, indicating damage to both bladder afferent and detrusor efferent nerves. Not all patients will recover bladder function, and recovery may take some months in those who do.

Pelvic nerve injury

Peripheral innervation of the pelvic organs may become damaged during pelvic surgery, such as anterior resection, radical prostatectomy or radical hysterectomy. Lower urinary tract dysfunction after the latter two is reported at rates between 10 and 60%, and in approximately one-fifth of these, the dysfunction may be permanent (McGuire, 1984). This injury may be the result of simple denervation, or nerve tethering or encasement in scar tissue, direct bladder or urethral trauma, or bladder devasularization.

The basis of the voiding dysfunction in patients with permanent dysfunction following radical pelvic surgery is a failure of detrusor contraction, with obstruction by the residual fixed striated urethral sphincter.

Urinary incontinence that follows a radical prostatectomy is due to damage to the innervation of the striated urethral sphincter.

Retention in women

Urinary retention and dysfunctional voiding in young women without any evidence of neurological disease has posed diagnostic difficulties for urologists and neurologists for some time, and such retention was often referred to as ‘psychogenic’, physicians believing that there was no organic underlying cause. The combination of urinary retention, abnormal sphincter EMG and polycystic ovaries was first described in 1988 (Fowler et al., 1988), and the hypothesis is that in these patients the primary abnormality exists in the striated urethral sphincter, which is overactive and which has impaired ability to relax.

Patients are typically premenopausal (mean age 26 years) and often present, following an operative procedure, in painless urinary retention, with a bladder capacity in excess of 1 litre. On direct questioning of these patients in one study, 78% claimed to have abnormal voiding prior to the onset of complete retention, and of those who had undergone pelvic ultrasonography, 50% were found to have polycystic ovaries (Swinn et al., 2002).

Urethral sphincter EMG of these patients typically reveals abnormal excitatory activity, with decelerating bursts and complex repetitive discharges. Many of these patients have to manage their voiding dysfunction by performing CISC, but this group of patients appears to respond particularly well to sacral neuromodulation (Swinn et al., 2000).

Investigation of bladder dysfunction in neurologic disease

When faced with a patient with bladder dysfunction and known neurological disease, it is important to ensure that the symptoms the patient is experiencing are not due to 'other' pathology, such as a bladder tumour, or bladder outflow obstruction caused, for example, by an enlarged prostate gland. A thorough history together with the investigations detailed below are sufficient in the initial evaluation of these patients.

History

Table 56.1 shows what bladder symptoms might be expected from neurological disease at different levels. Also shown are the other symptoms of pelvic organ dysfunction with a lesion at each level since clustering of symptoms is important in trying to decide if pelvic organ complaints are due to 'ordinary', local pathology or are neurogenic. For example, in a patient with spinal cord disease, bladder and sexual dysfunction are usually present together whereas, if bladder symptoms are due to prostatic outflow obstruction, sexual function is usually preserved. Therefore, when taking the history, attention should focus on identifying whether bladder complaints are isolated or are part of a pelvic organ symptom complex.

Investigations

Urine examination is important. A simple bedside dipstick test will help determine if the patient has a urinary tract infection accounting for, or resulting in, an exacerbation of their bladder symptoms. If positive, the urine should then be sent off for formal microscopy and culture. Dipstick examination may also reveal the presence of hematuria, a finding which, in the absence of an infection, requires full urological assessment. This is to investigate the possibility that local bladder pathology such as a ureteric or bladder stone or transitional cell cancer may be the cause of the patient's symptoms.

'Urodynamic investigations' is a term which includes all investigations of the lower urinary tract function, but it is often incorrectly used as a synonym of cystometry.

Uroflowmetry is the simplest urodynamic investigation. It is non-invasive and involves recording the rate of urine flow during voiding per unit time. A uroflow trace is generated during the test, and parameters of the flow rate calculated, including the maximum flow rate, mean flow rate, flow time and the volume voided. For a flow trace to be meaningful, the volume voided should be over 150 ml. Useful, but limited information may be ascertained from uroflowmetry. A normal flow curve is bell shaped, but may be flattened, with a low maximum flow rate (Q_{max}), in patients with either an element of bladder outflow obstruction, due to an enlarged prostate gland or a urethral stricture, or a hypocontractile detrusor muscle. A normal uroflow trace is shown in Fig. 56.1, with a trace below it showing the curve seen in a patient who has bladder outflow obstruction due to an enlarged prostate.

Ultrasonography is one of the most important investigations in a patient with neurogenic bladder dysfunction, and often this is combined with uroflowmetry. It is used to assess residual urine, with a postmicturition volume of greater than 100 ml being significant. Ultrasonography may also be used to assess upper tract dilatation, which may occur in some patients who have neurogenic bladder dysfunction. While residual urine volume may be measured with relative ease by clinic staff, an upper tract ultrasound needs to be performed by a radiologist.

Often uroflowmetry combined with an ultrasound scan of the bladder to assess residual urine volume is all that is required in patients who have established neurological disease and bladder dysfunction but in others, full cystometry is indicated. Such cases may be in patients with an unusual collection of urological symptoms, or in whom the neurological basis of their disease is unclear. Cystometry requires urethral catheterization with a filling catheter and an intravesical pressure catheter, although single dual lumen catheters are now available, which will provide both functions. A rectal pressure line is also inserted. Subtraction of the measured rectal pressure from the intravesical pressure gives the pressure generated by the smooth muscle of the bladder, the detrusor (Fig. 56.2). During the investigation, the bladder is filled at a controlled rate by an infusion pump, and while the rate of filling is variable, it should be remembered that rapid filling may provoke a rise in detrusor pressure. During the study, recordings are made of the intravesical and intra-abdominal pressures, and the detrusor pressure calculated from this. Once filling is complete, the patient voids with the pressure lines *in situ*, and the pressures are once again recorded, as is the flow rate.

The commonest abnormality shown by cystometry in neurogenic incontinence is detrusor hyperreflexia, which is an involuntary phasic rise in detrusor pressure associated with urgency. If this pressure exceeds urethral pressure, involuntary loss of urine will result (Fig. 56.2). However, bladder outflow obstruction which is indicative of an obstructing prostate or a urethral stricture may also be identified. This may mimic some of the bladder symptoms seen in patients with neurogenic bladder dysfunction which is important, as correct identification may allow treatment of the condition, thus alleviating the patient's symptoms.

Table 56.1. Pelvic organ dysfunction resulting from neurological pathology at different sites

Level of lesion	Neurological causes	Pelvic organ dysfunction
Suprapontine:	Dementia	DH
Cortical	CVA	Fecal incontinence (very rare)
	Tumour	Altered sexuality/sexual apathy
Extrapyramidal	IPD	DH (early in MSA)
	MSA	Incomplete emptying
		Constipation
		MED (early in MSA)
		Note: Signs of Parkinsonism advanced in IPD, minor in MSA
	Note: DH occurs without DSD	
Suprasacral:	Multiple sclerosis	DH
Spinal	Spinal cord injury (trauma)	Incomplete bladder emptying
	Compression (e.g. tumour)	Difficulty with bowel evacuation (in advanced disease), with poor sphincter control
	Transverse myelitis	
	AV malformation	MED, FSD
	Spina bifida[a]	
	Note: DH may occur with DSD	
Infrasacral:	Spina bifida[a]	Various forms of lower urinary tract dysfunction exist (see text)
Conus	Tethered cord	Constipation, soiling
		MED
Cauda equina	Trauma	Detrusor areflexia or DH
	Central disc prolapse	Stress urinary incontinence
	AV malformation	Constipation
	Congenital	Fecal incontinence/difficulty with evacuation
		MED, FSD
		Note also: Saddle sensory impairment and sexual sensory loss
Peripheral	Diabetes mellitus	Detrusor areflexia
innervation	Amyloid polyneuropathy	Diarrhea
	Immune-mediated neuropathy	MED (early)
Innervation	Pelvic surgery	Detrusor areflexia, with external sphincter damage and thus stress incontinence
within pelvis	Childbirth injury	
		MED, sometimes FSD

Note:

[a] Patients with spina bifida may have a combination of suprasacral and infrasacral pathologies.

DH = detrusor hyperreflexia, MED = male erectile dysfunction, FSD = female sexual dysfunction, IPD = idiopathic Parkinson's disease, MSA = multiple system atrophy, DSD = detrusor sphincter dyssynergia.

Neurophysiological investigations

Various neurophysiological investigations of the pelvic floor and the sphincters have been developed and used over the years. Currently, those thought to be useful include anal sphincter EMG to recognize changes of chronic reinnervation in MSA, and the use of urethral sphincter EMG to recognize a primary disorder of sphincter relaxation in young women with isolated urinary retention (Vodusek & Fowler, 1999).

Needle electrode EMG of either the anal or urethral sphincter can be performed to show evidence of sacral segment or root damage in much the same way as EMG is used at somatic sites. However, because motor units in the sphincter fire tonically it is difficult to recognize changes of denervation and most often changes of reinnervation are sought, based on the analysis of individual motor units captured using a trigger and delay line. In general, EMG is held to be the most valuable of the pelvic floor investigations to detect lower motor neuron damage. EMG of the

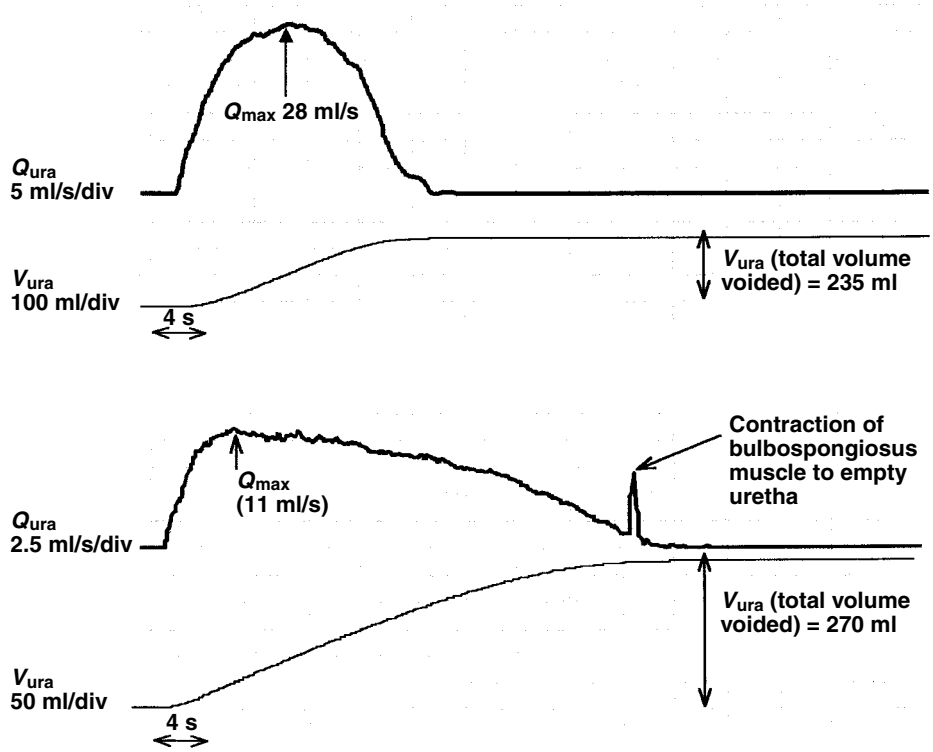

Fig. 56.1. Uroflow traces. The upper trace shows a normal uroflow trace. Note the smooth shape to the uroflow curve. The lower trace shows a flattened curve, as may be seen in a patient with a bladder outflow obstruction. Q_{ura} = urine flow rate (ml/s); Q_{max} = maximum urinary flow rate (ml/s); V_{ura} = volume voided.

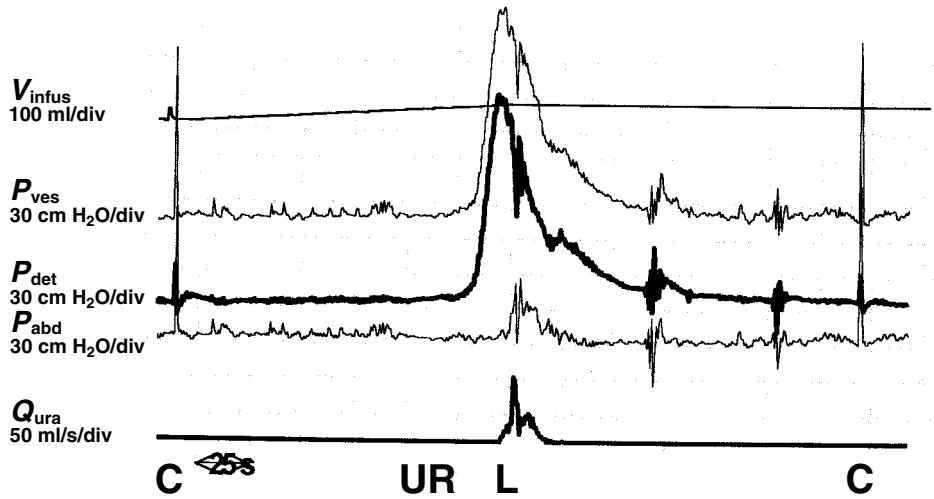

Fig. 56.2. Cystometrogram trace from a patient with MS, demonstrating detrusor hyperreflexia and urge incontinence. After 80 ml had been instilled (V_{infus}), the patient experienced urgency (UR) that was associated with an uninhibitable detrusor contraction (P_{det}) and involuntary leakage of urine occurred (L). The transient rises seen in P_{det} and P_{abd} are due to the patient coughing at intervals to ensure the lines are still in place and recording accurately (C). P_{ves} = intravesical pressure; P_{abd} = intra-abdominal pressure; P_{det} = detrusor pressure; Q_{ura} = urine flow rate.

striated musculature of the pelvic floor can demonstrate changes of denervation and chronic reinnervation in patients with cauda equina lesions as well as those with suspected MSA. Changes of reinnervation in MSA are non-specific and some caution must be exercised in interpreting EMG findings in multiparous women or in patients who have had extensive pelvic surgery. There is some controversy as to the value of the test in distinguishing between MSA and IPD, but extreme prolongation of the mean of ten motor units in a patient with early minor parkinsonism and severe urinary incontinence and erectile dysfunction is strongly indicative of MSA (Palace et al., 1997).

Urethral sphincter EMG may be used to further investigate young women with urinary retention. When a concentric needle electrode is used to record from the striated urethral sphincter in some of these women, abnormal EMG activity may be recorded. This consists of complex repetitive discharges and decelerating bursts (Fowler et al., 1985). A syndrome consisting of this abnormal activity, urinary retention, and polycystic ovaries has been described (Fowler et al., 1988), and the hypothesis is that the primary abnormality lies in the striated sphincter muscle, which is overactive and causes a feedback inhibition of the detrusor muscle, such that these patients are unable to void.

Treatment of bladder dysfunction in neurologic disease

The mainstay of management of neurological bladder dysfunction is a conservative approach consisting of first the treatment of detrusor hyperreflexia, and secondly the management of incomplete emptying.

Treatment of detrusor hyperreflexia (DH)

Oral agents

Most patients with detrusor hyperreflexia respond well to oral anticholinergics (Chapple, 2000), of which the most widely prescribed is oxybutynin (Yarker et al., 1995). It should be commenced at a dose of 2.5 mg twice daily, with the dosage being increased as necessary up to a maximum of 20 mg per day in divided doses. Oxybutinin, however, has the disadvantage of troublesome antimuscarinic side effects, which include a dry mouth, constipation and blurred vision. A dry mouth is the most problematic and common of these reported, even on low doses, and a patient not experiencing this is probably not achieving therapeutic concentrations. A single dose, taken when required, provides adequate treatment for patients who require treatment only occasionally, when for example they know that they will not have toilet access for a while, such as prior to a long car or train journey.

Controlled release oxybutinin is now available as a single daily dose of between 5 and 30 mg. The drug is released over a 24-hour time period, leading to a smoother plasma concentration–time profile, with a significantly reduced incidence of a dry mouth, and comparable efficacy to the immediate release formulation. A multicentre, prospective trial has shown that patients are able to tolerate a higher dose of controlled release oxybutinin than of the conventional preparation, which may lead to a more effective control of symptoms (Anderson et al., 1999).

More recently, tolterodine, a more 'bladder selective' anticholinergic has been introduced, which in clinical studies led to fewer treatment withdrawals compared to oxybutinin. In this study a troublesome dry mouth was reported in 60% of oxybutinin-treated patients, compared to 17% of those taking tolterodine (Appell, 1997). It may be given at a dose of up to 2 mg, twice daily.

Propiverine hydrochloride, at doses of up to 15 mg four times a day, is another effective treatment for DH (Madersbacher et al., 1999). It has both anticholinergic and calcium antagonistic properties, and has been shown to be as effective as oxybutinin in controlling urgency and urge incontinence. The drug is associated with a lower incidence of dry mouth compared to oxybutinin.

Propantheline may be used in some cases when other treatments are unavailable. The addition of a tricyclic antidepressant with antimuscarinic properties such as imipramine, amitriptyline or nortriptyline is sometimes helpful in patients who fail to respond to oxybutynin alone.

Desmopressin, an analogue of ADH, may be used as a nasal spray (Desmospray) or tablets (Desmotabs) to reduce troublesome nocturia in patients not responding to anticholinergics alone (Valiquette et al., 1996). It acts on the kidney, increasing water resorption at the collecting tubule, and thus reducing urine formation. Because of the risk of dilutional hyponatremia, which if it occurs usually does so within the first week or so of starting treatment, it is advisable to check serum sodium levels if the patient experiences any adverse effects. Even though recovery of sodium levels occurs promptly once the medication is stopped, it should be used with caution in patients with compromised renal or cardiovascular function, and avoided in the elderly.

Intravesical agents

There are a number of intravesical agents which have been used to treat detrusor hyperreflexia in patients who do not

respond to oral anticholinergic medication, or who find the side effects of such medication limiting (Fowler, 2000). Two different types of treatment have been used. The first of these blocks cholinergic transmission between the pelvic nerve and detrusor muscle and includes oxybutinin and atropine, while the second group includes agents which act on afferent innervation of the bladder, such as the vanilloids capsaicin and resiniferatoxin.

Oxybutinin acts intravesically by interfering with cholinergic transmission, as well as having a local anesthetic effect. It has been shown to be effective in children and adults with resistant detrusor hyperreflexia, and patients did not report the level of side effects that they experienced with the oral formulation of the drug. Thus for those patients unable to tolerate the oral preparation of the drug, intravesical oxybutinin may be advantageous, but with the normal dose being 5 mg (30 ml of solution) intravesically three times a day, it requires frequent catheterization and is only a realistic option for those patients who are performing clean intermittent self-catheterization already.

Intravesical capsaicin, a member of a group of compounds with a common chemical structure of a vanillyl ring called vanilloids, is a pungent ingredient of the red hot chilli pepper and has been used to treat intractable detrusor hyperreflexia due to spinal cord disease (Fowler et al., 1994). It is a C fibre neurotoxin, affecting those afferent neurons that are responsible for the signals that trigger detrusor activity in patients with DH. It has been shown to increase bladder capacity and reduce the amplitude of hyperreflexic contractions in some patients, with a benefit that lasts for an average of 3–4 months.

Resiniferatoxin is another member of the vanilloid group, and has been demonstrated to be 1000 times more neurotoxic than capsaicin. Initial reports of the use of RTX to deafferent the bladder of patients with detrusor hyperreflexia have been promising (Lazzeri et al., 1998; Silva et al., 2000).

Incomplete bladder emptying or urinary retention

In patients with detrusor hyperreflexia and a significant postmicturition residual, the treatment of incomplete bladder emptying is central, as any treatment to reduce detrusor overactivity is unlikely to be effective in the presence of large residual volumes. In patients with hypo- or acontractile bladders, ensuring bladder emptying is crucial.

Many neurological patients with voiding problems develop their own method of assisting bladder emptying but the best option to deal with significant residual volumes in these patients is clean intermittent self-catheterization (CISC). Patients are often unaware of the extent to which they fail to empty their bladder, and for this reason the measurement of residual volume is the single most important measurement to be made when planning bladder management (Fig. 56.3). A generally accepted figure for significant residual volume is 100 ml, with volumes greater than this requiring drainage.

The patient should be taught CISC by someone experienced in the method and nurse specialist continence advisors are particularly expert. A main requirement for success with this technique is patient motivation; a degree of physical disability may be overcome provided the patient is sufficiently determined. Sometimes impaired visual acuity or other symptoms related to their neurological disease such as spasticity, tremor or rigidity might make it impossible for the patient to perform self-catheterization and in such circumstances it may be performed by a partner if they and the patient are willing, or a care assistant. Most patients are advised initially to perform it at least twice a day.

In spinal cord disease, a combination of intermittent self-catheterization together with an oral anticholinergic manages both aspects of bladder malfunction, namely incomplete emptying and detrusor hyperreflexia. In a patient with a borderline significant residual volume, starting an anticholinergic may have the effect of further impairing bladder emptying. This should be suspected if the anticholinergic has some initial efficacy which then disappears. In any case, however, the residual volume should be checked after initiation of anticholinergic therapy. The management algorithm for the initial treatment of patients with neurogenic incontinence is summarized in Fig. 56.3.

Permanent indwelling catheters/collection devices

Although a combination of anticholinergic medication together with intermittent catheterization is the optimal management for patients with DH and incomplete bladder emptying, there comes a point with worsening neurological disease when the patient is no longer able to perform self-catheterization, or when urge incontinence and frequency are unmanageable. At this stage an indwelling catheter may help greatly with management of bladder symptoms.

Problems with permanent catheterization such as infection, catheter blockage, urinary leakage or expulsion are common. Another major problem may be leakage of urine around the catheter. Bladder stones and recurrent, resistant infections are also more common in patients with a

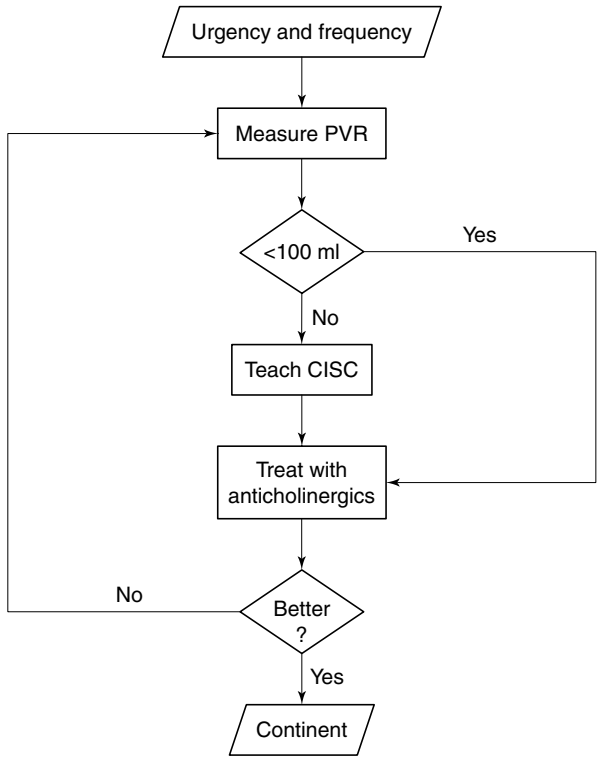

Fig. 56.3. Algorithm for management of detrusor hyperreflexia.

permanent indwelling catheter compared to those who perform CISC.

A preferred alternative to an indwelling urethral catheter is a suprapubic catheter, which can be inserted under local anesthetic. Although by no means a perfect system, a suprapubic catheter is a better alternative to an indwelling urethral catheter and is often the method of choice in managing incontinence in patients for whom other means are no longer effective.

There are some patients in whom medical management is not successful and who then require practical help with their continuing continence problems. The priority in most cases is usually containment of any urine leakage, and the continence advisor is best placed to recommend whether absorbent pads or, in men, an external collecting device may be the best option. A review of these can be found elsewhere (Dasgupta & Haslam, 1999).

Neural stimulation

At present, two different forms of treatment modalities are available. In patients with urge incontinence or voiding dysfunction, neuromodulation of the S3 nerve with an extradural implantable pulse generator (IPG) has been shown to be effective (Shaker & Hassouna, 1998; Swinn et al., 2000). In patients with spinal cord injury, posterior sacral root rhizotomies with implantation of Brindley stimulators on the anterior sacral roots may improve voiding (Brindley et al., 1986; van Kerrebroeck & Debruyne, 1993).

Urological surgery

Various urological procedures can be carried out to treat incontinence (Walsh et al., 1998). Although surgical procedures to deal with urine leakage in an otherwise fit patient are often successful, caution must be exercised before using such measures on those patients with progressive neurological disease. When the bladder symptoms of these patients are becoming unmanageable by using a combination of intermittent catheterization and anticholinergics or even intravesical agents, their neurological disease may be so advanced that urological surgery is not appropriate. However, in some cases, such as those patients with traumatic spinal cord injury, surgery may be the best option for long-term bladder management.

Control of sexual function

Similarities do exist in the neurological control of sexual function in men and women, though that of women is less well understood.

There are two major neurologic pathways of erection, reflexogenic and psychogenic. Reflexogenic erections are the result of direct genital stimulation, with afferent impulses carried in the pudendal nerve to S2–S4, and the efferent arm using the same pathway. Preservation of reflex erections is seen in men with lesions above T11.

Psychogenic erections occur in response to input from higher centres, and require intact long tracts between cortex, spinal cord and autonomic outflow. Somatic sensory afferents deliver information on tactile sexual stimuli which, after synapsing in the sacral spinal cord, pass information centrally leading to awareness of sexual stimulation, and locally to induce the sexual responses dependent upon increased blood flow. Parasympathetic efferents from S2–S4 spinal segments travelling through the pelvic plexus and cavernosal nerves, initiate erection. Blood flow in the penile artery, and the corresponding artery in the clitoris, increases. The smooth muscle of the cavernous sinuses in the penile corpora relax and the sinuses fill with blood. The increased pressure in the corporal bodies reduces venous outflow by compression of the subtunical veins, with the combined reaction resulting in erection. Continued sacral parasympathetic activity maintains this erection.

Seminal emission begins during arousal (Mitsuya et al., 1960) and with continued sensory stimulation, orgasm is triggered with ejaculation resulting from the rhythmic phasic contractions of perineal and pelvic floor muscles. Ejaculation is effected by integrated sympathetic outflow from T11–L2 segments travelling through the sympathetic chain and hypogastric plexus, and along the pelvic and pudendal nerves and somatic efferents travelling through the pudendal nerves. Sympathetic outflow causes smooth muscle contraction in the seminal vesicles, vas deferens and prostate to deliver seminal fluid to the posterior urethra, and bladder neck contraction to prevent retrograde ejaculation. In women parasympathetic activity causes clitoral erection, engorgement of labia, and vaginal lubrication. In the periphery, the main proerectile transmitter is nitric oxide which is colocalized with vasoactive intestinal peptide and acetylcholine (Rajfer et al., 1992). The same mechanisms are thought to be responsible for clitoral erection and nitric oxide synthetase activity has been demonstrated in nerve fibres within the human glans and corpora cavernosa of the clitoris (Burnett et al., 1997).

Orgasmic sympathetic activity results in rhythmic contractions of uterus, fallopian tubes, and paraurethral glands, and the somatic motor activation in rhythmic contractions of pelvic floor muscles (Berard, 1989; Bohlen et al., 1982). Motor innervation of the pelvic floor muscles as well as the ischiocavernosus and bulbocavernosus muscles is conveyed through pudendal nerve branches from below. However, there is also a motor innervation of the pelvic floor muscles directly from the sacral plexus.

Sensory information from the glans and the skin of the penis and clitoris is conveyed through bilateral branches of the pudendal nerve. The afferents from the root of the penis (and from the anterior part of scrotum) join the ilioinguinal nerve.

The role of the cerebral hemispheres, the brainstem, and even of the spinal cord in controlling human sexual behaviour has not been fully elucidated. The forebrain areas regulate initiation and execution of sexual behaviour; the medial preoptic area integrates sensory and hormonal signals, and the amygdala and other nuclei play a role in the execution and reward aspects of sexual function.

Sexual dysfunction in neurological disease

Cortical lesions

Much remains to be discovered about the cortical control of sexual function, and it is thought that cerebral processing determines libido and desire.

Animal experiments have shown that the limbic system is important for sexual responses, and the medial preoptic hypothalamic area has an integrating function. Observations of patients with brain lesions indicate that temporal or frontal disease may cause disturbances in sexuality.

Head injuries

Disability, cognitive impairment and personality change may occur often after a traumatic brain injury, and be accompanied by sexual dysfunction either as a consequence of the cerebral lesion or as a consequence of psychological factors (Elliott & Biever, 1996). In a group of patients with closed head injury admitted for 24 hours or more, an incidence of significant sexual dysfunction in 50% over a 15 years time span was found (O'Carroll et al., 1991). Decreased and increased sexual desire, erectile failure, and retarded ejaculation have been reported (Kreutzer & Zasler, 1989; Meyer, 1955). Lesions of the frontal and temporal lobe seem to result more often in sexual problems than do lesions of the parieto-occipital part of the brain. Hypersexuality, disinhibited and inappropriate sexual behaviour, and changes in sexual preference have been reported with basal frontal and limbic brain injury (Miller et al., 1986).

Cerebrovascular disease

One measure of sexual impairment following stroke is decline in frequency of intercourse. In some studies about 75% of patients who were sexually active before the stroke reported an abrupt and permanent decrease in coital frequency (Boldrini et al., 1991). Furthermore, the majority of men (50–65%) have erectile dysfunction after a stroke (Monga et al., 1986a; Boldrini et al., 1991) and orgasmic dysfunction after stroke is common in men. Whereas 88% of men were able to ejaculate before stroke, only 29% could achieve this afterwards in one study (Bray et al., 1981). However, in another study both erections and ejaculation returned to approximately 60% of men 8 months after the stroke (Boldrini et al., 1991).

Hypersexuality has also been reported after stroke, associated with temporal lobe damage and seizures (Monga et al., 1986b). An overall change in sexual life is reported more frequently by men but changes also occur in women after stroke. In one study 63% of women reported normal vaginal lubrication before, but only 29% did so after the stroke. Similarly only 34% failed to achieve orgasm before stroke, but 77% did so afterwards (Monga et al., 1986a). However, in another study, only one-third of women who

remained sexually active after a stroke suffered a decline in ability to achieve orgasm (Boldrini et al., 1991).

Epilepsy

Sexual dysfunction

It has long been known that epilepsy is associated with sexual problems, more so in men than women. Various types of abnormal behaviour, more commonly hyposexuality, but also hypersexuality, are reported, particularly in temporal lobe epilepsy (Shukla et al., 1979) and basal–medial frontal lobe lesions. Both men and women with epilepsy often suffer from loss of sexual desire, reduced sexual activity, or inhibited sexual arousal; percentages vary in different studies (Morrell et al., 1994; Guldner & Morrell, 1996). It has been suggested that subclinical hypogonadotrophic hypogonadism is the underlying condition, induced by temporal lobe dysfunction (Murialdo et al., 1995).

However, in some men with temporal lobe damage and epilepsy, desire may be preserved with loss of erectile function (Hierons & Saunders, 1966). Apart from inability to maintain an erection, ejaculatory dysfunction, decreased satisfaction with sexual life, and reduced sexual fantasies, dreams and initiatives have all been reported in patients with complex partial epilepsy and a mesiobasal temporal spike focus (Shukla et al., 1979). Loss of nocturnal tumescence has been reported in such patients (Guldner & Morrell, 1996). Surgery for epilepsy rarely restores function (Blumer & Walker, 1967), and antiepileptic drugs including carbamazepine, phenytoin, and phenobarbitone may influence both sexual desire and performance (Isojärvi et al., 1995).

Basal ganglia

Dopaminergic mechanisms are involved in both inducing penile erection and determining libido. The medial preoptic area of the hypothalamus has been shown to regulate sexual drive in animal studies, with D2 receptors being involved. Patients with Parkinson's disease commonly display decreased sexual desire, and sexual dysfunction is also frequent in their partners (Brown et al., 1990).

Erectile dysfunction (ED) is a considerable problem for patients with Parkinson's disease. In one study, 60% of a group of men with IPD were affected compared with 37.5% of an age-matched healthy group (Singer et al., 1992). ED usually affects men with IPD some years after the onset of neurological disease, whereas in men with MSA, ED may be the first symptom. Further adding to their sexual dysfunction, many men with IPD are also unable to ejaculate or to reach orgasm.

Treatment of Parkinson's disease with dopaminergic compounds may result in an apparent increase, or rather a normalization, of sexual desire (Uitii et al., 1989) without corresponding improvement of the movement disorder. Dopaminergic agonists have been shown to induce erection in animal species, and spontaneous erections have been seen in patients treated with L-dopa. Apomorphine, in both subcutaneous and sublingual preparations, has been reported to increase erectile function in some patients (O'Sullivan & Hughes, 1998). There are also reports of hypersexuality in a proportion of patients treated with anti-Parkinsonian medication (Uitti et al., 1989) and this can be of considerable concern to families looking after these patients.

Erectile failure is almost universal among patients with MSA and in a retrospective study of the duration of symptoms in 46 men clinically diagnosed as suffering from MSA, 96% had erectile dysfunction at the time of diagnosis. Erectile dysfunction alone was the first symptom in 37% but was part of the presenting symptom complex in 59% (Beck et al., 1994). The onset of ED usually predated the onset of other neurological symptoms by several years, many of the men having developed ED in their early 50s or late 40s. The reason for the early selective involvement of erectile function in patients with MSA is not known, but preserved erectile function is a clinical feature which suggests a diagnosis of MSA should be reconsidered. There are insufficient clinical grounds for attributing it to part of a general autonomic failure because symptomatic or laboratory-proven autonomic failure occurred much later in most instances (Kirchhof et al., 2000).

Spinal cord

In men, the level and completeness of spinal cord injury determines sexual function. In high spinal cord lesions, while the ability to have psychogenic erections may be lost, reflexogenic erections should be intact. In theory, a lesion below L2 should leave psychogenic erections intact, but in practice the quality of the erection is often insufficient for intercourse. Psychogenic erections are more likely to be preserved if spinal cord damage at any level is incomplete. With lower spinal cord damage, especially if the cauda equina is involved, there may be little or no erectile capacity.

Estimates of the prevalence of ED in MS vary between 35 and 80% (Mattson et al., 1995; Ghezzi et al., 1996), usually in combination with bladder dysfunction as well. Early in the disease process the initial complaint is of trouble sus-

taining erections, and with advancing disease, erectile function may totally cease. Problems with ejaculation are also common in men with MS, affecting approximately 40% of patients (Valleroy & Kraft, 1984) (Minderhoud et al., 1984). One paper (Vas, 1969) reported that all men with complete ED had lost ejaculation, and one-third of those with partial ED also had ejaculatory problems.

In women with MS, sexual dysfunction is a common problem affecting up to 60% of patients. A decrease in lubrication, altered pelvic sensation and inability to reach orgasm are three of the commoner complaints (Shaughnessy et al., 1997), and fatigue, lower limb spasticity and fear of urinary and bowel incontinence may contribute adversely to the situation. A reduction in sexual desire is also commonly reported.

Over 50% of all SCI men have ED (Bors & Comarr, 1960). Reflexogenic, psychogenic, and mixed erections are well described in SCI men, and the percentage of patients achieving such erections varies in different reports (Beretta et al., 1986; Tsuji et al., 1961; Yarkony, 1990). The level of SCI and the completeness of the lesions may have a bearing on the likelihood of ED, although there is much individual variation and an accurate prognosis for future sexual function in the individual may not be possible.

As well as ED, the ability to ejaculate by masturbation or sexual intercourse is impaired in most men with SCI and, consequently, men with SCI rarely father children without medical intervention (Martinez-Arizala & Brackett, 1994). Reduced fertility cannot be attributed completely to ejaculatory dysfunction because semen obtained from SCI men by methods of assisted ejaculation is of poor quality (Brackett et al., 1998; Sønksen et al., 1999). Ejaculation is generally more likely to be preserved among SCI men with incomplete rather than complete lesions.

Although orgasm has been noted to occur in men with SCI, it may differ in quality compared to before the injury (Alexander et al., 1993). Surprisingly, some women with complete SCI may retain their ability to achieve orgasm possibly because of afferents from cervix travelling with the vagus nerve (Whipple & Komisaruk, 1997).

Sympathetic thoracolumbar outflow

Retroperitoneal lymph node dissection may damage the sympathetic thoracolumbar outflow, which leaves the spinal cord at T10–L2 to pass retroperitoneally and enter the pelvic plexus. Loss of this innervation causes disorders of ejaculation, with the result that there is either no emission, or retrograde ejaculation occurs due to the inability of the normally sympathetically innervated bladder neck to contract. However, nerve sparing approaches in retroperitoneal dissection have been developed with considerable success (Donohue et al., 1990).

Spina bifida

As patients with spina bifida now have increased life expectancy and erectile dysfunction is a common problem, it is now recognized as an important quality of life issue (Joyner et al., 1998).

Cauda equina

Erectile dysfunction is commonly seen in men with cauda equina damage (Bors & Comarr, 1960), and sexual dysfunction in women is also a problem with both genders having a severe problem with loss of genital sensation.

Traumatic cauda equina lesions are generally considered with SCI. A complete lesion of the cauda equina will damage the parasympathetic erectile pathways to the penis. However, approximately one-quarter of men may still be able to achieve an erection psychogenically (Bors & Comarr, 1960). This is thought to be mediated by a sympathetic erectile pathway via the hypogastric plexus. Ejaculatory disturbances, penile sensory loss, and pain syndromes have also been described.

Women report loss of lubrication, dyspareunia, diminished sensation, difficulties in achieving orgasm, as well as changes in the qualities of orgasm. The effects on vaginal lubrication and orgasm are related to the level and completeness of the lesion (Berard, 1989). Patients with incomplete SCI retain the ability for psychogenic genital vasocongestion if pinprick sensation is preserved in the T11–12 segments; only reflexogenic responses are obtained in those with complete SCI (Sipski et al., 1995, 1997).

Peripheral innervation

Diabetic neuropathy

Diabetes is the commonest cause of erectile dysfunction, with this as the underlying diagnosis in approximately 25% of patients attending ED clinics. The prevalence of ED in diabetic men is between 30 and 60% (Kolodny et al., 1979; McCulloch et al., 1980) and is higher in patients with longstanding diabetes and in those who have developed some of the other complications of the disease. Neuropathy may not be the only cause, and both microvascular disease and the effect of formation of advanced glycation end products of neurotransmitters involved may play a role. Retrograde ejaculation may occur in patients who have diabetic cystopathy, due to neuropathy

of the sympathetic nerves supplying the bladder neck (Ellenberg, 1966).

Female sexual dysfunction has been studied to a lesser degree, but studies suggest that diabetic women may also be affected by specific disorders of sexual function, which may include decreased lubrication (Tyrer et al., 1983) and inability to reach orgasm, as well as dyspareunia and vaginal fungal infections.

Immune mediated neuropathies

Autonomic involvement may lead to ED in Guillain–Barré syndrome, and Guillain reported this in his original description.

Pelvic nerve injury

The peripheral autonomic nerves to the genital organs may be injured, for example by surgical procedures, leading to ED or ejaculatory problems in men, and loss of lubrication in women. The sympathetic thoracolumbar fibres may be injured by retroperitoneal lymph node dissections. Pelvic plexus and cavernosal nerves may be injured in surgery, such as by abdominoperineal resection of carcinoma, hysterectomy, radical prostatectomy, or sphincterotomy. Surgeons are increasingly aware of these possibilities and have developed 'nerve sparing' operations. In the case of radical prostatectomy, prior to development of nerve sparing techniques almost all patients were impotent post-operation. In one series of patients followed up after nerve sparing radical prostatectomy, erectile dysfunction was reported in almost 60% at 18 months (Stanford et al., 2000). ED has also been reported after injection of sclerosing agents to treat hemorrhoids (Bullock, 1997), and subtrigonal injections to treat a hypersensitive bladder (Bennani, 1994).

Investigation of sexual dysfunction in neurologic disease

In many patients with neurological disease and bladder dysfunction, sexual dysfunction often coexists (See Table 56.1). In some patients investigations are contributory, but in the majority a thorough history and clinical examination are sufficient to attribute the dysfunction to the established neurological disease.

History

In patients with sexual dysfunction secondary to neurological disease there are usually other neurological symptoms. The temporal association of sexual dysfunction with onset or progression of their neurological disease is often strong. Depression which may accompany neurological disease may result in sexual dysfunction as well, as may antidepressant medication or a range of other medications including some diuretics, antihypertensives, H2 antagonists, and a high intake of recreational drugs such as alcohol and marijuana. Normal sexual function with a different partner or during differing sexual activities strongly suggest a psychogenic explanation for erectile dysfunction. It is possible for patients with spinal cord disease to have reflexogenic erections from genital stimulation, but be unable to have psychogenic erections and thus preserved nocturnal and early morning erections need not mean that erectile dysfunction has a psychogenic basis.

Clinical examination

Sexual dysfunction has many different possible neurological causes. However there are also a number of non-neurological causes of which the clinician must be aware. In a neurological patient with sexual dysfunction in whom there are no clues from the history as to the underlying diagnosis, it is necessary to perform a full neurological examination, looking for evidence of neurological disease. Because normal sexual function is highly dependent on the integrity of the spinal cord, examination of the lower limbs should be especially thorough. This should include sensation and vibration perception which, if deficient, may indicate an underlying peripheral neuropathy. In cases of cauda equina injury sensation in the saddle area should be tested, as should anal tone. Erectile dysfunction may occur as the first symptom of multiple system atrophy, and early signs of extrapyramidal or cerebellar dysfunction should therefore be carefully sought.

Inspection of the distribution of body hair may indicate if there is an underlying hormonal basis for erectile dysfunction, as may the finding of gynaecomastia. The patient's leg pulses should always be checked to rule out the possibility of peripheral vascular disease as being the underlying cause of the dysfunction, and the patient's blood pressure checked. It should also be remembered that there are several urological causes of erectile dysfunction.

Investigations

Dipstick examination of the urine may reveal glycosuria, indicating that diabetes may be the underlying cause of sexual dysfunction. Routine laboratory tests should be performed, and these should include serum HbA_1C, also to

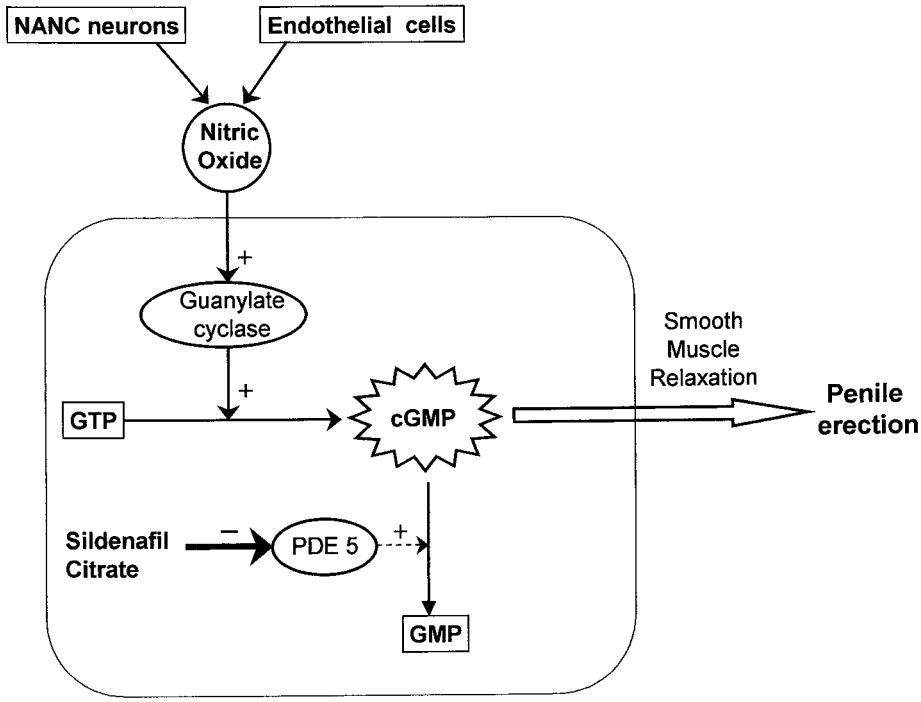

Fig. 56.4. Nitric oxide-cGMP mechanism of corpus cavernosal smooth muscle relaxation and penile erection. Sexual stimulation results in the release of nitric oxide from corporal vascular endothelium and non-adrenergic–non-cholinergic (NANC) neurons. PDE 5 = cGMP-specific phosphodiesterase type 5.

exclude underlying diabetes as a cause, as well as serum testosterone if the history or examination suggest possible hypogonadism. Prolactin should be measured if the serum testosterone is low, or if there is a loss in libido, and LH should be measured if testosterone is low. A hemoglobinopathy screen should be performed in Afro-Caribbean patients, to exclude sickle cell disease, as erectile dysfunction may follow an episode of priapism.

Other investigations, which are really the remit of a urologist with an interest in andrology may include nocturnal penile tumescence monitoring, a Rigiscan which is a home monitoring device capable of continuously monitoring penile circumference and rigidity, or a colour duplex Doppler ultrasound to investigate an underlying vascular cause.

Treatment of sexual dysfunction in neurologic disease

Recent advances in knowledge of the physiology and pharmacology of erection have led to the development of drug treatments by the oral, intracavernous and intraurethral routes. As a last resort, surgical treatment is also possible. Such treatment is available also for neurologically impaired patients.

Oral agents

Since the introduction of sildenafil citrate (Viagra) in 1997, the management of erectile dysfunction has been revolutionized. It is an orally active potent inhibitor of PDE5, thus prolonging the effect of cyclic GMP, increasing the relaxation of smooth muscle in the corpora cavernosa (See Fig. 56.4). In response to sexual stimuli, cavernous nerves and endothelial cells release nitric oxide, which stimulates the formation of cyclic GMP. In turn, this leads to smooth muscle relaxation, and the cGMP is then metabolized by cyclic GMP specific phosphodiesterase type 5 (PDE5). Viagra has been shown to be effective in treating erectile dysfunction of various different etiologies (Goldstein et al., 1998), and has been particularly effective in patients with MS. In one study, 90% of patients reported improvements in erections compared to 24% of those on placebo (Fowler et al., 1999) and had a demonstrable improvement in quality of life (Miller et al., 1999). In addition to MS, it has also been shown to successfully treat ED in men with spinal cord lesions (Guiliano et al., 1999; Schmid et al., 2000). However, the efficacy depended

on sparing of either sacral (S2–S4) or thoracolumbar (T10–L2) spinal segments which, in this study, was shown to be of relevance in mediating psychogenic erections in male SCI patients. Other studies have shown the beneficial effect of sildenafil in patients with spina bifida (Palmer et al., 2000), and Parkinson's Disease (Zesiewicz et al., 2000; Hussain et al., 2000). A note of caution should be sounded, however, in patients with MSA, as profound decreases in blood pressure have been shown following administration of sildenafil in these patients (Hussain et al., 2000).

The use of sildenafil in women with sexual dysfunction secondary to neurological disease is currently an area of research interest. It is believed that the nitric oxide–cGMP pathway which Viagra has been shown to affect so successfully by inhibition of phosphodiesterase type 5 (PDE5) in the male (Fig. 56.4) may be important in the female sexual response, producing clitoral engorgement and vaginal lubrication in the female during sexual stimulation. This may provide a treatment option for women with sexual dysfunction and multiple sclerosis, and trials are currently being undertaken.

Sildenafil is well tolerated with a low side effect profile, which includes headache, flushing and dyspepsia. It is however not suitable for those patients taking nitrates, or patients with severe hepatic disease or hereditary retinal disorders.

Intracavernous injection therapy

Now the most widely used agent for intracavernosal injection therapy is alprostadil, Prostaglandin E1. It is highly effective in treating erectile dysfunction, and produces erections satisfactory for intercourse in 66% of patients self-injecting at home (Godschalk et al., 1994) 94% of the time (Linet & Ogrinc, 1996). It has few contraindications or interactions, is rapidly effective and has high rates of partner satisfaction.

Potential problems with this treatment include the manual dexterity required to give such injections, which is particularly pertinent in a neurological patient population, together with penile pain on injection (Linet & Ogrinc, 1996), and the occurrence of fibrosis, which has reported incidences of up to 20%. There is also a reported incidence of priapism, a urological emergency, of up to 1% (Chew et al., 1997).

Intraurethral therapy

Transurethral therapy with alprostadil (MUSE) has been reported to be effective in the treatment of ED. In a study of over 1500 men with ED of various etiologies, use of MUSE resulted in 65.9% having erections satisfactory for intercourse (Padma-Nathan et al., 1997). However, other reports indicate that this treatment is not very effective, with 63% of men not achieving erections satisfactory for intercourse in one study (Werthman & Rajfer, 1997). Despite this, compared to intracavernosal treatment the risk of priapism is lower, and MUSE may be suitable for patients who have difficulty either in preparing or administering intracavernosal alprostadil. However, it is slower acting than injection therapy, with lower efficacy (Werthman & Rajfer, 1997; Porst, 1997). The reported side effects include mild penile pain and urethral discomfort.

Vacuum devices

A vacuum device consists of an external cylinder which fits over the penis, and then air is pumped out. This results in blood flow into the penis, following which a constriction ring is fitted around the base of the penis to maintain the erection. This type of treatment has a long history; achievement of adequate rigidity for penetration has been reported in 90% of patients with neurogenic ED (Seckin et al., 1996; Denil et al., 1996). The most common complaints are of premature loss of rigidity and difficulty in placing and removing the constriction bands and the most common complications are bruising, petechiae, and skin edema. Severe complications such as penile gangrene, severe erosions, and cellulitis can occur and are associated with prolonged constriction-band wearing (Rivas & Chancellor, 1994).

Penile prostheses

Penile prostheses are semirigid, inflatable or malleable implants that are surgically inserted into the penis to allow an erect state. They are suitable for patients who have an organic basis to their erectile dysfunction who have failed to respond to other treatments. Once placement of a prosthesis is undertaken, other treatments for erectile dysfunction are ruled out. Inflatable prostheses require manual dexterity by the patient or his partner. They allow a flaccid penis when not inflated, which is more practical for everyday life. Most reports in the literature deal with the semirigid type of prosthesis (Evans, 1998). Complications include prosthesis extrusion leading to explantation and prosthesis failure. However this incidence may be higher in neurogenic patients due to the increased risk of erosion because of sensory loss. The biggest disadvantage of this treatment is that it requires an operative procedure, which is invasive and has its own set of potential complications.

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57

Hypothalamic/pituitary function and dysfunction

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The hypothalamus and pituitary gland are a functional unit forming an interface between the nervous and endocrine systems. The hypothalamic–pituitary axes regulate several endocrine glands (e.g. thyroid, adrenal, and gonad) and many metabolic processes. Abnormalities of the pituitary gland present in three ways. First, a mass within the sella can compress the normal pituitary gland causing varying degrees of hypopituitarism. The spectrum of presentation includes non-specific complaints, slowly progressive constitutional symptoms and acute, life-threatening consequences of hormonal deficiencies. Secondly, an expanding sellar mass can injure continguous structures resulting in visual field abnormalities, diminished acuity, diplopia, headache, and other neurologic symptoms. Thirdly, secretory pituitary adenomas can cause unusual clinical syndromes including acromegaly, Cushing disease, amenorrhea/galactorrhea syndrome or thyroid toxicosis. Sellar abnormalities are also incidentally discovered when radiographic tests are ordered for other reasons. In rare patients, pituitary adenoma is part of the famililal multiple endocrine neoplasia syndrome, Type 1 (MEN 1), which also includes hyperparathyroidism and pancreatic islet cell adenomas.

Hypothalamic disorders (e.g. tumours, infiltrative disease or genetic abnormalities) often affect pituitary function, generally causing panhypopituitarism or monohormonal failure (e.g. Kallman's syndrome causing gonadal failure or growth hormone releasing hormone deficiency causing growth retardation). Less frequently hypothalamic disorders are associated with hyperfunction of the pituitary gland (e.g. precocious puberty).

Normal pituitary function

The pituitary gland receives its blood supply from the superior and inferior hypophysial arteries. The superior hypophysial artery, a branch of the internal carotid artery, forms a capillary plexus surrounding the hypothalamus and infundibulum and drains into the hypophysial–portal system. The hypothalamic releasing and inhibiting factors, which modulate anterior pituitary function, are secreted into this capillary plexus and are carried by the hypophysial–portal circulation to the anterior pituitary, their site of action. Once reaching the anterior pituitary, the hypothalamic releasing and inhibiting factors bind to specific membrane receptors and modulate synthesis, release and sometime posttranslational processing of anterior pituitary hormones. The pituitary gland synthesizes and secretes at least six hormones, and each is under some form of hypothalamic control (Table 57.1). In addition, it is possible for blood to flow retrograde up the infundibulum to the median eminence and thereby provide a route for pituitary hormones to control their own release by positive

Table 57.1. Hypothalamic factors and the pituitary hormones they regulate

Hypothalamic hormones	Anterior pituitary hormones
Growth hormone-releasing hormone (GHRH)	Stimulates growth hormone
Somatostatin	Inhibits growth hormone
Dopamine	Inhibits prolactin
Thyrotropin-releasing hormone (TRH)	Stimulates thyrotropin (TSH)
Corticotropin releasing hormone (CRH)	Stimulates ACTH and other POMC products
Gonadotropin-releasing hormone (GnRH)	Stimulates luteinizing hormone (LH) and follicle-stimulating hormone (FSH)

and negative feedback mechanisms. The posterior pituitary receives a direct arterial blood supply from the inferior hypophysial artery. This portion of the pituitary does not manufacture hormones but rather is a storage depot for vasopression and oxytocin synthesized in specific hypothalamic nuclei.

Hypothalamic–pituitary–adrenal (HPA) axis

The HPA axis is responsible for generating the glucocorticoid component of the stress response and for stimulating adrenal androgen production. Secretion of ACTH is primarily stimulated by corticotropin-releasing factor (CRH). In response to stress, the hypothalamus secretes CRH, which in turn stimulates the release of ACTH from the pituitary. ACTH is the primary regulator of adrenocortical function and increases cortisol, androgen and to a lesser extent, aldosterone secretion. Cortisol participates in its own regulation through a negative feedback loop inhibiting ACTH at the pituitary level and CRH at the hypothalamus. ACTH secretion has a diurnal cycle, with the highest levels occurring in the early morning before awakening and preceding the early-morning rise in cortisol.

ACTH is 49-amino acid peptide synthesized in the pituitary as part of a larger prohormone, proopiomelanocortin (POMC). POMC is a 265-amino-acid peptide that contains the sequence of ACTH, β-LPH, α-MSH, β-endorphin and other peptides. The endocrine role of ACTH is well understood, but the roles of β-LPH and the other mature peptide derived from POMC precursor are uncertain. The main hypothalamic regulator of ACTH is CRH. This peptide is expressed primarily in the paraventricular nucleus of the hypothalamus. The CRH neurons within the paraventricular nucleus are under regulation by several neurotransmitter systems. Hypothalamic β-endorphin and γ-aminobutyric acid (GABA) inhibit the release of CRH, whereas serotonin and α-adrenergic input stimulates CRH release. Vasopressin (AVP) is co-secreted from paraventricular neurons with CRH and potentiates the action of CRH on ACTH secretion. Angiotensin II, another neuropeptide released during stress, increases ACTH secretion.

Hypothalamic–pituitary–gonadal (HPG) axis

The HPG axis is responsible for maintaining normal gonadal function. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are the main regulators of gonadal steroidogenesis (e.g. estrogen and testosterone). Both hormones are glycoproteins composed of α and β subunits. The β subunits of LH, FSH, TSH, and the placental peptide human chorionic gonadotropin are identical. Immunologic activity for detection of the intact hormone in radioimmunoassys depends on the integrity of the β subunit, whereas biologic activity depends on association of the α and β subunits and appropriate post-translational glycosylation of the subunits.

The decapeptide, gonadotrophin-releasing hormone (GnRH) is the main hypothalamic-stimulating factor for the secretion of LH and FSH. GnRH stimulates the release of both LH and FSH. In turn, LH and FSH stimulate the gonads to produce sex-steroid hormones. Through a sensitive negative feedback loop, estrogen and testosterone participate in their own regulation by inhibiting LH, FSH and GnRH release. The pituitary hormone prolactin (PRL) can also inhibit the release of GnRH accounting for the hypogonadism associated with hypoprolactinemia.

Hypothalamic–pituitary–thyroid (HPT) axis

The HPT axis is responsible for maintaining normal thyroid homeostatis. Thyroid-stimulating hormone (TSH) is a glycoprotein that regulates thyroid gland function. It has a molecular weight of 28 000 and like LH and FSH is composed of two non-covalently linked chains, the α and β subunits. Triiodothyronine (T_3) is the main hormone regulating TSH secretion. Through negative feedback, this thyroid hormone inhibits TSH and hypothalamic thyroid releasing hormone (TRH) synthesis and release. Although some T_3 comes directly from the thyroid, most is derived from the conversion of L-thyroxine (T_4) into T_3 by type II thyroxine 5-deiodinase within the pituitary gland.

The most important peptide regulating TSH is hypothalamic TRH. This simple tripeptide is found throughout the nervous system, but is enriched in TRH-secreting neurons within the median eminence. Like TSH, TRH secretion is inhibited by T3. TRH administration induces a dose-dependent increase in TSH secretion. Although rarely needed, failure of TSH to respond to synthetic TRH is one of the most sensitive clinical tests for hyperthyroidism. TRH can also be used to assess TSH reserve in patients with pituitary disease. In addition to T3 and TRH regulation of TSH, the hypothalamic inhibitory factor, somatostatin, also inhibits TSH secretion.

Somatotroph axis

Somatic growth is regulated by growth hormone (GH), a 21 500 Da protein. Most of the growth promoting effects of GH are mediated through GH-induced release of insulin-like growth factor (IGF-I), a protein made predominantly by the liver but also by other tissues. GH and IGF-I are

required for normal growth and development during childhood. The presence of both factors is necessary for normal adult metabolic processes (e.g. muscle mass, lipid profile, and cognitive function).

Hypothalamic control of GH secretion is mediated by at least two peptides: somatostatin, which inhibits GH and growth hormone-releasing hormone (GHRH), which stimulates GH release. A recently identified third factor, Ghrelin, also stimulates GH secretion (Kojima et al., 1999). The GH inhibiting factor, somatostatin is a 14-amino-acid peptide present in the hypothalamus and distributed widely throughout the human central nervous system. Somatostatin blocks the release of GH induced by exercise, amino acids, and hypoglycemia. Somatostatin is also effective in reducing elevated GH and TSH levels in GH- and TSH secreting pituitary tumours, respectively. In normal humans, dopamine stimulates GH release. In patients with acromegaly (e.g. GH-secreting pituitary tumour), dopamine inhibits GH release. This inhibitory effect of dopaminergic agonists has been exploited in the treatment of acromegaly. Stress, exercise and slow wave sleep induce GH release. In normal individuals, glucose suppresses GH, whereas certain amino acids (e.g. arginine) stimulate GH secretion. In acromegalic patients glucose does not generally suppress GH and often, paradoxically stimulates GH. This difference in GH responses to a carbohydrate load between normals and patients with acromegaly forms the basis for the glucose-GH suppression test, a study employed to diagnosis acromegaly.

Prolactin

Prolactin, a 22 000 Da molecular weight protein, induces breast milk production in the presence of estrogens. In contrast to all other pituitary hormones, prolactin is primarily under inhibitory control by dopamine synthesized within tubero-infundibular neurons of the hypothalamus. In addition, the prohormone for GnRH contains a 56-amino-acid sequence that strongly inhibits the release of prolactin. This peptide is coreleased with GnRH and may serve to reduce prolactin levels.

The rise in prolactin induced by suckling, sleep, stress, and exercise is thought to be mediated through serotonergic input. Endogenous opioids (e.g. endorphin and enkephalins) stimulate prolactin secretion. Moreover, a variety of peptides (e.g. cholecystokinin, vasoactive intestinal polypeptide, neurotensin, and substance P) stimulate prolactin release. However, the physiologic significance of these effects remains uncertain. Estrogen modulates prolactin secretion. It acts on the hypothalamus to regulate dopamine turnover and at the level of the pituitary.

Disorders of the hypothalamic–pituitary unit

Precocious puberty

Precocious puberty results from the activation of the hypothalamic–pituitary–gonadal axis (Lee, 1999). While often observed after the development of a hypothalamic lesion, it can also be idiopathic. Precocious puberty has been described in the setting of various hypothalamic lesions but is most often observed in the presence of hamartomas, teratomas, germinomas and ependymomas. Other types of tumours associated with precocious puberty include optic nerve gliomas, astrocytomas, chorioepitheliomas, and neurofibroma (as part of von Recklinghausen's syndrome). These tumours both synthesize and secrete GnRH or stimulate the hypothalamus to prematurely release GnRH in a pulsatile manner.

Long-acting GnRH analogues are used to treat central precocious puberty because after a brief period of stimulation of LH and FSH, the analogues result in long-term inhibition of LH and FSH (Schally, 1999). GnRH analogues have the advantage of not causing other pituitary dysfunction, and prevent premature closure of the epiphyses (leading to short stature) that can be caused by the gonadal steroids.

McCune–Albright syndrome

The McCune–Albright syndrome is characterized by irregular pigmented areas (e.g. café-au-lait spots) on the trunk and polyostotic fibrous dysplasia of bone (De Sanctis et al., 1999). Precocious puberty and other endocrine hypersecretory syndromes (e.g. acromegaly, hyperthyroidism) can also be manifestations of the disorder. The hypersecretory states seen in McCune–Albright syndrome are the product of a somatic mutation in the Gs alpha gene leading to the constitutive activation of adenylyl cyclase signal transduction. This same mutation also accounts for approximately 30–40% of sporadically occurring GH-secreting pituitary tumours.

Pituitary adenomas

Pituitary adenomas are almost always benign accounting for 90% of sellar lesions and 10% of intracranial neoplasms. Pituitary adenomas are classified as microadenomas if their diameter is less than 1 cm, and macroadenomas if they are 1 cm or larger. This distinction is made because lesions greater than 1 cm often extend out of the sella and injure surrounding structures (e.g. optic chiasm). One can appreciate the potential symptoms (Table 57.2) created by

Table 57.2. Presentations of pituitary tumours

Increased hormone production
Hyperprolactinemia
Acromegaly (growth hormone)
Cushing's disease (adrenocorticotropin (ACTH))
Hyperthyroidism (thyroid-stimulating hormone (TSH))
Compression of adjacent structures
Headache
Visual field defects (classically, superior bitemporal)
Cranial nerve deficits
Hypopituitarism
Hypothyroidism
Hypogonadism
Adrenal dysfunction
GH deficiency
Incidental radiographic detection
Microadenoma
Macroadenoma

an expanding sellar mass by remembering the structures adjacent to the pituitary (Fig. 57.1). As a sellar lesion expands it may induce (i) sign/symptoms of hypopituitarism resulting from compression of the normal pituitary gland; (ii) signs/symptoms secondary to extension of the mass into surrounding structures (e.g. optic chiasm); and (iii) clinical manifestations resulting from excess hormone secretion by the sellar mass. The pituitary gland 'sits' in a cavity, the sella turcica (Turkish saddle). This boney structure surrounds the anterior, ventral (floor) and posterior portions of the pituitary gland. The gland is also attached to hypothalamus by the stalk or infundibulum. However, the pituitary is on the peripheral side of the blood-brain barrier. In the superior direction, the gland is separated from CSF, optic chiasm and hypothalamus by a thin section of dura, the diaphragm sellae. Under normal circumstances, this boundary does not allow CSF to enter the sella turcica. Laterally, the pituitary is separated from both cavernous sinuses by thickened dura. The cavernous sinus contains cranial nerves III, IV, VI and the first two divisions of cranial nerve V. The carotid artery passes through the cavernous sinus and parasympathetic nerves inducing pupillary constriction ride on the surface of the carotids within the cavernous sinus. Below the floor of the sella is the sphenoid sinus.

Similar to any mass within a closed space, the expanding pituitary adenoma usually takes the path of least resistance, which is the superior direction. The lesion may compress the normal pituitary cells and induce various degrees of hypopituitarism (e.g. hypothyroidism, hypogonadism, adrenal insufficiency and GH deficiency). The mass can also stretch the diaphragm sella and induce dull frontal headaches. If the lesion continues to expand in the superior direction, it will compress the optic chiasm causing visual abnormalities. Loss of vision can be the sole presenting symptom of pituitary adenoma. The subtlest visual abnormality is colour desaturation in the superior temporal fields, caused by compression of the medial inferior portion of the optic chiasm. However, some patients describe their vision as dim or foggy, or feel as though they have a veil over their eyes. Many patients have only vague complaints, like loss of depth perception. Some are unaware of their visual loss because peripheral vision is typically affected first. However, they may acknowledge problems with driving, which requires peripheral vision, or may complain that they are bumping into furniture or other people. If the tumour continues to grow, patients may suffer bitemporal hemianopia, optic atrophy, and loss of visual acuity. Papilledema is rare. In a few patients, an expanding tumour impinges on the hypothalamus, disturbing consciousness or temperature regulation, or causing hyperphagia. Tumour obstructing the third ventricle and cerebrospinal fluid flow can lead to hydrocephalus.

Less commonly the tumour will erode through the floor of the sella or into either cavernous sinus. Cavernous sinus invasion can result in injury to cranial nerves III, IV, V, and VI causing diplopia, ophthalmoplegias or facial numbness. Compression of the carotid artery may cause pupillary dilatation by injury to parasympathetic nerves on the surface of the vessel. Lastly, pituitary adenomas may cause a variety of syndromes secondary to excess hormone secretion.

Prolactin-searching and non-functional adenomas are the most common pituitary lesions. Less common are growth hormone-secreting adenomas, mixed prolactin- and growth hormone-secreting adenomas, ACTH secreting adenomas, and gonadotropin-secreting adenomas. Rare adenomas secrete TSH.

Prolactin-secreting adenomas and hyperprolactinemia

Patients with prolactin-secreting pituitary adenomas present with complaints resulting from the hormonal consequences of hyperprolactinemia and/or from tumour expansion (Molitch, 1995). The most common symptom is galactorrhea (non-puerperal lactation). However, this complaint is non-specific, affecting upwards of 20% of all previously pregnant premenopausal women. Most hyperprolactinemica women also have irregular menses. In fact,

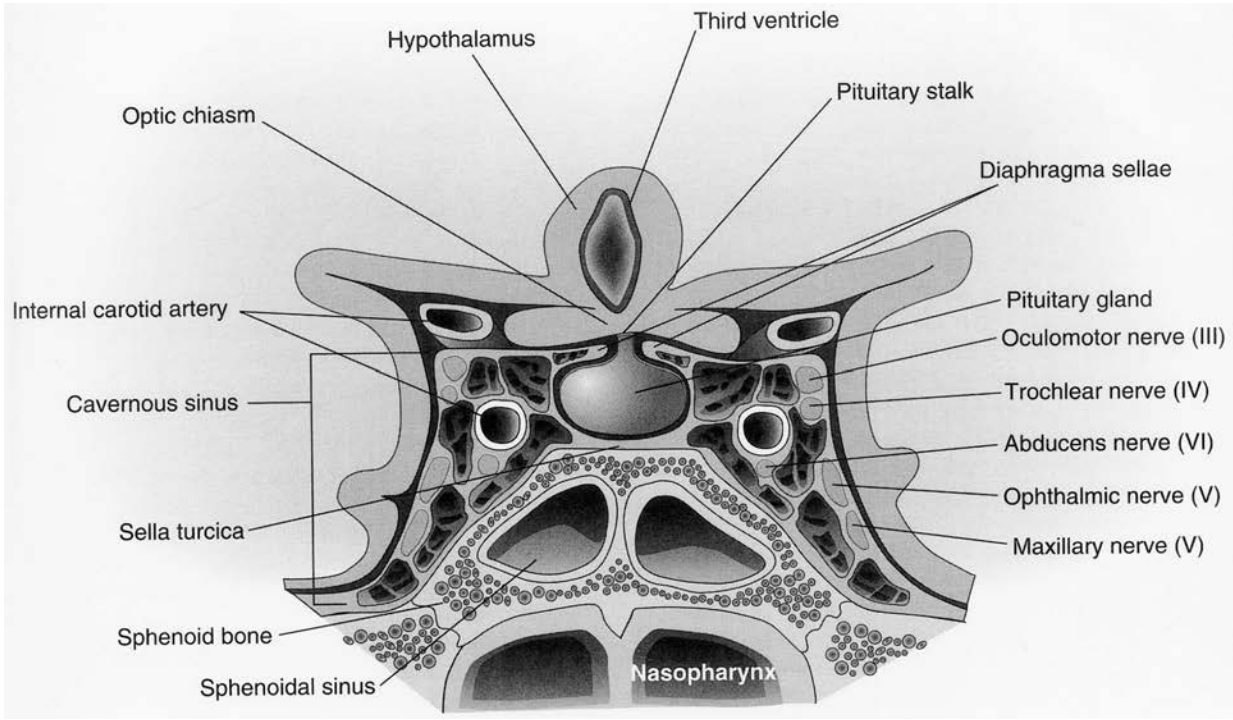

Fig. 57.1. Anatomy of the sellar region. (From Ward, 1996.)

15% of women presenting for evaluation of amenorrhea, 25% with galactorrhea, 35% with infertility and 75% with amenorrhea and galactorrhea have hyperprolactinemia. The prevalence of prolactinoma is approximately 5 cases per 10 000.

While menstrual dysfunction often leads women to seek medical help and permits early detection of prolactin-secreting adenomas, men less frequently complain to physicians about their core symptoms of hyperprolactinemia: impotence and decreased libido. At the time of diagnosis, men's tumours tend to be larger than women's. Hyperprolactinemia suppresses GnRH and therefore plasma LH and FSH levels, resulting in low circulating gonadal steroids causing diminished libido and vasomotor flushing in either sex. Relatively few men present with galactorrhea and gynecomastia.

It is important to consider physiologic and other pathologic causes of hyperprolactinemia and not assume that an elevated prolactin is always associated with prolactinoma (Table 57.3). The most common cause of hyperprolactinemia in women is pregnancy. Other important causes of hyperprolactinemia are (i) sellar or suprasellar lesions that block dopamine transport from hypothalamus to the pituitary (e.g. hypothalamic glioma, craniopharyngioma, and large non-functioning pituitary adenomas); (ii) medications that deplete dopamine synthesis or block the D2-dopamine receptor (e.g. phenothiazines, Reglan^{R}) (iii) kidney failure; and (iv) liver failure. In rare patients, severe primary hypothyroidism causes hyperprolactinemia. In this setting hypothyroidism may mimic a prolactin-secreting pituitary tumour by causing amenorrhea, galactorrhea, and even sellar enlargement due to thyrotropin-secreting cell hypertrophy. A TSH level should be checked in all patients with hyperprolactinemia to exclude primary hypothyroidism. In some patients, hyperprolactinemia is caused by chest wall injury or irritation (e.g. herpes zoster), which activate the neurologic circuitry responsible for elevations in prolactin induced by suckling.

Serum prolactin levels usually distinguish prolactin-secreting macroadenomas from other causes of hyperprolactinemia. Most prolactin-secreting macroadenomas produce serum prolactin levels above 250 ng/ml. Prolactin levels in microadenomas and other hyperprolactinemic disorders are generally lower.

Medical intervention with a dopamine agonist is first line treatment of prolactinoma regardless of size. Cabergoline (Dostinex^{R}) and bromocriptine (Parlodel^{R}) are the most frequently used dopamine agonists in this setting. Dopamine agonists normalize serum prolactin level in more than 90% of patients with microadenomas

Table 57.3. Causes of hyperprolactinemia

Physiologic
Pregnancy
Suckling
Exercise
Sleep
Postprandial
Pathologic
Prolactin-secreting tumours
Lesions interfering with hypothalamic dopaminergic tone
Hypothalamic diseases, e.g. sarcoidosis, tumour
Suprasellar lesions, e.g. craniopharyngioma
Non-functioning pituitary adenoma
Acromegaly (cosecretion of prolactin in 25% of patients)
Kidney failure
Liver failure
Hypothyroidism
Chest wall stimulation, e.g. by herpes zoster, surgery, trauma
Chronic anovulatory syndrome
Pharmacologic
Dopamine-blocking agents, e.g. phenothiazines, metoclopramide
Catecholamine-depleting drugs, e.g. reserpine
Certain other intravenous drugs, e.g. cimetidine, verapamil

and 75% with macroadenomas. In both sexes, unless the tumour has destroyed the gonadotroph cells, both drugs reverse the hypogonadotropic hypogonadism that accompanies hyperprolactinemia. By reversing hypogonadism, medical therapy can halt or partially reverse decreased bone mineralization associated with hyperprolactinemia (Schlechte et al., 1992). In women, estrogen deficiency and galactorrhea production stops. This is accompanied by a return in ovulatory menstrual cycles. In men, normalization in prolactin is accompanied by a return of serum testosterone into the normal range. This is followed by restoration of libido, potency, spermatogenesis and fertility.

Importantly, dopamine agonists significantly shrink more than two-thirds of prolactin-secreting tumours. In most cases the drug needs to be taken indefinitely. The most common side effects are nausea, dizziness, nasal congestion and headache. In most cases, the side effects will abate after several weeks of therapy. In cases where tumours are resistant to dopamine agonists or the patient cannot tolerate medical intervention, transphenoidal surgery should be considered. However, the surgical cure rate is 50% for microadenomas and less than that for macroadenomas. Radiation therapy is efficacious in preventing tumour growth but is not effective in normalizing the serum prolactin level.

Special consideration should be given to women with prolactinomas that become pregnant during medical therapy (Molitch, 1998). Under the influence of high estrogen levels, prolactinomas grow during pregnancy. Upward of 30% of macroadenomas and a small subset of microadenomas will grow to the extent that hypopituitarism or neurological defects occur. For this reason, most endocrinologists maintain macroadenoma patients on bromocriptine during pregnancy. Retrospective studies have strongly suggested that bromocriptine is not teratogenic nor does it induce spontaneous abortion. The safety of cabergoline during pregnancy has not been established at the time of this writing.

Growth hormone-secreting adenomas and acromegaly

Acromegaly is a syndrome caused by GH-secreting pituitary tumours (Klibanski & Zervas, 1991). The prevalence of acromegaly is approximately 7 cases per 100000. Acromegaly is easy to diagnose when the manifestations are severe, but more often, there is a considerable delay between disease onset and diagnosis. This is because GH-induced changes in appearance occur insidiously and these subtle alterations evolve gradually over time. Indeed, family members and physicians often do not notice the gradual change in appearance. It has been estimated that, on average, 8 years separate the time of diagnosis from the onset of the syndrome. It is helpful for physicians to review old photographs of the patient. Unfortunately, by the time most GH secreting tumours are discovered, they are larger than 1 cm (e.g. macroadenoma) and have already caused local compressive effects. Moreover, the larger tumours are more difficult to cure.

Although 99% of acromegaly results from GH-secreting pituitary tumours, if a pituitary tumour is not identified by MRI, the physician must consider other causes. For example, eutopic overproduction of growth hormone-releasing hormone by the hypothalamus or ectopic production of this hormone by a peripheral tumour (e.g. islet cell tumour) can cause excess GH secretion and the syndrome of acromegaly.

Acromegalic patients first develop soft-tissue hypertrophy causing a generalized coarsening of the facial features, thickening of lips, tongue (macroglossia), ear lobes and skin (Table 57.4). Malodorous hyperhidrosis is an early symptom. With time, undiagnosed patients may complain of increasing ring, glove or shoe size resulting from enlargement of hands and feet. They may also develop a

Table 57.4. Common clinical features of acromegaly

Headaches
Impaired glucose tolerance or overt diabetes mellitus
Acral growth and prognathism
Coarsening of facial features
Hypertrophy of the frontal sinuses (frontal bossing)
Deepening of the voice
Hypertension
Arthritic complaints
Menstrual irregularities
Carpal tunnel syndrome
Thick skin
Visceromegaly
Hyperhidrosis
Hypertrichosis

deepening voice (hypertrophy of the vocal cords), snoring, sleep apnea, carpal tunnel syndrome and organomegaly. Approximately 40% of growth hormone-secreting tumours also secrete prolactin and therefore patients may complain of breast secretion (galactorrhea). Over time significant boney changes occur resulting in arthritis, enlargement of the mandible (prognathism), wide spacing of the teeth, and hypertrophy of the frontal sinuses (frontal bossing). Metabolic abnormalities can include glucose intolerance, hypertension, hyperphosphatemia and hypercalciuria. If acromegaly begins prior to closure of the epiphyseal growth plates, then excess growth hormone secretion will result in gigantism.

Because GH is secreted in pulses, a single serum growth hormone determination is not an accurate indicator of acromegaly unless markedly elevated. Glucose challenge testing is more reliable. In normal people, 50–100 grams of glucose suppresses GH to undetectable levels; acromegalics typically have either inadequate suppression or a paradoxical rise in GH following a carbohydrate load. Insulin-like growth factor I (IGF-I) synthesized in the liver, is a major mediator of growth hormone action. This protein has a long plasma half-life and is not secreted in a pulsatile manner. Therefore a single elevated plasma IGF-I determination can also be diagnostic, although elevations are found in some normal young adults.

Growth hormone-secreting tumours are usually first treated surgically, by transphenoidal resection through the nasal cavity and sphenoid sinus (Laws & Thapar, 1999). In the hands of an experienced neurosurgeon, approximately 80–90% of microadenomas and 20–50% of macroadenomas are cured. Similar to transphenoidal surgery for any pituitary tumour, fewer than 5% of acromegalics will develop hemorrhage, infection, cerebrospinal fluid leak or injury to the anterior pituitary. However, transient diabetes insipidus occurs in about 25% of patients with permanent diabetes insipidus in fewer than 3%.

Recent studies have established new guidelines for defining cure of this syndrome. These guidelines were revised following reports showing that treated acromegalics still have two- to three-fold higher incidence of mortality compared to the general population unless serum GH levels are 1 μg or less and the IGF-I levels are in the normal range. Patients who still have elevated GH or IGF-I levels after surgery should be given a trial of a somatostatin analogue. Somatostatin analogs (e.g. Octreotide^{R}) normalize growth hormone levels in about two-thirds of patients and occasionally induce tumour shrinkage. Dopamine agonists also have some efficacy. Pegvisomant, a newly developed GH receptor antagonist, is a promising therapy for patients who had unsuccessful surgery (Trainer et al., 2000).

When patients are not cured by medical and surgical therapy, the remaining option is radiation therapy. However, conventional radiation may take 2–5 years to work, it does not cure all patients, and in 30–50% of patients it induces hypopituitarism. Radiotherapy for Acromegaly is often combined with medical treatment. All patients need periodic follow-up of their pituitary function. Ongoing studies are evaluating the efficacy of gamma knife radiation in the treatment of Acromegaly (Jackson & Noren, 1999).

ACTH-secreting adenomas and Cushing disease

Cushing syndrome results from hypercortisolism from any source: ACTH-secreting pituitary adenomas, ectopic production of ACTH by peripheral tumours, autonomies, cortisol secreting adrenal adenomas and autominously administered corticosteroids (Table 57.5). Cushing disease specifically defines hypercortisolism caused by an ACTH-secreting pituitary adenoma. It has a prevalence of approximately 4 cases per 100 000. Cushing disease accounts for approximately 80% of all causes of endogenous Cushing syndrome (Aron & Tyrrell, 1994). The ACTH-secreting pituitary tumour most often afflicts women in their childbearing years. Signs and symptoms include truncal obesity, cervicodorsal fat pad (buffalo hump), moon facies, plethora, purple striae, proximal muscle wasting and weakness, easy bruising, amenorrhea, psychiatric disturbances, and hirsutism (Table 57.6). Many ACTH-secreting pituitary adenomas are less than 0.5 cm in diameter and up to 70% cannot be visualized by MRI.

The diagnosis of Cushing syndrome requires the patient to undergo a low dose dexamethasone suppression test;

Table 57.5. Causes of Cushing's syndrome

ACTH dependent
Administration of exogenous ACTH
ACTH-producing pituitary adenoma
Corticotrophin cell hyperplasia
Idiopathic
Secondary to production of CRH
Ectopic ACTH production
ACTH independent
Administration of glucocorticoids
Associated with alcoholism
Adrenal
Benign adenoma
Adrenal carcinoma
Hyperplasia–non-ACTH induced (rare)

Table 57.6. Common clinical features of hypercortisolism

Obesity–centripetal
Hypertension
Impaired glucose tolerance or diabetes mellitus
Menstrual irregularities or amenorrhea; sexual dysfunction
Hirsutism and acne
Striae
Proximal muscle weakness
Osteoporosis
Easy bruisability
Psychiatric disturbance

the details of which are beyond the scope of this text. Once Cushing syndrome is firmly established, the diagnosis of Cushing disease is made by performing the high dose dexamethasone. Inferior petrosal sinus sampling can be used to diagnosis of Cushing disease, when results from the high dose suppression tests are ambiguous and there is no evidence of a pituitary lesion on MRI.

First-line therapy of Cushing's disease is transphenoidal resection of the tumour, curing upwards of 80% of patients. The remainder can be given a combination of pituitary radiation and 'medical adrenalectomy' with one or more drugs that inhibit adrenal glucocorticoid biosynthesis, for example, Ketoconazole^{R}, metyrapone, aminoglutethimide, Trilostane^{R}, and o,p-DDD. However, none of these agents easily normalizes glucocorticoid secretion, and all have side effects. By 5 years, radiotherapy cures only 50% of adults, but more than 50% of children.

If pituitary surgery, radiotherapy, and medical therapy fail to control hypercortisolism, the last option is bilateral adrenalectomy. This commits patients to lifelong glucocorticoid and mineralocorticoid replacement. About 10% of patients who undergo bilateral adrenalectomy develop Nelson's syndrome, which is a progressive enlargement of the pituitary tumour, hyperpigmentation, and very high plasma ACTH levels unleashed by loss of cortisol-negative feedback. Such tumours can be aggressive and difficult to cure. Tumours causing Nelson's syndrome can be detected radiographically as well as by extremely high ACTH levels. All patients who have undergone bilateral adrenalectomy should be monitored closely.

Gonadotroph-secreting tumours

Many pituitary tumours secrete immunoreactive LH and/or FSH (Snyder, 1995). At the time of diagnosis, most are large and cause local compressive symptoms. Typical patients present with hypogonadism despite their high serum FSH or LH levels, because the hormones produced by the tumour have reduced biological activity. The gonadotroph tumour does not respond to medical therapy and is managed with surgery followed by radiotherapy if a significant tumour remnant remains.

TSH-secreting tumours

The least common pituitary adenomas secrete TSH and usually cause hyperthyroidism (Mindermann & Wilson, 1993). Unlike typical patients with primary hyperthyroidism, for example, from Graves' disease, in whom circulating TSH levels are undetectable, patients with hyperthyroidism from TSH-secreting adenomas have either elevated or inappropriately normal serum TSH levels (inappropriate secretion of thyroid hormone) at the same time that they have high serum T4 and T3 levels. Most TSH-secreting adenomas are managed with surgery; many patients also need antithyroid drugs and radioactive iodine. Somatostatin analogues have been shown to reduce TSH secretion from these tumours.

A cause of inappropriate TSH secretion that is not associated with a pituitary adenoma is the thyroid hormone resistance syndrome, a rare genetic disorder (Refetoff, 1996). When thyroid hormone resistance is more pronounced in the pituitary gland compared to peripheral tissues, patients have an appropriate elevation in TSH and are either euthyroid or hyperthyroid. However, when thyroid hormone resistance exists in the periphery and in the pituitary gland, patients present

with unsuppressed TSH levels and features of hypothyroidism.

Non-functional pituitary tumours

Approximately 40% of pituitary adenomas are classified as non-functional because they produce no clinical syndrome resulting from hormone excess (Shimon & Melmed, 1998). However, the majority of non-functional adenomas do synthesize and secrete hormones, albeit at low levels. These tumours are managed with surgery followed by ratiotherapy if a significant tumour remnant remains. Medical therapy is not effective.

Pituitary incidentalomas

Pituitary adenomas that cause symptoms resulting from mass effect or hormone hypersecretion are uncommon. The prevalence of these lesions is approximately 20 cases per 100 000. However, clinicians are increasingly encountering incidental pituitary adenomas on CT and MRI scanning (Aron & Howell, 2000). The prevalence of pituitary incidentalomas found by CT ranges from 4% to 20%, and the prevalence found by MR imaging is approximately 10% (Katzman et al., 1999).

Given the high incidence of incidentalomas and the low incidence of potentially problematic lesions, an assessment algorithm would be helpful. Unfortunately, the optimal strategy for assessing patients with incidental adenomas has not been established. However, it has been suggested that any patient with an incidentaloma and clinical signs or symptoms suggestive of hormone hypersecretion should undergo appropriate testing as described above. Also, the asymptomatic patient with an incidentally discovered microadenoma should undergo limited hormonal testing. Most neuroendocrinologists would recommend that at least a serum prolactin be obtained. Evaluation of subclinical growth hormone or ACTH excess is not recommended in the absence of any signs or symptoms of these disorders. However, these patients require follow-up and if signs or symptoms of pituitary disease emerge, further evaluation is warranted.

In the presence of an incidentally discovered non-functional macroadenoma, some degree of hypopituitarism is not uncommon. Therefore, hormonal screening is suggested to detect potential deficiency of ACTH, TSH, GH, and gonadotropins. Patients with syndromes of hormonal excess should receive specific therapy as detailed below. These patients require formal visual field testing. Patient with evidence of visual field defects or cranial nerve injury should undergo surgery. For patients with non-functional macroadenomas and no signs of visual abnormalities or hypopituitarism, optimal management is unclear. If the lesion is abutting the optic chiasm, surgery is strongly suggested. If the lesion does not extend into the suprasellar cistern a 'watch and wait' approach is reasonable. However, evidence of tumour growth or hypopituitarism should result in surgical intervention. If there is no evidence of growth of the lesion, the time period between scans can be lengthened.

Empty sella syndrome

The empty sella syndrome is a symmetric enlargement of the sella turcica caused by invagination of the diaphgram sella by CSF, putting pressure on adjacent bone, and compressing the pituitary gland towards the floor of the sella (Vance, 1997). In spite of this pressure, pituitary function is generally normal, although hyperprolactinemia or some degree of hypopituitarism is observed approximately 5% of the time. The empty sella syndrome most often affects obese hypertensive women. It is also seen following pituitary apoplexy and rarely in patients with neurosarcoidosis. MRI of the sella can distinguish it from a pituitary tumour. Empty sella must be distinguished from a Rathke's cleft cyst since the former is never treated surgically whereas enlarging pituitary cysts may require surgical intervention.

Other sellar lesions

In addition to pituitary adenomas, the sellar and suprasellar regions can harbour other types of neoplasm (Albrecht et al., 1995). Craniopharyngiomas are squamous epithelial tumours that arise from the upper part of the pituitary stalk, hypothalamus or third ventricle (Hayward, 1999). They are partly cystic and the cysts often contain a viscous fluid. These lesions have a peak incidence in childhood but can occur any time in life. The craniopharyngioma is treated by surgery, often requiring craniotomy. Other hypothalamic lesions that can alter pituitary function include hamartomas, teratomas, germinomas, ependymomas, gliomas, astrocytomas, chorioepitheliomas and neurofibroma. Metastases from breast and lung cancers, lymphoma, and melanoma are other uncommon hypothalamic and pituitary lesions affecting pituitary function.

Rarely, autoimmune, infiltrative, and infectious diseases involve the pituitary, sometimes mimicking a tumour. Lymphocytic hypophysitis predominantly affects young women in late pregnancy or postpartum, and is thought to have an autoimmune pathogenesis (Beressi et al., 1999).

Infiltrative and infectious processes that can damage the hypothalamus and pituitary include sarcoidosis, Langerhans' histiocytosis, and tuberculosis.

Hypopituitarism

There are numerous causes and various ways patients present with hypopituitarism. Pituitary dysfunction can occur gradually with insidious symptoms or suddenly with a catastrophic event. The most frequent causes of hypopituitarism are listed in Table 57.7. As the posterior pituitary only functions as a storehouse for ADH and oxytocin, the presence of diabetes insipidus usually indicates the involvement of the hypothalamus in the pathological process (Freda & Post, 1999).

Presenting signs and symptoms

Injury to LH- and FSH-secreting cells causes secondary ('central') hypogonadism. In children, this delays or prevents puberty. In adult men, it causes impotence, decreased libido, and infertility. In women, it leads to menstrual irregularities, amenorrhea, infertility, hot flushes, decreased libido, vaginal dryness, and dyspareunia. Deficient prolactin secretion makes women unable to lactate postpartum.

Injury to ACTH-secreting cells causes secondary adrenal insufficiency. Many patients complain of weight loss, anorexia, nausea, weakness, arthralgia, and myalgia. The degree of adrenal insufficiency is often milder than observed in patients with primary adrenal failure, and it is not unusual to observe symptoms only during times of physical stress, when the cortisol requirements are higher (Oelkers, 1996). Decreased adrenal androgen production diminishes women's axillary and pubic hair. Patients with secondary adrenal insufficiency do not have hyperpigmentation, which is a common feature of primary adrenal insufficiency. Further, since ACTH is not the primary regulator of the mineralocorticoid axis, patients with secondary insufficiency do not have extracellular fluid volume depletion and hyperkalemia, which are often seen in primary adrenal insufficiency. Many patients do have hyponatremia; this is caused by impaired renal free water clearance, which is dependent on glucocorticoid action, and by the frequent co-existence of central hypothyroidism. Patients are typically sensitive to infection and other stresses, which can quickly precipitate hypoglycemia, hypotension, circulatory collapse, and death.

The most frequent cause of secondary adrenal insufficiency is long-term exposure to exogenous glucocorticoids, which may last for several months after glucocorticoids are discontinued. Every patient who has been treated with supraphysiological doses of glucocorticoids for 3 weeks or longer needs to be suspected to be adrenal insufficient (Krasner, 1999).

Injury to TSH-secreting cells causes secondary hypothyroidism. Symptoms include fatigue, cold intolerance, dry skin, constipation, weight gain, impaired mentation, and menstrual irregularities in women. These manifestations resemble those of primary hypothyroidism, but are usually less severe.

Growth hormone deficiency impairs skeletal growth if the epiphyses have not fused. Infants with GH deficiency

Table 57.7. Causes of pituitary failure

Hypothalamic
1. Developmental
   Kallman syndrome, septo-optic dysplasia, anencephaly
2. Traumatic
3. Neoplastic
   chraniopharingiomas, hamartomas, gliomas, astrocytomas, teratomas, germinomas, ependymomas, chorioepitheliomas
   metastatic disease (lymphomas, leukemias)
4. Inflammatory/infiltrative
   sarcoidosis, tuberculosis, histiocytosis X
5. Radiation therapy

Pituitary
1. Neoplastic
   pituitary adenomas or metastatic disease (breast, lung, melanoma)
2. Hereditary
   multi-hormonal: mutations in Pit-1 or Prophet of Pit-1 transcription factors
3. Developmental
   aplasia, ectopia, Rathke's cleft cyst, arachnoid cysts
4. Traumatic
5. Postsurgical
6. Inflammatory or infiltrative
   Tubercolosis, fungal, syphilis, sarcoidosis, hemochromatosis, lymphocytic hypophysitis
7. Vascular
   Sheehan's syndrome (postpartum pituitary necrosis), pituitary infarction or apoplexy
8. Other
   Empty sella syndrome

Extrasellar diseases
1. Parasellar neoplasms
   meningioma, chordoma, optic nerve glioma
2. Aneurysms of the internal carotid artery
3. Nasopharyngeal carcinoma

are prone to hypoglycemia. Growth hormone-deficient adults can lose muscle mass and strength, have reduced bone mineral density, increased adipose mass, hypercholesterolemia and reduced sensation of well being, often associated with emotional lability and feelings of social isolation (Carrol & Christ, 1998). Treatment with recombinant GH at a dose sufficient to normalize IGF-1 has been proven to improve all the above changes (Gibney et al., 1999).

Diagnosis of hypopituitarism

When a patient develops pituitary failure from compression by a sellar mass, the first anterior pituitary hormone to fail is usually GH, followed by LH and FSH, TSH and ACTH. However, especially in the case of radiation-induced-hypopituitarism, this order can be inverted, and it is not unusual to observe isolated deficit of TSH or ACTH.

If a patient is diagnosed with partial or complete hypopituitarism secondary to a pituitary macroadenoma, hormonal function needs to be reassessed after neurosurgical treatment, as it may improve or worsen postoperatively (Webb et al., 1999).

In evaluation of a patient with suspected hypopituitarism, the physician must identify the patient's hormone deficiencies and determine whether they are caused by pituitary failure (secondary, 'central' hormone deficiencies) or target gland dysfunction (primary, 'peripheral' hormone deficiencies). Levels of target gland hormones – T4, cortisol, and estradiol or testosterone – can be low in both primary and secondary endocrine disorders. Distinguishing between peripheral and central failure depends, then, on the level of the pituitary trophic hormone. For example, T4 levels are low in both primary and secondary hypothyroidism, so one must look to the pituitary trophic hormone, TSH. In primary hypothyroidism, diminished negative feedback causes the TSH to be high, while in secondary hypothyroidism, pituitary injury makes the TSH either low or inappropriately normal. Analogous patterns allow the physician to distinguish between primary and secondary adrenal insufficiency and between primary and secondary hypogonadism.

In addition to a careful history and physical examination, evaluation of patients with a possible sellar lesion usually requires a focused hormone assessment, imaging studies, and visual field analysis.

Suspected GH deficiency in children

Growth failure is particularly suspicious when a deflection in growth velocity is observed in a child with previously normal growth curve. Several systemic diseases can also cause growth failure. Therefore, renal failure, malabsorption or hypothyroidism, need to be ruled out before GH secretion is evaluated.

GH deficiency can be isolated or part of multihormonal pituitary failure. Isolated GH deficiency in children manifests itself as growth failure and may be caused by any hypothalamic or pituitary disease. However, structural abnormalities are evident via MRI only in 12.5% of children affected by isolated GH deficiency (Cacciari et al., 1990). Genetic abnormalities (mutations in the GH gene or the GHRH-receptor gene) are present only in a minority of patients, leaving the vast majority classified as idiopathic. The clinical presentation includes growth failure, abdominal fat accumulation and delayed bone age. Several genetic syndromes (such as Turner syndrome, Silver Russel syndrome or Noonan syndrome) also present with short stature, and a careful physical examination in search of dysmorphic characters needs to be performed. Insulin-like growth factor-1 (IGF-1) is produced by the liver under the influence of GH and mediates most of the effects of GH. It circulates as a ternary complex bound to IGF-binding protein 3 (IGF-BP3) and to the acid labile subunit (ALS), whose synthesis is also under control of GH. Therefore, an indirect evidence of GH deficiency may be provided by measurement of serum IGF-1 or IGF-BP3 levels (ALS is not routinely used at the present time). However, confirmation of GH deficiency needs to be obtained via one of the many stimulation tests (insulin-induced hypoglycemia, GHRH, arginine, L-dopa, clonidine or combinations of the above) (Vance & Mauras, 1999). Although the cutoff of normal response is debated, usually a peak value below 7 ng/ml is considered diagnostic of GH deficiency. As each one of these tests has false positives, it is preferable to confirm GH deficiency with two tests before committing a child to a long and expensive injectable therapy.

Suspected GH deficiency in adults

The vast majority of adults with GH deficiency have overt pituitary disease. Among patients with pituitary tumours, those with deficiency in other hormones are very likely to be GH deficient. The likelihood of GH deficiency is close to 100% in a patient with deficit of gonadotropins, TSH and ACTH. Adults with a history of childhood onset isolated GH deficiency need to be retested, as more than 50% have normal GH secretion when retested as adults (Tauber et al., 1997). Serum IGF-1 and IGFBP3 levels are not reliable in diagnosing GH deficiency in adult, particularly in older patients, as a large overlap exists between subjects with normal and abnormal GH secretory reserve. Stimulation tests are often needed: insulin-induced hypoglycemia is the 'gold standard' in adults as well (except for patients

with known or suspected coronary artery disease and in patients with history of seizures). Alternatively, arginine, GHRH or GHRH plus arginine or clonidine can be used. At present, as the long term side effects of GH therapy in adults are not known, it is recommended that only patients with severe GH deficiency (peak GH after insulin <3 ng/ml) be treated (Bengtsson et al., 2000). The usual starting dose is 3–4 mcg/kg/day for males and 4–5 μg/kg/day for females. Side effects are usually dose dependent, limited to edema and arthralgia or myalgia. Absolute contraindications to GH treatment are active malignancy, proliferative or preproliferative diabetic retinopathy and benign intracranial hypertension (Growth Hormone Research Society, 1998).

Suspected secondary adrenal insufficiency

A basal morning cortisol is generally not a useful screening test for adrenal insufficiency, unless the level is above 20 μg/dl (indicating normal HPA axis) or below 3 μg/dl during the morning hours (indicating adrenal insufficiency). Therefore, most patients need to have a dynamic test. The available tests are the ITT, the overnight metyrapone test, the CRF tests and the ACTH tests.

The insulin tolerance test is the gold standard for diagnosing secondary adrenal insufficiency because it assesses the integrity of the entire hypothalamic–pituitary–adrenal (HPA) axis (Abdu et al., 1999). It has the additional advantage of simultaneously testing GH reserve when needed. It is, however, dangerous in patients above 60, or with history of seizures or known or suspected coronary artery disease.

The metyrapone test is an accurate way to diagnose acute secondary adrenal insufficiency as it evaluates both the pituitary and the adrenal cortex. It takes advantage of the ability of metyrapone to reduce serum cortisol by blocking the enzyme 11-beta-hydroxylase, which catalyses the last step in cortisol biosynthesis. Metyrapone (30 mg/kg; maximal dose 3 gm) is given at midnight and a single blood sample is drawn at 8 am the following morning. When cortisol synthesis is inhibited, a normal pituitary responds by secreting more ACTH, thereby raising plasma levels of 11-deoxycortisol, the immediate precursor to cortisol, above 7.5 μg/dl. Patients with secondary adrenal insufficiency have blunted ACTH and 11-deoxycortisol responses. This test needs to be performed with overnight hospitalization because of the theoretical risk of inducing an adrenal crisis (Fiad et al., 1994).

The rapid ACTH stimulation test detects pituitary–adrenal dysfunction only when secondary adrenal insufficiency has been chronic (>6 weeks). Traditionally patients are given 250 μg of synthetic ACTH and one hour later a serum cortisol value >20 μg/dl defines a normal response. Even more sensitive is the low dose of ACTH test where patients receive 1 μg of synthetic ACTH and 30 minutes later a serum cortisol >18.6 μg/dl defines a normal response (Abdu et al., 1999).

The CRF test utilizes the ability of ovine CRF of causing a raise in ACTH and cortisol. It is safe but expensive (CRF costs about $300/vial) and it is not yet well standardized.

Suspected secondary hypothyroidism

The physician should measure the free T4 (by T4 radioimmunoassay or free T4 index) and serum TSH concentrations. In secondary hypothyroidism, the free thyroxine is low, while the serum TSH is low or inappropriately normal. A normal TSH level in a patient with secondary hypothyroidism is explained by the fact that TSH produced in patients with pituitary and hypothalamic diseases is less biologically active than normal. In rare cases a TRH stimulation test (showing reduced TSH response to TRH) may help confirming the diagnosis of central hypothyroidism. As opposed to the treatment of primary hypothyrodism, TSH is not a reliable marker in patients with central hypothyroidism. Appropriateness of L-thyroxine replacement therapy must be assessed clinically and by measuring free T4 levels.

Suspected secondary hypogonadism

The gonadal axis can be evaluated by measuring the LH, FSH, and estradiol or testosterone. Secondary deficiency is marked by LH and FSH levels that are inappropriately low relative to low sex steroid levels. Normal LH and FSH levels in a postmenopausal woman who is not on estrogen replacement, rather than the expected elevations, also suggest hypopituitarism, especially in the initial postmenopausal years (Santoro et al., 1998).

Imaging and visual field testing

Imaging of the sella turcica, preferably by MRI, reveals sellar lesions, defines their size, and occasionally suggests the specific tumour type. For example, a craniopharyngioma can often be predicted by calcification (better detected by CT than MRI) and cystic degeneration as well as by its suprasellar position (Naidich & Russell, 1999). Because many people have clinically irrelevant non-secretory pituitary adenomas ('pituitary incidentalomas', see above), pituitary imaging should be deferred until hormonal or neurologic findings confirm that there is reason to suspect a clinically significant sellar lesion.

If imaging studies show a macroadenoma, the patient should have visual field tests to detect possible optic nerve abnormalities. Although routine physical exam can reveal gross defects in peripheral vision, formal ophthalmologic

evaluation is essential to find subtle abnormalities. Furthermore, visual field test is a sensitive indicator of rapid changes in size of a pituitary mass (such as the growth that may occur after hemorrhage of a macroadenoma or the shrinkage of a macroprolactinoma in response to dopaminergic therapy).

Pituitary apoplexy

About 5–20% of pituitary adenomas hemorrhage spontaneously. About one-third of these hemorrhages are recognizable as pituitary apoplexy, a syndrome of sudden, severe headache, neurologic symptoms and signs, and acute adrenal insufficiency (Randeva et al., 1999). Neurologic problems characteristically include vision loss, diplopia, ptosis, and pupil abnormalities. Within hours, lack of ACTH and cortisol production (present in two-thirds of the cases) may cause nausea, vomiting, and hypotension. If necrotic tissue and blood enter the cerebrospinal fluid, the patient may also develop meningismus, hyperpyrexia, and coma. CSF analysis may show pleiocytosis and increased protein concentration. The diagnosis of pituitary apoplexy is often delayed because 60% of the patients presenting with this syndrome have previously undiagnosed pituitary adenomas. Furthermore, symptomatology often can mimic the symptoms of subarachnoid hemorrhage and meningitis; and differentiating these disorders requires imaging of the sella. Although CT scan of the brain reveals a pituitary mass in about 90% of the cases, MRI is superior in diagnosing pituitary hemorrhage. Treatment requires urgent administration of intravenous glucocorticoids to treat acute adrenal insufficiency. Surgical decompression of the sella is required in the presence of reduced vision (symptom of acute chiasmal compression) and altered level of consciousness (symptom of increased intracranial pressure). Extraocular motor palsies do not constitute indication for surgery, as they revert spontaneously in most cases. Some authors believe that early (within a week) surgical decompression reduces the incidence of long-term hypopituitarism (Arafah et al., 1988) and visual deficit (Bills et al., 1993), but no prospective study is available to support these opinions. Acute pituitary failure is often transient, and patient's hormonal function needs to be re-evaluated weeks after the acute event.

The posterior pituitary

The posterior pituitary is a storehouse for the hormones antidiuretic hormone (ADH) (or vasopressin) and oxytocin produced by neurosecretory cells whose bodies are located in the supraoptic and paraventricular nuclei of the hypothalamus. The axonal processes of these neurons extend into the posterior pituitary where they carry the secretory material, containing the hormones and the associated protein neurophysins. A second secretory pathway releases vasopressin in the portal hypophysial system, where this hormone is believed to play a role in the secretion of ACTH from the anterior pituitary.

The secretion of ADH is mainly regulated by osmotic factors. Osmotic receptors are present in the CNS, and can detect very subtle changes in serum osmolarity. The amount of ADH released is proportional to the increase in plasma osmolarity. Increased osmolarity also stimulates ADH gene expression. ADH causes increase in urinary osmolarity. A 2% increase or decrease in serum osmolarity causes maximal concentration ($>$1000 mmol/kg) or maximal dilution ($<$100 mmol/kg) of the urine, respectively. As the onset of thirst occurs at values of plasma osmolarity similar to those of the threshold of ADH release, in a normal subject with access to water plasma osmolarity is tightly regulated.

ADH release is also regulated by baroreceptors located in the left atrium, aortic arch and carotid sinus. Stimulation of these receptors via ascending neural pathways suppresses ADH release, while reduced activity, as seen in hypovolemia or hypotension, causes increase in ADH release. The threshold for activation is much higher than for osmotically stimulated thirst and ADH secretion. Finally, ADH release is negatively regulated by glucocorticoids and stimulated by opioids, nausea and vomiting.

The effects of ADH on the renal collecting ducts (increase in water permeability) is mediated by a specific V2 receptor which activates water channels called aquaporins (Agre, 2000). ADH has a dual effect: a short-term one, triggering the translocation of aquaporin-containing intracellular vesicles to the plasma membrane, and a long-term one, increasing the number of aquaporin-containing vesicles (Knepper et al., 1997). However, it is the inner medullary-concentrating gradient that determines the degree of urine concentration in the presence of maximal ADH activity.

The effect of oxytocin is to cause contraction of the myoepithelial cells in the lactating mammary gland and to stimulate uterine contraction during parturition and expulsion of the placenta. The only two known stimuli for oxytocin secretion are nipple suckling and vaginal distention.

Diabetes insipidus

Disorders of the posterior pituitary lead to syndromes caused by inadequate (diabetes insipidus) or excessive

(SIADH) secretion of ADH. Diabetes insipidus is a polyuric syndrome of excessive excretion of dilute urine, with secondary polydipsia (Bichet, 1995). Diabetes insipidus can result from either inadequate ADH production ('central' or 'neurogenic' diabetes insipidus) or renal disease impairing responsiveness to ADH ('nephrogenic' diabetes insipidus). Central diabetes insipidus develops when the posterior lobe of the pituitary fails to secrete sufficient amount of ADH. In 10–30% of the cases the disorder is idiopathic; the major known causes are hypothalamic tumours, head trauma, central nervous system infiltrative disorders (e.g. sarcoidosis) or infection (e.g. tuberculosis), and transphenoidal surgery. Primary disease of the pituitary gland is rarely the culprit, because the posterior pituitary is merely a storage site for ADH after its synthesis in the hypothalamus. Thus, diabetes insipidus accompanying anterior pituitary dysfunction suggests underlying hypothalamic disease. Rarely, diabetes insipidus can be caused by very large pituitary tumours, pituitary apoplexy or lymphocytic hypophisitis. Rare familial autosomal dominant forms have been described, caused by mutations in the ADH signal peptide or in the neurophysins.

Patients with central diabetes insipidus require MR imaging of the sellar region to rule out secondary causes. The posterior pituitary usually appears as a bright spot, corresponding to the presence of stored ADH. In patients with idiopathic diabetes insipidus such a bright spot is usually absent. However, the presence of a normal bright spot does not rule out the diagnosis of diabetes insipidus.

In contrast, nephrogenic diabetes insipidus is caused by kidney disorders in which the renal tubules do not respond normally to ADH. The condition can be familial or acquired through electrolyte derangements (e.g. hypokalemia, hypercalcemia), diseases of the renal interstitium that disrupt medullary concentrating mechanisms, or drugs that impair renal tubular function (e.g. lithium carbonate or demeclocycline). Familial nephrogenic diabetes insipidus can be transmitted as an X-linked character (due to defects in the ADH receptor gene) or, less frequently, autosomal recessive (due to defects in the gene encoding for the vasopressin-sensitive water channel aquaporin-2) (Bichet, 1998).

Differential diagnosis

Polyuria is not pathognomonic for diabetes insipidus, and the physician must consider other conditions when a patient presents with excessive urination. Polyuria can reflect primary renal diseases, diuretic therapy, and diabetes mellitus. The cause can also be compulsive water drinking, also known as 'psychogenic' or 'primary' polydipsia. Such chronic excessive water drinking can lead to temporary loss of renal medullary hypertonicity, which then impairs urine concentration even when the drinking is temporarily interrupted and plasma ADH levels rise, resembling nephrogenic diabetes insipidus. Primary polydipsia is usually diagnosed in young women with known psychiatric disease; in rare patients, the cause is a structural lesion in the hypothalamus. It needs to be suspected particularly in polyuric patients who have hyponatremia, never caused by diabetes insipidus.

The physician evaluating a patient with polyuria must first exclude an osmotic diuresis, such as the glycosuria of diabetes mellitus. The history and routine laboratory findings can generally exclude diabetes mellitus, primary renal diseases, drug effects, and electrolyte disturbances. The degree of polyuria can vary, up to 16–18 litres a day in case of total lack of ADH. Special tests are needed for certain systemic diseases that affect renal interstitial function, for example, sickle cell disease, amyloidosis, multiple myeloma, and Sjögren's syndrome. It is important to remember that lithium can cause a transient and a permanent form of nephrogenic diabetes insipidus. Therefore, lithium exposure needs to be considered as a possible etiology even if the medication has been discontinued.

Most patients need a water deprivation test to confirm diabetes insipidus and to distinguish central from nephrogenic diabetes insipidus. Fluids and food are withheld, starting in the morning to avoid dangerous nocturnal dehydration. Over the next 4–8 hours, hourly measurements of urine and plasma should show increasing osmolality and a two- to four-fold greater increase in urine osmolality than plasma osmolality. When plasma osmolality exceeds 295 mosm/l or urine osmolality stops rising, blood is drawn for ADH level and patients are given aqueous ADH or its analogue dDAVP. In normal people, endogenous ADH is already maximally stimulated, so exogenous ADH does not cause further urine concentration. Patients with complete central diabetes insipidus do not concentrate their urine despite a rising plasma osmolality, but do respond to exogenous ADH with a rise in urine concentration. Patients with nephrogenic diabetes insipidus also maintain dilute urines despite dehydration, and when they receive exogenous ADH, their urine osmolality does not rise above that of plasma. In selected cases with partial diabetes insipidus, a short administration of hypertonic saline may be needed to reach a serum osmolality of 295 mosm/l.

When central diabetes insipidus is diagnosed, patients should have a MRI scan to check the hypothalamic and pituitary regions for the presence of tumour or infiltrative diseases.

Patients with primary polydipsia may be difficult to identify with the water deprivation test because chronic dilution

Table 57.8. Distinguishing primary polydipsia from diabetes insipidus (DI)

Feature	Primary polydipsia	Diabetes insipidus
Onset of polyuria	Gradual	Sudden
Nocturia	Unusual	Common
Random plasma osmolality	Sometimes <285 mOsm/l	Normal or elevated
Morning plasma osmolality	Normal	Elevated
Morning urine osmolality	Normal	Inappropriately low
Plasma ADH concentration	Normal relative to plasma osmolality	Low relative to plasma osmolality (in neurogenic DI)

of their renal medullary osmolar gradient can prevent them from responding properly to either endogenous or exogenous ADH. However, other features may distinguish primary polydipsia from diabetes insipidus (Table 57.8). Polyuria usually begins gradually in primary polydipsia, but suddenly in diabetes insipidus. Patients with primary polydipsia may not have much nocturia, but most patients with diabetes insipidus have a constant urine output. Compulsive water drinkers do not share the high plasma osmolality and inappropriately low urine osmolality seen after overnight fasting in patients with central or nephrogenic diabetes insipidus. Most patients with primary polydipsia have at least one random plasma sample documenting an osmolality below 285 mosm/l (dilutional hyponatremia). Plasma ADH levels are normal relative to plasma osmolality in patients with primary polydipsia, but are low in patients with central diabetes insipidus.

Management

Patients with mild diabetes insipidus may not need drug treatment as long as they have an intact thirst mechanism and free access to water. However, patients with diabetes insipidus who are temporarily deprived of water can quickly develop circulatory collapse and hypertonic encephalopathy. Treatment is usually indicated when urine volumes exceed 5 l per day or when nocturia interferes with restful sleep.

DDAVP (Desmopressin^{R}), a long-acting synthetic analog of ADH, is the treatment of choice for central diabetes insipidus. The drug is usually given orally (0.1–0.2 mg once or twice a day) or by nasal insufflation (10 μg/spray, 1–2 spray a day). Subcutaneous injections (1 μg SQ 1–2 times a day) are available for situations in which oral or nasal administrations are not possible. The dose–effect equivalence between oral, intranasal and SQ administration is approximately 1/10/200. If patients with partial central diabetes insipidus require treatment, many can be successfully managed with chlorpropamide, which augments ADH release and potentiates its action on renal tubular cells. Most patients with normal glucose tolerance can take chlorpropamide in the low dose required, without developing symptomatic hypoglycemia. Clofibrate and carbamazepine can also augment ADH release. During pregnancy the dose requirement of DDAVP may increase, due to vasopressinase produced by the placenta.

There is no good treatment for nephrogenic Dl. Some patients show a partial response to high doses of DDAVP, but most are treated with volume contraction (thiazide diuretics) to decrease glomerular filtration rate.

Syndrome of inappropriate secretion of ADH (SIADH)

Differential diagnosis

Excessive secretion of ADH, termed the 'syndrome of inappropriate secretion of antidiuretic hormone' (SIADH), leads to excessive water retention and hyponatremia. SIADH is the most common cause of non-iatrogenic hyponatremia. The major causes of SIADH are ectopic secretion of ADH (e.g. by a small cell carcinoma), neurologic disorders, pulmonary diseases, and certain drugs (Table 57.9). Cardinal features of the syndrome are hyponatremia and serum hypo-osmolality resulting from an inappropriately concentrated urine.

Patients with mild SIADH may have few symptoms and signs, especially if hyponatremia develops slowly. But when the serum sodium falls below 130 meq/l, patients can become anorexic, lethargic, and confused, with nausea and muscle cramping. When the serum sodium falls below 115 meq/l, patients can become obtunded and develop seizures. The severity of symptoms generally corresponds to the degree of hypo-osmolality and the rate at which hyponatremia develops. Premenopausal women seem to be more sensitive to rapid fluxes in serum sodium than are men and postmenopausal women and have a higher risk of permanent neurologic damage following hyponatremic encephalopathy.

Table 57.9. Common causes of the syndrome of inappropriate secretion of antidiuretic hormone

1. Central nervous system diseases
Meningitis
Encephalitis
Brain abscess
Subarachnoid hemorrage
Postoperative (5–7 days after pituitary surgery)
2. Pulmonary diseases
Lung abscess
Pneumonia
Positive pressure ventilation
3. Tumours
Lung carcinoma (especially small cell)
Gastrointestinal malignancies
Prostate cancer
Thymoma
Lymphoma
4. Drugs
Vincristine
Chlorpropramide
Narcotics
Clofibrate
Carbamazepine
Nicotine
Phenothiazine
Cyclophosphamide

Hyponatremia is the most common form of electrolyte abnormality in hospitalized patients. Other causes of hyponatremia must be considered in the differential diagnosis of SIADH. Sodium may be falsely low ('pseudohyponatremia') in case of severe hypertriglyceridemia or marked increase in serum protein concentration. Hyperglycemia can cause hyponatremia by attracting free water in the extracellular space. Plasma glucose will generally decrease plasma sodium concentration by 1.6 meq/l for every 100 mg/dl increase in glucose above 100 mg/dl. The physician should determine clinically whether hyponatremic patients are euvolemic (normal water volume), hypervolemic, or hypovolemic. Although patients with SIADH do have modest volume expansion, they are not edematous. In patients with edema, the physician should consider the major causes of hypervolemic hyponatremia such as liver cirrhosis, heart failure, and kidney failure. Patients with glucocorticoid or thyroid hormone deficiencies can develop hyponatremia because these hormones are essential for normal renal tubular function and free water excretion by the kidney. Thus, the diagnosis of SIADH cannot be established until hypothyroidism has been excluded by measurement of the serum free T4 and TSH concentrations, adrenal insufficiency has been excluded, and kidney disease has been excluded by renal function tests. The physician should also seek a history of medications (chlorpropramide, carbamazepine, vincristin), neoplasia, pulmonary disease, and neurologic disorders known to be associated with SIADH.

In SIADH, urine sodium is generally above 20 meq/l, but it is usually below 20 meq/l in conditions with intravascular volume contraction or decreased effective plasma volume, for example, congestive heart failure, cirrhosis, and the nephrotic syndrome (Chung et al., 1987). The blood urea nitrogen and uric acid are low in SIADH but high in volume-contracted states. Lastly, in SIADH the urine is less than maximally dilute (50–100 mosm/kg) despite plasma hypo-osmolality. Occasionally the water load test helps the diagnosis of SIADH. After drinking 20 ml/kg of water, normal individuals reach maximally diluted urine ($<$100 mosm/kg) and eliminate 80–90% of the water load within 4 hours. This test should not be performed if serum sodium is $<$125 meq/l.

Management

The aims of treating SIADH are to correct hypo-osmolality and hyponatremia, and to diagnose and, when possible, treat the underlying disorder. It is important to understand that the brain can adapt to hyponatremia by releasing osmoles, provided that it develops slowly. Therefore, it is not unusual to find patients with marked hyponatremia who are absolutely asymptomatic. For the asymptomatic patient, water restriction to 500–1000 cc a day corrects hyponatremia at a rate of about 5 meq/l a day. Infusions of normal saline do not correct hyponatremia because the sodium is promptly excreted in the urine. Only symptomatic hyponatremia is treated with hypertonic saline (3% NaCl) until the serum sodium concentration reaches 125 meq/l (Verbalis & Martinez, 1991). An approximate way of calculating the rate (cc/hour) of hypertonic solution infusion is to multiply the ideal body weight by the desired hourly increase in serum sodium concentration. In a 70 kg patient, if an increase of 0.5 meq/l/hour is desired, the rate of infusion should be $70 \times 0.5 = 35$ cc/hour. Serum osmolarity should not be corrected faster than 12 meq/l in 24 hours, because of risk of potentially fatal central pontine myelolysis. Therefore, plasma sodium level should be monitored very closely during hypertonic solution infusion. Once a level of 125 is reached, hyptertonic solution should be discontinued and plasma osmolality is restored gradually by water restriction alone. For many patients with chronic SIADH in whom hyponatremia cannot be controlled with fluid restriction only, deme-

clocycline normalizes serum sodium by inhibiting ADH action in the kidney. Lithium carbonate acts similarly but is rarely used because it can be more toxic.

Fluid abnormalities after pituitary surgery

Manipulation of the pituitary gland during transphenoidal or transcranial pituitary surgery may cause transient or permanent abnormalities in ADH production, leading to diabetes insipidus or hyponatremia. Although a classical triphasic pattern is often reported when the posterior pituitary is permanently damaged (with transient diabetes insipidus followed by a SIADH phase and ultimately by permanent diabetes insipidus) the possible patterns are way more variable. In a large analysis of 1571 transphenoidal pituitary surgery done by Hensen et al. (1999) the classical triphasic pattern was observed only in 1.1% of patients. However, 8.4% developed hyponatremia (symptomatic in 2.1%) at some point during the first 10 postoperative days. Patients with Cushing's disease seem to have a particular high prevalence of polyuria and hyponatremia, and should be monitored particularly closely.

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Part VII

Headache and pain

58

Peripheral nociception and genesis of persistent pain

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Pain can be divided into two distinct categories, nociceptive and clinical. The detection of, or reaction to damaging or noxious stimuli, the phenomenon of nociception, is mediated in the periphery by highly specialized primary sensory neurons, the nociceptors. These have peripheral terminals that are activated only by high intensity mechanical, thermal and chemical stimuli. Nociceptive pain, the 'ouch' pain typically experienced on touching a hot object or stubbing a toe, is the readout from a protective system fundamental to maintaining bodily integrity in a potentially lethal environment. The key physiological role of this system is well illustrated by the tissue destruction produced both in the denervated (Charcot) joints and neuropathic ulcers in diabetic patients, or in the mutilating injuries seen in patients with congenital insensitivity to pain due to a loss of nociceptor sensory neurons during development, as a result of a mutation of the TrkA receptor (Indo et al., 1996). Nociceptive pain contributes to the pain associated with the onset of acute trauma and is amenable to a variety of therapies that directly target the nociceptor neuron. These include blocking input to the spinal cord with local anesthetic nerve blockade, epidural or spinal anesthesia or reducing transmission from the nociceptor to the CNS with high dose opioids.

Clinical pain has two general manifestations, that associated with tissue injury and inflammation, inflammatory pain, and that generated as a result of damage to the nervous system, neuropathic pain. Multiple distinct, but commonly coexisting pathophysiological mechanisms are responsible for the generation of clinical pain and these typically involve the recruitment of pain in response to sensory inputs other than just nociceptors (the pain is no longer purely nociceptive). Clinical pain, is moreover, the manifestation of profound alterations in sensory processing within the peripheral and central nervous systems, neuroplasticity. Two key features of clinical pain are that the pain may present in the absence of any obvious peripheral stimulus (spontaneous pain) and that there is typically an abnormal hypersensitivity to applied innocuous and noxious stimuli. Clinical pain can arise from insults to, or changes induced anywhere along, the somatosensory neuraxis from the peripheral innervation targets (as with osteo- or rheumatoid arthritis), in inflammatory pain, along peripheral nerves (postherpetic neuralgia and diabetic neuropathy), in the spinal cord (spinal cord injury) or the brain (stroke), for neuropathic pain. The aim of clinical pain treatment is the elimination of spontaneous pain and the normalization of sensibility, rather than the elimination of pain perception *per se*, but this can be achieved optimally only if the mechanisms responsible can be identified in individual patients and if treatments specific to each mechanism are available. At the moment, however, standard clinical techniques do not enable pain mechanisms to be unambiguously established, nor are there treatments suitable for each mechanism. Accelerating progress in the study of pain makes such a rational approach a realistic possibility for the near future, one that will require, however, considerable effort to translate molecular advances into new clinical diagnostic approaches and therapies. The aim of this chapter is to highlight the advances in our understanding of pain mechanisms and their clinical implications.

Primary sensory neurons and the dorsal horn

Sensory neurons are a heterogeneous group of neurons whose cell bodies are located within the dorsal root and trigeminal ganglia, and which have either myelinated A, or unmyelinated C, axons (Lawson, 1979). Making up approximately two-thirds of the population are the C-fibre neurons, the majority of which are nociceptors (some are

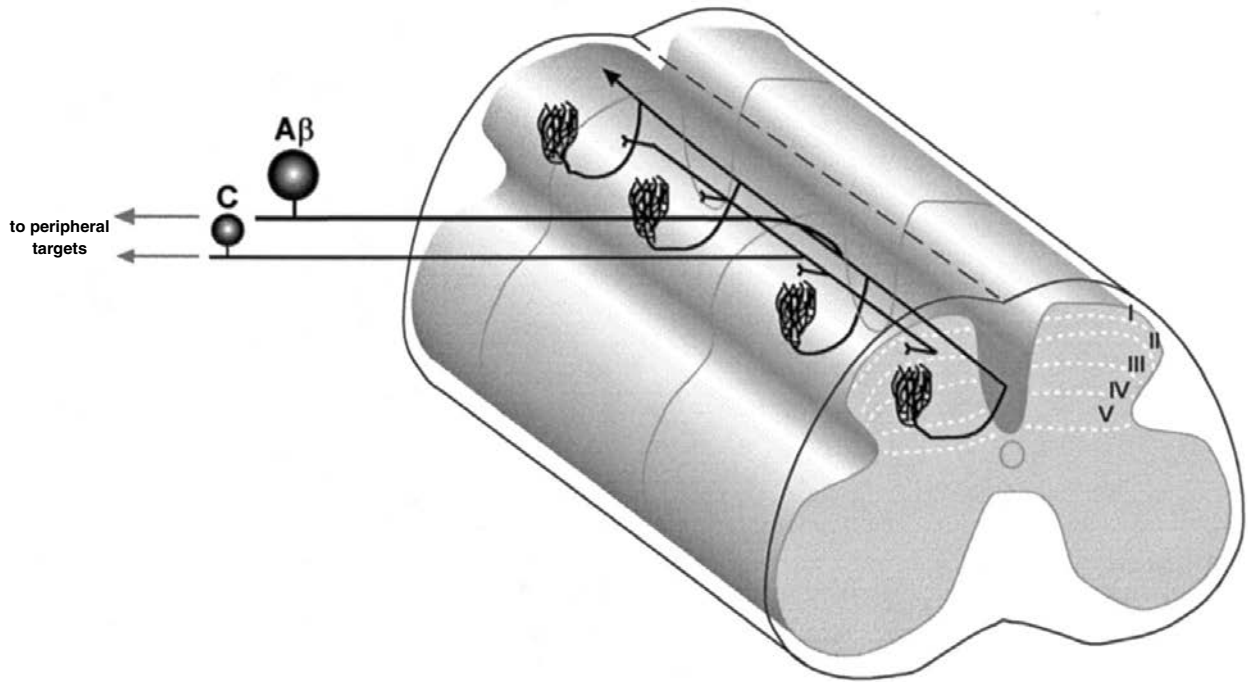

Fig. 58.1. Diagram showing Aβ- and C-fibre central axons entering the spinal cord. C-fibres synapse directly in the superficial dorsal horn. Aβ-fibre central axons enter the ipsilateral dorsal column pathway to travel up to the brain, synapsing in the dorsal column nuclei within the medulla. In addition, they give off multiple collateral axons that synapse within the deep dorsal horn over a few spinal segments.

innocuous warm receptors) (Willis & Coggeshall, 1991). Although some nociceptors are modality-specific, most are polymodal, responding to thermal, mechanical and chemical stimuli (Willis & Coggeshall, 1991). In addition, some are silent, unresponsive to all stimuli even at a very high intensities, but become active under pathological conditions, e.g. during inflammation (McMahon & Koltzenburg, 1990). The remaining sensory neurons (~30–40%) are the A-fibres, which are larger and are classified into three groups: the thinly myelinated Aδ fibres, which are predominantly nociceptive but include cool detectors; the myelinated Aβ fibres, many of which are cutaneous mechanoreceptors responsible for the detection of vibration, pressure and brush; and the large myelinated Aα fibres innervating muscle spindles and golgi-tendon organs, responsible for proprioceptive afferent input (Bonica, 1990).

The central terminal projections of primary sensory neurons in the dorsal horn of the spinal cord are highly ordered rostrocaudally, mediolaterally and dorsoventrally to form a somatotopic map of the body surface with minimal overlap between adjacent nerves (Willis & Coggeshall, 1991). C-fibres synapse directly onto second-order neurons in the ipsilateral dorsal horn either at the same spinal level that they enter the cord or within a few segments rostrocaudally. A-fibre central axons on entering the spinal cord via a dorsal root give off collateral axons to the dorsal horn before entering the dorsal column pathways and ascending to the brainstem (Fig. 58.1). Dorsoventrally, specific types of afferent innervate cytoarchitectonically distinct laminae in the dorsal horn. Aδ-fibres project to laminae I and V, Aβ-fibre collaterals project to the deeper dorsal horn laminae (III-V, with some input to lamina II inner (II_i)), while C-fibres project to lamina II. Lamina II outer (II_o), is therefore, innervated almost exclusively by C-fibres (Woolf, 1994) (Fig. 58.2(a), see colour plate section). In addition to producing excitation of pain projection pathways, afferent input also activates segmental inhibitory interneurons which feed back onto the projection neurons in a reciprocal arrangement to dampen down and functionally focus the effect of the input (Woolf, 1994) (Fig. 58.3(a)).

The spinal cord is the site of the first relay along the sensory neuraxis at which the transfer of sensory information can be controlled. The dorsal horn also receives descending innervation from brainstem regions like the periaqueductal grey via the raphe nuclei and locus ceruleus. These tonic and phasic inputs are both excitatory (e.g.

5HT) and inhibitory (e.g. NA and opioids) and act to modulate spinal transmission through the dorsal horn. In this way the amount and nature of sensory input transferred to the brain following a particular stimulus can be either facilitated or inhibited altering the relationship between peripheral stimulus and perceptual response. This form of sensory adaptability was a key feature of Melzack & Wall's gate control theory of pain (1965) and both increased facilitation and reduced inhibition have been implicated in persistent pain states.

Primary sensory neurons can be classified on the basis of their chemical phenotype (i.e. what genes they express). Sensory neuron phenotype is thought to be actively maintained by signalling molecules extrinsic to the neuron, such as growth factors expressed by cells in the peripheral targets and Schwann cells lining the axons (McMahon & Bennett, 1999), and molecules intrinsic to the neurons such as cell specific transcription factors (Wood et al., 1999). For unmyelinated C-fibres, one major phenotypic distinction made is that between peptidergic and non-peptidergic afferents, each forming approximately half of the population. The former express neuropeptide neuromodulators (e.g. SP, CGRP) while the latter do not. The former also express the high affinity NGF receptor TrkA, while the latter express the GDNF receptor binding complex and the $P2X_3$ purinoreceptor (McMahon & Bennett, 1999). The NGF and GDNF sensitive nociceptor populations terminate in laminae I / II_o and II_i respectively (Snider & McMahon, 1998) (Fig. 58.2(b), see colour plate section).

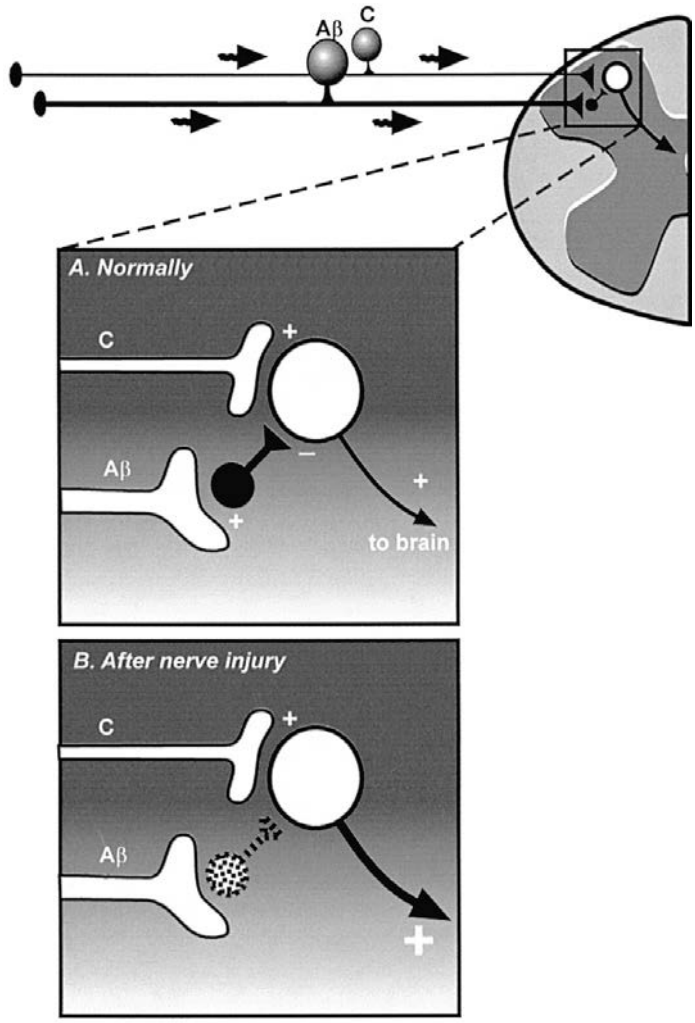

Fig. 58.3. (*a*) A noxious stimulus leads to the activation of both A- and C-fibres. C-fibres make monosynaptic connections with some spinal neurons that may also receive polysynaptic input from A-fibres that is relayed through an inhibitory interneuron (some Aβ input may also be relayed via excitatory interneurons). Thus, noxious input to spinal projection neurons through C-fibres is controlled to a certain extent by A-fibre activity. The inhibitory input acts to dampen down and functionally focus the effects of the C-fibre input. (*b*) Following nerve injury, many inhibitory interneurons in lamina II die leading to disinhibition of spinal projection neurons manifesting as increased excitation with a greater level of information being transferred to higher centres.

Activation: transduction, transmission and use-dependent augmentation

Primary nociceptor activation

For most of the time the 'protective pain system' lies quiescent, being activated only on exposure to damaging or potentially damaging events. The detection by nociceptors of noxious stimuli is the consequence of their selective expression of specialized transducer molecules, that when activated result in the opening of cation channels and the generation of inward currents at the peripheral terminal. Examples of these molecules are: the VR1 receptor for capsaicin (the active ingredient in chilli peppers), an ion channel that opens in response to heat (>42 °C); VRL1, another vanilloid receptor also activated by heat but at higher temperatures (>50 °C) (Caterina & Julius, 1999); chemosensitive molecules like $P2X_3$ purinoreceptors that detect ATP (released during tissue damage) and proton-gated ion channels like ASIC (acid-sensing ion channel) which respond to tissue acidosis (Wood et al., 1999); and molecules that transduce mechanical stimuli, candidates for which are the mDEG ion channels which are homologues of the degenerins, mechanotransducer proteins in the nematode *Caenorhabditis elegans* (Wood et al., 1999).

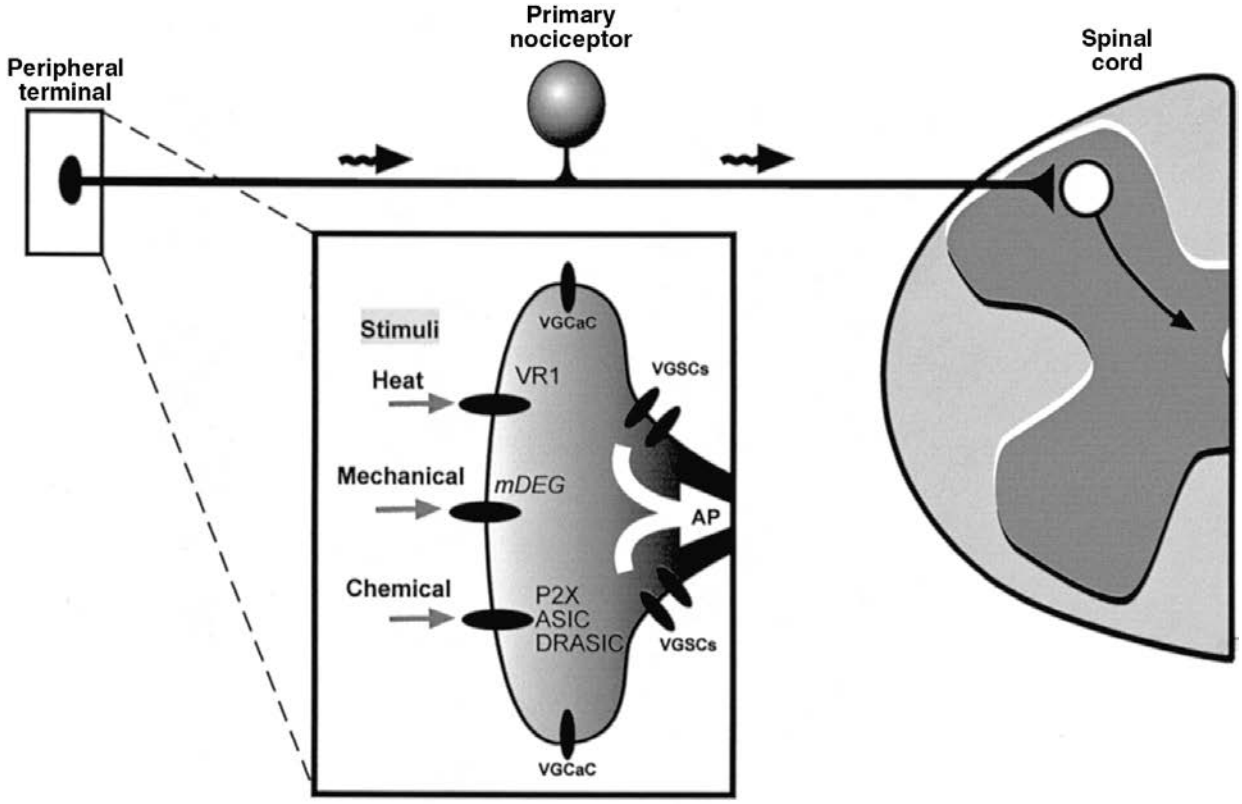

Fig. 58.4. Primary nociceptors responding to different stimulus modalities through the expression of specific transducer proteins on their peripheral terminal membranes. Activation of these proteins leads to the generation of inward currents that further activate voltage gated sodium channels (VGSCs). If stimulus intensity is sufficient to reach activation threshold, action potentials are generated and conducted orthodromically along the axon to the spinal cord. This represents pain normosensitivity.

Once specific transducer receptor/ion channels proteins are activated, depolarization of the nociceptor terminal by cation influx (the generator potential) activates voltage-gated sodium channels (VGSCs) in the terminal axon (Fig. 58.4). VGSCs are responsible for generating the upward phase of the action potential and in sensory neurons can be divided into two types based upon sensitivity to the puffer fish poison tetrodotoxin (TTX), either sensitive (TTXs) or resistant (TTXr) (Gold, 1999). TTXs sodium channels (there are up to six such channels in DRG neurons, most of which are expressed elsewhere in the CNS as well) play a major role in action potential conduction along the axon and are expressed by all sensory neurons. They are inserted into the membrane along unmyelinated axons or selectively at nodes of Ranvier along myelinated axons, mediating fast saltatory conduction (Waxman & Ritchie, 1993) (Fig. 58.5(a), see colour plate section). The TTXr channels, two of which have been cloned (SNS and SNS2) are however, expressed selectively by nociceptors and their electrophysiological properties are thought to mediate specific functional features of these neurons. For example, TTXr channels have higher activation and inactivation thresholds along with a rapid recovery when compared to TTXs channels, allowing them to remain active during sustained depolarization, a specific feature of nociceptor function (Bevan, 1999). The TTXr channels are likely to contribute both to the generator potential of nociceptors as well as to action potential conduction (Quasthoff et al., 1995).

The threshold of individual transducer proteins in the peripheral nociceptor terminal can be altered by prior activation, as with repetitive peripheral stimuli, an example of activation-dependent plasticity or autosensitization (Woolf & Salter, 2000). Such a lowering of threshold is observed in response to repeated thermal activation of the VR1 receptor producing a drop from 42 °C to about 38 °C and reverses rapidly. Similar thermal threshold changes for the VR1 receptor also occur after capsaicin or proton activation of the receptor. The increased sensitivity may be mediated either by conformational changes or by phos-

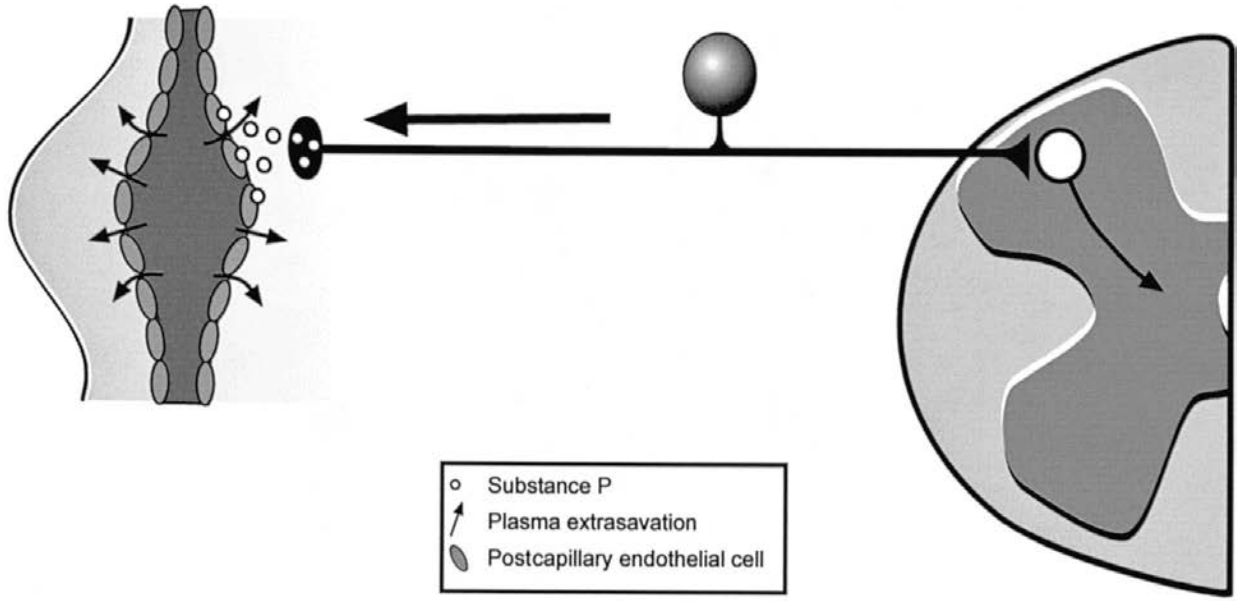

Fig. 58.6. Antidromic conduction of action potentials along nociceptor axons leads to the release of peptides such as CGRP and Substance P into the skin. These molecules bind to receptors on endothelial cells to cause vasodilatation and increase permeability leading to plasma extrasavation. This is known as neurogenic inflammation.

phorylation following calcium entry through the channel, which will activate intracellular kinases.

The selective expression of nociceptor-specific molecules such as VR1 has been exploited by clinicians for treatment targeted at the nociceptor. Topical capsaicin cream has been used to treat postherpetic neuralgia and painful diabetic neuropathy. Initially it results in nociceptor activation (through activation of the VR1 receptor), producing a burning sensation. However, with repeated application over days, the heightened pain is followed by a reduction in sensitivity, a consequence of nociceptor peripheral terminal degeneration that lasts for approximately 4–6 weeks and is thought to be due to prolonged calcium influx (Simone et al., 1998).

Local anesthetic nerve block produces a more rapid and reversible method of blocking primary nociceptor input, but sodium channel blockers such as lignocaine or bupivicaine are both non-selective (motor, sympathetic and proprioceptive sensory axons are also blocked) and limited by their cardiac and central nervous system side effects (they block all sodium channels in a use-dependent fashion). The recent identification of sensory neuron specific sodium channels offers the possibility for the development of highly selective nociceptor blockers/antagonists that will avoid unwanted side effects.

In addition to orthodromic action potentials moving from the peripheral terminal towards the spinal cord, C-fibres can conduct action potentials antidromically, i.e. from the spinal cord towards the periphery. This is important in producing neurogenic inflammation, where antidromic C-fibre activation causes the release of CGRP and SP from the peripheral terminals, acting on postcapillary venules to produce peripheral vasodilatation and increased capillary permeability respectively (Fig. 58.6). The exact role of neurogenic inflammation is controversial but it has been implicated in pain states, such as migraine, asthma, and arthritis as well as wound healing (Raja et al., 1999). It has also been suggested as a potential mechanism for the trophic skin and nail changes in Reflex Sympathetic Dystrophy (RSD)/Causalgia (Complex Regional Pain Syndrome type II) (Devor & Seltzer, 1999). It is not clear how this antidromic activation occurs; one possibility is that the central terminals of C-afferent fibres are depolarized by presynaptic axo-axonic synapses in the spinal cord, as part of presynaptic inhibition, and this can cause a backfiring of action potentials. Antidromic action potentials also occur as part of the axon reflex producing the flare response (Simone et al., 1998). This process is almost entirely absent in animals with a null mutation in genes for either Substance P or its receptor NK1, suggesting that this is a Substance P mediated phenonemon amenable to treatment with newly developed highly selective tachykinin antagonists (Woolf et al., 1998).

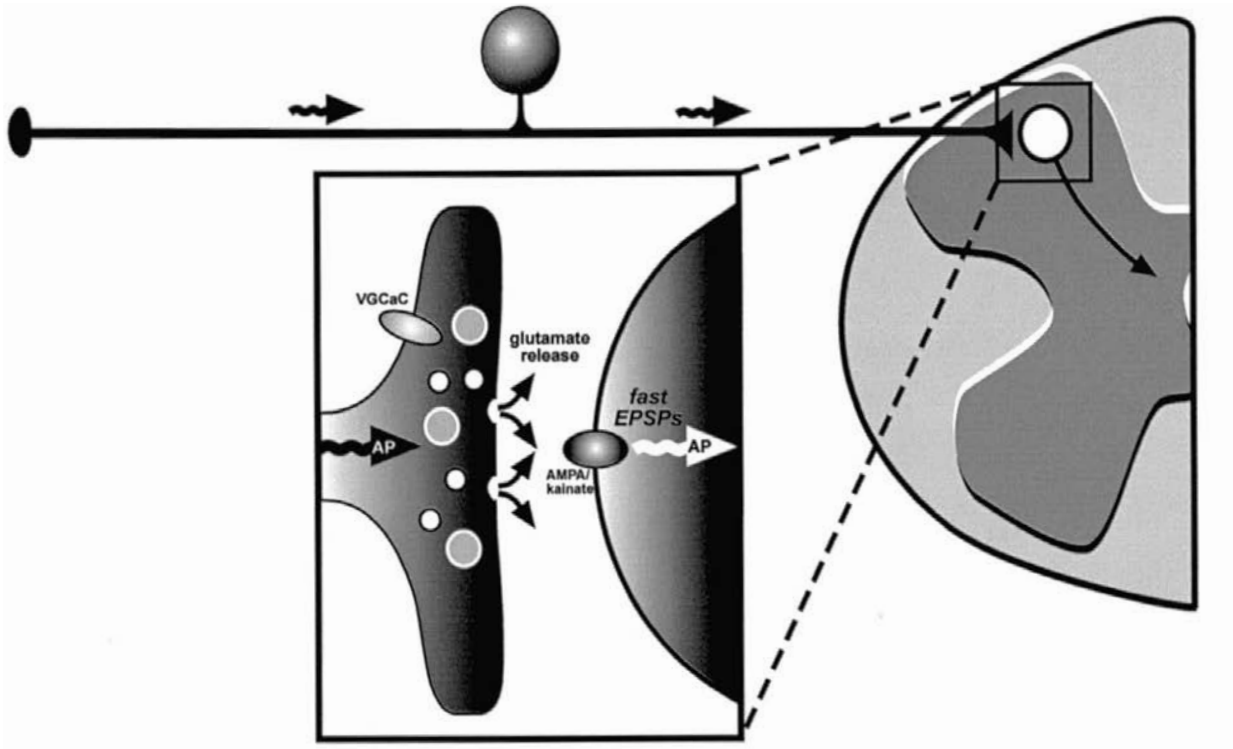

Fig. 58.7. Nociceptor activation leads to the release of glutamate, from primary afferent axon central terminals, that binds postsynaptically to AMPA receptors. If stimulus intensity is sufficient, action potential activation threshold is reached and the spinal projection neuron fires.

Activation of central pain pathways

Primary nociceptor activation leads to the propagation of action potentials to the spinal cord (the frequency of which codes for the intensity of the stimulus (Raja et al., 1999), where they invade central presynaptic terminals to elicit neurotransmitter release. Expressed upon the presynaptic terminal membrane are many different receptors for neurotransmitters/modulators whose activation (both as autoreceptors and from axo-axonic synapses) can alter intracellular calcium levels and the degree of transmitter release from the terminal, e.g. excitatory receptors such as the ionotropic glutamate receptors AMPA, kainate and NMDA, the metabotropic glutamate receptor mGluR, the NK1, P2X3, α_2-adrenoreceptors, 5-HT receptors, ACh_N receptors, EP (prostaglandin) receptors, and receptors which inhibit transmitter release, particularly those for GABA, adenosine and the opioids. A reduction in transmitter release is one of the major mechanisms underlying the analgesic actions of opioids.

Terminals of nociceptor neurons contain two types of synaptic vesicle, small clear glutaminergic vesicles, and large dense-core peptidergic vesicles (containing SP, BDNF, CGRP, etc). Terminal depolarization, with the influx of calcium through high threshold voltage dependent channels (e.g. N-type) results in the fusion of vesicles with the pre-synaptic membrane and the release of transmitters into the synaptic cleft. N-type calcium channels are inhibited by Ω-conopeptides which reduce inflammatory and neuropathic-related allodynia and hyperalgesia without affecting normal nociceptive responses (Vanegas & Schaible, 2000). The Ω-conopeptides have, however, a narrow therapeutic index and are associated with significant motor and sympatholytic side effects which limit their clinical use.

Following brief, noxious stimulation, spinal nociceptive transmission is mediated mainly, if not exclusively by glutamate released from small clear vesicles acting on AMPA and kainate receptors on postsynaptic dorsal horn neurons to produce fast excitatory post-synaptic potentials (EPSPs) (Yoshimura & Jessell, 1990). Much of this postsynaptic activity is subthreshold, but if stimulus intensity is sufficient, action potentials are generated and the spinal neuron fires at a discharge frequency that is linearly related to stimulus intensity (Fig. 58.7). It is this activity that signals the onset, intensity, and duration of transient

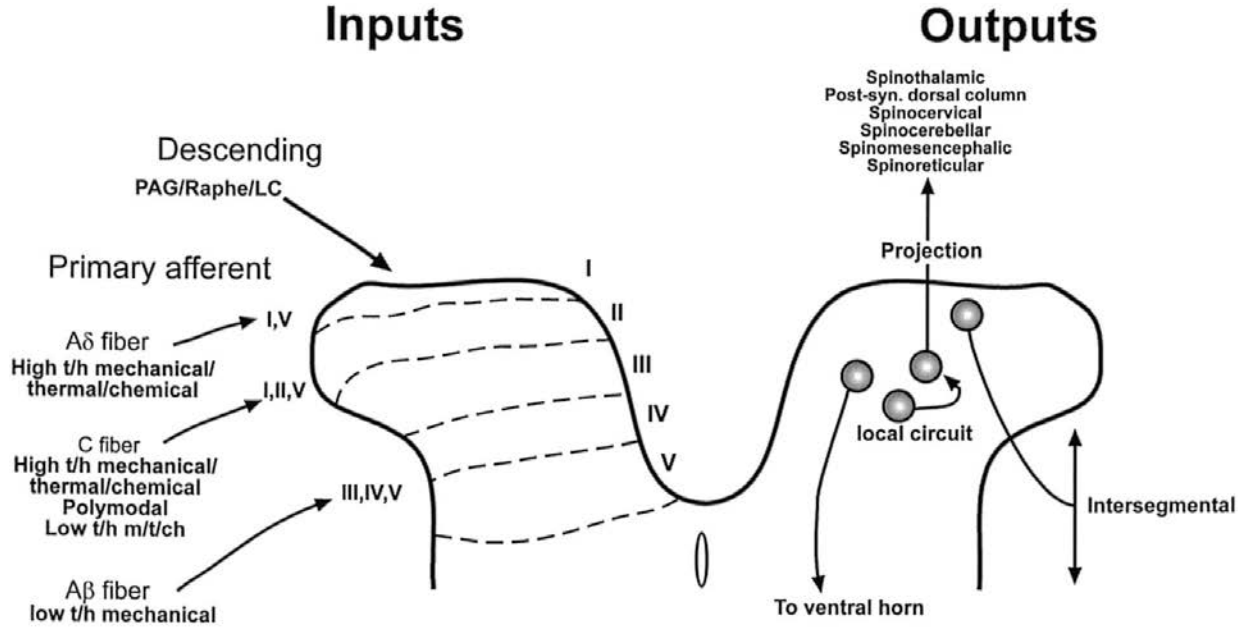

Fig. 58.8. A schematic diagram showing the major sources of inputs into and outputs from the dorsal horn.

noxious stimuli. Spinal neurons are a heterogeneous population often divided into those responding with an action potential output in response only to nociceptor input (nocispecific cells) situated predominantly within superficial regions of the dorsal horn, or those responding to C-, Aδ- and Aβ-fibre inputs, the non-nocispecific (also known as wide dynamic range) cells typically situated in deeper dorsal horn laminae. The electrophysiological properties of dorsal horn neurons are not fixed, however, and change dramatically under different situations such as after a sustained noxious stimulus, after nerve injury or in response to altered descending modulatory inputs. A nocispecific cell may, following a prolonged C-fibre input that induces increased membrane excitability and the recruitment of previously sub-threshold (e.g. Aβ) inputs, become a non-nociceptive specific cell. Similarly, a non-nociceptive cell may become unresponsive to Aβ input if descending modulatory inhibitory inputs increase following electrical stimulation of brain stem nuclei or pharmacologically with morphine (Fields & Basbaum, 1999).

Most neurons in the superficial dorsal horn that project to the thalamus via the spinothalamic tract express the NK1 (Substance P) receptor (Nichols et al., 1999). Neurons that project axons to the brain through the dorsal columns are implicated in visceral pain transmission. Some propriospinal neurons project a few segments along the spinal cord, allowing for the polysynaptic transfer of sensory input to the brain, a pathway implicated in somatosympathetic reflexes, and others project locally/segmentally, forming local excitatory and inhibitory networks (Fig. 58.8). Thus, although the anterolateral spinothalamic tract is sometimes referred to as the 'pain pathway', there actually exist multiple pathways by which primary nociceptor inputs are transferred to the brain. This is seen in patients suffering from chronic pain who, having been rendered 'analgesic' by an anterolateral cordotomy, commonly have their pain return after a period of months (Tasker, 1990). A 'twenty-first century' update of surgical anterolateral cordotomy, recently tested in animals, uses intrathecal infusion of a toxin conjugated to substance P. The substance P toxin conjugate, on binding to NK1 receptors on lamina I spinothalamic tract neurons, and following internalization, selectively kills only these cells (Nichols et al., 1999).

High frequency nociceptor activation following intense or prolonged noxious stimuli leads to the co-release, with glutamate, of neuromodulators such as SP, CGRP and BDNF, possibly controlled by intracellular calcium concentrations (Cao et al., 1998). The corelease of peptides/proteins results in the production of slow synaptic potentials due to activation of ionotropic (AMPA/kainate) and metabotropic (e.g. mGluR, NK1) receptors as well as the NMDA receptor (which at resting membrane potential is blocked by magnesium but opens during depolarization). These slow potentials last for seconds to minutes and have the potential to summate temporally, such that a repetitive noxious stimulation at $>$0.5 Hz produces a progressively

greater postsynaptic response (a cumulative depolarization), which is further augmented by the activation of postsynaptic voltage dependent calcium-activated cation channels. The increased action potential discharge that results is known as wind-up and is an example of spinal autosensitization and represents a short-lasting mechanism for boosting pain transmission. Psychophysical correlates of wind-up can be shown in humans both after repeated heat stimuli and in patients suffering from neuropathic pain (Arendt-Neilsen et al., 1995).

Modulation: reversible alterations in pain processing

The hypersensitivity that accompanies peripheral inflammatory disease or nervous system lesions arises as a consequence of alterations in sensory processing. These alterations can be divided into two mechanistic categories: modulation, a reversible alteration in primary and secondary nociceptor function, brought about by post-translational changes in specific signalling molecules (e.g. through phosphorylation) and modification, longer-term potentially irreversible changes in signalling within the sensory system, involving altered gene expression, neuronal and non-neuronal cell death and the structural reorganization of peripheral terminals and of interneuronal connectivity in the spinal cord (Woolf & Salter, 2000).

Modulating the sensitivity of primary nociceptors

The threshold at which nociceptors are activated determines basal pain sensitivity, the point at which neural activation may lead to the sensation of pain. Inflammatory pain is associated with an increase in nociceptor terminal membrane excitability, increasing basal sensitivity by reducing the activation threshold (enabling normally innocuous inputs to activate the terminal) and increasing suprathreshold responses of the nociceptor terminal to noxious stimuli (peripheral sensitization). This phenomenon accounts for the hypersensitivity to chemical and thermal stimuli at the site of tissue damage in inflammatory pain, but less so for mechanical hypersensitivity, which is largely a central phenomenon.

Peripheral sensitization occurs as a consequence of the local action of inflammatory mediators on the nociceptor terminal. Tissue injury results in the release of ATP and protons from damaged cells, 5-HT and histamine from mast cells, cytokines like TNF and IL-1 from macrophages, prostaglandins, bradykinin and growth factors like NGF and LIF (Woolf & Costigan, 1999) (Fig. 58.9). Some of these mediators (ATP, bradykinin) can directly activate the terminal eliciting pain, others (NGF, PGE_2) do not activate the terminal but sensitize it. The low levels of NGF produced normally in the target tissue maintain normal basal sensitivity to thermal stimuli (Bennett et al., 1998), but increased NGF increases pain sensitivity (Lewin & Mendell, 1993), which has limited its use as replacement therapy for neuropathies in humans. NGF does not directly depolarize the terminal but sensitizes it, on activation of its tyrosine kinase TrkA receptor, to subsequent thermal and chemical input, both through a short latency (seconds) effect on the VR1 receptor (Shu & Mendell, 1999) as well as slower onset changes (>6 hours) in the level of gene expression in the DRG following retrograde transport of the internalized NGF-TrkA complex to the cell body.

Other peripheral sensitizing agents include prostaglandins particularly PGE_2, 5-HT and adenosine, which activate protein kinase A (PKA), and noradrenaline and bradykinin, which activate PKC (Woolf & Costigan, 1999). The predominant mechanism responsible for peripheral sensitization is phosphorylation of membrane bound receptors and ion channels in the peripheral terminal by the kinases PKC and PKA. Activation of PKC results, for example, in phosphorylation of the TTXr sodium channel SNS/PN3, enhancing nociceptor excitability by increasing the inward current produced by any depolarizing stimulus (Gold, 1999). A similar phosphorylation of the VR1 receptor is likely. Although many PKC isoforms are expressed by primary nociceptors, the PKC′ isoform plays a pivotal role in bradykinin (BK), noradrenaline and heat-induced hypersensitivity without involvement in normal nociceptor activation (Cesare et al., 1999).

The molecules that contribute to the generation of this modulation of nociceptor terminal excitability represent potential targets for the development of antihypersensitivity/analgesic treatments for inflammatory pain which could be aimed at reducing the build up or action of inflammatory mediators (IL-1 / TNFα neutralizing antibodies or fusion proteins, NSAIDs, bradykinin antagonists, NGF antibodies/fusion proteins) or kinase inhibitors that block the phosphorylation of nociceptor signalling molecules. The use of cyclo-oxygenase (COX) inhibitors to treat inflammation by reducing prostaglandin synthesis is central to the current management of conditions like rheumatoid arthritis and the introduction of highly selective COX-2 inhibitors (the inducible cyclo-oxygenase isoform) designed to avoid the gastrointestinal and other side effects of COX-1 inhibitors (the constitutive isoform) has been a major advance.

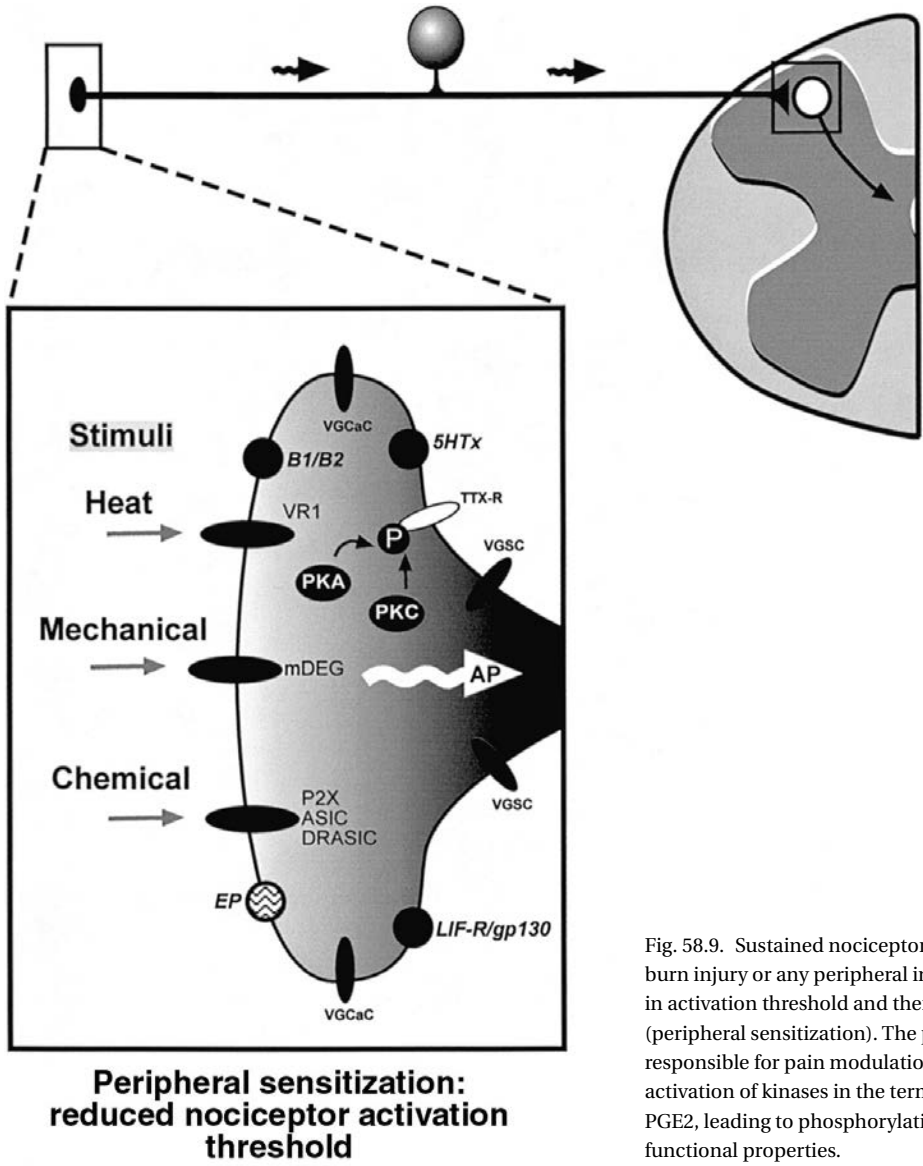

Fig. 58.9. Sustained nociceptor activation such as following a burn injury or any peripheral inflammation leads to a reduction in activation threshold and thereby to pain hypersensitivity (peripheral sensitization). The predominant mechanism responsible for pain modulation in primary nociceptors is activation of kinases in the terminal by sensitizing agents such as PGE2, leading to phosphorylation of ion channels, altering their functional properties.

Peripheral sensitization predominantly contributes to local hypersensitivity where there is local inflammation. In some patients with nerve lesions, however, an increased nociceptor terminal excitability has been detected clinically, particularly in a subgroup of patients with postherpetic neuralgia who can be identified by a reduction in thermal pain threshold at the site of their lesions (Fields et al., 1998). This has led to the recent development of lignocaine patches that can be applied directly to painful areas, limiting systemic action, and these have been used to treat that subtype of postherpetic neuralgia where 'irritable (overactive) nociceptors' are implicated (Fields et al., 1999).

Modulating central pain pathways:

If the intensity/duration of nociceptor input to the spinal cord increases beyond a critical threshold, in addition to the direct fast activation of the dorsal horn neurons during the input, a long-lasting facilitation of sensory transmission occurs in the spinal cord, which is known as central sensitization (Woolf, 1983). Central sensitization manifests as a reduction in the threshold of activation of the dorsal horn neurons, an increase in their receptive field size and an increased response to suprathreshold inputs and is due to a maintained increase in synaptic efficacy. This contributes,

with peripheral sensitization, to primary hyperalgesia but is exclusively responsible for the abnormal sensitivity to noxious and innocuous inputs to uninjured tissue adjacent to the site of injury, such as the production of pain on activation of low threshold Aβ fibres (tactile allodynia) and Aδ fibre mediated pin-prick hyperalgesia. In common with peripheral sensitization, this form of central modulation occurs as a consequence of the activation of specific intracellular signal transduction molecules that post-translationally modify receptors and ion channels, but in this case, on the postsynaptic membrane of dorsal horn neurons. This post-translational processing increases membrane excitability such that the stimulus–response relationship of the neuron is augmented, increasing the spinal response to both innocuous and noxious inputs.

The AMPA and NMDA glutamate receptors expressed on dorsal horn neurons are crucial to this functional synaptic plasticity, which may occur either at the activated synapse (homosynaptic facilitation) or spread to neighbouring synapses (heterosynaptic facilitation). Homosynaptic facilitation of spinal AMPA receptor-mediated responses to nociceptor inputs is thought to occur via a mechanism similar to long-term potentiation in CA1 hippocampal neurons. Brief high frequency (100 Hz) inputs lead to the summation of fast AMPA-mediated EPSPs that release the NMDA receptor magnesium block, increasing channel opening and intracellular calcium levels postsynaptically. Calcium-activated kinases, e.g. calcium/calmodulin dependent kinase II (CaMKII) or PKC can then phosphorylate the AMPA receptor on serine or threonine residues increasing AMPA mediated postsynaptic activity for a long period. These changes contribute to the facilitation of responses to subsequent inputs in the same nociceptors that initiated this form of synaptic plasticity. Heterosynaptic facilitation, in contrast, is initiated by much lower stimulation frequencies (1 Hz) in nociceptors and causes a spatially dispersed synaptic enhancement in dorsal horn neurons. This NMDA receptor-mediated increase in membrane excitability leads to the augmentation of the response to subsequent Aβ, Aδ and C-fibre inputs, the first of which leads to tactile allodynia, a major feature of inflammatory and neuropathic pain. This form of NMDA-mediated functional enhancement is the consequence of NK1, mGluR and TrkB receptor activation, secondary to the release from C-fibre terminals of substance P, glutamate and BDNF, followed by convergent activation of second messenger kinases (such as PKCγ) that in turn phosphorylate an intracellular tyrosine kinase src. Src when activated phosphorylates the NMDA receptor on tyrosine residues modifying its channel kinetics and voltage-dependent characteristics, increasing membrane excitability. Other postsynaptic kinase signalling cascades have also been implicated in central sensitization such as the mitogen-activated protein kinase (MAPK), whose activity is induced in the superficial dorsal horn by nociceptor activity and whose pharmacological inhibition reduces central sensitization experimentally (Ji et al., 1999). Not all the substrates of these kinases have been identified, nor have all the phosphatases involved in regulating their activity. Nitric oxide (NO) generated in dorsal horn neurons following calcium entry is also believed to facilitate NMDA-mediated central sensitization through a positive feedback onto the presynaptic membrane enhancing further transmitter release (Fig. 58.10).

Central sensitization represents a major area for potential new analgesics, ones that could be targeted presynaptically to block neuromodulator release, or postsynaptically to block receptor activation or inhibit intracellular kinases. Since the NMDA receptor is downstream of most of the signalling activity that leads to central sensitization, NMDA receptor antagonists may also have a major role as antihypersensitivity agents. NMDA receptor antagonists, such as ketamine or dextromethorphan, have been found to reduce hypersensitivity in patients with inflammatory and neuropathic pain, but their use is limited by psychotropic side effects due to the widespread distribution of these receptors. Antagonists for the glycine site on the NMDA receptor or those directed at the NR2a NMDA receptor subunit may have a greater therapeutic index and could make a major contribution to normalizing centrally generated pain hypersensitivity.

Central sensitization has been shown to contribute to the generation of both postsurgical and neuropathic pain hypersensitivity (Dahl et al., 1992; Stubhaug et al., 1997; Koltzenburg, 1998). Recently, both peripheral and central sensitization have also been implicated in the pathogenesis of migraine. Early on, pain and associated hypersensitivity in migraine is lateralized on the head, often around or above the orbit, a feature thought to be mediated by peripherally sensitized primary nociceptors (Strassmann et al., 1996). Within hours, hypersensitivity spreads over a much wider area and this has been correlated with the induction of central sensitization within brainstem (Burstein et al., 2000). Treatment early in attack should be targeted, therefore, at preventing/reducing peripheral sensitization, which will then prevent the establishment of central sensitization. If an attack is not aborted early, treatment will have to be targeted at the established central sensitization.

An area where targeting central sensitization contributes to clinical management is use of pre-emptive anal-

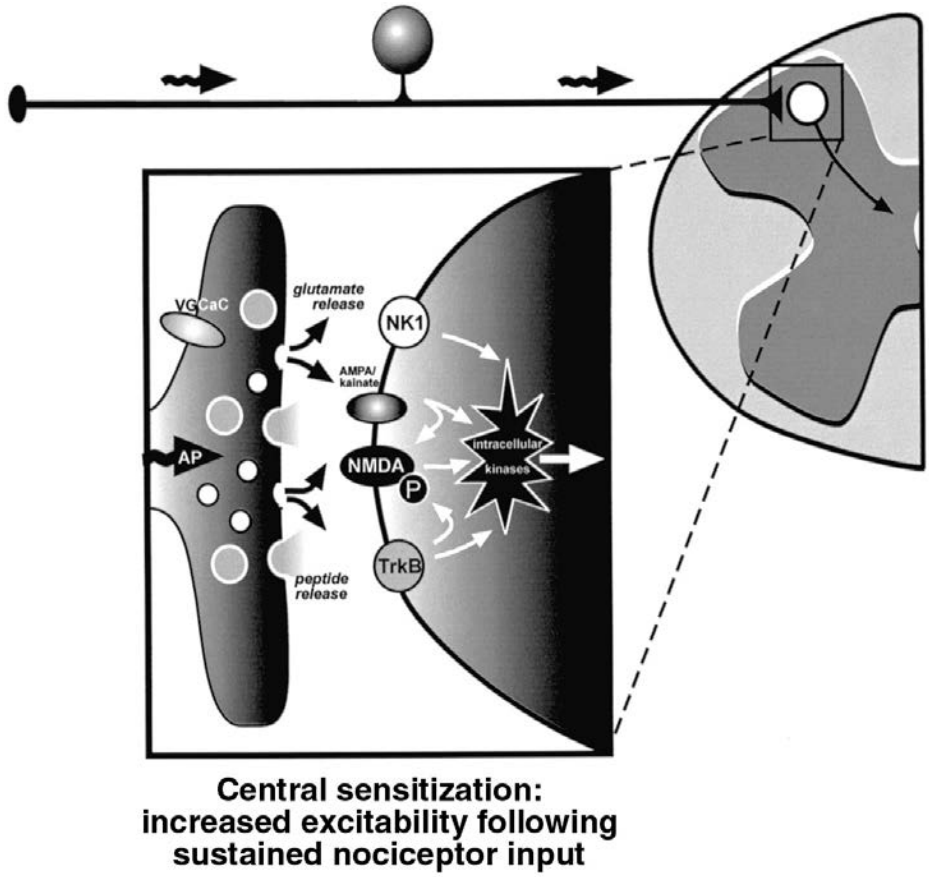

Fig. 58.10. Prolonged nociceptor input to the spinal cord leads to a use-dependent increase in neuronal membrane excitability that long outlasts the duration of the stimulus. A key molecule in this process, known as central sensitization, is the NMDA glutamate receptor. Other receptors such as the substance P receptor NK1 and the BDNF receptor TrkB are involved by means of activating many postsynaptic kinases, which then act to phosphorylate the NMDA and other receptor/ion channels.

gesia to reduce postoperative pain. The rationale is that by blocking C-fibre input to, or action on, the spinal cord before a surgical incision is made, the dorsal horn will remain in a state of normosensitivity and the patient will require less postoperative analgesia. Although this has been borne out in many carefully designed placebo controlled clinical trials using ketamine, opioids and regional anesthesia, this approach has not yet been fully optimized. One problem is that a sensory input sufficient to drive central sensitization will be generated both intraoperatively by surgically induced activation of nociceptors, and postoperatively by input arising from the injured and inflamed tissue. For this reason pre-emptive treatment administered preoperatively alone is insufficient, it needs to continue into the immediate postoperative period.

Modification: long-lasting alterations in pain processing

In addition to the reversible changes in nociceptor and dorsal horn neurons during peripheral and central sensitization, long-term and potentially irreversible changes can occur in these cells, which can be divided into two types: phenotypic and structural, including degeneration, cell death and sprouting and contribute to altered synaptic input, changes in synaptic connectivity as well as disinhibition.

Phenotypic modifications in the sensory system

Both peripheral inflammation and nerve injury can change the phenotype of primary sensory and dorsal horn

neurons. The raised levels of NGF at the site of the inflammation results in an increase in NGF-regulated peptide transmitters expressed by sensory neurons (substance P, CGRP and BDNF). This involves both an increase in those cells which normally express these synaptic neuromodulators, as well as novel expression in sensory neurons which normally do not contain them, such as neurons with myelinated axons, a switch from an A-fibre phenotype to a C-fibre phenotype (see Fig. 58.10). In addition to the retrograde transport of NGF, increased activity in sensory neurons appears to be sufficient to alter transcription (Mannion et al., 1999).

For nerve lesions, the disconnection of the neuronal body from its target cuts off the cell body from target-derived peripheral growth factor signals and introduces the neuron to novel signals (such as local inflammation at the site of injury, molecules produced by denervated Schwann cells and altered activity patterns) all of which can lead to a change in sensory neuron phenotype. Nerve injury results in increased excitability in the injured neurons as a consequence of transcriptionally and post-translationally mediated alterations in voltage gated sodium channel function as well as a reduction in potassium channel expression which may be sufficient to generate ectopic activity leading both to spontaneous burning pain and paresthesias (Waxman & Ritchie, 1993). Injured C-fibre afferents dramatically up-regulate a TTXs sodium channel, Brain III, normally only expressed by sensory neurons at high levels during development. This switch to a phenotype resembling developmental (embryonic) neurons is seen for many molecules including structural growth related proteins like growth associated protein-43 (GAP-43). A-fibre neurons distribute sodium channels differently following nerve injury and no longer are they found solely at Nodes of Ranvier (Waxman & Ritchie, 1993) (Fig. 58.5(*b*), (*c*), see colour plate section). In particular, sodium channels accumulate at the site of the neuroma and this alters the activation properties of cells and becomes a site for ectopic discharge, as can be demonstrated by tapping the neuroma site as in the Tinel sign in carpal tunnel syndrome. Peripheral nerve injury also results in the development of increased adrenoreceptivity, either due to increased local catecholamine levels following sympathetic axon sprouting into injured tissue and the DRG or following the up-regulation of α_2-adrenoreceptors by sensory neurons which may contribute to the development of sympathetically maintained pain (Devor & Seltzer, 1999).

Although the phenotypic changes in C-fibres after inflammation and nerve injury tend to be in opposite directions, remarkably, both nerve injury and inflammation induce substance P and BDNF expression *de novo* in those large A-fibre neurons normally involved in signalling low threshold innocuous stimuli (Fig. 58.11). A novel feature of both these clinical pain states is that contrary to the normal situation, where only C-fibre input can induce central sensitization, low threshold fibre stimulation can lead to central sensitization and in consequence a build up of pain hypersensitivity known as progressive tactile hypersensitivity (PTH) (Ma & Woolf, 1996). Apart from an increased synaptic drive by virtue of such phenotypic shifts, peripheral nerve injury also results in reduced inhibition as a result of the down-regulation of opioid receptors on injured primary afferents and this may contribute to the relative decrease in morphine sensitivity frequently found in patients with neuropathic pain.

Dorsal horn neurons also show phenotypic changes including up- and down- regulation of receptors such as NK1, TrkB and GABA-R. Alterations in dorsal horn transmitters also occur including increases in dynorphin, GABA and COX-2. These changes may be the result both of alterations in synaptic input as well as systemic signals from cytokines and they may contribute both to an alteration in responsiveness to primary afferent input as well as modifying intrinsic dorsal horn neuronal function.

Postinjury sensory neuron cell death and central sprouting

During development, primary sensory neurons are dependent for survival upon a limited supply of trophic factors expressed in peripheral targets, with around 50% of neurons undergoing apoptosis, known as programmed cell death. After experimental nerve injury in adult animals, although there are small increases in the number of cells undergoing apoptosis (Groves et al., 1998), there are no significant changes in DRG cell or axon number for up to 4 months (Coggeshall et al., 1996), suggesting that adult sensory neurons are independent of target-derived growth factors for survival. The cell death that does occur is predominantly in C-fibres leaving most A-fibre neurons intact. The degree and timing of cell death associated with other insults such as herpes zoster infection remains controversial (Oaklander, 1999) but there is a marked reduced innervation of the epidermis in many of these patients (Oaklander et al., 1998), which contributes to decreased thermal sensitivity and a loss of histamine-induced flare in such patients, while leaving A-fibre terminals in the dermis intact to signal tactile allodynia.

Although nerve injury does not at early time points result in neuronal cell death, it induces the transganglionic degeneration of C-fibre central terminals within the superficial dorsal horn (Doubell et al., 1999). Shortly after, Aβ-

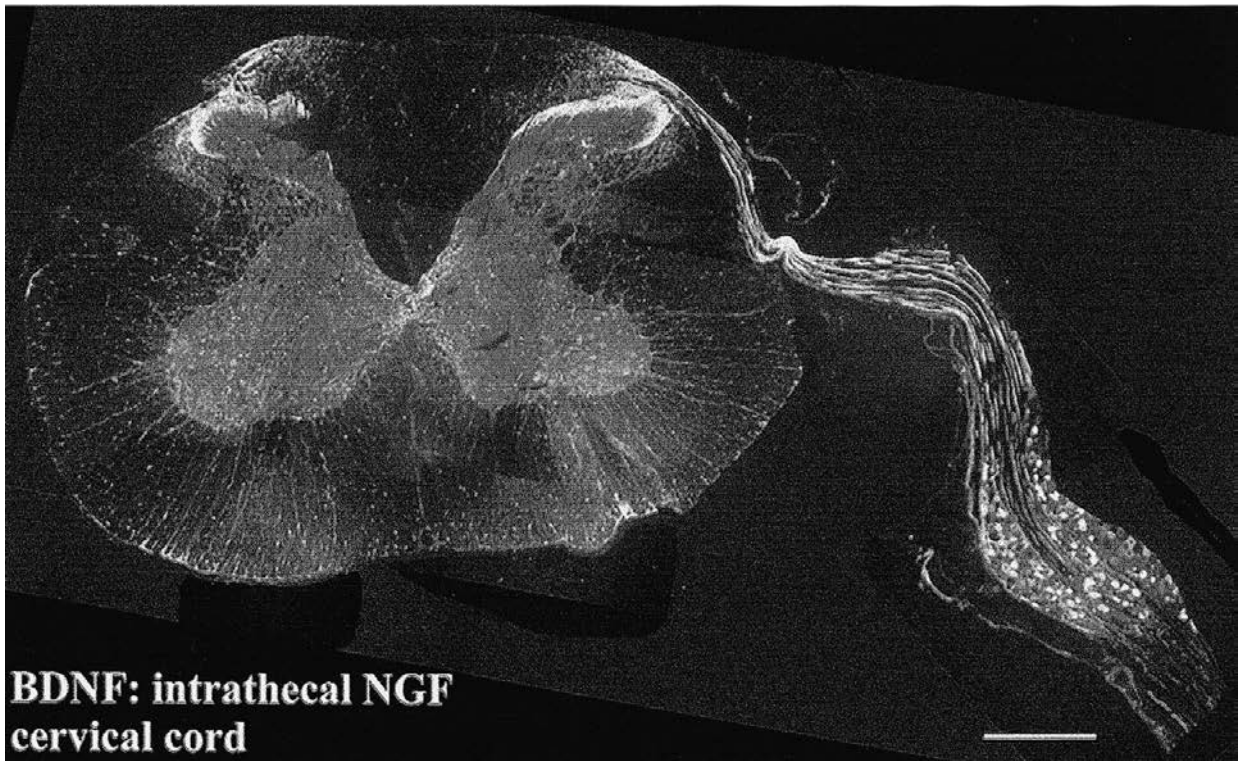

Fig. 58.11. BDNF is expressed by a subpopulation of sensory neurons in the DRG, predominantly those that express the NGF receptor TrkA. BDNF is synthesized in the cell body and transported centrally into the spinal cord where immunoreactivity can be seen in the superficial laminae of the dorsal horn. Following nerve injury and inflammation and intrathecal NGF administration, BDNF expression is increased and some A-fibres begin to express BDNF. (Printed with permission from Michael et al., 1997.)

fibre collateral central terminals sprout dorsally into superficial regions that normally are innervated specifically by C-fibre neurons (Woolf et al., 1992) (Fig. 58.12, see colour plate section). These sprouted collateral axons make novel synapses with dorsal horn neurons (Woolf et al., 1992; Kohama et al., 2000). Direct monosynaptic input to lamina II may result in the misinterpretation of A-fibre input as C-fibre input, an anatomical substrate for tactile allodynia (Koerber et al., 1999). The spinal A-fibre sprouting in animals is considered a consequence of C-fibre injury (Mannion et al., 1996) possibly as a consequence of peripherally derived growth factor deprivation as suggested by the prevention of the sprouting with intrathecal NGF or BDNF administration (McMahon & Bennett, 1999).

Tonic and phasic central inhibition of sensory transmission, a major part of normal sensory processing, is reduced in superficial laminae following nerve injury as a result of the decreased expression of inhibitory transmitters and receptors and direct cell death of local inhibitory interneurons in this region (Coggeshall et al., 1998; Fig. 58.3(b)). The novel presence of A-fibre terminals in lamina II after nerve injury may contribute to excitotoxic interneuron death in the superficial dorsal horn, manifesting as progressive disinhibition and worsening neuropathic pain. Such a disinhibition is functionally equivalent to an increase in excitation. In animal models, blocking glycine or GABA receptors locally in the spinal cord produces tactile allodynia. If similar changes occur in patients the issue then is how to prevent/treat this disinhibition. The former may be possible by blocking excitotoxic inhibitory interneuron loss soon after injury with NMDA receptor antagonists, the latter may require administration of GABAergic compounds.

In conclusion, the three functional states of the sensory system: activation, modulation and modification, are distinct but overlapping and will manifest in most patients with chronic pain, to a greater or lesser degree. Thus, successful treatment will never be achieved with single agents which act only on one state. Persistent pain is, therefore, a family of syndromes initiated by diverse etiological factors, the expression of which is a reflection of the activation of

diverse neurobiological mechanisms. These syndromes demand a multilayered management strategy targeting not just the mechanisms but also their evolution within the individual. The breakdown of complex symptoms into their cellular and molecular components is expanding our understanding of individual features of pain syndromes as well as identifying new targets to develop rational treatment plans. The key challenges for a rational mechanistically orientated treatment are to be able to identify individual mechanisms within patients using simple, reliable and reproducible clinical tests and to identify specific treatments that have the potential to treat individual mechanisms responsible for hypersensitivity, without the abolition or even reduction of pain normosensitivity. The challenge of conquering pain is enormous and will be difficult but the need is great, as are the opportunities.

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Central nervous system mechanisms of pain

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Chronic pain is an immense unsolved clinical problem. Current approaches to this condition are limited by uncertainty about mechanisms of acute and chronic pain in man. Although much progress has been made toward understanding peripheral neural mechanisms of human nociception (Willis, 1985; Price & Dubner, 1977), we have a poor understanding of CNS pain mechanisms. Spinal mechanisms of pain processing are the subject of the previous chapter. The purpose of the present chapter is to review the anatomy and physiology of the ascending spinal pathways and supraspinal centres with pain-related activity. This chapter will focus on the primate nervous systems since there are significant differences between pain transmission in primates and other species such as cats and rats.

It is widely recognized that there are different components to the pain sensation (Melzack & Casey, 1968; Casey, 1978). The sensory–discriminative aspect of pain refers to the intensity of the sensory experience of pain. The motivational–affective aspect of pain refers to the unpleasantness of the pain and how likely it is that the pain will motivate the organism to escape the pain. Throughout this chapter we will refer to these different components of the pain sensation.

Ascending spinal pathways

The two main output somatosensory tracts from the spinal cord are the anterior–lateral and the dorsal column spinal systems. The anterior–lateral system terminates in the brainstem and thalamus while the dorsal column system terminates in the dorsal column nuclei (Willis, 1985).

The anterior–lateral spinal column

Anatomy

The cell bodies of origin for the anterior–lateral system are found in the spinal dorsal horn, particularly in lamina I, outer layers of lamina II and in laminae III to V; though some cells are also found in laminae VI to IX (Willis, 1985; Willis & Coggeshall, 1991). The spinal pathway from the spinal cord to the thalamus, the spinothalamic tract (STT) is partly located in the anterior lateral column. The STT system consists of two tracts, one positioned in the ventral lateral and the other in the dorsal lateral spinal funiculus (Cusick et al., 1989; Apkarian & Hodge, 1989b; Craig, 1997; Ralston & Ralston, 1992) and most commonly referred to as the 'ventral' and 'dorsal' STTs, respectively (Ralston & Ralston, 1992; Zhang et al., 2000). The axons of cells in the deeper spinal laminae project via the ventral tract while those from more superficial laminae project in the dorsal STT (Apkarian & Hodge, 1989a,b).

Axons and axon collaterals of the spinal projection neurons that ascend in the ventro-lateral spinal quadrant terminate in a number of nuclei of the medulla, midbrain and diencephalon (Mehler, 1962; Mehler et al., 1960). These include in ascending order, the medullary reticular formation (via the spino-reticular tract) (Kevetter et al., 1982; Menetrey et al., 1982), the mesencephalic periaqueductal grey and neighbouring area (spino-mesencephalic tract) (Bjorkeland & Boivie, 1984; Mehler et al., 1960; Menetrey et al., 1982), the parabrachial nucleus (spino-parabrachial tract) (Saper, 1995; Saper & Loewy, 1980; Slugg & Light, 1994), and the hypothalamus (spino-hypothalamic tract) (Burstein et al., 1987, 1990).

Anterior–lateral spinal columns

Physiology

Neuronal responses

Both non-nociceptive and nociceptive spinoreticular (Blair et al., 1984; Fields et al., 1977; Haber et al., 1982), spinomesencephalic (Hylden et al., 1986; Yezierski & Schwartz, 1986; Yezierski et al., 1987), spinohypothalamic (Burstein et al., 1991; Katter et al., 1996), spino-parabrachial (Bernard & Besson, 1990), and spinothalamic (Craig & Hunsley, 1991; Palecek et al., 1992a, b; Surmeier et al., 1988), neurons have been demonstrated in many animal species. The non-nociceptive projection cells are termed low-threshold or LT neurons. These are an infrequently observed cell group, usually comprising no more than about 10% of dorsal horn neurons (Dougherty et al., 1993, 1998, 1999). The two types of nociceptive spinal projection neurons identified in the spinal cord include wide dynamic range (WDR) and nociceptive specific (NS) neurons. WDR cells are the most frequently encountered cell group, comprising about 70% of the cells sampled in the dorsal horn. WDR cells are especially concentrated in the deeper laminae of the dorsal horn (III to V) where they receive input from both low-threshold and nociceptive afferent fibres and hence are activated by both innocuous and noxious stimuli. However, the responses of WDR cells to these stimuli are graded so that the noxious stimuli evoke a greater response than non-noxious stimuli. It has been suggested that these properties of WDR neurons account for the discrimination of noxious from non-noxious stimuli (Bushnell et al., 1984; Dubner et al., 1989; Maixner et al., 1989) (the sensory-discriminative aspect of pain). In contrast to WDR cells, NS projection cells respond only to noxious stimuli under physiological conditions. The majority of NS cells are found in the superficial laminae of the dorsal horn (I and outer II).

The dorsal spinal column system

Anatomy

The second set of somatosensory inputs to the brainstem include those primary afferent fibres which ascend in the dorsal (posterior) columns of the spinal cord to form their first synapse at the dorsal column nuclei. In addition, there is input to the dorsal column nuclei from at least two groups of dorsal horn projection neurons, the postsynaptic dorsal column pathway and the spino-cervical tract (Wall & Melzack, 1984; Willis, 1985; Willis & Coggeshall, 1991). Both groups of inputs are organized so that the fibres from the lower extremities are most medial in the nucleus gracilis, and inputs from the upper extremities are most lateral in the nucleus cuneatus. The trunk is represented in a region between these nuclei. Inputs from the most distal body regions are dorsal and the more proximal body regions are ventral. The axons of the second-order cells in the dorsal column nuclei cross the midline and gather into the medial lemniscus on the contralateral side of the brainstem. These fibres then ascend through the brainstem and midbrain toward their site of termination in the ventral posterior lateral (VPL) nucleus of the thalamus.

The dorsal spinal column system

Physiology

The cells of the dorsal column nuclei largely respond to innocuous stimuli alone. The lemniscal system in primates does not appear to encode painful stimuli. The information carried in this path is primarily from hair follicle receptors, pacinian corpuscles, and types I and II slowly adapting receptors (Willis, 1985; Willis & Coggeshall, 1991). In addition, the nucleus cuneatus (but not gracilis) shows responses to muscle afferents (spindles and Golgi tendon organs). However, there are several lines of evidence which suggest a role of the dorsal column nuclei in nociceptive transmission. For example, the dorsal columns might account for the recurrence of pain sensitivity and reference of pain to other regions of the body after lesion of the anterolateral spinal quadrant (Vierck et al., 1990; Vierch, Jr. & Luck, 1979; Nagaro et al., 1993). Neuropathic pains are largely conveyed by myelinated fibre inputs (Campbell et al., 1988), which are the majority of fibres afferent to the dorsal column pathway. In addition, non-myelinated afferents have been shown to project to the dorsal column nuclei (Conti et al., 1990; Fabri & Conti, 1990; Garrett et al., 1992; Patterson et al., 1989, 1990). A small number of nociceptive dorsal column neurons have been reported (Cliffer et al., 1992; Ferrington et al., 1988). Finally, the postsynaptic dorsal column pathway and the spino-cervical tract ascend to the dorsal column nuclei and are often nociceptive (Brown et al., 1983; Brown & Franz, 1969).

Supraspinal nociceptive centres

Brainstem centres

Nociceptive neurons have been shown within the reticular formation (Barbaro et al., 1989; Guilbaud et al., 1973; Haws

et al., 1989; Nyquist & Greenhoot, 1974; Villanueva et al., 1990), and the periaqueductal grey (PAG) (Casey, 1971b; Eickhoff et al., 1978). Microstimulation in these nuclei produces a wide spectrum of pain-related responses (Bowsher, 1976; Carstens et al., 1980; Casey, 1971a; Gerhart et al., 1984; Janss et al., 1987; Bandler & Depaulis, 1988; Bandler & Carrive, 1988; Delgado, 1955; Fardin et al., 1984; Lovick, 1993; Nashold, Jr. et al., 1969; Spiegel et al., 1954;Walker, 1938; Wolfle et al., 1971). Electrical or chemical stimulation of the PAG or hypothalamus in animals and humans produces a spectrum of responses from overt nocifensive behaviour and associated cardiopulmonary changes to analgesia. This spectrum of effects in PAG is due to the activation of one of two subdivisions of the PAG, the dorsolateral and ventrolateral columns. Activation of the dorsolateral column of the PAG produces a behavioural response of vocalization, grimacing, attack or escape and a parallel tachycardia and pressor response (Bandler & Shipley, 1994; Lovick, 1993), while activation of the ventrolateral column produces behavioural quiescence, bradycardia and hypotension (Depaulis et al., 1994; Keay et al., 1994). Both of these response profiles have been observed by stimulation within the PAG of humans (Nashold, Jr. et al., 1969; Young, 1989; Young et al., 1985).

Lateral thalamic nuclei

Nociceptive neurons in humans have been observed in the mesencephalon (Amano et al., 1978), hypothalamus (Sano, 1977b; Sano, 1979) and thalamus (Lenz et al., 1993b; Lee et al., 1999). The region of Vc where the majority of cells respond to innocuous cutaneous stimulation is termed the core. Below and behind the core is a less cellular region arbitrarily termed the posterior inferior region in our studies. Receptive field locations for the cells in Vc remain unchanged over distances of several millimetres in the anterior–posterior and dorsoventral directions, but change markedly over similar distances in the mediolateral direction (Lenz et al., 1988). From medial to lateral the sequence of neuronal cutaneous receptive fields progresses from intraoral through face, thumb, fingers (radial to ulnar), and arm to leg. Cells with deep receptive fields are usually located anterior and dorsal in the core but sometime posterior to those with cutaneous receptive fields.

Several lines of evidence demonstrate that the region of Vc is important in human pain-signalling pathways. Studies of patients at autopsy following lesions of the STT show the most dense STT termination in Vc (Mehler, 1962; Mehler, 1966; Bowsher, 1957; Walker, 1943). Additionally, terminations are observed posterior to Vc in the magnocellular medial geniculate (Mehler, 1962; Mehler, 1969), limitans, and Vc portae nuclei (Mehler, 1966) and inferior to Vc in Vcpc (Mehler, 1966). STT terminations are found in monkey VMpo, posterior to medial Vc, which appears, by immunohistochemistry, to have a human analogue (Craig et al., 1994). It has been suggested that VMpo and the posterior nuclear group are specifically innervated by the dorsal STT (Craig, 1997; Craig et al., 1994), though not all studies have been in agreement (Apkarian & Hodge, 1989a,b; Ralston & Ralston, 1992; Zhang et al., 2000).

The cortical projections of these nuclei in monkeys are as follows: VP (corresponding to human Vc (Hirai & Jones, 1989a)) to primary (S1) and secondary (S2) somatosensory cortices (Jones, 1985; Burton, 1986; Kenshalo, Jr. & Willis, 1991), VPI (corresponding to human Vcpc) to S2 and granular and dysgranular insular cortex (Friedman & Murray, 1986), medial and oral pulvinar (corresponding to human Vcpor) to inferior parietal lobule and outer parietal operculum (7b) plus granular and dysgranular insular cortex (Burton & Jones, 1976; Burton, 1986; Friedman & Murray, 1986), posterior nucleus (as in humans) to retro-, granular and dysgranular insular cortex and S2 (Burton & Jones, 1976; Burton, 1986; Friedman & Murray, 1986), supragenicculate and limitans (as in humans) to granular insular cortex (Burton & Jones, 1976; Burton, 1986) and magnocellular medial geniculate to granular and dysgranular insular cortex (Friedman & Murray, 1986).

Fig. 59.1 shows an example of a cell in Vc with a differential response to painful thermal and mechanical stimuli and with a response to innocuous cool and mechanical stimuli (Lee et al., 1999). Cells in the posterior inferior region have been identified with a significant selective response to noxious heat stimuli (Lenz et al., 1993b) and to cold stimuli (Davis et al., 1999). These reports extend to humans the results of numerous monkey studies in which cells within VP (Casey & Morrow, 1983; Chung et al., 1986; Gautron & Guilbaud, 1982; Apkarian et al., 1991; Casey, 1966; Bushnell et al., 1993; Apkarian & Shi, 1994; Kenshalo et al., 1980; Bushnell & Duncan, 1987) and posterior and inferior to VP respond to noxious stimuli (Apkarian et al., 1991; Casey, 1966; Apkarian & Shi, 1994; Craig et al., 1994).

Cells in the region of Vc that respond to noxious stimuli probably signal pain based on temporary lesioning and stimulation studies. Blockade of the activity in this region by injection of local anesthetic into monkey VP, corresponding to human Vc (Hirai & Jones, 1989a), significantly interferes with the monkey's ability to discriminate temperature in both the innocuous and noxious range (Duncan et al., 1993). Stimulation within Vc and posterior-

inferior to it can evoke the sensation of pain (Dostrovsky et al., 1991; Halliday & Logue, 1972; Hassler & Reichert, 1959; Lenz et al., 1993a) and thermal sensations (Lenz et al., 1993a; Davis et al., 1999). Thus, there is strong evidence that the region of Vc is involved in pain signalling pathways: i. it receives input from pain signalling pathways, ii. it contains cells that respond to noxious stimuli, iii. stimulation can evoke pain, and iv. temporary lesioning of monkey VP disables the discrimination of pain and temperature.

Medial and intralaminar thalamic nuclei

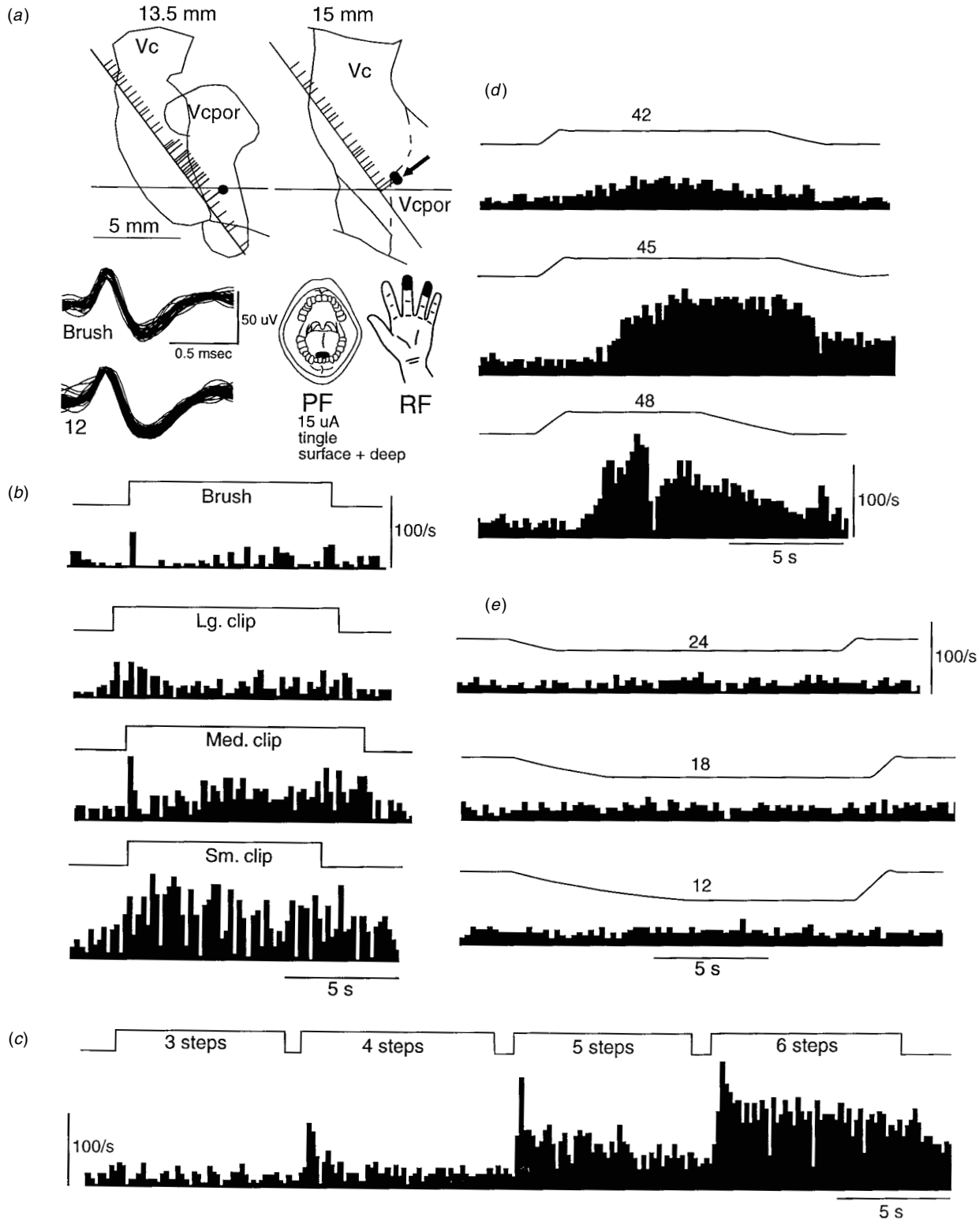
In the medial tier of human thalamic nuclei the most dense STT terminal pattern is found in intralaminar nucleus centralis lateralis (Bowsher, 1957; Mehler, 1962; Mehler, 1969) while a much less dense termination is found in other interlaminar nuclei central medial and parafascicularis (Mehler, 1962). These nuclei project to cortex diffusely (Le Gros Clark & Russell, 1940) and to striatum (Oppenheimer, 1967; Vogt & Vogt, 1941). STT terminations are also found in the medial dorsal nucleus (Mehler, 1969) which project to lateral prefrontal cortex (Meyer, 1947; Van Buren & Borke, 1972). An STT projection to human submedius has not been identified although regions of dense neurokinin staining in medial Vcpc (Hirai & Jones, 1989b) may correspond to monkey nucleus submedius (Burton & Craig, Jr., 1983). The nuclear pattern of STT terminations and projection patterns of these nuclei in humans is similar to that demonstrated in more precise anatomic studies in monkeys.

In monkeys, dense STT terminations are observed in central lateral (Mehler et al., 1960; Boivie, 1979; Mantyh, 1983; Berkley, 1980), while a light projection is found in central medial and parafascicularis (Mehler et al., 1960; Burton & Craig, Jr., 1983; Berkley, 1980; Apkarian & Hodge, 1989c; Kerr, 1975). These intralaminar nuclei project to caudate and putamen (Sadikot et al., 1990; Smith & Parent, 1986; Nakano et al., 1990; Kalil, 1978; Sadikot et al., 1992a,b) and diffusely to cortex (Macchi & Bentivoglio, 1986; Strick, 1975; Powell & Cowan, 1967). STT terminations are also found in monkey submedius (Apkarian & Hodge, 1989c), particularly the dorsal (Craig & Burton, 1981) and rostral (Mantyh, 1983; Craig, 1990) portion. The cortical projections of submedius have not been reported in monkey although projections to deep presylvian sulcus have been reported in cats (Craig et al., 1982). The medial dorsal nucleus receives STT input (Apkarian & Hodge, 1989c; Rothwell et al., 1983; Kerr, 1975) and projects to dorsolateral prefrontal cortex (Kievit & Kuypers, 1975; Tobias, 1975; Goldman-Rakic & Porrino, 1985). Therefore, the pattern of STT terminations in monkeys largely confirms that described in humans.

Nociceptive neurons have been identified in the human central medial nucleus (Ishijima et al., 1975; Jeanmonod et al., 1993, 1994; Rinaldi et al., 1991; Tsubokawa & Moriyasu, 1975). Ishijima et al. found that one-quarter (20/80) of the cells they recorded from the central medial/parafascicularis complex of man responded to noxious pinprick and two of these responded to application of noxious heat to the skin (Ishijima et al., 1975). None of these cells responded to non-noxious cutaneous stimuli. They identified nociceptive cells which responded at short latency to the application of stimuli, and terminated discharges shortly after discontinuation of the stimulus. A second group of cells responded with a long latency and showed prolonged after-discharges. Both types of cells had receptive fields that were large and often bilateral. The two types of cells were distributed in different areas of the central medial/parafascicularis, with the first type of cells in the medial basal parts of the nucleus, while the second type were scattered throughout the central medial and in the dorsal parts of parafascicularis. Tsubokawa and Moriyasu (Tsubokawa & Moriyasu, 1975) also found a relatively large number of nociceptive neurons which they localized to the central medial nucleus.

Studies by Rinaldi and coworkers ($n = 81$ cells (Rinaldi et al., 1991)) and Jeanmonod and coworkers ($n = 972$, (Jeanmonod et al., 1993, 1994)) in patients with deafferentation pain rarely found cells with receptive fields, in contrast to previous reports (Ishijima et al., 1975; Tsubokawa & Moriyasu, 1975). Instead cells with very high rates of spontaneous bursting discharge activity were reported ((Rinaldi et al., 1991; Jeanmonod et al., 1993, 1994), see below). The cells with receptive fields to tapping were found in two patients in whom bursting activity was absent (Rinaldi et al., 1991). The receptive fields were very large and often bilateral. Jeanmonod et al. (1993, 1994) found two cells with large, bilateral cutaneous receptive fields to innocuous and noxious stimuli. These cells were found in the medial dorsal nucleus.

Electrical stimulation of the medial regions of thalamus for localization prior to thalamotomy for pain (Amano et al., 1976; Choi & Umbach, 1977; Hithcock & Teixeria, 1981; Laitinen, 1988; Richardson, 1967; Rinaldi et al., 1991; Urabe & Tsubokawa, 1965; Voris & Whisler, 1975) evoked painful sensations (Sano, 1977a; Fairman & Llavallol, 1973; Fairman, 1966). Sano's group (Sano, 1977a, 1979) described two types of sensation evoked by stimulation in medial thalamus. The first type was a diffuse, burning pain


(a)
13.5 mm
15 mm
Vc
Vcpor
Vc
Vcpor
5 mm
Brush
50 uV
0.5 msec
12
PF
15 uA
tingle
surface + deep
RF
(b)
Brush
100/s
Lg. clip
Med. clip
Sm. clip
5 s
(c)
3 steps
4 steps
5 steps
6 steps
100/s
5 s
(d)
42
45
48
100/s
5 s
(e)
24
100/s
18
12
5 s

referred to the contralateral half of the body or on occasion the whole body. The sites at which these sensations were produced were usually concentrated near the posterior half of the internal medullary lamina, corresponding to the parvocellular regions of central medial, plus parafascicularis and limitans. The spontaneous pain of the patient was frequently exacerbated by macrostimulation at these sites. The other type of sensation produced by Sano and coworkers was a generalized 'unpleasant' sensation, not localized to a particular body part. The sites at which these sensations were produced were concentrated in the very medial and anterior regions, possibly the medial dorsal and periventricular nuclei. Rinaldi and coworkers have also produced sensations by microstimulation in the medial thalamus, but these were not considered painful (Rinaldi et al., 1991). Instead a sensation of 'pulling' was produced by stimulation in parafascicularis while throbbing was produced by stimulation in the central medial nucleus.

The medial or intralaminar thalamus has often been lesioned for treatment of chronic pain. A decrease in the level of pain was found in 73% of patients on average for these studies (Lenz & Dougherty, 1997). The sensation of pain evoked by an acute experimental paradigm was not altered. Therefore, it is assumed that the medial nuclei subserve the affective–motivational component of pain.

Cortex

Our understanding of cortical areas involved in pain perception has been dramatically altered by the results of functional imaging studies carried out during the application of painful stimuli (Jones et al., 1991; Talbot et al., 1991a; Casey, 1999; Casey & Bushnell, 2000). These studies have identified four areas metabolically activated by the application of painful stimuli. This section will review anatomy and physiology of each of these areas: primary somatosensory cortex (S1), secondary somatic sensory cortex (S2), insula, and cingulate cortex.

The primary somatosensory cortex (S1)

The S1 cortex located in post-central gyrus is the first cortical target of somesthetic information from the monkey VPL and VPM nuclei of the thalamus. Most of the thalamocortical neurons of VPL and VPM project to S1 cortex, including the fraction that receives input from the STT. Human studies suggest a similar picture, such that the ventral caudal nucleus (Vc; corresponding to monkey VP) projects to S1 (Van Buren & Borke, 1972). Multiple case reports describe lesions involving parietal cerebral cortex and underlying white matter, that are associated with hypalgesia (Marshall, 1951; Boivie et al., 1989). Lesions of S1 cortex in old world primates are reported to interfere with discrimination of stimuli into the noxious range (Kenshalo et al., 1991). These results suggest that S1 has a pain-related function.

Neurophysiological studies in primates have demonstrated the existence of nociresponsive neurons in the S1 cortex, although they appear to be a small fraction ($\geqslant$1%) of all somatosensory neurons in this area (Kenshalo, Jr. et al., 1988). Nociresponsive neurons in S1 demonstrate response magnitudes that are proportional to the intensity of noxious heat. Thus, these neurons have the capacity to encode the intensity of painful stimuli. This intensity encoding capacity is consistent with S1 being involved in the discriminative aspect of pain.

Fig. 59.1 *(Opposite).* Activity of cell (061093) in Vc responding to painful mechanical and thermal stimuli. (*a*) location of the cell (arrow) relative to the positions of trajectories, nuclear boundaries, and other recorded cells. The ACPC line is indicated by the horizontal line and the trajectories are shown by the oblique lines (left-anterior, up-dorsal). Nuclear location was approximated from the position of the ACPC line. Lateral location of the cell (in millimeters) is indicated above each map. Trajectories have been shifted along the ACPC line until the most posterior cell with a cutaneous RF is aligned with the posterior border of Vc. Since cells responding to innocuous sensory stimuli may be located posterior to Vc (Apkarian & Shi, 1994), this map represents a first approximation of nuclear location and dimensions. The locations of cells are indicated by ticks to the right of each trajectory. Cells with cutaneous RFs are indicated by long ticks, those without definable RFs by short ticks. Filled circles attached to the long ticks indicate that somatic sensory testing was carried out. The scale is as indicated. The shape of action potentials recorded at the beginning of the recording on this cell during application of the brush (upper) and at the end of the recording, during a 12 °C stimulus (lower). Data were collected from upgoing stroke of the action potential by using voltage threshold of 0.15 μV. The RF and PF for the natural, surface and deep, non-painful, tingling sensation evoked by TMIS at the recording site (threshold – 15 μA) are also shown.

(*b*) response to the brush, LC, MC, and SC. (*c*) the response of the neuron to progressive increase in pressure applied with the non-penetrating towel clip, indicated by the number of steps. (*d*) responses to heat stimuli at 42 °C, 45 °C, and 48 °C. (*e*) responses to cold stimuli at 12 °C, 18 °C, and 24 °C. The upper trace in each panel is a footswitch signal indicating the onset and duration of the stimulus in panels (*b*) and (*c*) and the thermode signal in panels (*d*) and (*e*). The scales for the axes for all histograms (binwidth 100 milliseconds) are indicated in each panel. (From Lee et al., 1999 with permission.)

S1 cortex is activated by either innocuous or noxious stimulation in humans, based on magnetoencephalography (MEG), evoked potentials, positron emission tomography (PET), and most recently, functional magnetic resonance imaging (fMRI; see review by Bushnell et al., 1999). Several laser evoked potential (LEP) studies have proposed that LEPs arise in part from generators localized to the contralateral S1 cortex (Tarkka & Treede, 1993). Recent studies have demonstrated that metabolic activation in S1 is significantly related to the magnitude of perceived pain evoked by stimuli of varying intensity (Coghill et al., 1999). Thus, there is clear evidence that S1 is involved in the discriminative dimension of pain.

The secondary somatosensory cortex (S2)

There are several regions in the posterior parietal operculum and posterior insula that show somesthetic responsive neurons in the non-human primate. A part of that area has been identified as S2 cortex, by nature of its connectivity to ventrobasal thalamus and the S1 cortex (Burton, 1986). It is located in the parietal operculum, immediately posterior to the most lateral aspect of S1 cortex. Surrounding S2 cortex are several other electophysiologically defined somatotopic maps, which have been identified as PV (parietal ventral – just anterior to S2 in the parietal operculum; (Krubitzer et al., 1995)), area 7b (lateral to S2), posterior insula (medial to S2), and retroinsula (in the lateral fissure posterior to the insula proper) (Burton, 1986). Together, these areas are referred to as parasylvian cortical areas. Neurophysiological studies in primates have identified cells responsive to painful stimuli in S2 and area 7b (Dong et al., 1989, 1994).

Human studies suggest that the subnuclei in and around Vc project to the posterior parietal operculum (including S2; (Van Buren & Borke, 1972)). Human LEP studies provide evidence of nociceptive inputs to this area. LEPs are the potentials evoked by cutaneous application of a laser which is a pure pain stimulus. Subdural studies demonstrate that LEPs arise from a generator between the sylvian and the central fissures anterior to auditory cortex and discrete from the generator for the P3 event-related potentials (Lenz et al., 1998b). This suggests that the positive component of the LEP is not a potential related to the P3, a potential related to the attention evoked by infrequent events (cf Zaslansky et al., 1996).

The maximum of the LEP is identified just above the sylvian fissure and just anterior to a generator of the AEP – the primary auditory cortex located in Heschl's transverse gyrus on the temporal operculum (Celesia & Puletti, 1969). The polarity of the AEP is opposite at recording sites on opposite sides of the sylvian fissure (Fig. 59.2), consistent with the known location of the AEP generator. If we assume a generator in S2 on the parietal operculum (Burton et al., 1993), facing the temporal operculum, the polarity of the LEP should be opposite on opposite sides of the sylvian fissure, by analogy to the AEP. However, LEPs recorded on opposite sides of the sylvian fissure have the same polarity (Fig. 59.2), suggesting that this generator of the LEP is not located in S2 (Kakigi et al., 1995; Tarkka & Treede, 1993). Comparisons of LEPs with auditory evoked potentials recorded through the same electrodes suggest that the LEP generator is not in S2 but in the dorsal insula at the level of the central sulcus (Lenz et al., 2000).

It has not been possible for PET studies to resolve those regions around the lateral sulcus which are activated by this painful stimulus. Recent fMRI studies have demonstrated multiple loci of activation on the parietal operculum–posterior insula region with both innocuous (Disbrow et al., 2000) and noxious stimuli (Moulton et al., 1999). Hypalgesia has been reported in patients with cerebral lesions involving the parietal operculum, posterior insula, and/or underlying white matter (thereby involving the S2 region), while apparently sparing S1 (Biemond, 1956; Greenspan & Winfield, 1992; Greenspan et al., 1999).

One major issue to be addressed is whether these somatosensory regions demonstrate intensity encoding capacity within the noxious range. Single-unit neurophysiological studies in primates show that some neurons in 7b (adjacent to S2) show responses that can encode for the intensity of noxious heat stimuli (Dong et al., 1994). One PET study reported that responses in the S2 regions (among other areas) were graded in relation to noxious heat intensity (Coghill et al., 1999). Thus there is strong evidence that nociceptive information reaches S2 cortex, and that the activity in this area is related to pain intensity.

The insular cortex

In monkey, portions of the insular cortex have neuroanatomical connectivity suggestive of a role in somatosensory information processing, including inputs from S1 and S2 (Mufson & Mesulam, 1982; Friedman et al., 1986). Additionally, the insula receives input from several thalamic nuclei, including VPI, the oral and medial pulvinar nuclei, the centromedian-parafasicular nuclei, the medial dorsal nucleus, and the VMpo portion of thalamus, which receive nociceptive input from the spinal cord (Burton & Jones, 1976; Jones & Burton, 1976; Friedman et al., 1980; Mesulam & Mufson, 1985; Friedman & Murray, 1986). Stimulation in human Vcpc can evoke previously experienced pain, and the emotional tone associated with that previously experi-

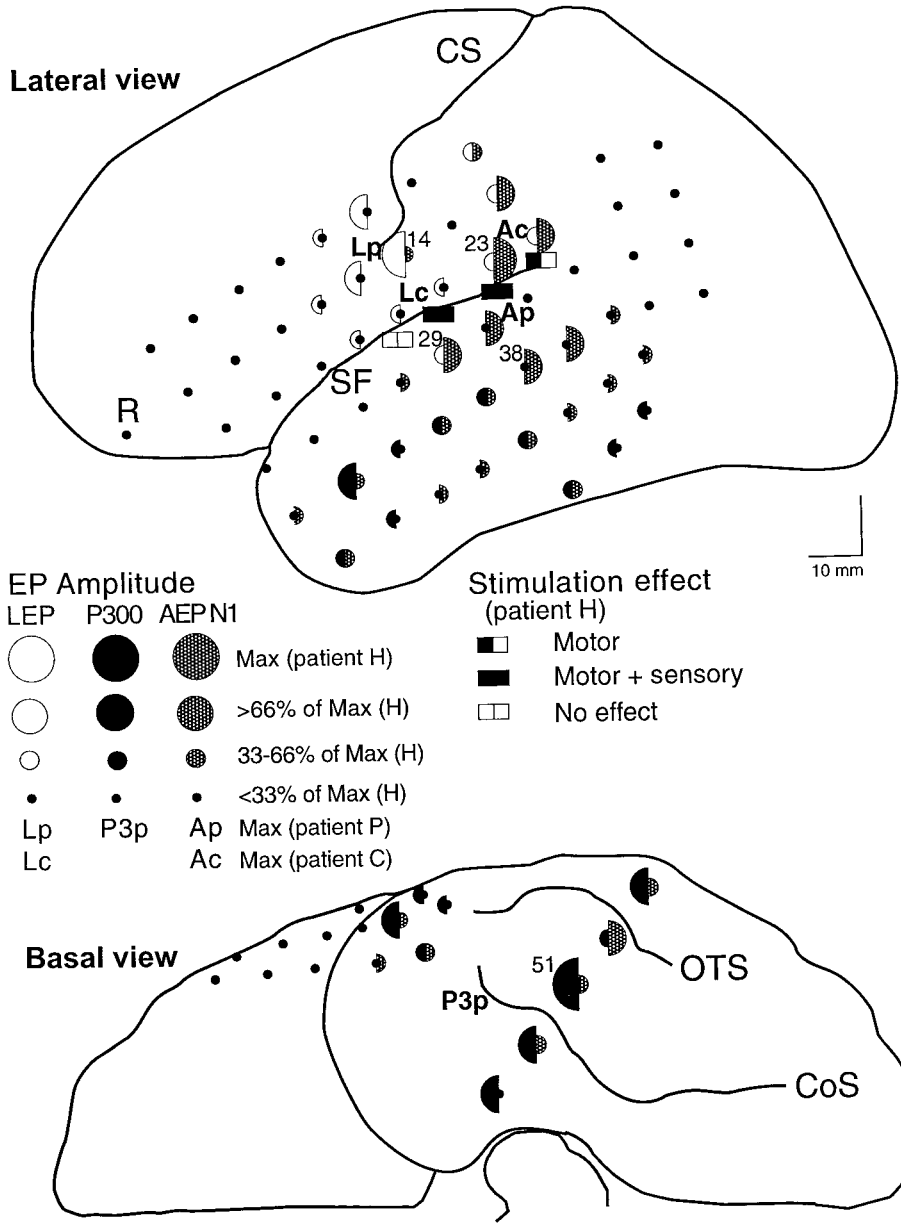


Fig. 59.2. Amplitude distribution of facial LEP P2, AEP, and P3 potentials in patient H and location of maximums for patients C and P. For patient H the LEP P2 amplitude was expressed as a percentage of the maximum (electrode 14) as indicated by the size of the circle. The same conventions were applied to circles for AEPs and P3s so that the location indicates electrode position, the size indicates amplitude as a percentage of the maximum, and the shading indicates the potential (LEP P2, AEP or P3) represented by the circle (Fig. 59.1, left inset). Amplitudes of greater than 33% of maximum were never found at the same electrode for both the LEP P2 and the auditory P3 so that the potentials not represented at any site were less than 33% of maximum.

In patient H, large LEP P2 potentials (>66% maximum) were seen over a restricted area adjacent to the inferior central sulcus, which was confirmed as facial sensorimotor area by stimulation mapping (right inset). LEP P2 maximums in patients C and P (Lc and Lp) were located close to that for patient H. AEPs were maximal posterior and superior to the maximum for LEPs. In patient H, large P3 potentials (>66% maximum) were widespread over basal, anterior, and lateral temporal areas with a maximum over the fusiform gyrus of the temporal base. CS, central sulcus; SF, sylvian fissure; OTS, occipital temporal sulcus; CoS, collateral sulcus. (From Lenz et al., 2000, with permission.)

enced pain. This finding suggests that nuclei in the posterior group may be connected to limbic structures (Lenz et al., 1994b, 1995), through insular connections to the medial temporal lobe (Mishkin, 1979). This suggestion is consistent with anatomic studies demonstrating that the granular portion of insula projects to limbic structures, including the amygdala and perirhinal cortex (Friedman et al., 1986).

There is also evidence that the insula plays a role in human somesthetic perception. Penfield and Faulk (Penfield & Faulk, Jr., 1955) documented somesthetic experiences evoked in patients by direct electrical stimulation of insular cortex. Berthier et al. (1987) described six patients with insular lesions who had reduced motivational–affective responses to pain, but normal sensory-–discriminative capacity. A recent report described the perceptual alterations in a group of people with lesions involving portions of the insula and the parietal operculum (Greenspan et al., 1999). Those individuals with lesions encompassing the posterior parietal operculum showed elevated pain thresholds contralaterally, regardless of whether the lesion involved the neighbouring insula. Those individuals with lesions involving the insula, but sparing the parietal operculum showed normal pain thresholds, but demonstrated greater pain tolerance contralaterally. This was interpreted to show that the parietal operculum (containing S2) has a role in the sensory–discriminative aspect of pain (evidenced by elevation of the pain threshold), while the insula has a role in the motivational–affective aspect of pain (evidenced by elevation of pain tolerance).

The insula's significance to thermal and nociceptive information processing has been highlighted by PET studies (Casey et al., 1994, 1996; Coghill et al., 1994; Craig et al., 1996). These reports describe significant activation of a mid/anterior region of insula, and a separate posterior region of insula, associated with noxious thermal stimuli. Both of these insular areas have been described as showing response levels proportional to stimulus and/or pain intensity (Coghill et al., 1999). It has been suggested that the more posterior region of insula, receiving thalamic input similar to S2 cortex, is more related to sensory discriminative functions.

The cingulate cortex

The anterior cingulate cortex (ACC) also appears to have a role in processing nociceptive input. Brodmann's area 24 in particular receives thalamic input from some of the nociresponsive medial thalamic nuclei and VPI (Craig, Jr. et al., 1982; Vogt et al., 1987; Musil & Olson, 1988; Yasui et al., 1988). Nociresponsive neurons have been recorded (Hutchison et al., 1999) in human ACC and LEPS have a maximum over this area (Lenz et al., 1998c). Surgical lesions have been made near the genu of the ACC in order to relieve chronic pain, and the effects are described as blunting the affective–motivational aspect of pain (Folz & White, 1962; Gybels & Sweet, 1989). Recently, two detailed psychophysical investigations reported sensory changes following cingulotomy or capsulotomy. In the first case pain intensity and unpleasantness was decreased postoperatively (Talbot et al., 1995); a more complex alteration in pain sensibility was observed in the second case who underwent both a capsulotomy and a cingulotomy (Davis et al., 1994).

Perhaps most compelling is the fact that the ACC is the region most consistently activated by noxious stimuli across all PET and fMRI studies (Casey, 1999; Casey & Bushnell, 2000), while innocuous tactile or thermal stimuli consistently fail to activate this region. It has been argued that the ACC activity associated with painful stimulation is not related to the pain experience *per se*, but rather is related to the attentional shift that occurs with an acute painful stimulus. However, the region of the ACC that is activated by painful stimulation is different from the region that is activated by directing attention to non-painful events (Davis et al., 1997). One PET study showed that hypnotic alteration of perceived unpleasantness of painful stimulation produced correlated changes in the ACC response, while producing no significant change in other cortical regions (Rainville et al., 1997). The part of ACC related to pain may be particularly involved in pain unpleasantness.

Central pain syndrome (CPS)

Although little is known of the fundamental pathophysiology of central pain (Boivie & Leijon, 1991), the condition is considered to involve a primary dysfunction of the somatosensory thalamus (Head & Holmes, 1912) that in turn involves cortical structures. The well-described relay of somatosensory information in the ventral posterior medial and lateral nuclei (VPM and VPL) (Guilbaud et al., 1980; Harris, 1980; Jasper & Bertrand, 1966; Jones, 1985; Mountcastle & Henneman, 1949) has historically been cited as evidence to implicate the thalamus in the paroxysmal pain evoked by acute peripheral stimuli in CPS patients (Head & Holmes, 1912). Consistent with this view, intraoperative studies have shown somatotopic rearrangement, abnormal responsiveness to peripheral stimuli, and abnormal spontaneous discharge patterns in thalamic neurons of CPS patients (Lenz et al., 1989, 1993a, 1998d; Radhakrishnan et al., 1999). Electrical stimulation in these zones of altered cellular activity, in lateral thalamus, provoked the sensation of pain at a higher frequency than

would be normally expected (Lenz et al., 1998a), and lesion in areas of altered activity in the medial thalamus successfully relieved CPS (Ishijima et al., 1975; Jeanmonod et al., 1993).

Psychophysical studies uniformly demonstrate that CPS is found in patients with impaired STT function (Boivie & Leijon, 1991; Vestergaard et al., 1997; Boivie et al., 1989; Beric et al., 1988) due to injuries to the STT and it's projections (Cassinari & Pagni, 1969). Acute lesion of the STT in humans produces insensitivity to pain but rarely produces pain (Boivie & Leijon, 1991; Bowsher, 1997; Casey, 1991; Cassinari & Pagni, 1969). However, chronic pain develops in an increasing percentage of patients with increasing length of survival following anterior lateral spinal lesion, so that the risk of CPS becomes a major limiting factor in use of cordotomy for pain relief with prolonged life expectancy (Beric et al., 1988; Casey, 1991). Unfortunately, the extent of spinal lesions was variable in the human neurophysiological studies and so, the specific contribution of STT damage to the observed changes in neurons of CPS patients could not be assessed. In monkeys, acute lesion of the STT reduced sensitivity to pain (Vierck, Jr. et al., 1971, 1983; Vierck, Jr., 1998; Vierck, Jr. & Luck, 1979; Willis, 1985). Over the next 6 months pain sensitivity returned for most in monkeys with STT lesions. In addition, one-third to one-half of all animals developed exaggerated responsiveness to nociceptive stimuli (Vierck et al., 1990). Therefore there is strong evidence that lesions of the STT can evoke features of the CPS.

Anatomic plasticity following peripheral neurological injury has been shown in the thalamus of several species (Albe-Fessard et al., 1983; Albe-Fessard & Rampin, 1991; Lombard & Larabi, 1983; Pollin & Albe-Fessard, 1979; Wall & Egger, 1971) (or for review, see Dougherty & Lenz, 1994). Anatomic rearrangements observed after cervical dorsal rhizotomy in non-human primates included loss of afferent terminals and decreased density of neurons (Rausell et al., 1992). Zones of parvalbumin and cytochrome oxidase staining, characteristic of lemniscal terminals, decreased in size while the calbindin positive zones, characteristic of the spinothalamic terminals, increased (Rausell et al., 1992). The affected areas also demonstrated a decrease in GABA-A receptors (GABA-B and -C receptors were not examined) without a decrease in the number of GABA positive interneurons. Marked changes in GABA synaptic morphology have also been shown following chronic dorsal column lesion (Ralston et al., 1996; Ralston & Ralston, 1994).

Thalamic neurons also show functional signs of plasticity after peripheral or central nervous system injury. Among these changes, receptive field reorganization (Kaas, 1991) and changes in the responses to mechanical and thermal stimuli are common (Koyama et al., 1993). Also, pain is evoked more commonly by stimulation in the region of Vc in patients with chronic pain than in patients with movement disorders (Lenz et al., 1998a). These changes may account for perceptual alterations which occur in patients with chronic pain secondary to peripheral deafferentation. For instance, changes in receptive and projected field organization could explain the telescoping of the limbs experienced by patients with amputations (Jensen & Rasmussen, 1994). Pain and hyperalgesia in patients with chronic pain could be explained by the increased likelihood of provoking pain by stimulation of the region of Vc.

An increase in the rate of action potential bursts has been widely reported in both the thalamus of humans (Jeanmonod et al., 1993; Lenz et al., 1989, 1994a) and in animals following lesion of the nervous system (Albe-Fessard et al., 1983, 1985; Lombard & Larabi, 1983; Rodin & Kruger, 1984). Particular significance has been assigned to the changes in spike train properties of thalamic neurons following deafferentation because the rate of neuronal spike bursts in pain patients is significantly higher in regions of the lateral thalamus (VPL/VPM) representing the painful part of the body (Lenz et al., 1994a). Microstimulation in areas of increased rates of neuronal bursting is more likely to produce pain in both post-amputation and post-stroke CPS patients than in other areas of VPL (Davis et al., 1996; Lenz, 1992; Lenz et al., 1998a). Lesions directed at medial thalamic regions of abnormal bursting have been used as a guide to relieve chronic pain surgically (Ishijima et al., 1975; Jeanmonod et al., 1993). The significance of these findings has been challenged by a study suggesting that the number of bursting cells is equal in patients with pain and in patients with movement disorders (Radhakrishnan et al., 1999). It is unclear how the two patient groups in that study would have compared if the rate of bursting in all cells (Lenz et al., 1994) rather than number of bursting cells were studied (Radhakrishnan et al., 1999).

A recently proposed mechanism of central pain proposes that central pain is the result of an imbalance between two ascending pathways. This hypothesis attempts to explain the burning pain and cold allodynia that can be observed in central pain syndromes. It is proposed that the burning pain of intense cold is mediated by the medial pathway from polymodal nociceptive lamina I spinothalamic neurons (HPC) in monkey lamina I to the cingulate gyrus via the ventral caudal portion of the medial dorsal nucleus (MDvc). It is further proposed that the medial pathway is inhibited by the lateral pathway from cold specific lamina I spinothalamic neurons (COLD) to

insula via the posterior portion of the ventral medial nucleus (VMpo) (Craig et al., 1996). Lesions of the lateral pathway are proposed to release inhibition of the medial pathway and so cause a burning pain similar to that evoked by intense cold. The site at which the lateral pathway may inhibit the medial pathway is unclear at present.

The idea that the ongoing pain of central pain syndromes resembles the burn of cold pain is the most basic tenet of this hypothesis. However, many patients with central poststroke pain (CPSP: 40–50%) do not experience a burning pain (Leijon et al., 1989; Bowsher, 1997). The cold allodynia which is predicted by this hypothesis is found in a minority of patients with CPSP (23% – 5/22) (Boivie et al., 1989). Thus, it is not clear that clinical features found in central pain syndromes are explained by this hypothesis done. Nevertheless, it is a useful construct for guiding research into central pain mechanisms.

In conclusion, studies in humans have demonstrated involvement of both lateral and medial thalamus in pain processing. In lateral thalamus, cells responsive to painful stimuli are located in the core area and in the postero-inferior area. Stimulation in the postero-inferior area or at the posterior aspect of the core can evoke pain or visceral pain suggesting involvement of this area in the mechanisms of somatic and visceral pain. Injections of local anesthetic into monkey VP blocks the ability of monkeys to discriminate temperature differences in the noxious and non-noxious ranges. These findings and particularly the presence of sensory loss following lesions of lateral thalamus suggest that the region of Vc signals the sensory discriminative aspect of acute pain in humans. Anatomic studies are consistent with this area projecting to parietal and parasylvian cortex.

In medial and intralaminar thalamus, some cells responsive to noxious stimuli have been recorded. Pain has been reported by macrostimulation at some sites. STT terminates in the nuclei where these recording and stimulation results are reported. These results provide support for the involvement of medial thalamic nuclei in pain signalling pathways in man. These structures project to cingulate cortex and diffusely to a wide area of cortex.

Abnormalities in lateral thalamus in patients with chronic pain point to involvement of this area in chronic pain in humans. Somatotopic reorganization of Vc occurs in patients who have chronic pain secondary to deafferentation or spinal cord injury. A reorganization of modalities occurs in patients with chronic pain so that the number of sites where thermal sensations are normally evoked by thalamic stimulation is decreased by an amount equal to the increase in the number of sites where pain is evoked. Increased rate of bursting is observed in the deafferented areas of thalamus and is probably related to loss of STT inputs. This abnormal burst firing is most pronounced in the posterior – inferior area of the thalamus involved in signalling pain, suggesting that this firing is involved in the sensation of chronic pain.

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Management of chronic pain

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Pain is the most common reason that patients seek medical attention. Most community-based surveys indicate that at least 15% of the population have chronic pain associated with adverse consequences in varied domains of functioning (Smith et al., 2001). The aggregate cost of unrelieved pain for health care systems and national economies is staggering.

All clinicians encounter patients with chronic pain. An understanding of the nature of pain provides a foundation for comprehensive assessment. Assessment, in turn, guides the long-term therapeutic strategy for enhancing the comfort of these patients and addressing their pain-related disability.

Definition of pain

Pain has been defined by the International Association for the Study of Pain (IASP) as 'an unpleasant sensory and emotional experience which we primarily associate with tissue damage or describe in terms of such damage, or both (Mersky & Bogduk, 1994)'. This definition underscores the potential contribution of sensory, emotional, and cognitive processes in the experience of pain, and the complex relationship between tissue injury and pain perception. Although pain is typically perceived to be a primary indicator of tissue injury, the relationship between pain and tissue damage is neither uniform nor constant. Pain may occur in association with progressive or stable chronic disease, or may occur in the complete absence of an identifiable lesion.

This complexity highlights the need to distinguish the neural processes initiated by tissue injury from pain. The mechanisms induced in neural pathways by potentially tissue-damaging stimuli are termed 'nociception', and are neither necessary nor sufficient for the experience of pain. Pain is the perception of nociception, and like other perceptions, is inherently subjective and can be influenced by a variety of non-nociceptive factors. These factors may be organic, e.g. the aberrant processes in the nervous system that result in neuropathic pain, or psychologic.

Given the subjective nature of pain, pain specialists generally believe that the clinician is best served by assuming that the patient is reporting a true experience, even when a causative lesion cannot be demonstrated. Clinical discussion focused on whether or not a pain is 'real' usually obscures the important issues and is unhelpful. Malingering or factitious pain is rare in clinical practice and, in almost all cases, the clinician is better served by assuming that the pain is truly experienced and then thoughtfully inferring the range of factors – ongoing tissue injury, neuropathic processes and psychologic processes – that may be sustaining the pain.

Early definitions of chronic pain used only a temporal measure, specifically pain persisting longer than 3 months or 6 months. More recently, a broader definition has been preferred. Pain is chronic if it persists for a month beyond the usual course of an acute illness or a reasonable duration for an injury to heal, if it is associated with a chronic pathologic process, or if it recurs at intervals for months or years (Bonica, 1990).

Pain assessment

The complexity of chronic pain underscores the critical importance of a comprehensive assessment as a first step in successful management. This assessment includes characterization of the pain, clarification of the relationship between the symptom and underlying diseases, and evaluation of the various comorbidities that may become important ancillary targets of therapy.

Table 60.1. Pain characteristics

Characteristic	Elements
Temporal	Acute, recurrent or chronic Onset and duration Course Daily variation (including breakthrough pain)
Intensity	Pain 'on average,' Pain 'at its worst,' Pain 'right now' Pain 'at its least'
Location	Focal or multifocal Referred Superficial or deep
Quality	Varied descriptors e.g., aching, stabbing, or burning Familiar or unfamiliar
Exacerbating/ relieving factors	Volitional ('incident pain') vs. non-volitional

Source: Adapted from Portenoy & Kanner (1996).

Evaluation of pain characteristics

Like all symptoms, pain is evaluated by the verbal reports used by patients to describe the experience (Portenoy & Kanner, 1996) (Table 60.1). Temporal descriptors are essential and include the onset and duration of the pain, the occurrences of episodic pain, and the fluctuation during the day.

Measurement of pain severity can be performed using simple unidimensional scales or multidimensional questionnaires. The choice of one or another method in clinical practice is probably less important than its systematic application repeatedly over time (Au et al., 1994). Because measuring pain enhances its visibility to clinicians, measurement and documentation are major elements in the new standards of institutional pain care adopted by the United States Joint Commission on the Accreditation of Healthcare Organizations. In clinical practice, the clinician is usually best served by selecting a simple approach, e.g. a four-point verbal rating scale such as 'none', 'mild', 'moderate', or 'severe', or an eleven-point, '0–10' numeric scale, and incorporating it into the routine. The time frame, e.g. 'pain right now' or 'pain during the past day', and the clinical context, e.g. after a dose of pain medication, must be defined to adequately measure pain.

Other important characteristics include pain location, quality, and factors that exacerbate or relieve the pain (Table 60.1). The medical record of patients with chronic pain should document these characteristics so that they can be tracked over time.

Etiology, inferred pathophysiology, and syndromes

The pain assessment, combined with information from the physical examination and radiographic or laboratory evaluations, may identify a pain syndrome or an etiology for the pain, and allow inferences about the broad set of mechanisms that might be sustaining it. These understandings may suggest additional investigations and guide therapeutic decision making.

If a discrete etiology can be reasonably identified as a cause for the pain, this information may be helpful in clarifying the nature of an underlying disease, indicating prognosis (for the pain or the disease itself), or suggesting the use of specific primary therapies. For example, the identification of a neoplasm impinging on a nerve plexus may allow use of an antineoplastic treatment, such as radiotherapy.

Although the classification of pain according to inferences about the underlying mechanisms oversimplifies complex pathophysiological processes, the approach has utility in clinical practice. Based on the characteristics of the pain and its etiologies, pathophysiology can be labeled 'nociceptive', neuropathic', psychogenic', or 'mixed' (Table 60.2). If pain persists in the absence of an identifiable organic substrate (nociceptive or neuropathic) and there is no evidence of a substantial psychologic contribution, it is best to label the pain 'idiopathic' and reassess in the future.

These pathophysiologic constructs have important therapeutic implications. For example, the response to opioids appears to be relatively better during treatment of nociceptive pains than neuropathic pains (Portenoy et al., 1990). Numerous drugs are now targeted specifically to the treatment of neuropathic pain (see below).

The pain assessment also may identify a discrete pain syndrome, identification of which can guide additional evaluation, indicate the likely etiology, or suggest a therapeutic approach. A very large number of disease-related pain syndromes have been defined and varied systems of classification have been proposed. For example, neuropathic pain may be classified by the presumed site of the sustaining pathophysiology – peripheral vs. central (Table 60.3) (Caraceni & Portenoy, 1998) – or by some combination or neurologic findings and etiology (Table 60.4) (Portenoy, 1996a,b).

In some cases, syndromic labels are imprecise and must be applied cautiously. For example, the generic terms 'chronic pain syndrome', 'chronic non-malignant

Table 60.2. Inferred pathophysiologies

Descriptor	Presumed mechanism	Characteristics
Nociceptive pain	Ongoing activation of somatic or visceral nociceptors as a result of persistent tissue injury; nervous system is presumed to be intact	Quality usually aching, sharp, throbbing; described as 'familiar' pain; evaluation typically reveals a source of tissue injury perceived to be commensurate with the pain
Neuropathic pain	Related to aberrant somato-sensory processing in the peripheral or central nervous systems; presumed to be sustained by neural processes that become independent, in part, from areas of tissue injury	Quality may be like nociceptive pain, e.g. aching from radiculopathy, or may be dysesthetic (abnormal, unfamiliar) and described as burning, shooting, electrical; evaluation may or may not reveal neurologic findings
Psychogenic pain	Predominantly determined by psychologic factors	Quality and characteristics variable; psychiatric assessment allows classification by specific diagnoses, e.g. pain disorder, somatization disorder, etc.
Mixed syndromes	Multiple mechanisms	Varied
Idiopathic pain	Unable to infer	Varied

Table 60.3. Pathophysiologic classification of neuropathic pains

Presumed to be primarily sustained by central mechanisms
Complex regional pain syndrome Type I (reflex sympathetic dystrophy) and type II (causalgia)
Deafferentation pain syndromes
Central pain
Postherpetic neuralgia
Root avulsion pain
Phantom pain
Miscellaneous syndromes (anesthesia dolorosa)
Presumed to be primarily sustained by peripheral mechanisms
Painful polyneuropathies
Compressive mononeuropathies, e.g. discogenic radiculopathy
Infiltrative or ischemic mononeuropathies, e.g. malignant plexopathies
Traumatic mononeuropathies, e.g. postamputation neuroma
Presumed to be sustained by both peripheral and central mechanisms
Lancinating neuralgias, e.g. trigeminal neuralgia

Source: Adapted from Caraceni & Portenoy (1998).

Table 60.4. Etiologic classification in two types of neuropathic pain

	Possible etiologies
Central pain (lesion in cord, brainstem, or cerebrum)	Trauma
	Ischemia
	Neoplasm
	Syrinx formation
	Focal demyelination
	Infection
	Other
Painful polyneuropathy	Metabolic disorders
	Diabetes
	Hypovitaminosis
	Hypothyroidism
	Uremia
	Amyloid
	Drugs or toxins
	Neoplasm
	Hereditary painful polyneuropathy
	Others

pain syndrome' and 'chronic intractable pain syndrome' are often used but not well defined in the literature. Typically, these terms refer to patients who have pain that is perceived to be excessive for the identifiable organic substrate and is associated with a high level of disability and psychiatric comorbidity. Although the challenge that such patients pose – to enhance analgesia while addressing serious functional disturbances – is very real, these labels can be stigmatizing and divert attention from potentially treatable nociceptive or neuropathic processes. The same risk applies to some site-specific terms, such as atypical facial pain, failed low back surgery syndrome, chronic tension headache, and chronic pelvic pain of unknown etiology.

Evaluation of associated phenomena

The assessment of the medical condition, physical impairments, psychological and social functioning, and prior therapies is an integral part of the pain evaluation, and is essential in developing the therapeutic strategy. The evaluation of pain-related disability as part of this process is particularly important. In a broad sense, the goal is to first clarify the degree to which pain is accompanied by disability, and then to deconstruct the latter phenomenon and understand the various physical and psychosocial factors that may be sustaining it. This assessment will identify patients whose pain syndromes would be most appropriately managed using a multimodality approach that includes interventions that specifically address functional disturbances or impaired quality of life. Some patients will be identified whose disability is sufficient to justify referral to a multidisciplinary pain management program.

The psychological assessment should address the interaction among pain and a spectrum of psychological concerns, including coping and distress, personality, and both present and past psychiatric disorders. When a significant psychiatric disorder (i.e. major depression, anxiety disorder, panic disorder, somatization, or severe personality disorder) is suspected, referral for psychiatric evaluation and specialized treatment is warranted.

The psychologic assessment also should attempt to identify behavioural contingencies and secondary gains that may be sustaining the pain and disability. Although families can be a source of great support for patients who are attempting to cope with pain, the dynamics in some homes have maladaptive consequences. Behavioural contingencies may be identified that reinforce pain, or pain-related behaviours (such as strong encouragement to stay in bed), and could be directly addressed as part of the treatment plan developed by the physician.

The history of prior drug use is an essential part of the assessment. This history should address all types of drug use, including prescription drugs, over-the-counter remedies, and both licit and illicit recreational drugs. A history of substance abuse is extremely important and deliberate questioning may be required to obtain sufficient detail (Passik and Portenoy, 1998). The history should clarify the use of specific drugs (including alcohol) and determine whether this use is remote, recent or ongoing.

Pain management

A comprehensive assessment allows the development of a therapeutic strategy that combines appropriate interventions from a very large number of potential candidates (Table 60.5). In some cases, the therapeutic strategy can include a primary treatment directed against an etiology of the pain. In others, the strategy can attempt to address disability and various medical and psychosocial comorbidities, the overall goal of which is to improve function and quality of life in tandem with enhanced comfort. There are many interventions that could be offered in a multimodality approach to the pain itself, and the decision to emphasize one type, e.g. pharmacotherapy, over another, e.g. rehabilitative, or to combine them from the start, must be individualized based on the priorities identified by the assessment.

Table 60.5. Interventions for pain and pain-related disability

Category	Examples
Pharmacotherapy	
Non-opioid	numerous NSAIDs,
Opioid	various opioids,
Adjuvant analgesic	antidepressants, anticonvulsants, and many other classes
Rehabilitative	physical/occupational therapy, orthoses
Neurostimulatory	transcutaneous electrical nerve stimulation
Psychologic	cognitive/behavioural therapy
Anesthesiologic	neural blockade, neuraxial infusion
Neurosurgical	neuroma resection, CNS lesions, deep brain stimulation
Complementary and alternative	acupuncture, massage, chiropractic, mind-body approaches, herbal therapies
Lifestyle changes	weight loss, exercise

Pharmacologic therapies

Analgesic drugs can be divided into the non-opioid analgesics, the so-called adjuvant analgesics, and the opioid analgesics. The non-opioid analgesics refer to acetaminophen, dipyrone, and all the non-steroidal anti-inflammatory drugs (NSAIDs). The term 'adjuvant analgesic' can be applied to any drug that has a primary indication other than pain but is known to be analgesic in specific circumstances.

Non-opioid analgesics: NSAIDs

The NSAIDs comprise an extremely diverse group of drugs (Table 60.6). They all inhibit the enzyme cyclo-oxygenase

Table 60.6. Non-steroidal anti-inflammatory drugs

Chemical class	Drug	Recommended starting dose (mg/d)	Recommended maximum dose (mg/d)
Non-selective COX inhibitors			
Salicylates	aspirin	2600	6000
	diflunisal	1000×1	1500
	choline magnesium trisalicylate	1500×1 then 1000	4000
	salsalate	1500×1 then 1000	4000
Propionic acids	ibuprofen	1600	4200
	naproxen	500	1500
	naproxen sodium	550	1375
	fenoprofen	800	3200
	ketoprofen	100	300
	flurbiprofen	100	300
	oxaprozin	600	1800
Acetic acids	indomethacin	75	200
	tolmetin	600	2000
	sulindac	300	400
	diclofenac	75	200
	ketorolac (IM)	30 (loading)	60
	ketorolac (PO)	40	40
	etodolac	600	1200
Oxicams	piroxicam	20	40
	meloxicam	7.5	15
Naphthyl-alkanones	nabumetone	1000	2000
Fenamates	mefenamic acid	500×1	1000
	meclofenamic acid	150	400
Pyrazoles	phenylbutazone	300	400
Selective COX-2 inhibitors			
	celecoxib	200	400
	rofecoxib	12.5–25	25

(COX) and reduce the synthesis of prostaglandins. Prostaglandins are key inflammatory mediators and sensitize primary afferent nerves that respond to noxious stimuli in the periphery. Although inhibition of these peripheral processes can explain both the analgesic and anti-inflammatory effects of the NSAIDs, prostaglandin inhibition in the central nervous system probably also contributes to the analgesia produced by these drugs (Willer et al., 1989). A central mechanism predominates in the analgesia produced by acetaminophen and dipyrone, which have minimal to no peripheral anti-inflammatory effects, and also presumably accounts for he observed disparity between the anti-inflammatory and analgesic potencies of some NSAIDs (McCormack & Brune, 1999).

Cyclo-oxygenase is produced in two isoforms, COX-1 and COX-2. COX-1 is relatively more constitutive and is involved in physiologic processes, whereas COX-2 is generally more inducible and involved in the inflammatory cascade. Although the commercially available NSAIDs vary in the extent which they affect COX-1 and COX-2 (some, such as meloxicam and nambumetone are relatively COX-2 selective), all are considered to be non-selective COX-1 and COX-2 inhibitors. The inhibition of the constitutive isoform produced by these drugs is associated with their gastrointestinal toxicities.

COX-2 selective inhibitors are now commercially available and substantially reduce the gastrointestinal risks associated with NSAID therapy (Simon et al., 1999; Langman et al., 1999). These drugs do not have demonstrably lesser renal toxicity than the non-selective COX-1 and COX-2 inhibitors.

Although the maximal efficacy of the NSAIDs varies with the type of pain, these drugs are generally considered to be non-specific analgesics. Nonetheless, clinical observation

suggests that they have relatively better efficacy in pain related to a grossly inflammatory process and bone pain, and relatively poorer efficacy in neuropathic pains. Their dose–response relationships are characterized by a minimal effective dose, dose-dependent analgesic effects, and a ceiling dose for analgesia. The existence of a ceiling dose implies that these drugs have limited maximal efficacy and are usually considered first-line for pains that are mild to moderate in severity.

There is large individual variation in the effective dose range and the dose associated with toxicity. Moreover, the maximal efficacy of the NSAIDs varies across drugs in any individual patient. Although an explanation for this phenomenon is lacking, it has important clinical implications. Sequential trials may demonstrate striking differences in effectiveness.

The potential for toxicity during NSAID therapy influences the decision to initiate therapy, the selection of drugs, and the approach to dosing and monitoring. Clinically important adverse gastrointestinal (GI) symptoms occur in about 10% of patients treated with the non-selective COX-1 and COX-2 NSAIDS, and ulcers occur in about 2% (Loeb et al., 1992). Although some surveys suggest that the risk is limited to gastric ulceration, other data implicate both gastric and duodenal lesions. Nausea and abdominal pain are poor predictors of serious GI toxicity; as many as two-thirds of NSAID users have no symptoms before bleeding or perforation.

The factors that have been associated with an increased risk of ulceration include advanced age, higher NSAID dose, concomitant administration of a corticosteroid, and a history of either ulcer disease or previous GI complications from NSAIDs (Loeb et al., 1992). Heavy alcohol or cigarette consumption may also increase the risk. A role for infection with the bacterium, *Helicobacter pylori*, in NSAID-related gastropathy has been suggested but never proved.

There are differences in the potential for GI toxicity among the various NSAIDs. As noted, the COX-2 selective drugs significantly reduce the risk of both GI symptoms and ulcer formation (Simon et al., 1999; Langman et al., 1999). However, comparative epidemiologic data, for these drugs and others, are limited. It is generally accepted that some NSAIDs have a relatively lesser risk of serious GI toxicity (such as the non-acetylated salicylates, choline magnesium trisalicylate and salsalate; ibuprofen and several other proprionic acids; diclofenac, and nabumetone), whereas others have a relatively greater risk (such as ketorolac, piroxicam and the fenamates).

The risk of ulcer can be reduced by concurrent administration of gastroprotective therapy (La Corte et al., 1999). Misoprostol, a prostaglandin analogue, reduces the incidence of NSAID-induced ulcers without reversing anti-inflammatory and analgesic effects. Proton pump inhibitors, such as omeprazole and lansoprazole, also have established efficacy. Studies of H2 blockers have been mixed, but a trial of higher dose famotidine was positive (Taha et al., 1996). Other interventions, such as antacids and sulcrafate, may reduce symptoms but do not decrease ulcer risk.

At the present time, it is reasonable to consider first-line use of the COX-2 selective drugs for patients at relatively high risk for GI toxicity, such as the elderly. Alternatively, co-administration of a gastroprotective therapy could be considered. There are no data presently by which to judge the relative cost-effectiveness of these approaches. Although changing practice patterns suggest that many clinicians are positioning the COX-2 selective drugs ahead of others in all types of patients, studies that confirm the advantages of doing so are still lacking.

All NSAIDs can cause serious renal toxicity (Murray and Brater, 1993). They must be used cautiously in patients who have nephropathies or are likely to have subclinical disease as a result of advanced age, prior treatment with nephrotoxic therapy (such as platinum-based chemotherapy), or an underlying disease.

Although there are large drug-to-drug differences in the degree to which various NSAIDs affect platelet function, the safety of these drugs in patients predisposed to bleeding has not been established in the clinical setting. All these drugs should be used cautiously in patients with a bleeding diathesis. The COX-2 inhibitors do not affect platelets.

Long-term NSAID therapy should be monitored for adverse effects. This monitoring might include periodic testing for occult fecal blood and an evaluation of hemoglobin, renal function and hepatic function. Patients who are predisposed to adverse effects and those who are receiving relatively high doses should be monitored relatively more frequently.

Although studies of dosing protocols in different patient populations are limited, it is prudent to initiate NSAID therapy with gradual dose escalation from a relatively low starting dose when patients have mild to moderate pain or a relatively increased risk of NSAID toxicity. During therapy, dose escalation can be considered if pain is uncontrolled, side effects are not intolerable, and the conventional maximal dose has not yet been reached. Dose escalation will not yield increased effects if the patient is at the ceiling dose. If a ceiling dose or conventional maximal dose is reached without achieving satisfactory analgesia, an alternative NSAID trial should be considered.

Adjuvant analgesics

The adjuvant analgesics include numerous drugs in diverse classes (Table 60.7) (Portenoy, 1998). The term

Table 60.7. Adjuvant analgesics

Multipurpose analgesics	Examples
Antidepressants	
Tricyclic antidepressants	amitriptyline
	desipramine
SSRIs/SNRIs[a]	paroxetine
	venlafaxine
Others	maprotiline
	buproprion
Alpha-2 adrenergic agonists	clonidine
	tizanidine
Corticosteroids	dexamethasone
	prednisone
For neuropathic pain	
Anticonvulsants	gabapentin
	carbamazepine
	phenytoin
	valproate
	clonazepam
	lamotrigine
	topiramate
	tiagabine
	oxcarbazepine
	zonisamide
	levetiracetam
Oral local anesthetics	mexiletine
	tocainide
NMDA receptor antagonists	ketamine
	dextromethorphan
	amantadine
Miscellaneous	baclofen
	calcitonin
Drugs used for CRPS or suspected SMP[b]	calcitonin
	corticosteroids
	clonidine
	prazosin
	phenoxybenzamine
	nifedipine
Topical agents	capsaicin
	local anesthetics
	NSAIDs
For headache	calcium channel blockers
	beta blockers
	antidepressants
	anticonvulsants
	ergot derivatives
	triptans
	ACE inhibitors
For cancer-related bone pain	bisphosphonates, e.g. pamidronate
	calcitonin
	radiopharmaceuticals, e.g. strontium-89 and samarium-153
For painful bowel obstruction	scopolamine
	glycopyrrolate
	octreotide

Notes:

[a] SSRI = serotonin-selective reuptake inhibitor; SNRI = serotonin- and norepineprine-selective reuptake inhibitors.

[b] CRPS = complex regional pain syndrome; SMP = sympathetically maintained pain.

'adjuvant', which was coined in the context of cancer pain management, has become a misnomer as the role of these drugs has been expanded to the primary treatment of many pain syndromes.

Multipurpose adjuvant analgesics

With clinical trials demonstrating efficacy in diverse types of chronic pain, some drug classes are best considered multipurpose analgesics. In this sense, they are similar to the opioids and the NSAIDs.

Antidepressants

The analgesic efficacy of the tricyclic antidepressants (TCAs) has been established in many painful disorders, including headache, arthritis, low back pain, postherpetic neuralgia, painful polyneuropathy, and fibromyalgia (Monks & Merskey, 1999). Both the tertiary amine TCAs (such as amitriptyline, imipramine and doxepin) and the secondary amine compounds (such as desipramine and nortriptyline) have analgesic effects. The supporting evidence is best for amitriptyline and desipramine (Max et al., 1992). Controlled trials also have established the efficacy of some of the serotonin-selective reuptake inhibitors (such as paroxetine), the serotonin- and norepinephrine-selective reuptake inhibitors (such as venlafaxine), and other antidepressant classes. Together, the extant data suggest that all antidepressants have the potential to be analgesic, and that the TCAs are likely to have higher analgesic efficacy overall than the newer drugs.

The analgesia produced by antidepressant drugs is believed to be due to their actions on endogenous monoaminergic pain modulating systems, particularly those that use norepinephrine or serotonin. Although positive mood effects may be beneficial, they are not required for analgesic efficacy.

It is reasonable to consider a TCA as the first-line drug if pain is a primary indication and the patient is likely to tolerate the drug. A tertiary amine, such as amitriptyline,

might be considered first, but avoided if the patient is likely to experience troublesome sedative, anticholinergic, or cardiovascular toxicity. The secondary amine TCAs have fewer side effects and are often used instead. The newer antidepressants usually are better tolerated than the TCAs overall, and should be considered for those who cannot tolerate TCAs or are substantially predisposed to side effects.

Variability in the analgesic responses to antidepressant drugs is common and sequential trials are appropriate in an effort to identify an effective and well tolerated drug. When a TCA is used, the analgesic effect is typically obtained at doses lower than the antidepressant dose and the onset of analgesia is more rapid (within a week) than effects on mood.

Alpha-2 adrenergic agonists

Clonidine and tizanidine are alpha-2 adrenergic agonists with established analgesic effects in a variety of pain syndromes (headache, diabetic neuropathy pain, postoperative pain, postherpetic neuralgia, and cancer pain). A study of systemic clonidine in patients with postherpetic neuralgia supported the potential for analgesia, but suggested that a relatively small proportion of patients respond (Byas-Smith et al., 1995). Tizanidine appears to be better tolerated than clonidine. Somnolence is the most difficult side effect associated with both of these drugs. As a result, it is prudent to initiate a trial with a low dose, then gradually increase the dose if tolerated.

Corticosteroids

The corticosteroids have been shown to improve pain, appetite, nausea, malaise, and overall quality of life in populations with advanced medical illness (Tannock et al., 1989). Non-malignant pain syndromes, including neuropathic pains and pains associated with inflammatory diseases, also may respond. Because the risks associated with this therapy increase with both the dose and duration of use, long-term administration is usually considered only for patients with advanced medical illnesses, such as cancer, and those with chronic inflammatory disorders who are administered the drug as a primary, rather than symptomatic, treatment. Current data are inadequate to evaluate drug-selective differences, dose-response relationships for the various effects, predictors of efficacy, or the durability of effects.

Adjuvant analgesics for neuropathic pain

The advent of a more sophisticated pharmacotherapy for chronic neuropathic pain has been one of the major recent advances in pain management (Sindrup and Jensen, 2000). Although the empirical use of many drugs is occurring before confirmatory trials are done, the clinical experience has been positive and the options for patients with challenging neuropathic pain have never been greater.

Chronic neuropathic pain of any type may be a target of one of the multipurpose adjuvant analgesics. Traditionally, the antidepressants and alpha-2 adrenergic agonists are considered to be among the first drugs considered for neuropathic pain characterized by continuous dysesthesias. Although these drugs also may benefit syndromes characterized by lancinating paroxysmal pains (such as trigeminal neuralgia), they usually are considered after the anticonvulsants or baclofen in this circumstance.

Anticonvulsants

There is extensive experience in the use of anticonvulsant drugs in the treatment of neuropathic pains (Ross, 2000). Concurrent with this role, these drugs also have found an expanding utility in the management of headache and varied psychiatric syndromes.

Older anticonvulsant drugs that have been used for neuropathic pain include carbamazepine, phenytoin, valproate, and clonazepam. These drugs have established analgesic effects in many syndromes characterized by lancinating or paroxysmal neuropathic pains, most notably in trigeminal neuralgia. In recent years, however, they have been administered conventionally for all types of neuropathic pain.

There is now a large and favourable experience with gabapentin, and data from experimental and clinical studies support potential efficacy in any type of neuropathic pain (Sindrup and Jensen, 2000; Ross, 2000). A favourable clinical profile has encouraged its use and, at the present time, it is generally considered a first- or second-line drug for all types of neuropathic pain. The effective dose range for pain appears to be very large. Although some patients respond at a total daily dose of 600 mg, many do not benefit until the daily dose is increased to 3600 mg, and some patients appear to benefit at doses substantially higher.

Other anticonvulsants, including lamotrigine, topiramate, oxcarbazepine, zonisamide, tiagabine, and levetiracetam, have more limited support from clinical trials but are nonetheless used in the management of neuropathic pain. At the present time, the best supporting evidence has been obtained for lamotrigine, which has established efficacy in both trigeminal neuralgia and central pain (Zakrewska et al., 1997; Vestergaard et al., 2001).

In the absence of any contrary data, the administration of the anticonvulsants for pain mirrors the approaches used to manage seizures. To use these drugs optimally, the clinician must appreciate their risks and side effect profiles, and understand appropriate dosing methods and monitoring techniques.

Oral local anesthetics

Systemic administration of local anesthetic drugs may produce analgesia in diverse pain syndromes, including neuropathic pains (Deigard et al., 1988). The availability of oral local anesthetic drugs offers an acceptable approach for long-term therapy. In controlled clinical trials, these drugs have been effective in relieving both continuous and paroxysmal pains. Given the relatively limited experience with these drugs as analgesics, and their side effect profiles, they should be considered second-line approaches. In the United States, mexiletine has been the preferred oral local anesthetic for the treatment of pain, based on a relatively better therapeutic index for serious cardiac and neurological toxicity. Alternative drugs, such as tocainide and flecainide, are also used.

Brief intravenous local anesthetic infusions also are analgesic. This approach, which usually involves the administration of lidocaine in doses of 2–4 mg/kg over 20–30 minutes, may be used in an effort to relieve very severe or rapidly progressive pain, or provide a local anesthetic trial in those patients unable to tolerate the oral drugs. It may be possible to predict the effect of oral therapy with a brief infusion, but the validity of this technique has not yet been sufficiently established to apply it routinely.

Given the side effect and toxicity profiles, oral local anesthetic therapy is best initiated at a low starting dose. Gradual dose escalation should proceed until favourable effects occur, side effects become problematic, or the usual maximal daily dose is reached. The electrocardiogram should be monitored at higher doses and measurement of plasma drug concentrations may be informative.

NMDA receptor antagonists

Recent preclinical studies have established that binding of the excitatory amino acid glutamate at the N-methyl-D-aspartate (NMDA) receptor is involved in the mechanisms that may underlie some neuropathic pains. On the basis of these findings, NMDA receptor antagonists are undergoing intensive investigation as potential analgesics.

Three drugs commercially available in the United States, the antitussive dextromethorphan, the dissociative anesthetic ketamine, and the antiviral amantadine, act at this receptor and may be potentially useful in neuropathic pain (Persson et al., 1995; Nelson et al., 1997). A trial of dextromethorphan may be initiated using a commercially available product that contains neither alcohol nor guaifenasin. It is likely that the analgesic dose will be at least 250 mg per day. Ketamine has been used both via brief infusion and orally. The side effect profile of this drug, which includes nightmares, hallucinations and delirium, is problematic and its use is likely to be limited to patients with severe and refractory neuropathic pain. Experience with amantadine is yet very limited.

Other drugs for neuropathic pain

The GABA agonist baclofen has been shown to be effective in the treatment of trigeminal neuralgia and is now often administered for diverse types of neuropathic pain (Fromm et al., 1984). Similar to its use for spasticity, the usual effective dose range is very broad. Although most patients appear to respond at doses lower than 100 mg per day, some require more than twice this dose to achieve a favourable effect. A serious abstinence syndrome, which includes status epilepticus, can occur with abrupt discontinuation of this drug and the dose always should be tapered before treatment is stopped.

Calcitonin may be effective as a treatment for complex regional pain syndrome (reflex sympathetic dystrophy and causalgia) (Gobelet et al., 1992). Its mode of action in this disorder is unknown. Given the favourable safety profile of this drug, it is empirically considered for a trial in other types of neuropathic pain as well. There are no data by which to judge a dose-response or long-term efficacy.

Other drugs are sometimes used in the treatment of complex regional pain syndrome. Prednisone or some other corticosteroid may be administered on the basis of limited data from clinical trials. Other drugs, such as prazocin and phenoxybenzamine, have been tried based on the observation that sympathetic blockade can help a subset of these patients. Still other drugs, such as nifedipine, are used based on anecdotal observation only.

Topical therapies

The role of topical therapy for pain is enlarging. A lidocaine impregnated patch has now been approved by the U.S. Food and Drug Administration for the treatment of postherpetic neuralgia (Galer et al., 1999). It is being tried more generally for all types of neuropathic pain and other pain syndromes related to injury to skin. Patients with neuropathic pain due to peripheral nerve injury can also be considered for trials of topical local anesthetic creams and gels, which may begin with lidocaine in varied concentrations and extend to a trial of a commercially available eutectic mixture of lidocaine and prilocaine. The latter cream has the ability to produce cutaneous anesthesia with sufficient contact time (Ehrenstrom-Reiz & Reiz, 1982).

Despite equivocal findings in some studies, capsaicin, which depletes peptides in nociceptors and other small primary afferent neurons, continues to be used for both neuropathic and arthritic pain (McCleane, 2000). An adequate trial is generally believed to require three to four applications daily for one month. Musculoskeletal pains of

Table 60.8. Opioid analgesics used during long-term treatment of chronic pain

	Equianalgesic dose (mg)		Half-Life		
Drug	P.O.	I.M./I.V	(Hrs)	(Hrs)	Duration comment
Morphine	20–30[a]	10	2–3	2–4	Standard for comparison; although a single-dose study showed a P.O.: I.M. ratio of 6: 1, the ratio of 2–3: 1 is appropriate for chronic dosing
Morphine CR	20–30	10	2–3	8–12	Various formulations are not bioequivalent
Morphine SR	20–30	10	2–3	24	—
Oxycodone	20	—	2–3	3–4	
Oxycodone CR	20	—	2–3	8–12	
Hydromorphone	7.5	1.5	2–3	2–4	Potency may be greater, i.e. IV hydromorphone: IV Morphine = 3: 1 rather than 6.7: 1, during prolonged use.
Methadone	20	10	12–190	4–12	Although 1: 1 IV ratio with morphine was in single dose study, there is a change with chronic dosing and large dose reduction (75–90%) is needed when switching to methadone.
Fentanyl	—	—	7–12	—	Can be administered as a continuous IV or SQ infusion; based on clinical experience, 100 μg/hr is roughly equianalgesic to IV morphine 4 mg/h.
Fentanyl TTS	—	—	16–24	48–72	Based on clinical experience, 100μg/hr is roughly equianalgesic to IV morphine 4 mg/h. A ratio of oral morphine: transdermal fentanyl of 70: 1 may also be used clinically.

Notes:

[a] Although the PO: IM morphine ratio was 6: 1 in a single dose study, other observations indicate a ratio of 2–3: 1 with repeated administration.

Source: Adapted from Derby et al. (1998).

all types also are candidates for trials of topical NSAIDs, which can be commercially compounded in various formulations (Galer et al., 2000).

Topical opioids, antidepressants (McCleane, 2000), sodium channel blockers such as mexiletine, ketamine, and other drugs are being tried in challenging cases. The relatively low risk of side effects associated with topical therapy ensures that further efforts will be made to identify drugs that may be effective by this route. Studies are needed to establish the benefits and define appropriate therapeutic candidates.

Opioid analgesics

Opioids are mainstay analgesics for acute pain and chronic pain related to cancer, and the role of these drugs in the management of chronic non-malignant pain is rapidly evolving (Portenoy, 1996). Numerous pure mu agonists are available and are the preferred agents for the treatment of acute and chronic pain (Table 60.8).

Opioid drugs have no long-term major organ toxicity and no ceiling effect to analgesia. During dose titration, analgesia increases until unconsciousness or some other intolerable side effect imposes a practical limit. The goal of therapy is to identify a favourable balance between analgesia and side effects. Responsiveness varies with characteristics of the patient and pain syndrome, but there is no characteristic that imparts opioid resistance. Accordingly, any severe chronic pain is potentially a candidate for an opioid trial. Selection of a patient for a trial must be based on a careful assessment and is influenced by the pain syndrome and conventional practice (first-line therapy for moderate or severe cancer pain, but generally not first-line for non-malignant pains), availability of safe alternative therapies, the risk of side effects, and the likelihood that the patient is able to use the drug responsibly.

The most important opioid side effects are constipation, nausea, vomiting, sedation and mental clouding. Tolerance develops to many side effects, usually in the first

Table 60.9. Common strategies to manage opioid side effects

Constipation
– best managed with combination of cathartic and stool softener
– osmotic or lavage agents can be useful
– refractory constipation can be treated with a trial of oral naloxone
Nausea, Vomiting
– metoclopramide or other dopamine antagonists
– scopolamine or other anticholinergic drugs
– ondansetron or other 5-HT antagonists
– change route of administration
– switch opioid
Sedation
– methylphenidate or other psychostimulant
– switch opioid

Source: Adapted from Caraceni & Portenoy (1998).

weeks of therapy. There are numerous strategies for the treatment of common opioid side effects (Table 60.9) (Caraceni and Portenoy, 1998). Long-term opioid therapy is fully consistent with functional restoration. Cognitive impairment can usually be avoided and successful therapy is marked by the capacity to drive, work, enjoy social activities and avocations, and otherwise capitalize on analgesia to improve quality of life.

Opioid therapy may be compromised by confusion concerning the phenomena of tolerance, physical dependence and addiction (Portenoy & Payne, 1997). Tolerance refers to a process by which exposure to a drug at a constant dose results in a decreasing effect, or the need for a higher dose to maintain an effect. It is entirely distinct from addiction. In humans, tolerance to non-analgesic opioid effects, such as somnolence, is favourable and allows safe escalation of the opioid dose. Tolerance to analgesic effects is a concern, but large surveys have established that loss of analgesia rarely occurs in opioid-treated patients with stable pain syndromes.

Physical dependence is a physiological phenomenon characterized by the development of an abstinence syndrome following abrupt discontinuation of therapy, substantial dose reduction, or administration of an antagonist drug. It is distinct from addiction and the term 'addicted' should never be used to refer to the capacity for abstinence. If abstinence is avoided, physical dependence is clinically irrelevant.

A task force of the American Medical Association defined addiction as 'a chronic disorder characterized by the compulsive use of a substance resulting in physical, psychological or social harm to the user and continued use despite that harm' (Rinaldi et al., 1988). This statement emphasizes that addiction is a psychological and behavioural syndrome with several fundamental features: (i) loss of control over drug use, (ii) compulsive drug use, and (iii) continued use despite harm. The syndrome is characterized by a genetic predisposition, which interacts in complex ways with psychosocial factors, situational factors and access to abusable drugs. In treating pain patients, addiction is suggested by the development of aberrant drug-related behaviours consistent with these features (Portenoy & Payne, 1997).

Information about addiction liability derives from limited published surveys that report clinical experience in selected populations. In populations with acute pain and those with chronic cancer pain, iatrogenic addiction is rare. In populations with non-malignant pain, the likelihood of iatrogenic addiction is unknown and presumably relates to various risk factors, such as a prior history of drug abuse, a family history of drug abuse, major psychiatric pathology, and social disruption (Compton et al., 1998). Clinicians who are considering the use of an opioid must assess for these factors and monitor patients for the development of aberrant drug-related behaviours over time. Monitoring is particularly important if treatment is offered to patients with a prior or current history of substance abuse (Portenoy & Payne, 1997).

Guidelines for the long-term administration of opioid drugs are well accepted for populations with cancer pain (Jacox et al., 1994). Although additional guidelines should be considered when treating patients with non-malignant pain (Table 60.10) (Portenoy, 1994), the approach to optimizing pharmacologic outcomes is the same irrespective of the clinical population. The most important principle is individualization of therapy, which is accomplished through gradual dose titration. Doses should be increased until a favourable outcome is achieved or treatment-limiting side effects occur. The absolute dose is immaterial as long as there is a favourable balance between analgesia and side effects. The use of extended-release opioids or opioids of long half-life (particularly methadone) is preferred during chronic therapy.

Other analgesic therapies

Patients with chronic pain may be appropriate for any of a very large number of alternative analgesic therapies (Loeser, 2001). Many patients benefit from a multimodality strategy that combines systemic pharmacotherapy with other approaches (Table 60.5).

Psychological interventions and rehabilitative therapies may improve comfort and are essential elements in a

Table 60.10. Guidelines for opioid therapy in populations with non-malignant pain

1. Therapy is based on a comprehensive assessment, which should judge the nature and consequences of the pain, the availability of alternative therapeutic strategies, and the likelihood of opioid responsiveness and responsible drug use.
2. A history of substance abuse or other factors that may predispose to abuse or addiction suggest the need for a more detailed evaluation and the use of strategies during therapy to improve monitoring of drug-taking behaviour.
3. A single practitioner should take primary responsibility for treatment.
4. Patients should give informed consent before starting therapy; accurate information about addiction liability and the occurrence of physical dependence should be provided and the potential for cognitive impairment and constipation should be discussed.
5. After drug selection, doses should be given around-the-clock; several weeks should be agreed upon as the period of initial dose titration, and although improvement in function should be continually stressed, all should agree to at least partial analgesia as the appropriate goal of therapy.
6. Failure to achieve at least partial analgesia at relatively low initial doses in the non-tolerant patient raises questions about the potential treatability of the pain syndrome with opioids.
7. Emphasis should be given to capitalizing on improved analgesia by gains in physical and social function; opioid therapy should be considered complementary to other analgesic and rehabilitative approaches.
8. In addition to the daily dose determined initially, patients should be permitted to escalate dose transiently on days of increased pain; two methods are acceptable: a) prescription of additional 'rescue doses' of the same drug or an alternative short-acting opioid; b) instruction that one or two extra doses may be taken on any day, but must be followed by an equal reduction of dose on subsequent days.
9. Initially, patients must be seen and drugs prescribed at least monthly. When stable, less frequent visits may be acceptable.
10. Evidence of drug hoarding, acquisition of drugs from other physicians, uncontrolled dose escalation, or other aberrant behaviours must be carefully assessed. In some cases, tapering and discontinuation of opioid therapy will be necessary. Other patients may appropriately continue therapy within rigid guidelines. Consideration should be given to consultation with an addiction medicine specialist.
11. At each visit, assessment should specifically address (a) comfort (degree of analgesia), (b) opioid-related side effects, (c) functional status (physical and psychosocial), and (d) occurrence of aberrant drug-related behaviours; these four outcomes should be documented repeatedly in the medical record.

Source: Adapted from Portenoy (1994).

broader approach that addresses pain-related disability. There is strong evidence that the psychological approaches benefit patients with pain. Support for the various rehabilitative therapies derives from an extensive clinical experience. The psychological approaches usually include cognitive, e.g. relaxation training, biofeedback, hypnosis, and varied other techniques, and behavioural therapies. The rehabilitative interventions include therapeutic exercise, the use of orthoses, and various modalities such as heat and cold. Transcutaneous electrical nerve stimulation also is widely used and supported by abundant clinical experience.

Invasive therapies for pain are typically performed by anesthesiologists (sometimes others) with advanced training in pain management. These techniques include injection therapy, neural blockade, neuraxial analgesia techniques, and central nervous system stimulation approaches. Despite very limited data from controlled clinical trials, local anesthetic and corticosteroid injections are widely used to manage neuropathic pain, myofascial and joint pain, and spinal pain syndromes. There is an extensive experience with long-term intraspinal therapy and dorsal column stimulation, and the utility of both these approaches is expanding with improved technology and new drug development. The availability of these techniques to manage pain that has not responded to conservative therapies has relegated the use of chemical and surgical neuroablative interventions to rare patients.

Many patients with chronic pain seek complementary and alternative medicine approaches. Pain specialists, whose practice includes many conventional interventions supported only by clinical experience, are usually open to those modalities for which there is some limited evidence and a high likelihood of safety. Acupuncture, lumbar chiropractic manipulation, and therapeutic massage are widely used.

Conclusion

The past three decades have witnessed an extraordinary increase in knowledge concerning the neurobiology of pain and the potential of diverse types of analgesic interventions. All clinicians should be able to perform a comprehensive pain assessment that clarifies the nature of the pain and pain-related comorbidities, and facilitates a therapeutic strategy that may enhance comfort and function. The non-specialist can implement and monitor many components of this strategy. Patients with refractory pain, and those with pain associated with severe disability, should be considered for referral to specialists in pain management.

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61

Migraine

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Migraine is a common, chronic, multifactorial, neurovascular disorder, typically characterized by attacks of severe headache, associated autonomic and neurological symptoms, and general malaise (Ferrari, 1998). The disease is beset by myths, including that it is mainly 'a psychological response to stress'. Despite that migraine is among the chronic diseases with the highest disability and socioeconomic impact (Menken et al., 2000), it also is among the most undertreated neurological conditions. More than two-thirds of patients either have never consulted a physician for their migraine, or have stopped doing so. Recent progress in the scientific basis of the diagnosis, epidemiology, pathophysiology, and pharmacology of migraine has, however, significantly improved the diagnostic and therapeutic options for this enigmatic brain disorder.

Clinical features and diagnosis

The International Headache Society (IHS, 1988) has considerably improved the diagnosis of migraine and other headache syndromes. Different types of headache, rather than patients, are diagnosed. Patients may have concurrent types of headache (e.g. migraine and tension-type headache), which should be treated separately. The two main types of migraine are migraine without aura (previously known as common migraine), occurring in 75% of migraineurs, and migraine with aura (previously classic migraine), occurring in one-third of patients (Table 61.1). Up to 33% of migraineurs experience both types of attacks during their lifetime (Russell et al., 1995).

Aura symptoms nearly always include visual (99% of patients), together with sensory (31%) or aphasic (18%) symptoms and, rarely, motor ones (6%) (Russel & Olesen, 1996). Aura symptoms typically progress over minutes, or different symptoms succeed one another. They usually occur at alternating body sides in different attacks, nearly always precede the headache and usually last between 5 and 60 minutes; motor symptoms may last longer. Up to 42% of patients may have attacks of migraine aura without headache. In patients with a typical history of migraine and an uneventful standard neurological examination, ancilliary investigations are redundant. The following 'alarm symptoms' may warrant a CT- or MRI-scan: aura symp-

Table 61.1. Simplified diagnostic criteria for migraine with and without aura

Migraine without aura
- Attacks lasting 4–72 hours[a]
- At least two of the following four headache characteristics:
  - unilateral
  - pulsating
  - moderate to severe[b]
  - aggravated by movement
- At least one associated symptom:
  - nausea or vomiting
  - photophobia
  - phonophobia

Migraine with aura[c]
- One or more transient focal neurological aura symptoms[d]
- Gradual development of aura symptom over >4 minutes, or several symptoms in succession
- The aura symptoms last 4–60 minutes
- Headache follows or accompanies aura within 60 minutes

Notes:
[a] duration applies to untreated or unsuccessfully treated attacks
[b] disturbing or precluding daily activities
[c] criteria for typical aura only; for atypical aura see IHS (1988)
[d] referring to focal cortical or brainstem dysfunction
Source: Adapted from IHS (1998).

toms always at the same body side or with acute onset without spread or either very brief (<5 min) or unusually long (> 60 min) duration; sudden change in migraine characteristics or a sudden, substantial increase in attack frequency; onset above age 50; aura without headache; or abnormal neurological examination. EEG is seldomly useful, except in the rare cases when epilepsy is suspected.

Differential diagnosis

Migraine may be difficult to differentiate from tension-type headache (previously known as stress-, tension-, or muscle contraction headache), and many patients have both headache types. The diagnostic criteria are opposite to those for migraine (IHS, 1988). Thus, tension-type headache has at least two of four characteristics: bilateral, non-pulsating, mild to moderate, and no aggravation by movement; there is no or only mild nausea or photophobia and phonophobia.

Overuse of antimigraine or analgesic drugs, especially those which also contain caffeine, frequently complicates migraine. The overuse syndrome is characterized by gradual increase of headache frequency and drug consumption, and a change of the headache characteristics. Ultimately, patients use 'painkillers' or other headache medication daily, to treat daily occurring atypical headaches, alternating with migraine-like aggravations. Anyone who has frequent headaches, should be specifically asked about their consumption of caffeine and analgesics, particularly those obtained without prescription (as these are usually not considered a medication by patients). The number of doses used, rather than the total weekly amount of drug, is important. Thus, daily use of a low dose is much riskier than a very large amount on one day a week. Frequent headache sufferers who regularly use headache drugs more often than 1 or 2 days per week should withdraw abruptly from all these drugs (and caffeine) (Hering & Steiner, 1991). After a few weeks of withdrawal symptoms, the severity and frequency of the headaches usually decrease and after 2 to 3 months the original headache characteristics return, enabling a correct diagnosis and treatment (see Chapter 64).

Epidemiology

Migraine patients are defined as individuals who have had at least two attacks with aura or at least five attacks without aura (IHS, 1988). One-year prevalence figures, i.e. migraine patients who have had at least one attack in the previous year, are remarkably similar across western countries and are primarily dependent on sex and age. Between age 10 and 19 there is a sharp but transient rise of the 1-year prevalence of migraine, with a peak around age 14–16 (Stewart et al., 1994); for women this is followed by a less abrupt second rise until age 40 (Stewart et al., 1994). Thus, overall 10–12% of the general population are active migraineurs. From age 16, migraine is 2–3 times more frequent in females than in males; females around age 40 have the highest prevalence (24%). The lifetime prevalence of migraine is at least 18% of the general population, but these figures are deflated by recall bias at older age (Russell et al., 1995). Onset of migraine may be at all ages, but is nearly always (90%) below age 50; the peak incidence is around puberty. The median attack frequency is 1.5 attacks per month; at least 10% of patients have weekly attacks (Stewart et al., 1994). The median attack duration is just under 1 day; one fifth of the patients have attacks lasting 2–3 days. Thus, more than 5% of the general population have at least 18 migraine days per year and more than 1% at least 54 days.

Pathophysiology

Anyone can have a migraine attack occasionally without necessarily being a migraine patient. It is not the attack but the repeated occurrence that is abnormal. Attacks seem to involve physiological mechanisms, initiated by migraine- and patient-specific triggers. Attacks recur only when the threshold for triggers is reduced or when the triggers are particularly strong and frequent. Genetic factors, most likely involving ion channel and receptor function, appear to set the individual threshold; internal and environmental factors such as hormonal fluctuations, fatigue, relaxation following stress, and substance misuse may modulate this set-point (Haan et al., 1996; Ferrari, 1998; Montagna, 2000).

Complex genetic factors are involved in migraine (Russell & Olesen, 1995; Haan et al., 1996; Montagna, 2000). The study of genetic factors in migraine has mainly focused on familial hemiplegic migraine (FHM), a rare, autosomal dominant subtype of migraine with aura, often misdiagnosed as epilepsy. Attacks are characterized by hemiparesis during the aura (IHS, 1988; Haan et al., 1996; Montagna, 2000). FHM is part of the migraine spectrum and can thus be used to identify candidate genes for migraine. In the majority of patients, FHM is caused by missense mutations in the so-called CACNA1A gene on chromosome 19p13, encoding the α_{1A} subunit of a P/Q type voltage-dependent calcium channel (Ophoff et al., 1996). These neuronal calcium channels are involved in cortical spreading

depression (see below) and release of neurotransmitters, including acetylcholine, neuroexcitatory aminoacids such as glutamate and aspartate, monoamines such as 5-HT, and calcitonin-gene-related-peptide (CGRP). Both clinical, genetic, and neurophsyiological evidence is accumulating that dysfunction of ion channels is involved in the pathophysiology of migraine (Ferrari, 1998).

Neurophysiological, magnetic resonance spectroscopy, biochemical, and epidemiological data suggest that migraineurs have an interictal state of cortical hyperexcitability, characterized by a reduced threshold and increased responses (Welch & Ramadan, 1995; Ferrari, 1998; Schoenen & Thomsen, 1999). The excitability level is proportional to the attack frequency. Its physiological basis may be defective mitochondrial oxidative phosphorylation, low intracellular magnesium, increased levels of neuroexcitatory amino acids, inherited dysfunction of calcium or other ionchannels, or a combination of these factors (Ferrari, 1998).

During attacks, PET studies have identified an area of increased cerebral blood flow in the upper brain stem (Weiler et al., 1995). This brainstem area may represent the 'migraine generator' involved in the initiation and maintenance of migraine attacks (Fig. 61.1, see colour plate section).

The migraine aura is most likely caused by 'cortical spreading depression' (CSD) (Lauritzen, 1994), a depolarization wave that propagates across the brain (mainly occipital) cortex at 2–3 mm/min and is associated with transient depression of spontaneous and evoked neuronal activity. The depression wave lasts several minutes and is preceded by a front of brief neuronal excitation and intense spike activity. During CSD there is dramatic failure of brain ion homeostasis and efflux of excitatory amino acids from nerve cells.

Activation of the trigeminovascular system (TVS; Fig. 61.1, see colour plate section) is pivotal to the pathogenesis of the migraine headache and associated symptoms. Afferent fibres, arising from the ophthalmic division of the trigeminal nerve and the upper cervical spinal cord segments, innervate the proximal parts of the large cerebral vessels, the pial vessels, large venous sinuses, and dura mater. These sensory fibres carry nociceptive information and project centrally, terminating within the trigeminal nucleus caudalis in the lower brain stem and upper cervical cord. The information is relayed further via the quintothalamic tract to the thalamus and cortical pain (perception) areas.

Depolarization of the trigeminal ganglion or its perivascular nerve terminals activates the TVS. This gives rise to central transmission of nociceptive information and retrograde release of powerful vasoactive neuropeptides from the perivascular nerve terminals. In animal experiments, these neuropeptides promote a sterile neurogenic inflammation response, consisting of two components: (i) dural vasodilation, mediated via release of CGRP from trigeminal A-delta-fibres; and (ii) dural plasma extravasation, mediated via release of neurokinin A and substance P from trigeminal C-fibres. Neurogenic inflammation has yet to be demonstrated in migraine.

Non-pharmacological treatment

Non-pharmacological treatments for migraine, including avoidance of putative migraine triggers, have no demonstrated efficacy, and are usually disappointing. Migraineurs have an inherited tendency to attacks, which may be triggered by a wide variety of factors. Complete avoidance seems impossible. There is no good evidence that specific diets ameliorate migraine. When overuse of analgesics and caffeine is present, stopping can reduce migraine attack frequency and severity.

Prophylactic drug-treatment

Preventive efficacy has been demonstrated for the β adrenoceptor-blockers propranolol and metoprolol (and probably also atenolol, timolol and nadolol), and the antiepileptic drug valproate (which has GABA-ergic and ion channel activity). Other β-blockers or antiepileptic drugs have no demonstrated efficacy. The 5-HT receptor antagonists pizotifen and methysergide, and the non-selective calcium-channel blocker flunarizine, are probably also effective, but formal evidence is limited (Goadsby, 1997a). The widespread use of amitriptyline is largely based on its efficacy in concurrent tension-type headaches, rather than on preventing migraine attacks. In North America such headaches are often referred to as 'minor migraines', which may explain the confusion. The calcium channel blockers nifedipine, nimodipine and verapamil, the α2-adrenoceptor agonist clonidine, some NSAIDs, the herbal drug feverfew, riboflavin, and hormonal manipulation, are often recommended, but evidence for preventive efficacy is lacking or unconvincing. Verapamil, however, is highly effective in preventing cluster headache attacks, and NSAIDs are effective symptomatic treatments of migraine.

The efficacy of the current migraine prophylactics is limited: at most 55% of patients will have a 50% or more reduction of the attack frequency (Ramadan et al., 1997; Goadsby, 1997b). The individual reponse is unpredictable

and must be determined by 'trial and error', taking into account individual (contra-)indications. Due to the non-specific pharmacology, there is a high risk of adverse events. Therefore, only patients with two attacks or more per month, which respond unsatisfactory to symptomatic treatment, should be considered for preventive treatment. There is a great need for better prophylactic agents.

Attack treatment

Specific and non-specific symptomatic antimigraine drugs treat the headache and associated symptoms only, not the aura. Non-specific drugs include analgesics such as aspirin and paracetamol, rapidly absorbable NSAIDs, prokinetic and antiemetic compounds such as metoclopramide and domperidone, and narcotics such as codeine, pethidine and morphine (Welch, 1993; Ferrari & Haan, 1997). The use of narcotics and barbiturates is highly controversial, not supported by scientific evidence, and is associated with prominent side effects and a high risk of abuse and dependency. Most patients who require narcotics are in fact overusing headache or migraine agents. After withdrawal, they rarely require narcotics anymore.

In migraine attacks, oral resorption is impaired because of vomiting or gastrointestinal stasis and dilatation, even in not nauseated patients. Thus, to optimize drug administration the parenteral route is usually preferred. However, most patients prefer tablets. Use of metoclopramide or domperidone 30 minutes prior to analgesics, improves their oral resorption and combats the nausea, but there is no evidence that analgesic efficacy is improved. The choice of drug, dose, and route of administration, depends on the characteristics and frequency of the attacks, and on the preferences of and contraindications for the patient. Not all attacks in a given patient are necessarily treated with the same drug or dose. Mild attacks may be treated with analgesics or NSAIDs, while severe, disabling ones usually respond better to specific antimigraine drugs. The Migraine Disability Assessment Scale (MIDAS) has proven to be a useful and easy to use clinical instrument to predict acute treatment needs (Lipton et al., 2000).

Ergot alkaloids

For decades ergots were the only drugs specifically for migraine. Most of our so-called knowledge is, however, based on 'authoritative reviews' and textbooks, largely summarizing uncontrolled studies and personal experiences. This surprising lack of scientific evidence contributes to the striking differences between countries in frequency of use, recommended dosing, formulations, and combinations with other compounds. Recent reviews conclude that ergot derivatives display a complex pharmacology and erratic pharmacokinetics, have poorly justified dose recommendations and only limited evidence for efficacy, and show potent and sustained generalized vasoconstrictor effects (Dahlöf, 1993; Tfelt-Hansen et al., 2000). As a result, their clinical use is complicated, results are unpredictable, and complications (including ischemia of organs and limbs, overuse syndromes, and rebound headaches) are frequent; ergot derivatives are strictly contraindicated in the presence of cardiovascular disease. The major reasons for prescribing ergots today seem to be that they have been around for a long time and are much cheaper than the newer drugs. The European Consensus Committee concluded that generally triptans (see below) are to be preferred but when patients have a satisfactory response to ergots it is not necessary to switch as long as there is no escalation of the use of ergots beyond 1–2 days per week.

Table 61.2. The triptans (5-$HT_{1B/1D}$ receptor agonists)

Triptan	Recommended oral doses (mg)	Company
In clinical use (year)		
Sumatriptan (1991)	25; 50; 100	GlaxoSK**
Zolmitriptan (1997)	2.5; 5	AstraZeneca
Naratriptan (1997)	2.5	GlaxoSK**
Rizatriptan (1998)	5; 10	Merck
Almotriptan (2001)	12.5	Almirall-Prodesfarma
Approved for registration		
Eletriptan (2001)	20; 40; 80	Pfizer
Frovatriptan (2001)	unknown	Vernalis

Triptans

Advances in the understanding of the neurobiology of migraine have resulted in the development of the novel class of selective 5-$HT_{1B/1D}$ (serotonin; 5-hydroxytryptamine$_{1B/1D}$) receptor agonists, known as the triptans (Table 61.2). It is likely that the 5-$HT_{1B/1D}$ agonist activity is the major basis for their therapeutic effects, although 5-HT_{1F} action may be involved as well. Triptans have three potential mechanisms of action, cranial vasoconstriction, peripheral neuronal inhibition, and inhibition of transmission through second order neurons of the trigeminocervical complex (Ferrari 1998; Goadsby et al., 2002). The relative importance of each

of these mechanisms remains uncertain (Fig. 61.1, see colour plate section).

In comparison to ergot derivatives, triptans have a number of distinct advantages. These include selective pharmacology, simple and consistent pharmacokinetics, evidence-based prescribing instructions, established efficacy based on an enormous body of well-designed placebo-controlled and direct comparative clinical trials, modest side effects, and a well-established safety record; their most important disadvantage is the higher price (Goadsby et al., 2002; Ferrari et al., 2001). The triptans are now the leading class of acute migraine medications in many western countries. They have proven to be very effective and generally well-tolerated acute migraine treatments, which have made an enormous difference for many patients. However, although the triptans currently are the most effective antimigraine drugs available, they certainly are no wonder drugs.

Sumatriptan was the first triptan available and undoubtedly is the most extensively investigated antimigraine drug (Plosker & McTavish, 1994; Visser et al., 1996a,b,c; Goadsby et al., 2002; Ferrari et al., 2001). Since its launch, first as a 6 mg subcutaneous auto-injector and 100 and 50 mg oral formulations, and later as 20 mg nasal and 25 mg rectal formulations, six other triptans have been marketed all in oral formulations (Table 61.2). For the oral triptans, the following effects can be expected (Goadsby et al., 2002; Ferrari et al., 2001). Approximately 60% of migraine patients improve by 2 hours postdose and up to 40% are pain free at that time. Up to one-third of the responders may experience recurrence of the headache (relapse) within 24–48 hours; repeated drug administration is then usually effective. Prescribing physicians should explain this to their patients. The mechanism of headache relapse is unknown, but seems, contrary to earlier belief, unrelated to the drug plasma half-life. Adverse events (AEs) are frequent, but in the great majority very mild and of short duration. The most frequent AEs include tingling, paresthesias, and warm and hot sensations in head, neck, chest, and extremities; less frequent AEs are dizziness, flushing, and neck pain or stiffness. Of more relevance are the so-called 'chest symptoms' which mainly consist of short-lived heaviness or pressure in the arms and chest, shortness of breath, anxiety, palpitations, and, very rarely, chest pain (Visser et al., 1998a,b,c; Ferrari et al., 2001). When patients are warned about these events, they rarely cause problems. However, they sometimes closely mimic angina and cause alarm. Severe and sustaining sumatriptan-associated chest symptoms should be taken seriously and should prompt cardiovascular investigation.

The mechanism of triptan-induced chest symptoms is unknown. Triptans may cause constriction of the coronary arteries, which is usually short-lived and mild. In atherosclerotic arteries, however, the constrictor effect of triptans may clinically be more important. Furthermore, use of triptans has been associated with myocardial or cerebral ischemia in some individuals, although very few given the very substantial total human exposure to triptans and mainly with pre-existing coronary or cerebral artery disease (Wilkinson et al., 1995; Welch et al., 2000). Myocardial ischemia can thus not be excluded in some patients with chest symptoms, though it seems an unlikely mechanism in most. Other mechanisms such as esophageal spasms, pulmonary vasoconstriction, intercostal muscle spasm, or bronchospasm, seem more likely (Ferrari, 1998). Thus, when prescribed prudently, i.e. not in patients with cardio- or cerebrovascular disease or risk factors, the triptans are safe. The risk of triptan-induced myocardial ischemia in migraineurs without clinical evidence of cardiovascular disease appears no greater than the risk is of exercise-induced myocardial ischemia in sportsmen (Ferrari, 1998).

A large meta-analysis investigated the relative efficacy and tolerability of the oral triptans (Ferrari et al., 2001; Goadsby et al., 2002). Rizatriptan 10 mg (especially to rapidly and consistently achieve freedom of pain), eletriptan 80 mg (especially when high efficacy and low recurrence are favoured over tolerability) and almotriptan 12.5 mg (especially when very good tolerability in combination with good efficacy are favoured) offer the highest likelihood of success. The lower doses of rizatriptan (5 mg) and eletriptan (40 mg) may be good starting doses in many patients. Sumatriptan 100 mg and 50 mg provide good efficacy and tolerability and by far the longest clinical experience; the 50 mg dose has a slightly better efficacy/tolerability ratio but also a slightly lower consistency. In addition, sumatriptan offers the widest range of formulation options (oral, suppositories, nasal, and subcutaneous), allowing tailor-made treatments for individual patients. Naratriptan 2.5 mg offers very good tolerability coupled to a slower onset of improvement; this can be useful in patients with mild or moderate migraine. Zolmitriptan 2.5 mg and 5 mg are good alternatives in many patients; they offer no specific advantages but there are also no specific flaws. Frovatriptan cannot be fully judged in view of the lack of data but doesn't seem to offer any particular advantage; available efficacy data suggest inferior results compared to most of the other oral triptans.

Sumatriptan is also available in parenteral formulations (for review, see Goadsby et al., 2002). Of all triptans, subcutaneous sumatriptan has the best pharmacokinetic profile (Tmax = 10 min; bioavailability = 96%). It is unaffected by

gastro-intestinal disturbances during migraine attacks and has excellent clinical efficacy (response of 76% and pain free of 48% already at 1 hour post dose) and within-patient consistency over multiple attacks (up to 90% for headache response in two out of three treated attacks. The main disadvantages are that patients need to inject themselves, and that the incidence of AEs is higher and the intensity is generally greater than for oral triptans, although still usually acceptable and short-lived. This may be related, among other factors, to the fixed 6mg dose; a 3–4mg dose may suffice in many patients. Subcutaneous sumatriptan is also highly effective in the acute treatment of cluster headache attacks. The efficacy and tolerability profiles of rectal and intranasal sumatriptan are very similar to those of the oral formulation, although many users of the nasal formulation complain about the bitter taste. Both formulations may be useful in nauseated and vomiting patients. Intranasal sumatriptan 20 mg is so far the only triptan with at least some demonstrated efficacy in adolescents. A number of studies of oral triptans in adolescent migraine have failed, most likely because adolescent attacks usually are short lasting and associated with prominent gastrointestinal symptoms; spontaneous early remissions generate high placebo responses.

When selecting a triptan, it is important to realize that patients' characteristics and preferences vary and that response to and tolerability for a triptan cannot be predicted in individual patients. As a consequence, optimizing therapy involves trial-and-error: if the first triptan is not successful one may successfully switch to another. Physicians thus need more than one triptan in their repertoire to optimally treat migraine patients. Differences in efficacy and tolerability among the oral triptans at optimal doses are relatively small, but clinically relevant for individual patients.

In conclusion, migraine is a common, very disabling, multifactorial, neurovascular disorder. Prophylactic treatment to prevent attacks may prove highly effective in individual patients, but often provides rather disappointing results, associated with prominent adverse events. There is a great need for specific and better migraine prophylactic drugs. In contrast, acute attack treatment with the novel class of triptans has greatly improved the life of many patients. They often provide very good efficacy and tolerability. Highest likelihood of consistent success is offered by 6mg subcutaneous sumatriptan (highest efficacy with reasonable tolerability); 10 mg oral rizatriptan (very good efficacy and very good tolerability), 80 mg eletriptan (very good efficacy and good tolerability), and 12.5 mg almotriptan (good efficacy and excellent tolerability). Sumatriptan provides the longest clinical experience and widest range of formulations allowing tailor-made treatments for individual patients. Other triptans and dosages are also good alternatives in many patients. When prescribed prudently (i.e. not in patients with cardio- or cerebrovascular disease or major risk factors), triptans are safe.

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62

Cluster headache, other trigeminal autonomic syndromes and the short-lived headaches

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Of the primary headache syndromes, cluster headache and the related trigeminal autonomic cephalgias, as well as some of the short-lived headache syndromes (Table 62.1), stand out for their very well-defined phenotypes and considerable associated disability. The trigeminal autonomic cephalgias (Goadsby & Lipton, 1997) offer some exceptional physiological insights (see also Chapter 79 (Volume 2)) (May & Goadsby, 1999) and are very rewarding to treat. Books have been written on cluster headache (Kudrow, 1980; Olesen & Goadsby, 1999; Sjaastad, 1992), and readers are referred to these for greater detail. A further issue arises as to what is short-lived; in this context attacks that commonly are measured in minutes (Table 62.2) will fulfil that definition.

Table 62.1. Primary headache – cluster headache, other TACs and short-lasting headaches

Trigeminal autonomic cephalgias (TACS)	Other short-lasting headaches
Cluster headache	Primary stabbing headache[b]
Paroxysmal hemicrania	Benign cough headache
SUNCT[a] syndrome	Hypnic headache
Hemicrania continua	

Notes:

[a] Shortlasting unilateral neuralgiform headache with conjunctival injection and tearing.

[b] Currently known as idiopathic stabbing headache but due for change in the second edition of the International Headache Society classification.

Cluster headache

Cluster headache is a relatively rare very severe episodic primary headache with a population prevalence at about 0.1%. It has been recognized for many years with among the earliest known description appearing in Gerhard van Swieten's medical textbook (Isler, 1993):

A healthy robust man of middle age [was suffering from] troublesome pain which came on every day at the same hour at the same spot above the orbit of the left eye, where the nerve emerges from the opening of the frontal bone: after a short time the left eye began to redden, and to overflow with tears; then he felt as if his eye was slowly forced out of its orbit with so much pain, that he nearly went mad. After a few hours all these evils ceased, and nothing in the eye appeared at all changed.

This description fulfils the International Headache Society diagnostic criteria (Table 62.3) for cluster headache (Headache Classification Committee of The International Headache Society, 1988). Before the term cluster headache was widely used, the disease was known by a large number of names (Table 62.4), with perhaps the most remarkable understatement being that of Sir Charles Symons (1956b), who called it a particular variety of headache. It has been suggested for many years that cluster headache was a disorder of the carotid artery at the base of the skull (Moskowitz, 1988) on the basis of inflammation (Hardebo, 1994) and vascular change (Ekbom & Greitz, 1970; Waldenlind et al., 1993). However, neuroendocrine studies (Leone & Bussone, 1993) suggest hypothalamic dysfunction in pacemaker regions of the brain, the suprachiasmatic nucleus (Hofman et al., 1996). Recently, activation on functional imaging with positron emission tomography (PET) in the region of the posterior hypothalamic grey (May et al., 1998), as well as a structural difference in the brain of cluster headache patients when compared with controls (May et al.,1999a), confirms this region of the brain to be pivotal to the syndrome (Fig. 62.1,

Table 62.2. Differential diagnosis for short-lasting primary headaches

With autonomic features	Without autonomic features
Cluster headache	Idiopathic stabbing headache
Paroxysmal hemicrania	Trigeminal neuralgia
SUNCT[a] syndrome	Migraine
	Benign cough headache
	Hypnic headache

Notes:
[a] Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

Table 62.3. Diagnostic features of cluster headache modified from the International Headache Society

Headaches must have each of:

Severe unilateral orbital, supraorbital, temporal pain lasting 15 minutes to 3 hours;

Frequency: 1 every second day to 8 per day;

Associated with 1 of:
- lacrimation
- nasal congestion
- rhinorrhea
- forehead/facial sweating
- miosis
- ptosis
- eyelid edema
- conjunctival injection

Source: From Headache Classification Committee of The International Headache Society (1988).

see colour plate section). The physiology of the pain and cranial autonomic activation has been reviewed recently (May & Goadsby, 1999).

Clinical features and differential diagnosis (Table 62.5)

Cluster headache is characterized by intermittent, repeated, brief attacks of very severe unilateral pain that is most usually reported to occur over or behind one eye. There are usually associated autonomic features such as lacrimation, nasal congestion, conjunctival injection and a partial Horner's syndrome (Headache Classification Committee of The International Headache Society, 1988). By these criteria each attack may last from 15 minutes to 3 hours and the frequency of attacks varies from one every other day to eight per day. Clearly, these are arbitrary rules that human biology breaks from time to time and when broken may be a sign that a more refractory clinical problem is emerging. Most patients with cluster headache have them in a bout or cluster that may last from 6 weeks to several months and are thus designated episodic cluster headache. Some 10–15 of patients have no substantial breaks and are classified as chronic cluster headache. These can be the most challenging of cases being frequently resistant to simpler treatments.

Table 62.4. Older terms for cluster headache

Histaminic cephalagia
Sphenopalatine neuralgia
Petrosal neuralgia
Migrainous neuralgia
Hemicrania periodic neuralgiformis
Erythroprosopalgia of Bing
Horton's headache

Emerging clinical features

Two recent large cohorts of cluster headache (Bahra et al., 2002; Silberstein et al., 2000) have revealed clinical aspects of cluster headache that are noteworthy. The reported ratio of males to females has dropped over the last 15 years from 9:1 to 3.5:1, due probably to better case ascertainment with studies from non-clinic populations. While clearly a predominately male disorder, female cases are readily seen. A key feature of acute cluster headache that occurs in more than 90% of patients is restlessness or agitation, which contrasts with acute migraine where slightly more than 90% of patients report aggravation of pain with movement. While not perfect, this completely opposite behaviour is an extremely helpful differentiating factor in clinical practice. It has also become clear that migrainous symptoms, such as nausea, photophobia and phonophobia, which occur in 70–80% of migraineurs, can occur in about 50% of cluster headache sufferers. Lastly, typical migrainous aura can be seen in about 15% of patients with cluster headache and should not preclude the diagnosis of cluster headache.

It is important to differentiate cluster headache from similar conditions, which most often consist of shorter more frequent attacks (Goadsby & Lipton, 1997), and to be aware of the rare but recognized causes of secondary cluster headache (Table 62.5) as they guide logical investigation. It can be both diagnostically profitable and clinically reassuring to the patient to investigate or even

Table 62.5. Differential diagnosis of secondary cluster-like headache

Similar secondary headaches	Secondary cluster headaches
	Lesion involving vessels
Tolosa–Hunt syndrome	vertebral artery dissection (Cremer et al., 1995) or aneurysm (West & Todman, 1991)
Maxillary sinusitis	pseudoaneurysm of intracavernous carotid[a] (Koenigsberg et al., 1994)
Temporal arteritis	aneurysm anterior communicating artery (Greve & Mai, 1988)
Raeder's paratrigeminal neuralgia	carotid aneursym (Greve & Mai, 1988)
	occipital lobe AVM (Mani & Deeter, 1982)
	AVM middle cerebral territory (Muoz et al., 1996)
	Lesions involving the caudal medulla or cervical spinal cord
	high cervical meningioma (Kuritzky, 1984)
	unilateral cervical cord infarction (de la Sayette et al., 1999)
	lateral medullary infarction (Cid et al., 2000)
	Intracranial lesions
	pituitary adenoma (Tfelt-Hansen et al., 1982)
	prolactinoma (Greve & Mai, 1988)
	meningioma of the lesser wing of sphenoid (Hannerz, 1989)
	Facial lesions
	facial trauma (Lance, 1993)
	orbito-sphenoidal aspergillosis (Heidegger et al., 1997)
	Other
	head or neck injury (Hunter & Mayfield, 1949)

Note:
[a] SUNCT, Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

reinvestigate the most refractory patients. It is certainly conceivable that they may harbour a secondary headache, since secondary cluster can respond to routine treatments (Cremer et al., 1995), and it certainly can be difficult to differentiate on clinical grounds.

Management of cluster headache

Many medical treatments in cluster headache can be used in both episodic and chronic cluster headache patients. In general, the acute medications may be used in both settings, although in chronic cluster headache long-term safety issues make the use of the medicines sometimes problematic. Key issues in difficult cluster headache include providing acute treatment when there are several attacks a day, particularly because of the limits on the use of injectable sumatriptan; finding a drug, or combinations of drugs, that are useful in preventing attacks and making decisions about the place and timing of surgery.

Preventative treatment

Preventative treatments in cluster headache can be used to either arrest a bout of episodic cluster headache or to ameliorate symptoms in patients with chronic cluster headache. Although each of the preventatives would probably be useful in either situation, certain practical limitations favour the clinical use of each drug. It is useful to think of preventatives as either being short term, limited usually by side effects and useful in episodic and less so in chronic cluster headache; and long term, usually used for longer bouts of episodic cluster headache or chronic cluster headache.

Short-term prevention: Oral ergotamine may be useful as a regular night-time dose to avoid nocturnal attacks (Ekbom, 1947) and at a dose of 1–2 mg nightly can be very useful. Ergotamine is at its best when given well before the attacks and is ideal for the patient with predictable nocturnal attacks and a short bout. It is problematic in patients with vascular disease although, in contrast to migraine sufferers, ergotamine-induced headache seems relatively uncommon in patients with cluster headache. Another useful strategy can be daily or even twice dihydroergotamine (1 mg) which can suppress attacks very effectively. The author has found both injectable dihydroergotamine and the dihydroergotamine nasal spray useful.

A short burst of oral corticosteroids has been recommended for some years (Jammes, 1975) and is certainly

effective. The problem of aspectic necrosis of the hip must be clearly explained to the patient. In this regard bony problems with steroid use have been reviewed by Mirzai and colleagues (Mirzai et al., 1999). The shortest course of prednisolone reported to be associated with osteonecrosis of the femoral head is a 30-day course of 16 mg/day (Fischer & Bickel, 1971). Furthermore, courses of adrenocorticotropic hormone (Good, 1974) have produced osteonecrosis after 16 days and dexamethasone at 16 mg per day after 7 days (Anderton & Helm, 1982). Thus a tapering course of prednisolone for 21 days is effective and seems prudent.

Methysergide can be an extremely effective anticluster agent and, because the bouts are usually short, the exposure can be limited. Patients may require up to 12 mg daily but usually respond reasonably quickly and in up to 70% of cases (Curran et al., 1967).

Longer-term prevention: The first-line treatment for longer-term prevention in cluster headache is verapamil. In an open trial employing large doses of 240–720 mg daily in episodic cluster and 120–1200 mg daily in chronic cluster headache, an improvement of more than 75% was noted in 69% of 48 patients treated with verapamil (Gabai & Spierings, 1989). Since this early report, verapamil has been established as among the most effective preventative agents in cluster headache. It is superior to placebo (Leone et al., 2000), and at least equal to lithium (Bussone et al., 1990). It is generally true that the regular verapamil preparation is more useful than the slow-release preparations and that the upper limit of dosing relates to side effects, particularly cardiac conduction problems. Although most patients will start on doses as low as 40 mg twice daily, doses up to 960 mg daily are now employed (Olesen & Goadsby, 1999). Side effects, such as constipation and leg swelling, can be a problem (Silberstein, 1994), but more difficult is the issue of cardiovascular safety.

Verapamil can cause heart block by slowing conduction in the atrioventricular node (Singh & Nademanee, 1987) as demonstrated by prolongation of the A–H interval (Naylor, 1988). Given that the PR interval on the ECG is made up of atrial conduction, A–H and His bundle conduction, it may be difficult to monitor subtle early effects as verapamil dose is increased. This question needs study in this group of patients but for the moment it seems appropriate to do a baseline ECG and then repeat the ECG at least 10 days after a dose change, usually 80 mg increments, when doses exceed 240 mg daily.

Lithium carbonate has been reported to be useful in up to 40% of patients (Carolis et al., 1988; Kudrow, 1977) and its use requires careful monitoring. Unfortunately, its most recent study was limited by practical problems and came to no clear conclusions on the drug's efficacy (Steiner et al., 1997). More recently, each of valproate (Hering & Kuritzky, 1989), gabapentin and topiramate (Wheeler & Carrazana, 1999) have been suggested to be useful. Blinded studies are required before these can be widely recommended.

Acute attacks of cluster headache

Perhaps the over-riding problem in acute cluster headache is that the attacks come on rapidly and reach a peak very quickly so that therapy to be of any value must be rapid in onset and thus oral preparations used in migraine may not be effective. Parenteral dihydroergotamine (1 mg intramuscularly) (Horton, 1952) and intranasal dihydroergotamine (Andersson & Jespersen, 1986) are effective for some but not all patients. Inhalation of 100% oxygen (10–12 l/min) for 15 minutes has been clearly shown to be of benefit in arresting attacks (Fogan, 1985; Kudrow, 1981). Other options include instillation of lidocaine nasal drops (4–6%) ipsilateral to the side of pain (Kitrelle et al., 1985; Robbins, 1995) or injection of the ipsilateral greater occipital nerve (Anthony, 1987). Sumatriptan, a 5-$HT_{1B/1D}$ receptor agonist developed for the treatment of migraine (Humphrey et al., 1991), has proved highly efficacious and rapid in onset of action (Hardebo, 1993) in the treatment of acute attacks of cluster headache (Ekbom & The Sumatriptan Cluster Headache Study Group, 1991). It has been shown that increasing the dose from 6 mg to 12 mg does not result in either more responders or a quicker effect (Ekbom et al., 1993). It is important clinically that the response is not diminished with time (Ekbom et al., 1992) and the side effect profile is modest as it is for migraine (Goadsby, 1994).

Pre-emptive treatment with sumatriptan in a regimen of 100 mg three times daily does not alter either the timing or frequency of headaches (Monstad et al., 1995). These data are in accordance with published data for migraine with aura that has shown pretreatment of patients prior to headache does not prevent headache (Bates et al., 1994). Rather, sumatriptan is only effective when headache has commenced even if the headache is mild (Aube, 1995; Lipton et al., 2000). Sumatriptan nasal spray has been studied in an open-label fashion and had modest effects (Hardebo & Dahlof, 1998). Recently, it was shown that zolmitriptan 5 mg and 10 mg were effective treatments of acute cluster headache but only in patients with the episodic form (Bahra et al., 2000).

Paroxysmal hemicrania (PH)

Sjaastad et al. first reported cases (Sjaastad & Dale, 1974), 7 of whom were female, of a frequent unilateral severe but short-lasting headache without remission coining the

term chronic paroxysmal hemicrania (CPH) (Sjaastad & Dale, 1976). The mean daily frequency of attacks varied from 7 to 22 with the pain persisting from 5 to 45 minutes on each occasion. The site and associated autonomic phenomena were similar to cluster headache, but the attacks of CPH were suppressed completely by indomethacin. A subsequent review of 84 cases showed a history of remission in 35 cases whereas 49 were chronic (Antonaci & Sjaastad, 1989). CPH usually begins in adulthood at the mean age of 34 years with a range of 6 to 81 years. Children with CPH have been reported (Broeske et al., 1993; Gladstein et al., 1994; Kudrow & Kudrow, 1989), although at least one case has been considered to be cluster headache (Solomon & Newman, 1995). The author has seen a 4-year child with an otherwise typical indomethacin-sensitive case. A typical case responding to acetazolamide has been reported (Warner et al., 1994).

By analogy with cluster headache the patients with remission have been referred to as episodic paroxysmal hemicrania (Kudrow et al., 1987). Pareja (1995) has recorded attacks which swap sides, just as is known for cluster headache, and attacks of autonomic features without pain. This has been observed in cluster headache after trigeminal nerve section, by this author and others, and is excellent evidence for a primarily CNS disorder. Event-related potentials which have been reported to be abnormal in migraine (Wang & Schoenen, 1998) are normal in CPH (Evers et al., 1997) as is cognitive processing (Evers et al., 1999).

Some recent cases have broadened our understanding of paroxysmal hemicrania. Boes and colleagues reported otalgia and an interesting sensation of fullness of the external auditory meatus responding to indomethacin (Boes et al., 1998). There has been some interesting speculation from Dodick about extra-trigeminal pain in episodic paroxysmal hemicrania (Dodick, 1998), and I doubt that the full clinical dimensions of these syndromes have been defined.

The essential features of paroxysmal hemicrania as it is now understood are:

- female preponderance;
- unilateral, usually fronto-temporal, very severe pain;
- short-lasting attacks (2–45 mins);
- very frequent attacks (usually more than 5 a day);
- marked autonomic features ipsilateral to the pain;
- robust, quick (less than 72 hours), excellent response to indomethacin, generally.

Other issues

The therapy of CPH has been discussed in relation to its responses to triptans. The issue is not clearly settled and may be both variable and dependent on the length of the attacks (Antonaci et al., 1998b; Dahlof, 1993; Pascual & Quijano, 1998). Greater occipital nerve injection is not useful in CPH (Antonaci et al., 1997). Piroxicam has been suggested to be helpful (Sjaastad & Antonaci, 1995), although again not as effective as indomethacin. By analogy with cluster headache verapamil has been used in CPH (Shabbir & McAbee, 1994), although the response is not spectacular and higher doses require exploration. An important and as yet unresolved issue is whether COX (cycloxygenase) II-selective blockers, such as celecoxib (Mathew et al., 2000) or rofecoxib, would be useful in CPH. An early impression is that some patients will benefit from these compounds.

CPH can coexist with trigeminal neuralgia (Caminero et al., 1998; Hannerz, 1993, 1998), just as does cluster headache (Pascual & Berciano, 1993; Watson & Evans, 1985). Both conditions must be treated to control the entire phenotype of the disorder. Similarly, secondary CPH has also been reported with a syndrome like Tolosa–Hunt (Foerderreuther et al., 1997) and in patients with a pituitary microadenoma and a maxillary cyst (Gatzonis et al., 1996), as well as as a first manifestation of cerebral metastasis of parotid epidermoid carcinoma (Mariano et al., 1998). Although extremely rare, a patient with CPH and typical migraine aura is reported.

Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) (Fig. 62.6)

This condition was first described by Sjaastad et al. (1989) and its basis has been the subject of speculation, although recently posterior hypothalamic activation with BOLD contrast fMRI has been observed (May et al., 1999b), suggesting a disorder of the central nervous system. The patients are mostly males (Pareja & Sjaastad, 1994) with a gender ratio of approximately 4 to 1 (Pareja & Sjaastad, 1997). The paroxysms of pain usually last between 5 and 250 seconds (Pareja et al., 1996b) although longer duller interictal pains have been recognized, as have attacks up to 2 hours in two patients (Pareja et al., 1996a). Patients may have up to 30 episodes an hour although more usually would have 5–6 per hour. The frequency may also vary in bouts. A systematic study of attack frequency demonstrated a mean of 28 attacks per day with a range of 6 to 77 (Pareja et al., 1996a). The conjunctival injection seen with SUNCT is often the most prominent autonomic feature and tearing may also be very obvious. Other less prominent autonomic symptoms include sweating of the forehead or

Table 62.6. Differential diagnosis of short-lasting headaches

Feature	Cluster headache	Chronic paroxsymal hemicrania	Episodic paroxsymal hemicrania	SUNCT[a]	Idiopathic stabbing headache	Trigeminal neuralgia	Hypnic headache
Gender (M:F)	5:1	1:2	1:1	2:1	F>M	F>M	5:3
Pain							
– type	boring	boring	boring	stabbing	stabbing	stabbing	throbbing
– severity	very severe	very severe	very	severe	severe	very	moderate
– location	orbital	orbital	orbital	orbital	any	V2/V3>V1	generalized
Duration	15–180 min	2–45 min	1–30 min	15–120 s	<5 s	<1 s	15–30 min
Frequency	1–8/d	1–40/d	3–30/d	1/d–30/h	any	any	1–3/night
Autonomic	+	+	+	+	−	−[b]	−
Trigger	Alcohol nitrates	Alcohol	Alcohol nitrates	Cutaneous	none	Cutaneous	sleep
Indomethacin	?	+	+	−	+	−	+

Notes:

[a] Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing.

[b] Cranial autonomic activation may be seen in first division trigeminal neuralgia.

rhinorrhoea. The attacks may become bilateral but the most severe pain remains unilateral.

Secondary SUNCT and associations

There have been several reported patients with SUNCT syndromes secondary to homolateral cerebellopontine angle and brainstem arteriovenous malformations diagnosed on MRI (Bussone et al., 1991; De Benedittis, 1996). One patient had a cavernous hemangioma of the cerebellopontine angle seen only on MRI (Morales et al., 1994), so that MRI of the brain should be part of the investigation of this syndrome when it is recognized. Extratrigeminal pain typical of SUNCT is reported (Wingerchuk et al., 2000) and is a syndrome which bears some consideration.

Management

Unlike some of the other short-lasting headache syndromes, such as the paroxsymal hemicranias that are highly responsive to indomethacin, SUNCT is remarkably refractory to treatment, including indomethacin (Pareja et al., 1995). The relationship between trigeminal neuralgia and SUNCT remains unclear (Sjaastad et al., 1997). There is a single report of a patient with trigeminal neuralgia who developed a SUNCT syndrome (Bouhassira et al., 1994). SUNCT patients may respond to carbamazepine in a partial sense. Case reports of responses with gabapentin, lamotrigine and topiramate can be found; of these topiramate and lamotrigine seem most promising.

Hemicrania continua

Sjaastad and Spierings (1984) reported two patients, a woman aged 63 years and a man of 53, who developed unilateral headache without obvious cause. One of these patients noticed redness, lacrimation and sensitivity to light in the eye on the affected side and the other described superadded 'jabs and jolts'. Both patients were relieved completely by indomethacin while other NSAIDs were of little or no benefit. Newman and colleagues (1994) reviewed the 24 previously reported cases and added 10 of their own, some with pronounced autonomic features resembling cluster headache. They divided their case histories into remitting and unremitting forms. Of the 34 patients reviewed, 22 were women and 12 men with the age of onset ranging from 11 to 58 years. The symptoms were controlled by indomethacin 75–150 mg daily.

Goadsby and Lipton (1997) compared the clinical presentation of hemicrania continua with that of chronic and episodic paroxysmal hemicrania, cluster headache and the SUNCT syndrome, concluding that it is likely to best fit under the general heading of 'trigeminal-autonomic cephalgias' to respect some of the likely shared pathophysiology. Silberstein et al. (1996) proposed that patients with hemicrania continua be subdivided into those with and without medication overuse. Apart from this secondary cause, analgesic overuse (Warner, 1997), and a report in an HIV-infected patient (Brilla et al., 1998), the status of secondary hemicrania continua is unclear.

Treatment

Sjaastad and Antonaci (1995) regard responsiveness to indomethacin as being essential for the diagnosis. Antonaci et al. (1998a) proposed the 'indotest' by which the intramuscular injection of 50 mg of indomethacin could be used as a diagnostic tool. In hemicrania continua, pain was relieved in 73 ± 66 minutes and the pain-free period was 13 ± 8 hours. The time elapsed between the oral administration of 25–50 mg t.i.d. and relief varied from 30 minutes to 48 hours (Pareja & Staastad, 1996). In practice, intramuscular indomethacin can be easily done as a single-blind placebo-controlled crossover *n-of-*1 study to clarify the best clinical management. Some patients may also respond to piroxicam and other NSAIDs (Sjaastad & Antonaci, 1995). Acute treatment with sumatriptan has been employed and reported to be of no benefit (Antonaci et al., 1998b). A useful effect from the COX (cycloxygenase) II-selective blocker, rofecoxib, is reported (Peres & Zukerman, 2000).

Primary (idiopathic) stabbing headache

Short-lived jabs of pain, defined by the International Headache Society as idiopathic jabbing headache (Headache Classification Committee of The International Headache Society, 1988) to be known as primary stabbing headache after the next revision, are well documented in association with most types of primary headache. The essential clinical features are:

- pain confined to the head, although rarely is it facial;
- stabbing pain lasting for a fraction of a second and occurring as a single stab or a series of stabs;
- recurring at irregular intervals (hours to days).

Raskin and Schwartz (1980) first described sharp, jabbing pains about the head resembling a stab from an ice-pick, nail, or needle. They compared the prevalence of such pains in 100 migrainous patients and 100 headache-free controls and only three of the control subjects had experienced ice-pick pains compared with 42 of the migraine patients, of whom 60% had more than one attack per month. The pains affected the temple or orbit more often than the parietal and occipital areas and often occurred before or during migraine headaches. Drummond and Lance (1984) obtained a history of ice-pick pains in 200 of 530 patients with recurrent primary headache. The sites of the ice-pick pains were recorded for 92 patients and coincided with the site of the patients' habitual headache in 37.

Retroauricular and occipital region pains are well described and these respond promptly to indomethacin (Martins et al., 1995). Ice-pick pains have been described in conjunction with cluster headaches (Lance & Anthony, 1971), and generally are experienced in the same area as the cluster pain. Ekbom (1975) noted that ice-pick pains may become more frequent as the attack abates. Sjaastad described what he called 'jabs and jolts' lasting less than a minute in patients with chronic paroxysmal hemicrania (Sjaastad et al., 1979). These seem more the exception, since idiopathic stabbing headache is generally truly stabbing: it is likely that longer lasting pains are a part of this overall spectrum. It is of interest that jabbing pains generally are not accompanied by cranial autonomic symptoms and can be seen with each of the trigeminal-autonomic cephalgias described in this chapter. The response of idiopathic jabbing headache to indomethacin (25–50 mg twice to three times daily) is generally excellent (Matthew, 1981; Medina & Diamond, 1981). As a general rule the symptoms wax and wane, and after a period of control on indomethacin it is appropriate to withdraw treatment and observe the outcome.

Benign cough headache

The clinical features of benign cough headache as defined by the IHS are (Headache Classification Committee of The International Headache Society, 1988):

- bilateral headache of sudden onset, short-lasting (usually < 1 min, but may last 30 min) and precipitated by coughing;
- may be prevented by avoiding coughing;
- may be diagnosed only after structural lesions such as posterior fossa tumour have been excluded by neuroimaging.

The presence of an Arnold–Chiari malformation or any lesion causing obstruction of CSF pathways or displacing cerebral structures must be excluded before cough headache is assumed to be benign. Cerebral aneurysm (Smith & Messing, 1993), carotid stenosis (Britton & Guiloff, 1988; Rivera et al., 1991) and vertebrobasilar disease (Staikov & Mattle, 1994) may also present with cough or exertional headache as the initial symptom.

Sharp pain in the head on coughing, sneezing, straining, laughing, or stooping has long been regarded as a symptom of organic intracranial disease, commonly associated with obstruction of the CSF pathways. Symonds (1956a) presented the case histories of six patients in whom cough headache was a symptom of a space-occupying lesion in the posterior fossa or of basilar impression from Paget's disease. He then described 21 patients with the same symptom in whom no intracranial disease became apparent. Cough headache disappeared in nine patients and improved spontaneously in another six patients. Two patients died of heart disease, and four were

lost to follow-up. Symonds (1956a) concluded that there was a syndrome of benign cough headache, which he attributed to the stretching of a pain-producing structure in the posterior fossa, possibly the result of an adhesive arachnoiditis. Of Symonds' 21 patients, 18 were males, and ages ranged from 37 to 77 years, with an average age of 55 years (Symonds, 1956a).

Rooke (1968) considered cough headache as a variety of exertional headache and recorded his experienced with 103 patients who experienced transient headaches on running, bending, coughing, sneezing, lifting, or straining at stool in whom no intracranial disease could be detected and who were followed for 3 years or more. During the follow-up period, reinvestigation discovered structural lesions such as Arnold–Chiari malformations, platybasia, subdural hematoma, and cerebral or cerebellar tumour in 10 patients. Of the remaining 93, 30 were free of headache within 5 years, and 73 were improved or free of headache after 10 years. This type of headache was found in men more often than in women at a ratio of 4:1. Rooke observed that this form of headache may appear for the first time after a respiratory infection with cough and that some patients reported an abrupt recovery after the extraction of abscessed teeth, which had also been noted by Symonds (1956a).

Pathophysiology

Williams (1976) recorded cerebrospinal fluid (CSF) pressures from the cisterna magna and lumbar region during coughing. He found that there was a phase in which lumbar pressure exceeded cisternal pressure, followed by a phase in which the pressure gradient was reversed. He postulated that cough headache may be caused by a valve-like blockage at the foramen magnum, which interferes with the downward or rebound pulsation. Williams (1980) followed up this observation by studying two patients with cough headache whose cerebellar tonsils descended below the foramen magnum without any obvious obstruction and confirmed a severe craniospinal pressure dissociation during the rebound after a Valsalva manoeuvre. Decompression of the cerebellar tonsils relieved the headache and eliminated the steep pressure gradient on coughing. Williams (1980) commented that coughing increased intrathoracic and intra-abdominal pressure, which was transmitted to the epidural veins, causing a pressure wave and CSF to move rostrally. The headache was presumably caused by temporary impaction of the cerebellar tonsils when the subject relaxed and the pressure gradient then reversed. Whether this explanation applies to those patients without an Arnold–Chiari type I malformation remains uncertain.

The possibility of a sudden increase in venous pressure being sufficient by itself to cause headache must be considered. Lance (1991) reported the case of a man with a goitre sufficiently large to cause sudden headache when his arms were elevated and the jugular veins distended. Calendre et al. (1996) suggested the term 'Benign Valsalva's manoeuvre-related headache' to cover headaches provoked by coughing, straining or stooping but *cough headache* is more succinct and unlikely to be displaced.

Management

Mathew (1981) reported two patients with benign cough headache (one of whom had proved unresponsive to ergotamine, propranolol, and methysergide) who improved with indomethacin 50 mg three times daily. When this therapy was compared with placebo, the reduction in cough headache with the active drug was 95% in one case and 85% in the other, while the reductions on placebo medication were 0% and 18%, respectively. One patient who had particularly severe cough headaches unresponsive to indomethacin responded completely to the i.v. injection of dihydroergotamine (Hazelrigg, 1986). Raskin (1995) has reported that some patients with cough headache are relieved by lumbar puncture which is a simple option when compared to prolonged use of indomethacin. The mechanism of this response remains unclear.

Hypnic headache

This syndrome was first described by Raskin (1988) in patients aged from 67–84 who had headache of a moderately severe nature that typically came on a few hours after going to sleep. These headaches last from 15 to 30 minutes, are typically generalized, although may be unilateral (Gould & Silberstein, 1997; Morales-Asin et al., 1998), and can be throbbing (Newman et al., 1990). Patients may report falling back to sleep only to be awoken by a further attack a few hours later with up to three repetitions of this pattern over the night. In a large and very carefully presented series of Dodick's (1998) 19 patients, 16 (84%) were female and the mean age at onset was 61 ± 9 years. Headaches were bilateral in two-thirds and unilateral in one-third and in 80% of cases mild or moderate. Three patients reported similar headaches when falling asleep during the day. None had photophobia or phonophobia (Dodick et al., 1998).

Management

Patients with this form of headache generally respond to a bedtime dose of lithium carbonate (200–600 mg) (Newman et al., 1990; Raskin, 1988) and in those that do

not tolerate this verapamil or methysergide at bedtime may be alternative strategies. Two patients who responded to flunarizine 5 mg at night have now been reported (Morales-Asin et al., 1998). Dodick and colleagues (1998) reported that one to two cups of coffee or caffeine 60 mg orally at bedtime was helpful. This author has recently successfully controlled a patient poorly tolerant of lithium using verapamil at night (160 mg) and others have reported a case controlled by indomethacin (Ivanez et al., 1998). This is an important observation in the context of trigeminal autonomic cephalgias (Goadsby & Lipton, 1997). Other strategies are important since, in the age group affected by the condition, lithium may have significant side effects.

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63

Orofacial pain

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Orofacial pain presents clinicians with a daunting task. The most critical task in treating patients is to establish the correct diagnosis. Often with chronic pain, we are faced with limited understanding, resulting too often in patients being labelled psychogenic. Pain as defined by The International Association for the Study of Pain is 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (Mersky, 1986). This definition allows for the pain to be present without nociception (the recordable neural activity in Aδ and C-fibres). Thus the clinician is encouraged to consider assessing the associated suffering and pain behaviour in understanding and treating pain. Pain in the face is often referred, owing to the trigeminal nerves' complex distribution. It is suggested therefore, that an organ system classification may simplify the problem enabling a quick and accurate diagnosis.

Classification

The International Headache Society published a classification system that can be used to describe many orofacial pains (Olesen, 1988). This classification separates many conditions that may produce facial pain and classifies them independently. For this discussion Table 63.1 provides an organ-based classification system that simplifies differential diagnosis. The orofacial pains are divided into six categories and will be reviewed separately.

Extracranial

The eyes, ears, nose, throat, sinuses, teeth, lymph glands, salivary glands may produce pain when infectious, degenerative, edematous, neoplastic or destructive processes trigger noxious stimulation. While the musculoskeletal system is an extracranial structure, they are separated in the classification as they are considered as a very common pain condition worthy of special attention.

Table 63.1. Organ system classification for orofacial pain

Organ	Presence	Quality	
A	Extracranial	Continuous	Dull
B	Intracranial	Continuous	Variable
C	Psychogenic	Variable	Variable
D	Neurovascular	Intermittent	Throbbing
E	Neuropathic	Intermittent	Sharp, shooting, electric
		Continuous	Burning
F	Musculoskeletal	Continuous	Dull, aching

Eye

Pain in and around the eye usually is caused by local disease but may also be referred from the teeth, jaw or sinuses. In addition migraine and other neurovascular pains are often perceived in the eye. An inflammatory pseudotumour in the orbit associated with Tolosa–Hunt syndrome may produce eye pain. Pseudotumour cerebri, also called benign intracranial hypertension, or idiopathic intracranial hypertension, classically presents with headache, associated with papilledema and sometimes 6th nerve palsy. These patients are best followed by neurophthalmologists to ensure vision is not lost due to persistent papilledema. Eye pain may be differentiated into superficial or corneal pain, deep or inflammatory pains. Eye disease includes iritis, acute angle glaucoma. Other eye disease may involve optic neuritis, eye strain and enucleation. Pain quality is variable depending on the cause or

pathology location. It is suggested that localized eye pain be evaluated by an ophthalmologist.

Ear

Pain in the ear is often referred from musculoskeletal structures such as the temporomandibular joint or mastication muscles. Additionally, the teeth or temporomandibular joint may refer pain to the ear. In these cases the pain is described as a dull, achy, or stopped-up sensation. Because the ear is complexly innervated by cranial nerves V, VII, IX, X, and cervical roots C2–3, referred pain to the ear needs to be carefully considered. Ear pain may arise from the external ear canal as an acute inflammatory process, or due to an accumulation of wax producing pressure. Middle ear or mastoid problems are often due to infection of the mucous membranes causing otitis media. If inflammation spreads to the petrous bones, a petrositis may develop or meningitis. Acoustic neuroma, a benign tumour involving the neural sheath of cranial nerve VIII, is associated with hearing loss, a tingling sensation deep in the ear and, if there is trigeminal nerve involvement, pain in the ear or face.

Nose

Pain in the nose may also be refereed from the teeth, sinuses or other structures, but is more likely caused by inflammation or local tumour. When there is inflammation present, it is useful to differentiate inflammatory, allergic, vasomotor or atrophic rhinitis. Referral to an ear nose and throat specialist is recommended if dental etiology is ruled out.

Throat

Throat pain is most often a local inflammatory reaction secondary to infection. Certainly, other local problems such as tumor need be considered. Some neurological problems like glossopharyngeal neuralgia, stomatodynia (burning mouth syndrome) and Eagles syndrome will be discussed under neurogenous pains. Throat tumours may invade various structures and produce pain, often associated with neurological or functional change. Diagnosis requires imaging and careful tissue exploration.

Sinus and paranasal pain

It has been established that pain can emanate from nasal and paranasal structures. Wolff, using mechanical stimuli and faradic current at various sites, elicited an aching or sharp, burning sensation from nose and sinus mucosal linings. The referred pain, following stimulation, occurred in specific patterns. The referral patterns are summarized in Table 63.2.

Table 63.2. Pain referral from nasal and paranasal mucosa

Site stimulated	Site pain reported
Nasal floor and septum	Local, zygoma, towards ear, outer and inner eye canthus, eye
Nasal turbinates	Lateral wall inside nose, upper teeth, below eye
Maxillary sinus	Local, nasopharynx, posterior teeth, zygoma, temple
Frontal sinus	Local
Ethmoid sinus	Eye, deep in the inner eye canthus
Sphenoid sinus	Pharynx, deep in the head, maxillary teeth, vertex

Sinus inflammation may be acute or chronic. Acute sinusitis is characterized by symptoms indicating active nasal membrane and sinus inflammation. Symptoms including dull persistent pain, associated with a purulent discharge, usually into the nose or pharynx. Malaise and fever are also usually present. Inflammatory sinus disease commonly produces toothache. Usually the maxillary sinus is implicated and pain is felt in the maxillary teeth on the involved side. The pain presents as a continuous dull toothache, accompanied by a feeling that the tooth is extruded.

Chronic sinusitis is characterized by persistent sinus mucous membrane inflammation. Hypertrophy, may induce permanent changes to the nasal ciliary action and mucous glands. There is no evidence that these changes produce headache. Chronic sinusitis may relapse into acute inflammation and then may present with pain.

Sinus evaluation may include sinus transillumination, which often reveals pus in acute sinusitis. Plain radiographs may show fluid levels. Specific radiographic techniques may be needed to clearly identify each sinus, e.g. a Waters view is used for the maxillary sinus. A computerized tomogram (CT) scan or MRI may be helpful in differentiating cystic from solid lesions, but differentiating acute from chronic sinusitis requires the presence of clinical features. Treating acute sinusitis and the presenting orofacial pain is best accomplished with antibiotics and systemic or topical decongestants. Surgical drainage may be required.

Teeth

The most common orofacial pain involves the teeth and their supporting structures. Most frequently the pain is related to dental caries, presenting as a reversible pulpitis. The reversible pulpitis is characterized by poorly localized pain, often sensitive to hot or cold stimuli. The reaction to the noxious stimulus (hot or cold) disappears soon after its removal. Eventually when the carious lesion invades the pulp an irreversible pulpitis begins. This is characterized by a lingering reaction to noxious stimuli such as hot or cold. If the microorganisms and inflammatory products invade the area around the root apex (periapical) this is called a periodontitis and may present with toothache associated with chewing, touch and percussion sensitivity. Periapical pathology may be observed as an area of increased radiolucency on radiograms. The tooth may have an abnormal response to pulp testing where applying heat, cold or electrical stimulus is not perceived. In clinical practice differentiating reversible and irreversible pulpitis is difficult. In situations where the diagnosis is not obvious, careful observation over days or weeks is recommended. Too often endodontic therapy is performed when not indicated.

An intermittent pain that is triggered by biting on an offending tooth characterizes cracked tooth syndrome. Unfortunately the cracks are often difficult to find and don't show on all X-ray images. This pain is often confused with pulpitis or trigeminal neuralgia resulting in frustration and unnecessary treatment. Tomographic imaging 1 mm apart through the tooth's long axis may be beneficial in defining the crack. Further careful clinical examination including meticulous bite tests on each tooth cusp or staining may be useful. Graff-Radford and Gratt have studied cracked teeth with thermography and it appears there is a difference in the patients with cracked teeth and neuropathic facial pain. The cracked tooth patients have normal thermograms and the neuropathic pain patients display asymmetrical thermograms (Graff-Radford et al., 1995). Chronic toothache may be a referred phenomenon. Where no obvious local etiology is evident, neuropathic, muscular or vascular etiologies should be considered (Graff-Radford et al., 1995).

Burning mouth syndrome

Burning mouth syndrome (BMS) is characterized by a burning sensation in one or several oral structures (Tourne & Fricton, 1992). Although no obvious cause has been established, numerous possibilities exist. The pathogenesis may be summarized into local, systemic and psychological etiologies. Local factors include contact allergy, denture irritation, oral habits, infection, and possible reflux esophagitis. The systemic factors include menopause, vitamin and mineral deficiency, diabetes, oral infection and chemotherapy. Psychogenic factors have often been cited but are mostly anecdotal. An essential component to rule out is candida infection. Although this may not be obvious to the eye, swabbing the oral mucosa and culture for fungus often reveals an incipient infection. Patients with fungal infection respond quickly to antifungal preparations such as clotrimazole or fluconazole. The author's experience indicates approximately half the patients with BMS have a candida infection. This often follows steroid, antibiotic or chemotherapy. For those patients where no systemic or local pathology is identified, it is postulated that the cause is neuropathic. Topical clonazepam (0.5 –1.0 mg three times per day) has been effective in reducing a burning oral pain (Woda et al., 1998). Patients are instructed to suck a tablet for three minutes (and then spit out) 3 times per day for at least 10 days. Serum concentrations are minimal (3.3 ng/ml) 1 and 3 hours after application. Woda hypothesized clonazepam produced a peripheral not central action disrupting the neuropathologic mechanism. Additional treatments for BMS include medications ranging from tricyclic antidepressants, antiepileptic drugs, benzodiazepines, folic acid and oral rinses. Treatment outcome is varied.

Intracranial

Intracranial pathology presenting as orofacial pain is exceedingly rare. The pain is usually associated with additional neurological signs and symptoms. The meninges, cranial nerves and blood vessels are the pain sensitive structures intracranially. Traction, inflammation, distention or pressure on these structures produces pain referral to distant sites.

Thalamic pain is described as 'unilateral facial pain and dysesthesia attributed to a lesion of the quintothalamic pathway or thalamus. Symptoms may also involve the trunk and limbs of the affected side' (Mersky, 1986). Infarcts in the thalamus involving the primary sensory nuclei, or damage in other sensory pathways, may lead to thalamic pain syndrome. The pain quality is moderate to severe, burning or aching, and localized to the face contralateral to the infarct. The clinical presentation may include a hemiplegia and associated allodynia, hyperesthesia and hyperpathia. MRI or CT scans are used to confirm the diagnosis. Treatment is difficult, but patients respond best to the tricyclic antidepressants or membrane stabilizing

medications such as listed in Table 63.5. Stimulation produced analgesia such as acupuncture or TENS or even deep brain stimulation may be treatment considerations.

Intracranial neoplasms produce pain in approximately 60% of cases. This is typically a dull, non-pulsatile, persistent pain aggravated by exertion or postural changes (Bulitt & Tew, 1986). In the patient who presents with non-odontogenic face pain where other cranial nerve abnormalities are present, intracranial pathology must be considered. While certain intracranial tumours are more likely to produce neurological problems, all do not present with the same neurological signs (Rushton & Rooke, 1962). Tumours producing facial pain include meningiomas, schwannomas, neurofibromas, acoustic neuromas and cholesteatomas. Pituitary tumours may result in pain when they erode the sella or place pressure on the gasserian ganglion due to invasion of the cavernous sinus (Cueneo & Rand, 1952). It is suggested that tumours arising from the trigeminal ganglion produce pain, and those arising from the root do not (Schisano & Olivercrona, 1960).

Psychogenic

Labelling a disease process psychogenic without clear documented objective criteria is grossly unfair to the patient. Fordyce has pointed out that too often a patient's pain experiences are labelled 'psychogenic pain' when repeated failures using the biomedical model result in a lengthy medical history (Fordyce & Steger, 1978). Fordyce suggests it is the system that has not provided adequate diagnosis. Psychogenic pain may be interpreted in many ways. Some consider psychogenic pain when the pain behaviour is in excess or is discrepant from the physiological sensation or apparent nociceptive cause. A more useful manner in which the psychogenic pain label may be employed, is when the emotional and psychological factors are the pain's primary. The latter alternative requires positive inclusion criteria and Fordyce suggests these may be divided into four groups (i) somatic delusions, (ii) somatization disorder, (iii) conversion, (iv) depression. Fordyce points out that psychogenic diagnosis is a philosophical one. The fact that the International Association for the Study of Pain's (Mersky, 1986) definition of pain provides an emotional component, should not allow us to confuse the emotional overlay with a psychogenic etiology.

It would be better to label pain problems in which no obvious pathology can be determined as idiopathic rather than psychogenic or atypical. Further in-depth, systematic and objective study of these disorders needs to be carried out so as to understand their etiology. It has been reported that patients described as 'atypical' or 'idiopathic' all have an ascribable diagnosis if evaluated by someone with more experience (Fricton, 1999).

Table 63.3. Orofacial pains of neuro-vascular origin

Migraine
Migraine with aura
Migraine without aura
Exertional migraine
Cluster headache
Chronic paroxysmal hemicrania
Hemicrania continua
Severe unilateral neuralgiform headache with conjunctival injection and tearing, rhinorrhea and subclinical sweating (SUNCT)

Neurovascular

The problems discussed under the neurovascular organ system may not originate in this system but have the trigemino-vascular pathway as the nociceptive mediator (Moskowitz et al., 1988). Neurovascular pains are largely intermittent and involve a complex mechanism, which is still not fully understood. Table 63.3 lists the neurovascular pains that may present in the orofacial region.

Migraine

Although migraine is traditionally considered to present above the oculo-tragus line, facial migraine is documented well (Lovshin, 1960; Raskin & Prusiner, 1977). Migraine is discussed elsewhere in this text. Exertional migraine is described as 'migraine symptoms lasting minutes and presenting with the other associated symptoms attributed to migraine' (Rooke, 1968). The exertional migraine may also be subclassified into benign cough headache (BCH) and benign exertional headache. BCH is defined as an intermittent pain, usually bilateral, with severe bursting explosive pain brought on by coughing. The pain location is usually in the vertex, occipital, frontal or temporal regions, but has been described as presenting in the tooth (Symonds, 1956; Moncada & Graff-Radford, 1993). This pain is responsive to 25–225 mg / day indomethacin doses. Patients are required to maintain the treatment indefinitely. If decreased, the symptoms usually reoccur. When evaluating BCH, Symonds emphasizes the need to rule out intracranial pathology (Symonds, 1956).

Lovshin (Lovshin, 1960) was the first to describe migraine as a facial pain problem that could occur without headache. This has been further described by Raskin (1988). The pain is described as dull pain with superimposed throbbing occurring once to several times per week. Each attack lasting minutes to hours. In the facial migraine, Raskin describes ipsilatertal carotid tenderness, a finding also present when migraine presents in the head. This condition has also been refereed to as carotidynia (Raskin & Prusiner, 1977). Raskin feels that dental trauma may be a precipitant.

Cluster headache

Cluster headache is described as 'attacks of severe strictly unilateral pain orbitally, supraorbitally and/or temporally, lasting 15–180 minutes and occurring from once every other day to 8 times per day. The pains are associated with one or more of the following autonomic signs: conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, meiosis, ptosis, eyelid edema. Attacks occur in series lasting for weeks or months (so-called cluster periods) separated by remission periods usually lasting months or years. About 10% of the patients have chronic symptoms' (Olesen, 1988).

Cluster headache has been described by Brooks as 'periodic migrainous neuralgia' when it presents as orofacial (Brooke, 1978). Brooke's facial cluster included 53% with toothache and 47% with jaw pain. Bittar and Graff-Radford described 42 cases of cluster headache where 42% received unnecessary dental procedures, provided as therapy (Bittar & Graff-Radford, 1992).

Cluster often presents in the orofacial region especially in the maxilla. Using sphenopalatine ganglion block with local anesthetic is useful as a temporary abortive therapy.

Chronic paroxysmal hemicrania (CPH) is described as 'attacks with largely the same characteristics of pain and associated symptoms and signs as cluster headache, but they are shorter lasting, more frequent, occur mostly in females, and there is absolute effectiveness of indomethacin' (Olesen, 1988). CPH may also present as face pain or involve the teeth. The clinical presentation is unchanged, as is the response to indomethacin (Delcanho & Graff-Radford, 1993).

SUNCT syndrome is described as a pain that is associated with short lasting unilateral neuralgiform headache attacks with conjunctival injection, tearing, rhinorrhea and subclinical sweating. Sjaastad and co-workers in 1978 first described SUNCT (Sjaastad et al., 1978). Most attacks are reported as moderate to severe, 30 to 120 second pain paroxysms. Pain is usually localized to the eye and may occur in a cluster fashion with some quiet periods. Attack frequency may be up to 30 per day or many per hour (Sjaastad et al., 1989; Sjaastad et al., 1991). Although SUNCT is clinically well identified it is poorly treated. Carbamazepine may be effective in controlling some symptomatology, but not consistently (Sjaastad et al., 1991). Gabapentin may also offer relief in some patients (Graff-Radford, 2000a).

Table 63.4. Neuropathic orofacial pain

Intermittent
Trigeminal neuralgia
Glossopharyngeal neuralgia
Nervous intermedius neuralgia
Occipital neuralgia
Continuous
Trigeminal dysesthesia
Trigeminal dysesthesia – sympathetically maintained

Neuropathic

Neuropathic pain suggests there has been some tissue or nerve injury. With injury there is a permanent peripheral nerve and or central nervous system change. It is surprising that with all that the human endures; falls, scrapes, fractures, surgery, etc., that so few chronic pain patients develop. This is likely due to the brain's ability to inhibit or control the permanent changes seen following tissue injury.

We should start out by differentiating 'transient pain' from 'chronic pain'. Short-lived pain following a stimulus that is potentially tissue damaging, also referred to as acute pain is a protective mechanism. Acute pain resolves in an appropriate time period and then normal function is restored. What happens when the stimulus results in a chronic pain? Once the injury appears to have healed there is pain that is non-protective. It is postulated that this may be due to central and peripheral nervous system change (Ren & Dubner, 1999). These changes may include the presence of ongoing peripheral nociception, CNS sensitization or down-regulation of CNS inhibition.

Clinically neuropathic pain can be divided into continuous and intermittent and may present simultaneously or independently. Table 63.4 is a clinical classification for neuropathic facial pain.

Neuropathic pain presents clinically as an intermittent bright, stimulating, electric sharp or burning pain. This is

typically seen in trigeminal neuralgia, glossopharyngeal neuralgia, nervous intermedius neuralgia and occipital neuralgia. These intermittent neuralgias are triggerable, usually by non-noxious stimuli. Vascular nerve compression is the proposed etiology (Fromm & Sessel, 1991). Compression may also be secondary to other structures, including tumours and bony growths (e.g. Eagles syndrome) (Janetta, 1977; Massey & Massey, 1979).

Trigeminal neuralgia

Trigeminal neuralgia (TIC) is described as 'a painful unilateral affliction of the face, characterized by brief electric shock-like (lancinating) pain limited to the distribution of one or more divisions of the trigeminal nerve. Pain is commonly evoked by trivial stimuli including washing, shaving, smoking, talking and brushing the teeth, but may also occur spontaneously. The pain is abrupt in onset and termination may remit for varying periods' (Olesen, 1988). Symptomatic trigeminal neuralgia is described as 'pain indistinguishable from trigeminal neuralgia, caused by a demonstrable structural lesion'. This lesion is usually a tumour such as an acoustic neuroma, or may be due to demyelination as seen in multiple sclerosis. If there is tissue or nerve injury there may be an ensuing continuous trigeminal neuralgia, which is usually referred to as traumatic trigeminal neuralgia or trigeminal dysesthesia (TD) (Graff-Radford, 2000b).

TIC is usually unilateral and only occurs bilaterally in 4% of subjects. There is no genetic link to the disorder. The average age at onset is between the sixth and seventh decades, with women slightly more affected than men in a 3: 2 ratio. The bright stimulating pain perceived is short-lived lasting seconds to minutes. If not questioned carefully the patient may report the pain lasts all day as there is often a dull pain associated with TIC, or the sharp volleys come and go continuously. The author believes the persistent aching pain may be secondary to a reflex muscle splinting and can be controlled with stretching exercise and a vapocoolant spray. Mechanical manoeuvring the trigeminal sensory system usually triggers TIC pain. The area from which the pain is activated has been described as a trigger zone. Characteristically, trigger zones occur around the supraorbital, infraorbital foramina, the inner canthus of the eye, lateral to the ala and over the mental foramen. Trigger zones are also common intraorally. Pain is not elicited from the trigger zone if deep pressure is used or during a latency period between paroxysms. The second and third trigeminal nerve divisions are most commonly affected. The first division cases occur less frequently than 5% (Fromm & Sessel, 1991). Often there is ipsilateral reflex facial spasm hence the term 'tic douloureux' which has been used synonymously with TIC (Andre'N, 1756).

It is postulated that TIC may be due to a trigeminal nerve focal demyelination at any point along its course. Exploring the posterior cranial fossa reveals between 60 and 88% of cases have trigeminal nerve root vascular compression. The compression is present in the posterior cranial fossa as it exits the pons (Gardner, 1962). This has been postulated to set up a centrally mediated disinhibition of pain modulation and/or peripheral repetitive ectopic action potentials. Once there is sensitization there may be increased afferent fibre activity and enhanced tactile stimulation resulting in trigeminal nucleus interneuron discharge and trigeminothalamic neuron producing pain. Taarnhoj (1982) have described tumours as a possible cause in up to 6% of cases. These include acoustic neurinomas, cholesteatomas, meningiomas, osteomas and angiomas. Aneurysms and adhesions have also been implicated. Although the pain may be typical of TIC usually there are additional symptoms or cranial deficits present. When patients are in the 20–40-year age range and present with trigeminal neuralgia multiple sclerosis should be ruled out. Fromm suggests that all patients with trigeminal neuralgia obtain a brain MRI or CT scan, with particular attention paid to the posterior cranial fossa (Fromm & Sessel, 1991).

Ratner and Roberts have proposed that bony cavities found in the alveolar bone may be the cause of trigeminal neuralgia and that repetitive curettage of these cavities is curative (Ratner et al., 1976, 1979; Roberts et al., 1984) Graff-Radford et al., have demonstrated, using 15-half-maxillae and 12 half-mandibles from cadavers, that cavities in bone larger than 2 mm in diameter occur throughout normal bone (Graff-Radford et al., 1988b). The cavities do not appear to be unique to trigeminal neuralgia patients. This sheds doubt on the bony cavity theory. Rather, it may be postulated that the curettage may be effective through central mechanisms or peripheral denervation.

TIC treatment may be divided into pharmacological and surgical. Table 63.5 outlines the drugs that may be used in TIC therapy.

The anticonvulsant action in pain management is not well understood. Some like carbamazepine block use dependent sodium channels, inhibiting sustained repetitive firing. There is also an effect in the spinal cord reducing post-tetanic synaptic transmission potentiation. There is also decreased synaptic transmission in the trigeminal nucleus, which may explain anticonvulsants effectiveness in facial pain. Valproic acid increases brain concentrations of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system as well as affecting sodium channels. The action of phenobarbital is not at

Table 63.5. Common membrane stabilizing drugs used in neuralgia therapy

Generic	Trade name	Dosage (mg/day)	Blood level (ug/ml)	Serum half-life (h)
Lioresal	Baclofen	10–80	–	
Carbamazepine	Tegretol (XR) Carbitrol	100–2000	4–12	12–17
Phenytoin	Dilantin	200–600	10–20	18–24
Valproic acid	Depakote	125–2500	50–100	6–16
Gabapentin	Neurontin	100–5000	–	
Lamotragine	Lamictal	50–500	2–5	14–59
Klonopin	Clonazepam	0.5–8	–	22–33
Orap	Pimozide	2–12	–	55–154
Depakote	Valproic acid	125–2000	50–100	6–16
Topiramate	Topamax	50–400	–	21
Oxcarbazepine	Trileptal	200–2400	–	9

the trigeminal nucleus but rather in the brain. It is therefore not effective for TIC. Gabapentin may increase GABA by preventing its breakdown or may affect the NMDA receptor.

All drugs used in TIC have side effects and great care must be used in their administration. Baclofen perhaps has the least side effects, but also may be less effective than carbamazepine. Fromm has also described the baclofen L isomer are the effective component (Fromm et al., 1984). Therefore, non-response may be secondary to metabolizing the D isomer only. Baclofen is initiated at 10 mg per day and increased every 2 days to a maximum of 80 mg per day usually in four doses. Drowsiness and confusion are the major side effects and many patients will not tolerate it for this reason. Carbamazepine is without doubt the most effective drug. It is suggested that one begins at 100 mg per day and increases by 100 mg every two days to a maximum of 1200 mg. The side effect of aplastic anemia, although rare, needs to be monitored carefully with routine blood tests. Should there be no relief a carbamazepine blood level should be obtained to ensure a therapeutic blood concentration. A rough level should be obtained and is usually in the range of 5–10 μg/ml. The sustained preparations (Tegretol XR, Carbitrol) have improved compliance and reduced the sedating side effects. Gabapentin, although not formally studied has been useful in doses from 300 mg per day to 3000 mg per day. Phenytoin is a good alternative in doses ranging from 100 – 400 mg per day. Fromm (Fromm & Sessel, 1991) has suggested using some of these drugs in combination to either maximize effect or minimize side effects. Pimozide has been described as more effective than carbamazepine in a double blind cross over design using 48 subjects with trigeminal neuralgia refractory to medical treatment. Side effects were reported in 83% of subjects who received pimozide and included physical and mental retardation, hand tremors, memory impairment, involuntary movements during sleep and slight Parkinson's disease manifestations. None of the patients stopped treatment because of side effects. It is felt therefore by Lechin et al. (1989) that it is effective but because of the adverse effects it should be reserved for severe and intractable trigeminal neuralgia. A new preparation oxcarbazepine (Trileptal) has proven effective and has fewer side effects than carbamazepine.

The surgical treatments for TIC are summarized in Table 63.6. Less traditional treatments reported for trigeminal neuralgia include the curettage of the bony cavities described above. Ratner and Roberts report a long-term success of 80% (Ratner et al., 1976, 1979; Roberts et al., 1984). Sokolovic et al., have described the using peripheral streptomycin and lidocaine injections (Sokolovic et al., 1986). They studied 20 patients in whom five injections of 2% lidocaine and 1 g of streptomycin sulfate were deposited adjacent to peripheral nerves at one month intervals; 16 of the 20 patients remained pain free after 30 months. No side effects were reported and the authors report there was no loss of sensation after the local anesthetic wore off. Bittar and Graff-Radford completed a double-blind placebo-controlled cross-over study using streptomycin, and the results were not favourable. They also reported significant swelling associated with the injections (Bittar & Graff-Radford, 1993).

Although not suggested as a therapeutic modality for trigeminal dysesthesia, surgery is an excellent alternative for trigeminal neuralgia. The most effective surgical approach

Table 63.6. Surgical management of trigeminal neuralgia

Procedure	Effectiveness	Comment
Alcohol block	Excellent	relief is typically 8–16 months paresthesia or dysesthesia occur in 48%
Alcohol gangliolysis	88% at 4 years	corneal anesthesia occurs in 15% neuroparalitic keratitis in 4–7% postoperative paresthesia in 55% paresthesia in 38% herpetic outbreak in 26% transient masticatory muscle weakness in 45%
Neurectomy	Excellent	relief is typically 26–38 months anesthesia dolorosa and corneal anesthesia are rare
Glycerol gangliolysis	89–96%	7–10% have early recurrence 7–21% develop recurrence over extended follow-up facial hyperesthesia occurs in 24–80% corneal anesthesia occurs in 9% facial dysesthesia occurs in 8–29%
Radiofrequency gangliolysis	78–100%	1–17% early recurrence 4–32% develop recurrence over extended follow-up masseter weakness occurs in 7–23% trigeminal dysesthesia in 11–42% corneal hyperesthesia in 3–27% neuroparalytic keratitis in 1–5% anesthesia dolorosa in 1–4%
Microvascular compression	96–97%	16–29% develop recurrence over extended follow-compression mortality occurs in 1% morbidity occurs in 10–23%
Rhizotomy	85%	15% develop recurrence over extended follow-up mortality occurs in 0.5–1.6% facial weakness occurs in 7–8% paresthesia occurs as a minor complaint in 56% paresthesia occurs as a major complaint in 5% neuroparalytic keratitis occurs in 15%
Trigeminal Tractotomy		ipsilateral limb ataxia occurs in 10% contralateral limb sensory loss occurs in 14%
Gamma knife	80–95%	onset may be 6 weeks or longer facial numbness trigeminal dysesthesia rare

remains microvascular decompression (Janetta, 1996). Advances in microvascular decompression include the use of an endoscopic approach. This allows clearer observation and is less traumatic (Jarrahy & Shahinian, 2000). Gamma knife radiosurgery is a recent advance for trigeminal neuralgia (Young et al., 1997). This technique offers a relatively non-invasive means for lesioning the trigeminal nerve adjacent to the pons using a 4 mm collimator helmet. Complications are rare and to date the author has seen one case of trigeminal dysesthesia attributed to the procedure.

Pretrigeminal neuralgia

Sir Charles Symonds first described pretrigeminal neuralgia (PRE TIC)(Symonds, 1949). Mitchell later reviewed it (Mitchell, 1980). Fromm et al. (1990) have described a further 16 cases in which patients initially present with a dull continuous aching toothache in the upper or lower jaw and in whom the pain changed to classic trigeminal neuralgia. Further, they describe seven cases in which the continuous pain was successfully treated with traditional trigeminal neuralgia therapies. The diagnosis of pretri-

geminal neuralgia is based on the following criteria: (i) description of pain as dull toothache; (ii) normal neurological and dental examination; (iii) normal CT or MRI scan of the head. Of note is that the pain of pretrigeminal neuralgia can be interrupted with somatic anesthetic blockade. Merrill and Graff-Radford have described 61 patients treated for pretrigeminal or trigeminal neuralgia. Of these 61% were incorrectly diagnosed and treated with traditional dental therapies (Merrill & Graff-Radford, 1992). The clinician should be aware of PRE TIC prior to surgical intervention in orofacial pain where the etiology is unclear.

Glossopharyngeal neuralgia

This pain presents with similar quality and characteristics to trigeminal neuralgia, but in the distribution of the glossopharyngeal nerve. It may be confused with Eagles syndrome (Massey & Massey, 1979). This syndrome presents as described in glossopharyngeal neuralgia but is associated with an elongated stylohyoid process that irritates or compresses the glossopharyngeal nerve. Rotation of the head, swallowing, chewing are all triggering factors. Patients may complain of persistent sore throats. This pain can be decreased with neural blockade and confirmation of the diagnosis requires demonstration of the calcified stylohyoid ligament on radiogram. Treatment is best achieved with surgical resection of the ligament.

Nervous intermedius neuralgia

This pain is described as similar to trigeminal neuralgia but localized to the middle ear. Patients often complain of 'hot poker' in the ear (Walker, 1966). Treatment is usually similar to that for trigeminal neuralgia.

Occipital neuralgia

Occipital neuralgia is pain located in the distribution of the greater and lesser occipital nerves. Pain is described as paroxysmal, sharp electric-like. There is usually an associated trauma at the onset of pain. Graff-Radford et al., have described myofascial trigger points in the splenius cervicus and capitis muscles that may mimic occipital neuralgia and it is suggested that trigger point injections be used to help rule out this possibility (Graff-Radford et al., 1988a,b). Surgical neurectomy has been described for occipital neuralgia, but the results are often short lived.

The neuropathic pain following tissue or nerve injury in the trigeminal nerve distribution may be called a trigeminal dysesthesia (TD). TD is defined as a continuous pain following complete or partial damage to a peripheral nerve. The pain is described as a continuous, burning numbness and often pulling pain (see Table 63.7).

Table 63.7. Criteria for trigeminal dysesthesia

History of trauma
Continuous pain
Associated hyperalgesia and allodynia
Temperature change
Block effect (sympathetic vs. somatic)

In TD the initiating trauma is usually quite obvious, e.g. postwisdom tooth removal or postimplant placement, but may occur with minor traumas such as crown preparation or following viral infection such as herpes zoster. The discomfort can be self-limiting, depending on nerve regeneration. Campbell has described approximately 5% of patients undergoing root canal therapy have persistent pain (Campbell et al., 1990) which may be attributed to the nerve damage. Elies described 17% of patients with mandibular implants as developing persistent sensory change or pain (Ellies & Hawker, 1993; Ellies, 1992). Thermographic studies of TD reveal all patients have abnormal thermograms with some being hot in the pain distribution and some cold. None are normal. Graff-Radford et al. (1995) have described a hypothesis for these temperature changes that may be helpful in selecting a treatment.

There are three peripheral mechanism, which may be involved in chronic trigeminal neuropathic pain development. These are (i) nerve compression, (ii) nerve regeneration and (iii) sympathetically maintained pain.

Nerve compression

When a peripheral nerve is compressed or injured there is a sustained firing that may be persistent. The closer the damage is to the central nervous system, the longer is the spontaneous neural discharge. The pain following nerve compression can be temporarily relieved with local anesthetic blockade. Following neural trauma receptor sprouting occurs on the damaged nociceptor, on dorsal horn cells and peripheral blood vessels. These receptors may include alpha-receptors, NPY receptors and possibly others. There is also an increased release in trigeminal nucleus substance P, CGRP and other neurotransmitters, resulting in further neurogenic inflammation and chronic pain (Bennett & Xie, 1988). When neural inflammation occurs, a neuritis ensues. The pain presentation is a continuous dull, burning pain with associated allodynia and hyperalgesia. A neuritis involving the facial nerve (cranial nerve VII) may present as a Bell's palsy. There is no pain in Bell's palsy unless the herpes zoster involves the geniculate ganglion. Ramsy Hunt Syndrome requires a facial

palsy associated with herpes zoster eruption around the ear (Karnes, 1984).

Nerve regeneration

Neuroma formation is essentially created by nerve regeneration where the path for regrowth is obstructed. The nerve resprouting and the continuous nerve irritation may result in pain. As in nerve compression, receptor sprouting, and neurotransmitter presence will increase the pain. Injecting the neuroma with local anesthetic will temporarily block the pain. The sprouting axons fire spontaneously, develop abnormal sensitization to norepinepherine, cold and mechanical stimulation. This occurs in dorsal root ganglion cells as well as peripheral terminals. Clinically, the neuroma may only produce pain following mechanical stimulation. The pain is an aching, burning pain with associated sharp pain volleys.

Sympathetically maintained pain (SMP)

Campbell best summarizes this phenomenon (Campbell et al., 1992). He reports that the initial trauma to the peripheral nervous system activates nociceptors and produces a sprouting of alpha-adrenergic receptors on the nociceptors. Additionally, the initial sensory barrage sensitizes the CNS causing sympathetic afferent activation, and increased response to non-noxious stimulus. This causes peripheral norepinepherine release, which activates the peripheral nociceptors and keeps the cycle active. There is evidence that following neural injury the sympathetic innervation in the dorsal root ganglia increases with age (Roberts & Foglesong, 1988). It is not surprising that there is a higher incidence of neuropathic pain as we age. SMP is aggravated by non-noxious stimuli and interrupted temporarily by sympathetic block or alpha-adrenergic block with phentolamine.

Most orofacial trigeminal dysesthesia occurs in females usually in their 4th decade (Vickers et al., 1998; Solberg & Graff-Radford, 1988). There must be a lesion in the trigeminal nervous system, peripherally or centrally to cause the continuous dysesthesia (Vickers et al., 1998). Sex-based differences have been seen in many pain disorders. The relationship and role of sex hormones in the generation and perpetuation of central sensitization is not fully understood but is obviously important (Ren & Dubner, 1999). In a neuropathic pain model using partial sciatic nerve legation, female rats were more likely to develop allodynia (Coyle et al., 1995). In studies comparing female rats that have been ovariectomized, there is a greater chance that those with estrogen were more likely to develop allodynia after injury than those without estrogen (Coyle et al., 1996).

The therapy for trigeminal dysesthesia is aimed at reducing peripheral nociceptive inputs and simultaneously enhancing central nervous system pain inhibitory systems (Graff-Radford, 1995).

Topical applications

The use of topical therapies has not been well studied. There is some evidence that capsaicin (Zostrix) applied regularly will result in desensitization and pain relief (Scrivani et al., 1999). The recommended dose is five times per day for 5 days then three times per day for 3 weeks. If the patient cannot withstand the burning produced by the application, the addition of topical local anesthetic, either 4% lidocaine or EMLA is useful. A Lidoderm patch has been useful in postherpetic neuralgia and other neuralgias where it is convenient to apply the material to the skin. Clonadine can be applied to the hyperalgesic region by placing the proprietary subcutaneous delivery patch where it is most tender. Alternatively, a 4% gel can be compounded and delivered over a larger area. For local intraoral application a neurosensory stent has been conceived. After an oral impression, an acrylic stent is manufactured to cover the painful site (Graff-Radford, 1995). The topical agent is applied to the gingival surface and placed intraorally 24 hours per day.

Topical clonazepam (0.5 –1.0 mg three times per day) has been effective at reducing a burning oral pain (Woda et al., 1998). Patients were instructed to suck a tablet for three minutes (and then spit out) three times per day for at least 10 days. Serum concentrations were minimal (3.3 ng/ml) one and three hours after application. Woda hypothesized there was a peripheral not central action at disrupting the neuropathologic mechanism.

Procedures

Neural blockade is very effective in differentiating SMP from sympathetically independent pain. It may also be effective in controlling SMP if used repetitively. Stellate ganglion blocks, phentolamine infusion and sphenopalatine blocks have been described as useful in obtaining a chemical sympathetic block. The author has not had significant benefit using phentolamine infusion in facial pain. Scrivani who used 30 mg infusion without benefit (Scrivani et al., 1999) supports this.

Lidocaine infusion (200 mg over 1 hour) may be used therapeutically in various forms of neuropathic pain (Boas et al., 1982; Rowbotham et al., 1991). It is suggested that response to intravenous lidocaine may predict who responds to the lidocaine analogue mexilatine. Sinnott et

Table 63.8. Common antidepressants used in trigeminal dysesthesia

Medication trade name	Route	Dosage per day
Amitriptyline	PO	10–150
Desipramine	PO	10–150
Doxepin	PO	10–150
Imipramine	PO	10–150
Nortriptyline	PO	10–150
Trazedone	PO	50–300

al., used an animal model to demonstrate that there is a minimal lidocaine concentration (2.1μg/ml) to abolish allodynia (Sinnott et al., 1999). They also describe a ceiling effect. Many animals with experimentally induced allodynia did not obtain persistent relief. They suggest separate physiological mechanisms, with differing pharmacologies, may account for variability and postulate there are different aspects of neuropathic pain.

Pharmacology

Tricyclic antidepressants

It is well documented that tricyclic antidepressants are effective in many pain problems. Solberg and Graff-Radford have studied the response to amitriptyline in traumatic neuralgia. It is noted that the effective range is 10–150 mg per day usually taken in a single dose at bedtime (Solberg & Graff-Radford, 1988). Many antidepressants may be used, see Table 63.8.

Membrane stabilizers

These medications include the anticonvulsants, lidocaine derivatives and some muscle relaxants. They have been classically used in intermittent sharp electric pains (see Table 63.5).

Behavioural strategies

Prior to beginning therapy, it is common to perform a behavioural assessment with appropriate testing. Following the behavioural evaluation, management is directed at the factors which may impact treatment and determining the most appropriate interventions. Consideration should be given to the following factors: (i) behavioural or operant; (ii) emotional; (iii) characterlogical; (iv) cognitive; (v) side effects; (vi) medication use and (vii) compliance. Therapy such as cognitive and behavioural management techniques, relaxation, biofeedback and psychotherapeutic and psychopharmacological interventions may be useful.

Surgery

Although not suggested as a therapeutic modality for trigeminal dysesthesia, surgery is an excellent alternative for trigeminal neuralgia.

Postherpetic neuralgia

Postherpetic neuralgia (PHN) is a complex problem whose treatment has frustrated clinicians and patients (Loeser, 1986; Watson & Evans, 1986). Herpes zoster (HZ) is primarily a disease affecting older people with some predilection for males (67% males: 33% females to 53% males: 47% females) (Molin, 1969). The localization of HZ in the face is between 15% and 30% of reported cases, this includes involvement of the facial nerve (Molin, 1969). The duration of pain after outbreak of the vesicles varies, but with an increase in age of the subject the pain appears to last longer. The number of subjects who go on to having postherpetic neuralgia (PHN), defined as pain after the vesicles are healed, ranges from 14% of males to 25% of females but almost all are older than 60 years (Molin, 1969). No studies to date have suggested that the subset of HZ patients who go on to have PHN is predictable. The mechanism whereby the herpetic virus produces the neuralgia condition has not yet been determined, reports by Head (Head & Campbell, 1900), and Denny-Brown (Denny-Brown & Adams, 1944), reveal that changes occur in the skin and peripheral nerve endings producing anesthesia or dysesthesia in the dorsal root ganglion characteristic of hemorrhage and lymphocytic infiltration. The adjacent proximal nerves and sensory nerve roots show demyelination and rarely in the spinal cord is cell death evident. There are few controlled studies assessing treatment outcome in this relentless disease. Watson has described the use of amitriptyline, which has by and large been the treatment of choice (Watson & Evans, 1986). This was confirmed by Max who showed amitriptyline but not lorazepam was effective in treatment of PHN (Max et al., 1988). Phenothiazines have been suggested as helpful in the treatment of chronic pain, and in five case studies Taub reported the combination of amitriptyline and fluphenazine to be effective (Taub, 1973). In this report there was a mix of acute (active lesions) and chronic cases (pain lasting longer than 6 months). Graff-Radford has studied the effects of amitriptyline and fluphenazine using a double-blind protocol and found no significant benefit in combining amitriptyline with fluphenazine (Graff-Radford et al., 1986). Sympathetic nerve

block is considered by many to be effective in preventing PHN, when used in the first 3–6 months following the outbreak of zoster. It is suggested between 1 and 6 blocks be performed, depending on the effects. There is little purpose in doing more than 3 blocks if the pain relief is not outlasting the anesthetic effects. It may be more appropriate for this category to be in the autonomic nervous system category, but in some situations sympathetic block does not reduce the pain and this may suggest a sympathetically independent pain.

Musculoskeletal system

Musculoskeletal pain is the most common cause for chronic orofacial pain. Broadly speaking the disorders may be divided into arthrogenous and muscular referred to as temporomandibular disorders (TMD). The temporomandibular joint (TMJ) is different from other body joints. The most recognizable difference between the TMJ and other synovial joints is the non-innervated avascular fibrous connective tissue articular covering. This is not hyaline in nature, possibly to aid withstand twisting, turning and compressive forces. The fibroconnective tissue covering may also allow for significant remodelling to occur in the TMJ. Other significant differences include the diarthroidal structure. There is an intracapsular disc dividing the joint into upper and lower compartments providing for the complex hinge and gliding action. The mandible produces a reciprocal effect of one articulation on the other by joining the TMJ's. Also interacting in this system is the dental occlusion, which will result in altered forces on the system if not in equilibrium. The teeth provide a solid end point to joint movement unlike any other joint in which end range of motion is somewhat elastic. Due to the structure's nature, the intracapsular anatomy can remodel when subjected to extraneous forces. Such remodelling can be brought about through tooth loss, poor dental restoration, macro trauma and parafunctional habits such as tooth clenching and grinding. The remodelling may lead to dysfunction if the tissues are unable to compensate for the abnormal load. In addition, muscular hyperactivity may be initiated also as a compensation for the lack of equilibrium.

The joints hinge action allows for about a 25 mm interincisal opening, which occurs primarily in the lower joint space (condylar rotation). The next 20–25 mm requires the disc condyle complex to slide down the temporal eminence, with the disc moving posterior relative to the condyle (translation). Remodelling resulting in a deviation in articular form may interrupt this rhythmic function. The articular tissues are usually characterized by smooth rounded surfaces until subject to extraneous forces, which produce remodelling (Solberg et al., 1985). The mechanical interferences that are produced by the remodelling may cause noise as they move over each other. Remodelling is an ongoing process and results in a disease process continuum beginning with soft tissue change and progressing to involve the bony structures. One might view the process as a failure for the adaptive process to compensate for the extraneous forces exerted on the joint. If there is sufficient change the articular disc may become displaced. The usual direction for displacement is in an anteromedial direction (Ireland, 1953; Farrar, 1972) although displacement has been reported in a posterior direction (Blankestijn & Boering, 1985). The disc displacement may reduce if the individual can manipulate the condyle onto the disc, producing joint noise. This noise is usually heard after the initial 25 mm rotation in the opening movement and again just before the teeth occlude in the closing path. The closing noise is usually much quieter and may be produced by the relocation of the disc in the anterior position. Joint noise occurs in 20–30% of individuals over the age of 15 years (Egermark-Eriksson et al., 1981; Solberg et al., 1979). Pain associated with joint pathology is usually intermittent and associated with function. In order to confirm an articular TMD, patients should display at least three of the following four criteria: (i) limited range of motion $<$40 mm); (ii) joint noise (clicking, popping or crepitus); (iii) tenderness to palpation; (iv) functional pain. Continuous pain associated with an articular TMD is unusual and usually is produced by associated inflammation or secondary muscle pain. Pain emanating from the ligamentous attachments, the synovium and fibrous capsules is usually secondary to infection or trauma to these structures. The differences between synovitis and capsulitis is almost impossible to determine clinically (Bell, 1995).

Articular remodelling is a direct result of adaptive changes that help to establish a status quo between joint form and function (Moffett et al., 1964). Osteoarthrosis results when there is destruction of articular tissues secondary to excessive strain on the remodelling mechanism. The problem is therefore non-painful and usually only produces mechanical interference's. De Bont has suggested that the degenerative process is due to disruption of the collagen fibre network and fatty degeneration (De Bont et al., 1985). Inflammation of the articular tissue does not occur due to the unvascularized surface. For inflammation to occur a fundamental arthropathic change must occur such as the proliferation of inflamed synovial membrane into the articular tissue, or the exposure of innervated and vascularized osseous tissue (De Bont et al., 1985).

Osteoarthrosis is a common condition that seems to progress with age. It also appears to affect females more than males (Davis, 1981). Osteoarthrosis is insidious in onset, usually not associated with systemic disease, but perhaps initiated through repetitive loading or a variety of factors that occur over a lifetime. The inflammation that occurs in osteoarthritis requires an innervated and vascular surface. This suggests that the adaptive remodelling that continues has been overwhelmed and the tissues below the fibroconnective tissue surface are exposed allowing the inflammatory process to begin.

Muscle disorders

The disorders involving muscle may be independent of the articular problems but more often than not are involved when joint dysfunction exists. Their involvement may be mild and produce minimal dysfunction or severe and markedly disabling. When muscle pain problems occur, the treatment may differ depending on the subgroup defined below.

Myofascial pain syndromes, as classified by the International Association for the Study of Pain Subcommittee on Taxonomy (Mersky, 1986), may be found in any voluntary muscle, and are characterized by trigger points (TPs) which may cause referred pain and local and referred tenderness (Clark et al., 1981; Moller, 1981). When 'active', TPs are painful to palpation and spontaneously refer pain and autonomic symptoms to remote structures in reproducible patterns characteristic for each muscle (Travell & Simons, 1984). It is this referred pain that is usually the presenting complaint. When 'latent', TPs are still locally tender but do not produce referred phenomena. The pain quality is pressing, tightening, deep, aching, and often poorly circumscribed (Travell & Simons, 1984). It may be associated with sensations of swelling, numbness and stiffness. Pain, although usually constant, may fluctuate in intensity and shift anatomical site (Travell & Simons, 1984). Associated symptoms may include autonomic phenomena, most commonly reactive hyperemia or erythema, although photophobia and phonophobia are described (Butler et al., 1975).

The primary basis for myofascial pain is the referred pain. The referral patterns often do not make neurological sense. As an example, pain from a trigger point in the trapezius, innervated by cranial nerve 11, may refer to the forehead, innervated by cranial nerve 5. Despite the poor mechanistic understanding, clinically myofascial pain is widely accepted. It is imperative that we understand how this referral may take place.

Men described a hypothesis for muscle pain referral to other deep somatic tissues remote from the site of the original muscle stimulation or lesion (Mens, 1994). He criticizes the convergence: projection pain referral theory, by pointing out there is little convergence in the dorsal horns associated with deep tissues. Mens' hypothesis adds two new components to the convergence: projection theory. First, the convergent connections from deep tissues to dorsal horn neurons are opened only after nociceptive inputs from muscle are activated. The connections opened after muscle stimulus are called silent connections. Secondly, the referral to muscle outside the initially activated site is due to spread of central sensitization to adjacent spinal segment (Mens, 1994). The initiating stimulus requires a peripheral inflammatory stimulus. In the animal model described by Mens the noxious stimulus was bradykinin injected into the muscle. It is unclear what triggers the muscle referral in the clinical setting where there is usually no obvious inflammation-producing incident.

This Mens theory has been used by Simons to discuss a neurophysiological basis for trigger point pain (Simons, 1994). Simons hypothesizes that when the tender area in the muscle is palpated there are neurotransmitters released in the dorsal horn (trigeminal nucleus) resulting in nociceptive inputs, openings that were previously silent. This causes distant neurons to produce a retrograde referred pain (Simons, 1994). This model accounts for most of the clinical presentation and therapeutic options seen in myofascial pain, but does not account for what initiates the peripheral tenderness, that must be present to activate the silent connections.

Fields has described a means whereby the central nervous system may switch on nociception (Fields & Heinricher, 1989). He describes the presence of 'on' cells which when stimulated may produce activation of trigeminal nucleus nociceptors. Olesen has used Fields' model to describe a hypothesis for tension-type headache (Olesen, 1991). This model describes the interaction of three systems, the vascular, supraspinal and myogenic. The proposed hypothesis suggests that perceived headache pain is facilitated by the central nervous system depending on inputs from either muscle or blood vessel. In migraine the inputs are proposed as primarily vascular whereas in tension-type headache there are primarily muscular inputs. This model helps explain why the clinical presentation and therapeutic options in migraine and tension-type headache are often similar, as well as why there is temporary relief seen with peripheral treatments such as trigger point injections.

The resultant hyperalgesia or trigger point sensitivity may represent a peripheral sensitization related to serum levels on serotonin (5H-T). Ernberg et al. (1999) showed a significant correlation with serum 5H-T and allodynia associated with muscular face pain (Alstergen et al., 1999). In

rheumatoid temporomandibuar pain serum 5H-T concentrations correlated with pain. There was no correlation with circulating serum levels of neuropeptide Y (NPY) or interleukin–1B (Alstergen et al., 1999).

It is therefore proposed that patients presenting with facial pain where the etiology is not obvious may have myofascial pain. In these patients careful physical examination will allow the clinician to reproduce the pain by digitally palpating the muscles. Confirmation with trigger point injections is also helpful. It is suggested that the trigger point be injected with 1–2 cc of 1% procaine for best results.

The therapy for myofascial pain requires enhancing central inhibition through pharmacology or behavioural techniques and simultaneously reducing peripheral inputs through physical therapies including exercises and trigger point specific therapy (Travell & Simons, 1986; Graff-Radford et al., 1987; Davidoff, 1998). It is essential that patients are aware that the goals in therapy are to manage the pain and not to cure. It is important to stress the role patients' play in managing the perpetuating factors (Graff-Radford et al., 1987; Davidoff, 1998).

Discussion

Prior to making the diagnosis of orofacial pain, the evaluation must begin with an in-depth medical history which should include the chief complaint and a narrative history of the complaint, its progression and prior treatment. Not all chronic pain conditions require a psychological evaluation, but it should be kept in mind that all pain, no matter what the etiology, is subject to behavioural and emotional factors. These behavioural issues should be considered and, where there is any doubt as to their contribution, a psychological evaluation is suggested. The psychological evaluation is not done to determine weather the pain is psychogenic, rather, for the purpose of selecting specific cognitive and behavioural strategies useful in pain management. Once these data are gathered, a neurological screening examination, temporomandibular joint examination and myofascial palpation should be carried out. At this time, a differential diagnosis can be established and specific tests outlined above may be required to provide a definitive diagnosis. This process permits effective treatment, for an appropriate diagnosis.

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Chronic daily headache

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There is no consensus on the classification of chronic daily headache (CDH). Some authors use the term CDH to refer to chronic or transformed migraine; others use it for any headache disorder that occurs on a daily or near-daily basis, regardless of cause. We use CDH to refer to the broad group of very frequent headaches (15 or more days a month) not related to a structural or systemic illness, but we include those headaches that are associated with medication overuse. Population-based studies in the United States, Europe, and Asia suggest that 4 to 5% of the general population has headache 15 or more days per month (Scher et al., 1998; Castillo et al., 1999; Wang et al., 2000) and that chronic tension-type headache (CTTH) is the leading cause (Rasmussen, 1992). CDH patients account for most consultations in headache subspecialty practices (Silberstein et al., 1994).

An approach to thinking about CDH is presented in Table 64.1. Once secondary headache has been excluded, we subdivide frequent headache sufferers into two groups, based on headache duration. When headache duration is less than 4 hours, the differential diagnosis includes cluster headache, chronic paroxysmal hemicrania, idiopathic stabbing headache, hypnic headache, and other miscellaneous headache disorders. When the headache duration is greater than 4 hours, the major primary disorders to consider are transformed migraine (TM), hemicrania continua (HC), CTTH, and new daily persistent headache (NDPH) (Silberstein et al., 1994).

In this chapter, we discuss the classification and treatment of primary CDH of long duration, highlighting the four categories outlined above. We propose revisions to the International Headache Society (IHS) system and offer criteria for TM, CTTH, NDPH, and HC (Silberstein et al., 1994). We also discuss the role of medication overuse in the development and treatment of these disorders, as well as their mechanisms and treatment.

Table 64.1. Chronic daily headache

Primary chronic daily headache
Headache duration >4 hours
Chronic migraine (transformed migraine)
Chronic tension-type headache
New daily persistent headache
Hemicrania continua
Headache duration <4 hours
Cluster headache
Paroxysmal hemicranias
Hypnic headache
Idiopathic stabbing headache
Secondary chronic daily headache
– Post-traumatic headache
– Cervical spine disorders
– Headache associated with vascular disorders (arteriovenous malformation, arteritis (including giant cell arteritis), dissection, and subdural hematoma)
– Headache associated with non-vascular intracranial disorders (intracranial hypertension, infection (EBV, HIV), neoplasm)
– Other (temporomandibular joint disorder; sinus infection)

Transformed (chronic) migraine

Transformed migraine has been variously called transformed or evolutive migraine, chronic migraine or mixed headache (Silberstein et al., 1995; Mathew, 1982; Mathew et al., 1982, 1987; Olesen et al., 1993; Saper, 1983). Patients with TM often have a history of episodic migraine that began in their teens or twenties (Silberstein et al., 1995). Most patients with this disorder are women, 90% of whom have a history of migraine without aura. Patients often report a process of transformation characterized by headaches that have grown more frequent over months to years

Table 64.2. Revised criteria for transformed migraine

1.8 Chronic migraine

A. Daily or almost daily (>15 days/month) head pain for >1 month
B. Average headache duration of >4 hours/day (if untreated)
C. At least one of the following:
   1) History of episodic migraine meeting any IHS criteria 1.1 to 1.6
   2) History of increasing headache frequency with decreasing average severity of migrainous features over at least 3 months.
   3) Headache at some time meets IHS criteria for migraine 1.1 to 1.6 other than duration
D. Does not meet criteria for new daily persistent headache (4.7) or hemicrania continua (4.8)
E. No evidence of organic disease.

Note:
The clinician should attempt to distinguish the coincidental occurrence of migraine and CTTH based on the pattern of headache evolution. If the patient cannot recall the pattern of evolution differentiating the coincidental occurrence of two disorders may be difficult.
Source: Modified from Silberstein et al. (1996).

Table 64.3. Proposed criteria for chronic tension-type headache

2.2 Chronic tension-type headache

Diagnostic criteria

A. Average headache frequency >15 days/month (180 days/year) with average duration of >4 hours/day (if untreated) for 6 months fulfilling criteria B-D listed below.
B. At least 2 of the following pain characteristics:
   1. Pressing/tightening quality
   2. Mild or moderate severity (may inhibit, but does not prohibit activities)
   3. Bilateral location
   4. No aggravation by walking upstairs or similar routine physical activity
C. History of episodic tension-type headache in the past (needs to be tested).
D. History of evolutive headaches which gradually increased in frequency over at least a 3 month period (needs to be tested).
E. Both of the following:
   1. No vomiting
   2. No more than one of nausea, photophobia, or phonophobia (needs to be tested).
F. Does not meet criteria for hemicrania continua (4.8), new daily persistent headache (4.7), or chronic migraine (1.8).
G. No evidence of organic disease.

Source: Modified from Silberstein et al. (1996).

while the associated symptoms of photophobia, phonophobia, and nausea have, on average, become less severe and less frequent (Mathew, 1982; Mathew et al., 1982; Mathew, 1987; Saper, 1983). Patients often develop (transform into) a pattern of daily or nearly daily headaches that resemble CTTH. That is, the pain is mild to moderate and not associated with photophobia, phonophobia, or gastrointestinal features. Other features of migraine, including aggravation by menstruation and other trigger factors, as well as unilaterality and gastrointestinal symptoms, may persist. Many patients have attacks of full-blown migraine superimposed on a background of less severe headaches. Migraine transformation most often develops when there is medication overuse, but transformation may occur without overuse (Mathew et al., 1982, 1990).

Eighty per cent of patients with TM have depression (Mathew, 1993; Saper, 1983) which often lifts when the pattern of medication overuse and daily headache is interrupted. We proposed criteria for TM (Table 64.2). We believe that TM is a form of migraine and that the diagnosis is best made in patients who have a past history of IHS migraine and a process of transformation (Silberstein et al., 1995). Our criteria provide three alternative diagnostic links to migraine: (i) a prior history of IHS migraine; (ii) a clear period of escalating headache frequency with decreasing severity of migrainous features (which were both required in the 1994 criteria); or (iii) current superimposed attacks of headaches that meet all the IHS criteria for migraine except duration. Pascual et al. pointed out that individuals with coincidental migraine and CTTH could meet criteria for TM. If a patient has episodic migraine and independent, coincidental CTTH, there is a risk that the headache may be misclassified as TM.

Chronic tension-type headache (Table 64.3)

Daily headaches may also develop in patients with a history of episodic tension-type headache (ETTH). These headaches are more often diffuse or bilateral, frequently involving the posterior aspect of the head and neck. Prior or coexistent episodic migraine is absent in patients with CTTH, as are most features of migraine. We proposed several modifications to the current classification of CTTH. CTTH (2.2) requires head pain on at least 15 days a month for at least 6 months. Although the pain criteria are identical to ETTH, the IHS classification allows nausea, but not

vomiting. The need to include any of these migrainous features in the IHS definition of CTTH may be a result of the practice of including TM under the rubric of CTTH. Coexistent migraine and CTTH might exist with the caveat that the non-migrainous headaches have no migrainous features. Guitera et al. (1999) have suggested, based on population-based epidemiologic data, that CTTH and migraine can coexist if, and only if, the current headache has no migrainous features and there is a remote history of migraine.

Calcitonin gene-related peptide (CGRP) is involved in the pathophysiology of migraine and cluster headache. Its role in CTTH is unknown. Ashina et al. (2000) found that plasma levels of CGRP are normal and unrelated to headache state in patients with CTTH. CGRP levels measured in the peripheral circulation of patients on days without headache, 63±5 pmol/l, tended to be higher than CGRP levels of controls, 53±3 pmol/l, but the difference was not statistically significant ($P=0.06$). No differences were found between CGRP levels assessed ictally and interictally in either the cranial ($P=0.91$) or the peripheral ($P=0.62$) circulation. Plasma CGRP was higher in the external jugular vein than in the antecubital vein on days without headache ($P=0.03$), but not on days with headache ($P=0.82$). Interictal plasma CGRP was increased in patients whose pain quality was pulsating. This study suggests that TTHs that fulfill IHS criteria may be related to migraine, if the headache has a pulsating quality.

Russell et al. (1999) evaluated CTTH in a family study of 122 probands and 377 first-degree relatives. Sensitivity, specificity, predictive values, and chance-corrected agreement rate for the diagnosis of CTTH were 68%, 86%, 53% (PVpos), 92% (PVneg), and 0.48, respectively. The low sensitivity for CTTH in a family member, assessed by a proband report, indicates that 32% of CTTH cases are missed using this method. They concluded that direct interviews of family members are necessary to determine case status, as was previously shown for migraine (Ottman & Lipton, 1994). Clinically interviewed parents, siblings, and children had a 2.1- to 3.9-fold increased risk of CTTH compared with the general population. The proband's gender did not influence the risk of CTTH among first-degree relatives. The significantly increased familial risk, with no increased risk found in spouses, suggests that genetic factors are involved in CTTH, although familial environmental factors are also possible.

New daily persistent headache (Table 64.4)

NDPH is characterized by the relatively abrupt onset of an unremitting CDH (Vanast, 1986); that is, a patient develops a headache that does not remit. NDPH is likely to be a heterogeneous disorder. Castillo et al. (1999) conducted a population study of over 2000 patients; they identified only two cases of this disorder, indicating that it is rare. Some cases may reflect a postviral syndrome (Vanast, 1986). The daily headache develops abruptly, over less than 3 days. Patients with NDPH are generally younger than those with TM (Vanast, 1986).

Table 64.4. Proposed criteria for new daily persistent headache

4.7 New daily persistent headache
A. Average headache frequency >15 days/month for >1 month
B. Average headache duration >4 hours/day (if untreated). Frequently constant without medication but may fluctuate.
C. No history of tension-type headache or migraine which increases in frequency and decreases in severity in association with the onset of NDPH (over 3 months).
D. Acute onset (developing over <3 days) of constant unremitting headache
E. Headache is constant in location? (Needs to be tested)
F. Does not meet criteria for hemicrania continua 4.8
G. No evidence of organic disease.

Source: Modified from Silberstein et al. (1994).

Since NDPH is not defined by the characteristics of the headache, this disorder overlaps with CTTH. The presence or absence of a past history of headache distinguishes the disorders. NDPH requires the relatively abrupt onset of near daily headache in the absence of a history of evolution from migraine or ETTH. Excluding all patients with a history of ETTH is problematic, as almost 70% of men and 90% of women have had a TTH in the past. We allow a diagnosis of NDPH in patients with migraine or ETTH if these disorders do not increase in frequency to give rise to NDPH. The constancy of location is uncertain and needs to be field-tested. NDPH may or may not be associated with medication overuse (4.7.1., 4.7.2.). A diagnosis of NDPH takes precedence over TM and CTTH.

Hemicrania continua (Table 64.5)

HC is a rare, indomethacin-responsive headache disorder characterized by a continuous, moderately severe, unilateral headache that varies in intensity, waxing and waning without disappearing completely (Newman et al., 1993). It rarely alternates sides (Bordini et al., 1991). HC is frequently associated with jabs and jolts (idiopathic stabbing headache). Exacerbations of pain are often associated with

Table 64.5. Proposed criteria for hemicrania continua

4.8 Hemicrania continua[a]
A. Headache present for at least 1 month
B. Strictly unilateral headache
C. Pain has all 3 of the following present:
1. Continuous but fluctuating
2. Moderate severity, at least some of the time
3. Lack of precipitating mechanisms
D. 1) Absolute response to indomethacin or
2) One of the following autonomic features with severe pain exacerbation
(a) Conjunctival infection
(b) Lacrimation
(c) Nasal congestion
(d) Rhinorrhea
(e) Ptosis
(f) Eyelid edema
E. May have associated stabbing headaches
F. No evidence of organic disease.

Notes:

[a] HC is usually non-remitting, but rare cases of remission have been reported.

Source: Modified from Goadsby and Lipton (1997).

autonomic disturbances, such as ptosis, miosis, tearing, and sweating. HC is not triggered by neck movements, but tender spots in the neck may be present (Table 64.5). Some patients have photophobia, phonophobia, and nausea.

Although HC almost invariably has a prompt and enduring response to indomethacin, the requirement of a therapeutic response as a diagnostic criterion is problematic. It effectively excludes the diagnosis of HC in patients who were never treated with indomethacin (perhaps because another agent helped) and in patients who failed to respond to indomethacin. Cases have been described that did not respond to indomethacin but meet the phenotype; for this reason a characteristic pattern or a response to indomethacin (Table 64.5) provides an alternative means of diagnosis.

HC exists in continuous and remitting forms. In the remitting variety, distinct headache phases last weeks to months, with prolonged pain-free remissions (Newman et al., 1993; Iordanidis & Sjaastad, 1989; Pareja et al., 1990). In the continuous variety, headaches occur on a daily, continuous basis, sometimes for years. A bilateral case and a patient whose attacks alternated sides (Newman et al., 1993) have been described. HC takes precedence over the diagnosis of other types of primary CDH. Many patients with this disorder overuse acute medication; it must be differentiated from TM.

The relative rarity of HC has made it difficult to study its pathophysiology. In a population study of nearly 2000 patients, no cases were identified (Castillo et al., 1999). Pain pressure thresholds are reduced in patients who have HC, as they are in those who have chronic paroxysmal hemicrania (Antonaci et al., 1994). In contrast, orbital phlebography is relatively normal compared with patients who have chronic paroxysmal hemicrania (Antonaci, 1994), although it should be observed that this area is controversial (Bovim et al., 1992). Pupillometric studies have shown no clear abnormality in HC (Antonaci et al., 1992), and studies of facial sweating have shown modest changes, similar to those seen in chronic paroxysmal hemicrania (Antonaci, 1991).

Espada et al.(1999) reported five men and four women who had HC (eight continuous, one remitting) that was diagnosed using proposed diagnostic criteria (Goadsby & Lipton, 1997). The mean age of onset was 53.3 years (range 29 to 69). All nine patients had initial relief with indomethacin (mean daily dose 94.4 mg, range 50 to 150). Follow-up was possible in eight patients. Indomethacin could be discontinued after 3, 7, and 15 months respectively, and patients remained pain free. Three patients discontinued treatment because of side effects and had headache recurrence; two had relief with aspirin. Two other patients continue to take indomethacin with partial relief.

Drug overuse and rebound headache

Patients with frequent headaches often overuse analgesics, opioids, ergotamine, and triptans (Katsarava et al., 1999). Medication overuse may be both a response to chronic pain and a cause of chronic pain. In headache-prone patients, medication overuse may produce drug-induced 'rebound headache' that is accompanied by dependence on symptomatic medication. In addition, medication overuse can make headaches refractory to prophylactic medication (Mathew et al., 1990; Mathew, 1990; Diamond & Dalessio, 1982; Wilkinson, 1988; Saper, 1987a, 1989). Although stopping the acute medication may result in the development of withdrawal symptoms and a period of increased headache, there is generally subsequent headache improvement (Saper, 1989; Andersson, 1988; Baumgartner et al., 1989; Rapoport et al., 1986; Saper & Jones, 1986).

In subspecialty centres, most patients with drug-induced headache have a history of episodic migraine that has been converted into TM as a result of medication overuse (Mathew et al., 1987, 1990; Mathew, 1990; Rapoport, 1988; Kudrow, 1982; Diener et al., 1984; Rasmussen et al., 1989).

Patients with TTH, HC, and NDPH may also overuse symptomatic medications.

In European headache centres, 5 to 10% of the patients have drug-induced headache. One series of 3000 consecutive headache patients reported that 4.3% had drug-induced headaches (Micieli et al., 1988). Experiences in the United Kingdom (Goadsby, P. personal communication) suggest that drug-associated headache is more common than the literature suggests. In American specialty headache clinics, as many as 80% of patients who presented with primary CDH used analgesics on a daily or near-daily basis (Rapoport, 1988; Solomon et al., 1992). In India, in contrast, medication overuse is less common (Ravishankar, 1997). Diener and Tfelt-Hansen (1993) summarized 29 studies, which included 2612 patients with chronic drug-induced headache. Migraine was the primary headache in 65%, TTH in 27%, and mixed or other headaches in 8% (for example, cluster headache). Women had more drug-induced headache than men (3.5 : 1; 1533 women, 442 men). The number of tablets or suppositories taken daily averaged 4.9 (range 0.25 to 25). Patients averaged 2.5 to 5.8 different pharmacologic components simultaneously (range 1 to 14) (Diener & Tfelt-Hansen, 1993).

Clinical features of rebound headache

Rebound headache has not been demonstrated in placebo-controlled trials. However, stopping daily low-dose caffeine frequently results in withdrawal headache (Silverman et al., 1992). In a controlled study of caffeine withdrawal, 64 normal adults (71% women) with low-to-moderate caffeine intake (the equivalent of about 2.5 cups of coffee a day) were given a two-day caffeine-free diet and either placebo or replacement caffeine. Under double-blind conditions, 50% of the patients who were given placebo had a headache by day two, compared to 6% of those given caffeine. Nausea, depression, and flu-like symptoms were common in the placebo group. This study is relevant since caffeine is frequently used by headache sufferers for pain relief, often in combination with analgesics or ergotamine. The study is a model for short-term caffeine withdrawal but does not demonstrate the long-term consequences of detoxification. In a community-based telephone survey of 11 112 subjects in Lincoln and Omaha, Nebraska, 61% reported daily caffeine consumption, and 11% of the caffeine consumers reported symptoms upon stopping coffee (Potter et al., 2000). A group of those who reported withdrawal were assigned to one of three regimes: abrupt caffeine withdrawal; gradual withdrawal; and no change. One-third of the abrupt-withdrawal group and an occasional member of the gradual-withdrawal group had symptoms that included headache and tiredness.

The actual dose limits and the time needed to develop rebound headaches have not been defined in rigorous studies, nor is the relationship of drug half-life to rebound development known. It is believed that overuse occurs when patients take three or more simple analgesics a day more often than 5 days a week, triptans or combination analgesics containing barbiturates, sedatives, or caffeine more often than 3 days a week, or opioids or ergotamine tartrate more often than 2 days a week (Mathew et al., 1990; Diamond & Dalessio, 1982; Mathew, 1990; Saper, 1987a; Wilkinson, 1988). Rebound headache can develop in patients taking as little as 0.5 to 1mg of ergotamine three times a week (Silberstein, 1993; Wilkinson, 1988; Saper, 1983, 1987b; Saper & Jones, 1986; Baumgartner et al., 1989).

The triptans are selective 5-HT_1 agonists that are effective in acute migraine treatment and all of them (sumatriptan, rizatriptan, naratriptan, and zolmitriptan) have been reported to induce rebound headache (Catarci et al., 1994; Diener et al., 1991; Gaist et al., 1996; Katsarava et al., 1999). The weekly dosages necessary to initiate drug-induced headache with the centrally penetrant triptans may be lower than with ergotamines or sumatriptan and the time of onset might be shorter. Increasing attack frequency can be the first sign that drug-induced headache is developing. We recommend limiting triptan use to 3 days a week.

Medication overuse may be responsible, in part, for the transformation of episodic migraine or ETTH into daily headache and for the perpetuation of the syndrome. However, medication overuse is not the sine qua non of TM or CTTH. Some patients develop TM or CTTH without overusing medication, and others continue to have daily headaches long after the overused medication has been discontinued. Medication overuse is usually motivated by a patient's desire to treat the headaches (Kaiser, 1999). However, some headache patients overuse combination analgesics to treat a mood disturbance. Medication overuse rarely represents a form of primary substance abuse.

In addition to exacerbating the headache disorder, drug overuse has other serious effects. The overuse of acute drugs may interfere with the effectiveness of preventive headache medications. Prolonged use of large amounts of medication may cause renal or hepatic toxicity in addition to tolerance, habituation, or dependence.

Psychiatric comorbidity

Anxiety, depression, panic disorder and bipolar disease are more frequent in migraineurs than in non-migraine

control subjects (Merikangas et al., 1990; Breslau & Davis, 1993). Since TM evolves from migraine, one would expect to find a similar profile of psychiatric comorbidity in TM. In clinic-based samples, depression occurs in 80% of TM patients. The Minnesota Multiphasic Personality Inventory was abnormal in 61% of primary CDH patients, compared with 12.2% of patients with episodic migraine. Zung and Beck Depression Scale scores were significantly higher in primary CDH patients than in migraine controls (Mathew, 1990, 1991; Mathew et al., 1990; Saper, 1987b). Comorbid depression often improves when the cycle of daily head pain is broken.

Mitsikostas and Thomas (1999) found that the average Hamilton rating scores for anxiety and depression were significantly higher in headache patients. Patients with CTTH, mixed headache, or drug abuse headache had the highest Hamilton rating scores for depression and anxiety. Verri et al. (1998) found current psychiatric comorbidity in 90% of primary CDH patients. Generalized anxiety occurred in 69.3% of patients and major depression in 25%.

Psychiatric comorbidity is a predictor of intractability. The Minnesota Multiphasic Personality Inventory was abnormal in 100% of CDH patients who failed to respond to aggressive management (31% of the primary CDH group), compared to 48% of the responders. Physical, emotional, or sexual abuse, parental alcohol abuse, and a positive dexamethasone suppression test also correlated highly with a poor response to aggressive management. Curioso et al. (1999) found that 31 of 69 (45%) CDH patients had an adjustment disorder, 16 (23%) had major depression, 12 (17%) were dysthymic, 6 (9%) had generalized anxiety disorder, 1 (2%) was bipolar, and 3 (4%) were normal. The risk of a bad outcome after treatment was significantly greater for patients with major depression than those without. CDH patients who have major depression or abnormal Beck Depression Inventory scores have worse outcomes at 3 to 6 months compared with patients who are not depressed.

Epidemiology

In population-based surveys, primary CDH occurs in 4.1% of Americans, 4.35% of Greeks, 3.9% of elderly Chinese, and 4.7% of Spaniards. Population-based estimates for the one-year period prevalence of CTTH are 1.7% in Ethiopia (Tekle Haimanot et al., 1995), 3% in Denmark (Rasmussen, 1995), 2.2% in Spain (Castillo et al., 1999), 2.7% in China (Wang et al., 2000), and 2.2% in the United States (Scher et al., 1998).

Scher et al. (1998) ascertained the prevalence of primary CDH in 13, 343 individuals aged 18 to 65 years in Baltimore County, Maryland. The overall prevalence of primary CDH was 4.1% (5.0% women, 2.8% men; 1.8: 1 women to men ratio). In both men and women, prevalence was highest in the lowest educational category. More than half (52% women, 56% men) met criteria for CTTH (2.2%), almost one-third (33% women, 25% men) met criteria for TM (1.3%), and the remainder (15% women, 19% men) were unclassified (0.6%). Overall, 30% of women and 25% of men who were frequent headache sufferers met IHS criteria for migraine (with or without aura). On the basis of chance, migraine and CTTH would co-occur in 0.22% of the population; the fact that TM occurred in 1.3% of this population would suggest that their co-occurrence is more than random.

Castillo et al. (1999) sampled 2252 subjects over 14 years of age in Cantabria, Spain. Overall 4.7% had CDH. Using the criteria of Silberstein et al. (1994), none had HC, 0.1% had NDPH, 2.2% had CTTH, and 2.4% had TM. Overuse of symptomatic medication occurred in 19% of CTTH and 31.1% of TM patients. Eight patients had a previous history of migraine without aura and now had primary CDH with only the characteristics of TTH. These headaches met the criteria of TM but could have been migraine and coincidental CTTH.

Wang et al. (2000) looked at the characteristics of primary CDH in a population of elderly Chinese (over 65 years of age) in two townships on Kinmen Island in August 1993. Person-to-person biannual follow-up of the primary CDH patients was done in June 1995 and August 1997. Sixty patients (3.9%) had CDH. Significantly more women than men had primary CDH (5.6% and 1.8%, $P<0.001$). Of the primary CDH patients, 42 (70%) had CTTH (2.7%), 15 (25%) had TM (1%), and 3 (5%) had other CDH. By multivariate logistic regression, the significant risk factors of primary CDH included analgesic overuse (OR = 79), a history of migraine (OR = 6.6), and a Geriatric Depression Scale-Short Form score of 8 or above (OR = 2.6). At follow-up in 1995 and 1997, approximately two-thirds of patients still had CDH. Compared with the patients in remission, the patients with persistent primary CDH in 1997 had a significantly higher frequency of analgesic overuse (33% vs. 0%, $P=0.03$) and major depression (38% vs. 0%, $P=0.04$).

Pathophysiology of chronic daily headache

The nucleus caudalis (NC) of the trigeminal complex, the major relay nucleus for head and face pain, receives nociceptive input from cephalic blood vessels and pericranial muscles, as well as inhibitory and facilitatory suprasegmental input. Recent evidence suggests that central pain

facilitatory neurons (on-cells) are present in the ventromedial medulla. In addition, neurons in the trigeminal NC can be sensitized as a result of intense neuronal stimulation. Chronic pain may be due to ongoing peripheral activation of nociceptors (for example, chronic inflammation), although it may occur in the absence of painful stimuli. Although the source of pain in primary CDH is unknown and may be dependent on the subtype of CDH, recent work suggests several mechanisms that could contribute to the process: (i) abnormal excitation of peripheral nociceptive afferent fibres (perhaps due to chronic neurogenic inflammation); (ii) enhanced responsiveness of the NC neurons (central sensitization); (iii) decreased pain modulation; (iv) spontaneous central pain; or (v) a combination of these.

Peripheral mechanisms

In migraine, trigeminal nerve activation is accompanied by the release of vasoactive neuropeptides, including calcitonin gene-related peptides, substance P (SP), and neurokinin A from the nerve terminals. These mediators produce mast cell activation, sensitization of the nerve terminals, and extravasation of fluid into the perivascular space around the dural blood vessels. Intense neuronal stimulation causes induction of c-fos (an immediate early gene product) in the trigeminal NC of the brainstem. Neurotropins such as nerve growth factor are synthesized locally and can also activate mast cells and sensitive nerve terminals. Prostaglandins and nitric oxide (a diffusible gas that acts as a neurotransmitter) (Edelman & Gally, 1992) are both endogenous mediators that can be produced locally and can sensitize nociceptors. Repeated episodes of neurogenic inflammation may chronically sensitize nociceptors and thus contribute to the development of daily headache.

Central sensitization is manifested by increased spontaneous impulse discharges, increased responsiveness to noxious and non-noxious peripheral stimuli, and expanded receptive fields of nociceptive neurons. Does central sensitization play a role in headache? Brief chemical irritation of the dura with a cocktail of four inflammatory mediators (histamine, serotonin, bradykinin, and prostaglandin E2) made meningeal perivascular neurons pain-sensitive for a period of one to two hours, becoming more sensitive to mechanical forces (>2 g) (Strassman et al., 1996). This can explain the intracranial hypersensitivity (i.e. the worsening pain during coughing, bending over, or any head movement) and the throbbing pain of migraine (Anthony & Rasmussen, 1993).

Brief dural chemical irritation may also result in temporary changes in the central trigeminal neurons that receive convergent input from the dura and the skin. Their threshold decreased and their excitability increased in response to brushing and heating (<42 °C) of the periorbital skin – stimuli to which they showed only minimal or no response prior to chemical stimulation (Burstein et al., 1998). Sensitization may be the basis of the extracranial tenderness that accompanies migraine. In addition, the threshold of cardiovascular responses to facial and intracranial stimuli is reduced (Yamamura et al., 1999). The enhanced neuronal responses represent a state of central sensitization and the enhanced cardiovascular responses represent a state of intracranial hypersensitivity and cutaneous allodynia.

Burstein et al. (1998) predicted that cutaneous allodynia is present in migraine patients during attacks. They examined the pain thresholds of patients during and between migraine attacks. Many patients had periorbital cutaneous allodynia ipsilateral to the headache. Patients with allodynia were significantly older than those without cutaneous allodynia, hinting at a possible correlation between age and sensitization. These findings provide a neural basis for the pathophysiology of migraine pain and suggest a basis for continued head pain.

Bendtsen et al. (1996b) found evidence for sensitization in CTTH patients. Pericranial myofascial tenderness, evaluated by manual palpation, was considerably higher in patients than in controls ($P<0.00001$). The stimulus–response function from highly tender muscle was qualitatively different than from normal muscle, suggesting that myofascial pain may be mediated by low-threshold mechanosensitive afferents projecting to sensitized dorsal horn neurons.

Lassen et al. (1997) discovered that nitroglycerin, a nitric oxide (NO) donor, can induce more headache in CTTH patients than in healthy volunteers. Ashina et al. (1999) found that a NO synthesis inhibitor (L-NMMA) reduced headache and muscle hardness in CTTH. CTTH patients may have sensitization of second-order neurons due to prolonged nociceptive input from myofascial tissues. The decrease in muscle hardness following treatment with L-NMMA may be caused by decreased central sensitization.

Pain modulation

The mammalian nervous system contains networks that modulate nociceptive transmission. In the rostroventromedial medulla are so-called off-cells that inhibit, and on-cells that facilitate nociception (Fields et al., 1991). Increased on-cell activity could enhance the response to both painful and non-painful stimuli. Opiate withdrawal

results in increased firing of the on-cells, decreased firing of the off-cells, and enhanced nociception (Fields et al., 1991). A similar mechanism may occur during drug-induced headaches. Primary CDH may result, in part, from enhanced neuronal activity in the NC as a result of enhanced on-cell or decreased off-cell activity.

Jensen and Olesen (1996) used sustained teeth-clenching to trigger TTH in 58 patients with frequent CTTH or ETTH and 58 matched controls. Within 24 hours, 69% of patients (more than would be expected) and 17% of controls developed TTH. Shortly after clenching, electromyography (EMG) amplitude was significantly increased in the trapezius but not in the temporal muscle, and tenderness (which was increased at baseline in the headache patients) was further increased only in the patients who subsequently developed headache. Mechanical pain thresholds remained unchanged in the group that developed headache but increased in the group that did not develop headache. Pain tolerance decreased in the patients who developed headache, was unchanged in the remaining patients, and increased in controls, suggesting that headache patients do not effectively activate their antinociceptive system. This study clearly shows that peripheral mechanisms alone cannot explain TTH, but they could act as a trigger for a central process. Tenderness, not muscle contraction, correlates to headache development.

Exteroceptive suppression (ES) is the inhibition of voluntary EMG activity of the temporalis muscle induced by trigeminal nerve stimulation (Schoenen et al., 1987). There are two successive periods of ES (ES1 and ES2) (silent periods). ES2, a multisynaptic reflex subject to limbic and other modulation, was originally reported to be absent in 40% of patients with CTTH and reduced in duration in 87%, whereas ES1, an oligosynaptic reflex, was normal (Paulus et al., 1992; Makashima & Takahashi, 1991; Pritchard, 1989). More recent studies have not confirmed these findings. Zwart and Sand found normal ES2 values in a small blinded study of 11 patients with CTTH (Zwart & Sand, 1995). Bendtsen et al. (1996a) and Lipchick et al. (1996, 1997) did not find abnormalities in ES2 in blinded studies of patients with CTTH. Measures of ES2 duration depend on tricky methodologic variables. ES2 may be absent in headache-prone patients (Paulus et al., 1992; Nakashima & Takahashi, 1991).

Schoenen et al. (1987) measured the ES2, pain threshold, EMG activity, anxiety scores, and response to biofeedback in 32 women with CTTH, and found an abnormal EMG in 62.5% of the patients if three different muscles and three states were tested. The EMG was abnormal in only 40% if only one muscle and one state were tested. A decreased pain threshold was found in half the patients tested in one of three muscles but in only 34% if only one muscle was tested. ES2 duration was reduced in 87% of patients

Schepelmann et al. (1998) found that the duration of ES2 (+SD) in fibromyalgia syndrome patients was 30.6 + 7.5 ms and was not significantly different from the control group (33.1 + 7.8 ms), whereas it was significantly shortened in CTTH patients (22.9 + 11.5 ms). Lipchik et al. (1996) evaluated masseter ES2 suppression and tenderness in the pericranial muscles of young adults with CTTH, ETTH, migraine without aura, migraine with aura, and controls. Pericranial muscle tenderness better distinguished diagnostic subgroups and better distinguished recurrent headache sufferers from controls than did masseter ES2. CTTH sufferers had the highest pericranial muscle tenderness and controls exhibited the lowest tenderness ($P<0.01$). The association between pericranial muscle tenderness and CTTH was independent of the intensity, frequency, or chronicity of headaches. Pericranial muscle tenderness may be present early in the development of tension headache, while ES2 suppression may only emerge later.

Reduced Achilles tendon pain thresholds were found in half of CTTH patients when compared with headache-free controls (Schoenen et al., 1991). Biofeedback moderately but significantly increased the pain threshold, perhaps by normalizing limbic input to the brainstem pain modulating system. Increased EMG activity or decreased pain thresholds were found in 72% of the patients (Schoenen et al., 1991), consistent with a diagnosis of 'CTTH associated with disorder of pericranial muscles', but these findings were not present in the remaining 28% of patients, consistent with a diagnosis of 'CTTH unassociated with such disorder'. Headache severity, anxiety, ES2, and response to biofeedback did not differ between these two groups, suggesting that their separation may be artificial or a consequence of the headache.

Spontaneous central pain activation

Post and Silberstein (1994) suggested the kindling model for epilepsy as a model for non-epileptic, progressive disorders such as mania. Post and Silberstein (1994) suggested that spontaneous recurrent migraine headaches might be analogous to the low levels of electrical stimulation in the kindling model in the process of headache transformation. Preventive migraine treatment could provide a dual benefit by preventing the occurrence of episodes and blocking the sensitization process that could lead to syndrome progression.

In primary CDH, hypersensitivity of neurons in the trigeminal NC may exist as a result of supraspinal facilitation. The vascular nociceptor may be hypersensitive in TM; in

CTTH associated with a disorder of the pericranial muscles, the myofascial nociceptor may be hypersensitive. In CTTH not associated with a disorder of the pericranial muscles, there may be less myofascial nociceptor hypersensitivity and a general increase in nociception. CTTH and TM may result from a defective interaction between endogenous nociceptive brainstem activity and peripheral input. Physical or psychologic stress or non-physiologic working positions can increase nociception from strained muscles that could trigger or sustain an attack and produce CTTH in an individual with altered pain modulation. Emotional mechanisms may also reduce endogenous antinociception. Long-term potentiation of nociceptive neurons and decreased activity in the antinociceptive system could cause primary CDH. Sensitization of the trigeminal NC neurons can result in normally non-painful stimuli becoming painful, production spots, an overlap in the symptoms of migraine and TTH, and activation of the trigeminal vascular system.

Drug-induced headache mechanisms

Overuse of analgesics, opioids, barbiturates, ergotamine-containing compounds, or triptans may contribute to the transformation of episodic into transformed migraine. Formulations of drugs that maintain sustained, non-fluctuating levels might avoid the development of drug-induced headache (Post & Silberstein, 1994). Continued high fluctuating doses of ergots, analgesics, opioids, or triptans could result in resetting the pain control mechanisms in susceptible individuals, perhaps by enhancing on-cell activity, enhancing central sensitization through NMDA receptors, or blocking adaptive antinociceptive changes.

Cerebral blood flow increases in the brainstem and cortex of patients with migraine without aura. During the headache, the increased cerebral blood flow in the cortex (but not the brainstem) is reversed by sumatriptan, as is the headache. This area of the brainstem is rich in opioids and includes the pain control centres. Dihydroergotamine (DHE) and centrally penetrant triptans selectively bind to this area of the brainstem, while sumatriptan may not. Perhaps this area of the brainstem integrates the phenomenon we call migraine, or it could be activated as a result of the migraine attack. If the first explanation is correct, ongoing activity in this area of the brainstem could produce recurrent or daily headache. If this area is responsible for controlling pain, then its failure to activate could explain ongoing headache activity. Acute migraine medications may induce daily headache by preventing the development of adaptive changes and perhaps by maintaining brainstem activation (Weiller et al., 1995).

Treatment

Overview

Patients suffering from CDH can be difficult to treat, especially when the disorder is complicated by medication overuse, comorbid psychiatric disease, low frustration tolerance, and physical and emotional dependency (Mathew et al., 1987; Saper, 1987b). The following steps should be taken. First, exclude secondary headache disorders; secondly, diagnose the specific primary headache disorder (i.e. TM, HC); and thirdly, identify comorbid medical and psychiatric conditions, as well as exacerbating factors, especially medication overuse. Limit all symptomatic medications (with the possible exception of the long-acting non-steroidal anti-inflammatory drugs (NSAIDs)). Start the patient on a programme of preventive medication (to decrease reliance on symptomatic medication), with the explicit understanding that the drugs may not become fully effective until medication overuse has been eliminated and detoxification completed (Silberstein & Saper, 1993). Outpatient detoxification options, including outpatient infusion in an ambulatory infusion unit, are available. If outpatient detoxification proves difficult or is dangerous, hospitalization may be required. We have proposed guidelines for hospitalization (Table 64.6). Patients need education and continuous support during this process.

Patients who overuse acute medication may not become fully responsive to acute and preventive treatment for 3 to 8 weeks after overuse is eliminated. Withdrawal symptoms include severely exacerbated headaches accompanied by nausea, vomiting, agitation, restlessness, sleep disorder, and (rarely) seizures. Barbiturates and benzodiazepines must be tapered gradually to avoid a serious withdrawal syndrome (Silberstein et al., 1990; Mathew et al., 1990; Baumgartner et al., 1989; Raskin, 1986).

Psychophysiologic therapy involves reassurance, counselling, stress management, relaxation therapy, and biofeedback. Physical therapy consists of modality treatments (heat, cold packs, ultrasound, and electrical stimulation), improvement of posture through stretching, exercise, and traction, trigger point injections, occipital nerve blocks, and a programme of regular exercise, stretching, balanced meals, and adequate sleep (Silberstein, 1984). It has been our experience that treating painful trigger areas in the neck can result in improvement of intractable primary CDH.

Acute pharmacotherapy

Choice of acute pharmacotherapy depends upon the diagnosis. Transformed migraine patients who do not overuse

Table 64.6. Criteria for hospitalization

I. Emergency or urgent admission

A. Certain migraine variants (e.g. hemiplegic migraine, suspected migrainous infarction, basilar migraine with serious neurologic symptoms such as syncope, confusional migraine, etc.)
   1. When a diagnosis has not been established during a previous similar occurrence
   2. When a patient's established outpatient treatment plan has failed.

B. Diagnostic suspicion of infectious disorder involving CNS (e.g. brain abscess, meningitis) with initiation of appropriate diagnostic testing.

C. Diagnostic suspicion of acute vascular compromise (e.g. aneurysm, subarachnoid hemorrhage, carotid dissection) with initiation of appropriate diagnostic testing.

D. Diagnostic suspicion of a structural disorder causing symptoms requiring an acute setting (e.g. brain tumour, increased intracranial pressure) with initiation of appropriate diagnostic testing.

E. Low cerebrospinal fluid headache when an outpatient blood patch has failed and an outpatient treatment plan has failed or there is no obvious cause.

F. Medical emergency presenting with a severe headache.

G. Severe headache associated with intractable nausea and vomiting producing dehydration or postural hypotension, or unable to retain oral medication, and unable to be controlled in an outpatient setting or with admission to observation status.

H. Failed outpatient treatment of an exacerbation of episodic headache disorder with:
   1. Failure to respond to 'rescue' or backup medications or
   2. Failure to respond to outpatient treatment with IV DHE on a schedule of a minimum of twice daily.

II. Non-emergent admission:

A. Coexistent psychiatric disease documented by psychologic or psychiatric evaluation with sufficient severity of illness such that failure to admit could pose a health risk to the patient or impair the implementation of outpatient treatment.

B. Coexistent or risk of disease (e.g. unstable angina, unstable diabetes, recent transient ischemic attack, myocardial infarction in the past 6 months, renal failure, hypertension, age >65) necessitating monitoring for treatment of headache significant enough to warrant admission.

C. Severe chronic daily headaches involving chronic medication overuse when there is:
   1. Daily use of potent opioids and/or barbiturates
   2. Daily use of triptans, simple analgesics, or ergotamine in a patient with a documented failed trial of withdrawal of these medications.

D. Impaired daily functioning (e.g. threatened relationships, many lost days at work or school due to headache), with a failure to respond to 2 days of outpatient treatment with i.v./DHE, i.v. neuroleptics, or i.v. corticosteroids on a schedule of a minimum of twice daily or equivalent treatment.

Source: S.D., Silberstein, W.B., Young, T.D., Rozen & J. Lenow, Personal communication.

symptomatic medication can treat acute migrainous headache exacerbations with triptans, DHE, and NSAIDs. These drugs must be strictly limited to prevent superimposed rebound headache that will complicate treatment and require detoxification. The risk of rebound is much lower for DHE and triptans than for analgesics, opioids, and ergotamine. CTTH and NPDH can be treated with nonspecific headache medications, and HC can be treated with supplemental doses of indomethacin.

Preventive pharmacotherapy

Patients with very frequent headaches should be treated primarily with preventive medications, with the explicit understanding that their medications may not become fully effective until the overused medication has been eliminated. It may take 3 to 6 weeks for treatment effects to develop. The following principles guide the use of preventive treatment: (i) from among the first-line drugs, choose preventive agents based on their side effect profiles, comorbid conditions, and specific indications (for example, indomethacin for HC); (ii) start at a low dose; (iii) gradually increase the dose until you achieve efficacy, until the patient develops side effects, or until the ceiling dose for the drug in question is reached; (iv) treatment effects develop over weeks and treatment may not become fully effective until rebound is eliminated; (v) if one agent fails, choose an agent from another therapeutic class; (vi) prefer monotherapy, but be willing to use combination therapy; (vii) communicate realistic expectations (Silberstein & Lipton, 1994).

Table 64.7. Summary of preventive drugs for use in transformed migraine

Drug	Clinical efficacy	Side effects	Clinical evidence[a]
Antidepressants			
Amitriptyline	+++	++	+++
Doxepin	+++	++	++
Fluoxetine	++	+	+++
Anticonvulsants			
Divalproex	+++	++	++
Topiramate	+++	++	++
Beta-blockers			
Propranolol, Nadolol, etc.	++	+	+
Calcium channel blockers			
Verapamil	++	+	+
Miscellaneous			
Methysergide	+++	+++	+

Notes:
All categories are rated from + to ++++ based on a combination of published literature and clinical experience.
[a] Ratings of +++ for clinical evidence indicate at least one double-blind, placebo-controlled study. A rating of ++ indicates open well-designed studies and + indicates ratings based on clinical experience. A rating of ++++ requires at least two double-blind placebo-controlled trials.
Source: Modified from Tfelt-Hansen and Welch (2000).

Most preventive agents used for primary CDH have not been examined in well-designed double-blind studies. Table 64.7 summarizes an assessment of the efficacy, safety, and evidence for a number of agents (Silberstein & Saper, 1993).

Antidepressants are attractive agents for use in TM, CTTH, and NDPH, since many patients have comorbid depression and anxiety. The most widely used tricyclic antidepressants are nortriptyline (Aventyl, Pamelor), doxepin (Sinequan) (Morland et al., 1979), and amitriptyline (Elavil), which has been effective in many but not all studies (Bussone et al., 1991; Couch et al., 1976; Diamond & Baltes, 1971; Holland et al., 1983; Lance & Curran, 1964; Pluvinage, 1994; Pfaffenrath et al., 1986, 1994; Holroyd et al., 1991; Gobel et al., 1994; Cerbo et al., 1998; Mitsikostas et al., 1997; Bonuccelli et al., 1996). In an open-label study in 82 non-depressed patients with either ETTH or CTTH, Cerbo et al. (1998) found that amitriptyline (25mg a day) significantly reduced ($P<0.05$) analgesic consumption and the frequency and duration of headache in CTTH but not in ETTH.

Fluoxetine (Prozac), a selective serotonin reuptake inhibitor, is coming into wider use for daily headaches; evidence from a double-blind study demonstrates its efficacy in primary CDH (Bussone et al., 1991; Saper et al., 1994). Fluvoxamine appears to be effective (Manna et al., 1994) and may have analgesic properties (Palmer & Benfield, 1994). Other selective serotonin reuptake inhibitors including paroxetine (Foster & Bafaloukos, 1994) and monoamine oxidase inhibitors may have a therapeutic role, but this has not been proven to date (Langemark & Olesen, 1994).

Beta-blockers (propranolol, nadolol) remain a mainstay of therapy for migraine (Silberstein & Saper, 1993) and are used for primary CDH (Pfaffenrath et al., 1986; Mathew, 1981). Clinicians fear that beta-blockers may exacerbate depression; however, this issue is controversial (Bright & Everitt, 1992). Beta-blockers are relatively contraindicated in patients who have asthma and Raynaud's disease.

Calcium channel blockers are very well tolerated (Silberstein & Saper, 1993); anecdotal evidence supports their use for TM. Verapamil (Calan) is the most widely prescribed agent in this family. Diltiazem (Cardizem) and nifedipine (Procardia) may also be considered. Flunarizine (Silberstein & Saper, 1993; Lake et al., 1993) is widely used in Canada and Europe but is not available in the United States.

The anticonvulsant divalproex sodium (Depakote) (Jensen et al., 1994) is an important drug in migraine prophylaxis, even for patients who have failed other agents. Four double-blind placebo-controlled studies have demonstrated its efficacy in migraine (Jensen et al., 1994; Mathew et al., 1995; Hering & Kuritzky, 1998; Klapper, 1995). Smaller open studies support its utility in TM (Mathew & Ali, 1991). Doses lower than those used for epilepsy (250 mg twice a day) may be sufficient. In an open-label study, Edwards et al. (1999) assessed the possible benefit of sodium valproate in 20 consecutive CDH patients who were refractory to multiple standard treatments. Eleven (55%) had a response (mild or no headaches within one to four weeks). The doses ranged from 375 mgs to 1500 mg a day. Two patients (10%) discontinued medication due to side effects (nausea and difficulty thinking).

Topiramate is a new antiepileptic agent that has GABA-agonist properties and few side effects when used in low doses. Its chronic use has been associated with weight loss, not weight gain. In an open-label study, Shuaib et al. (1999) used topiramate (25 to 100 mg per day) to treat 37 patients who had more than ten migraine headaches a month. Most patients had CDH in addition to migraine; all had failed previous preventive treatment. Over a 3- to 9-month follow-up, 11 patients had an excellent result (headache

frequency decreased by over 60%); 11 patients had a good result (headaches frequency decreased 40% to 60%); three patients discontinued therapy due to side effects; and eight patients had no improvement. This uncontrolled study suggests that topiramate may be useful for TM.

The NSAIDs can be used for both symptomatic and preventive headache treatment. Naproxen sodium is effective for prevention at a dose of one or two 275 mg tablets twice a day (Miller et al., 1987). Other NSAIDs found to be effective include tolfenamic acid, ketoprofen, mefenamic acid, fenoprofen, and ibuprofen (Johnson & Tfelt-Hansen, 1993; Mylecharane & Tfelt-Hansen, 1993). Aspirin was found to be effective in one study (Kangasniemi et al., 1983) and equal to placebo in another (Scholz et al., 1987). We believe that the short-acting NSAIDs such as ibuprofen and aspirin cause rebound and their use should be limited. The rebound potential of the other NSAIDs is uncertain. Indomethacin is the drug of choice for HC, and the response to this medication defines the disorder. We give indomethacin a therapeutic trial to rule out HC, but otherwise limit the use of NSAIDs.

Although monotherapy is preferred, it is sometimes necessary to combine preventive medications. Antidepressants are often used with beta-blockers or calcium channel blockers and divalproex sodium may be used in combination with any of these medications.

Other treatments

Open and small placebo-controlled trials have suggested that CTTH may improve following injection with botulinum toxin A (Botox® (BTX-A)); whether this is due to paralysis of muscles or to unknown mechanisms is uncertain. Botulinum toxin has been shown to be effective in decreasing the frequency of migraine attacks (Gobel et al., 1999).

Porta et al. (1999), in a randomized, single-blind trial, compared BTX-A to methylprednisolone. Injections were given in the tender points of cranial muscles, which were determined using pressure pain threshold measurements with an electronic algometer. Inclusion criteria included a diagnosis of IHS ETTH or CTTH, age between 18 and 70 years, and no preventive treatment. At 30 and 60 days postinjection, both treatment groups had a significant reduction in pain scores (using a visual analogue scale) compared with baseline. At 60 days postinjection, the reduction in pain scores was statistically significantly greater in BTX-A-treated patients compared with those who received steroid.

Smuts et al. (1999) conducted a double-blind, placebo-controlled, randomized study of 40 CTTH patients (29 women, 11 men) who had previously been unsuccessfully treated with either amitriptyline or sodium valproate. Patients received intramuscular injections of either BTX-A (100U in 2 ml saline) or placebo (2 ml saline) at predefined areas in the neck and temporal muscles. The number of headache-free days was significantly increased in the BTX-A group 3 months following treatment compared with controls. A clear shift toward the lower headache score counts for the BTX-A group was retained throughout the study period. A statistically significant reduction in the average pain score was achieved for the BTX-A group compared with the placebo group over the 3-month period. No serious adverse events were reported.

In a double-blind trial, Gobel et al. (1999) treated ten CTTH patients with either 10 i.u. Botox® injected into the frontal muscle and the auricular muscle on each side and 20 i.u. injected into the splenius capitis muscle on each side, or the corresponding quantity of NaCl as placebo. No significant change in headache intensity, headache hours per day, or frequency of analgesic intake was observed between the treatment groups. Relja and Korsic (1999) reported a significant and rather long-lasting decrease in headache intensity in 16 CTTH patients in a double-blind, placebo-controlled study. Botox® and/or placebo (saline) were injected into the most tender pericranial muscle. Botulinum toxin A treatment resulted in a significant decrease of the total tenderness score, obtained by the palpation method, two weeks, four weeks, and eight weeks after injections. Placebo had no effect. According to patients' diaries, the severity and the duration of the attacks decreased significantly during the BTX-A treatment period (Relja & Korsic, 1999).

Outpatient treatment of medication overuse

Two general outpatient strategies are employed. One approach is to taper the overused medication, gradually substituting a long-acting NSAID as effective preventive therapy is established. The alternative strategy is to abruptly discontinue the overused drug, substitute a transitional medication to replace the overused drug, and subsequently taper the transitional drug. Drugs used for this purpose include NSAIDs, DHE, corticosteroids and triptans (Diener et al., 1991; Bonuccelli et al., 1996; Drucker & Tepper, 1998). Serious withdrawal syndromes that can be produced by the overused drug must be prevented. For example, if high doses of a butalbital-containing analgesic combination are abruptly discontinued, phenobarbital should be used to prevent barbiturate withdrawal syndrome. Similarly, benzodiazepines must be gradually tapered. Outpatient treatment is preferred for motivated patients, but is not always safe or effective.

Patients who do not need hospital-level care but cannot be safely or adequately treated as outpatients can be considered for ambulatory infusion treatment. Outpatient ambulatory infusion must be done in a hospital or a supervised medical setting where the patient can be monitored frequently (as often as every 15 minutes). Under these circumstances, repetitive i.v. treatment can be given twice a day for several days in a row. Although ambulatory infusion is better for many patients than outpatient treatment, major concerns still exist. Contraindications to outpatient ambulatory infusion include the likelihood of withdrawal symptoms at night when patients are withdrawn from long-acting or potent drugs; psychiatric disorders that interfere with treatment (these patients cannot be treated aggressively as outpatients); and comorbid medical illness that requires prolonged monitoring. No long-term observation is available, and many problems manifest themselves in an intensely monitored interactive environment.

Inpatient treatment of medication overuse

If outpatient treatment fails or is not safe, or if there is significant medical or psychiatric comorbidity present, inpatient treatment may be needed (Silberstein & Saper, 1993). The goals of inpatient headache treatment include: (i) medication withdrawal and rehydration; (ii) pain control with parenteral therapy; (iii) establishment of effective preventive treatment; (iv) interruption of the pain cycle; (v) patient education; and (vi) establishment of outpatient methods of pain control. The detoxification process can be enhanced and shortened and the patient's symptoms made more tolerable by the use of repetitive i.v. DHE coadministered with metoclopramide (Raskin, 1986), which helps control nausea and is an effective antimigraine drug in its own right. Following 10 mg of IV metoclopramide, 0.5 mg of DEH is administered i.v. Subsequent doses are adjusted based on pain relief and side effects. Patients who are not candidates for DHE or do not respond to this medication can be given repetitive i.v. neuroleptics, such as chlorpromazine, droperidol, and prochlorperazine, and/or corticosteroids. These agents may also supplement repetitive i.v. DHE in refractory patients (Silberstein et al., 1990). Hospitalization is also used as a time for patient education, for introducing behavioural methods of pain control, and for adjusting an outpatient programme of preventive and acute therapy.

Silberstein et al. (1990) showed that repetitive i.v. DHE is a safe and effective means of rapidly controlling intractable headache. Of 214 patients suffering from daily headache with rebound, 92% became headache free, usually within 2 to 3 days, with an average hospital stay of 7.3 days. With more aggressive treatment, the average length of stay is now 3 days. Pringsheim and Howse (1998) reported similar but less robust results.

Prognosis

The 'natural history' of primary CDH, and rebound headache in particular, has never been studied and probably never will be for ethical and technical reasons. Recognition of the rebound process probably is itself therapeutic and could affect the patient's behaviour or the physician's approach. Retrospective analysis suggests that there may be periods of stable drug consumption and periods of accelerated medication use. Patients who are treated aggressively generally improve. There are no literature reports of spontaneous improvement of rebound headache, although this may happen. Silberstein and Silberstein (1992) performed follow-up evaluations on 50 hospitalized primary CDH drug overuse patients who were treated with repetitive i.v. DHE and became headache free. Once detoxified, treated and discharged, most patients did not resume daily analgesic or ergotamine use. Seventy-two per cent continued to show significant improvement at 3 months, and 87% continued to show significant improvement after 2 years. This would suggest at least a 70% improvement at 2 years in the initial group (35/50), allowing for patients lost to follow-up.

Silberstein and Silberstein (1992) reported a 2-year success rate of 87%, consistent with other reports. In a series of 22 papers (Hering & Steiner, 1991; Andersson, 1975, 1988; Tfelt-Hansen & Krabbe, 1981; Schoenen et al., 1989; Isler, 1982; Dichgans et al., 1984; Granella et al., 1998; Baumgartner et al., 1989; Mathew, 1990; Mathew et al., 1990; Rapoport et al., 1986; Lake et al., 1990; Henry et al., 1984; Diener et al., 1988, 1989, 1992; Silberstein & Silberstein, 1992; Pini et al., 1996; Schnider et al., 1996; Pringsheim & Howse, 1998; Monzon & Lainez, 1998; Suhr et al., 1999) published between 1975 and 1991, the success rate of withdrawal therapy (often accompanied by pharmacologic and/or behavioural intervention) in patients overusing analgesics, ergotamine, or both, ranged from 48% to 91%; success rates of 77% or higher were reported in ten papers (45%).

Why treatment fails (Table 64.8)

When patients fail to respond to therapy or announce at the first consultation that they have already tried everything and nothing will work, it is important to try to identify the reason or reasons that treatment has failed. The

Table 64.8. Why treatment fails

The diagnosis is incomplete or incorrect
An undiagnosed secondary headache disorder is present
A primary headache disorder is misdiagnosed
Two or more different headache disorders are present
Important exacerbating factors may have been missed
Medication overuse (including over-the-counter)
Caffeine overuse
Dietary or lifestyle triggers
Hormonal triggers
Psychosocial factors
Other medications that trigger headaches
Pharmacotherapy has been inadequate
Ineffective drug
Excessive initial doses
Inadequate final doses
Inadequate duration of treatment
Other factors
Unrealistic expectations
Comorbid conditions complicate therapy
Inpatient treatment required

Source: Modified from Lipton et al. (2000).

cause of treatment failure may be an incomplete or incorrect diagnosis (Lipton et al., 2000). For example: (i) an undiagnosed secondary headache disorder is the major source of the head pain; (ii) a primary headache disorder has been misdiagnosed (i.e. HC is mistaken for TM, episodic paroxysmal hemicrania or hypnic headache is mistaken for cluster); or (iii) two or more different headache disorders are present. In addition, pharmacotherapy may have been inadequate or important exacerbating factors such as medication overuse may have been missed.

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Index

Note: this is a complete two-volume index

Note: page numbers in *italics* refer to figures and tables; 'Fig.' refers to illustrations in the plates section

Abbreviations of conditions used in subheadings (without explanation):
AD Alzheimer's disease
AIDS Acquired immune deficiency syndrome
ALS Amyotrophic lateral sclerosis
CJD Creutzfeldt–Jakob disease
FTD Frontotemporal dementia
HIV Human immunodeficiency virus
HD Huntington's disease
PD Parkinson's disease
SIADH syndrome of inappropriate secretion of antidiuretic hormone

Part VIII

Neuromuscular disorders

65

Pathophysiology of nerve and root disorders

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The peripheral nervous system (PNS) represents the final common anatomical pathway linking the brain with the outside world. This chapter deals with the pathological basis of disorders of the PNS, including symptoms and signs related to abnormalities of peripheral nerves, spinal roots, and sensory and autonomic ganglia. Specific neurological disorders are discussed here only in the context of their representative value in understanding PNS dysfunction. Readers are directed to other chapters within this section and the section on Degenerative Disorders for more complete discussions of PNS diseases.

Anatomical organization

The neuronal cell bodies for the PNS are located within the dorsal root ganglia (primary sensory neurons), the cranial and spinal sympathetic and parasympathetic ganglia, and the anterior horn of the spinal cord (motor neurons). The perikaryal organization reflects the enormous synthetic requirements for maintaining the axonal and dendritic processes that may represent many times the volume of the perikaryon itself. Prominent within the perikaryal cytoplasm are mitochondria which are responsible for the production of ATP, and the Nissl substance which is made up of free and membrane-bound ribosomes (rough endoplasmic reticulum). The pattern of Nissl staining seems to reflect the metabolic state of the neuron, and changes in the staining pattern are associated with injury to the neuron. The classic example of these changes is chromatolysis (Fig. 65.1), where axonal injury leads to swelling of the cell body, eccentric displacement of the nucleus, and margination of the Nissl substance (for review see Peters et al., 1991). These changes are not necessarily associated with the death of the neuron; to the contrary they frequently reflect a reparative and regenerative stage after neuronal injury (Bodian & Mellors, 1945). Chromatolytic changes are stimulated by a variety of injuries including root avulsion, axonal transection, and even peripheral neuropathy.

Neurons communicate with one another and with their effector organs by transmitting chemical and electrical signals via dendrites and axons. Dendrites and axons may be distinguished by a variety of structural and functional characteristics (Table 65.1), however a practical distinction is that dendrites are responsible for input to and axons are responsible for output from the cell body.

In clinical neurology, few disorders are defined neuropathologically as diseases of dendrites. Diseases of axons, however, are recognized as the neuropathological substrate for neurological dysfunction in a large array of CNS and PNS disorders. This holds true for primary disorders of axons as well as for demyelinating diseases where secondary axonal degeneration correlates with the chronic loss of sensory and motor functions.

The axon

The axon emerges from the cell body as a unique structure that can be distinguished from the perikaryon on the basis of both morphological and functional features (Berthold & Rydmark, 1995). Within the axon, neurofilaments and microtubules are organized in parallel arrays along the axis of the nerve fibre, in contrast to the complex cytoskeletal structure of the cell body. Other organelles found within the axoplasm are mitochondria, smooth endoplasmic reticulum, and a variety of vesiculotubular and membranous structures. Axons are devoid of the machinery for protein synthesis (ribosomes and granular endoplasmic reticulum), and must depend on transport mechanisms for replenishment of proteins. (For an alternative view, see Alvarez et al., 2000.) Functionally, the axon is the wire that connects the cell body with its targets, and the intimate

Table 65.1. General features of axons and dendrites

	Number	Cytoskeletal elements	Function	Electrical activity	Presence of ribosomes	Protein markers
Axon	Single (except DRG)	Neurofilament rich (except in small axons)	Output from cell body	Saltatory in myelinated fibres	No[a]	Tau
Dendrite	Multiple	Microtubule rich	Input to cell body	Cable	Yes	MAP-2

Note:

[a] Ribosomes and local protein synthesis in axons are controversial topics; however, both have been described (Alvarez et al., 2000).

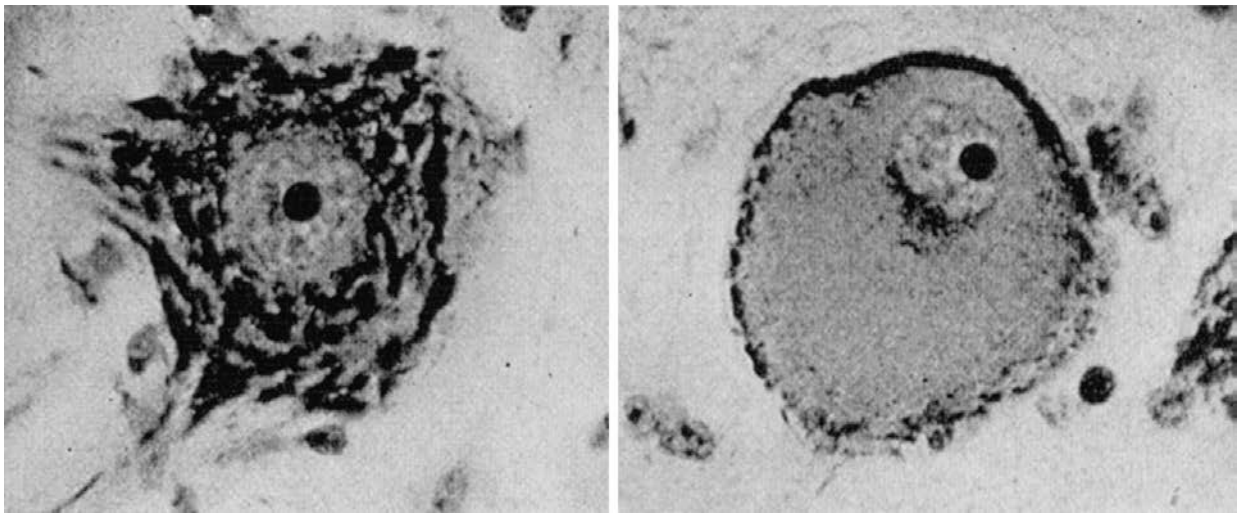


Fig. 65.1. Chromatolysis in motor neurons. As compared to the normal neuron on the left, the neuron on the right shows typical chromatolytic changes in response to axonal transection, including swelling, margination of the Nissl substance, and eccentric displacement of the nucleus. (From Bodian & Mellors, 1945.)

relationship between the axon and Schwann cell (in the PNS) allows for rapid electrochemical communication along that wire. The relationship with the Schwann cell also has major influences on the underlying axonal structure, including axonal calibre and degree of phosphorylation of neurofilaments (see below).

Axonal transport

The enormous volume of axoplasm in relation to perikaryal size, a feature particularly prominent in PNS axons, requires that proteins be transported over long distances for effective axonal and synaptic maintenance. For this purpose, axonal transport systems have evolved for shuttling proteins to and from the perikaryon (for reviews, see Vallee & Bloom, 1991; Goldstein & Yang, 2000). Axonal transport can be viewed metaphorically as a rail system, complete with tracks (axonal cytoskeleton), trains (vesicles), and engines (kinesin and cytoplasmic dynein), operating with express and local schedules (fast and slow transport). Passengers (proteins) board the rail system at both ends of the line. Axons and their presynaptic terminals are completely dependent on this transport system for the delivery of neurotransmitter-related enzymes and other proteins from the cell body. The cell body relies on retrograde transport for growth factors originating within muscle and skin, and the recycling of membrane constituents. Disruptions in either the slow or fast components of axonal transport are likely to underlie a variety of disorders including toxic and nutritional peripheral neuropathies (Griffin & Watson, 1988), and possibly some motor neuron diseases (Lee et al., 1994). A summary of axonal transport systems and their relationship to disease is outlined in Table 65.2.

The Schwann cell and organization of the myelinated nerve fibre

The Schwann cell is the glial cell of the PNS. Like the oligodendrocyte of the CNS, Schwann cells provide the myelin sheath that insulates large calibre axons and allows for the

Table 65.2. Axonal transport systems

	Fast transport	Slow transport
Direction	Bidirectional	Anterograde[a]
Rate of transport	Anterograde 100–400 mm/ day Retrograde: ≃300 mm/day	Component A: 0.2–2 mm/day Component B: 1–5 mm/day
Motors	Anterograde: kinesin Retrograde: dynein (MAP 1C)	Unknown
Components	Anterograde: smooth ER, vesicles, synaptic proteins, membrane components Retrograde: lysosomes, multivesicular bodies, synaptic ligands (e.g. – NGF)	Component A: neurofilament (NF) subunits, tubulins Component B: tubulins
Representative disorders	Delivery to perikaryon of toxins and infectious agents via retrograde transport: tetanus, poliovirus, rabies virus	Altered NF transport resulting in axonal swelling and distal axonal atrophy: hexacarbon, IDPN intoxication ?motor neuron diseases

Note:

[a] retrograde slow transport in special pathological preparations (Glass & Griffin, 1994).

phenomenon of saltatory conduction of action potentials (see below). Schwann cells and oligodendrocytes are clearly separate populations of cells that have structural, morphological and functional distinctions (Peters et al., 1991).

Axons and Schwann cells maintain a complex and interactive structure/function relationship both during development and within the adult PNS. There is a tight mathematical correlation between axonal calibre, myelin thickness, and internodal length (Friede & Samorajski, 1971; Friede & Bischhausen, 1982; Friede & Beuche, 1985; Berthold & Rydmark, 1995). A change in any of these features may influence the physiological characteristics of the fibre, including rate of axonal transport (Hoffman et al., 1984, 1985) and conduction velocity (Ritchie, 1995). Overall control of this relationship was, until recently, believed to rest with the axon, where calibre, as determined by neurofilament number and degree of phosphorylation, regulated myelination (Griffin & Hoffman, 1993; Griffin et al., 1981, 1988). Recent data, however, demonstrate that there is a major influence of Schwann cells, and specifically myelination, on axonal structure and function. In the normal PNS, examples of this relationship are found at the nodes of Ranvier and at proximal sites of dorsal root ganglion axons. In these regions, lack of myelination is correlated with reduction of axonal calibre, tighter packing of neurofilaments, and reduced neurofilament phosphorylation (Mata et al., 1992; Hsieh et al., 1994). Axons can also be modified in response to local demyelination, as has been demonstrated in xenograft studies using the Trembler mouse (de Waegh et al., 1992) and human sural nerves from patients with type-1 Charcot–Marie–Tooth disease (Sahenk, 1999). In both of these studies, axons from the recipient mouse regenerated through grafts containing the mutant Schwann cells. Axons in these regions, as compared to the regions containing normal host Schwann cells, showed reduced calibre, tighter neurofilament packing, and reduced phosphorylation of neurofilaments.

From a functional standpoint, the structural relationship between axons and Schwann cells is important for the very existence of large mammals. In mammals, neurological function depends on the rapid and efficient conduction of action potentials over long distances (sometimes many metres). The phenomenon of saltatory conduction has evolved to provide for rapid conduction of action potentials. This evolution includes the tight mathematical relationship between axonal calibre, myelin thickness, and internodal length which, taken together, are the determinants of conduction velocity in myelinated fibres.

Clinical nerve disorders demonstrate that the relationship between axons and Schwann cells is even more complex. Primary disorders of myelin or Schwann cells invariably result in some degree of axonal degeneration. A clear example is found in patients with type-1 (demyelinating) Charcot–Marie–Tooth disease (CMT). Children in these families frequently are asymptomatic even though their nerve conduction velocities are as slow as those in their symptomatic parents (Gutmann et al., 1983; Garcia et al., 1998). Symptoms of CMT, that is sensory loss and weakness, are correlated not with degree of demyelination or

conduction slowing, but with axonal degeneration that progresses over time in a distal to proximal fashion (Krajewski et al., 2000). An example in the CNS is multiple sclerosis, a primary demyelinating disorder in which the long term clinical deficits are best correlated with underlying degeneration of axons (Trapp et al., 1998).

Experimentally, primary disorders of Schwann cells frequently result in degeneration of underlying axons. In animal models of CMT, including the P-zero knockout mouse (CMT 1B) (Giese et al., 1992; Martini et al., 1995; Shy et al., 1997) the PMP-22 overexpressing rat (CMT 1A) (Sereda et al., 1996), the PMP-22 null mouse (CMT 1A) (Sancho et al., 1999), and the PMP-22 deficient mouse (HNPP) (Adlkofer et al., 1995), axonal degeneration is found, as it is in humans, in older mice. Similarly, mice deficient in the gene for myelin-associated glycoprotein (MAG) demonstrate age-related axonal degeneration (Fruttiger et al., 1995; Sheikh et al., 1999), and also show reduction in axonal calibre and degree of neurofilament phosphorylation. These experimental and clinical observations emphasize the importance of the axon–Schwann cell relationship for normal axonal maintenance.

Deficits due to primary demyelination without axonal degeneration are often either short term or easily reversible. Here, loss of function is due to the physiological disconnection between the cell body and effector organ by the phenomenon of conduction block. Conduction block occurs when the membrane potential at the node of Ranvier cannot reach threshold to generate an action potential, resulting in the loss of electrical propagation along the axon. This may occur because of a structural alteration of the internode (e.g. segmental demyelination or nodal expansion, Fig. 65.2), or through a block of ion channels at the node. Normally, the properties of myelin allow for propagation of the membrane potential from node to node with little loss of amplitude (saltatory conduction), so that each node easily reaches 'threshold' for the regeneration of the action potential. Demyelinated or inadequately myelinated internodes lose their capacity for saltatory conduction and must depend on the propagation of action potentials along the formerly myelinated internode, a process which is inefficient and slow (Felts et al., 1997). Conduction failure is due to insufficient sodium current density to offset the leak and capacitative currents along the demyelinated internode. This results in a dwindling of the membrane potential over distance to below the threshold for generation of an action potential (see Waxman et al., 1995). Remyelination, which may occur over days to weeks, re-establishes the anatomical structure of the internode, thus physiologically reconnecting the cell body with its target.

Biological toxins such as tetrodotoxin or saxitoxin cause the reversible blockade of sodium channels at the node of Ranvier, resulting in loss of propagation of action potentials along the axon (Brown & Ironton, 1977; Oda et al., 1989). This form of conduction block occurs in the absence of structural changes in myelin, and is practically reversible within minutes of the removal of the toxin.

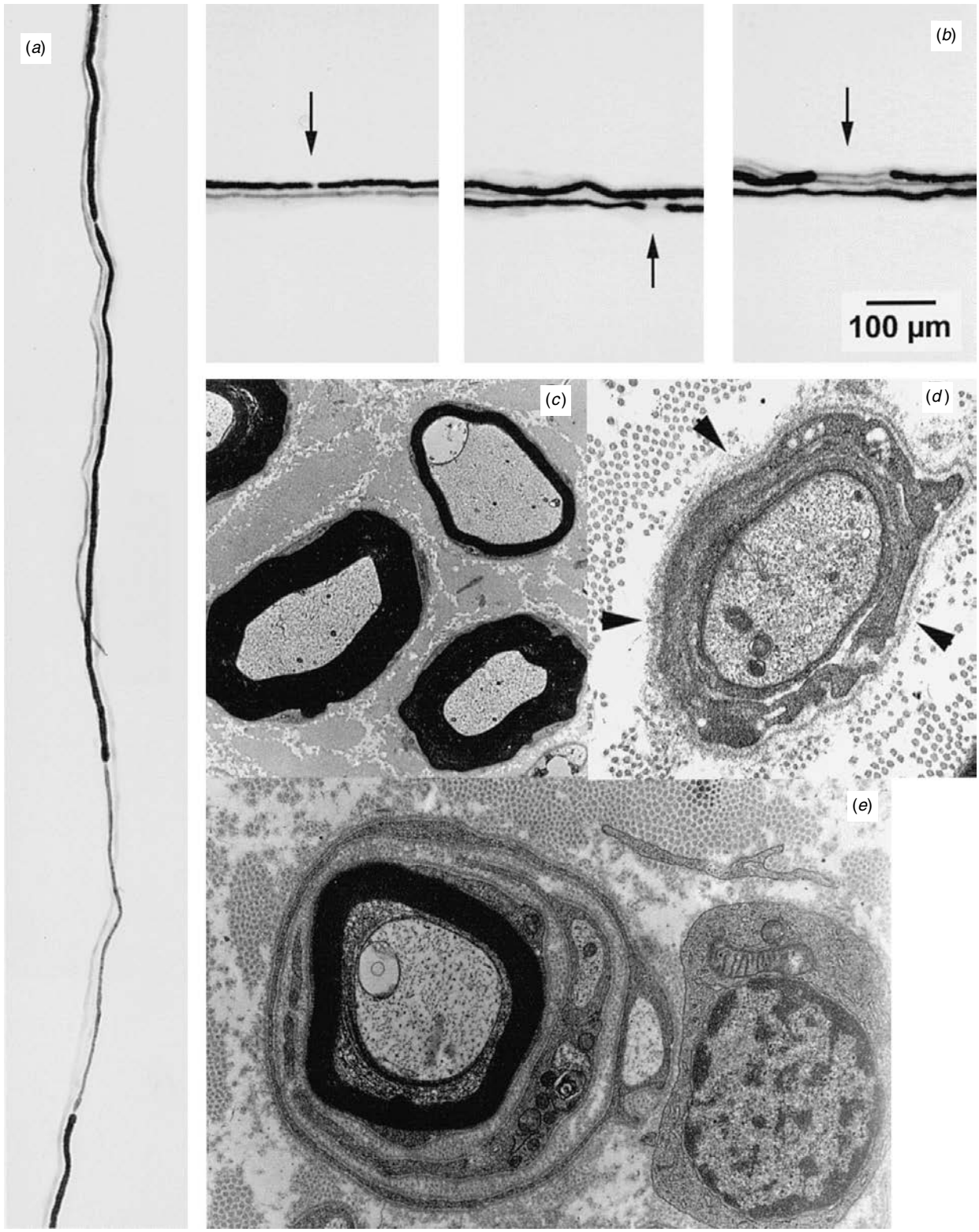
Examples of conduction block are encountered frequently in clinical practice. Patients with immune-mediated demyelinating neuropathies, such as Guillain–Barré Syndrome and CIDP (Brown & Feasby, 1984), frequently demonstrate rapid loss and recovery of neurologic function which correlates well with the electrodiagnostic findings of conduction block. There are also many cases in the literature documenting patients with long-standing weakness, sometimes lasting many years, who show recovery after only a few days of immunomodulatory therapy. This pattern of disease and recovery, with electrodiagnostic demonstration of conduction block and reversal has been seen in patients with multifocal motor neuropathy (MMN) (Pestronk et al., 1988; Chaudhry et al., 1993). The rapidity of recovery, perhaps too rapid for the process of remyelination, probably reflects the unblocking of ion channels at the nodes. The mechanism of blocking and unblocking has not yet been delineated, however the binding of immunoglobulin at the node of Ranvier is suspected.

Axonal degeneration

Wallerian degeneration

Axonal degeneration is the most common pathological finding in patients with nerve and root disorders. Even though primary disorders of Schwann cells may lead to

Fig. 65.2. Neuropathological features of demyelination in human sural nerve biopsies. (*a*) Teased nerve fibre demonstrating a demyelinated and thinly remyelinated internode. Note that the internodal length is shorter than the adjacent normal internode. (*b*) Mild and severe paranodal demyelination in centre and right panels, respectively. Normal node shown in left panel. Measurement bar for panels (*a*) and (*b*). (*c*)–(*e*) Electron micrographs showing features of demyelination and remyelination. In (*c*), a thinly remyelinated fibre is shown next to normally myelinated fibres of similar calibres. In (*d*), a 'naked' axon is shown with surrounding Schwann cell cytoplasm. The Schwann cell basal lamina is depicted by the arrowheads. In (*e*) a well-formed 'onion bulb' created by multiple layers of Schwann cell cytoplasm surrounds a thinly myelinated axon. The cell on the right without a basal lamina is likely an inflammatory cell.


(a)
(b)
100 µm
(c)
(d)
(e)

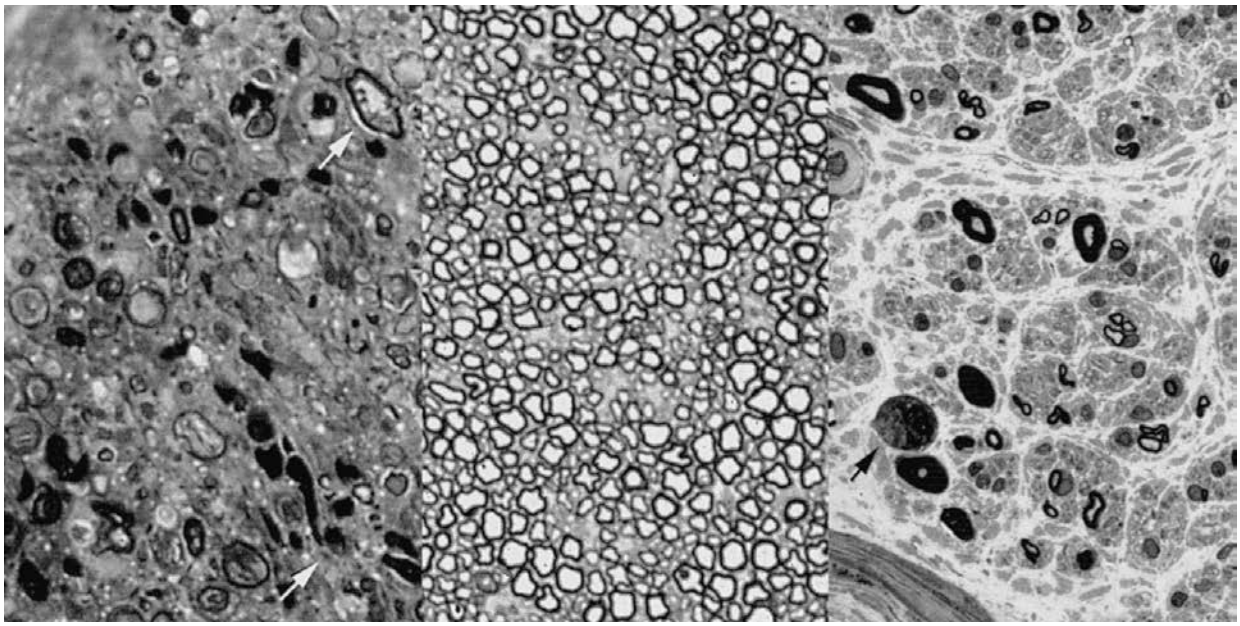


Fig. 65.3. Comparison of Wallerian degeneration in an axotomized rat nerve(left) and Wallerian-like nerve degeneration from a patient with diabetic neuropathy(right). Axonal loss and myelin ovoids are seen in both (arrows), but are more prominent in the rapidly progressing lesion due to axotomy. A normal rat sciatic nerve is demonstrated in the center panel (all 1 µm plastic sections stained with toluidine blue).

axonal degeneration, as described above, in the majority of cases axonal degeneration results from diseases of the axon or perikaryon. The simplest model of axonal degeneration is Wallerian degeneration (Waller, 1850) which results from physical separation of the axon from its cell body. After axotomy, Wallerian degeneration begins with a latency period during which the separated distal stump is relatively quiescent, showing only minor pathological changes. This latency period lasts from 1–7 days in mammals, roughly directly corresponding to the size of the organism (i.e. 1–2 days in mice, and 5–7 days in humans). The latency period ends with explosive degradation of the axonal cytoskeleton, triggering a sequence of events which includes myelin degradation and digestion, Schwann cell proliferation (in the PNS), and remodelling of the distal stump in preparation for regeneration (for review see Chaudhry et al., 1992). Axonal transection, and thus Wallerian degeneration, is not an uncommon factor in neurological diseases, including traumatic, ischemic, and inflammatory injuries. However, the importance of understanding the pathophysiology of Wallerian degeneration is markedly amplified by the apparent similarities between the rapid degeneration occurring after axotomy and the slowly evolving degeneration seen in neurodegenerative disorders (Wang et al., 2000a,b,c). Neuropathologists have long recognized these similarities, describing the changes seen in a wide spectrum of CNS and PNS disorders as 'Wallerian-like' in nature (Fig. 65.3).

Until recently, Wallerian degeneration was believed to represent the inevitable consequence of interruption of communication between the axon and perikaryon. The prevailing hypothesis was that the axon died passively due to starvation for 'trophic' substances from the cell body (Ramon y Cajal, 1928). Examples of prolonged survival of transected axons (weeks to months) were unknown in mammals, although were seen in invertebrates and poikilotherms (Bittner, 1991). In 1989, however, a spontaneous mouse mutant was discovered that demonstrates prolonged axonal survival after nerve injury (Lunn et al., 1989). In this mouse mutant, named Wld^S for 'slow Wallerian degeneration', the entire sequence of Wallerian degeneration is delayed, including macrophage recruitment, myelin clearance, and Schwann cell proliferation. Once axonal degeneration occurs, however, Wallerian degeneration progresses at a normal rate (Glass & Griffin, 1991; Hall, 1993). The phenotype of the Wld^S can thus be considered one of prolongation of the latency period after injury. Transected axons from the PNS or CNS of this remarkable animal remain structurally intact for up to 4 weeks (Glass & Griffin, 1991; Ludwin & Bisby, 1991; Crawford et al., 1995), support action potentials for at least 2 weeks, and will continue anterograde and retrograde transport of pro-

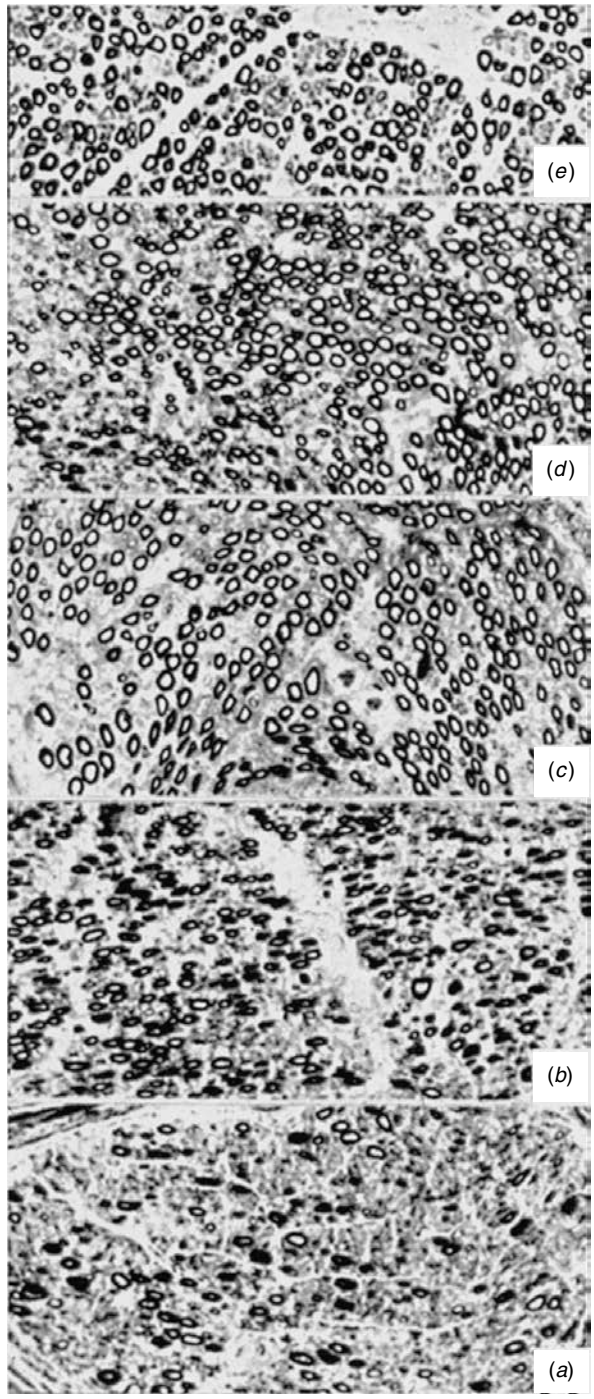


Fig. 65.4. Distal axonal degeneration ('dying-back' neuropathy). These sections of nerves were taken from an autopsy of a patient dying with AIDS complicated by peripheral neuropathy. Sections (*a*)–(*e*) were taken from progressively more proximal sites and demonstrate the distal predominence of pathological changes, correlating well with clinical symptoms and signs: (*a*) sural at ankle; (*b*) peroneal at fibular head; (*c*) peroneal at mid thigh; (*d*) lumbosacral plexus; (*e*) L5 root. 1 μm plastic sections stained with toluidine blue.

teins for similar amounts of time (Smith & Bisby, 1993; Glass & Griffin, 1994). The phenotype is carried as an autosomal dominant trait (Perry et al., 1990a), and the 'defect' which allows for prolonged survival of transected axons is inherent to the nervous system (Perry et al., 1990b; Glass et al., 1993). Remarkably, no other phenotypic markers of this mutation have been identified. The mutation lies within an 85 kB DNA triplication on chromosome 4 (Lyon et al., 1993; Coleman et al., 1998) which creates a new gene by splicing portions of two normally non-contiguous genes, *Ufd2* and *NMNAT* (Conforti et al., 2000). The existence of this gene, and its novel protein product, impart protection against axonal degeneration (Wang et al., 2001b). At the time of this writing, the mechanism of protection is unknown.

The existence of the Wld^s mutant reinforces the concept that axonal biology is more complex than previously believed, and has re-energized research interest in the mechanisms of axonal degeneration. The prolonged survival of anucleate axons suggests that axonal degeneration is not a passive process, but is a 'programmed' response to injury. This concept, that neuronal and axonal degeneration are independent processes, is supported by experimental studies on cultured sympathetic neurons from Wld^s mice (Deckwerth & Johnson, 1994). In these preparations, neuronal cell bodies deprived of nerve growth factor (NGF) die by the process of apoptosis, as expected for normal sympathetic neurons. Axons, however, remain intact long after their cell bodies have disappeared.

Mechanisms of axonal degeneration

Calcium entry into neurons is a common feature of experimental models of acute and chronic neurologic diseases (Choi, 1993; Nixon et al., 1994; Nixon, 1989; Caner et al., 1993; Meldrum & Garthwaite, 1990; LoPachin et al., 1990). There are data in both the CNS and PNS that calcium entry and elevated intracellular calcium levels are required for axonal degeneration. In a model of hypoxia/ischemia of rat optic nerve axons, Waxman and colleagues demonstrated that requirements for axonal injury (degradation) are the presence of calcium, and entry of calcium into the

intra-axonal space (Waxman et al., 1991, 1993; Stys et al., 1990, 1991; Lehning et al., 1996). Similarly, Schlaepfer and colleagues showed that calcium is required for degeneration of peripheral nerve fibres, and that calcium entry is associated with the structural and biochemical degradation of axonal neurofilaments (Schlaepfer, 1971, 1977; Schlaepfer & Hasler, 1979; Schlaepfer & Micko, 1979). Given that calcium is an essential component in the process of axonal degeneration, important considerations are how and when calcium enters an injured axon, and what role calcium plays in cytoskeletal degradation.

Elevation of intracellular calcium likely occurs by a variety of mechanisms that are both tissue and injury dependent. For example, in the model of optic nerve hypoxia/ischemia calcium enters as a result of energy failure, resulting in the reverse operation of a calcium pump (sodium–calcium exchanger) which under normal conditions works to keep intracellular calcium levels low. In an axotomy model of PNS axons, calcium entry proceeds through L-type calcium channels and not via energy dependent mechanisms (George et al., 1995). A third model of axonal degeneration caused by closed head trauma showed that increases in intracellular calcium levels may occur as a delayed phenomenon due to release of bound calcium from internal stores (calcium binding proteins, cytoskeletal proteins, and mitochondria) (Maxwell et al., 1997; Okonkwo & Povlishock, 1999).

Therapeutic intervention by reduction of extracellular calcium levels successfully prevents axonal degeneration in all of these models, but this strategy is only practical in in vitro situations. More important for designing rational preventative therapies is understanding the mechanism(s) by which elevated intracellular calcium leads to cell death. A current hypothesis is that elevated calcium levels in injured cells leads to pathologic activation of calpains (for review see Bartus, 1997).

Calpains are ubiquitous neutral cysteine proteases that are implicated in both physiological and pathological cellular processes (for review see Croall & DeMartino, 1991). The two major forms, μ-calpain (calpain I) and m-calpain (calpain II) are activated by micromolar and millimolar calcium concentrations, respectively (Melloni & Pontremoli, 1989; Sorimachi et al., 1994). Cytoskeletal proteins, and specifically neurofilaments, are excellent calpain substrates (Bernier et al., 1999; Castejon et al., 1999). It is likely that calpains act as the executors of cytoskeletal degradation during axonal degeneration. Experimental models of Wallerian degeneration (Kamakura et al., 1983), toxic peripheral neuropathy(Wang et al., 2000), ischemic stroke (Bartus et al., 1995), spinal cord injury (Li et al., 1995), and traumatic brain injury (Saatman et al., 1996), support a role for calpains in cellular degradation, and suggest that calpain inhibitors may be protective against axonal and neuronal death. Clinical applications of calpain inhibitors, as of this writing, have not been tested.

Calpains may not be the only proteases involved in axonal degeneration, and there is a growing interest in the presence and activity of the caspases in axons. Caspases are typically thought of as important in the process of apoptosis, which occurs within cell bodies. Axons, however, contain caspases (specifically caspase-3), which become active after brain trauma (Buki et al., 2000). Wallerian degeneration, however, may not require caspase activation (Finn et al., 2000). Interactions between calpains and caspases have been demonstrated, and may be important in some forms of axonal degeneration (Wang, 2000).

Distal axonal degeneration ('dying back')

The majority of slowly evolving axonal degenerations progress in a distal to proximal pattern, affecting the longest nerve fibres first (Fig. 65.4) (Cavanagh, 1964). Examples of this phenomenon are seen in a variety of peripheral and central disorders, including diabetic polyneuropathy in the PNS (Dyck & Giannini, 1996), and spinocerebellar degeneration in the CNS (Greenfield, 1954). Bipolar neurons in the dorsal root ganglion may show simultaneous distal degeneration of their peripheral and central processes, as demonstrated experimentally by Spencer and Schaumburg (for review see Spencer & Schaumburg, 1976), and termed 'central–peripheral distal axonopathy'. Clinically this pattern is seen in a number of toxic neuropathies and in the gracile tract degeneration of AIDS (Rance et al., 1988). This pattern of progression underlies the typical 'stocking and glove' clinical presentation and early loss of ankle reflexes in patients with peripheral neuropathies.

The pathophysiology of distal axonal degeneration is not understood in any disorder. Conceptually, the most satisfying explanation for length-dependent vulnerability is the 'distal watering' hypothesis (see Spencer et al., 1979). In this model, the highest metabolic demand for 'watering' the distal regions of the axon exists within the longest and largest calibre nerve fibres. During disease, alteration in the metabolic capabilities of the perikaryon, or inadequate function of the axonal transport system leads to undernourishment of the most distal regions, just as low water pressure leads to lack of irrigation of the most distant flower-bed. Experimental data supporting this model of distal axonal degeneration exists for acrylamide neuropathy, where pathologic alterations in the cell body are seen

early after exposure (Sterman, 1983; Cavanagh & Gysbers, 1983), and for 2, 5 hexanedione, where abnormalities of axonal transport are seen exclusively within the distal axon (Sahenk & Mendell, 1981; Watson et al., 1991). Perhaps the most compelling data supporting this hypothesis are those from experimental pyridoxine intoxication (Xu et al., 1989). In these studies, large single doses of pyridoxine caused acute neuronal death, whereas chronic low-dose exposure resulted in axonal atrophy along peripheral nerves. Large neurons with the longest processes were preferentially affected, creating the picture of a distally predominant neuropathy. These findings suggest that sublethal disruption of neuronal metabolism may underlie some distal axonopathies.

This 'neurocentric' model of distal axonal degeneration does not easily account for other experimental and clinical observations. For example, Spencer and Schaumburg (for review see Spencer & Schaumburg, 1976) studied ultrastructurally the spatio-temporal progression of a number of toxic neuropathies and made the important observations that: (i) the longest and largest calibre fibres are not always the earliest to degenerate, and (ii) in several neurotoxic disorders the preterminal region of the axon degenerates before the terminal. A clinical observation that is not easily explained by the 'watering' hypothesis is the distal to proximal progression of neuropathy in primary demyelinating disorders, the most prominent of which is type-1 CMT (Krajewski et al., 2000). Patients with CMT 1 typically show symptoms and signs first in the feet and toes, even though demyelinating physiology can be demonstrated throughout the PNS. All of these observations suggest that the distal axon is a highly vulnerable region of the nerve fibre, and is susceptible to insults either from systemic toxins or even from some nourishing effect of the Schwann cell.

Relationship between Wallerian and Wallerian-like degenerations

Although it seems likely that the same or similar pathogenetic mechanisms are involved in true Wallerian degeneration and slowly evolving Wallerian-like degeneration, the evidence is mostly indirect. As described above, there are distinct pathological similarities between the two, and a distal to proximal pattern of axonal loss has been demonstrated in some models of Wallerian degeneration (Weddell & Glees, 1941; Miledi & Slater, 1970; Lunn et al., 1990), but not in others (Lubinska, 1982; George & Griffin, 1994). The best evidence linking the mechanisms of Wallerian and Wallerian-like degeneration come from therapeutic models and the Wld^S mouse. In a dorsal root ganglion model of Wallerian degeneration and vincristine neuropathy, calpain inhibitors are protective against both types of injury (Wang et al., 2000) (Fig. 65.5). Similarly, the Wld^S mouse which shows delayed Wallerian degeneration also shows delayed axonal degeneration after vincristine exposure, demonstrating that a genetic mutation has a similar affect on axonal degeneration seen in these two distinct types of injuries (Wang et al., 2001a). It appears clear that Waller's conclusion from his original axotomy remains true*: 'It is impossible not to anticipate important results from the application of this inquiry . . . with reference to nervous diseases . . .'* (Waller, 1850).

Symptoms and signs

The symptoms of nerve and root disorders are directly related to the loss of normal functional connectivity between the CNS and PNS and are conveniently divided into positive and negative symptoms. Positive symptoms are typically sensory in nature and include spontaneous pain or disturbed sensory phenomena including paresthesia, hyperesthesia and allodynia. Negative symptoms are sensory loss and weakness. Physiologically, negative symptoms result from complete disconnection of the cell body from its target, as may occur in axonal degeneration, demyelination or with conduction block.

Positive motor symptoms may have their origins in muscle, nerve, or within the CNS, and include cramps, fasciculations, and myokymia. A few rare disorders such as neuromyotonia ('Isaacs syndrome'), continuous motor unit activity ('stiff person syndrome'), and tetanus, demonstrate positive motor symptoms as their major manifestation. In neuromyotonia (for review see Newsom-Davis & Mills, 1993), motor unit activity is eliminated after administration of curare but is not affected by centrally-acting inhibitory agents or epidural block, suggesting a peripheral nerve origin for ectopic discharges. Neuromyotonia is frequently associated with antibodies to voltage-gated potassium channels occurring either in isolation or as a paraneoplastic process. It is hypothesized that antibody-mediated destruction of voltage-gated potassium channels, which are responsible for repolarization of the nerve following the action potential, may result in repetitive firing at the motor end plate due to incomplete repolarization of the axonal membrane (Vincent, 2000). The positive motor symptoms in Stiff Person syndrome (Moersch & Woltman, 1956) originate in the CNS. In these patients, stiffness is likely to be associated with systemic autoimmune abnormalities including diabetes mellitus, adrenal insufficiency, thyroiditis, and pernicious anemia.

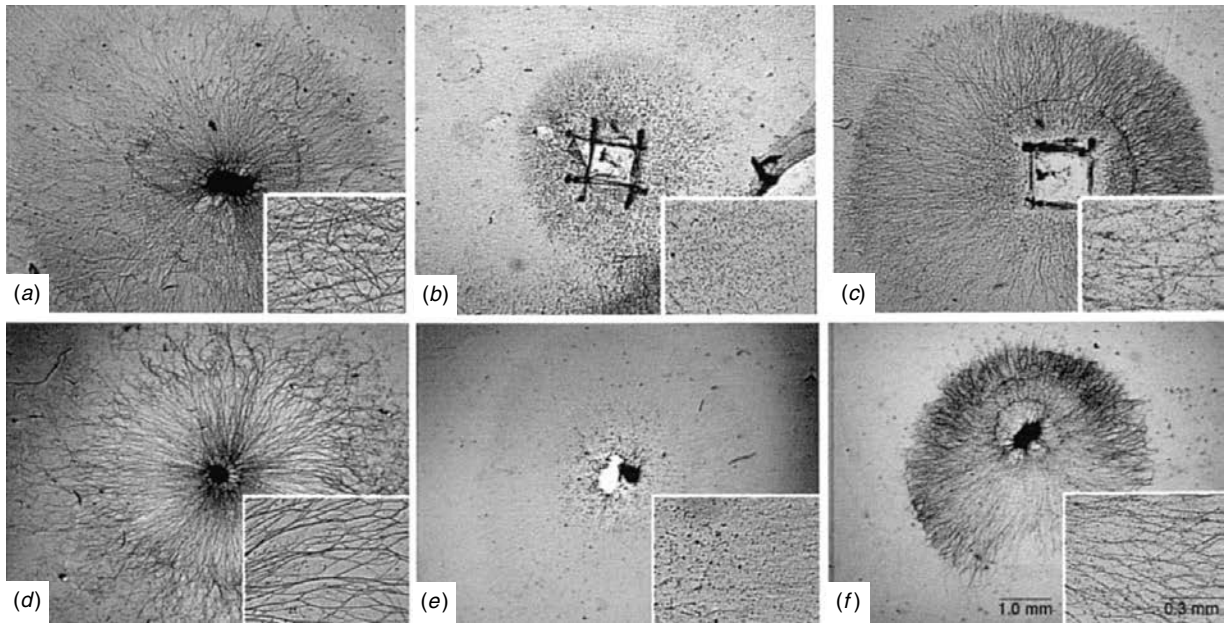


Fig. 65.5. Demonstration of protective effect of calpain inhibition against axonal degeneration after axotomy (*a*)–(*c*) and after exposure to the neurotoxin vincristine (*d*)–(*f*). Uninjured dorsal root ganglion cultures are shown in (*a*) and (*d*). Axonal degeneration 5 days after axotomy (*b*) or after 6 days exposure to 0.01 μM vincristine (*e*). Axonal degeneration is significantly prevented when injured axons exposed to 50 μM AK295, an experimental calpain inhibitor ((*c*) and (*f*)). (From Wang et al., 2000a,b,c with permission.)

Circulating antibodies to glutamic acid decarboxylase, found in about 70% of cases, are believed to target GABAergic neurons or their terminals, releasing motor neurons from the normal inhibitory tone through suppression of spinal inhibitory circuits (Floeter et al., 1998). Immunosuppressive and immunomodulatory therapies are effective in a subset of these patients.

Positive sensory symptoms are possibly the most frequent motivation for neurological consultation. In the PNS they are associated with the same types of pathologic processes as negative symptoms, but require a degree of intact communication between the cell body and the nerve terminal. Painful or disturbed sensory phenomena are typically associated with underlying axonal degeneration, although it is not clear why some patients with axonal neuropathies experience pain while others describe only numbness. Experimental studies have shown that action potentials that are normally generated at sensory terminals, may arise spontaneously along the axis of diseased nerve fibres (Rasminsky, 1987). There may also be 'cross-talk' (ephaptic transmission) between adjacent nerve fibres so that a normally non-painful stimulus may elicit activity in fibres destined for neurons perceiving pain (Granit et al., 1944). Physical stimulation of otherwise normal nerve fibres, as may occur in compression neuropathies or in compressive radiculopathies will generate ectopic discharges perceived as sensory symptoms ranging from tingling to severe pain. Common clinical examples are Tinel's sign in carpal tunnel syndrome and Lasegue's sign in lumbar radiculopathy. Similarly, inflammatory or neoplastic processes that infiltrate peripheral nerves or roots may generate pain through compression of fibres or destruction of the axon or myelin sheath (Fig. 65.6).

It is clear that the generators of abnormal or painful sensory symptoms in patients with nerve and root disorders may lie outside of the peripheral nerve or even within the CNS. Dorsal root ganglion cells or central sensory neurons may become 'sensitized' after nerve injury, potentially overreacting to incoming stimuli or displaying spontaneous discharge (Wall & Devor, 1983). Complex regional pain syndromes (CRPS) categorized under the headings of 'causalgia' (CRPS type 2) or 'reflex sympathetic dystrophy' (CRPS type 1) (Stanton-Hicks et al., 1995) combine pain with symptoms and signs of vasomotor instability. A role for sympathetic nerve fibres in the pathophysiology of these disorders has been demonstrated, with some patients responding to pharmacological sympathetic blockade or surgical sympathectomy (Jadad et al., 1995; Ramamurthy & Hoffman, 1995). A number of hypotheses describing the mechanism of sympathetically maintained

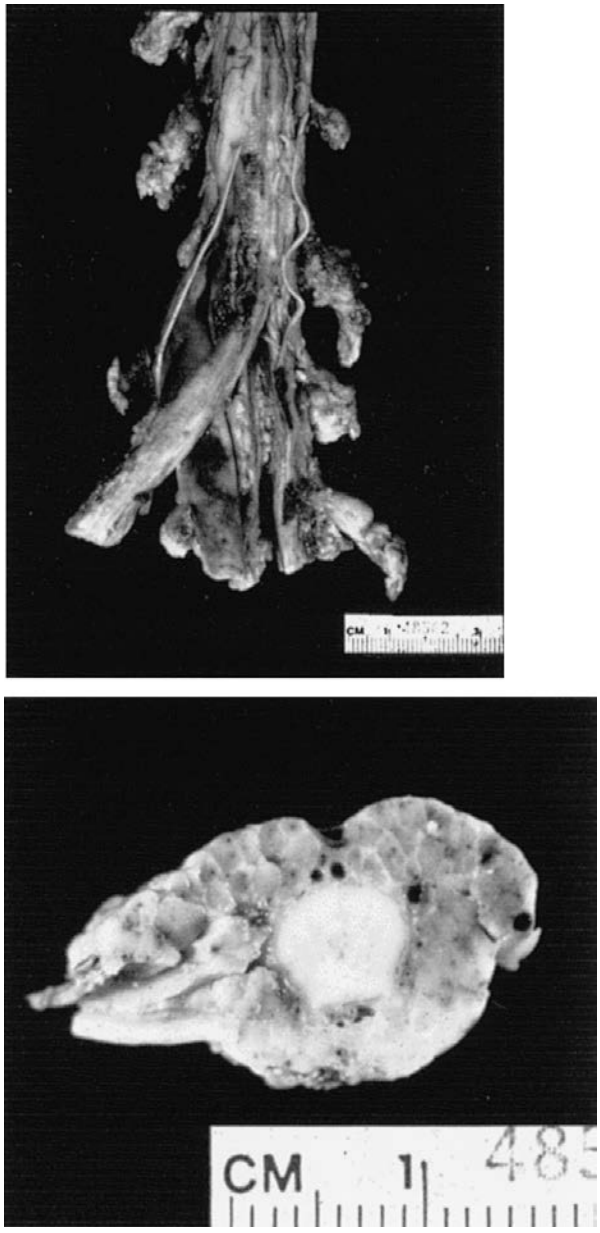


Fig. 65.6. Infiltrative and compressive radiculopathy caused by infection with cytomegalovirus (CMV polyradiculitis). This patient dying with AIDS had urinary retention and painful dysesthesias in the lower extremities, accompanied by reflex loss. He progressed to paraplegia.

pain are currently being investigated (Treede et al., 1992; McLachlan et al., 1993), and some controversy exists regarding the peripheral vs. central etiology of these disorders (Verdugo et al., 1994; Verdugo & Ochoa, 1994). The lack of satisfactory treatments for these patients speaks to the complexity of the disorder.

Primary disorders of neuronal cell bodies cause symptoms and signs that are distinguished from diseases affecting the nerve or root by their pure motor or pure sensory characteristics, and their irreversibility. Sensory neuronopathies are mediated by an immune attack as part of a systemic connective tissue disease (Griffin et al., 1990) or a paraneoplastic syndrome (Denny-Brown, 1948; Dalmau et al., 1999), as a toxic effect of antibiotics (Asbury, 1987), antineoplastic agents (Thompson et al., 1984; Verdu et al., 1999) or pyridoxine (Schaumburg et al., 1983; Windebank et al., 1985; Xu et al., 1989), or as part of heritable degenerative diseases such as Friedreich's Ataxia (Mott, 1907). In distinction to peripheral nerve disorders, the acquired sensory neuronopathies frequently demonstrate a rapid onset of days to weeks and may affect proximal and distal sites simultaneously. Sensory neurons are susceptible to immune attack because of the presence of specific antigens, including Hu in the case of paraneoplastic neuronopathy, and extractable nuclear antigens in the case of neuronopathy associated with Sjögren's syndrome. Motor neuronopathies are most commonly associated with sporadic and heritable degenerative disorders (spinal muscular atrophies and ALS), the pathophysiology of which is covered in other chapters. Poliovirus and other enteroviruses cause motor neuron destruction through their recognition of specific viral receptors on motor neurons (Ren & Racaniello, 1992; Racaniello & Ren, 1996). Paraneoplastic and HIV-related motor neuronopathies have also been described (Schold et al., 1979; Moulignier et al., 2001).

Areflexia and ataxia

Sensory receptors within muscle (spindle afferents and Golgi tendon organs) are a rich source of kinesthetic information important for normal proprioceptive function and balance. Neuropathies frequently result in disconnection of these receptors from the CNS ('sensory deafferentation') resulting in areflexia and ataxia. Both axonal and demyelinating neuropathies cause areflexia and ataxia, however the nature of demyelination makes these signs a more prominent feature of demyelinating neuropathies.

Axonal neuropathies are typically characterized as distal axonal degenerations. Deafferentation of proprioceptors occurs through distal axonal loss, which is noticed first as loss of the ankle jerk since it is the most distal, clinically tested reflex. For example, in vincristine neuropathy the ankle jerk is lost before loss of the H-reflex, which anatomically is only slightly more proximal (Guiheneuc et al., 1980). As axonal degeneration progresses, more proximal reflexes may be lost as well. Sensory ataxia is rarely a major

problem in peripheral axonal neuropathies, except in sensory neuronopathies where deafferentation occurs both proximally and distally. Axonal neuropathies preferentially affecting small myelinated and unmyelinated fibres, such as the small fibre sensory neuropathies or amyloid neuropathies, may not show reflex loss until late in the course of disease.

Demyelinating disorders preferentially affect the large calibre afferent nerve fibres, causing temporal dispersion of the nerve impulse or conduction block. Since demyelination typically occurs all along the nerve or root, reflexes are lost both proximally and distally. The physiological explanation for reflex loss in demyelinating neuropathies is that the afferent limb of the reflex arc cannot provide the necessary stimulus to fire the corresponding motor neurons. Temporal dispersion and conduction block degenerate the normally synchronized volley of action potentials into an impulse with insufficient amplitude and duration to fire the corresponding motor neurons. Compressive or infiltrative disorders of nerve roots that block electrical impulses destined for the spinal cord similarly cause loss of tendon jerks. Electrodiagnostically these types of lesions are recognized as prolongation or loss of the F-wave and H-reflex.

Ataxia in demyelinating neuropathies is also a manifestation of loss of proprioceptive input from large myelinated fibre populations through conduction abnormalities. Since proprioceptors are affected at all levels, sensory ataxia is a much more prominent feature in demyelinating neuropathies.

Muscle atrophy

In patients with peripheral neuropathies, the presence or absence of muscle atrophy and electrical changes of denervation are used as criteria to distinguish between axonal and demyelinating pathologies. Experimental denervation of muscle fibres leads to muscle atrophy and changes in the properties of the muscle fibre membrane such as partial loss of resting membrane potential and generation of spontaneous action potentials (fibrillations). Changes in muscle gene expression include an increase in acetylcholine receptors throughout the muscle with development of extrajunctional receptors (Purves & Lichtman, 1985), and re-expression of the embryonic type voltage-dependent sodium channels causing decreased sensitivity to the blocking action of tetrodotoxin (Kallen et al., 1990; Yang et al., 1991). These changes in gene expression are at least partially driven by increases in the levels of transcription factors in the MyoD family which are crucial for normal development but are present at low levels in adult muscle (Arnold & Braun, 1996). Changes in MyoD recapitulate the embryonic programme, and may be important for successful reinnervation.

There has been some controversy concerning the mechanism of denervation-induced changes in muscle. Several lines of evidence, however, suggest that loss of muscle activity and not physical separation of the terminal from the end-plate is the most significant factor. Blockade of impulse conduction alone is enough to stimulate denervation changes in muscle (Eftimie et al., 1991; Buonanno et al., 1992), and direct stimulation of muscle following denervation prevents changes in muscle gene expression (Lomo & Rosenthal, 1972; Lomo & Westgaard, 1975). How atrophy relates to this sequence of events is unknown, and whether inhibition of denervation programs in muscle will also prevent atrophy remains to be investigated.

Autonomic dysfunction

Autonomic function is served in the PNS by the small calibre myelinated and unmyelinated fibre populations (Groups B and C). Autonomic symptoms, which include abnormal bowel and bladder function, abnormal reflex control of blood pressure and heart rate, and abnormalities of sweating, occur in many neuropathies. Diseases such as familial and acquired amyloid neuropathies affect these fibre populations disproportionately, and autonomic neuropathy may be a presenting feature and a major factor in morbidity. Demyelinating disorders which typically affect large calibre fibres, such as Guillain–Barré syndrome, may cause autonomic dysfunction by demyelination of small myelinated fibres. Clinical symptoms, which are usually transient, may be tachycardia and hypertension or urinary retention. The populations of nerve fibres responsible for autonomic function show significant overlap with those serving sensory, and particularly pain, function. Patients with diabetic neuropathy may show either clinical or electrophysiological evidence of autonomic dysfunction as a major feature of their disease. In patients with small fibre sensory neuropathy without diabetes, where standard nerve conduction studies are typically normal, tests of autonomic function may be the only objective evidence for the presence of peripheral neuropathy.

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66

Toxic and metabolic neuropathies

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Peripheral neuropathies caused by exogenous toxins or dysmetabolic states are relatively common. Most present as motor–sensory polyneuropathy, usually axonal in type. The underlying pathophysiology of such polyneuropathies is discussed in the previous chapter (Chapter 65).

Clinical features

First noticeable symptoms tend to be sensory and consist of tingling, prickling, burning, or band-like dysesthesias in the balls of the feet, in the tips of the toes, or generally over the soles. Symmetry of symptoms and findings in a distal graded fashion is the rule, but occasionally dysesthesias appear in the sole of one foot a brief time before the other one, or perhaps are more pronounced in one foot at first. Care must be used to avoid confusion with a mononeurothapy multiplex, in which initial sensory symptoms tend to appear in the distributions of individual digital nerves, usually asymmetrically, and in either a hand or a foot.

As a polyneuropathy worsens, both weakness and usually pansensory deficit and loss of tendon jerks spread more or less concurrently in a centripetal and symmetrical fashion, and if severe enough, involve even the torso and the axial parts of the body as well as the limbs. Numbness and imbalance are the main sensory features and are usually accompanied by positive symptoms, dysesthesias and pain. As a rule, pain in polyneuropathy is dysesthetic in character and is most prominent distally, but there is often an accompanying nerve trunk component. The character of this is deep aching pain and is generally experienced more proximally than the dysesthetic pain (Asbury, 1990; Asbury & Fields, 1984).

When sensory disturbance is severe and ascends to midthigh in the legs and to the elbows, a tent-shaped area of hypesthesia on the lower abdomen may be demonstrated. This grows broader and the apex extends rosterally toward the sternum or higher as the neuropathy worsens. This tent-shaped sensory disturbance on the anterior torso is nerve-length dependent and in this case involves dying back of the segmental truncal nerves. It can be mistaken for sensory deficit of spinal cord origin if care is not taken to check for a sensory level posteriorly on the back and to outline with care the precise area of deficit.

Variations on the pattern and sequence of progressive polyneuropathies are diverse and virtually endless. Variables are the rate of evolution of symptoms; the symmetry of signs and symptoms; their distribution in terms of proximal vs. distal, arms vs. legs, and motor vs. sensory; the relative proportion of sensory dysfunction attributable to either large nerve fibre deficits or to small nerve fibre deficits; and the determination, principally by electrodiagnostic examination, of the relative contributions of axonal vs. demyelinating processes.

Evaluation of patients with neuropathy

Clues to the diagnosis of toxic and metabolic neuropathies may be subtle, and even forgotten in the weeks or months before the onset of symptoms. Inquiries should be made about recently prescribed or self-prescribed medications, systemic symptoms that accompany the neuropathic symptoms, potential toxic exposures to solvents, pesticides, or heavy metals; the concurrence of similar symptoms in coworkers or family members; habits concerning alcohol ingestion; the presence of known underlying medical disorders. It is always useful to ask patients if they would otherwise feel well if free of their neuropathic symptoms to determine the presence or absence of underlying systemic features.

Axonal polyneuropathies of toxic or metabolic origin tend to evolve over several weeks to a year or perhaps even longer. Exceptions are diabetic polyneuropathy and para-

proteinemic neuropathies in which the progress may be insidious for five to ten years, and in which most of the manifestations are sensory. Rate of progression of demyelinating neuropathies is highly variable, depending upon the basis. Relatively few toxic and metabolic neuropathies are demyelinating, although paraproteinemic neuropathies are an exception. If major fluctuations occur in the course of the neuropathy, two possibilities come to mind: the first is a relapsing form of neuropathy, usually immune mediated, but not always. For instance, porphyric neuropathy may be relapsing in type. Also, repeated toxic exposures can give the appearance of a relapsing-type neuropathy and should be kept in mind. Slow fluctuation in symptoms taking place over weeks to months, reflecting changes in the activity of a particular neuropathy, should not be confused with the more commonplace variability from day to day or diurnal undulation of symptoms. The latter are common to all neuropathic disorders.

In most toxic or metabolic polyneuropathies, the legs are more severely affected than the arms and distal muscles more than the proximal ones. There are exceptions, as in lead neuropathy, in which manifestations of bilateral wrist drop may occur early and dominate the clinical picture.

Electrodiagnosis

Electrodiagnosis is a key part of the evaluation of any neuropathy. It allows one to be certain about the presence or absence of sensory deficit when this is unclear from clinical examination alone. It provides information about the distribution of subclinical findings thus sharpening the diagnostic focus. More general issues, more fully discussed elsewhere (Asbury, 1980), may be raised by the clinician and posed to the electrodiagnostician, including the following:

(i) The distinction between disorders primary to nerve or to muscle.
(ii) The distinction between root involvement and more distal nerve trunk involvement.
(iii) The distinction between generalized polyneuropathic processes and widespread multifocal nerve trunk involvement.
(iv) The confirmation of a clinical impression that a particular neuropathic disorder is purely motor or purely sensory which often suggests that the primary process is a neuronopathy.
(v) The distinction between upper and lower motor neuron weakness.
(vi) The distinction, in a given generalized polyneuropathic process, between a primary demyelinating neuropathy and an axonal degeneration.
(vii) The assessment, in both primary axonal and demyelinating neuropathies, of many factors bearing on the nature, activity, and likely prognosis of the neuropathy.
(viii) The assessment, in mononeuropathies, of the site of the lesion and its major effect on nerve fibres, especially the distinction between conduction block and wallerian degeneration.
(ix) The characterization of disorders of the neuromuscular junction.
(x) The identification, often in muscle of normal bulk and strength, of chronic partial denervation, fasciculation, and myotonia.

Pure motor or sensory presentations

In pure lower motor neuron syndromes, the diagnostic possibilities are relatively few, and even fewer of these are of toxic or metabolic causation. Neuropathies associated with lead intoxication or dapsone toxicity tend to be purely motor in presentation. Disorders of presynaptic neuromuscular transmission, such as the Lambert–Eaton myasthenic syndrome, tick paralysis, and organophosphate intoxication may be confused clinically on occasion with motor neuropathies, but these can be distinguished electrodiagnostically.

Pure sensory neuropathy or neuronopathy are much more frequently associated with toxic and metabolic disorders. The predominant nerve fibre type involved (large or small diameter) may be helpful in identifying the underlying disorder (see Tables 66.1, 66.2, and 66.3). Selected damage to small sensory fibres, with diminished pain–temperature sensation and frequently autonomic dysfunction, occurs with certain axonal neuropathies, most commonly in those associated with diabetes mellitus. An almost equally frequent type of small fibre sensory neuropathy is the idiopathic variety (Wolfe & Barohn, 1998), but this usually does not have an autonomic component. Other possibilities include amyloid polyneuropathy, sensory perineuritis (which is multifocal), sensory neuropathy associated with hyperlipidemia or primary biliary cirrhosis, and the chronic sensory neuropathy associated with acquired immunodeficiency syndrome (AIDS), which is inflammatory in nature. Neuropathy caused by ciguatera toxin (reef fish poisoning) and chronic metronidazole or misonidazole administration may also present as a primarily cutaneous, small fibre, sensory neuropathy. There are relatively few causes of large fibre sensory neuropathy (manifesting by proprioceptive loss and ataxia) that are toxic or dysmetabolic in origin. Certain dysproteinemic neuropathies

Table 66.1. Polyneuropathy associated with systemic diseases

		Axonal[a]			Demyelinating[a]					
Systemic Disease	Occurrence[b]	Ac	Sub	Chr	Ac	Sub	Chr	Sensory vs. Motor[c]	Autonomic	Comment
Diabetes mellitus	C	–	±	+	–	±	+	S, SM, rarely, M	± to +	See text
Uremia	S'	±	+	+	–	–	–	SM	±	Controllable with proper dialysis; curable with successful renal transplant; see Ch. 124
Porphyria (three types)	R	+	±	–	–	–	–	M	± to +	May be proximal, distal and may have atypical proximal sensory deficits
Hypoglycemia	R	±	+	+	–	–	–	M	–	Usually with insulinoma; arms often > legs
Vitamin deficiency, excluding B_{12}	S'	–	+	+	–	–	–	SM	±	Involves thiamine, pyridoxine, folate, pantothenic acid; probably others
Vitamin B_{12} deficiency	S'	–	±	+	–	–	–	S	–	Neuropathy overshadowed by myelopathy
Chronic liver disease	S'	–	–	–	–	–	+	S or SM	–	Usually mild or subclinical
Primary biliary cirrhosis	R	–	±	–	–	–	–	S	–	Intraneural xanthomas; dysesthesias
Hypothyroidism	R	–	–	–	–	±	+	S	–	May respond to thyroid replacement
Chronic obstructive pulmonary disease	S'	–	±	+	–	–	–	S or SM	–	Often subclinical; severe pulmonary insufficiency
Acromegaly	R	–	–	+	–	–	–	S	–	Carpal tunnel syndrome also frequent
Malabsorption (sprue, celiac disease)	S'	–	±	+	–	–	–	S or SM	±	Basis for neuropathy unclear; deficiency suspected
Carcinoma (sensory)	R	–	+	+	–	–	–	Pure S	–	Due to ganglionitis; mostly small cell lung and breast cancer
Carcinoma (sensorimotor)	S'	–	+	+	–	–	–	SM	±	Sensorimotor axonal neuropathy; mostly with lung cancer
Carcinoma (late)	C	–	+	+	–		–	S > M	±	Mild, probably related to weight loss and wasting
Carcinoma (demyelinating)	S'	–	–	–	+	+	±	SM	–	Acute or relapsing demyelinating neuropathy
Lymphoma, including Hodgkin's	S'	–	+	+	+	+	±	See earlier	±	Same as carcinomatous types
Polycythemia vera	R	–	±	+	–	–	–	S	–	Also CNS manifestations; often shooting pains in limbs
Multiple myeloma, lytic type	S	–	±	+	–	–	–	S, M or SM	±	Symptomatic neuropathy uncommon, subclinical neuropathy more frequent
Osteosclerotic myeloma	S	–	–	±	–	±	+	SM		Significant nerve conduction velocity slowing
MGUS	S									
IgA		–	±	+	–	–	–	SM	–	IgM binds to myelin-associated glycoprotein in half
IgG		–	±	+	–	–	±	SM	–	
IgM		–	–	–	–	±	+	SM	–	

Table 66.1 (*cont.*)

		Axonal[a]			Demyelinating[a]					
Systemic Disease	Occurrence[b]	Ac	Sub	Chr	Ac	Sub	Chr	Sensory vs. Motor[c]	Autonomic	Comment
Cryoglobulinemia	R	–	±	+	–	–	–	SM	–	May be mononeuropathy multiplex in presentation

Notes:
[a] +, usually; ±, sometimes; –, rare, if ever.
[b] R, rare; S', sometimes; C, common.
[c] S, sensory; M, motor; SM, sensorimotor.
Ac, acute; Sub, subacute; Chr, chronic; Ig, immunoglobulin; MGUS, monoclonal gammopathy of undetermined significance.
For other neuropathies: See Ch. 67 (Immune mediated), Ch. 103 (HIV infection), Ch. 108 (Lyme disease), Ch. 124 (Renal failure).

Table 66.2. Polyneuropathy associated with drugs or environmental toxins

	Axonal[a]			Demyelinating[a]						
Systemic Disease	Ac	Sub	Chr	Ac	Sub	Chr	Sensory vs. Motor[b]	Autonomic	CNS	Comment
Drugs										
Amiodarone (antiarrhythmic)	–	–	+	–	–	+	SM	–	–	Dose-dependent neuropathy, reversible by decreasing dose
Aurothioglucose (antirheumatic)	±	±	–	+	+	–	SM	–	–	Idiosyncratic reaction; ? immune mediated
Cisplatin (antineoplastic)	–	+	+	–	–	–	S	–	–	Severe sensory neuropathy, also ototoxicity; dose related
Dapsone (dermatologic including leprosy)	–	±	+	–	–	–	M	–		Dose-related pure motor neuropathy
Disulfiram (antialcoholism agent)	±	+	+	–	–	–	SM	–	±	Usually occurs after months of treatment
Hydralazine (antihypertensive)	–	±	+	–	–	–	S>M	–	–	A pyridoxine antagonist; rarely neurotoxic
Isoniazid (antituberculous)	–	±	+	–	–	–	SM	±	–	A pyridoxine antagonist; neurotoxic in slow acetylators
Metronidazole (antiprotozoal)	–	–	±	–	–	–	S	–	+	Dose-related central–peripheral distal axonopathy
Misonidazole (radiosensitizer)	–	±	+	–	–	–	S	–	–	Neurotoxicity is the limiting factor
Nitrofurantoin (urinary antiseptic)	–	±	+	–	–	–	SM	–	–	Generally total dose related; renal failure enhances toxicity
Nucleoside analogues (ddC, ddI, d4T) (antiretroviral)	–	+	+	–	–	–	S>M	–	–	Dose related; painful
Pyridoxine (vitamin)	—	±	+	–	–	–	S	–	–	Occurs with megadose intake; may occur with only 200 mg/d

Table 66.2 (*cont.*)

	Axonal[a]			Demyelinating[a]						
Systemic Disease	Ac	Sub	Chr	Ac	Sub	Chr	Sensory vs. Motor[b]	Autonomic	CNS	Comment
Phenytoin (anticonvulsant)	–	–	+	–	–	–	S>M	–	–	After 20–30 y of phenytoin use
Taxol (antineoplastic)	+	+	–	–	±	–	S>M	–	–	Dose-related neuropathy
Vincristine (antineoplastic)	–	+	+	–	–	–	S>M	–	–	Sensory symptoms common, hands>feet; motor signs ominous
Toxins										
Acrylamide (flocculant, grouting agent)	–	±	+	–	–	–	S>M	±	+	Large-fibre neuropathy; sensory ataxia
Arsenic (herbicide, insecticide)	±	+	+	–	–	–	SM	±	±	Skin changes, Mees' lines in nails; painful, systemic effects
γ- diketone hexacarbons (solvents)	–	±	+	–	–	+	SM	±	+	Neurofilamentous swellings of axons; these solvents in restricted use
Dimethylamino-propionitrile (industrial)	–	–	+	–	–	–	S>M	+	–	Small-fibre neuropathy with prominent bladder symptoms and impotence in males
Diphtheria toxin	–	–	–	+	+	–	SM	–	–	Clinically rare; can be confused with GBS
Inorganic lead	–	–	+	–	–	–	M>S	–	±	Selective motor neuropathy with prominent wristdrop
Organophosphates	–	±	+	–	–	–	SM	–	+	Brain and spinal cord are also affected, the latter irreversibly
Thallium (rat poison)	–	+	+	–	–	–	SM		+	Also alopecia, Mees' lines in nails; painful

Notes:

[a] +, usually; ±, sometimes; -, rare, if ever.

[b] S, sensory; M, motor; SM, sensorimotor.

The following drugs and environmental toxins are also neurotoxic, mainly to the peripheral nervous system:
Drugs: amitriptyline, chloramphenicol, colchicine, ethambutol, nitrous oxide, perhexiline maleate, sodium cyanate, L-tryptophan
Environmental toxins: allyl chloride, buckthorn berry, carbon disulfide, dimethylaminoproprionitrile (DMAPN), ethylene oxide, metallic mercury, methyl bromide, polychlorinated biphenyls, styrene, trichloroethylene, vacor.

(antimyelin-associated glycoprotein (MAG) antibody associated) may present as a relatively pure large fibre sensory neuropathy.

Sensory neuronopathies are usually distinctive and recognizable. They may be associated with malignancies as a paraneoplastic disorder (see Chapter 90). Usually, they present as symmetrical, acral, or body-wide sensory loss and areflexia in contradistinction to the length-dependent changes seen in most motor–sensory polyneuropathies. Unlike the case with sensory axonal neuropathies, there is little likelihood of recovery. This is because of irreplaceable loss of sensory nerve cell bodies in the dorsal root ganglia, and trigeminal ganglia when affected. The type of sensory disturbance reflects the size of the sensory nerve cell bodies involved.

The rate of progression of sensory neuronopathies varies greatly, from acute to chronic, and the rate at which sensory disturbance evolves is quite helpful in arriving at the appropriate diagnosis (Asbury & Brown, 1990). Acute sensory neuronopathies evolve dramatically over days and in some cases may be related to the use of semisynthetic penicillins (Sterman et al., 1980). In other cases no apparent cause is found. Subacute sensory neuronopathies are associated with the remote malignancies as paraneoplastic syndromes, or are associated with Sjogren's syndrome or are idiopathic. Certain neurotoxins (see Table 66.2) affect primarily the sensory system and in high doses result in subacute neuronopathy. These include cisplatin, pyridoxine (vitamin B6), and taxol. Chronic sensory neuronopathies are usually either idiopathic or hereditary in nature (Table 66.3).

Table 66.3. Sensory neuropathies and neuronopathies

Cause or association	Course	Nerve fibre size affected: Small	Nerve fibre size affected: Large	Neuronopathy	Comment
Toxins/drugs					
Cisplatin (antineoplastic)	Sub/Chr	+	++	+	Dose related
Pyridoxine (vitamin, in megadose amounts)	Sub/Chr	+	++	±	Dose related
Taxol (antineoplastic)	Acu/Sub	++	+	−	NGF may be protective
Systemic diseases					
Paraneoplastic	Sub	+	++	++	Most SCLC and breast
Sjögren's syndrome	Sub/Chr	±	+	++	Variable presentation
Dysproteinemia (mainly IgM_k)	Chr	+	++	−	Demyelinating; may bind to MAG and other myelin glycoproteins
Idiopathic					
Acute sensory neuronopathy	Acu	±	++	++	Poor recovery; persistent deficit
Chronic ataxic neuropathy	Chr	±	++	Prob.	Gradual progression
Hereditary					
Many varieties (see Chapter 68)	Chr	Variable		Some	Progressive

Notes:
++, most; +, some; ±, occasionally; Prob., probable; Acu, acute; Sub, subacute; Chr, chronic; NGF, nerve growth factor; MAG, myelin-associated glycoprotein; SCLC, small cell lung carcinoma.

Metabolic neuropathies

Diabetic neuropathies

Polyneuropathies

Classification of the neuropathies of diabetes have been put forward (Brown & Asbury, 1984; Thomas & Tomlinson, 1993; Bird & Brown, 1996) (For a thorough monograph devoted to diabetic neuropathy, see Dyck & Thomas, 1999). The classification in Table 66.4 is a variation of these schemes. Diabetes affects the peripheral nervous system in several distinctive patterns, the most common being the chronic primarily sensory polyneuropathy. Its occurrence appears to be mainly a function of the duration of diabetes. There are rare forms of acute diabetic polyneuropathy in which rapid (weeks) onset of severe burning pain and small fibre-type sensory loss predominates. This is often in the setting of weight loss or changing glycemic control, for example, starting insulin therapy. Proximal diabetic neuropathy (diabetic amyotrophy) is a distinctive motor syndrome with asymmetrical proximal leg weakness, usually preceded by weight loss and leg pain. Diabetics may develop acute cranial, truncal or limb mononeuropa-

Table 66.4. Classification of diabetic neuropathies

- Chronic diabetic polyneuropathy (diabetic polyneuropathy)
  - Mixed sensory-autonomic-motor polyneuropathy
  - Other patterns of chronic polyneuropathy
    - Predominantly sensory
      - Small fibre (painful)
      - Large fibre (ataxic)
    - Predominantly autonomic
    - Subclinical polyneuropathy
- Acute diabetic polyneuropathy
  - With worsening diabetic control (diabetic neuropathic cachexia)
  - With improved control (insulin neuritis)
- Proximal diabetic neuropathy (diabetic amyotrophy)
- Diabetic mononeuropathies and radiculopathies
  - Cranial neuropathies
  - Truncal neuropathies
  - Limb mononeuropathies
- Focal compression neuropathies associated with diabetes
  - Carpal tunnel syndrome
  - Other focal neuropathies

thies. Finally, patients with diabetic polyneuropathy are particularly susceptible to carpal tunnel syndrome and possibly other focal compression neuropathies. Some patients have a combination of these neuropathies.

Clinically overt polyneuropathy will develop in over half of all diabetic patients during the course of their disease. Even more have polyneuropathy if asymptomatic individuals with diabetes are screened with a careful neurological examination, nerve conduction studies (NCS), or quantitative sensory tests (QST) (Vinik et al., 2000). Diabetic polyneuropathy is a progressive predominantly sensory neuropathy that usually develops and progresses slowly after years of hyperglycemia. A varying combination of sensory and reflex loss and some weakness begins distally and slowly ascends as the neuropathy worsens. Autonomic dysfunction may become increasingly important as the neuropathy progresses, with erectile dysfunction, gastroparesis, and orthostatic hypotension. If a diabetic has an axonal polyneuropathy, it is important to consider whether the severity of the neuropathy is consistent with the likely duration of diabetes. Since diabetes is common, neuropathy may occur coincidentally, so other causes of polyneuropathy must be considered. Electrophysiologic tests can determine whether the neuropathy has multifocal or demyelinating features, either of which would suggest another diagnosis.

The pathogenesis of diabetic polyneuropathy is a subject of controversy. Pathologic studies of distal nerve show loss of both large and small-calibre axons (Giannini & Dyck, 1999), and endoneurial capillaries are often thickened. Microvascular occlusions and infarct-like lesions have been observed in the proximal nerves of patients with diabetic polyneuropathy (Johnson et al., 1986; Dyck et al., 1986) suggesting that in some cases endoneurial vascular factors play a role. Studies in experimental diabetic animals, summarized in recent reviews (Dyck & Thomas, 1999; Vinik et al., 2000), have pointed to several potential mechanisms. Metabolic alterations, or even elevated blood glucose itself, may be toxic to peripheral nerves. Glucose may bind non-enzymatically to endoneurial structures, with a deleterious effect on nerve function (Brownlee, 1999). Chronic hyperglycemia leads to reduced nerve blood flow and endoneurial hypoxia (Zochodne, 1999). As a result of altered glucose metabolism there is an increase in nerve polyols, such as sorbitol, and reduced myoinositol (Greene et al., 1987, 2000). Nerve growth factors are suppressed after hyperglycemia, and could contribute to the distal axonal degeneration of diabetic polyneuropathy. How and whether all of these factors converge to damage peripheral nerve insidiously in diabetes remains uncertain.

The best evidence that polyneuropathy is the result of chronic hyperglycemia was shown by two landmark diabetes trials (DCCT, 1993; UKPDS, 1998). In the Diabetes Control and Complications Trial, 1440 type 1 diabetics were followed for 5 or more years. They demonstrated that intensive treatment substantially reduced the incidence of polyneuropathy, as well as retinopathy and nephropathy. The incidence of neuropathy was reduced from 10% to 3% (a 69% risk reduction). To date, the only treatment proven to slow the course of diabetic neuropathy is rigorous control of blood glucose.

Acute diabetic polyneuropathy

Acute axonal polyneuropathy occurs in two settings. One form, acute painful diabetic neuropathy or 'diabetic neuropathic cachexia', generally follows a period of unintentional weight loss and is heralded by severe, cutaneous pain. The clinical sensory loss and nerve conduction abnormalities are mild. Weight gain usually precedes, and may be necessary for, recovery. The other form, 'insulin neuritis', starts coincident with the initiation of improved glycemic control. There is intense burning pain that is difficult to control, with mild objective signs of neuropathy. The painful period generally passes after 6 months or so, but the underlying mild polyneuropathy remains.

Proximal diabetic neuropathy (diabetic amyotrophy)

This disorder is much less common than diabetic polyneuropathy. Garland and Taverner (1953) characterized it as a distinct clinical entity seen in the setting of diabetes and manifested by asymmetric pain and proximal leg weakness, with little demonstrable sensory loss. Garland was uncertain of the underlying pathology so he termed this entity diabetic amyotrophy (Garland, 1955). Since the initial reports, other names have been proposed emphasizing different aspects of the presentation and possible localization (Goodman, 1954; Skanse, 1956; Raff & Asbury, 1968; Raff et al., 1968; Asbury, 1977; Bastron & Thomas, 1981; Chokroverty, 1982; Barohn et al., 1991). One suggestion is that diabetic amyotrophy be discarded in favour of the term proximal diabetic neuropathy, highlighting the presence of proximal leg weakness without implying a localization or pathogenesis (Asbury, 1977).

Proximal diabetic neuropathy (PDN) is a disorder of older adults with Type 2 diabetes (Coppack & Watkins, 1991; Chokroverty et al., 1977; Casey & Harrison, 1992). Substantial weight loss occurs before or during the progressive phase of the neuropathy, with a mean weight loss of 18 kg in one study (Pascoe et al., 1997). The characteristic presentation is one of severe thigh pain, followed within weeks by mild to severe hip girdle and thigh muscle weak-

ness. The muscles most often affected are the iliopsoas, quadriceps, and thigh adductors, and less so the hip extensors and hamstrings. Distal muscles, particularly peroneal-innervated ones, may be involved. However, proximal muscles are affected more than distal ones, the reverse of the usual pattern with polyneuropathy. Cutaneous sensory loss over the thigh may be demonstrated in half of patients and distal sensory loss may be seen if there is coexistent polyneuropathy. The majority of patients with PDN have clinical signs of a distal symmetric polyneuropathy as well (Said et al., 1994; Subramony & Wilbourn, 1982). Pain is often severe, requiring treatment with long-acting oral narcotics. The progressive phase of weakness may develop over a few days or more slowly, over months. Some authors report patients with a relatively symmetric, slowly progressive disorder (Chokroverty, 1982; Williams & Mayer, 1976), but this presentation is much less common in practice (Said & Thomas, 1999). It has been suggested that there is a rapid phase associated with pain followed by a slower phase of weakness that progresses over weeks or months (Barohn et al., 1991). Electrophysiologic studies are helpful in confirming the diagnosis or distinguishing it from another disorder that may mimic PDN and present with proximal leg weakness in the setting of diabetes, such as chronic inflammatory demyelinating polyneuropathy, polymyositis, or motor neuron disease.

Electrophysiologic evidence of a distal neuropathy is found in the majority of those patients who present with PDN (Subramony & Wilbourn, 1982). There is no convincing evidence of a difference in the distal electrophysiologic features of those with distal polyneuropathy with or without PDN. In the first few months, there are needle EMG signs of acute denervation (fibrillation potentials and positive sharp waves). The abnormalities are typically most prominent in the quadriceps, iliopsoas, and thigh adductor muscles, but may also involve the hamstrings, glutei and lumbar paraspinal muscles. Electrodiagnostic involvement of clinically uninvolved contralateral proximal muscles is variable.

The pathogenesis of this disorder has been controversial, but recent evidence supports the role of an inflammatory vasculopathy. An autopsy study of a diabetic with acutely developing leg weakness by Raff and colleagues described microinfarcts and an epineurial inflammatory cell infiltrate in the nerve to affected muscles (Raff et al., 1968b), but the most convincing evidence of an inflammatory vasculopathy comes from recent work of Said and colleagues (Said et al., 1994, 1997). They performed biopsies of the intermediate cutaneous nerve of the thigh in patients with PDN and found inflammation and vasonecrosis, perivascular inflammatory infiltrates and nerve lesions felt to be consistent with ischemia. The presence of inflammatory cell infiltrates or vasculitis in this disorder has been reported by others (Younger et al., 1996; Llewelyn et al., 1998; Kelkar et al., 2000).

Proximal diabetic neuropathy has an initial phase of progression, followed by improvement. The mean time to the beginning of recovery has been reported to be 3 months (range 1–12 months), and improvement ceases after 18 months (Coppack & Watkins, 1991). There are anecdotal reports that patients who regain a portion of the lost weight seem to improve faster than those who remain cachectic. Intravenous immunoglobulin (IVIG) therapy has been reported as effective in uncontrolled studies, but at this time there is no established role for immunotherapy.

Diabetic mononeuropathies

Diabetes is associated with the development of acute cranial mononeuropathies and often coexist with diabetic polyneuropathy. The cranial nerves most frequently affected are III, IV, VI, and VII. Ocular motor neuropathies appear suddenly, over hours or a few days, with ocular pain or unilateral headache in more than half of patients. Third nerve palsies manifest with ptosis and paresis of third nerve-supplied extraocular muscles. Pupillary function is typically spared. The usual explanation is that the pupillary fibres lie on the surface of the third nerve and therefore are less susceptible to ischemia. Pupillary sparing helps to differentiate this from a compressive lesion such as a cerebral aneurysm or tumour, but alternatively, pupil function may be partially spared in the presence of a compressive lesion in up to 20% of cases. The prognosis for vasculopathic ocular motor mononeuropathies is excellent. The majority recover completely or partially in 4 to 6 weeks, with a mean time to recovery of 2.5 months (Richards et al., 1992; Goldstein & Cogan, 1960). There is pathological evidence to support acute focal peripheral nerve ischemia as the cause of acute diabetic ophthalmoplegia. In a postmortem histopathologic study of a patient with diabetic third nerve palsy, findings supportive of nerve ischemia and centrofascicular fibre loss in the mid-cavernous portion of the nerve, were identified (Asbury et al., 1970).

Idiopathic facial neuropathy (Bell's palsy) appears to be more common in older diabetics than in non-diabetics in the same age groups (Aminoff & Miller, 1972; Adour et al., 1975). The clinical and electrophysiologic features are that of any other case of idiopathic facial palsy, with an acute onset of facial weakness that may progress further over several days. A disturbance of taste is seen in 14% of those with diabetes compared to 83% of those with no diabetes (Pecket & Schattner, 1982), suggesting that the lesion in diabetic patients is most often distal to the chorda

tympani. The prognosis for recovery is more variable than with the ocular motor mononeuropathies and depends on the degree of axonal loss.

Diabetic patients and others with chronic polyneuropathy are considered more susceptible to conventional compression neuropathies than persons with neither of these conditions. Such mononeuropathies are clinically and electrophysiologically similar to those occurring in the absence of diabetes. The best evidence for increased susceptibility to the development of compressive neuropathy exists for carpal tunnel syndrome (CTS) where the overall prevalence in persons with diabetes is about 30%, but only about 10% are symptomatic (Dyck et al., 1993; Albers et al., 1996). Ulnar neuropathy at the elbow, although much less common than CTS, also occurs more frequently in diabetics. Peroneal neuropathy at the fibular head is infrequent enough that it may be a coincidental occurrence with diabetic polyneuropathy. The limbs must be carefully examined clinically and electrophysiologically to determine the extent of coexistent polyneuropathy.

Truncal neuropathies

Acute truncal radiculoneuropathy, also called thoracic polyradiculopathy, truncal neuropathy, or diabetic thoracoabdominal neuropathy, is a distinctive complication of diabetes and often occurs in the setting of weight loss (Sun & Streib, 1981). It presents with pain, cutaneous hypersensitivity, sensory loss and sometimes weakness in the distribution of one or more thoracic or abdominal nerves or roots. The pain location may incorrectly suggest a myocardial infarction, acute cholecystitis, or acute appendicitis. The affected segments usually are contiguous and can be bilateral (Stewart, 1989). Focal abdominal wall weakness may produce a local bulge, simulating an abdominal hernia (Parry & Floberg, 1989). Cutaneous skin biopsies in diabetic truncal radiculoneuropathy show a loss of intraepidermal nerve fibres with a return of the fibres after clinical recovery, suggesting a lesion distal to the dorsal root ganglion (Lauria et al., 1998). The lesion in this disorder is likely at the level of the thoracic roots and the intercostal or abdominal nerve in varying combinations.

Chronic renal failure

A subacute or chronic motor–sensory polyneuropathy is seen in up to 70% of patients who require therapy for long-standing renal failure. It has been extensively and critically reviewed (Bolton & Young, 1990; Burn & Bates, 1998; see also Chapter 124). The degree of motor nerve conduction velocity slowing parallels the fall in creatinine clearance, even when the neuropathy is subclinical (Nielsen, 1974). Pathologically, the neuropathy is marked by axonal atrophy, secondary demyelination, and eventual axonal degeneration in a centripetal pattern (Asbury et al., 1963; Dyck et al., 1971; Thomas et al., 1971). There is pathophysiologic evidence of axolemma dysfunction (decreased resting membrane potential, sodium channel abnormality, and slowing impulse propagation) (Nielsen, 1974). This neuropathy is not seen with acute renal failure, and chronically does not develop if the glomerular filtration rate remains above 12 ml/min. The polyneuropathy can be stabilized, even improved, by adequate hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) unless the neuropathy is already advanced (Burn & Bates, 1998; Laaksonen et al., 2000). This has implicated several possible dialyzable 'middle molecular weight' neurotoxins, as well as guanidino compounds, polyamines, myoinositol, and parathyroid hormone, although there is no clear correlation between neuropathy and any one of these. Successful renal transplantation usually reverses uremic neuropathy, often with complete recovery (Bolton et al., 1971).

Hepatic and gastrointestinal disorders

Four different conditions are known in which a hepatic disorder may have a neuropathic consequence (Asbury, 1993). These are a mild polyneuropathy that seems to occur in chronic hepatic failure of many causes (Chari et al., 1977; Kardel & Nielson, 1974; Knill-Jones et al., 1972; Seneviratne & Peiris, 1970). Chaudhry and colleagues found evidence of neuropathy in 71% of patients with end-stage liver disease of various causes, although it was subclinical or mild in almost all patients (Chaudhry et al., 1999). The electrophysiological features indicate a predominantly sensory axonal neuropathy. Half also had evidence of autonomic neuropathy. Autonomic neuropathy occurs in association with liver disease of any cause and is thus not necessarily a toxic effect of alcohol (Thuluvath & Triger, 1989; Szalay et al., 1998; Fleisher et al., 2000).

Less commonly, other forms of neuropathy are seen, such as acute demyelinating polyneuropathies of the Guillain–Barré type that may occur during the course of acute or chronic viral hepatitis (Berger et al., 1981; Tsukada et al., 1987). In the setting of primary biliary cirrhosis, two distinctive neuropathies occur. One is a patchy cutaneous sensory neuropathy in cases of far advanced primary biliary cirrhosis (Thomas & Walker, 1965), in whom xanthomatous deposits in cutaneous nerves may be demonstrated. The other syndrome has been described in women with primary biliary cirrhosis and no cutaneous nerve xanthomata (Charron et al., 1980; Illa et al., 1989). Rather, a

widespread sensory neuronopathy with severe large fibre sensory deficits dominates the clinical picture. Finally, large-fibre sensory neuropathies with axonal lesions of the posterior columns in the spinal cord can be seen in children with cholestatic liver disease and secondary vitamin E deficiency (Rosenblum et al., 1981; Sokol et al., 1985a; Traber et al., 1987). Vitamin E replacement can cause neurologic stabilization or improvement (Sokol et al., 1985b).

Peripheral neuropathy may be seen in association with inflammatory bowel disease, mostly with ulcerative colitis (Pfeifer, 1996; Lossos et al., 1995). It has been reported in the setting of Crohn's disease as well (Nemni et al., 1987; Humbert et al., 1989). Most cases are mild sensory axonal polyneuropathies, but on occasion a mononeuropathy multiplex-like presentation is seen. In one patient the neuropathy appeared to wax and wane with the clinical course of the inflammatory bowel disorder (Nemni et al., 1987).

Chronic respiratory insufficiency

A mild distal polyneuropathy may accompany chronic respiratory insufficiency, primarily with advanced chronic obstructive pulmonary disease (COPD) (Appenzeller et al., 1968; Kinsman et al., 1983; Malik et al., 1990). About 10% of these patients are symptomatic, usually with mild distal sensory loss (Faden et al., 1981; Stoebner et al., 1989; Malik et al., 1990; Jann et al., 1998). Electrophysiologically the changes are consistent with an axonal neuropathy, as are the sural nerve biopsy specimens examined (Appenzeller et al., 1968; Paramelle et al., 1986). Autonomic dysfunction can be demonstrated as well (Stewart et al., 1991, 1994). The peripheral neuropathy associated with COPD is typically far overshadowed by the pulmonary dysfunction. However, this minor polyneuropathy may interact with potentially neurotoxic agents, in an additive or synergistic fashion.

Microangiopathy of the endoneurial vessels in patients with hypoxic COPD has been recently reported. This includes thickening of the basement membrane and perineurium, endothelial cell hyperplasia and hypertrophy, and narrowing of the endoneurial capillary lumens (Stoebner et al., 1989; Malik et al., 1990). These endoneurial microvascular changes may accelerate injury to nerves that are already hypoxic.

Critical illness polyneuropathy

Two distinct syndromes, critical illness polyneuropathy and critical illness myopathy, develop in critically ill patients as a consequence of the illness and/or its treatment. A sensorimotor axonal polyneuropathy that develops in association with sepsis and critical illness was first described by Bolton and colleagues (Bolton et al., 1984). They described five patients who developed a severe sensorimotor polyneuropathy in the setting of sepsis and multiorgan failure. Using serial nerve conduction studies, they were able to characterize this as a distal sensorimotor axonal polyneuropathy, eventually termed critical illness polyneuropathy (CIP). Subsequently, the clinical, electrophysiologic and pathologic features of this disorder have been characterized by many observers (Bolton et al., 1986; Bolton, 1987; Williams et al., 1986; Witt et al., 1991; Zochodne et al., 1985, 1987; Zifko et al., 1998).

Patients may develop CIP in the setting of the systemic inflammatory response syndrome (SIRS), which is a response that occurs in the wake of infection or burns or trauma (Tran et al., 1990). When SIRS occurs in the setting of infection, this is termed sepsis. The major risk factor for the development of critical illness polyneuropathy is sepsis. Witt and coworkers (1991) prospectively evaluated 43 patients with sepsis and multiorgan failure. These patients were all noted to be encephalopathic and 70% had electrophysiologic evidence of axonal polyneuropathy when evaluated at a mean of 28 days (range 5–89). Half of the patients with electrophysiologic signs of neuropathy had clinical findings consistent with polyneuropathy as well. These latter clinical signs were defined as distal weakness and hyporeflexia or difficulty weaning from mechanical respiration. The severity of the neuropathy correlated with the length of time in the intensive care unit setting. For survivors of the period of critical illness (almost half), the degree of neurologic recovery correlated with the severity of the axonal loss. Over the past decade, critical illness myopathy has also been better delineated and distinguished from CIP (Bird & Rich, 2000). A recent study by Lacomis and coworkers (1998) of 92 patients in the ICU determined that myopathy was the more common cause (42%), but neuropathy was frequently found and was the cause of weakness in 13%.

The electrophysiological and pathological studies of CIP indicate an axonal basis (Bolton et al., 1984, 1986; Bolton, 1987; Witt et al., 1991; Zochodne et al., 1987). Nerve conduction studies demonstrate reduced or absent sensory responses and some degree of reduction in the motor responses. There are no features of demyelination (conduction block or significant conduction velocity slowing) and CIP is easily distinguished from the Guillain–Barré syndrome. Repetitive nerve stimulation studies of neuromuscular transmission are unremarkable, unless there is persistent pharmacological neuromuscular blockade.

Needle EMG examination of limb muscles is often notable for spontaneous activity (fibrillation potentials and positive sharp wave) in distal muscles at rest. With voluntary activation, there may be an excess of polyphasic and motor unit action potentials with abnormal recruitment. These features are consistent with acute denervation, but often are difficult to assess in patients with little voluntary movement due to encephalopathy and/or sedation. Phrenic nerve conduction studies as well as needle EMG of the diaphragm may demonstrate phrenic nerve involvement (Bolton, 1993). These can be helpful in confirming the neuromuscular basis for failure to wean from mechanical respiration in patients.

Nerve biopsy, as well as autopsy studies, have demonstrated axonal changes in CIP. Axonal degeneration is observed in both sensory and motor nerves without evidence of significant inflammation or demyelination (Bolton et al., 1984; Zochodne et al., 1987).

The pathogenesis of critical illness polyneuropathy is uncertain. Evidence is lacking to show that drugs, toxins, nutritional deficiencies, autoimmune disorders, or specific infectious agents are causative. Speculation has been advanced that the systemic inflammatory response syndrome produces a humoral product that disturbs the microcirculation of brain and nerve (Glauser et al., 1991).

Toxic neuropathies

Many of these disorders are summarized in Table 66.2, and are well described in recent reviews (Schaumburg & Kaplan, 1995; Spencer & Schaumburg, 2000).

Drugs and vitamins

Amiodarone

Amiodarone is an antiarrythmic drug that produces a sensory–motor polyneuropathy, often associated with tremor and ataxia (Charness et al., 1984). It generally occurs at doses at, or above, 400 mg/day and after 6 to 36 months of use, but it may occur earlier and at lower doses (Martinez-Arizala et al., 1983). An unusual feature for a toxic neuropathy is that amiodarone may produce electrophysiologic features of demyelination, as well as axonal loss (Fraser et al., 1985). If the neuropathy is not too severe, it may resolve following discontinuation of medication or even reduction of dose.

Cisplatin (platinum)

Cisplatin is a chemotherapeutic agent that produces a cumulative dose-dependent sensory neuropathy. Neuropathy develops in 50% of patients at a cumulative dose of 900 mg and in all by 1200 mg (Riggs et al., 1988). Newer cisplatin congeners are considerably less neurotoxic. The neuropathy is large-fibre selective with sparing of motor axons, even at higher doses. This produces loss of reflexes distally with prominent abnormalities in proprioception and vibratory sensation with locomotor ataxia (Krarup-Hansen et al., 1993). Pain and thermal sensation are relatively spared (Roelofs et al., 1984). A 'coasting effect', with worsening for a few weeks after drug discontinuation, has been described. When severe, the deficits may be irreversible, suggesting that this is a sensory neuronopathy at higher doses, much like pyridoxine excess (see below).

Colchicine

A polyneuropathy and myopathy may develop in those taking colchicine at standard doses, particularly if there is renal dysfunction (Kuncl et al., 1987). Colchicine is primarily a myotoxin; clinical myopathy is generally more severe than the neuropathic component. The combination of proximal weakness, distal paresthesias and mild sensory loss, and an elevated serum CK, although confusing, may be produced by colchicine. Electrophysiologically, there is evidence of a myopathy often with mildly reduced sensory nerve action potential amplitudes. It has been suggested that this drug exerts its toxic effect by the mechanism proposed for vincristine neuropathy, namely impaired microtubule assembly resulting in defective axonal transport (Kuncl et al., 1987).

Dapsone

Dapsone is used for leprosy and certain dermatologic conditions. It is an unusual neurotoxin in that it produces a pure motor neuropathy manifesting particularly by distal arm weakness (Gutmann et al., 1976). This may be mistaken for motor neuron disease clinically and electrophysiologically. The mechanism is unknown.

Disulfuram

Disulfiram is an agent used to treat alcoholism. A sensory–motor polyneuropathy may develop after many months at standard doses. The neuropathy may be hard to distinguish from that due to chronic alcoholism and other nutritional comorbidities. The electrophysiologic and pathologic features are those of an axonal neuropathy (Moddel et al., 1978; Mokri et al., 1981).

Isoniazid

Isoniazid (INH) is used to treat tuberculosis including prophylaxis for a positive PPD test. INH can cause a sensory–motor polyneuropathy in a dose-dependent

fashion. Distal sensory symptoms appear first from 1 to 6 months after starting therapy and progress if the drug is continued. INH is deactivated by acetylation, so slow acetylators are particularly at risk for the development of this neuropathy (Paulson & Nilsson, 1985). Neuropathy is due to the inhibition of pyridoxal phosphokinase by INH, thus acting as a pyridoxine inhibitor. The neuropathy can be prevented by the addition of 100 mg daily of pyridoxine (Ochoa, 1970). Hydralazine, an antihypertensive drug, may on occasion be associated with a mild neuropathy presumably due to a similar pyridoxine-inhibitor effect.

Metronidazole and misonidazole

Metronidazole is a commonly used antimicrobial agent used in the treatment of gram-negative infections. It is not a problem when used for short courses (e.g. 2 weeks), but when used for a chronic infection or Crohn's disease for weeks or longer it may produce neuropathy. This is particularly the case for total cumulative doses of 30 grams or more. The neuropathy is primarily a sensory axonal neuropathy affecting both large and small-diameter fibres (Bradley et al., 1977; Hahn & Feasby, 1989). Misonidazole is a cell sensitizer used in radiation therapy and a congener of metronidazole. It also produces a distal sensory axonopathy that is dose related, and this is the dose-limiting side effect of the drug (Urtasun et al., 1978).

Nitrofurantoin

This antibiotic is often used chronically for the suppression of recurrent urinary tract infections. The neurotoxic effect is dose related and tends to occur more readily in the presence of renal failure, presumably due to higher serum levels (Toole et al., 1968). The sensory–motor polyneuropathy is generally mild, although cases of more severe and subacute onset have been reported. Studies of human sural nerve biopsies and experimental animals given this agent are consistent with a distal axonopathy (Yiannikas et al., 1981).

Nucleoside analogues (ddC, ddI, d4T)

These agents, zalcitabine (dideoxycytidine, or ddC), didanosine (dideoxyinosine, or ddI), and stavudine (d4T) are antiretroviral agents used in HIV-infected patients (Hirsch & D'Aquila, 1993; Berger et al., 1993). At currently used doses, fewer than 10% of patients develop toxic neuropathy. The axonal sensory neuropathy secondary to nucleoside analogues may be difficult to differentiate from the painful, sensory neuropathy seen in late HIV infection. Both present early with distal paresthesias, pain and small-fibre sensory loss. They may be distinguished by the speed of onset and improvement after withdrawal of the drug. When these drugs are withdrawn, the neuropathy generally improves. A delay of a few weeks (a 'coasting-effect') is frequent, and may erroneously suggest that drug discontinuation was not beneficial. The degree of recovery after drug withdrawal depends on the severity of the neuropathy and whether there is coexistent HIV sensory neuropathy. The pathogenesis of nucleoside analogue neuropathy is uncertain.

Phenytoin

Neuropathy due to this anticonvulsant agent is uncommon, and generally does not occur until after 20 to 30 years of use. A sensory–motor axonal polyneuropathy insidiously develops and only slowly worsens. Recovery can follow drug discontinuation (Lovelace & Horowitz, 1968).

Pyridoxine (vitamin B6)

Vitamin B6 (pyridoxine) can produce a dose-dependent sensory neuropathy that at high doses is a neuronopathy. The severity and reversibility of the neuropathy is dose dependent (Schaumburg et al., 1983). Neuropathy has been reported at doses of 1000 mg per day in a few months or at 200 mg per day over a longer time period (Berger et al., 1992; Parry & Bredesen, 1985). Massive intravenous doses have been noted to produce a profound sensory neuronopathy with irreversible proprioceptive loss and ataxia (Albin et al., 1987). Pyridoxine has a preferential toxic effect on large-fibre sensory modalities. On electrophysiologic examination, sensory nerve action potential amplitudes are reduced or absent, with normal motor findings.

Pyridoxine, cisplatin (see above), and taxol are important examples of neurotoxins that produce a selective involvement of large sensory neurons (sensory neuronopathy). Dose–response studies using pyridoxine (Xue et al., 1989) demonstrated that the pyridoxine given to rats can cause a neuronopathy in large doses but an indolent distal sensory axonopathy in smaller doses. Megadose pyridoxine given to rats produced a neuronopathy with necrosis of dorsal root ganglion cells, whereas lower doses produced reversible neuropathy with perikaryal and axonal atrophy.

Statins

Statins are widely used cholesterol-lowering medications that act by inhibiting hydroxymethylglutaryl coenzyme A (HMG–CoA) and are now widely used. Recent reports suggest that these drugs may result in an axonal sensory polyneuropathy (Phan et al., 1995; Jacobs, 1994; Jeppesen et al., 1999; Ziajka & Wehmeier, 1998). In most case reports the neuropathy is mild and predominantly sensory, and reverses after drug withdrawal. One patient had recurrence of neuropathic symptoms after the drug was reintroduced

(Jacobs, 1994). It is probably an uncommon side effect since it was not observed in several large clinical trials of these agents. It is difficult in an individual patient to differentiate a possible toxic effect of these drugs from idiopathic sensory polyneuropathy. A reasonably long trial of drug withdrawal, 6 months or more, may be necessary to answer the question.

Taxol (paclitaxel)

Taxol is a chemotherapeutic agent used to treat several solid tumours. Neuropathy has been the limiting side effect and is dose related. Neuropathy tends to occur above 200 mg/m^2 total dose and is more severe when used with cisplatin (Kaplan et al., 1993a; Chaudhry et al., 1994). The neuropathy, like cisplatin and pyridoxine, is a selective for sensory fibres. Sensory symptoms and distal sensory and reflex loss predominate. Nerve conduction studies show loss of sensory nerve action potentials without demyelination. Taxol promotes increased microtubule assembly after binding to tubulin. In tissue culture, this results in abnormal bundles of microtubules. This presumably interferes with axoplasmic transport and thus results in an axonopathy (Lipton et al., 1989).

Thalidomide

Thalidomide is used in certain dermatological conditions, as well as Behcet's disease, and when used chronically, produces neuropathy. The initial symptoms are sensory, but as neuropathy worsens distal motor involvement appears. Neuropathy generally occurs at doses of 25–50 mg per day for a year or longer. The electrophysiological findings are those of an axonal sensory–motor polyneuropathy (Fullerton & O'Sullivan, 1968; Chaudhry et al., 1996).

Vincristine

Vincristine is a chemotherapeutic agent used to treat many malignancies. Toxic neuropathy begins with sensory symptoms in the distal limbs, often first or more prominently in the hands (Casey et al., 1973). The length-related pattern of sensory loss is evident on examination by the early loss of ankle reflexes and sensory deficit in the toes. As the neuropathy worsens, distal weakness develops. More severe neuropathy can be accompanied by autonomic involvement, with gastroparesis and urinary dysfunction. The neuropathy is axonal and may be reversible if not too severe (Bradley et al., 1970). Vincristine binds to tubulin and inhibits microtubule assembly, the opposite effect of taxol which promotes microtubule assembly. Both mechanisms disrupt fast axonal transport (Sahenk et al., 1987) and produce neuropathy.

Other

A number of other drugs have been associated with neuropathy (see Spencer & Schaumburg, 2000). These include amitriptyline, chloramphenicol, chloroquine, doxorubicin, hydralazine, nitrous oxide, perhexiline maleate, sodium cyanate, suramin and L-tryptophan.

Environmental toxins

The toxic effects of lead (inorganic), mercury, and other metals are discussed in Chapter 112 and alcohol in Chapter 113.

Acrylamide

The monomer of acrylamide is a grouting agent and may be neurotoxic. Polyacrylamide is not neurotoxic. Neuropathy may occur following absorption through the skin and be preceded by palmar desquamation. Acrylamide produces mainly a large-fibre sensory neuropathy (Spencer & Schaumburg, 2000). Distal reflex and proprioceptive loss, and ataxia, may be followed later by distal weakness. Recovery following removal from exposure is often incomplete and may reflect a central–peripheral process. Electrophysiologic studies are consistent with a distal sensory–motor axonopathy (Sumner & Asbury, 1975).

Arsenic

The neurotoxic effects occur usually after the ingestion of inorganic arsenic in a suicide or murder attempt. Acute ingestion of a massive dose produces nausea, vomiting, and hypotension. This is followed 1 to 3 weeks later by the development of a subacute axonal sensory–motor polyneuropathy (Spencer & Schaumberg, 2000; LeQuesne & McLeod, 1977). Neuropathy can be quite severe, and the ascending quadripareis may be confused with the Guillain–Barré syndrome (Donofrio et al., 1987). Chronic or repeated exposure results in a more indolent axonal sensory–motor polyneuropathy. Other effects are characteristic white lines in the fingernails and toenails (Mees' lines) and a pigmented dermatitis. Recovery from arsenical neuropathy depends on the severity of the axonal loss at its peak. The diagnosis may be confirmed by laboratory evaluation of the urine during acute exposure, but this rapidly normalizes. With chronic exposure or later after an acute one, an assay of hair is best since arsenic binds to keratin. The use of chelating agents to treat an acute exposure has been suggested but no clear role has been established.

Hexacarbons

Hexacabons (n-hexane and methyl n-butyl ketone (MBK)) can produce neuropathy. n-Hexane is a solvent widely

used in glues and thinners; methyl n-butyl ketone is now a rarely used industrial solvent. Chronic industrial exposure produces a length-related, sensory–motor polyneuropathy (Allen et al., 1975; Altenkirch et al., 1977). The pace and completeness of recovery, as with most toxic neuropathies, depends on the severity of the axonal loss. Central nervous system involvement may be seen with hyperreflexia and abnormal evoked potential studies of central conduction (Oge et al., 1994). The neuropathy may be also be seen as a result of inhalation abuse (glue sniffing). The inhalation, called huffing, may produce a subacute, severe neuropathy (Prockop et al., 1974; Smith & Albers, 1997). This presentation, with nerve conduction studies showing significant slowing and even conduction block (see below), may be confused with the Guillain–Barré syndrome or CIDP. Coasting, with progression for a few weeks, is commonly seen after exposure ceases.

The pathogenesis is uncertain, but one thought is that the γ-diketone form of these drugs causes cross-linking of neurofilaments. Pathologically, there is focal axonal enlargement due to neurofilament accumulation. These areas of giant axonal swelling result in multifocal myelin thinning and underlies the electrophysiologic findings consistent with demyelination (motor conduction velocity slowing and conduction block).

Organophosphates

Organophosphorus esters (OPs) are acetylcholinesterase inhibitors that are used as pesticides. Acute poisoning produces a picture of cholinergic excess with prominent muscarinic and nicotinic symptoms, due to the action as an inhibitor of acetylcholinesterase. Muscarinic effects include increased secretions, gastrointestinal cramps and diarrhea, and miosis. Neuromuscular weakness, and even diaphragm paralysis, can occur as part of the nicotinic effects.

These OPs also produce a delayed central and peripheral axonopathy, generally 2 to 3 weeks after acute exposure (Namba et al., 1971; Senenayake & Johnson, 1982; Gutmann & Besser, 1990; Kaplan et al., 1993b). The course is acute with a peak deficit at 14 days. The neuropathy is a sensory–motor disorder, but there are signs of myelopathy as well. The neuropathy generally recovers, whereas the disability due to the myelopathy does not. As a result there may be residual proprioceptive loss and spasticity. Drugs used to counteract the acute poisoning, such as atropine, have no effect on this late sequela once it has developed.

Other toxins

Other environmental toxins that are toxic to peripheral nerve (Spencer & Schaumburg, 2000) include allyl chloride, buckthorn berry, carbon disulfide, dimethylaminopropionitrile (DMAPN), ethylene oxide, methyl bromide, polychlorinated biphenyls (PCBs), styrene, thallium, trichlorethylene, and vacor (PNU).

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67

Guillain–Barré syndrome (GBS)

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With the eradication of polio, GBS is now the commonest cause of acute flaccid paralysis. GBS is an acute immune mediated polyradiculoneuropathy with an incidence of 1–1.5 per 100 000 per year. It occurs in all age groups, with peaks in young adulthood and in late life where a gradual increase in incidence is seen with advancing age (Kennedy et al., 1978; Hankey, 1987; Rees et al., 1998).

Criteria for diagnosis

GBS is an acute, monophasic, predominantly motor polyneuropathy. The currently accepted criteria for the diagnosis of Guillain–Barré syndrome (Asbury et al., 1978) include the following.

Features required for diagnosis

- Progressive motor weakness of more than one limb
- Areflexia which is usually universal but distal areflexia with more proximal hyporeflexia is adequate if other features are consistent

Features strongly supportive of the diagnosis

- Rapid progression of weakness which has ceased by 4 weeks
- Relative symmetry of involvement
- Mild sensory involvement, cranial nerve involvement, autonomic involvement
- Recovery usually beginning 2 to 4 weeks after progression stops

Features that rule out the diagnosis

- A diagnosis of botulism, toxic neuropathy or poliomyelitis
- Abnormal porphyrin metabolism
- Recent diphtheric infection

Antecedent events

This immune-mediated polyradiculoneuropathy often follows an acute infective illness. One-half to two-thirds of GBS patients report symptoms of a respiratory tract or gastrointestinal infection within the month preceding neurological symptoms (Winer et al., 1988a; Jacobs et al., 1998). The most commonly identified organism is *Campylobacter jejuni*; recent infection being detected by bacteriologic or serologic techniques in 26–40% of patients (Kaldor & Speed 1984; Rees et al., 1995). Other identified antecedent infections include Cytomegalovirus (CMV), Epstein–Barr virus, *Mycoplasma pneumoniae* and *Haemophilus influenza* (Winer et al., 1988a; Jacobs et al., 1998; Mori et al., 2000). GBS may be an early manifestation of HIV infection, presenting at the time of seroconversion or in the immunocompetent phase of the disease. A small proportion of GBS cases follow surgery by an interval of 1 to 4 weeks, in the absence of identifiable infection.

An increased incidence of GBS was reported with the no longer used rabies vaccines containing neural tissue (Arnason & Soliven 1993), with swine influenza vaccination in the United States in 1976 (Schonberger et al., 1979) and with oral poliovirus vaccine (Kinnunen et al., 1989). However, more recent large studies have failed to demonstrate an increased incidence after any currently administered vaccines, including influenza, measles, measles/rubella, oral polio, or tetanus toxoid containing vaccines (Roscelli et al., 1991; Hughes et al., 1996a; da Silveira et al., 1997; Tuttle et al., 1997; Lasky et al., 1998; Kinnunen et al., 1998; Ropper & Victor, 1998; Salisbury, 1998). Whether vaccination is associated with relapse of GBS remains uncertain, but it would seem reasonable to follow the recent advice of Hughes and avoid vaccination in the first 12 months after an episode of GBS (Hughes et al., 1996b).

Variants

In the past, the terms GBS and acute inflammatory demyelinating polyradiculoneuropathy (AIDP) have been used synonymously. However, in recent years it has become increasingly clear that GBS is not a single pathophysiological entity. The acute demyelinating form remains the most common type in Europe, North America and the rest of the developed world, accounting for 85–90% of patients. An axonal form, first described by Feasby et al. (1986) is now widely recognized (Yuki et al., 1990; McKhann et al., 1993). A pure motor axonal subtype (acute motor axonal neuropathy or AMAN) has been extensively characterized in Northern China (McKhann et al., 1993) and is more common in developing countries, although it may represent 10–15% of cases of GBS in the developed world (Visser et al., 1995). AMAN is strongly linked to preceding *Campylobacter* infection (Ho et al., 1995, Visser et al., 1995). The motor–sensory axonal type is a more severe form with less complete recovery (Feasby et al., 1986). The Miller Fisher variant of GBS (MFS), which represents approximately 5% of cases, has been recognized for many years (Fisher, 1956). In pure MFS, patients present with ataxia, ophthalmoplegia and areflexia without significant weakness, although overlap forms, with bulbar, facial and/or generalized weakness are also seen.

Clinical features

The most common initial symptom is weakness, usually beginning in the lower limbs and characteristically involving both proximal and distal muscles. The time from onset to nadir of neurological deficit varies from hours to weeks, but most patients develop maximal deficit within 14 days and over 90% reach a nadir by 4 weeks (Winer et al., 1988b). This is followed by a plateau phase, characteristically of 1 to 2 weeks, and then recovery. Pain, particularly low back, buttock or thigh pain, is an early symptom in approximately 50% of patients. Complete areflexia is found in over 80% of patients, and some reflexes are lost in virtually all. Numbness and paresthesiae are frequently reported, but abnormalities on sensory examination are often minimal, with reduced light touch or pinprick sensation evident in only one quarter of cases and some loss of vibration sensation in 60%. Cranial nerve involvement is seen in two-thirds of cases, most commonly facial weakness, ophthalmoplegia, difficulty swallowing or altered taste. Facial weakness occurs in just over one-half of cases and is usually bilateral. Ophthalmoplegia is evident in 10–15% of patients (Winer et al., 1988b; Hankey, 1987). Autonomic nervous system involvement is present in 30% of patients, and can be manifest as reduced sinus arrhythmia, sinus tachycardia, arrhythmias, hypertension, labile blood pressure, orthostatic hypotension, abnormal sweating or pupillary abnormalities (Tuck & McLeod, 1981; Fuller et al., 1992).

Investigations

Cerebrospinal fluid

The characteristic finding on examination of the CSF is increased protein without a significant increase in cells (cytoalbuminemic dissociation). CSF protein is increased in 80–90% of cases (Winer et al., 1988b; Hankey, 1987) and is more likely to be abnormal if the spinal tap is performed more than seven days after the onset of neurological symptoms. A mild increase in white cells in the CSF is evident in approximately 10% of patients. The CSF findings are not predictive of disease severity or outcome.

Electrodiagnostic studies

Nerve conduction studies may be normal early, particularly within the first week. The characteristic findings in AIDP are those of a demyelinating neuropathy, with prolonged distal motor latencies, slowing of motor conduction velocity and often evidence of conduction block or dispersion of the compound muscle action potential (CMAP) (Cornblath, 1990). F waves, which enable assessment of conduction in the more proximal segments of nerves and in the spinal motor roots, are the most sensitive parameter in the early stages of the disease, with abnormal lower limb latencies evident in 90% of patients (Winer et al., 1988b; Kimura, 1978). Sensory abnormalities are variable, but reduced or absent sensory nerve action potentials and slowing of sensory conduction velocity are common.

In AIDP, a reduction in the amplitude of the distal CMAP to 20% or less of the lower limit of normal is the most powerful electrodiagnostic predictor of protracted recovery and poor eventual outcome (Cornblath et al., 1988; Miller et al., 1988), and usually indicates significant axonal degeneration. However, cases of GBS with decreased distal CMAP amplitude, very distal demyelination and rapid recovery are recognized (Hall et al., 1992). Electromyography is helpful in determining the extent of acute denervation in cases where axonal degeneration is suspected and the presence of abundant fibrillation potentials is associated with a poor prognosis (McLeod, 1981). In the primary axonal forms of the disease, motor (AMAN) or motor and sensory (AMSAN) responses are absent or reduced in amplitude, with normal distal motor latencies and normal or only mildly reduced conduction velocities. Inexcitable nerves can be seen in severe demyelinating or

axonal forms. A gradual return of nerve conduction studies to normal is seen in most patients, however residual conduction abnormalities sometimes persist even in the absence of clinical disability (McLeod et al., 1976).

Clinical course

Approximately one-fifth of patients remain ambulant throughout, one-half become chair- or bed-bound, one-third require intensive care admission and one-quarter mechanical ventilation (Winer et al., 1988b; Sheth et al., 1996; Rees et al., 1998; Hankey, 1987). The severity of disease increases with increasing age (Sheth et al., 1996) and antecedent infection with either *Campylobacter* (Winer et al., 1988a; Kaldor & Speed, 1984) or CMV (Visser et al., 1996) is also associated with more severe disease.

Complete functional recovery is seen in two-thirds of patients, but 20–30% are left with significant disability and approximately 10% are unable to walk unaided. With modern intensive care facilities, the mortality rate has been significantly reduced, but remains 3–8% in recent series with most deaths a result of cardiac arrest (attributed to autonomic disturbance), respiratory failure or infection, or pulmonary embolism (Winer et al., 1988b; Rees et al., 1998; Guillain–Barré Study Group, 1985).

A number of factors have been associated with poor outcome, including a short interval from onset to being bedbound, the need for mechanical ventilation, age >40 and small ($\leq 20\%$ of normal) or absent distal CMAPs (Winer et al., 1988b; McKhann et al., 1988). The outcome is better in children (Delanoe et al., 1998; Bradshaw & Jones, 1992), and the presence of decreased CMAP amplitudes and denervation potentials may not predict poor outcome in this group, though a prolonged interval to commencement of recovery does correlate with a poor outcome (Eberle et al., 1975).

GBS recurs in 1–10% of untreated patients. Recurrent episodes have been reported 4 months to 8 years after the initial presentation in association with varying antecedent infections, pregnancy and the early post-partum period, and vaccination with tetanus toxoid (Grand'Maison et al., 1992; Pollard & Selby, 1978). Treament related fluctuations are noted in the acute phase of the disease in 5–10% of patients treated with either plasmapheresis or intravenous immunoglobulin (see treatment below) (Visser et al., 1998).

Pathology

In AIDP the primary abnormality is segmental demyelination. Perivascular lymphocytic infiltrates and endoneurial edema are evident early in the disease, and areas of vesicular myelin breakdown and phagocytosis correspond to the areas of inflammatory cell infiltrate (Fig. 67.1) (Asbury et al., 1969; Prineas, 1972; Carpenter, 1972). The earliest myelin lesion is retraction of myelin at the nodes of Ranvier (paranodal demyelination) which evolves to loss of myelin over complete internodes (segmental demyelination) (Asbury et al., 1969). Demyelination is macrophage mediated (Fig. 67.1) (Prineas, 1972; Carpenter, 1972). Axonal degeneration may be present, especially in cases with more intense inflammatory changes. All levels of the peripheral nervous system are involved, with multiple foci of inflammation scattered from spinal roots and ganglia to the terminal motor nerves and also involving cranial nerves and sympathetic chains and ganglia. Recent immunohistochemical studies on autopsy specimens from patients dying early in the disease have demonstrated dep-

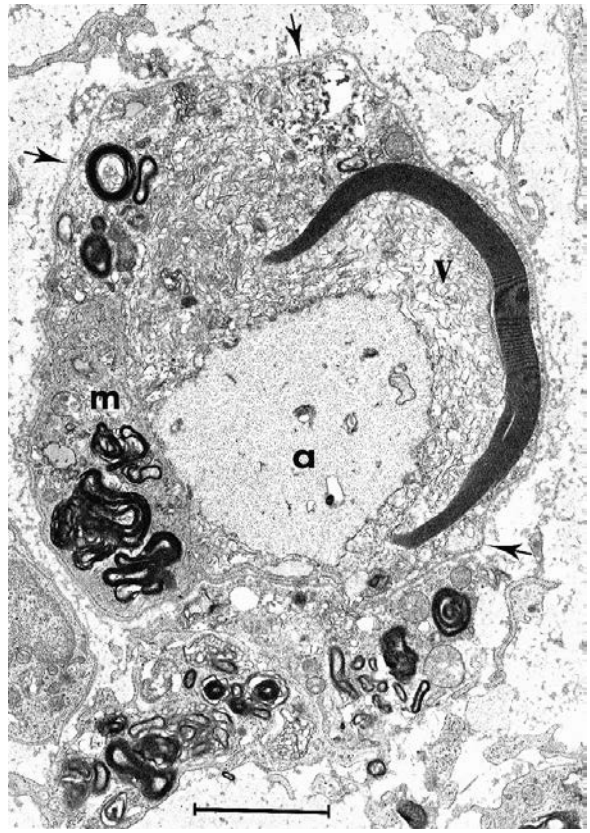

Fig. 67.1. Vesicular demyelination in GBS. An electron micrograph of a sural nerve biopsy specimen showing vesicular dissolution of the myelin sheath (v) surrounding an axon (a). A macrophage (m) containing myelin debris is replacing effete Schwann cell cytoplasm within the Schwann cell basal lamina (arrows). Bar = 5 μm

osition of immunoglobulin and complement activation products on the Schwann cell surface, suggesting that the Schwann cell plasmalemma is the site of primary immune attack in this form of GBS (Hafer-Macko et al., 1996).

In AMAN, there is axonal degeneration of motor fibres in the spinal roots and peripheral nerves, but little lymphocytic inflammation or demyelination (Griffin et al., 1995). The earliest and mildest changes are lengthening of the nodes of Ranvier, with distortion and sometimes breakdown of the paranodal myelin. Macrophages are evident overlying the nodes, extending processes through the Schwann cell basal lamina to the axolemma, entering the periaxonal space and ultimately surrounding the axon (Griffin et al., 1996). The final stage is Wallerian degeneration of the axon. In the ventral roots of early fatal cases, immunoglobulin and complement activation markers are deposited on the axolemma suggesting that the axon is the site of primary immune attack in this form.

Pathogenesis

In AIDP, there is evidence that both humoral immune responses and T-cell activation are important in pathogenesis. Complement fixing antibodies directed against peripheral nerve myelin are detected in the serum of GBS patients (Koski et al., 1986) and immunoglobulin and complement deposition is evident on the Schwann cell surface consistent with a primary immune attack directed against the Schwann cell or myelin (Hafer-Macko et al., 1996).

Lymphocytic infiltration is evident in AIDP nerve, and there is systemic evidence of T-cell activation (Hartung et al., 1990). The pro-inflammatory cytokine TNF-α is up-regulated in AIDP and levels correlate with disease severity and electrophysiological evidence of demyelination (Sharief et al., 1993, 1997). Other inflammatory markers are also up-regulated, including vascular adhesion molecules, matrix metalloproteinases and B-7 costimulatory molecule (Créange et al., 1999; Kiefer et al., 2000).

In AMAN, lymphocyte infiltration of nerve is minimal, but there is deposition of immunoglobulin and complement on the axolemma, consistent with the axon being the site of primary immune attack. Given the lack of lymphocytic infiltration, humoral factors may be relatively more important in AMAN but this remains to be fully determined.

Molecular mimicry and antiganglioside antibodies

Recent evidence suggests that the heterogeneity of the clinical picture in GBS may reflect different antecedent infections and consequent immune responses. The concept of molecular mimicry is best established for *Campylobacter*-associated GBS. The lipopolysaccharide component of *Campylobacter* contains ganglioside-like epitopes, and antibodies directed against these bacterial epitopes can cross react with ganglioside epitopes on peripheral nerve (Yuki et al., 1993a; Sheikh et al., 1998). If a similar mechanism exists for other preceding infections, the antigenic specificities of the resultant antibodies and the distribution of specific ganglioside epitopes in the peripheral nervous system may, at least in part, determine the variable clinical features of the disease.

One-quarter to one-third of patients with GBS have high serum titers of anti-ganglioside antibodies, usually IgG. The occurrence of GBS, with high levels of antiganglioside antibodies, after parenteral therapy with gangliosides (Illa et al., 1995) adds weight to the hypothesis that these anti-ganglioside antibodies are pathogenic but their precise significance remains to be determined. There are a number of associations between different clinical variants of GBS, and antibodies to particular gangliosides. The strongest association is that of anti-GQ1b antibodies with Miller Fisher syndrome and GBS with ophthalmoplegia (Willison et al., 1993) and these antibodies have been shown to block neuromuscular transmission (Plomp et al., 1999). There is also a strong association between anti-GM1 antibodies and antecedent infection with *C. jejuni*, pure motor GBS and axonal involvement (Yuki et al., 1990; Rees et al., 1995). On the other hand, preceding CMV infection is associated with more marked sensory involvement and antibodies against GM2 ganglioside (Visser et al., 1996; Jacobs et al., 1997b). Some antiganglioside antibodies have also been associated with more severe disease (Yuki et al., 1993b) but at this stage the antiganglioside profile of individual patients is not helpful in making treatment decisions. The role of these antibodies is the subject of intense research that will probably yield further insights into the immunopathogenesis and treatment of the Guillain–Barré syndromes.

Treatment

Patients with GBS require admission to hospital as weakness can progress rapidly, and up to one-third of patients will require ICU admission for ventilatory support or as a result of hemodynamic instability secondary to autonomic dysfunction. Both plasmapheresis (Guillain–Barré Study Group, 1985; French Cooperative Group on Plasma Exchange in Guillain–Barré Syndrome, 1987) and intravenous immunoglobulin (IVIg) (van der Meché et al., 1992; Plasma Exchange/Sandoglobulin Guillain–Barré Syndrome Trial Group, 1997) are effective therapy if started within the

first two weeks of neurological symptoms. Both treatments improve the time to onset of recovery and outcome. No benefit has been demonstrated for either treatment over the other and no benefit is derived from combined therapy (Plasma Exchange/Sandoglobulin Gullain–Barré Syndrome Trial Group, 1997). High dose corticosteroids are ineffective in the treatment of GBS (Gullain–Barré syndrome Steroid Trial Group, 1993).

Standard plasmapheresis schedules involve a total of 200–250 ml/kg of plasma being exchanged in 4 to 5 sessions over 7 to 14 days. The dose of IVIg used in the treatment trials was 0.4 g/kg/day for 5 days although the same total dose (2 g/kg) is now given over two days in some centres. Treatment related fluctuations are seen in 5–10% of patients treated with either plasmapheresis or IVIg, with no significant differences between treatment modalities (French Cooperative Group on Plasma Exchange in Guillain–Barré Syndrome, 1987; Dutch Guillain–Barré Study Group, 1998). Retreatment with the original modality is the usual approach in patients who have improved and then relapsed. Those patients who fail to improve after an initial course of IVIg may respond to a second course (Farcas et al., 1997).

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Diagnosis and definition

CIDP, as the name implies, is a chronic demyelinating neuropathy affecting particularly nerve roots and plexuses as well as distal nerves, the onset of which in most cases evolves over a period of more than 4 weeks. The diagnosis is usually considered in patients who present with an appropriate history (progression over more than 4 weeks) and in whom the electrodiagnostic studies show changes consistent with an acquired demyelinating pathology when other causes of demyelination (drugs, paraproteins, etc.) have been excluded.

In considering the differential diagnosis, hereditary demyelinating neuropathies may not be easily distinguished on clinical grounds when no family history is available. Demyelinating neuropathy may occur in association with malignancy, in carcinoma, lymphoma and myeloma including POEMS Syndrome. Neuropathies associated with paraproteinemia, particularly IgM, need to be excluded by immunofixation or gel electrophoresis. Electrophysiological and histological features of demyelination may occur in diabetes and other metabolic disorders, including uremia, hypothyroidism and acromegaly and drug-induced causes include amiodorone, perhexilene, n-hexane and 2.5 hexanedione (glue sniffing neuropathy). HIV infection may be associated with demyelinating neuropathy (usually accompanied by CSF pleocytosis) as may Lyme disease and it may occur in graft vs. host disease. When CIDP presents in a multifocal fashion, it needs to be differentiated from multifocal motor neuropathy with persistent conduction block.

Clinical features

Most patients present with a mixed motor and sensory neuropathy with proximal and distal weakness, although motor and sensory signs may be mostly distal.

Occasional patients present with an ataxic sensory or purely motor neuropathy (McCombe et al., 1987a; Barohn et al., 1989). CIDP may also present with limb or back pain (Gorson et al., 1997; Bouchard et al., 1999). Postural or action tremor may occur even when power or sensation remains intact. Cranial nerve involvement occurs less commonly than in the Guillain–Barré syndrome. Hypertrophy of peripheral nerves (including cranial nerves), nerve roots or plexus is relatively common in CIDP particularly after a long time course and massive hypertrophy of nerve may be evident clinically and cause nerve root or limb pain (Duggins et al., 1999). Disturbances of micturition (urgency, difficulty voiding) occur in about 25% of cases (Sakakibara et al., 1998). Rarely CIDP may be associated with a multifocal central demyelinating disorder resembling multiple sclerosis. Patients fulfilling diagnostic criteria for CIDP may occasionally be shown to have an IgG and or IgA paraprotein (Bleasel et al., 1993). However, patients with IgM-associated neuropathies usually differ in clinical, electrophysiological and pathological features and in response to treatment (Yeung et al., 1991; Maisonobe et al., 1996).

Prevalence, course and prognosis

The prevalence of CIDP is between 1 and 2 per 100 000 whereas the incidence has been estimated to be 0.15 per 100 000 (Lunn et al., 1999; McLeod et al., 1999).

CIDP follows either a relapsing and remitting or progressive course whilst occasional patients experience a subacute monophasic illness although a chronic progressive course is more common (Dyck et al. 1993). Relapses may occur related to changes in therapy or intercurrent illness. A majority of patients present with a gradual onset of symptoms but some present acutely as GBS and CIDP is diagnosed retrospectively because of their subsequent relapsing or progressive course (McCombe et al., 1987b). Given appropriate treatment the prognosis for recovery is

excellent in most patients but is better in those with relapsing than with progressive disease (McCombe et al., 1987b; Bouchard et al., 1999). A major long-term prognostic factor in CIDP is axonal loss in sural nerve biopsy (Bouchard et al., 1999).

Electrodiagnostic studies

These studies provide the cornerstone of diagnosis in CIDP, since it is the finding of electrodiagnostic features of demyelination that, in practice, suggests the diagnosis. Electrophysiological criteria for the diagnosis of CIDP have been described by several authors (Lewis et al., 1982; Albers & Kelly, 1989; Ad hoc Sub Committee, 1991; Sumner, 1994). These include:

(i) motor conduction velocity less than 75% of the lower limit of normal/or less than 40 m/s in median and ulnar nerves and less than 30 m/s in common peroneal nerves;
(ii) terminal motor latencies greater than 140% of normal (or greater than 7 ms in median and ulnar nerves or 10 ms in common peroneal nerve);
(iii) conduction block and/or temporal dispersion of the compound muscle action potential;
(iv) F wave latency increased to greater than 120% of normal.

It is important to exercise care in the diagnosis of conduction block since severe conduction slowing and temporal dispersion may result in phase cancellation of action potentials of different motor units causing 'pseudoblock' (Rhee et al., 1990). Short segment stimulation to determine whether block occurs abruptly over a limited distance of nerve is a useful technique to facilitate the diagnosis of conduction block (Krarup et al., 1990). Moreover, since the pathological changes in inflammatory neuropathy have a predilection for proximal regions (nerve roots, plexuses, proximal nerve trunks) it is important to examine for proximal conduction block and conduction abnormalities within this region of the PNS despite the technical difficulties involved (Fig. 67.2) (Menkes et al., 1998). Assessment of F wave responses and spinal evoked potentials may reveal proximal demyelinating lesions in motor or sensory fibres respectively.

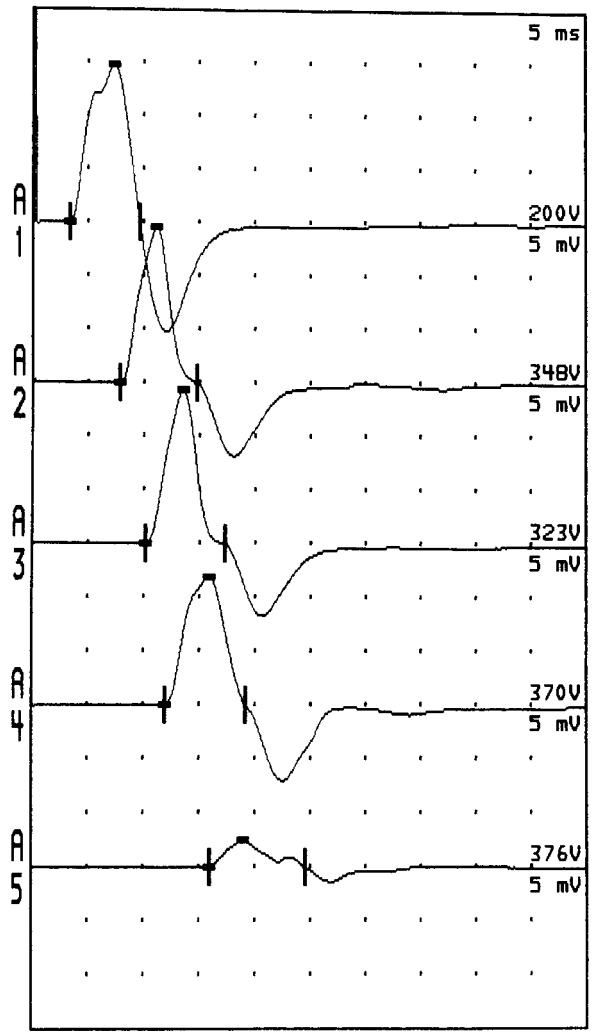

Fig. 67.2. Proximal conduction block in CIDP. Compound muscle action potentials (CMAPs) recorded from the ADM muscle following stimulation of the ulnar nerve at increasing proximal sites. A_1 = wrist, A_2 = below elbow, A_3 = above elbow, A_4 = axilla, A_5 = Erb's point. Note that amplitude and area are maintained until the most proximal stimulation site is reached. This patient who was quadriplegic had near normal routine conduction studies.

Pathology

The lesions of CIDP consist of patchy regions of edema and demyelination associated with a variable inflammatory infiltrate of T-cells and macrophages, occurring mainly within spinal nerve roots, plexuses and proximal nerve trunks (Prineas & McLeod, 1976). In sural nerve biopsy studies the findings may include endoneurial edema, thinly myelinated or demyelinated fibres, active demyelination (myelin stripping or vesicular dissolution in the presence of mononuclear phagocytes) onion bulb formation, varying degrees of axonal degeneration, and mononuclear cell infiltrates (Figs 67.3, 67.4) (Pollard, 1994). Analysis of nerve fibres teased from sural nerve biopsies showed demyelinating changes in 71%, mixed axonal and demyelinating in 21%, and purely axonal in 5% (Bouchard et al., 1999).

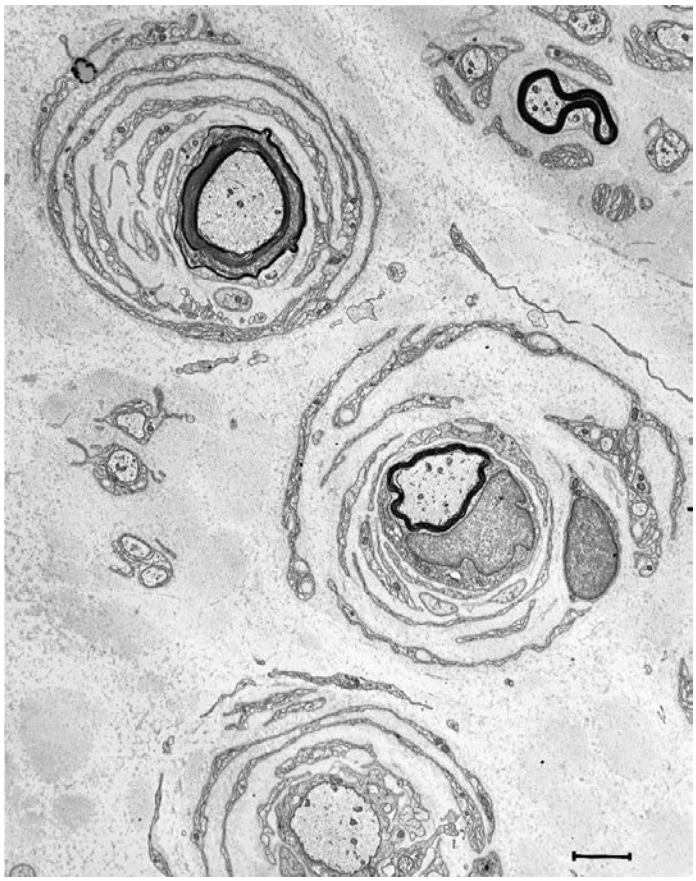

Fig. 67.3. Onion bulb formation in CIDP. An electron micrograph of a sural nerve biopsy specimen showing marked onion bulb formation in a CIDP. Note the variability of myelination of central axons, unlike CMT1a. Bar = 2.5 μm.

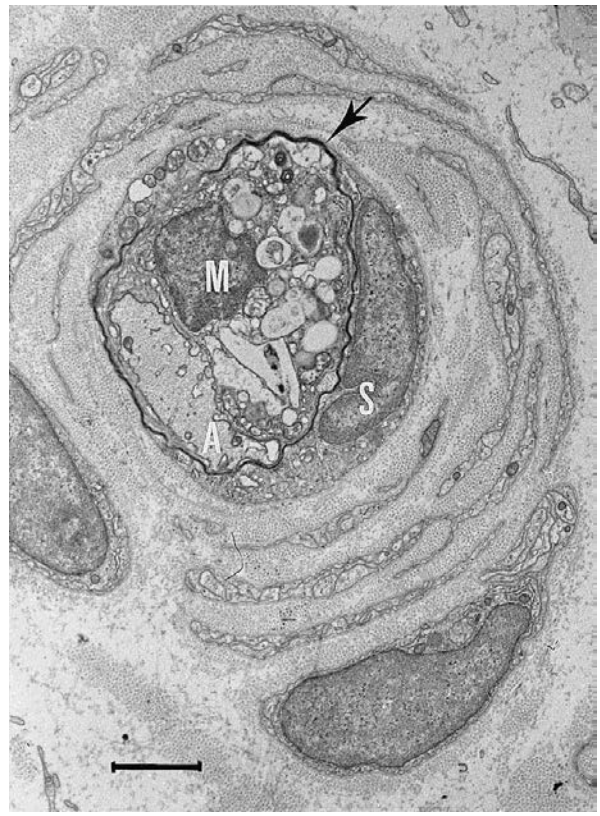

Fig. 67.4. Demyelination within an onion bulb. An electron micrograph of a sural nerve biopsy showing active demyelination within an onion bulb in a CIDP patient who was biopsied during a relapse. Arrow head points to myelin that has been lifted away from the axon (A) by a macrophage (M). The Schwann cell (S) has been pushed to the right side. Bar = 2 μm.

Immunopathological studies have shown deposition of C_3d or immunoglobulin (IgG or IgM) on myelinated fibres in a small percentage of patients and up-regulation of major histocompatibility antigens Class I and II (Yan et al., 2000; Rizzuto et al., 1998). Activation markers are found on endoneurial macrophages in CIDP but not in hereditary or other neuropathies (Kiefer et al., 1998).

Pathogenesis

An association with preceding illness and the presence of antiganglioside antibodies is less evident than with GBS (McCombe et al., 1987a,b). Nevertheless since a majority of CIDP patients respond to plasma exchange or intravenous immunoglobulin, an important role for humoral mediators such as antibody has long been suspected in CIDP. Antiglycolipid antibodies have been reported in CIDP in only small numbers of cases and pathogenicity has not been demonstrated (Melandez & Vasquez et al., 1997; Yuki et al., 1996). Anti GM-1 antibodies however are clearly associated with the related disorder multifocal motor neuropathy with persistent conduction block (MMN).

Recent evidence of a role for antimyelin protein antibodies has been shown by passive transfer studies using purified IgG from a select group of patients responsive to plasma exchange (Yan et al., 2000). IgG purified from patients whose serum bound to normal myelinated nerve fibres by indirect immunofluorescence, caused conduction block and demyelination in rat sciatic nerve in the presence of complement. The antigenic target of these antibodies was the P zero (P0) protein of peripheral myelin (Yan et al., 2001), which is largely responsible for compaction of the myelin sheath.

CIDP is a heterogeneous disease and it is likely that other target antigens and pathogenic pathways will be defined. For instance whereas some patients are easily maintained by regular plasma exchange or intravenous immunoglobulin infusion others respond only to high dose immunosuppressive therapy. In the animal model experimental autoimmune neuritis (EAN) and its chronic counterpart (CEAN) a role for both T- and B-cell mechanisms is evident. Even when antimyelin antibodies can be demonstrated, the involvement of T-cells, macrophages and mast cells is necessary for the production and regulation of cytokines, toxic mediators, proteinases and metalloproteinases that are implicated in vascular (blood–nerve barrier) and Schwann cell damage (Hartung et al., 1998; Mathey et al., 1999).

Although the etiology and pathogenesis of CIDP remains obscure, these findings provide early insight into why, for most patients, effective therapy can be provided. It may be that in patients readily responsive to plasma exchange antibody or other circulating mediators play a major role whereas T-cell mechanisms are dominant in those patients needing intense immunosuppression with cyclosporin or cyclophosphamide.

Treatment

Intravenous immunoglobulin (IVIg)

IVIG is effective, as shown by a randomized, double-blind, placebo-controlled study. In many centres it is first-line therapy since it is easy to administer, has few contra-indications or serious side effects and improvement has been reported in 62–63% of cases (Hahn et al., 1996a,b; Van Doorn et al., 1991). Although maintenance therapy is required for most patients, some chronic progressive cases have a prolonged remission following a single course. The recommended but empirical dose is 0.4 g/kg body weight daily for 5 days. Maintenance therapy may be given as a single dose of 0.4 g/kg every 2–3 weeks or at less frequent intervals as clinically indicated. IVIg has clear advantages over plasma exchange in small children, patients with venous access difficulties and cardiovascular instability and in patients in remote areas.

Plasma exchange (PE)

The efficacy of PE has also been shown by randomized controlled studies (Dyck et al., 1986; Hahn et al., 1996a,b). It is safe therapy in centres experienced in its use, but is time consuming and unsuitable for small children. In one randomized controlled study (Hahn et al., 1996a,b) 80% of patients responded but the majority required long-term immunosuppression (steroids ± azathioprine) for stabilization. PE may be given two to three times weekly until improvement is established and then the frequency tapered over several months until an appropriate maintenance program is established, usually one exchange every 3 to 4 weeks. Patients may be maintained with PE alone, but concomitant immunosuppression may allow the interexchange interval to be increased.

Corticosteroids

Steroids are efficacious (Dyck et al., 1982), cheap and convenient, but their well-known side effects have led to a significant reduction in their use for CIDP. They are useful when expensive and complicated therapies are unavailable, to induce remissions in relapsing and subacute cases and in combination with immunosuppressive agents when first line therapies prove ineffective. High dose intravenous methylprednisone (1 g daily for 3–5 days) or dexamethasone 40 mg daily for 4 days given monthly for 6 months has been reported to be beneficial in anecdotal cases (Molenaar et al., 1997).

Immunosuppressive agents

There is no class one evidence available for the use of immunosuppressive agents in CIDP. Azathioprine is nevertheless widely used, often in combination with steroids, in a starting dose of 2.5 mg/kg. Cyclophosphamide (Good et al., 1998) may be administered orally (2–3 mg/kg) or intravenously as pulse therapy 3–5 mg/kg twice weekly or 10–15 mg/kg every 7–10 days, but adverse side effects are considerable and include hemorrhagic cystitis, alopecia, sterility, mucosal ulceration, interstitial fibrosis and cancer.

Cyclosporin (CsA) has been used successfully in resistant CIDP (Barnett et al., 1998). It may be given in a starting dose of 5 mg/kg with a gradual dose reduction to a maintenance level of 2 mg/kg. Nephrotoxicity is the most serious side effect and is dose dependent. Whole blood CsA levels, creatinine clearance and serum creatinine should be monitored.

Interferons

Interferon beta has been reported in anecdotal cases only although a multicentre trial is currently in progress. Interferon 2A was given to 16 patients in an open prospective study in which 50% of patients improved (Gorson et al., 1998).

Recommended approach

Treatment should be initiated with IVIg or PE if available. These have high efficacy and few side effects. If one of these is ineffective the other should be tried. If PE is effective but

needed too frequently, an immunosuppressive regime such as azathioprine and steroid may allow an increase in the interexchange interval. Failing these measures immunosuppression with cyclosporin or cyclophosphamide may be used. Occasional patients need intense immunosuppression, i.e. CAA, azathioprine and steroids (in an organ transplant-like regime) before improvement is seen.

Multifocal motor neuropathy (MMN)

A chronic multifocal neuropathy with persistent conduction block was first described by Lewis and Sumner (Lewis et al., 1982). Parry and Clarke (1985) later reported a group of patients with a purely motor syndrome who had been diagnosed as motor neuron disease but were shown to have a pure motor neuropathy with motor conduction block. Other workers later pointed out a relationship between anti GM-1 antibodies and patients with motor neuropathies with persistent conduction block (Nordelli et al., 1988; Pestronk et al., 1988). Differences in clinical, electrophysiological and antibody profiles suggest that MMN can be differentiated from CIDP.

Clinical features

MMN is characterized by slowly progressive asymmetric limb weakness with muscle wasting often accompanied by cramps and fasciculations. Weakness often begins in the arms and prominent changes are seen in the forearms. There is a predilection for young adults. Reflexes may be preserved in normal or mildly weak muscles. Some muscles of normal bulk may be very weak. The clinical picture of muscle wasting, fasciculations and cramps with preserved reflexes often suggests the diagnosis of motor neuron disease. However, clinical examination may show that the pattern of muscle weakness follows the distribution of individual nerves rather than a spinal segmental pattern, particularly in the early stages (Parry, 1993).

Diagnosis

Electrophysiological studies

The hallmark of this disorder is persistent localized motor conduction block. However the diagnosis of conduction block in these chronic neuropathies needs to be made with care as described under CIDP (Parry, 1993).

Conduction block in MMN is confined to motor axons and may occur at any level of the peripheral nervous system although proximal segments are frequently affected (Kaji et al., 1993). Conduction velocity through the blocked segments is usually markedly slowed and the proximal CMAP markedly dispersed. The distal motor latency is usually normal and the region of slowing within the nerve confined to a short segment (Krarup, 1990). Frequent, asynchronous fasciculations can often be recorded in affected muscles and signs of chronic partial denervation may be found in clinically unaffected muscles.

Antiganglioside antibodies

High levels of IgM anti GM-1 antibodies have been reported in 18–84% of patients in various series (Pestronk, 1991; Kornberg et al., 1994; Bouche et al., 1995). Most antibodies are polyclonal and recognize the Gal(beta 1–3)GalNac epitope shared by GM-1 and GD1b. However the role of these antibodies remains uncertain. Although GM-1 and other Gal(beta 1–3)GalNac bearing glycoproteins are located in the vicinity of the node of Ranvier, the application of GM-1 antibodies from humans or experimental animals to single ventral root nerve fibres in the rat did not cause conduction block or blockade of sodium channels (Hirota et al., 1997). This finding is contrary to previous studies in which human and rabbit sera containing GM-1 antibodies were injected intraneurally (Santoro et al., 1992; Arasaki et al., 1993).

Histology

Pathological examination of nerve biopsied from identified sites of conduction block showed thinly myelinated and demyelinated axons and small onion bulb formations (Auer et al., 1989; Kaji et al., 1993).

Therapy

No placebo-controlled trials of therapy in MMN have been published. However this disorder is a progressive one, and many open studies have shown benefit from intravenous immunoglobulin and cyclophosphamide. Patients do not benefit from plasma exchange or prednisone and may worsen when so treated. Intravenous immunoglobulin has been repeatedly shown to be beneficial although maintenance therapy is necessary. Initial therapy is 0.4 g/kg for 5 consecutive days. A maintenance dose of 0.4 g/kg should be given as necessary to maintain the improvement, but optimal frequency has not been determined (Nobile-Orazio et al., 1993; Chaudry et al., 1993; Van den Berg, 1995).

Cyclophosphamide may be given orally or intravenously, alone or following plasma exchange (Pestronk et

al., 1994). In a recent study of six patients treated with both cyclophosphamide and IVIg all patients improved and improvement was associated with reduction of antibody level and lessening of conduction block (Meucci et al., 1997). Patients required periodic immunoglobulin to maintain improvement, but after 3–7 months of cyclophosphamide (1–3 mg/kg/day) the interval between immunoglobulin doses could be progressively increased. Thus intravenous immunoglobulin can induce and maintain remission but does not eradicate the disease whereas cyclophosphamide may help to induce a sustained remission. Because of the significant side effects of cyclophosphamide it should be reserved for patients who require frequent immunoglobulin or are severely disabled.

Most recently Levine and Pestronk (1999) reported improvement in a small group of patients following the use of a B-cell (anti-CD 20) monoclonal antibody (Rituximab). Clinical improvement correlated with reduced levels of serum antibodies.

Neuropathies associated with monoclonal gammopathy

This group of neuropathies is characterized by the presence of monoclonal serum proteins, some of which react with components of the myelin sheath or axolemma. Although usually they are associated with monoclonal gammopathy of uncertain significance (MGUS) they may accompany or precede certain systemic malignancies including multiple myeloma, osteosclerotic myeloma, Waldenstrom's macroglobulinemia, Castlemann's disease, POEMS Syndrome, primary amyloidosis, cryoglobulinemia and lymphoma.

Peripheral neuropathy associated with MGUS

IgG paraproteins are considerably more common than IgM or IgA, but peripheral neuropathy is more frequently seen in IgM paraproteinemia (Gosselin et al., 1991). M proteins have been reported to occur with an incidence of 10% among patients with idiopathic neuropathy (Kelly et al., 1981); 6% of these patients had MGUS, 2.5% primary amyloid and 1.1% multiple myeloma and there was one patient each with Waldenstrom's macroglobulinemia and heavy chain disease.

Neuropathy associated with IgM paraproteinemia

Clinical features

Most cases present with a slowly progressive distal sensorimotor neuropathy that predominantly affects men in the sixth or seventh decade. The signs are those of a distal and symmetrical sensorimotor neuropathy in the majority although a purely sensory neuropathy is occasionally seen and a multifocal neuropathy has rarely been described. An upper limb postural tremor resembling essential tremor and ataxia are prominent features (Smith et al., 1983; Gosselin et al., 1991, Yeung et al., 1991). Relatively few patients become severely disabled. In a prospective study of 18 patients followed for up to 14 years only 2 were unable to walk within 10 years of symptom onset (Smith, 1994).

Laboratory investigations

The CSF protein level is often raised and monoclonal IgM and anti MAG antibodies may be found. The M protein is shown by serum electrophoresis or immunofixation. Antibodies reacting with myelin associated glycoprotein MAG (and associated epitopes) are found in about 50% of patients with IgM monoclonal gammopathy and about 70% of those with IgM MGUS (Nobile-Orazio, 1998). The IgM reactivity is directed to a carbohydrate moiety in MAG that is shared by other glycoconjugates in nerve including P0 and PMP22 glycoproteins, and the glycosphingolipids, sulphoglucuronyl lactosaminyl paragloboside (SGLPG) and sulphoglucuronyl paragloboside (SGPG). The epitope is closely related to the HNK-1 epitope expressed on human natural killer cells. Anti MAG antibodies are detected by ELISA or immunoblot (Nobile-Orazio, 1998).

Electrophysiology

Slowing of motor conduction velocity is found in most patients and characteristically there is a marked prolongation of distal latencies representing a pronounced distal accentuation of conduction slowing (Kaku et al., 1994).

Pathology

Sural nerve studies show nerve fibre loss without inflammatory infiltrates. On teased fibre examination segmental demyelination is prominent and tomacula may be found (Sanders et al., 2000). On electron microscopy widened myelin lamellae, most pronounced in the outer lamellae, may be evident (Fig. 67.5). This change presumably results from deposition of the M protein since it is particularly pronounced in paranodal regions and Schmidt/Lantermann incisures where the target antigen MAG is located (Trapp & Quarles, 1982). Direct immunofluorescence shows binding of IgM and complement to surviving myelin sheaths (Fig. 67.6).

The mechanism by which anti MAG antibodies cause demyelination has not been clearly defined but there is strong evidence for their pathogenicity. The antibodies are deposited where MAG is located; intraneural injection of

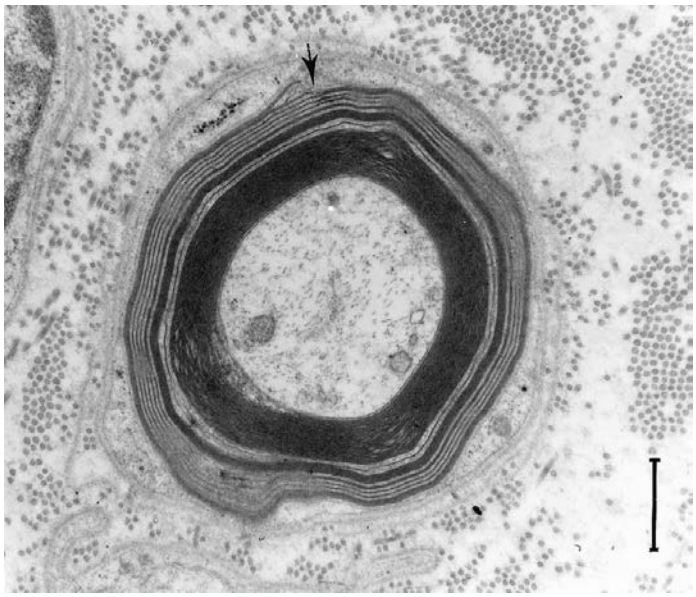

Fig. 67.5. Widened myelin lamellae in IgM paraprotein-associated neuropathy. An electron micrograph from a sural nerve biopsy specimen taken from a patient with high titre anti MAG antibodies. Note outer lamellae of myelin are widened (arrow). Bar = 5 μm.

the antibody causes focal demyelination. Passive transfer in the new born chick, in which blood–nerve barrier is defective has produced the electrophysiological and pathological features of the disease (Tatum, 1993).

Neuropathy associated with IgM paraproteins of non-MAG specificity

Less common paraproteins (polyclonal and monoclonal) react with GM-1 gangliosides causing a purely motor syndrome, multifocal motor neuropathy, discussed above. These antibodies mostly react with the terminal Gal (β1–3) GalNac structure. Other patients have antibodies with specificity for disialosyl groups on gangliosides GD1b, GT1b, GQ1b and related molecules and present with a chronic and progressive ataxic neuropathy. A subgroup of these patients develop ophthalmoplegia and the syndrome has been designated CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, M protein, agglutination and disialosyl antibodies). Purified antibody from such a patient bound to human dorsal roots and dorsal root ganglia and to femoral and oculomotor nerves (Jacobs et al., 1997b). GQ1b antibodies as found in the Miller Fisher syndrome may be responsible for sensory symptoms by virtue of their cross reactivity with other disialosyl moieties (O'Leary & Willison, 1997).

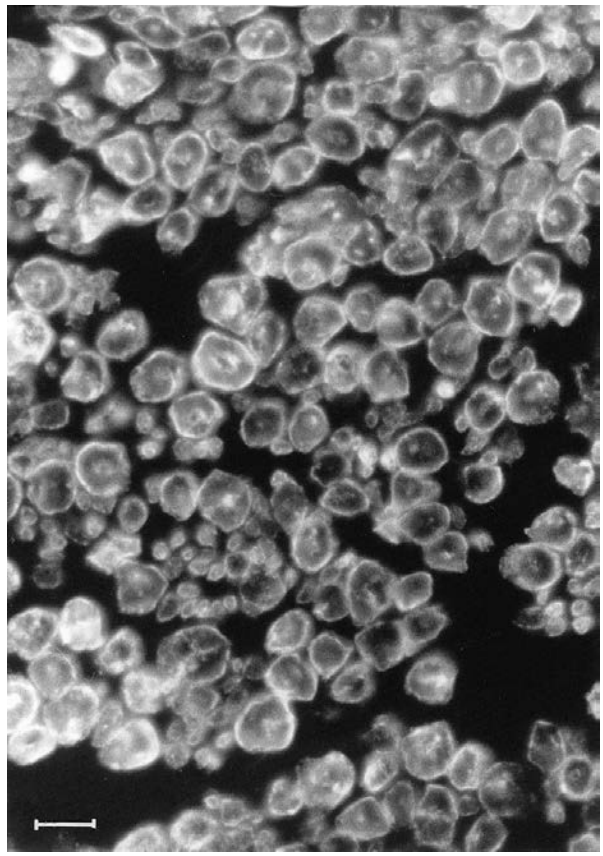

Fig. 67.6. Direct immunofluorescence showing binding of IgM to surviving myelin sheaths (arrow). Transverse section of sural nerve from a patient with IgM paraproteinemia. IgM is also evident within the perineurium (arrowhead). Bar = 20 μm.

In occasional patients paraproteins reacting with sulphatide and chondroitin sulphate are found. These patients have a chronic sensory neuropathy characterized by axonal degeneration (Sherman et al., 1983; Pestronk et al., 1991).

Neuropathy associated with IgG and IgA paraproteins

Neuropathy associated with IgG paraproteins is usually a sensorimotor neuropathy that may follow a progressive or relapsing course. Five cases described by Bleasel et al. (1993) were, in all respects apart from the paraprotein, similar to patients with CIDP. Mainly sensory neuropathies have been described (Gosselin et al., 1991; Yeung et al., 1991). Evidence for reactivity of the M protein to defined antigens is lacking in this group of patients. IgG reactivity to a neurofilament determinant was reported in

three patients with sensorimotor axonal neuropathy (Fazio et al., 1992).

Few cases of IgA paraprotein associated neuropathy have been reported and their clinical features have been similar to patients with IgG paraproteinemic neuropathy (Gosselin, 1991).

Treatment

Patients with IgG or IgA neuropathy respond to similar treatment regimes as used in CIDP; intravenous immunoglobulin, plasma exchange or immunosuppressive therapy (steroids with or without azathioprine, cyclosporin, cyclophosphamide) (Yeung et al., 1991; Pollard & Young, 1997). Treatment of IgM paraprotein-associated neuropathy is controversial. Improvement following plasma exchange has been reported in several uncontrolled trials, but not in one controlled trial (Yeung et al., 1991; Dyck et al., 1991; Kyle & Dyck, 1997; Gorson et al., 1998). Several uncontrolled studies have shown improvement when the IgM level is decreased by 50% but since IgM levels rapidly rise following plasma exchange, it needs to be accompanied by some form of immunosuppression. Chlorambucil and cyclophosphamide have been used successfully in open studies (Nobile-Orazio, 1998) and more recently fludarabine (Sherman et al., 1994) and rituximab, a monoclonal antibody directed against the B-cell surface marker CD20 (Levine & Pestronk, 1999).

Neuropathies associated with malignant plasma cell dyscrasias

There is no general agreement as to whether these neuropathies are autoimmune. Peripheral neuropathy occurs uncommonly in multiple myeloma. It is usually sensorimotor in type but purely sensory forms have been reported and relapsing and remitting forms occur. The presence of autonomic features in such patients may indicate the presence of systemic amyloidosis (Ropper & Gorson, 1998; Pollard & Young, 1997).

In patients with macroglobulinemia a sensorimotor neuropathy is frequently seen with features very similar to those described above for neuropathy with IgM paraproteinemia.

In contradistinction to the rarity of neuropathy complicating myeloma of the common osteolytic variety, in osteosclerotic myeloma a mainly motor demyelinating neuropathy is seen in almost half the patients. The neuropathy may be part of the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes). In addition to neuropathy, peripheral edema, hyperpigmentation and hypertrichosis are common. Gynecomastia, amenorrhea, impotence, testicular atrophy and finger clubbing may occur and ascites or pleural effusion are seen occasionally. Early weight loss is characteristic and facial lipoatrophy may be striking (Gherardi et al., 1994).

Reactivity of the M protein with myelin has not been firmly established in these patients. Increased serum levels of TNF-α have been reported in patients with POEMS and may be related to the weight loss (Gherardi et al., 1994). In addition IL-1 and IL-6 are increased and since both TNF-α and IL-1 have been implicated in increased vascular permeability within nerve, they may contribute to the neuropathy.

Stabilization or improvement of the neuropathy may be seen in half the patients who are treated. Treatment includes resection of solitary bone lesions, focused radiation or chemotherapy in patients with widespread lesions. Prednisone and melphalan or prednisone and cyclophosphamide have been shown to improve the neuropathy of some patients with POEMS (Nakanishi et al., 1984).

Vasculitic neuropathy

Vasculitic neuropathy results from ischemic nerve injury secondary to inflammatory cell infiltration of blood vessel walls and subsequent occlusion of those vessels. It occurs in association with systemic vasculitis or, less commonly, as an isolated vasculitis of peripheral nerve. In biopsy series of vasculitic neuropathy, the three most common diagnoses are polyarteritis nodosa, rheumatoid arthritis and isolated peripheral nerve vasculitis (Said et al., 1988; Kissel et al., 1985).

Neuropathy associated with systemic necrotizing vasculitis

Peripheral neuropathy is common in systemic vasculitis; it is seen in approximately 50% of patients with polyarteritis nodosa, Churg-Strauss vasculitis or rheumatoid vasculitis and in 10–20% of patients with Wegener's granulomatosis (Scott et al., 1981; Moore & Cupps, 1983; Cohen & Hurd, 1981; Guillevin et al., 1988). Sjögren's syndrome is associated with distal sensorimotor neuropathy, trigeminal sensory neuropathy and a sensory ataxic neuropathy or ganglionopathy. Vasculitis is seen in the majority of cases of distal sensorimotor neuropathy, the most common form (Mellgren et al., 1989). Vasculitic neuropathy also occurs in systemic lupus erythematosus (SLE) (Cohen & Hurd 1981; McCombe et al., 1987a), but probably represents a minority of SLE-associated neuropathies. Similarly, vasculitic

neuropathy can be seen with undifferentiated connective tissue disease, giant cell arteritis, and Behçet's syndrome.

Peripheral neuropathy is reported in 25–50% of patients with essential Type II (mixed) cryoglobulinemia, and nerve biopsy frequently shows evidence of vasculitis (Gemignani et al., 1992). Vasculitic neuropathy also occurs with secondary cryoglobulinemia, for instance, in association with hepatitis C infection.

Vasculitis secondary to malignancy, infection (including HIV) and serum sickness can also be complicated by vasculitic neuropathy and vasculitic neuropathy has recently been reported in association with chronic graft-vs.-host disease (Gabriel et al., 1999).

Isolated peripheral nerve vasculitis (non-systemic vasculitic neuropathy)

Vasculitis confined to the peripheral nerves represents 31–44% of cases of vasculitic neuropathy in biopsy series. The clinical features of the neuropathy are not different to those of the neuropathies associated with systemic vasculitis (Dyck et al., 1987) but clinical and laboratory evidence of systemic disease is lacking. The response to treatment and prognosis may be better than that of the systemic vasculitides (Kissel et al., 1985; Dyck et al., 1987; Said et al., 1988; Davies et al., 1996).

Clinical features

Vasculitic neuropathy characteristically has an acute or subacute onset. It may present across a wide age range, however it is more common in older patients, with the mean age at presentation in several series being in the vicinity of 60 years. The classical clinical picture of multiple mononeuropathies is seen in only 50–66% of patients, and it is important to note that up to one-quarter of patients present with a distal symmetric sensory or sensorimotor polyneuropathy. Most of the remaining patients present with an asymmetric polyneuropathy (Kissel et al., 1985; Said et al., 1988; Hawke et al., 1991; Chia et al., 1996). Rare patients have been described with an isolated small fibre sensory neuropathy associated with vasculitis (Lacomis et al., 1997). Local pain is a feature in 50–70% of patients. Although most patients have both sensory and motor disturbance, the sensory abnormalities are usually more extensive.

Electrodiagnostic studies

The characteristic findings are those of an axonal neuropathy: low amplitude sensory and compound muscle action potentials with preserved or only minimally reduced conduction velocities. Sensory nerve conduction is more often and more severely affected than motor. As with the clinical findings, the electrophysiological abnormalities may be multifocal, asymmetric or diffuse. There have been reports of conduction block in vasculitic neuropathy (Mohamed et al., 1998; Ropert & Metral, 1990) but the presence of widespread conduction block with relatively preserved distal compound muscle action potential amplitudes is more suggestive of an inflammatory demyelinating neuropathy. Needle electromyography typically shows evidence of denervation (positive sharp waves and fibrillation potentials) in muscles supplied by affected nerves. In the systemic vasculitides, peripheral neuropathy is more common than is suggested by clinical examination alone, and electrodiagnostic studies are helpful in detecting subclinical neuropathy.

Laboratory investigations

Non-specific markers of inflammation such as the erythrocyte sedimentation rate (ESR) are often elevated. Kissel et al. (1985) found a moderately elevated ESR in 88% of patients with vasculitic neuropathy, with no difference between isolated nerve vasculitis and cases with underlying vasculitis or connective tissue disease. In our patients with isolated peripheral nerve vasculitis, 63% had mild to moderate elevation of the ESR, antinuclear antibodies were present (in low titre) in only 20% and rheumatoid factor was positive in less than 10% (Davies et al., 1996). In patients with systemic vasculitis, laboratory findings largely reflect the underlying disease.

Pathology

The dominant finding in nerve biopsies is axonal degeneration. The degree of involvement may vary between fascicles or there may be segmental loss of fibres within individual fascicles. The diagnostic features of active vasculitis are a transmural inflammatory cell infiltrate with associated segmental necrosis of the blood vessel wall. The internal elastic lamina of the vessels is disrupted. The presence of perivascular inflammatory infiltrates in association with active axonal degeneration, especially with intra- or interfascicular variation or with all fibres at the same stage of degeneration consistent with a 'point source' insult, is suggestive of vasculitis, but inflammatory cell invasion and necrosis of the vessel wall is required for a firm pathological diagnosis. The vasculitic process most commonly involves epineurial and, to a lesser extent, perineurial vessels. Occlusion of the vessel lumen, some-

times with recanalization and evidence of hemorrhage, may also be seen. Subperineurial edema is often prominent in the acute phase. Healed vasculitis may appear as concentric fibrous scarring and intramural thickening of the vessel wall. In patients with a suspected vasculitic neuropathy, performing both nerve and muscle biopsy may increase the diagnostic yield (Hattori et al., 1999; Said et al., 1988).

Pathogenesis

The eventual cause of vasculitic neuropathy is occlusion of the vasa nervorum, leading to nerve ischemia and consequent axonal degeneration. The pathogenesis of the inflammatory vascular lesion is not fully elucidated, but there is evidence that both cellular and humoral mechanisms are involved. Deposition of immunoglobulin and complement in vessel walls is a frequent finding, and the fact that these deposits are evident only in vessels with inflammatory cell infiltration does suggest a role for immune complexes in the pathogenesis of the vascular lesions (Kissel et al., 1989; Hawke et al., 1991).

Treatment and prognosis

There are no large scale studies of the treatment of vasculitic neuropathy. Most series have reported the results of variable regimens of prednisone alone or in combination with other immunosuppressive agents, most frequently azathioprine or cyclophosphamide. The results of treatment are somewhat variable from series to series. Kissel et al. (1985) reported a moderate to substantial improvements in 75% of patients; 20% of these subsequently developed a remitting relapsing course; a significant proportion of these patients had isolated peripheral nerve vasculitis. On the other hand, Hawke et al. (1991) showed a 5-year survival rate of only 37% for a mixed group of patients with vasculitic neuropathy predominantly in association with systemic vasculitis. A favourable response is reported in 43–53% of patients with vasculitic neuropathy associated with Churg–Strauss or rheumatoid vasculitis, but one-third of those surviving 5 years had moderate sensorimotor sequelae (Hattori et al., 1999; Puéchal et al., 1995). Evidence of more systemic organ damage and increased age are consistently associated with poor outcome.

The prognosis appears to be better for isolated peripheral nerve vasculitis. In the series reported by Davies et al. (1996) and treated with steroids alone or in combination with azathioprine or cyclophosphamide, 24 of 25 patients had survived at a mean of 3.4 years follow-up and 20 of 23 patients were ambulant without walking aids. Thirty per cent of patients had at least one relapse, which is not dissimilar to the rate reported by Kissel et al. (1985).

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68

Hereditary neuropathies

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The hereditary neuropathies consist of a large group of conditions that for descriptive purposes are conveniently separable into the hereditary motor and sensory neuropathies, the hereditary sensory and autonomic neuropathies and conditions in which the neuropathy is associated with a generalized metabolic disorder. The hereditary motor neuropathies (spinal muscular atrophies) are discussed elsewhere (see Chapters 116, 117).

Hereditary motor and sensory neuropathies

The hereditary motor and sensory neuropathies comprise a miscellaneous group of disorders in which a number of different clinical patterns are recognizable. Broadly speaking, these are the Charcot–Marie–Tooth (CMT) syndrome, Dejerine–Sottas disease (DSD) and congenital hypomyelination neuropathy (CHN) (Reilly, 2000). In addition, there are two examples of inherited recurrent neuropathy, namely hereditary neuropathy with liability to pressure palsies (HNPP) and hereditary neuralgic amyotrophy (HNA) and a number of other rare but important more complex disorders that deserve consideration.

Charcot–Marie–Tooth disease

Charcot–Marie–Tooth (CMT) disease is divisible into three categories, in two of which, types 1 and 2, the inheritance is autosomal and in the third it is X-linked. CMT disease is the commonest inherited neuropathy with a prevalence of about 20–40 : 100 000 (Dyck et al., 1993).

Charcot–Marie–Tooth disease type 1

CMT1 or type 1 hereditary motor and sensory neuropathy (HMSN I) usually begins in the first decade of life, less often in the second and rarely at later ages. The onset is commonly with difficulty in walking or foot deformity with later involvement of the upper limbs. Variable disability develops during childhood and adolescence following which deterioration is slow or sometimes negligible. Inheritance is most frequently of autosomal dominant pattern, less often autosomal recessive. In dominantly inherited families clinical severity is highly variable (Thomas et al., 1997). Some heterozygous gene carriers may be asymptomatic and others may just display foot deformity. The characteristic clinical features are distal muscle wasting and weakness in the limbs giving rise to a 'stork leg' appearance accompanied by atrophy of the small hand muscles. Patients with prominent upper limb postural tremor have been referred to as the Roussy–Lévy syndrome. The distal lower limb weakness gives rise to a drop-foot gait. There is usually accompanying distal sensory loss in the limbs which may affect all modalities, and tendon areflexia. Most patients remain ambulant but rarely they can become wheelchair bound. Diaphragmatic weakness sometimes develops. The peripheral nerves may be enlarged. Associated skeletal deformity is frequent, usually pes cavus or pes equinovarus, clawing of the toes and claw hand, and occasionally kyphoscoliosis.

Motor nerve conduction velocity is characteristically reduced, to less than 38 m/s in the upper limbs, and sensory nerve action potentials are absent. Nerve biopsy shows evidence of axonal loss and widespread demyelination. There are hypertrophic 'onion bulb' changes (Fig. 68.1) consisting of the circumferential proliferation of Schwann cells around axons related to repeated cycles of demyelination and remyelination (Thomas et al., 1997).

Inheritance is usually autosomal dominant. In the majority the disorder is due to a 1.5 megabase duplication on chromosome 17p11.2 – p12 leading to the presence of an extra copy of the gene for peripheral myelin protein 22 (*PMP22*). Such cases are referred to as CMT1A (or HMSN

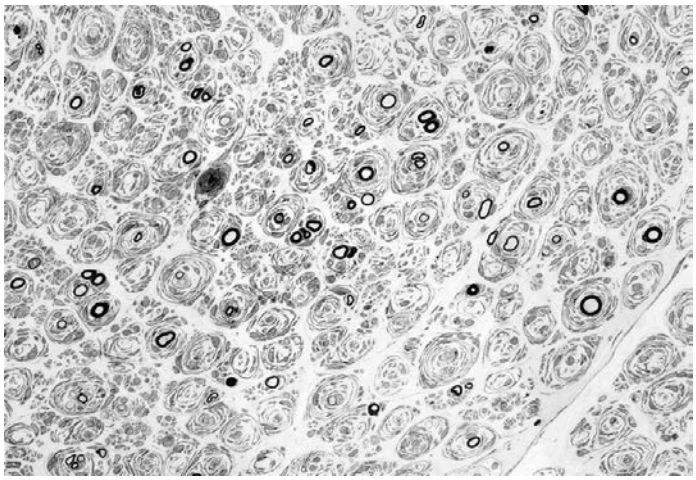

Fig. 68.1. Transverse section of sural nerve biopsy, from cases of CMT1A showing profuse concentric Schwann cell proliferation ('onion bulbs') and a severe loss of myelinated nerve fibres. Thionin and acridine orange stain. ×400.

Ia). The duplication is flanked by a repeat sequence, 17–29 kb in length, termed CMT1A-REP. The duplications appear to arise from misalignment of the distal repeat during meiosis and are usually of paternal origin (Keller & Chance, 1999). Rarely the cause of CMT1A is a point mutation in the *PMP22* gene. PMP22 is a relatively minor component of myelin, the function of which is not yet established. It may have a role both during the early stages of myelination and in the maintenance of compact myelin.

In patients with a chromosome 17p11.2 duplication myelin sheath thickness is initially excessive for axon diameter. This is associated with overexpression of the *PMP22* gene, as assessed by the *PMP22* mRNA content in Schwann cells on nerve biopsy (Vallat et al., 1996). From observations on transgenic mice with extra copies of the *PMP22* gene, it has been established that overexpression of *PMP22* results in demyelination, but what leads to the axonal loss that is the main cause of disability in CMT1A is so far uncertain. Active demyelination tends to be confined to childhood (Gabreëls-Festen et al., 1992) and this is succeeded by axonal loss. Cases with point mutations in the *PMP22* gene are usually more severely affected and nerve biopsy shows hypomyelination rather than hypermyelination (Gabreëls-Festen et al., 1995).

Less commonly, type 1 CMT disease is the result of mutations in the gene for myelin protein zero (P_0, MPZ) (Hayasaka et al., 1993). MPZ is the major myelin structural protein. It is a 30 kDa protein and a member of the immunoglobulin superfamily. It has transmembrane, extracellular and cytoplasmic domains and is probably involved in homophilic interactions between adjacent myelin lamellae and thus controls myelin periodicity. CMT disease related to MPZ mutations is categorized as CMT1B (HMSNIb). The clinical features closely resemble those of CMT1A. The original Roussy–Lévy family has been shown to have CMT1B, but this phenotype can also be a manifestation of CMT1A.

Rarely mutations in the *early growth response 2* (*EGR2/Krox 20*) gene are responsible for a CMT phenotype (Warner et al., 1998). This gene is located on chromosome 10q23 and codes for a protein with a zinc finger domain.

Type I HMSN or CMT1 disease can also be of autosomal recessive inheritance. These disorders are designated CMT4 in the gene-mapping literature. Several different entities have now been identified (Reilly, 2000; Thomas, 2000). A severe sensorimotor neuropathy with an onset in early childhood, has been mapped to chromosome 8q13–21.1. Pathologically the peripheral nerves show hypomyelination and multiple basal laminal onion bulbs, i.e. the central axons are surrounded not by circumferential Schwann cell processes but by concentric double layers of empty basal laminae. Another disorder, mapped to chromosome 5q23–33, again begins in early childhood. Scoliosis is a prominent feature. It is again characterized pathologically by hypomyelination and basal laminal onion bulbs but also by elongated processes extending from the Schwann cells of both myelinated and unmyelinated fibres. A further recessive demyelinating neuropathy identified in a Lebanese kindred has been linked to chromosome 19q13.1–13.3.

Hereditary neuropathy with focally folded myelin is distinguished by the presence of demyelination accompanied by multiple regions where the myelin sheath is thrown into complex folds (Fig. 68.2), either from the external aspect of the sheath or protruding into the axon (Ohnishi et al., 1989). Clinically these patients have a severe early onset sensorimotor neuropathy with involvement of the masticatory, facial and bulbar muscles and also the diaphragm. This disorder is genetically heterogeneous. In some families that have been linked to chromosome 11q23, there are mutations in the *myotubularin related protein 2* (*MTMR2*) gene (Bolino et al., 2000). They have been categorized as CMT4B1. Other families (CMT4B2) have been linked to chromosome 11p15. Although designated as CMT disease, the clinical phenotype, with severe involvement and an early onset, more closely resembles Dejerine–Sottas disease.

Hereditary motor and sensory neuropathy Lom (HMSNL), a disorder recognized in Balkan gypsies and named after the Bulgarian city Lom, combines a severe CMT phenotype with deafness. It has been shown to be due to mutation in the *N-myc downstream regulated gene 1*

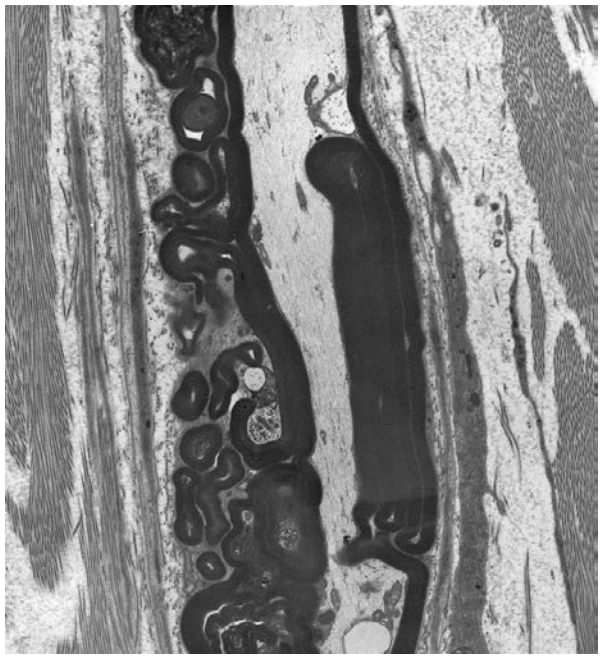

Fig. 68.2. Electron micrograph of longitudinal section through a myelinated nerve fibre showing multiple folds of the myelin sheath both outwards and into the axon. ×5000.

(NDRG1) on chromosome 8q24. NDRG1 is a signalling protein involved in growth arrest and terminal cell differentiation but its role in myelination and axon maintenance is not yet understood.

Charcot–Marie–Tooth disease type 2

CMT2 (HMSN II) shows similar clinical features to those of CMT1 but onset tends to be later, being most often in the second decade and sometimes delayed until late life. Upper limb involvement, the degree of sensory loss and the occurrence of skeletal deformity are less pronounced. Motor nerve conduction velocity is either within normal limits or only mildly reduced. The underlying pathology is an axonopathy of dying-back type in which the axons initially degenerate distally, this progressing proximally towards the cell bodies. Onion bulbs are not present. Inheritance is usually autosomal dominant or rarely autosomal recessive. Three loci for dominantly inherited CMT2 disease have been established, mapping to chromosomes 1p35–36 (CMT2A), 3q13–q22 (CMT2B) and 7p14 (CMT2D). (Reilly, 2000). CMT2B tends to have prominent sensory loss which may lead to a mutilating acropathy, resulting in a phenotypic overlap with type 1 hereditary sensory neuropathy. CMT2C is clinically distinct, the presentation being with vocal cord and diaphragmatic paralysis. It has not yet been localized. A further autosomal dominant disorder with a proximal distribution has been mapped to chromosome 3q13.1. CMT2 can also be the result of mutations in the neurofilament light gene on chromosome 8q24. Occasionally *MPZ* mutations produce a CMT2 phenotype.

Autosomal recessive forms of CMT2 are less well characterized. Onset tends to be in childhood, leading to severe disability (Gabreëls-Festen et al., 1991). One form has been mapped to chromosome 1q21.2–21.3. An X-linked variety associated with deafness also exists.

'Complex' CMT disease

A number of so far poorly characterized disorders combine a CMT phenotype with additional neurological features. These include pyramidal signs (Dyck et al., 1993), optic atrophy (Vizioli type), deafness, optic atrophy and deafness (Rosenberg & Chutorian type) and pigmentary retinopathy (Massion–Verniory disease).

X-linked Charcot–Marie–Tooth disease

CMTX (or HMSNX) produces a similar phenotype to that of CMT1 in males. Carrier females are asymptomatic or less severely affected (Hahn et al., 1990). Motor nerve conduction velocity tends to be intermediate between that of CMT1 and CMT2. Nerve biopsy demonstrates axonal loss with some associated demyelination (Hahn et al., 1990).

The disorder has been shown to be due to mutations in the gene for connexin 32 (Bergoffen et al., 1993). This is a gap junction protein present in Schwann cells at the nodes of Ranvier and Schmidt-Lanterman incisures. It may provide communication between the compartments of the Schwann cell on either side of the myelin sheath.

Dejerine–Sottas disease (DSD)

DSD is genetically heterogeneous. It has been defined as a mixed motor and sensory neuropathy of congenital or childhood onset. Motor milestones are delayed and disease progression leads to severe disability, often with prominent foot and spinal deformities. The peripheral nerves may be enlarged. Motor nerve conduction velocity is markedly reduced, to less than 10 m/s, and sensory nerve action potentials are absent. Nerve biopsy demonstrates chronic demyelination with hypertrophic changes and also hypomyelination so that myelin sheaths are consistently of reduced thickness.

DSD, or type III HMSN, was initially thought to be of autosomal recessive inheritance. Most cases are now known to represent new dominant mutations in the *PMP22* (DSDA) or *MPZ* (DSDB) (Tyson et al., 1997) genes or sometimes in the *EGR2* gene (Warner et al., 1998).

Congenital hypomyelination

This is an uncommon type of neuropathy. Affected children present with hypotonic weakness at birth and show generalized hyporeflexia. They have markedly delayed motor development and remain severely disabled, often with skeletal deformities. It is difficult or impossible to obtain motor responses on nerve stimulation because of a high electrical threshold but if motor conduction velocity is recordable it is very severely reduced at 1–2 m/s. Sensory nerve action potentials are unobtainable. Nerve biopsy shows hypomyelination with extremely thin myelin sheaths or a total lack of myelin. The disorder is genetically heterogeneous and may result from *PMP22, MPZ* or *EGR2* gene mutations (Warner et al., 1998), or from other so far undiscovered mutations. EGR2 has been shown to be involved in the early stages of enwrapment of axons by Schwann cells (Topilko et al., 1994).

Inherited recurrent neuropathies

Hereditary neuropathy with liability to pressure palsies

HNPP is characterized by the occurrence of repeated focal nerve lesions related to external compression or to nerve damage at the common entrapment sites. Painless acute lesions affecting the brachial plexus may occur. Individual lesions usually improve but not always fully so that the patient may gradually acquire persisting neurological deficits. Sometimes a distal neuropathy with a CMT-like phenotype of gradual onset is encountered. Nerve conduction studies, in addition to confirming focal lesions, may or may not demonstrate the presence of a generalized neuropathy. Nerve biopsy shows evidence of widespread demyelination together with multiple focal myelin thickenings referred to as tomacula (tomaculum = sausage in Latin) (Madrid & Bradley, 1975).

The disorder is of autosomal dominant inheritance. Most cases are related to a deletion on chromosome 17p11.2–p12 so that this is a reciprocal of CMT1A with a duplication. *PMP22* gene expression is reduced in Schwann cells (Vallat et al., 1996). Occasionally there is a point mutation in the *PMP22* gene or a mutation at another undiscovered locus.

Hereditary neuralgic amyotrophy

The clinical features in this autosomal dominant disorder are very similar to those encountered in sporadic cases (see pp. xx-xx) but multiple episodes tend to be encountered more frequently and in some families dysmorphic facial features with hypotelorism have been described. The disorder has been mapped to chromosome 17q25 (Pellegrino et al., 1996), but it is probably genetically heterogeneous.

Hereditary sensory and autonomic neuropathies

This is a miscellaneous group of disorders (Dyck, 1993), most examples of which show a predominant sensory neuropathy, sometimes associated with minor motor and varying degrees of autonomic involvement. One example, familial dysautonomia or the Riley–Day syndrome, is characterized both by a sensory neuropathy and by prominent autonomic dysfunction.

Hereditary sensory neuropathies

Type I hereditary sensory neuropathy (HSN I) is an autosomal dominant disorder that has been mapped to chromosome 9q22.1–22.3 (Nicholson et al., 1996). Onset of symptoms is most commonly in the second or third decades and usually begins with painless foot ulceration although spontaneous neuropathic pain may be a feature. Examination reveals distal sensory loss mainly affecting pain and temperature sensibility which is more prominent in the lower limbs. Minor distal motor involvement may be evident and also slight distal anhidrosis. Other autonomic dysfunction is not seen. The disorder is slowly progressive and may lead to the development of neuropathic joint degeneration and to secondary osteomyelitis following chronic foot ulceration. Nerve biopsy shows depletion of unmyelinated axons and a predominant loss of small myelinated fibres. A genetically distinct variant presents with familial 'burning feet' in midlife.

Type II hereditary sensory neuropathy (HSN II) is of congenital or early childhood onset. There is a distal loss of all sensory modalities, often leading to a pronounced mutilating acropathy in all four limbs. Again, there is only minor motor and autonomic involvement. Nerve biopsy shows a severe loss of myelinated fibres of all sizes and also of unmyelinated axons (Ohta et al., 1973). The disorder is of autosomal recessive inheritance.

A further syndrome is congenital insensitivity to pain with anhidrosis (CIPA) which is again of autosomal recessive inheritance. It has been shown to be due to mutations in the gene for TRKA, the high affinity nerve growth factor receptor (Masdy et al., 1999). Onset is congenital or in early infancy with episodes of fever related to high ambient temperature. There is loss for pain and temperature sensibility which leads to a distal acropathy. Self mutilation may be observed. There is also widespread anhidrosis. Affected children may be of reduced intelligence. Pathologically

there is a predominant loss of small myelinated axons and a virtually total absence of unmyelinated axons.

Hereditary sensory neuropathy with selective loss of small myelinated nerve fibres resembles CIPA (Dyck, 1993). It consists of a sensory neuropathy selectively affecting pain and temperature sensibility, together with widespread anhidrosis leading to a mutilating acopathy and sometimes keratitis. Nerve biopsy shows a predominant loss of small myelinated nerve fibres and relative preservation of unmyelinated axons.

Familial dysautonomia

Familial dysautonomia or the Riley–Day syndrome (Dyck, 1993) is of autosomal recessive inheritance and has been mapped to chromosome 9q31–33. It is most commonly encountered in individuals of Ashkenazi Jewish descent. Onset is in infancy with poor feeding, repeated episodes of vomiting, pulmonary infections and failure to thrive. Autonomic dysfunction becomes evident early in life with alacrimia, skin blotching, defective temperature control and labile blood pressure. Prolonged respiratory depression after anesthesia may be encountered. Bladder function is preserved but disorders of esophageal and gastric motility may be demonstrable, as may megacolon. Fungiform papillae on the tongue are absent. There is evidence of widespread reduced pain appreciation including corneal ulceration. Visual impairment and optic atrophy may be present. Growth is impaired and affected children remain of small stature, often with kyphoscoliosis. Intellectual development is probably unaffected.

Neuropathological studies have shown loss of autonomic neurons in autopsied cases and of unmyelinated axons on nerve biopsy.

Inherited motor and sensory neuropathies with multisystem involvement

This group of rare hereditary motor and sensory neuropathies comprises disorders in which the neuropathy is accompanied by characteristic abnormalities affecting other systems.

Giant axonal neuropathy

Giant axonal neuropathy is of autosomal recessive inheritance and has been mapped to chromosome 16q24.1. Onset is in childhood with a slowly progressive distally-accentuated neuropathy which is predominantly motor in type. There are accompanying CNS features including ataxia, nystagmus and mild signs of corticospinal tract dysfunction. A high proportion of the affected children have abnormally curly hair (Fig. 68.3). Nerve conduction studies demonstrate an axonopathy with reduced or absent sensory action potentials. Pathologically the peripheral nerves show axonal loss with multiple focal axonal swellings packed with accumulations of neurofilaments and associated with secondary demyelination. The precise mechanism of the neurofilamentous accumulations has not been established but there appears to be a generalized disorder of intermediate filaments. Mutations of the gene for the cytoskeletal protein gigaxonin have recently been described.

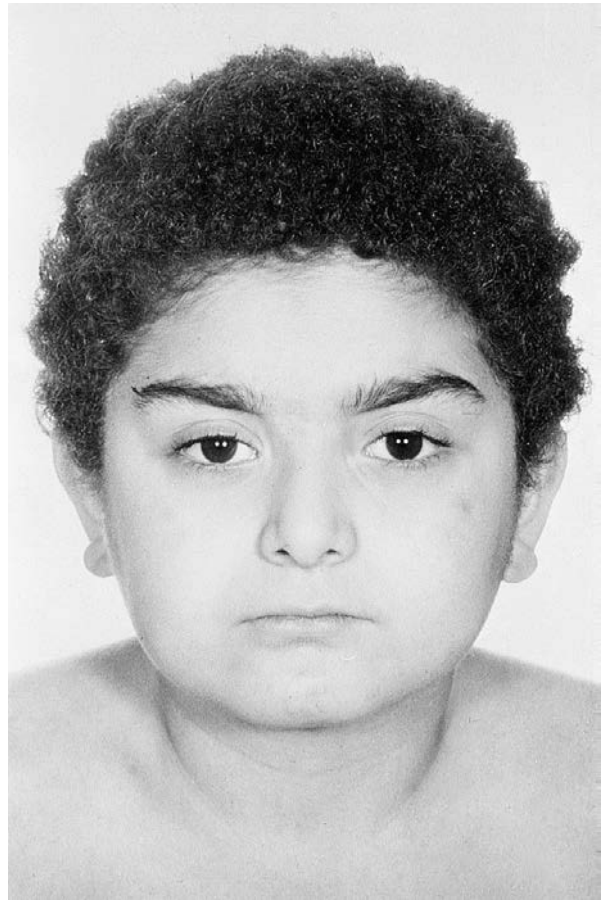

Fig. 68.3. Child aged 9 years with giant axonal neuropathy showing curly hair.

Multiple endocrine neoplasia type 2B

MEN 2B is a complex disorder characterized by the combination of medullary carcinoma of the thyroid, pheochromocytoma, ligamentous laxity and a marfanoid habitus. The disorder is of autosomal dominant inheritance. Peripheral nerve involvement (Dyck et al., 1993) mainly affects the autonomic nervous system and has been referred to as

ganglioneuromatosis. There is a non-neoplastic proliferation of nerves and ganglion cells leading to multiple nodular swellings on the lips, tongue, buccal mucosa, palate and alimentary tract including the salivary glands, pancreas and gall bladder. A variety of gastrointestinal symptoms occur, such as vomiting, diarrhea, constipation, megacolon and dilation of the small intestine and stomach. The somatic nerves are less affected but limb weakness may be present.

MEN2B is a neurocristopathy related to mutations in the RET proto-oncogene. These result in a gain of function leading to constitutive activation of the receptor.

Andermann's syndrome: agenesis of the corpus callosum and neuropathy

Confined to French Canadian families from Quebec, this autosomal recessive disorder combines mental retardation, dysmorphism, and agenesis of the corpus callosum with a progressive axonal sensorimotor neuropathy. The neuropathy can occur in the absence of callosal agenesis. The disorder has been mapped to chromosome 15q13–q15.

Multiple symmetric lipomatosis

Otherwise known as Madelung's disease, many individuals with this disorder develop a progressive distal sensorimotor neuropathy of axonal type (Enzi et al., 1985). The disease is characterized by the presence of a massive rufflike lipoma of the neck together with symmetric lipomas over the shoulders, trunk and proximal limbs. The inheritance is probably autosomal recessive. The disorder may involve disturbed mitochondrial function.

Chédiak–Higashi disease

This autosomal recessive disorder has an onset in childhood with partial oculocutaneous albinism associated with giant melanosomes. Giant peroxidose-positive lysosomes are found in leukocytes. There is defective hair pigmentation, anemia, leukopenia, thrombocytopenia and a liability to lymphoreticular malignancy. Mental retardation, a distal sensorimotor axonal neuropathy or a syndrome resembling a spinocerebellar degeneration, may be accompanying features.

Congenital cataracts facial dysmorphism neuropathy (CCFDN) syndrome

The CCFDN syndrome is a complex autosomal recessive disorder, so far only identified in gypsies. It combines congenital cataracts, a characteristic facial dysmorphism, small stature, moderate mental retardation and hypogonadotrophic hypogonadism with a progressive distal sensorimotor neuropathy. Some patients also show evidence of corticospinal tract dysfunction, mild ataxia and chorea. The disorder has been mapped to chromosome 18qter.

Treatment of CMT and HSN

Treatment for the hereditary motor and sensory neuropathies should include regular neurological or orthopedic supervision during childhood and adolescence for cases with an early onset in an attempt to prevent the development of skeletal deformity. Orthoses to compensate for foot drop may be required as may orthopedic procedures to correct foot deformity or scoliosis, or to improve foot drop or manual dexterity by tendon transfer procedures. Patients with HNPP should be advised to avoid athletic or other activities that would put their peripheral nerves at risk.

The commonest inherited neuropathy is CMT1A, due to a duplication on chromosome 17p11.2–p12. As already stated, this has been shown to result in overexpression of the *PMP22* gene. Definitive treatment will therefore require reducing the expression of this gene. Progress in this direction has been achieved in a transgenic mouse model of CMT1A in which extra copies of the *PMP22* gene are introduced into the mouse genome. This leads to a demyelinating neuropathy in which the severity of the neuropathy is related to the number of copies of the transgenes. To explore the possibility of treatment, a conditional mouse model has been developed in which the *PMP22* transgenes are under the control of a tetracycline-responsive promoter. It has been shown that turning off the expression of the transgenes can prevent the development of the neuropathy and improve established neuropathy (Perea et al., 1999), providing encouragement for the further development of this approach.

In the demyelinating forms of CMT disease, disability is not the direct result of demyelination but of associated axonal loss. Any effective treatment must therefore prevent this axonal loss. There are indications that the loss may be secondary to lack of growth factor support from Schwann cells. A possible treatment approach would therefore be the delivery of growth factors to the axons.

Occasional patients with HMSN may develop an abrupt deterioration and are improved by treatment with corticosteroids or intravenous immunoglobulin. It is likely that such cases represent superimposed chronic inflammatory demyelinating polyneuropathy (CIDP) as a secondary immunological reaction.

In the hereditary sensory neuropathies, education is required to avoid the development of foot ulceration. This includes the provision of suitable footwear and the avoid-

ance of walking on sharp objects or hot surfaces. Appropriate medication may be required for neuropathic pain.

Neuropathies related to generalized metabolic disorders

Familial amyloid polyneuropathy

The amyloidoses are a group of disorders characterized by the deposition of a fibrillar protein with an abundant β-pleated structure in the extracellular space. There are many different proteins that can form amyloid and it is the individual constituent protein that defines the disease. The hereditary peripheral nervous system amyloidoses are called the familial amyloid polyneuropathies (FAP). FAP is classified into three different types based on the constituent fibril protein. The first description of FAP was by Andrade in 1953 when he described an autosomal dominant disorder, characterized by a small fibre neuropathy with autonomic involvement and variable cardiac dysfunction, in a group of Portuguese kindreds (Andrade, 1952). Subsequently the constituent fibril protein for this type of FAP was shown to be transthyretin, previously known as prealbumin (TTR-related FAP). FAP can also occur secondary to apolipoprotein A-1 (apolipoprotein A-1 related FAP) and to gelsolin (gelsolin-related FAP) mutations.

TTR is the product of a single gene on chromosome 18q11.2–q12.1, containing four exons coding for a 127 amino acid mature protein and an 18 residue signal peptide. To date, there have been at least 80 point mutations and one trinucleotide deletion identified in exons 2, 3 and 4 of the TTR gene (Planté-Bordeneuve & Said, 2000), most of which are associated with FAP. The TTR mutations usually exist in the heterozygous state and are inherited in an autosomal dominant manner. The Met 30 mutation is the commonest, accounting for all the original Portuguese cases and other large clusters of the disease in Sweden and Japan and also more recently described in association with FAP in many different countries. Haplotype studies have confirmed multiple founders for this mutation. Although the actual mechanisms whereby TTR mutations lead to the formation of amyloid are not clearly understood, the amyloidogenic potential of TTR is presumed to be partly due to its extensive ß-pleated structure. There is also evidence that mutations in TTR may make conditions more favourable to form an amyloidogenic intermediate.

The clinical features of TTR-related FAP are best described for the TTR Met 30 mutation. The cardinal feature is a length-dependent sensory and motor neuropathy that usually starts in the lower limbs and in the small fibres. The neuropathy eventually progresses to affect all sensory and motor modalities. Autonomic involvement can be very severe and can occur early in the course of the disease. Other features include cardiomyopathy and vitreous deposits. Recently, a few TTR mutations have been shown to present rarely with a central nervous system syndrome, oculoleptomeningeal amyloidosis (OLMA), clinically characterized by vitreous deposits, strokes, progressive dementia, ataxia and hydrocephalus (Brett et al., 1999). Careful genotype–phenotype studies have failed to demonstrate a direct phenotype correlation with any particular mutation although certain mutations, e.g. TTR Ser 84 and TTR His 58, tend to present with upper limb involvement and others, e.g. TTR Ala 60, with cardiac involvement. It is not understood why TTR is deposited in peripheral nerves or how it causes a neuropathy. Transgenic mice have so far failed to answer these questions. Amyloid deposits can be found in any part of the peripheral nervous system including nerve trunks, plexuses, and the sensory and autonomic ganglia and are most commonly found around blood vessels. The neuropathy is an axonal neuropathy and the amyloid deposits are often localized and patchy. Unmyelinated and small myelinated fibres are lost first followed later by the large myelinated fibres.

The diagnosis of FAP relies on a high level of clinical suspicion. Amyloid can be diagnosed on a biopsy from nerve, heart, rectum or other tissues, depending on the clinical presentation. The most widely used technique is a combination of alkaline congo red and polarizing filters to demonstrate the characteristic apple green birefringence. The constituent fibril protein can be identified by immunohistochemistry, although this technique is not completely reliable. Molecular diagnosis has benefited this area enormously with most mutations being detected either by using polymerase chain reaction (PCR) related techniques or by methods used for mutation screening or direct sequencing. The extent of the systemic deposits (excluding the nervous system) can be ascertained using scintigraphic studies with ^{123}iodine labelled serum amyloid protein (SAP).

Until the 1990s symptomatic treatments (e.g. pacemakers) and rehabilitative measures were the only treatments available for FAP and still remain important. Liver transplantation was first considered as 90% of TTR is synthesized in the liver. This procedure was first performed in 1990 and is now available in most large centres dealing with this condition. The biochemical effect of liver transplantation is good, as demonstrated by a dramatic

reduction in variant TTR in plasma and scintigraphic evidence of reduced amyloid deposits postoperatively (Holmgren et al., 1993). The general well being, gastrointestinal symptoms, autonomic symptoms and nutritional state are generally reported to improve. The sensory motor and autonomic neuropathy usually stops or slows its rate of deterioration and a recent study has shown a lower rate of myelinated axon loss postoperatively compared to non-transplanted patients. The cardiomyopathy, especially in non-Met 30 TTR mutations can progress postoperatively. The global mortality (in first 6 months postoperatively) for liver transplantation in TTR-related FAP is 20% and is mainly related to autonomic involvement, cardiac complications, infections and organ rejection (Planté-Bordeneuve et al., 2000). The length of disease preoperatively, the nutritional status of the patient, the severity of the autonomic involvement and comorbidities are important factors in the outcome. It is not known if the different TTR mutations respond differently to this treatment as most of the experience is with TTR Met 30. Liver transplantation is accepted to be the only effective treatment for TTR-related FAP at present. Life expectancy with TTR-related FAP without a transplant is about 10 years. The estimated 5-year survival rate in recent studies in patients after transplantation is 60%. The timing of the transplant should be early in the course of the disease and research is ongoing to see if there are other factors to help select the best candidates and reduce mortality. Treatments that might prevent amyloid deposition are also being investigated.

Apolipoprotein A-1-related FAP

This type of FAP is associated with deposition of a variant of apolipoprotein A-1 in which there is an arginine for glycine substitution at position 26. It has only been described in one kindred from Iowa (Van Allen et al., 1969) and the phenotype is similar to FAP TTR Met 30 except for a higher incidence of renal amyloidosis and gastric ulcers.

Gelsolin-related FAP

Gelsolin-related FAP was first described in a Finnish kindred in 1969 (Meretoja, 1969) and it is still most commonly seen in Finland but has been identified in other countries including the Netherlands, Japan and Czechoslovakia. It usually presents with a corneal lattice dystrophy in the fourth decade followed later by a progressive cranial neuropathy and a mild sensory and autonomic neuropathy. The constituent fibril protein for this type of FAP is an abnormal fragment of gelsolin. The gene for gelsolin is on chromosome 9 and two point mutations in the gene have been associated with this type of FAP, asparagine for aspartic acid at residue 187 and tyrosine for aspartic acid also at position 187.

Porphyria

The porphyrias are a heterogeneous group of disorders caused by a disruption of heme biosynthesis and are a rare cause of peripheral neuropathy. Heme is synthesized in the liver and bone marrow but neuropathy is only encountered with disorders of liver heme synthesis (hepatic porphyrias). Neuropathy is seen in four types of hepatic porphyrias; acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP) and aminolevulinic acid (ALA) deficiency (Fig. 68.4).

Figure 68.4 shows the eight enzymes involved in heme synthesis. Deficiency of any of these enzymes causes decreased heme production with resulting accumulation of porphyrins and porphyrin precursors in various tissues. ALA deficiency is a rare autosomal recessive disorder caused by a homozygous deficiency of the enzyme ALA dehydrase. Mutations in the gene for this enzyme on chromosome 9 have been shown to be responsible for this condition (Kaya et al., 1994). Deficiency of ALA dehydrase results in elevation of urinary ALA, minimally elevated urinary porphobilinogen and a marked reduction in ALA dehydrase activity. The most common form of porphyria is AIP, an autosomal dominant disorder caused by a partial deficiency of porphobilinogen (PBG) deaminase. Over a hundred different mutations of the gene for PBG deaminase on chromosome 11 have been described in AIP (Grandchamp, 1998). A rise in urinary and serum PBG and ALA during acute attacks with a reduction of erythrocyte PBG deaminase activity is seen with partial PBG deaminase deficiency. A partial deficiency of coproporphyrinogen oxidase causes the autosomal dominant condition HCP. This is much rarer than AIP and mutations in the gene for coproporphyrinogen oxidase on chromosome 3 have been shown to cause HCP (Cacheux et al., 1994). During acute attacks, the reduction in coproporphyrinogen oxidase activity that can be shown in leukocytes, results in elevation of urinary and fecal coproporphyrin and an elevation of urinary ALA, PBG and uroporphyrin. The fourth neuropathy-associated porphyria is VP, an autosomal dominant disorder due to a partial deficiency of protoporphyrinogen oxidase. The gene for this enzyme is on chromosome 1 and several mutations have been found to be associated with VP with one founder mutation accounting for the high prevalence of this disease in South Africa (Meissner et al., 1996). The biochemical profile here during acute attacks is an increase in urinary ALA, PBG and coproporphyrin with an increase in fecal coproporphyrin and

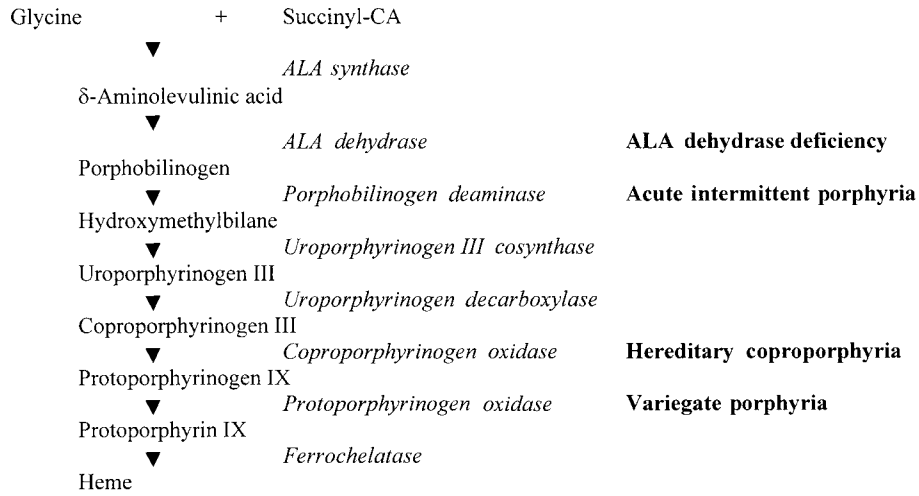

Fig. 68.4. Heme biosynthetic pathway. The eight enzymes in the heme biosynthetic pathway are shown in italics followed by the type of porphyria deficiency of each enzyme causes. Only the porphyrias associated with peripheral neuropathy are shown and are in bold.

protoporphyrin. The activity of protoporphyrin oxidase can be shown to be reduced in leukocytes.

Acute porphyric attacks are associated with neuropathy, CNS symptoms and abdominal symptoms with the addition of skin involvement in HCP and VP. An acute attack usually starts with abdominal symptoms, such as pain, constipation and vomiting. The CNS symptoms include agitation, psychosis, seizures and coma. The neuropathy follows a few days later and is characteristically a patchy motor neuropathy with bulbar involvement mimicking Guillain–Barré syndrome. Autonomic involvement is frequent. Axonal degeneration and chromatolysis are the pathological features described in porphyria. A recent study of motor neuropathy in porphobilinogen deficient mice suggests that heme deficiency may be important in the development of the neuropathy. Acute attacks can be precipitated by drugs, hormonal changes, fasting, alcohol, stress and infection. The list of drugs that can provoke an attack is constantly being updated and includes any drug, e.g. barbiturates, that induces the hepatic microsomal cytochrome P450 system.

A rapid screening test for urinary PBG should be performed when an acute porphyric attack is suspected. If positive the diagnosis should be confirmed by specific quantitative assays in urine, feces and serum. In the latent phase and family studies, enzymatic assays and molecular studies are very useful.

Acute attacks, especially if severe, are now treated with intravenous heme, preferably heme arginate. Carbohydrate administration in the acute attack is also important. Other symptomatic measures, including pain relief, nasogastric feeding, ventilation and seizure treatment may be necessary. The careful use of drugs is important. Prevention of attacks requires the identification of at risk individuals and avoidance of precipitating factors. The mortality from acute attacks has reduced from 30% to less than 10% with modern treatments but the neuropathy, especially if severe, may not recover completely.

Lipid metabolic defects

Metachromatic leukodystrophy

The metachromatic leukodystrophies (MLD) are a group of autosomal recessive disorders characterized by a pathological syndrome of central and peripheral nervous system demyelination and a metabolic abnormality of accumulation of galactosyl sulfatide (cerebroside sulfate) in glia, Schwann cells and macrophages. There are three main types of MLD, late infantile, juvenile and adult onset, which are all caused by a deficiency of arylsulfatase A (cerebroside sulfatase). Mutations in the arylsulfatase A gene on chromosome 22 have been described in all three types of MLD (Gieselmann et al., 1998). Two other rare variants have been described; multiple sulfatase deficiency secondary to deficiencies of arylsulfatases A, B and C and another variant of MLD due to a deficiency of the cerebroside sulfate activator protein, sapsosin B.

The late infantile is the most severe form with onset between 1 and 2 years, starting with ataxia, weakness and hypotonia and gradually progressing to dementia, quadriplegia, blindness, deafness and seizures. Juvenile onset is between 3 and 20 and adult onset is very rare presenting after the age of 21. The adult-onset cases often present with

intellectual deterioration, behavioural disturbances and a peripheral neuropathy. The neuropathy is demyelinating and pathologically shows segmental demyelination and remyelination with the accumulation of metachromatically staining material within Schwann cells and macrophages. Three types of inclusions, Zebra bodies, tuffstone bodies and prismatic inclusions have been shown to account for the metachromatic inclusion material ultrastructurally. The diagnosis is made by assay of arylsulfatase activity in blood leukocytes and serum. MR brain imaging reveals widespread white matter disease. Although the juvenile and adult onset cases progress slowly, the infantile cases usually die before the age of 6. Bone marrow transplantation has been used to replace deficient enzyme activity with varying success (Krivit et al., 1999). Later age of onset and minimal involvement prior to transplantation are the best prognostic factors.

Globoid-cell leukodystrophy (Krabbe disease)

Globoid-cell leukodystrophy (Krabbe disease) is an autosomal recessive disease caused by a deficiency of galactosylceramide ß-galactosidase. The pathological hallmark of the disease is the finding of multinucleated globoid cells in cerebral white matter containing prismatic and tubular inclusions composed of galactosylcerebroside. Many different mutations have been described in the gene for galactosylceramide ß-galactosidase on chromosome 14 (De Gasperi et al., 1996).

The classic form of the disease presents between the ages of 3 and 6 months with motor and intellectual regression. Examination findings include hypertonicity, hyperreflexia, optic atrophy, deafness and evidence of a neuropathy and death usually occurs by 2 years of age. Later-onset cases and even rarely adult-onset cases have been described including presentations with a demyelinating sensory motor neuropathy. Segmental demyelination is seen in the peripheral nerves and a reduction in the myelinated nerve fibre density. Similar inclusions to those seen in the CNS are found in Schwann cells and macrophages. MRI of brain either shows diffuse cerebral atrophy or more distinct white matter changes but the diagnosis is established by the assay of galactosylceramide ß-galactosidase in leukocytes or cultured fibroblasts.

Bone marrow transplantation to replace deficient enzyme activity has been performed successfully in late-onset disease cases.

Adrenoleukodystrophy (ALD) and adrenomyeloneuropathy (AMN)

Adrenoleukodystrophy (ALD) is an X-linked recessive disorder which affects the nervous system and adrenal cortex and is due to an accumulation of very long chain fatty acids (VLCFAs C26: 0 to C22: 0). This accumulation occurs due to defective peroxisomal ß oxidation and ALD is one of a group of disorders, which include classical Refsum disease, in which there is a single peroxisomal enzyme deficiency. Over a hundred mutations have been described in the ALD gene at Xq28 (Moser, 1998), and the protein is located in the peroxisomal membrane and is a member of the family of ABC transporters.

Although many different phenotypes have been described in X-linked ALD, there are two common phenotypes. Classical ALD presents in young males (between 4 and 8 years) and is characterized by progressive dementia, spasticity, deafness and blindness and sometimes adrenal failure. Adrenomyeloneuropathy (AMN) usually presents in adolescence or adult life and may be preceded by hypoadrenalism. It is characterized by a spastic paraplegia and a peripheral neuropathy. Isolated adrenal insufficiency or cerebral dysfunction in adult life are rarer phenotypes. Crucially, there is no evidence for genotype–phenotype specificity even in the same kindred. Pathologically, extensive demyelination is seen in the CNS with lamellar inclusions found in brain macrophages, Schwann cells and the adrenal glands. Nerve conduction studies in AMN cases show a predominant axonal neuropathy and nerve biopsies confirm the presence of Schwann cell inclusions and show loss of all axon types. MRI brain studies show a demyelinating pattern often characteristically involving the parieto-occipital lobes. The diagnosis is based on finding increased VLCFAs in plasma, red blood cells or cultured skin fibroblasts.

Treatment of adrenal deficiency if present is crucial. Restriction of dietary VLCFAs does not cause clinical improvement. 'Lorenzo's oil' (a combination of oleic acid and erucic acid thought to normalize the plasma concentration of C26:0) has not shown improvement in patients with ALD or AMN but is still being assessed in asymptomatic carriers. Immunosuppression has been tried to no effect. Bone marrow transplantation has shown encouraging results in children with classical ALD if they are transplanted when the cerebral involvement is mild.

Neonatal ALD is a rare autosomal recessive progressive neurological disorder belonging to a group of disorders, which includes infantile Refsum disease, in which there is an abnormality of peroxisomal biogenesis rather than a single enzyme defect.

Phytanic acid storage diseases

The main phytanic acid storage disease, classical Refsum disease, is an autosomal recessive disease characterized biochemically by the accumulation of the branched chain

fatty acid, phytanic acid, in serum and tissues. This accumulation occurs because of a deficiency of the peroxisomal enzyme phytanoyl-CoA hydroxylase, which catalyses the first step in the α-oxidation of phytanic acid to α-hydroxyphytanic acid. Mutations in the gene (PAHX) for phytanoyl-CoA hydroxylase on chromosome 10 have been described in Refsum disease (Mihalik et al., 1997).

Patients usually present in the second or third decade with night blindness due to retinitis pigmentosa and subsequently develop a demyelinating sensory motor neuropathy with or without thickened nerves and a cerebellar ataxia. Other features may include deafness, pupillary changes, cataracts, anosmia, ichthyosis and skeletal abnormalities. CSF protein is generally high with no increase in CSF white cells. The nerve pathology demonstrates diffuse hypertrophy, segmental demyelination, Schwann cell onion bulbs and non-specific inclusions in Schwann cells. The diagnosis is suggested by the finding of raised serum phytanic acid and defective α-oxidation of cultured skin fibroblasts and can be confirmed by genetic analysis. A diet low in phytanic acid is the recognized treatment and if started early and adhered to is very successful. If symptoms suddenly worsen secondary to an increase in phytanic acid (e.g. due to infection), plasma exchange can be beneficial.

Infantile Refsum disease presents early with mental retardation, deafness, retinopathy, hepatomegaly and occasionally a demyelinating neuropathy and is due to abnormal peroxisomal biogenesis.

Fabry disease (alpha-galactosidase deficiency)

Fabry disease is an X-linked disease due to deficiency of the enzyme, α-galactosidase, with resulting accumulation of neutral glycosphingolipids with terminal α-galactosyl moieties especially in vascular lysosomes. Mutations in the α-galactosidase gene on chromosome Xq22 have been described in Fabry disease (Desnick et al., 1995).

The clinical features of the disease, which usually begins in childhood or adolescence, include burning pain secondary to a neuropathy, a maculopapular rash (angiokeratoma corporis diffusum) in the 'bathing trunk' area, hypertension, renal failure, cardiovascular and cerebrovascular disease and corneal opacification. Pathologically, loss of unmyelinated and small myelinated fibres is described and lipid deposition in the nervous system is seen in vascular elements supplying the nerves, perineurial cells and ganglion cells. The diagnosis is suggested by reduced α-galactosidase activity in leukocytes or cultured skin fibroblasts and can be confirmed by genetic studies. Treatment is largely symptomatic including renal dialysis and renal transplantation, management of pain, hypertension and cardiovascular and cerebrovascular complications. Trials of treatment including direct replacement of the deficient enzyme look promising and gene therapy studies in mice suggest that gene therapy may be a viable future treatment.

Hereditary lipoprotein deficiencies

Hereditary high density lipoprotein deficiency (Tangier disease) is a rare autosomal recessive disorder, originally described on Tangier island, characterized biochemically by very low levels of plasma high density lipoprotein (HDL) and pathologically by deposition of cholesteryl esters in many tissues. This disease is due to mutations in the gene encoding the ATP-binding cassette transporter (ABC1) on chromosome 9q31 (Brooks-Wilson et al., 1999).

The most common clinical manifestations of the disease are a neuropathy, hypersplenism, hyperplastic orange tonsils and premature coronary artery disease in some patients. The neuropathy can present in three different ways; a relapsing asymmetric mononeuritic type of neuropathy, a slowly progressive symmetric polyneuropathy and finally a slowly progressive neuropathy characterized by facial and small hand muscle weakness with a dissociated loss of pain and temperature sensation in a syringomyelic-like manner. Pathologically, clear vacuoles are seen in Schwann cells of unmyelinated and small myelinated fibres. The diagnosis is suggested by very low plasma HDL levels, very low plasma cholesterol levels and normal or increased triglyceride levels. Genetic testing can also be done. The prognosis is usually good.

Abetalipoproteinemia (Bassen–Kornzweig disease) is a rare autosomal recessive disease characterized by the virtual absence of apolipoprotein B (ApoB)-containing lipoproteins (that is low density lipoproteins (LDL) and very low density lipoproteins (VLDL)) from plasma. This disease is associated with mutations in a gene encoding a microsomal triglyceride transfer protein (MTP) on chromosome 4q22–24 (Sharp et al., 1993).

The disorder may present in infancy with fat malabsorption or failure to thrive and most people have neurological involvement by age 20. The main neurological features are ataxia, dysarthria, areflexia and proprioceptive loss. A pigmentary retinopathy and extensor plantar responses may also be found. Clinical evidence of a peripheral neuropathy is rarely seen but sensory action potentials may be reduced. Pathologically the neurological features are due to the degeneration of the large sensory neurons of the spinal ganglia. The neurological manifestations are thought to be due to a secondary deficiency of vitamin E. The diagnosis is suggested by characteristic lipoprotein findings (very low VLDL and LDL and normal HDL) in

association with reduced cholesterol and triglycerides. Acanthocytes are commonly seen and vitamin E levels are reduced. Mutational analysis can also be performed. The treatment is vitamin E supplementation. Vitamins A and K are also given when neccessary.

Familial hypobetalipoproteinemia is another rare disorder with the same lipid/lipoprotein profile and the same, if less severe, neurological features in affected patients as abetalipoproteinemia but it is caused by mutations in the ApoB gene. Chylomicron retention disease is another rare ApoB deficient disease in which chylomicrons are absent in plasma.

Cholestanolosis (cerebrotendinous xanthomatosis)

Cholestanolosis (CTX) is a rare autosomal recessive disorder characterized by the accumulation of cholestanol and cholesterol in many tissues especially the nervous system (Thomas, 1993), secondary to a deficiency of the enzyme 27-hydroxylase. Mutations in the gene (*CYP27*) for this enzyme on chromosome 2 have been reported to cause cholestanolosis (Shiga et al., 1999). The disease starts in adolescence or late childhood and the clinical features include dementia, ataxia, a peripheral neuropathy, premature atherosclerosis and the finding of tendon and tuberose cutaneous xanthoma. The neuropathy is mainly sensory and is predominantly an axonopathy on nerve biopsy. The diagnosis is suggested by the finding of a high plasma cholestanol and normal plasma cholesterol and can be confirmed genetically. The treatment is with oral chenodeoxycholic acid to reduce the formation of cholestanol.

Sphingomyelin lipidoses (Niemann–Pick disease)

There are four types of autosomal recessive Niemann–Pick disease (NPD types I to IV or types A to D). Types A and B are true sphingomyelin lipidoses where there is a deficiency of sphingomyelinase (ASM) and accumulation of sphingomyelin in tissues. The gene for ASM is on chromosome 11 and mutations in this gene have been described in NPD types A and B. NPD types C and D have normal ASM activity and are due to abnormalities in cholesterol transport with accumulation of cholesterol in lysosomes. Mutations in the NPC1 gene on chromosome 18q11 account for most cases of NPD C and D. Type A is a fatal degenerative disorder of infancy characterized by dementia, seizures, retinal cherry red spots, hepatosplenomegaly and rarely a peripheral neuropathy. The neuropathy is characterized by segmental demyelination and remyelination, Schwann cell and axon lipid inclusions and endothelial foam cells. Type B is milder with no neurological involvement. Neurological involvement is seen in types C and D but neuropathy has only been described in type D. Types A and B are diagnosed by deficient ASM activity in leukocytes and genetic analysis. Gene therapy and enzyme replacement therapy are being researched as future treatments.

Other inherited neuropathies

Disorders with defective DNA repair

Ataxia telangiectasia (AT) is an autosomal recessive disorder characterized at the cellular level by radiosensitivity and chromosomal instability. Mutations in the gene for AT (ATM) on chromosome 11q22–23 have been described in AT. Clinically, a neurological disorder, oculocutaneous telangiectasia and immunological deficiency are seen. The neurological disorder starts in early childhood with cerebellar ataxia, oculomotor dyspraxia and oculocutaneous telangiectasia. Choreoathetosis and a neuropathy may occur. The neuropathy is characterized pathologically by a loss of large myelinated fibres. Impaired humoral and cellular immunity cause an increased incidence of infections and lymphoreticular malignancies. Endocrine abnormalities such as delayed sexual maturity and glucose intolerance may occur. The diagnosis is suggested by raised α-fetoprotein and can be confirmed by lymphocyte and fibroblast irradiation sensitivity studies and genetic analysis. There is no specific treatment.

Xeroderma pigmentosum (XP) is also a rare autosomal recessive disorder in which there is an increased frequency of sunlight-induced skin cancers as a result of defects in DNA repair or replication after damage by ultraviolet irradiation (UV) or various chemical carcinogens. XP has been divided into seven forms with defective excision repair (XPA to XPG) and another form with a defect in replication of damaged DNA sites (XPV). Eight genes have been identified in XP (Cleaver et al., 1999). The neurological forms of XP (XPA, B, D and G) can have mental retardation, spasticity, seizures, deafness, ataxia, dystonia and a neuropathy. Pathologically the sensory fibres are involved to a greater degree and there is loss of both myelinated and unmyelinated axons. Laboratory testing of the UV sensitivity of fibroblasts and of excision repair are the mainstay of diagnosis although genetic testing will become increasingly available. Treatment is aimed at early diagnosis, genetic counselling and crucially skin care.

Cockayne syndrome (CS) is another very rare condition in which a neurological disorder, short stature and an increased frequency of skin cancer is seen. There are three types of CS (A, B and C) and the genes for types A and B have been cloned (on chromosomes 5 and 10q11–21,

respectively) (Cleaver et al., 1999). The clinical syndrome includes early presentation with sun sensitivity, progeria, growth retardation, mental retardation, deafness, pigmentary retinopathy, ataxia and a demyelinating neuropathy. Segmental demyelination is seen on nerve biopsy. Although genetic analysis will become increasingly available, the diagnosis presently is made by the demonstration of hypersensitivity to killing by UV in cultured CS cells and by delayed recovery of DNA and RNA synthesis following UV radiation.

Neuroacanthocytosis

Neuroacanthocytosis is characterized by a combination of a movement disorder, cognitive dysfunction, an axonal neuropathy and the finding of acanthocytes on blood film. The genetics of this disease are believed to be heterogeneous but most cases are thought to be autosomal recessive. There is one recent report of linkage to chromosome 9q31 in one patient thought to have autosomal recessive neuroacanthocytosis. The age of onset is usually between the third and fifth decade. The movement disorder is variable with chorea, dystonia and tics all being described but the most frequent finding is an orofacial dyskinesia, often with tongue and lip biting. Although the tendon reflexes are often depressed or absent and there may be distal amyotrophy, there is usually no weakness. Sensory action potentials are reduced and denervation changes are seen with normal motor conduction velocities. The pathology is that of an axonopathy. The diagnosis depends on examining fresh blood films for acanthocytes in appropriate clinical circumstances.

A neuropathy can be seen in other inherited diseases such as the hereditary ataxias and the mitochondrial disorders and these are covered elsewhere in this volume.

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69

Disorders of neuromuscular junction transmission

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Basic concepts and classification

The neuromuscular junction (NMJ) is undoubtedly the most intensively studied, best understood, and arguably the simplest of mammalian synapses. Its role is to amplify the relatively weak electrical impulses that travel down the motor nerve sufficiently to trigger electrical impulses in the much larger muscle cell, and thereby lead to muscle contraction. It accomplishes this by translating the neural electrical impulse to a chemical signal, acetylcholine (ACh), which in turn elicits an amplified electrical depolarization at the level of the muscle. A single event of neuromuscular transmission takes place in less than a millisecond. Although this process is normally powerful, swift and efficient, it is highly vulnerable to a wide variety of insults, including genetic errors, autoimmune diseases, biological poisons made by bacteria, plants and animals, and pharmacological drugs or chemical warfare agents manufactured by humans. Any alteration in the highly complex and coordinated processes of ACh synthesis, storage and release; transmission across the junction; structure or function of the acetylcholine receptors (AChRs); termination of the event by the enzyme acetylcholinesterase (AChE); or impairment of neighbouring ion channels, can lead to muscular weakness. In this sense, the junction is the Achilles heel of the neuromuscular system. In order to understand the many disorders that can affect the NMJ, it is important to review the basic anatomy and physiology of neuromuscular transmission.

Although one motor nerve cell may innervate as few as 3 or as many as 1500 muscle fibres, each mature muscle fibre is innervated by only a single axonal branch, and has only a single NMJ. The junction is comprised of contributions from both the motor nerve and the muscle cell, including: a motor nerve fibre which branches to form specialized nerve terminals; the basal lamina which intervenes between nerve terminals and muscle cells; the highly invaginated postsynaptic membrane, with concentrations of AChRs at the peaks of the primary folds; AChE in secondary folds; and Schwann cells that roof over the NMJ (Fig. 69.1). In simplest outline, the process of neuromuscular transmission begins with an action potential that depolarizes the motor nerve terminal, triggering the entry of calcium, which leads to the release of ACh from storage vesicles in the nerve terminals. The released ACh binds to AChRs on the apposed muscle membrane. This produces opening of the AChRs' cation channels, which depolarizes the muscle membrane, and triggers muscle contraction. Every aspect of the biology of the NMJ has turned out to be far more complex than was previously envisioned (Boonyapisit et al., 1999; Lindstrom, 2000). The following section summarizes the basic concepts that relate to disorders covered in this chapter.

Presynaptic events

Acetylcholine synthesis, storage, and release

ACh is synthesized in the motor nerve terminal by the enzymatic action of choline acetyltransferase, and is stored in synaptic vesicles for subsequent release. It has been estimated that each vesicle, or 'quantum', normally contains approximately 10 000 ACh molecules, termed the 'quantal size'. ACh release occurs by exocytotic fusion of the vesicles with the nerve terminal membrane at 'preferred' release sites, that are situated directly opposite the areas of highest concentration of AChRs on the postsynaptic membrane. The vesicle's cycle involves synthesis and loading of ACh, docking of the vesicle at the release site, fusion of the vesicle and nerve terminal membranes, release of ACh and finally recycling of the vesicle. The processes involved in quantal

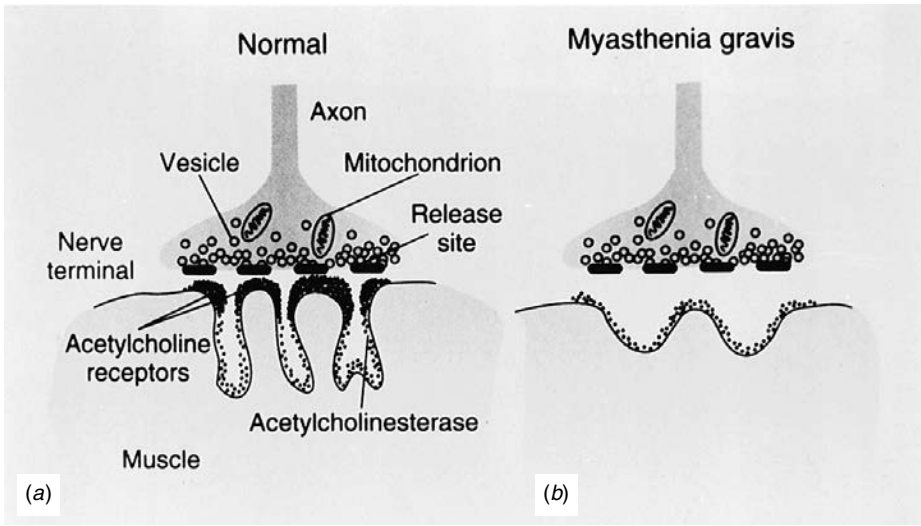

Fig. 69.1. (*a*) Normal (left) and myasthenic (right) neuromuscular junction. In neuromuscular junctions, vesicles release acetylcholine at specialized release sites of the nerve terminal. Acetylcholine crosses the synaptic space to reach receptors that are concentrated at the peaks of junctional folds. Acetylcholinesterase in the clefts rapidly terminates transmission by hydrolyzing acetylcholine. The myasthenic junction has reduced numbers of acetylcholine receptors, simplified synaptic folds, a widened synaptic space, and a normal nerve terminal. (From Drachman, 1994. Reprinted with permission. Copyright 1994 Massachusetts Medical Society. All rights reserved.)

ACh release are now known to involve more than a dozen identified proteins. Destruction of any of these proteins, for example by specific enzymatic cleavage produced by the different strains of botulinum toxin, results in blockade of quantal ACh release and paralysis (see below).

Normally, quantal release of ACh occurs both spontaneously, and in response to nerve impulses. Spontaneous release of ACh involves single vesicles, and gives rise to local low-amplitude depolarizations of the muscle membrane, or 'miniature end-plate potentials' (mepps). When an electrical impulse invades the motor nerve terminal much greater numbers of ACh vesicles (50 to 300, termed the 'quantal content') are released . This results in a larger muscle membrane depolarization, the 'endplate potential', which normally elicits an action potential that is propagated along the muscle membrane, and triggers muscle contraction. Impulse-dependent ACh release is initiated by the influx of calcium through voltage-gated calcium channels (VGCC), which are situated near the release sites, and are arranged in parallel double rows. Interference with the VGCC, for example by autoantibodies in the Lambert–Eaton Myasthenic Syndrome (LEMS), impairs ACh release, and results in muscle weakness (see below). Several toxins, produced by the Funnel web spider and certain cone snails also bind to these calcium channels and block their function. These toxins are useful in diagnostic assays of autoantibodies to the VGCCs in LEMS.

Postsynaptic events

The acetylcholine receptor

The structure, molecular biology, and function of skeletal muscle AChRs are now known in exquisite detail, and have led to the understanding and treatment of autoimmune myasthenia gravis (MG), the genetically determined congenital myasthenic syndromes, and the effects of numerous pharmacological and toxic agents (Lindstrom, 2000). The AChR is a glycoprotein with a molecular weight of approximately 250 000, that is composed of five subunits arranged like barrel staves around a central channel, and projects through the NMJ membrane. In adult innervated muscle the AChR is comprised of two α-subunits, one β-subunit, one δ-subunit, and one ε-subunit (Fig. 69.2). In immature or denervated muscle, a γ-subunit substitutes for ε (Kistler et al., 1982; Unwin, 1995). Each of the subunits has four hydrophobic domains, implying that they traverse the muscle membrane four times, with both the amino and carboxyl termini located extracellularly. The genes for all the subunits have been completely sequenced (Stevens, 1987). Although each subunit is encoded by a distinct gene, the different subunits have considerable homology to each other, suggesting a common ancestral origin. Each α-subunit has one binding site for ACh, that is located extracellularly, centred around amino acids 192 and 193, at

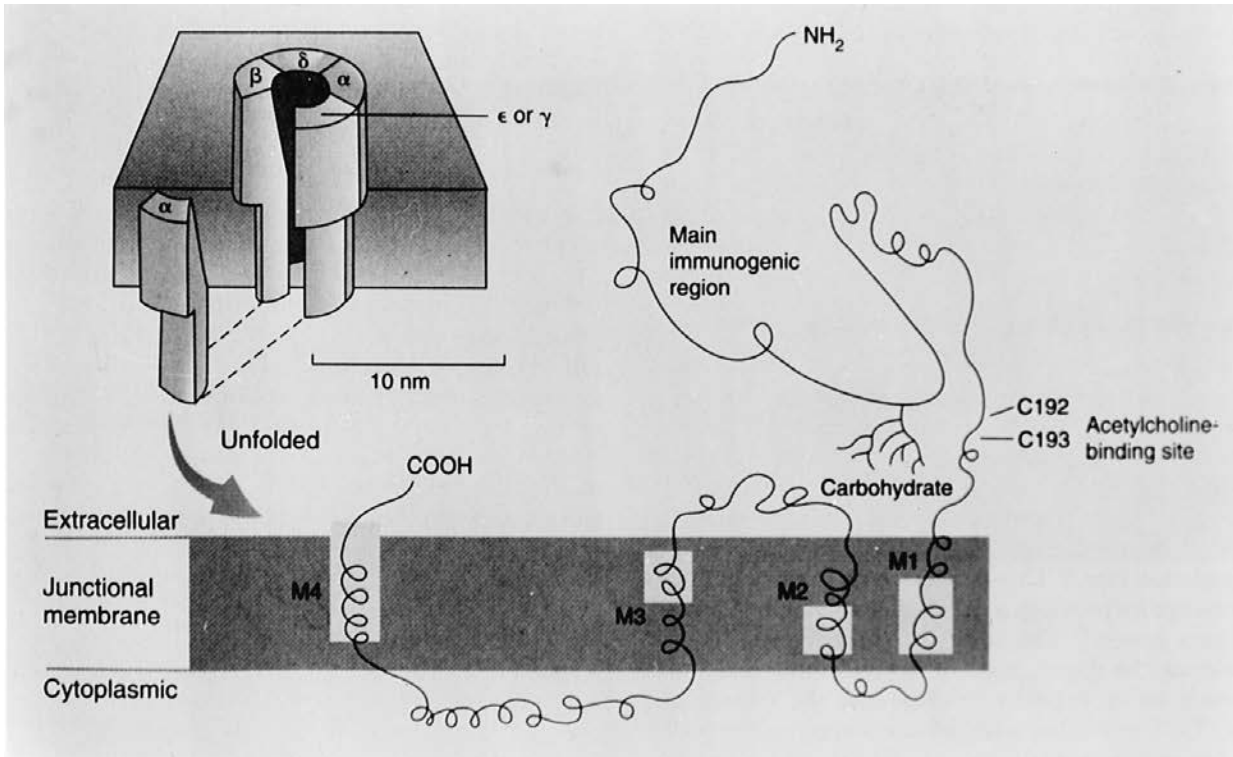

Fig. 69.2. The acetylcholine receptor. The subunits of the acetylcholine receptor – α, β, δ, and λ or ε – are arranged like barrel staves around the central iron pore. Each subunit winds through the junctional membrane four times (sites M1, M2, M3, and M4). In the unfolded view of the α subunit, the amino terminal end of the α subunit is extracellular, where it is accessible to the acetylcholine, which binds at the site shown (amino acids 192 and 193). In myasthenia gravis, autoantibodies may bind to various epitopes of all subunits, but a high proportion of antibodies bind to the main immunogenic region of the α subunit. (From Drachman, 1994. Reprinted with permission. Copyright 1994 Massachusetts Medical Society. All rights reserved.)

the interfaces between the α- and δ-subunits, and the α- and γ- or ε-subunits. Functionally, the ion channel of the AChR is closed in the resting state. When both α subunit binding sites are occupied, the AChR molecule twists slightly like a Chinese purse, opening the channel transiently, and allowing the rapid passage of cations. The channel properties of normal and pathologic AChRs have been studied by patch clamp techniques and noise analysis. Abnormalities of AChR channel properties are responsible for some of the congenital myasthenic syndromes (see below.)

AChRs are normally clustered at high concentrations (15 000 to 20 000/μ^2) at the peaks of folds of the NMJ, opposite the motor nerve's ACh release sites. Clustering of AChRs at the NMJ is dependent on motor innervation, and involves the interaction of several anchoring proteins, including rapsyn, agrin, utrophin, dystroglycan, and MuSK (muscle specific receptor protein kinase). MuSK is of particular interest, since it has recently been shown to be a target for antibodies in patients with 'antibody negative MG' (Hock et al., 2001).

AChRs normally undergo continual turnover at the neuromuscular junction. Motor nerves have an important role in this process, regulating the synthesis, subunit composition, distribution, and degradation of AChRs. In muscles with an intact nerve supply, AChRs are localized nearly exclusively at the NMJ, have an ε-subunit rather than a γ-subunit, and are quite stable (half-life of 11 days in mice). Following denervation, the rate of AChR turnover increases (<24 hrs in mice), and new AChRs are also synthesized at an increased rate. The AChRs in denervated muscles contain γ-subunits instead of ε-subunits. These AChRs are distributed over the entire length of the muscle cell membrane (Lindstrom et al., 1988). There is substantial evidence that ACh transmission plays a key role in the neural regulation of these properties. Impairment of neuromuscular transmission in MG may be responsible for increased transcription of AChR genes that has been

reported in an experimental animal model of MG. These processes of turnover and renewal of junctional AChRs permit virtually complete recovery in MG once the autoimmune attack has been brought under control.

Synapse

Acetylcholinesterase

AChE is a glycoprotein enzyme that is is bound to the basal lamina at the postsynaptic membrane of the NMJ, and is most highly concentrated in the secondary clefts. Its function is to hydrolyse ACh rapidly, and thus terminate the process of neuromuscular transmission, permitting repeated activation of the muscle fibre. The molecular structure and function of AChE are now known in detail, and this knowledge has facilitated the understanding of genetic mutations causing endplate AChE deficiency (see below). Drugs that inhibit AChE permit the released ACh to interact repeatedly with AChRs, and are used to improve neuromuscular transmission in MG and some of the congenital myasthenic syndromes. However, failure to remove ACh may cause the AChRs to become desensitized, or unresponsive to further application of ACh. Over the longer term, persistent cholinergic stimulation results in excitotoxic damage to the endplate. This may result from the use of excessive amounts of anti-AChE drugs; from exposure to organophosphate insecticides or war gases, which produce paralysis by irreversibly blocking AChE; or as a consequence of one of the genetic defects in the AChE molecule (see below).

Safety margin of neuromuscular transmission

The concept of the 'safety margin' is useful in understanding disorders of neuromuscular transmission (Waud, 1971). Under normal circumstances, the amplitude of the endplate potential is more than necessary to produce an action potential that triggers muscle contraction. The excess, termed the 'safety margin', depends on several factors: the amount of ACh released by a nerve impulse, the number and functional integrity of AChRs present at the NMJ, and the sensitivity of the neighbouring muscle membrane to propagate an action potential (Vincent et al., 2000). Any reduction in the safety margin may result in failure of neuromuscular transmission. When transmission fails at many junctions, the power of the whole muscle is reduced, which is clinically manifested as weakness. If the safety margin is borderline, repeated stimulation may result in a progressive decline in muscle power, or 'neuromuscular fatigue'. This is a consequence of the reduced safety margin, in combination with the normal phenomenon of ACh 'rundown': During repeated nerve stimulation, the amount of ACh released per impulse normally declines (runs down) after the first few impulses, since the nerve terminal is not able to sustain its initial rate of release (Stalberg et al., 1976). When the number of ACh–AChR interactions falls below the threshold, transmission fails, resulting in progressive failure of contraction of muscle fibres, or 'fatigue'. In healthy individuals, the safety margin is sufficient so that transmission failure and fatigue do not occur except at very rapid rates of nerve stimulation, above 40 or 50 Hz.

Classification of disorders of neuromuscular junction

For the purpose of classifying disorders of the neuromuscular junction, it is convenient to consider those that interfere with presynaptic functions, including the synthesis, storage and release of ACh; abnormalities at the postsynaptic level, involving the AChRs or their channels; and disorders at the synaptic level, which disturb the function of AChE. A classification of the different disorders based on this scheme is given in Table 69.1.

Postsynaptic acquired disorders of neuromuscular transmission

Autoimmune myasthenia gravis

Myasthenia gravis is an autoimmune disorder characterized clinically by weakness and fatigability of skeletal muscles. The pathogenesis of MG involves a reduction in the number of available AChRs at neuromuscular junctions, due to an antibody-mediated immune response. It is not rare, with a prevalence that has recently been assessed to be as high as 2 to 7 per 10 000 population in Great Britain (MacDonald et al., 2000) to ~1.5/10 000 in central and Western Virginia (Phillips et al., 1992). The disease may present at any age, but there is a bimodal peak of incidence, involving younger women (third decade) and older men (sixth and seventh decades). Although the clinical features were first recognized more than 300 years ago, important progress in our understanding of the pathophysiology, immunology and molecular basis of MG has been made during the past 30 years, and this knowledge has been applied directly to the effective diagnosis and treatment of this formerly 'grave' disease. Clinically, the cardinal features of MG are weakness and fatigability of skeletal muscles, often in a characteristic distribution. Diagnosis

Table 69.1. Classification of disorders of neuromuscular transmission

1. Postsynaptic
   (a) *Acquired*
      (i) Autoimmune myasthenia gravis
      (ii) Transient neonatal myasthenia gravis
      (iii) Drug -induced myasthenia gravis
      (iv) Postsynaptic blockade: snake toxins
   (b) *Congenital*
      (i) AChR deficiency
      (ii) Slow-channel syndrome
      (iii) Fast-channel syndrome
2. Presynaptic
   (a) *Acquired*
      (i) Lambert–Eaton myasthenic syndrome
      (ii) Botulism
      (iii) Black widow spider venom (latrotoxin)
   (b) *Congenital*
      (i) Familial infantile myasthenia
      (ii) Congenital Lambert–Eaton-like syndrome
3. Synaptic
   (a) *Acquired*
      Organophosphate intoxication
   (b) *Congenital*
      End-plate acetylcholinesterase deficiency

Table 69.2. Modified Osserman grading for myasthenia gravis (Jablecki, III et al., 2000)

	Any ocular muscle weakness	Limb or/ and axial muscles	Oropharyngeal or/and respiratory muscles	Intubation ± mechanical ventilation
I	+ to +++	−	−	−
IIa	± to +++	+	±	−
IIb	± to +++	±	+	−
IIIa	± to +++	++	±	−
IIIb	± to +++	±	++	−
IVa	± to +++	+++	−+	−
IVb	± to +++	−+	+++	+/−
V	± to +++	±	± to +++	+ to +++

Notes:
+ = present; − absent; ± = may be present; + = mild; ++ = moderate; +++ severe.

involves electrophysiological and immunological testing. Treatment is directed toward enhancing neuromuscular transmission, and especially toward suppressing the underlying autoimmune process. Properly treated, the great majority of myasthenic patients can be restored to fully productive lives.

Clinical features

The clinical symptoms may be so characteristic that the diagnosis can be made on history alone, though atypical cases may go undiagnosed for years. The presenting complaint consists of muscle weakness, often in a distinctive distribution, with increasing fatigue following repeated or sustained exertion. The elevators of the eyelids and the extraocular muscles are affected very early in about 60% of patients, and ptosis of the lids and diplopia occur at some time in the course of the disease in about 90%of myasthenic patients. Weakness remains confined to these muscles in a small minority (about 15%) of patients, and if it does not involve other muscle groups for 3 years or more, there is a good probability that it may persist as purely 'ocular MG' (Grob et al., 1987). In about 85% of patients, symptomatically significant weakness spreads to affect other areas as well. Involvement of the facial and bulbar muscles may give rise to a characteristic 'snarling' expression on attempting to smile, 'mushy' or nasal speech, and difficulty in chewing and swallowing. Generalized weakness often affects the limb muscles, commonly in a proximal distribution, as well as the diaphragm and neck extensor muscles. If impairment of respiration or swallowing becomes so severe as to require mechanical assistance with respiration or feeding, the patient is said to be in 'crisis'.

On physical examination, the findings are limited to the motor system, without alteration of reflexes, sensation or coordination. There are often distinctive patterns of selective weakness. Asymmetrical ptosis is a common feature. When the examiner lifts one eyelid, ptosis of the other lid may increase ('Cogan's see-saw sign'). The combination of ptosis (weakness of levator palpebrae) and weakness of eyelid closure (orbicularis oculi) muscles is characteristic of MG. Diplopia may occur on gaze in several different directions, due to weakness of more than one extraocular muscle, which may be variable and difficult to define. The baseline strength of the patient should be documented quantitatively, for later evaluation of the results of treatment. The most useful quantitative measures include timed forward arm abduction and lid elevation (up to 5 minutes), vital capacity, and dynamometry of selected weak muscles. The overall severity of MG is usually graded functionally and regionally, according to a modification of a scale proposed originally by Osserman, and recently standardized by an ad hoc committee (Table 69.2) (Jablecki, III et al., 2000): Class I: any ocular muscle weakness; may have weakness of eye closure; all other muscle strength is

normal; Class II: mild weakness affecting other than ocular muscles; may also have ocular muscle weakness of any severity (IIa: predominantly affecting limb, axial, or both, may have lesser involvement of oropharyngeal muscles; IIb: predominantly affecting oropharyngeal, respiratory muscles, or both: may have lesser or equal involvement of limb, axial muscles); class III: moderate weakness affecting other than ocular muscles; may also have ocular muscle weakness (IIIa: predominantly affecting limb, axial, or both, may have lesser involvement of oropharyngeal muscles; IIIb: predominantly affecting oropharyngeal, respiratory muscles, or both, may have lesser or equal involvement of limb, axial muscles); class IV: severe weakness affecting other than ocular muscles; may also have ocular muscle weakness of varying severity (IVa: predominantly affecting limb, axial, or both, may have lesser involvement of oropharyngeal muscles; IVb: predominantly affecting oropharyngeal, respiratory muscles, or both- may have lesser or equal involvement of limb, axial muscles); class V: defined by intubation with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

Pathophysiology

The basic abnormality in MG is a reduction in the number of available AChRs at neuromuscular junctions (Drachman, 1994). This was originally demonstrated by the use of a radioactively labelled snake toxin, α-bungarotoxin (αBuTx), which binds specifically, quantitatively, and irreversibly to AChRs of skeletal muscles, permitting accurate measurement of the numbers of AChRs. Studies of muscle biopsies showed that NMJs of myasthenic patients had on average only one third as many AChRs as those of normal individuals. In general, the clinical severity of MG correlated with the reduction of AChRs, although even patients with purely ocular weakness had reduced numbers of AChRs in clinically strong limb muscles. Neuromuscular junctions from myasthenic patients also show morphological changes of simplification of the postsynaptic membranes, and an increase in the width of the gap between pre- and postsynaptic membranes, visualized by electron microscopy. These changes at the NMJ produce a reduced 'safety margin' for NM transmission, and account fully for the clinical and electrophysiological features of MG. The amplitude of endplate potentials is reduced, with failure of transmission at some fibres, and a decrease in the overall power of muscular contraction, clinically manifested as weakness. Fatigue on repeated or sustained contraction (or a decremental response to electrical stimulation of the nerve) results from the abnormally reduced safety margin in MG in conjunction with the normal phenomenon of ACh 'rundown', described above.

Immune pathogenesis of MG

It is widely accepted that the neuromuscular abnormalities in MG are due to antibody mediated processes (Lindstrom et al., 1988; Ragheb & Lisak, 1998). Many lines of evidence support this concept: First, 80 to 90% of myasthenic patients have antibodies directed against AChR, that are detected by a standard radioimmunoassay (RIA). The RIA measures serum IgG that binds to human AChR that has been solubilized and tagged with ^{125}I-labelled αBuTx. Secondly, the pathogenic antibody binds to the target antigen, AChR at neuromuscular junctions, in myasthenic patients. Thirdly, passive transfer of IgG from myasthenic patients to experimental mice reproduces the disease features. Fourthly, immunization of a wide variety of experimental animals with purified AChR produces an experimental model of MG (experimental autoimmune MG, or EAMG) that has proven useful for testing new therapeutic strategies. Finally, treatments that lower AChR antibody levels result in improvement of the disease.

AChR antibodies have been shown to reduce the number of available AChRs by three different mechanisms (Drachman et al., 1982: (i) cross-linking of AChRs by the divalent antibodies, which accelerates endocytosis and degradation of the AChRs by the muscle cells; (ii) blockade of the receptors' ACh binding sites by antibody; (iii) complement-mediated damage to neuromuscular junctions. Antibodies from some myasthenic patients have a more pronounced effect on degradation of AChRs, while others produce more marked blockade of receptors. Their particular functional properties are probably related to the specific epitopes of the AChR to which they bind. However, the ability of the serum to induce loss of available AChRs by a combination of these mechanisms corresponded most closely to the clinical severity of the patient's MG.

Antibody-negative MG

About 10 to 20% of patients with acquired MG do not have AChR antibodies detectable by RIA. Although this includes patients with mild localized MG, there is also a subgroup with generalized MG, whose disease corresponds to conventional MG with respect to most other clinical, diagnostic, and therapeutic properties (Mossman et al., 1986). Actually, these patients have circulating antibodies that are not detected by the conventional RIA, but do cause accelerated degradation of AChRs in culture systems, and are capable of inducing features of MG by passive transfer to mice. A recent report suggests that at least some of these sera have antibodies that bind to MuSK, a muscle specific

protein kinase that plays a key role in anchoring AChRs at the neuromuscular junction (Hoch et al., 2001). Taken together, these findings indicate that 'antibody-negative' MG is an antibody-mediated autoimmune disorder directed against one or more components of the NMJ that are not detected by the standard anti-AChR RIA.

Role of T-cells in MG

Although production of the pathogenic antibodies in MG is directly attributable to B-cells, T-cells play a pivotal role in the disease process by providing help that is essential for the antibody production (Ragheb & Lisak, 1998). The requirement for T-cells has been formally demonstrated in EAMG in rats, and there is extensive evidence that T-cells play a key role in the autoantibody response in human MG (Newsom-Davis et al., 1989). T-cells from myasthenic patients respond to stimulation with AChR, and augment the production of AChR antibody in vitro. AChR-reactive T-cell lines or clones have been isolated from the peripheral blood lymphocytes or thymuses of myasthenic patients. In contrast to their role in AChR antibody production, T-cells do not act as effector cells in MG. It is noteworthy that lymphocytes from some normal individuals can also respond to AChR, although AChR-specific T-cells are more numerous in myasthenic patients. This is consistent with the concept that potentially autoreactive T-cells can exist in the normal immune system.

Analysis of AChR-specific T-lymphocytes from myasthenic patients has revealed striking heterogeneity in their patterns of responsiveness. The T-cells of each individual respond to a great variety of AChR epitopes, and there are significant differences in the epitopes to which T-cells of different patients respond. The majority of T-cell recognition sites are on the α subunit, but T-cells recognize epitopes on the other subunits as well. Attempts to analyse the repertoire of T-cell receptors that recognize AChRs have not shown a consistent or restricted pattern. The striking heterogeneity of AChR-specific T-lymphocytes must be taken into account when designing specific immunotherapeutic approaches aimed at these T-cells.

Etiology of MG

The origin of the autoimmune response in MG remains an unsolved problem, as is also true in virtually all human autoimmune diseases. The heterogeneity of the repertoires of the AChR-specific autoantibodies and T-cells argues that multiple different factors may trigger MG. The thymus has been implicated as a possible site of origin of MG for several reasons. Approximately 75% of MG patients have thymic abnormalities. Of these, 85% have hyperplasia (germinal centre formation), and 15% have thymic tumours. Thymectomy results in improvement in a majority of patients. Both T- and B-lymphocytes from the thymus of myasthenic patients are more responsive to stimulation with AChR than are peripheral blood lymphocytes from the same patients. In addition to lymphocytes, thymus glands from normal and myasthenic individuals contain muscle-like ('myoid') cells that express surface AChRs. Because of their strategic location within the thymus, surrounded by antigen presenting cells (APCs), and helper T-cells, these AChR-bearing myoid cells are thought to be the source of the autoantigen, AChR. Some alteration of the myoid cells or the lymphocytes may break tolerance, and lead to the autoimmune response. Attempts to implicate viruses as possible agents in precipitating the autoimmune response have been unsuccessful. Viruses could not be cultured from MG thymus tissue in recent onset cases, and antibody titres against a number of common viruses do not differ from those in matched controls. The hypothesis that MG may be triggered by 'molecular mimicry', that is, an immune response to an infectious agent that resembles the AChR, has some support. Antibodies from 6 of 40 patients with MG recognized a peptide sequence of herpes simplex virus that is similar to a sequence of the AChR α-subunit. Cross-reactivity between bacteria and the AChR has also been reported. Genetic factors may influence the likelihood of developing MG. There is a weak to moderate association of MG with the HLA antigens B8 and Drw3 in Caucasians, but Japanese and Chinese patients have different HLA associations. A wide variety of other autoimmune diseases have been reported to occur in some myasthenic patients and their relatives, supporting a defect in immune regulation as a possible causative factor, and suggesting that the predisposition may be inherited.

Diagnosis of MG

The diagnosis of MG usually commits both the patient and the physician to long-term medical treatment and/or surgery, and entails substantial risks. It is therefore essential: (i) to establish the diagnosis unequivocally; (ii) to exclude other conditions that may masquerade as MG; and (iii) to search for associated conditions that may influence the choice of treatment. The history and physical examination (above) are usually the most important initial clues to the clinical diagnosis of MG. However, the clinical impression must be confirmed by further diagnostic testing before initiating treatment.

Anticholinesterase (AChE) test

Inhibition of the enzyme AChE allows the ACh released from the motor nerve to interact repeatedly with the limited number of AChRs at myasthenic NMJs, resulting in

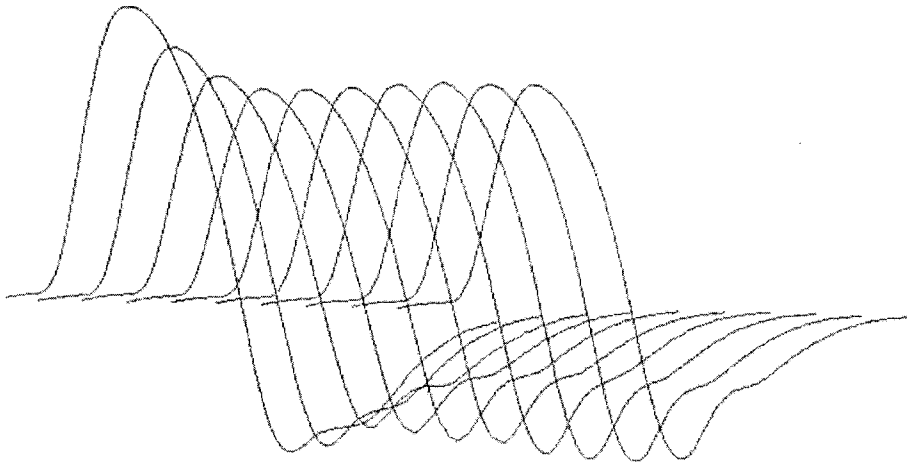

Fig. 69.3. Repetitive nerve stimulation at 3 Hz. shows a decrement of 27% from the first to the fourth response.

at least partially improved muscle strength. Edrophonium (Tensilon®) is commonly used intravenously for diagnostic testing, because of the rapid onset (30 seconds) and short duration (~5 minutes) of its anti-AChE effect (MacDonald et al., 2000). It is essential to select one or more muscles that are unequivocally weak for observation before and after administration of edrophonium. Because edrophonium occasionally produces side effects of bradycardia or hypotension, atropine sulfate (0.6 mg) should be on hand for i.m. or i.v. injection. Initially, 2 mg of edrophonium is injected i.v., and the muscle response is observed for 60 seconds. If there is definite improvement in an objectively weak muscle, the test is considered positive. If the result is doubtful or negative, further injections of 4 to 8 mg are carried out. False-positives may occur in a number of non-myasthenic conditions including brainstem lesions, oculomotor denervation and even in normal control subjects. False-negatives may also occur in myasthenic patients.

Electrophysiologic testing

The *repetitive nerve stimulation* (RNS) test is carried out by supramaximal electrical stimulation of a nerve, while recording the compound muscle action potentials from surface electrodes over the muscle (CMAPs). At low rates of stimulation (3 Hz) the CMAPs of normal individuals do not change appreciably. A rapid reduction in the amplitude of the CMAP (decremental response $\geq$10% by the fourth stimulus) is characteristic of MG, and is considered a positive response (Fig. 69.3). The yield of positive responses is increased when weak muscles, or several proximal muscles are tested. As discussed above, the basis for the decremental response is the reduced 'safety margin' at myasthenic endplates, in conjunction with the normal phenomenon of ACh 'rundown'. As the amount of ACh released by the motor nerve normally diminishes on successive stimuli, the EPPs fail to reach threshold levels at NMJs of myasthenic patients, and there is progressive failure of activation of MAPs (Sanders, 1993; Jablecki, 1991). *Single fibre EMG (SFEMG)* is an electrophysiological technique developed to record action potentials from individual muscle fibres (Stalberg & Trontelj, 1997). By recording several consecutive firings of two or more muscle fibre action potentials belonging to the same motor unit, one can assess the 'neuromuscular jitter', which is the fluctuation in time between activation of the related muscle fibres. Jitter is increased when the safety margin of neuromuscular transmission is reduced (Fig. 69.4). When the defect in neuromuscular transmission is severe, some nerve impulses fail to elicit action potentials, termed 'impulse blocking'. Single fibre EMG is a highly sensitive test, and may be helpful in difficult diagnostic situations. It is positive in 88 to 92% of myasthenic patients, but its specificity is limited, with increased jitter or blocking in other disorders of nerves, muscles, and neuromuscular junctions.

AChR antibody assay

The gold standard for diagnosis of MG is a radioimmunoassay (RIA) that measures antibodies that bind to detergent solubilized human AChR, which is labelled by ^{125}I-α-BuTx (Vincent & Newsom-Davis, 1985). A positive RIA test for AChR antibodies is specific for MG, but antibodies are detectable in only about 80 to 85% of patients with acquired autoimmune MG, and in a lower proportion (~50%) of patients with pure ocular MG. Other tests for

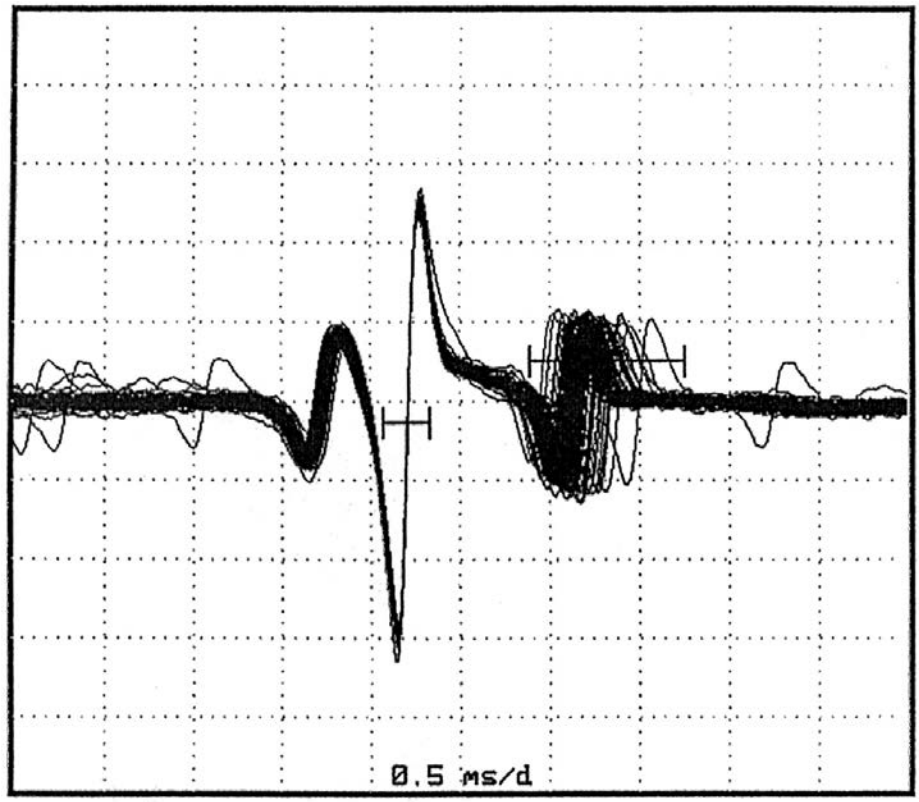

Fig. 69.4. Single fibre EMG shows 2 pairs, one with normal jitter (left) and the other with abnormal jitter (right).

antibodies, measuring accelerated degradation or blocking of AChRs may be helpful in antibody-negative MG. A newly developed test for antibodies to MuSK may prove useful in patients with 'antibody-negative MG', although it is limited to research purposes at present (Hoch et al., 2001). There are few, if any, false-positive RIAs, and a positive test in a patient with compatible clinical features essentially confirms the diagnosis.

Differential diagnosis

Other conditions that may cause weakness of the cranial and somatic muscles must be considered in the differential diagnosis of MG, including LEMS, the congenital myasthenias, and botulism (which will be discussed below), drug-induced myasthenia (penicillamine, aminoglycosides, magnesium), intracranial mass lesions or vascular malformations, progressive external ophthalmoplegia, oculopharyngeal dystrophy, and thyrotoxic ophthalmopathy. Each of these conditions should be considered, and appropriate diagnostic testing carried out. Especially when weakness is confined to the cranial musculature, it is essential to obtain MRI imaging of the brain and orbits to exclude other conditions that can cause similar features.

Associated conditions

Several clinically important conditions may be associated with MG. As noted above, thymic tumours occur in approximately 12% of myasthenic patients, and are reliably detected by CT or MRI imaging. The thymus is normally detectable until mid-adulthood, but persistence of a thymus shadow in a patient with MG who is over 40 years of age, or an increase in its size in any patient on repeated scanning, raises the possibility of a thymoma. Hyperthyroidism occurs in 3% to 8% of patients with MG, and either hyperthyroidism or hypothyroidism may aggravate myasthenic weakness. We routinely screen for other autoimmune disorders, because they may add to the diagnostic picture of immune dysregulation, and because they may complicate therapy. Conditions that may influence the choice of immunosuppressive therapy include unsuspected

Table 69.3. Drugs, dosages, costs, onset of actions, and side effects to be monitored for the immunomodulatory agents used for MG

Drug	Dosage	Costs	Onset	Monitor
Prednisone	60 mg/d	$0.40[a]	3 weeks	BP, BS, Na/K, Wt, Bone density, eyes, stool guiacs
Azathioprine	2–3 mg/kg/d	$4/-[b]	3–6 mos.	MCV, lymphocytes, LFTs
Cyclosporine	5 mg/kg/d (2 divided dosages)	$20/-[c]	4 weeks	Creatinine, BP, CsA levels
Mycophenolate mofetil	1 gm bid	$18/-[d]	3–6 mos.	WBC
Cyclophosphamide	2–3 mg/kg/d	$11/-[e]	4 weeks	CBC, urine, lytes
Plasmapheresis	250 ml/kg qod × 5	$8000/-[f]	3rd exchange	Asepsis, calcium
IVIG	2 g/kg (over 2–5 days)	$6000/-[g]	3–4th day	Infusion rate, creatinine

Notes:
Based on average wholesale prices: [a]60 mg; [b] 150 mg; [c] 300 mg; [d] 2 g; [e]150 mg; and [f]144 mg (does not include pharmacy or nursing costs). [g] five treatments.

infections such as tuberculosis, diabetes, peptic ulcer disease, occult gastrointestinal bleeding, renal disease, and hypertension.

Treatment

The outlook for myasthenic patients has improved dramatically as a result of advances in treatment. At present, with optimal treatment, the mortality rate is essentially zero, and virtually all myasthenic patients can be returned to full, productive lives (Grob et al., 1987). The most important methods used in the treatment of MG include anticholinesterase (anti-ChE) medications, immunosuppressive agents, thymectomy, and the short-term treatments such as plasmapheresis or intravenous immunoglobulin (IVIg) (Tables 69.3 and 69.4) (Drachman et al., 1993).

Cholinesterase inhibitors

Anticholinesterase (anti-ChE) agents inhibit the enzymatic elimination of acetylcholine, thereby prolonging its action at the postsynaptic membrane, and enhancing neuromuscular transmission. They are often the initial agents used for treatment. There is no substantial difference in efficacy among the various anti-ChE drugs; oral pyridostigmine bromide (Mestinon®) is the one most widely used in the United States. Its beneficial action begins within 15 to 30 minutes, and lasts for 3 to 4 hours, but individual responses vary. The dosage schedule must be tailored to the needs of the patient, and should be timed to maximize strength prior to anticipated activities, such as 30–60 minutes before meals. The initial dosage of pyridostigmine bromide is 30 to 60 mg every 4–6 hours. The dose may be increased to 60 or 90 mg every 3 hours when awake. The maximum useful dosage rarely exceeds 120 mg every 3

Table 69.4. Step-wise approach to management of MG

Step 1. Firmly establish the diagnosis, by history, examination, anti-AChR antibody, repetitive nerve stimulation, or single-fiber EMG study.

Step 2. Document the severity into ocular; mild, moderate, or severe generalized; and whether bulbar and respiratory functions are involved. Follow with regular vital capacity, ptosis and arm abduction time.

Step 3. Evaluate the thymus by CT scan or MRI of the chest.

Step 4. Test for associated disorders, especially thyroid function tests and CK measurement.

Step 5. Explain the nature of the disease to the patient, especially its variable nature and the known precipitating factors, including certain drugs, temperature, stress, and the premenstrual period in some females.

Step 6. Start treatment with Mestinon®

Step 7. Perform thymectomy in patients with thymoma or generalized myasthenia gravis, if < 60 years of age after stabilizing MG.

Step 8. Use corticosteroids in patients with disabling ocular or generalized myasthenia gravis/ Switch gradually to alternate-day therapy.

Step 10. Start azathioprine, mycophenolate mofetil, or cyclosporine as 'steroid sparing agents'.

Step 11. Use plasmapheresis or intravenous immunoglobulin in myasthenic crisis, before or after thymectomy, to tide over periods of severe weakness while waiting for other immune drugs to take effect.

hours, and higher doses may produce increased weakness. A long-acting pyridostigmine preparation (Timespan® 180 mg) should be used only at bedtime, for patients who are symptomatic at night or in the early morning. The side effects of anti-ChE drugs include gastrointestinal hyperactivity with abdominal cramping or diarrhea, and increased oral and upper respiratory secretions. Anticholinergic medications such as diphenoxylate (Lomotil®) may overcome these muscarinic side effects without diminishing the nicotinic benefit. As a rule, anti-ChE drugs provide only partial improvement in most patients, and their effects often wane after weeks or months of treatment.

Thymectomy

As noted above, the thymus gland is believed to play an important role in the development of autoimmune myasthenia gravis. There are two different indications for thymectomy in MG: (i) Surgical removal of a thymic tumour; and (ii) thymectomy as a treatment for MG. Thymic tumours must be removed because they may spread locally and involve important structures within the chest, although they are usually histologically benign. In the absence of a tumour, there is now broad consensus that patients with generalized MG who are between the ages of puberty and about 60 years should have thymectomy, because up to 85% of patients eventually experience improvement in their MG after thymectomy (Bulkley et al., 1997). Of these, about 35% achieve drug-free remission, while the remaining 50% show some improvement. The advantage of thymectomy is that it offers the possibility of long-term benefit, after months or years, in some cases diminishing or eliminating the need for continuing medical treatment. In view of these potential benefits, and of the negligible risk in skilled hands, thymectomy has gained widespread acceptance in the treatment of MG, even though the evidence for this fails to come from controlled studies (Gronseth & Barohn, 2000). Thymectomy should *never* be performed as an urgent procedure. Unless absolutely necessary, thymectomy should be performed before beginning treatment with immunosuppressive drugs, so as to minimize the risks of infection and delayed wound healing. If MG is severe, or in patients with bulbar or respiratory dysfunction, thymectomy should be carried out only after stabilization of the disease with plasmapheresis, IVIg treatment, or other immunomodulatory therapy (see below). Although various surgical approaches to thymectomy, transcervical, transsternal, or 'maximal', continue to be used at different centres, median sternotomy with cervical exploration is most widely used, since it permits maximal removal of all thymic tissue. Potential complications from thymectomy include the general risks of anesthesia, impaired wound healing, sternal instability, pleural effusion, atelectasis, pneumonia, pulmonary embolism, paresis of phrenic or recurrent laryngeal nerve, and precipitation of myasthenic crisis. To minimize the risk of these complications, thymectomy should always be carried out in a hospital where it is performed regularly, and where the staff is experienced in the pre- and postoperative management, anesthesia, and surgical techniques of total thymectomy.

Immunosuppressive drugs

Most patients can be restored to full activity with optimum immunosuppressive therapy. An increasing number of immunosuppressive agents including glucocorticoids, azathioprine, cyclosporine-A, mycophenolate mofetil, methotrexate, cyclophosphamide, and others are now available (Cornelio et al., 1993; Lanska, 1990). The choice of which drugs or other immunomodulatory treatments to use should be guided by their relative benefits and risks for the individual patient, and the urgency of treatment. It is helpful to develop a treatment plan based on (i) short-term, (ii) intermediate-term, and (iii) long-term objectives. For example, if immediate improvement is essential either because of the severity of weakness or because of the patient's need to return to activity as soon as possible, plasmapheresis or IVIg treatment should be undertaken. For the intermediate term, adrenal corticosteroids and cyclosporine generally produce clinical improvement within a period of 1 to 3 months. The beneficial effects of azathioprine and mycophenolate usually begin after many months (up to a year), but these drugs have advantages for the long-term treatment of patients with MG. The side effects of each drug may preclude its use in some patients, as indicated below.

Steroid therapy

Adrenal corticosteroids, when used properly, produce improvement in myasthenic weakness in the great majority of patients (Johns, 1987). The initial dose of prednisone should be relatively low (15 to 20 mg/d) to avoid the early weakening that occurs in about one-third of patients treated initially with a high-dose regimen. It is then increased by 5 mg every 2 to 3 days as tolerated, until a total dose of 60 mg a day is reached. Prednisone should be administered in a single dose in the morning so as to minimize side effects (which are more pronounced when it is given in divided doses throughout the day), and to mimic the natural diurnal cortisol cycle. After reaching an optimal dose, treatment is continued for 1 to 3 months or until near-maximal or maximal improvement occurs. The treatment schedule is then modified gradually to an alternate-day

regimen over weeks to months. Occasionally, a small dose of prednisone must be given on the 'off' day to prevent fluctuations in strength. The ultimate aim of therapy is to maximize the benefits while minimizing the risks. Since the risks are directly related to the dose and duration of steroid use, the smallest effective dose given on alternate days should be determined for each patient by gradually tapering the dose (usually by no more than 5 mg every month or so). The combination of other immunosuppressive agents (see below) with corticosteroids facilitates the reduction of the steroid dose, while maintaining the therapeutic effect on MG. Potential side effects of steroid therapy include weight gain, cataracts, gastrointestinal irritation and ulcers, psychological changes, hyperglycemia, hypertension, osteoporosis, aseptic necrosis of the hip, suppression of pituitary ACTH secretion, impaired wound healing and increased risk of infection. Because of these side effects, consistent follow-up with close monitoring of blood pressure, blood glucose, electrolytes, bone density, weight, occult infections, stool for occult blood, advice regarding an exercise program, a low fat low sodium diet, calcium and vitamin D supplementation or the use of biphosphonates to prevent osteopenia, and surveillance or treatment for hyperglycemia, should all be part of management of MG patients on corticosteroids. Inability or unwillingness of a patient to be followed closely is an absolute contra-indication to the use of steroid therapy.

Other immunosuppressive drugs

Azathioprine, cyclosporine, mycophenolate mofetil, or occasionally cyclophosphamide, are effective in many patients, either alone or in combination with glucocorticoid therapy.

Azathioprine has been the most widely used of these drugs because of its relative safety in most patients, and long track record (Gajdos et al., 1997). Its therapeutic effect may add to that of glucocorticoids and usually allows the steroid dose to be reduced. However, up to 10% of patients are unable to tolerate azathioprine because of idiosyncratic reactions consisting of flu-like symptoms of fever and malaise, bone marrow depression, or abnormalities of liver function. An initial dose of 50 mg/d should be used to test for adverse side effects. If this dose is tolerated, it is increased gradually until the white blood count falls to approximately 3000 to 4000/μl. In patients who are receiving steroids concurrently, leukocytosis precludes the use of the WBC as a measure of treatment. A reduction of the lymphocyte count below 1000/μl and/or an increase of the mean corpuscular volume of red blood cells may be used as indications of adequacy of azathioprine dosage. The typical dosage range is 2 to 3 mg/kg total body weight (including fat in obese patients). The beneficial effect of azathioprine takes at least 3 to 6 months to begin and even longer to peak.

Cyclosporine is approximately as effective as azathioprine, and is being used increasingly in the management of MG (Goulon et al., 1989; Tindall et al., 1987). Its beneficial effect appears more rapidly than that of azathioprine. It may be given alone but usually is used as an adjunct to steroids, to permit reduction of the steroid dose. The usual dose of cyclosporine is 4 to 5 mg/kg per day, given in two divided doses (to minimize side effects). Side effects of cyclosporine include hypertension and nephrotoxicity, which must be closely monitored. The blood pressure and serum creatinine levels should be monitored on a regular basis. 'Trough' blood levels of cyclosporine are measured 12 h after the evening dose; the therapeutic range, as measured by radioimmunoassay, is 150 to 200 ng/l.

Mycophenolate mofetil, which has been used for immunosuppression in transplant patients, has now proven useful in the treatment of MG (Ciafaloni et al., 2000; Hauser et al., 1998; Chaudhry et al., 2001). Its mechanism of action involves inhibition of purine synthesis by the de novo pathway. Since only lymphocytes lack the alternative 'salvage pathway' that is present in all other cells, mycophenolate inhibits proliferation of lymphocytes, but not proliferation of other cells. It does not kill or eliminate pre-existing autoreactive lymphocytes, and therefore clinical improvement in autoimmune diseases like MG may be delayed for many months to a year, until the pre-existing autoreactive lymphocytes spontaneously die. The advantage of mycophenolate lies in its relative lack of adverse side effects, with only occasional production of diarrhea, and rare development of leukopenia. This drug may become the choice for long-term treatment of myasthenic patients. Unfortunately, the present cost of mycophenolate is high.

Cyclophosphamide is reserved for occasional patients refractory to the other drugs, because of its relatively high risk of adverse side effects, including late development of malignancies (Niakan et al., 1986).

Plasmapheresis and intravenous immunoglobulin

In view of the antibody-mediated pathogenesis of MG, plasmapheresis has been used therapeutically. The plasma, which contains the pathogenic antibodies, is mechanically separated from the blood cells, which are returned to the patient. Plasmapheresis produces a short-term reduction in anti-AChR antibodies, with clinical improvement in many patients (Keesey et al., 1981). It is useful as a temporary expedient in seriously affected patients or to improve the patient's condition prior to surgery (e.g., thymectomy).

The indications for the use of intravenous immunoglobulin are the same as those for plasma exchange: to produce rapid improvement in order to help the patient through a difficult period of myasthenic weakness, or prior to surgery (Gajdos et al., 1984, 1997; Arsura, 1989). This treatment has the advantages of not requiring special equipment or large-bore venous access. The usual dose is 2 g/kg, which is typically administered over 5 days (400 mg/kg/day). If tolerated, the course of IVIg can be shortened to administer the entire dose over a 3-day period. Improvement occurs in about 70% of patients, beginning during treatment or within a few days thereafter, and continuing for weeks to months. The mechanism of action of intravenous immunoglobulin is not known; the treatment has no consistent effect on the measurable amount of circulating AChR antibody. Adverse reactions are uncommon, but include headache, fluid overload, and rarely aseptic meningitis or renal shutdown.

Management of myasthenic crisis

Myasthenic crisis is defined as an exacerbation of weakness sufficient to endanger life, due to respiratory failure caused by diaphragmatic and intercostal muscle weakness. Treatment should be carried out in an intensive care unit staffed with physicians experienced in the management of MG, respiratory insufficiency, infectious disease, and fluid and electrolyte therapy. The most common cause of crisis is intercurrent infection. This should be treated immediately, because the mechanical and immunologic defences of the patient can be assumed to be compromised. The myasthenic patient with fever and early infection should be treated like other immunocompromised patients. Early and effective antibiotic therapy, respiratory assistance, and pulmonary physiotherapy are essentials of the treatment program. As discussed above, plasmapheresis or IVIg is frequently helpful in hastening recovery. Crisis is occasionally due to the improper use of excessive anticholinesterase medication ('cholinergic crisis'). This is best evaluated by temporarily stopping anti-ChE drugs.

Transient neonatal MG

Transient neonatal MG is due to the placental transfer of anti-AChR antibodies from the mother reacting with the infant's AChR (Ohta et al., 1981; Lefvert & Osterman, 1983; Morel et al., 1988). However, even though circulating anti-AChR antibodies can be detected in most infants born to myasthenic mothers, only 10–15% of such children display symptoms or signs of MG. The risk is higher if previous siblings have been affected. There is no correlation between the severity of myasthenia in the mother or the maternal titre of anti-AChR antibodies and the occurrence and severity of transient neonatal myasthenia gravis. Affected newborns manifest hypotonia, weak cry and suck, and respiratory difficulty, usually within the first few hours of life. Rarely, arthrogryposis and polyhydramnios can occur and are due to myasthenic weakness in utero, with virtual immobility of the fetus. Transient neonatal myasthenia requires supportive treatment along with Mestinon® at a dose of 1–2 mg/kg orally/nasogastric tube given every 3–4 hours. Symptoms resolve spontaneously within 1–3 weeks, with mean duration of illness being 18 days. The diagnosis is made on the basis of maternal history, clinical manifestations, AChR antibody assays in mother and infant, and the clinical response to anti-ChE treatment. Electrophysiological study shows decremental response with RNS, but is rarely necessary.

Drug-induced myasthenia gravis

D-Penicillamine is a drug that may be used in the treatment of rheumatoid arthritis, scleroderma, or Wilson's disease. During treatment with D-penicillamine, anti-AChR antibodies, typical clinical manifestation of MG, identical to those of acquired immune myasthenia gravis, may occur (Penn et al., 1998; Wittbrodt, 1997). The symptoms subside gradually after the drug is stopped.

Postsynaptic blockade: snake toxins

The paralytic syndromes of cobra, and krait snake bites are due to blockade of AChRs at neuromuscular junctions, and thus resemble myasthenia gravis (Naphade & Shetti, 1977; Mitrakul et al., 1984). Weakness develops soon after the bite and reaches a peak in 4 hours. Weakness proceeds in the order of ocular, masticatory, facial, palatal, neck, and proximal and distal limb paralysis, with recovery in the same direction. Treatment with antivenom and supportive care is required.

Postsynaptic congenital disorders of neuromuscular transmission

Acetylcholine receptor deficiency

This is a heterogeneous group of disorders caused by inherited autosomal recessive mutations in the AChR subunits (Engel, 1999; Engel et al., 1993; Middleton et al., 1999; Quiram et al., 1999; see Table 69.5). Sporadic cases have also been described. A wide variety of mutations have been identified in each of the subunits, but the ε subunit is

Table 69.5. Congenital myasthenic syndromes

Type	Clinical features	Electrophysiology	Genetics	Endplate effects	Treatment
1. Postsynaptic					
(i) Severe AChR Deficiencies[b]	Early onset (infant to childhood Variable severity (hypotonia, respiratory insufficiency, ocular,bulbar weakness), skeletal deformities	Decremental response to repetitive nerve stimulation Decreased MEPP amplitudes	Autosomal recessive ε mutations most common Heteroallelic	Increased span of endplates Variable synaptic folds	Anti-ChE 3,4- DAP
(ii) Slow Channel[a] (increased response to ACh)	Onset 2–3rd decade Most common Fatigable ptosis, ophthalmoparesis, trunk or extremity (especially forearm extensors) weakness	Repetitive responses on single nerve stim Prolonged channel opening and prolonged MEPPs	Autosomal dominant α,β,ϵ mutations Gain of function	Excitotoxic Endplate myopathy Decreased AChRs Postsynaptic damage	Quinidine Made worse by anti-ChE
(iii) Fast Channel[b] (decreased response to ACh)	Onset early (neonate or infantile) Moderate severity Ptosis, EOM involvement; weakness and fatigue	Brief and infrequent channel openings Opposite of slow channel syndrome	Autosomal recessive May be hetero-allelic	Normal endplate structure Normal AChR	Anti-ChE 3,4- DAP
2. Pre Synaptic					
(i) Familial Infantile MG[a] (Congenital MG with episodic apnoea)	Infancy or early childhood Intermittent hypotonia, fatigable generalized weakness, ptosis, dysphagia, respiratory insufficiency – precipitated by infection or excitement	Decrement at low rates – 10 Hz stimulation for 5–10 min may be required before decrement appears MEPPs decreased	Autosomal recessive	Morphology of synapse normal Defect in synthesis, storage or release	Anti-ChE
(ii) Congenital LEMS[b]	Infants and children Hypotonia, ptosis, fatigable weakness including respiratory	Decrement low rates Increment at high rates Low amplitude CMAP	Case reports	Paucity of ACh vesicles Defects in quantal release	Some respond to guanidine
3. Synaptic					
AChE deficiency[a]	Early onset. Variable severity. Scoliosis. May have normal EOM, absent pupillary responses	Repetitive muscle response on nerve stim. Decremental response	Mutant gene for AChE's collagen anchor	Small nerve terminals; degenerative junctional folds	Worse with anti-ChE meds.

Notes:

[a] Clinical features distinct

[b] Clinical features similar – diagnosis requires in vitro physiologic, morphologic, and molecular genetic studies.

affected in about 75% of these cases. In most, the mutations are heteroallelic; that is, different mutations affecting each of the affected alleles are present. Over 56 AChR subunit gene mutations in 69 congenital myasthenic syndrome kinships have been described. The age of onset ranges from infancy to adulthood. Clinical manifestations include hypotonia, respiratory insufficiency, weakness of ocular and bulbar muscles and skeletal deformities. The majority of patients respond to AChE inhibitors. The findings on electrodiagnostic studies are indistinguishable from those of autoimmune myasthenia gravis. Repetitive nerve stimulation at low rates results in a decremental muscle response. The decrement is partially repaired with exercise, tetanic stimulation or AChE inhibitors as in acquired MG. A reduction in the number of ^{125}I- α-BuTx binding sites on the postsynaptic membrane, and a decrease in MEPP ampli-

tude are seen in patients with congenital AChR deficiency syndrome. Patients with congenital AChR deficiency may respond to a combination of anti-AChE agents, and 3,4-diaminopyridine (3,4-DAP) which acts by enhancing the release of ACh from the motor nerve terminal.

Slow channel syndrome

This is a postsynaptic congenital myasthenic syndrome, characterized by prolonged AChR channel open time (Engel et al., 1982; Harper & Engel, 1998). It is inherited as an autosomal dominant, with mutations having been described in the α, β, or ε subunits (Table 69.5). Clinically, slow channel syndrome is manifested by fatigable ptosis, ophthalmoparesis, trunk or extremity weakness which may be asymmetric, and often selectively involves the forearm extensors. The age of onset and clinical severity are variable. Patients may present from infancy to adulthood with a slowly progressive myopathy with superimposed fatigable weakness. Arms and trunk are often more involved than legs. Weakness does not improve and may worsen with anti-ChE agents. With a single supramaximal motor nerve stimulus, one or more repetitive CMAPs are observed ('double hump') as is also seen with AChE deficiency (see below). The repetitive discharges are accentuated by administration of edrophonium (Tensilon®). Low rate repetitive nerve stimulation produces a decrement with little or no repair on postactivation. Patients do not improve with administration of anti-ChE agents. Microelectrode studies have shown prolonged duration of MEPPs and reduced MEPP amplitudes, but the quantal content is normal. More than 10 single nucleotide mutations have been found in the α, β, and ε subunits of the AChR. Each mutation results in a 'gain of function' abnormality, with prolonged open time of the AChR ion channel due either to increased affinity of the receptor for ACh, or to slow closure of the AChR channel. In addition to sodium, excess calcium passes through the open AChR cation channel. Calcium-mediated activation of catabolic enzymes produces degeneration of the junctional folds and junctional sarcoplasm, resulting in 'endplate myopathy'. Treatment with quinidine, which blocks AChR open channels, not only helps to prevent the endplate damage, but reportedly produces improvement in the weakness.

Fast channel syndrome

This disorder is the opposite of slow channel syndrome, with abnormally brief channel opening responses to ACh, as demonstrated by patch clamp studies (Uchitel et al., 1993) (Table 69.5). This autosomal recessive disorder is symptomatic in the neonatal or infantile period, with hypotonia, ptosis, dysphagia, dysarthria and generalized fatigable weakness. The symptoms are partially responsive to cholinesterase inhibitors. Responses to repetitive nerve stimulation resemble those of autoimmune myasthenia gravis, with a decrement at low frequencies and partial repair following exercise. There is a decrease in the amplitude and duration of MEPPs, and increased resistance to desensitization by ACh. Mutation analysis has revealed a common mutation at ε P121L with the fast channel syndrome, associated with low affinity of the receptor for ACh. Patients with fast channel syndrome respond to a combination of pyridostigmine and 3,4-DAP. A second type of fast channel syndrome has been reported, with both a reduction in the number of AChRs at the motor end plate and reduced affinity for ACh. In some patients the decreased open time is combined with a deficit of AChRs (Walls et al., 1993).

Presynaptic acquired disorders of neuromuscular transmission

Lambert–Eaton myasthenic syndrome

Lambert–Eaton myasthenic syndrome (LEMS) is an acquired presynaptic disorder of the NMJ that can cause weakness similar to that of MG (O'Neill et al., 1988; Sanders, 1995). The proximal muscles of the lower limbs are most commonly affected, but other muscles may be involved as well. Cranial nerve findings, including ptosis of the eyelids and diplopia, occur in up to 70% of patients and resemble features of MG. However, the two conditions are readily distinguished, since patients with LEMS have depressed or absent reflexes, show autonomic disturbances such as dry mouth, impotence and anhidrosis, and have dramatically different electrophysiological findings. LEMS is caused by IgG autoantibodies directed against P/Q type calcium channels at motor nerve terminals and parasympathetic postganglionic nerve terminals, which can be detected in the serum of approximately 85% of patients by radioimmunoassay. These antibodies block and/or damage the calcium channels at the nerve terminal, and interfere with Ca^{2+} influx. As a result, ACh release is impaired, and the safety margin of neuromuscular transmission is reduced. EPPs fail to reach the critical threshold, producing low CMAPs. However, brief exercise or rapid (50 Hz) nerve stimulation facilitate calcium entry and ACh release, resulting in increased CMAP amplitudes. The most characteristic electrophysiologic findings in LEMS are low amplitude CMAPs in weak muscles, with striking facilitation of 100% or more on rapid rates of nerve stimulation or

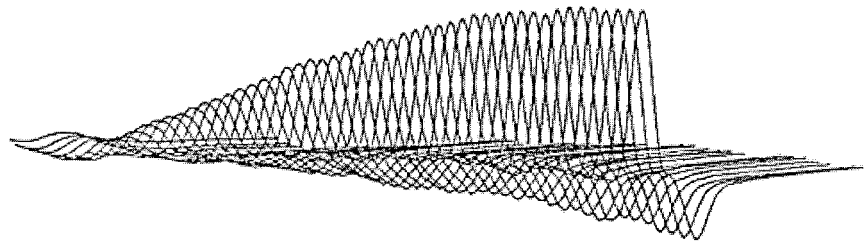

Fig. 69.5. Repetitive nerve stimulation at 50 Hz showing an incremental response in a patient with Lambert–Eaton myasthenic syndrome.

after exercise (Fig. 69.5). At low rates of nerve stimulation, decremental responses occur, as in MG. SFEMG shows increased jitter and blocking. In a majority of patients, LEMS is associated with small cell carcinoma of the lung, which is thought to trigger the autoimmune response. The diagnosis of LEMS may signal the presence of the tumour long before it would otherwise be detected, permitting early removal. However the tumour may not be detected for as long as 5 years after the neurological manifestations. Treatment of the neurological disorder involves plasmapheresis and immunosuppression, as for MG (Chalk et al., 1990). Patients often respond to 3,4-DAP, which increases ACh release (McEvoy, 1994). Treatment with anti-ChE drugs may also be helpful, but the results are usually less effective than those in MG.

Botulism

Clostridium botulinum, an anaerobic bacterium that is virtually ubiquitous in soils throughout the world, produces botulinum toxin, 'the most poisonous poison'. Seven different serotypes of botulinum toxin, and the closely related tetanus toxin, are recognized. Types A, B, E, and F have been associated with human disease; types A and B are the most common. These toxins are highly evolved zinc-containing proteases that enter motor nerve terminals by a 'Trojan horse' mechanism, and then interfere with the complex molecular events of synaptic vesicle docking and release (Pellizzari et al., 1999). As noted above, the release of ACh from vesicles involves at least 12 proteins. Each of the botulinum toxins cleaves one of these proteins in a highly specific manner. For example, synaptobrevin is a protein that is normally associated with and coats the ACh containing vesicle, and is essential for its docking and release. Botulinum toxins of types B, D, F, and G, and tetanus toxin, cleave synaptobrevin, but at different and highly specific cleavage sites. *SNAP25*, another of the synapse-related proteins, is localized at the nerve terminal's vesicle release site, and binds the synaptobrevin-coated ACh vesicle just prior to its release. Botulinum toxins type A and E cleave SNAP25 at different specific sites. The consequence of enzymatic destruction of either of these proteins is paralysis, due to the inability of the motor nerve to release quanta of acetylcholine from the presynaptic terminal in response to an action potential. One of the striking properties of botulinum toxin is its ability to maintain blockade of ACh release for months! The blocked nerve terminals are induced to sprout extensively and develop new endings, which gradually results in recovery of function.

Cl. botulinum is an obligate anaerobe, which forms hardy spores under unfavourable conditions. However, when introduced into an anaerobic nutritious environment, such as is provided by canned food, that has not been sufficiently cooked to kill the spores, the spores replicate and produce toxin. Clinically, patients who ingest botulinum toxin present with weakness involving the ocular and bulbar as well as limb and respiratory muscles, with dilated unresponsive pupils. When paralysis due to botulism begins acutely, it may be confused with a brain stem infarct or encephalitis, but the intact level of consciousness and the decreased reflexes in patients with botulinum poisoning differentiate the two, although imaging and spinal fluid studies may be necessary. The rapid generalization of paralysis and areflexia may mimic the Guillain-Barré syndrome. However, the early loss of pupillary reflexes in botulism and the descending (rather than ascending) paralysis distinguish the two disorders. Weakness resulting from botulism is prolonged, lasting for months, because the toxin permanently impairs the presynaptic release of acetylcholine from the terminals after toxin entry. Infant botulism is a rare but widespread acute paralytic illness caused by the intra-intestinal production of toxin by *Clostridium botulinum* organisms in the GI tract of the infant (Arnon et al., 1977; Cherington, 1990). Clinically, infant botulism presents in otherwise healthy infants at the age of 10 days to 6 months with paucity of movement, poor feeding, weak cry, and respiratory insufficiency occurring over hours to day. There may be a history of painless constipation for several days to 3 weeks before the onset of weakness. Examination reveals an afe-

brile, lethargic, non-irritable infant with diffuse hypotonia, weakness, ptosis, ophthalmoplegia with pupillary dilatation and paralysis, reduced gag and hypoactive reflexes. Many infants progress rapidly to require assisted ventilation. The mean duration of required assisted ventilation is 23 days. Patients typically recover in a pattern that is the reverse of their presentation, with limb movements reappearing before respiration.

Diagnosis by culture or isolation of toxin is slow and has poor sensitivity (Pickett, 1988; Shapiro et al., 1998). The principal electrodiagnostic test for botulism is the demonstration of an incremental compound muscle action potential (CMAP) response to high-rate repetitive nerve stimulation (RNS) in over 90% of patients (Clay et al., 1977).

The management of patients with botulism involves mainly supportive management of ventilation and nutrition. Patients should be watched closely in an intensive care setting and intubated early when signs of airway compromise, bulbar dysfunction, or respiratory insufficiency first arise. Administration of 3,4-DAP has been reported to improve function in some patients by enhancing ACh release.

Black widow spider venom (latrotoxin)

Black widow spider bite results in presynaptic ACh release, followed by blockade (Plomp et al., 1999; Grishin, 1998; Muller, 1993). The 'latrotoxin' binds to synaptotagmin (one of the proteins involved in the calcium-mediated ACh vesicle release process), causing fusion of synaptic vesicles with the terminal axon membrane and release of their contents. The ACh release causes severe muscle contraction and pain, and local erythema, swelling and urticaria also occur at the bite site. The main muscular symptoms are cramping, rigidity, trismus and tremor; and autonomic symptoms include vomiting, salivation, hypertension, urinary retention and diaphoresis. Eventually, exhaustion of the ACh results in inexcitability and presynaptic blockade. Treatment with antitoxin and support of vital function leads to eventual resolution.

Presynaptic congenital disorders of neuromuscular transmission

Familial infantile myasthenia (FIM)

Familial infantile myasthenia is an autosomal recessive disorder defined by default to be presynaptic given that the postsynaptic function including the number of ACh receptors, and the synaptic AChE levels are normal (Robertson et al., 1980; Mora et al., 1987). The precise presynaptic defect is unknown but is thought to be due to an abnormality of synthesis, packaging or release of ACh. The disorder presents in infancy or early childhood with intermittent hypotonia and fatigable generalized weakness, ptosis, dysphagia, weak suck, weak cry and respiratory insufficiency. Because intermittent episodes of severe weakness and respiratory failure precipitated by infection or excitement can occur, the disorder has also been named congenital myasthenia with episodic apnea. Sudden infant death or anoxic encephalopathy can occur during these crises. However, these intermittent crises lessen in frequency and severity in early to mid-childhood, leading to a clinical syndrome that is very similar to autoimmune myasthenia gravis. The symptoms respond to anti-ChE agents at all ages. Repetitive nerve stimulation usually shows a decrement of the CMAP at rest, repair with brief exercise, and the reappearance of the decrement a few minutes later. In mild cases, it may be necessary to carry out prolonged nerve stimulation at 10 Hz continuously for 5–10 minutes before a decrement can be demonstrated. Microelectrode studies show normal MEPP amplitudes and quantal content at rest, but a gradual fall in both after 10 Hz stimulation for 5–10 minutes. The morphology of the synapse, the concentration of AChE, and the number and kinetics of AChRs have all been shown to be normal by ultrastructural and histochemical studies, suggesting that FIM is caused by a defect in either the reuptake of choline into the nerve terminal or the synthesis, storage or mobilization of ACh.

Congenital Lambert–Eaton-like syndrome (LEMS)

Infants and children who present with hypotonia, ptosis, fatigable weakness, including respiratory insufficiency, and demonstrate electrophysiological features like those of LEMS have been reported (Table 69.4). On repetitive nerve stimulation, they show a decrement of the CMAP at slow rates and facilitation following brief tetanic stimulation, similar to that seen in adult LEMS . Microelectrode studies in some have shown a presynaptic defect with very low quantal content. A defect in the synthesis, mobilization or storage of ACh has been postulated. There are individual case reports, but a unified syndrome has not been defined (Albers et al., 1984; Bady et al., 1987).

Synaptic acquired disorders of neuromuscular transmission

Organophosphate and other intoxications

Certain organophosphate anti-ChE agents bind to AChE, producing virtually irreversible blockade of the enzyme,

and resulting in failure to hydrolyze ACh released at the NMJ (Besser et al., 1989; Namba et al., 1971). Their primary use is as insecticides, but extremely potent versions have been devised as nerve gases for chemical warfare (e.g. Sarin, Tabun, Soman). After initial binding to AChE, the organophosphate compounds can establish chemical bonds that cannot be reversed. Intoxication by organophosphates may occur by accidental ingestion, attempted suicide or chemical warfare. Clinically, patients present with the features of cholinergic crisis, with nicotinic and muscarinic overstimulation because of the exaggerated effects of ACh on neuromuscular junctions and autonomic ganglia. Generalized paralysis, cramps, fasciculation, miosis, wheezing, nausea, vomiting, diarrhea, sweating, increased salivation, bradycardia, hypotension and CNS effects such as confusion and seizures can all occur. The electrophysiological findings resemble those of AChE deficiency (see below) and slow channel syndrome, with multiple repetitive CMAPs in response to single supramaximal stimulus. If treated very early with oxime agents (such as 2-pralidoxime) and atropine, the blockade of AChE may be partially reversed. Supportive care is required until regeneration of AChE occurs (Besser et al., 1990).

Synaptic congenital disorders of neuromuscular transmission

End-plate acetylcholinesterase deficiency

Acetylcholinesterase deficiency is an autosomal recessive disease characterized by a deficiency of the asymmetric form of AChE at the neuromuscular junction (Hutchinson et al., 1993a,b; Ohno et al., 1998, 1999, 2000). A defect in the collagen-like tail that anchors the AChE to the basal lamina has been implicated by genetic studies. Patients usually present in the neonatal period or early infancy with severe generalized weakness, hypotonia, poor feeding, weak cry and respiratory insufficiency requiring mechanical ventilation. In some cases, the manifestations may be delayed until later infancy or childhood, and include symptoms similar to those of MG, including fatigable asymmetric ptosis, ophthalmoparesis, dysarthria, dysphagia and weakness of axial and limb musculature. Sluggish pupillary response to light may be seen. Spinal deformities such as scoliosis or lordosis may be present and characteristically worsen after the patient stands for few minutes. In contrast to MG, the symptoms of AChE deficiency are unresponsive to anti-ChE drugs. Electrophysiological findings may suggest the diagnosis, with repetitive CMAPs produced in response to single supramaximal stimuli. Other conditions with similar findings include pyridostigmine overdose, organophosphate poisoning, and the slow channel congenital myasthenic syndrome. The common underlying physiological feature of these conditions is prolongation of the endplate potentials (EPP), which may remain above threshold beyond the refractory period, and thereby trigger one or more additional action potentials. Repetitive nerve stimulation at 2 Hz produces a decrement of the CMAP that is minimally repaired after exercise and is not repaired following the administration of AChE inhibitors. Single fibre EMG shows increased jitter and blocking.

Histochemical studies have revealed the absence of the asymmetric form of AChE at the end plate. Because of the lack of AChE, excitotoxic effects of ACh produce endplate damage (endplate myopathy) similar to that seen with anti-ChE poisoning. There is widening of the synaptic cleft, reduction in the number and complexity of the junctional folds, and degeneration of the subcellular components of the sarcoplasm. Most of the nerve terminals are small in size, and the Schwann cells often extend into the synaptic space. In addition to the above factors, AChR desensitization and depolarization block of the endplate may contribute to the reduced safety margin of neuromuscular transmission in this disease. Quantal content and MEPP amplitude are reduced in most patients.

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70

Disorders of striated muscle

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Muscle cells develop from mesenchymal cells in the embryo. They differentiate into two distinct morphologies, striated and non-striated. Striated muscle has an organized structure, and is able to contract rapidly. This is most commonly found as skeletal muscle, but also as cardiac muscle. Non-striated muscle, or smooth muscle, is generally not under voluntary control, maintains slow contraction, and is found in organs such as blood vessel walls, gastrointestinal tract, and urinary tract. In this chapter we deal with the skeletal form of striated muscle.

The basic unit of skeletal muscle is the muscle fibre. This is a single cell, with many nuclei. The muscle fibres are arranged in fascicles. Connective tissue within the fascicle is termed endomysium, the fascicle is surrounded by perimysium, and the whole muscle is surrounded by epimysium. Individual muscle fibres are 10–60 μ diameter, but are elongated, and may extend the full length of the muscle, up to 30 cm. The cytoplasm of the muscle fibre, or sarcoplasm, is composed of longitudinal threads of myofibrils, 1 μ diameter. In longitudinal section the myofibrils are transected by striations, or Z bands, which divide the myofibril into sarcomeres, 2.5 μ long at rest, and lead to the classification as striated muscle (Williams et al., 1989).

Within the sarcomere, two types of myofilament are present. Actin (5 nm diameter) attached to the Z band, and interdigitating myosin (12 nm diameter). In contracting muscle the actin filaments slide in relation to myosin. It is the making and breaking of connections between lateral projections on the myosin, and the actin, filaments, which causes the mechanical muscle contraction.

Within the muscle fibre are organelles and enzymes to provide the high level of energy necessary for muscle contraction. These include mitochondria, lipid vacuoles, and glycogen granules. Two main physiological groups of muscle fibres are recognized: slow (Type I) and fast (Type II). Slow muscles are more red than fast, and are rich in mitochondria and oxidative enzymes, but poor in phosphorylation. Slow fibres perform aerobic metabolism, in addition to the glycolytic metabolism which predominates in fast fibres. Slow muscles are particularly suited to sustained contraction, as in postural muscles, and fast muscle to more rapid movements. Most muscles contain a mixture of the two types of fibre.

Muscle fibres develop from embryonic mesenchymal cells of the myotomes, forming myoblasts. The myoblasts fuse to form the long multinucleate cylinder, or myotube. Some myoblasts persist into adult life as satellite cells, which lie below the basement membrane. When a muscle fibre is damaged, satellite cells may fuse to form part of the new fibre. Skeletal muscle is capable of regeneration, but with progressive damage may degenerate and be replaced by connective tissue, which may be fibrous, and cause contracture.

Skeletal muscle is dependent on innervation for its development, maintenance and function. The terminal branches of the motor nerves end at the motor end plate on individual muscle fibres. Skeletal muscle is organized at a functional level into motor units. The motor unit is a single alpha motor neuron and the muscle fibres it innervates. In muscles requiring precise control, for example the extrinsic ocular muscles, the motor unit may comprise only 6–13 muscle fibres, while in large limb muscles there may be up to 2000 muscle fibres. The muscle fibres of an individual motor unit may be spread diffusely in the muscle. The nerve impulse releases the neurotransmitter acetylcholine at the motor end plate, causing depolarization of the sarcolemma (the end plate potential), and at a critical level a massive depolarization (the action potential) occurs. This depolarization spreads at 5 m/s over the whole muscle fibre membrane, causing a contraction of the muscle fibre, lasting 25–75 ms. Repeated action potentials cause sustained contraction, but with a refractory

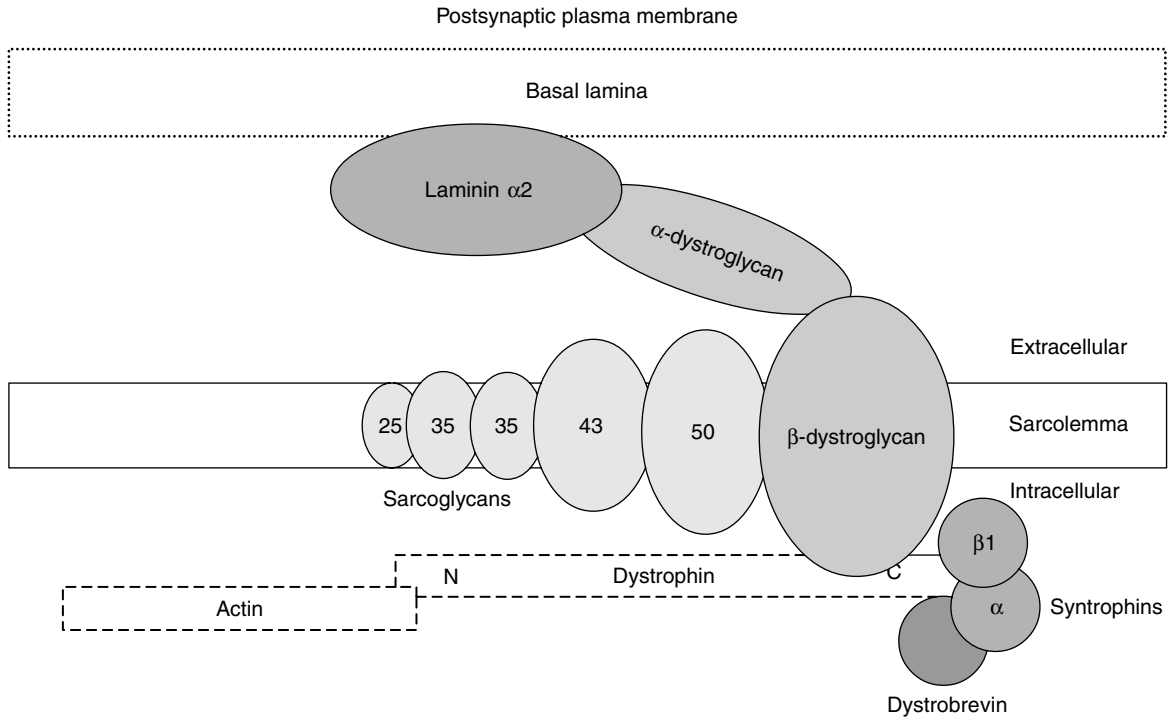


Fig. 70.1. Diagrammatic representation of the dystrophin-associated complex in the muscle fibre membrane.

period of around 10 ms. Isolated muscle fibres attain an 'all or none' contraction, the variable contraction force of a muscle being determined by the recruitment of motor units.

The clinical disorders of human skeletal muscle reflect the organization of the skeletal muscle described above. The muscular dystrophies are predominantly disorders of muscle fibre structural proteins. The molecular pathology of many of these has become clearer in recent years. Other muscle diseases remain defined at a morphological level, for example the core diseases. The inflammatory myopathies place muscle fibres in the context of systemic diseases, with generalized or targeted immunological mechanisms. In some of these, the primary mechanism may be ischemia as a result of vasculitis. Muscle fibres are dependent on an efficient metabolism, and acquired myopathies may be associated with endocrine, toxic, pharmacologic, and other disruptions of the metabolic process. Separate chapters in this book deal with other specific disorders of skeletal muscle, i.e. metabolic myopathies (including mitochondrial disorders), channelopathies (including periodic paralyses), and disorders of the peripheral nerve, motor neuron, or neuromuscular junction, which may cause secondary skeletal muscle dysfunction and disease.

Muscular dystrophies

The muscular dystrophies are genetically determined myopathies, characterized by progressive weakness. They comprise a wide range of disorders, of varying severity. Some present in severe form at birth, and others in mild form in adult life. Original descriptions referred to the clinical presentation, for example limb girdle muscular dystrophy, distal myopathy, facioscapulohumeral dystrophy, and other distinct phenotypes for example Duchenne muscular dystrophy, and Becker muscular dystrophy. The determination of clinical phenotype remains important, but the identification of the molecular basis for many of the muscular dystrophies is leading to a revision of classification based on molecular diagnostics. It is through identification and clarification of the molecular basis for these conditions that effective therapy may be developed in the future (Orrell & Griggs, 1999).

The understanding of the muscular dystrophies requires consideration of the proteins of the sarcolemma related cytoskeleton (Fig. 70.1) (Molnar & Karpati, 1999). These include dystrophin, the sarcoglycans and dystroglycan (Sunada & Campbell, 1995; Beckmann, 1996). The current classification based on identified proteins and genes is given in Table 70.1.

Table 70.1(*a*). A classification of muscular dystrophies based on identified gene and protein abnormalities

Group	Disease	Inheritance	Gene	Gene product
Calpain	Limb–girdle	AR	LGMD3A (CAPN3)	calpain 3
Caveolin	Limb–girdle	AD	LGMD1C (CAV3)	caveolin-3
Collagen	Bethlem myopathy	AD	COL6A1–3	collagen type VI subunit a1, 2 or 3
αB-crystallin	Desmin-related myopathy	AD	CRYAB	αB-crystallin
Desmin	Desmin-related myopathy	AD	DES	desmin
Dysferlin	Limb–girdle	AR	LGMD2B	dysferlin
	Miyoshi distal myopathy	AR	MM	dysferlin
Dystrophin	Duchenne/Becker	XR	DMD (DYS)	dystrophin
Emerin	Emery–Dreifuss	XR	EMD	emerin
Fukutin	Fukuyama congenital muscular dystrophy	AR	FCMD	fukutin
Integrin	Congenital muscular dystrophy with integrin deficiency	AR	ITGA7	integrin α7
Lamin	Emery–Dreiguss	AD	LMNA	lamin A/C
	Limb–girdle	AD	LMNA (LGMD1B)	lamin A/C
Merosin	Congenital muscular dystrophy with merosin deficiency	AR	LAMA2	merosin, or laminin α2 chain
Myotubularin	Myotubular myopathy	XR	MTMX	myotubularin
Nebulin	Nemaline myopathy	AS	NEM2	nebulin
Plectin	Epidermolysis bullosa simplex associated with late-onset muscular dystrophy	AR	MD-EBS	plectin
Polyadenyl binding protein	oculopharyngeal	AD	OPMD (PABP2)	polyadenyl binding protein 2
Protein kinase	Myotonic dystrophy	AD	DMPK	myotonin protein kinase
Sarcoglycan	Limb–girdle	AR	LGMD2D (SGCA)	α-sarcoglycan, or adhalin
		AR	LGMD2E (SGCB)	β-sarcoglycan
		AR	LGMD2C (SGCG)	γ-sarcoglycan
		AR	LGMD2F (SGCD)	δ-sarcoglycan
Skeletal muscle alpha actin	Nemaline myopathy	AR	ACTA1	skeletal muscle alpha actin
Ryanodine receptor	Central core disease	AD	CCD (RYR1)	ryanodine receptor
Tafazzin	Barth syndrome	XR		tafazzin
Telethonin	Limb–girdle	AR	LGMD2G	telethonin
α tropomyosin	Nemaline myopathy	AD	NEM1 (TPM3)	α tropomyosin

Notes:
AR = Autosomal recessive; AD = Autosomal dominant; XR = X-linked recessive.
Source: Based on the neuromuscular disorders gene location table compiled by Jean-Claude Kaplan and Bertrand Fontaine (Kaplan & Fontaine, 2000).

Table 70.1(*b*). A classification of muscular dystrophies where the gene and protein abnormality have not yet been identified

Disease	Inheritance	Gene	Gene location
Gacioscapulohumesal	AD	FSHD	4q35
Limb–girdle	AD	LGMD1A	5q23–q34
	AD	LGMD1D	6q23
	AD	LGMD1E	7q
	AR	LGMD2H	9q31–q34.1
	AR	LGMD2I	19q13.3
Distal myopathies			
Nonaka–hereditary inclusion body myopathy	AR	DMRV	9
Markesbery–Griggs-Udd	AD	TMD	2q31–33
ADDM–Welander	AD	MPD1	14q11.2–13
Other myopathies			
Vocal cord and pharyngeal weakness with autosomal dominant distal myopathy	AD	VPDMD	5q31
Autosomal dominant myopathy with proximal muscle weakness and early respiratory muscle involvement	AD	MPRM1	2q24–31
	AD	MPRM2	2q21
Myotonic			
Myotonic dystrophy type 2	AD	DM2	3q

Notes:
AR = Autosomal recessive; AD = Autosomal dominant.
Source: Based on the neuromuscular disorders gene location table compiled by Jean-Claude Kaplan and Bertrand Fontaine (Kaplan, 2000).

Table 70.2. The clinical presentations of dystrophinopathies

Classical childhood onset Duchenne muscular dystrophy
Milder Duchenne muscular dystrophy
Manifesting Duchenne muscular dystrophy in female carriers
Becker muscular dystrophy
Quadriceps myopathy
Cramps with myoglobinuria
Phenotypically normal individuals (including hypercemia)

Dystrophinopathies

Duchenne and Becker muscular dystrophies are dystrophinopathies. The dystrophin gene is very large, with around 2.4 million bases (Koenig et al., 1987). It is located on the short arm of the X chromosome. The gene encodes the dystrophin protein, which is a rod shaped molecule, accounting for around 5% of the muscle membrane-associated cytoskeletal protein (Koenig et al., 1988). Dystrophin is especially present at the neuromuscular junction. The function is probably related to mechanical reinforcement of the sarcolemma, and an anchor for the other proteins, such as sarcoglycans. The clinical presentations of dystrophinopathies are shown in Table 70.2.

The most typical presentation of Duchenne muscular dystrophy (Emery, 1993) is of a normal boy at birth, but with delayed motor milestones, and increasing difficulty walking by age 5 years. Muscle weakness is mainly proximal, and leads to Gowers' sign on rising from the floor. Hypertrophy of the calf muscles is often present (Fig. 70.2). Typically the boy is unable to walk by age 10 years, and subsequently respiratory insufficiency is progressive. Cardiomyopathy also develops, with death usually by his 20s (Brooke et al., 1989).

Duchenne muscular dystrophy is X linked, but may present in milder forms in carrier females, and sometimes in a form indistinguishable from that in males (Hoffman et al., 1992). Becker muscular dystrophy is a variant of Duchenne muscular dystrophy, with a milder phenotype, explicable by the molecular mechanisms (Baumbach et al., 1989; Koenig et al., 1989; Medori et al., 1989). Age of onset is usually later than for Duchene muscular dystrophy, up to 20 years, and may be walking to age 40 years, with death from respiratory insufficiency or cardiomyopathy usually between 30 and 60 years age. Milder forms of dystrophinopathy may present with muscle cramps (Gospe et al., 1989), or quadriceps myopathy (Sunohara et al., 1990).

In most individuals with Duchenne muscular dystrophy there is an out-of-frame deletion (Gillard et al., 1989; Abbs & Bobrow, 1992; Bushby, 1992), producing an unstable truncated dystrophin protein. In others there may be a point mutation (Roberts et al., 1992). In-frame mutations are associated with the Becker phenotype, with a less severe disruption of dystrophin (Koenig et al., 1989; Beggs et al., 1991).

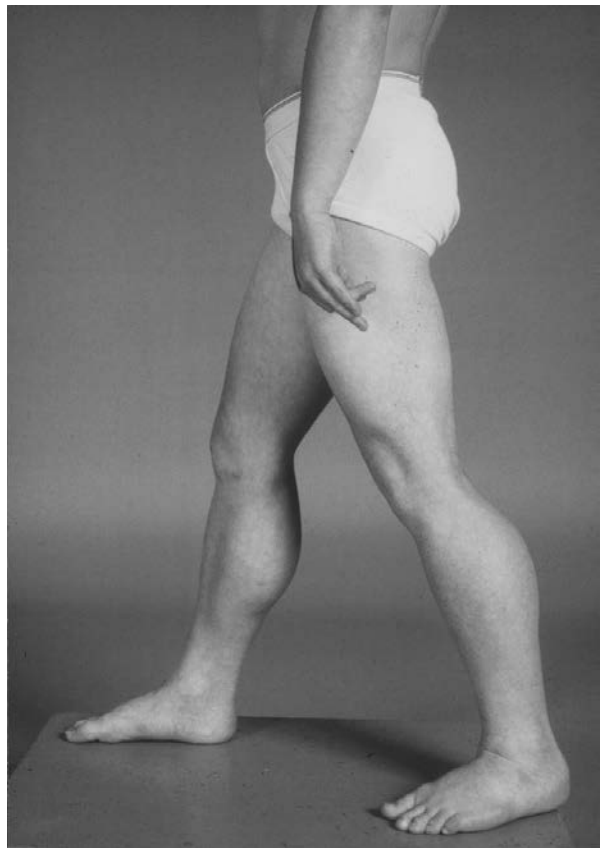


Fig. 70.2. Dystrophinopathy. Calf muscle enlargement is evident in this boy with a partial deficiency of dystrophin. Note that the hand position (palms facing backwards) indicates the presence of shoulder girdle weakness.

Creatine kinase is markedly elevated, EMG will show myopathic features, and ECG may show cardiomyopathy. Multiplex PCR (polymerase chain reaction) will detect common gene deletions (Chamberlain et al., 1988). Total or partial dystrophin deficiency may be identified by Western blot protein analysis (Bulman et al., 1991). Muscle biopsy immunohistochemistry will show absent dystrophin staining. In addition, there is secondary deficiency of immunostaining for α and β dystroglycan, all sarcoglycans, but preserved merosin (Ohlendieck et al., 1993). (In primary sarcoglycanopathy, dystrophin staining is normal.)

Management of patients with Duchenne muscular dystrophy includes attention to issues such as physiotherapy, respiratory support, cardiac care, bracing, and orthopedic surgical procedures. The education and other social needs of the patient and family also require attention. Treatment

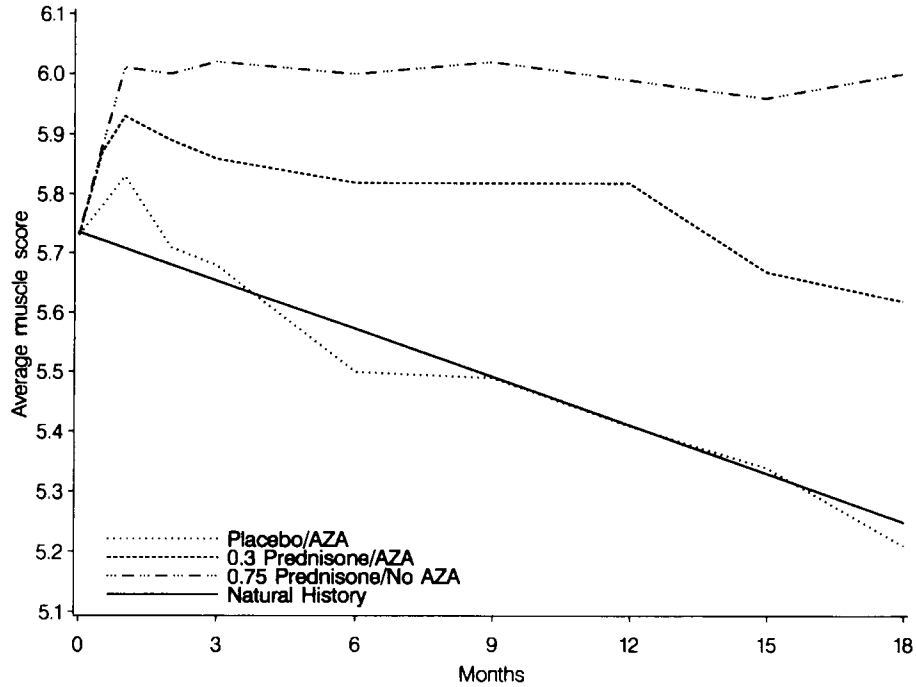


Fig. 70.3. Treatment of Duchenne muscular dystrophy. Comparison of average muscle score on manual muscle testing in the three groups. Azathioprine alone or added to prednisone 0.3 mg/kg/d resulted in no improvement additional to that of prednisone. (From Griggs et al., 1993.)

with steroids has been shown to have benefit in Duchenne muscular dystrophy (Fig. 70.3) (Griggs et al., 1991). Gene therapy is being explored, using various techniques, but has not yet shown clinical benefit (Karpati & Ascadi, 1993). Techniques initially included myoblast transfer (Mendell et al., 1995), and now virus vector transfer, and utilization of utrophin (Blake et al., 1996). Around 70% of dystrophin mutations are inherited from the mother, but in 30% the mutation is new. The genetic implications for the patient and family require careful consideration.

Dystrophin-associated proteinopathies

There are an increasing number of sarcolemmal proteins associated with human muscular dystrophy (Fig. 70.1). The dystrophin-associated sarcolemmal proteins appear to stabilize the membrane during contraction (Ozawa et al., 1995). They also attach the intracellular actin to the extracellular basal lamina.

Sarcoglycanopathies

The sarcoglycan complex is a group of membrane integrated proteins. It contains a number of subunits, including α, β, γ and δ (Roberds et al., 1994). α-Sarcoglycan has been called adhalin (Kaplan & Campbell, 1994; Eymar et al., 1997). An abnormality in one of the subunits may lead to loss of the full complex. In severe childhood autosomal recessive muscular dystrophy (SCARMD), there is loss of the sarcoglycan complex, with mutations in any of the individual subunits. Sarcoglycanopathies account for around 10% of autosomal recessive limb girdle muscular dystrophies (Duggan et al., 1996, 1997).

The clinical presentation of sarcoglycanopathy may be indistinguishable from dystrophinopathy. Phenotypes include SCARMD, Duchenne muscular dystrophy like muscular dystrophy, and limb girdle muscular dystrophy. Age at onset and severity is variable, usually between 2 and 20 years age. There is no cardiac involvement. Five to 10% of patients with dystrophin-positive muscular dystrophies have α-sarcoglycanopathy (adhalin deficiency) (Duggan et al., 1997). Creatine kinase is elevated (10–100×), EMG is myopathic, and muscle biopsy shows dystrophic features. Dystrophin immunostaining of muscle is usually normal. α-, β-, γ-, and δ-sarcoglycans may all be deficient on immunostaining (Sewry et al., 1996; Barresi et al., 1997). Western blot and gene analysis is necessary to determine the primary genetic abnormality. The mutations are in the α (Ljunggren et al., 1995; Piccolo et al., 1995), β (Lim et al., 1995), γ (Noguchi et al., 1995; McNally et al., 1996), and δ (Nigro et al., 1996) genes. Mutations must be identified in both alleles of the gene. Mutations are most commonly found in α sarcoglycan (Hayashi & Arahata, 1997), including

Table 70.3. Genetic classification of limb–girdle muscular dystrophies (LGMD)

	Gene	Gene locus	Gene product
Autosomal dominant LGMD	LGMD1A	5q22–24	?
	LGMD1B	1q11–1	Lamin A/C (LMNA)
	LGMD1C	3p25	Caveolin 3 (CAV3)
	LGMD1D	6q23	?
	LGMD1E	7q	?
Autosomal recessive LGMD			
Calpain deficient LGMD	LGMD2A	15q15.1–21.2	Calpain 3 (CAPN3)
Dysferlin deficient LGMD	LGMD2B	2p13	Dysferlin (DYSF)
Telethonin mutant LGMD	LGMD2G	17q11–12	Telethonin
Sarcoglycanopathies			
α-sarcoglycanopathy	LGMD2D	17q12–21.33	α-sarcoglycan (adhalin)
β-sarcoglycanopathy	LGMD2E	4q12	β-sarcoglycan (SGCB)
γ-sarcoglycanopathy	LGMD2C	13q13	γ-sarcoglycan (SGCG)
δ-sarcoglycanopathy	LGMD2F	5q33–34	δ-sarcoglycan (SGCD)
Unknown protein			
	LGMD2H	9q31–33	?
	LGMD2I	19q13.3	?

Notes:
Based on Bushby (1999), and Kaplan and Fontaine (2000).
? = gene and product unknown at present.

missense and nonsense point mutations, deletions, and duplications. The clinical management of patients is similar to that of Duchenne muscular dystrophy, although steroids are generally not effective.

Calpainopathy

Calpain 3 (calcium activated neutral protease) is an intracellular protein. Mutations are associated with limb girdle muscular dystrophy (LGMD2A) (Richard et al., 1997). The clinical features are similar to the sarcoglycanopathies, with increased creatine kinase, calf hypertrophy, and weakness especially in the pelvic girdle. Scapuloperoneal weakness may be present.

Merosin-deficient congenital muscular dystrophy

The basal lamina includes a number of laminin proteins. Muscle fibre laminin complex comprises α2 heavy chain, and β1 or β2 and γ1 light chain (Wewer & Engwall, 1996). Laminins that contain α2 heavy chain (laminins 2 and 4) are termed merosin. The dystroglycans link laminin 2 to the dystrophin–actin complex. The complex of actin, dystrophin, dystroglycan and laminin is involved in linking the plasmalemma to the basal lamina, and may mechanically stabilize the sarcolemma during contraction of the muscle fibre.

Congenital muscular dystrophy is a clinical presentation with hypotonicity, wasting and weakness of face and limb muscles, and joint contractures (Dubowitz & Fardeau, 1995). Up to 40% of neonatal-onset congenital muscular dystrophy is due to merosin (laminin α2) deficiency (Sewry et al., 1995). The patient with merosin deficiency shows features of congenital muscular dystrophy from birth, and never walks. Creatine kinase is normal or mildly elevated. EMG is myopathic. MRI of the brain shows high signal lesions in the white matter. Muscle biopsy is dystrophic. Laminin α2 immunostaining is negative, but sarcoglycan immunostaining is positive. Nonsense and splice site mutations of the LAMA2 gene have been identified (Helbing-Leclerc et al., 1995; Guicheney et al., 1997). Clinical management is similar to the muscular dystrophies. Genetic counselling is appropriate, and prenatal diagnosis is possible.

In Japan, Fukuyama congenital muscular dystrophy should be considered (Fukuyama et al., 1981), with mutations in the gene encoding fukutin identified (Kobayashi et al., 1998). Severe mental retardation and other structural brain abnormalities may be associated.

Other dystrophin complex-associated proteinopathies

An increasing number of muscular dystrophies with abnormalities of dystrophin-associated proteins are recognized, as summarized in Table 70.1. Whilst the classification of muscular dystrophies in terms of proteinopathy is helpful for understanding the pathogenesis of the condi-

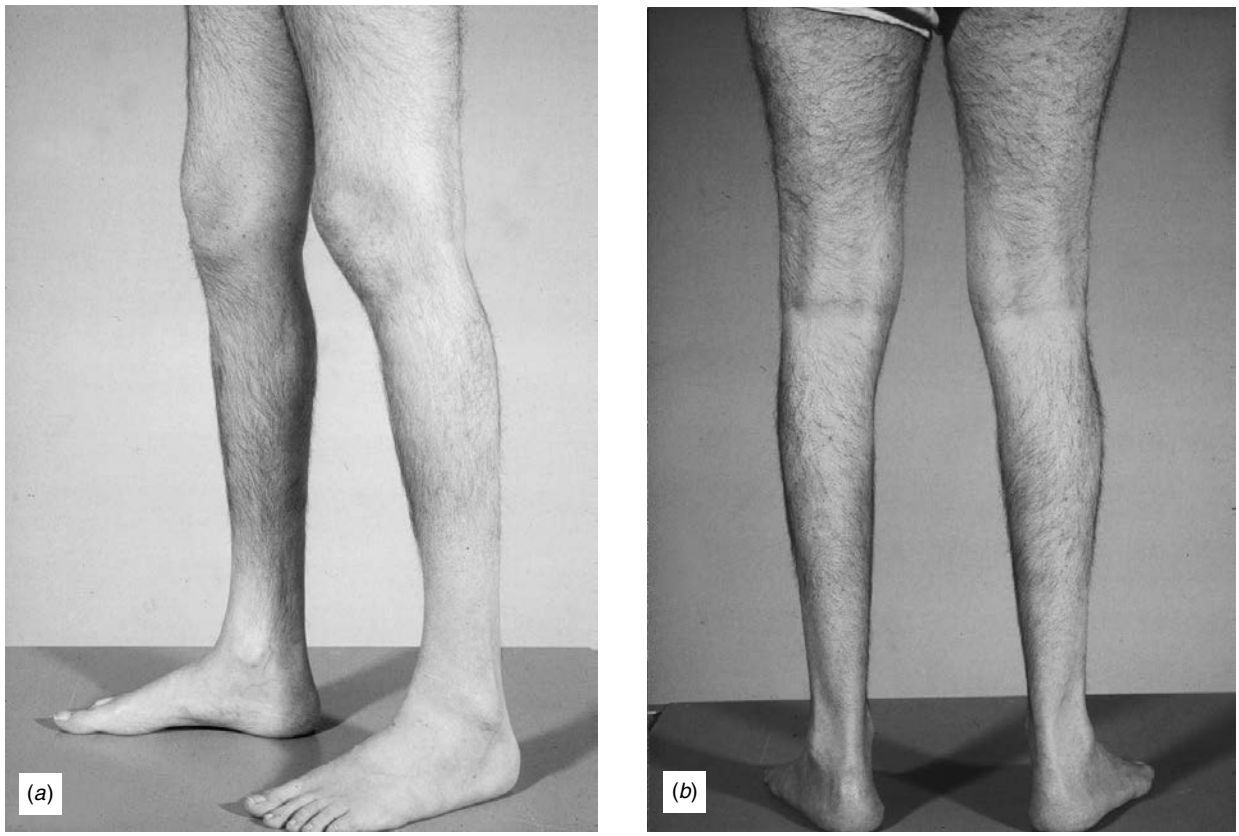


Fig. 70.4. (*a*) (*b*). Distal myopathy. There is striking atrophy of posterior>anterior compartment muscle atrophy in this man with Miyoshi myopathy.

tions, the clinical phenotype classification remains important. This is illustrated by the limb girdle muscular dystrophies, which are summarized in Table 70.3.

Distal myopathies

This difficulty in classifying on a molecular basis is also reflected in the distal myopathies, where the gene for autosomal recessive distal muscular dystrophy (ARDMD, Miyoshi myopathy) (Miyoshi et al., 1977; Linssen et al., 1997), is the same as that for the limb girdle muscular dystrophy, LGMD2B, and encodes the dysferlin protein (Liu et al., 1998).

The distal myopathies are primary muscle disorders with progressive muscle weakness and wasting, commencing in the hands or feet (Fig. 70.4). They are rare conditions, but genetic abnormalities have been identified in a number of these (Table 70.4) (Orrell & Griggs, 1999).

Facioscapulohumeral muscular dystrophy

Facioscapulohumeral muscular dystrophy has a distinctive pattern of progressive muscle weakness, involving the face, scapular stabilizers, proximal arms, and peroneal muscles (Fig. 70.5). Age at onset is from infancy to middle age. Clinical signs are present in more than 90% of those affected by age 20 years (Lunt et al., 1989). Muscle biopsy shows dystrophic changes, and sometimes inflammatory changes (Orrell & Griggs, 1999).

A reduction in the number of repeats of a 3.3 kb sequence, termed D4Z4, on the terminal region of chromosome 4q, is associated with facioscapulohumeral muscular dystrophy (Wijmenga et al., 1992; Van Deutekom et al., 1993). Molecular diagnostic testing is available (Deidda et al., 1996; Tawil et al., 1998; Orrell et al., 1999). Inheritance is autosomal dominant. Principles of symptomatic management are similar to those of the other muscular dystrophies. Clinical trials of albuterol, a β-adrenergic agonist, showed some initial possible benefit (Fig. 70.6) (Kissel et al., 1998), but more extensive trials have not yet supported its routine clinical use.

Emery–Dreifuss muscular dystrophy

Emery–Dreifuss muscular dystrophy is an X-linked disorder, characterized by slowly progressive wasting and

Table 70.4. Distal muscular dystrophies

Type	Inheritance	Initial weakness	CK	Biopsy	Gene
Nonaka – early adult – onset type I (familial IBM[a])	Autosomal recessive or sporadic	Legs: anterior compartment	Slightly to moderately increased, usually <5× normal	Vacuolar myopathy	9p1–q1
Miyoshi – early adult – onset type II (LGMD 2B[b])	Autosomal recessive or sporadic	Legs: posterior compartment	Increased 10–150× normal	Myopathic, usually without vacuoles; gastrocnemius often 'end stage'	2p13 dysferlin
Laing – early adult – onset type III	Autosomal dominant	Legs: anterior compartment Neck flexors	Slightly increased, <3× normal	Moderate myopathic changes/no vacuoles	14q
Welander–late adult type I	Autosomal dominant	Hands: fingers/wrist extensors	Normal or slightly increased	Myopathic; vacuoles in some cases	2p13
Markesbery–Griggs/ Udd Late adult onset type II	Autosomal dominant	Legs: anterior compartment	Normal or slightly increased	Vacuolar myopathy	2q

Notes:

[a] Autosomal recessive familial inclusion body myopathy (IBM), also known as quadriceps sparing myopathy, has been genetically linked with Nonaka distal myopathy.

[b] Limb–girdle muscular dystrophy type 2B colocalizes with Miyoshi distal myopathy.

weakness of the scapulohumeral, anterior tibial, and peroneal muscle groups. A distinctive feature is early development of muscle contractures, especially in the elbows, Achilles tendons, and posterior cervical muscles. Cardiomyopathy with conduction defects is common. Onset is usually around age 4 years (Emery & Dreifuss, 1966).

Serum creatine kinase may be normal or moderately elevated (10×). EMG and muscle biopsy are myopathic. Deficiency of emerin may be identified on immunostaining of muscle, and mutations of the EDMD gene identified (Bione et al., 1995; Klauck et al., 1995). Emerin is ubiquitously expressed. It is normally localized to the nuclear membrane. Carrier females may show clinical manifestations. Heart block is a common cause of death, and regular cardiac assessment may allow appropriate insertion of a cardiac pacemaker. Active and passive stretching may delay the development of muscle contractures.

A similar phenotype may be present in autosomal recessive and dominant forms, and not all patients with clinical features of Emery–Dreifuss muscular dystrophy have abnormalities of emerin immunostaining. Other genes are involved. Mutations in the LMNA1 gene, encoding the lamin A and C proteins, are present in some autosomal dominant (Bonne et al., 1999) and recessive (Barletta et al., 2000) forms.

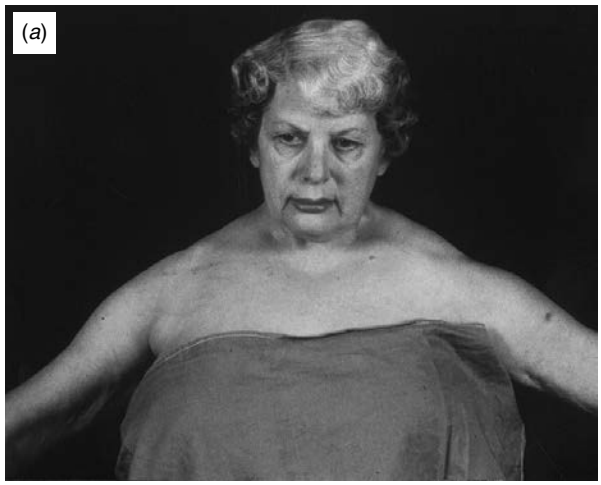
Bethlem myopathy should also be considered (Bethlem & van Wijngaarden, 1976). This is an autosomal dominant myopathy, associated with contractures, but without cardiac involvement. Mutations have been found in type VI collagen genes (Jobsis et al., 1996).

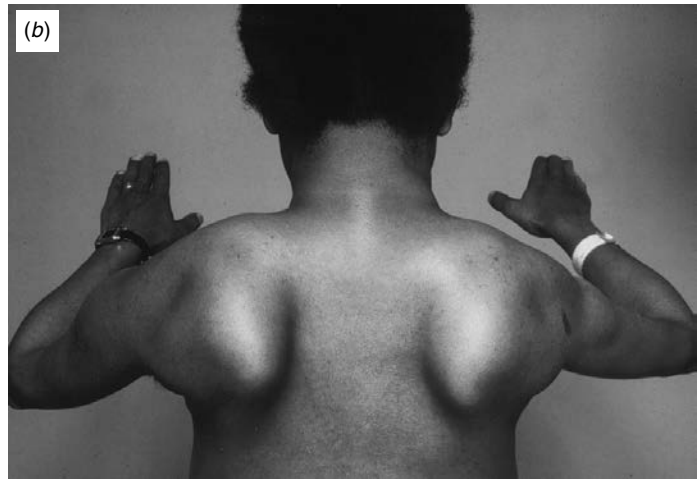
Oculopharyngeal muscular dystrophy

Oculopharyngeal muscular dystrophy (Fig. 70.7) affects ocular and pharyngeal muscles, causing ptosis, dysphagia, and dysarthria, but may also affect other limb girdle and distal limb muscles. Muscle weakness progresses slowly, and is rarely disabling (Victor et al., 1962). Ptosis may obstruct vision, and dysphagia may lead to weight loss, unless treated. Muscle biopsy shows myopathic features, and rimmed vacuoles. Inheritance is autosomal dominant, and a short GCG repeat expansion is present in the *PABP2* gene (poly[A]binding protein 2) (Brais et al., 1998). PABP2 protein is involved in mRNA polyadenylation.

Morphologically defined myopathies

A number of rare myopathies remain defined by their morphological features. These include the core diseases, centronuclear myopathy, nemaline myopathy, and desmin myopathy. Many present as congenital myopathies.





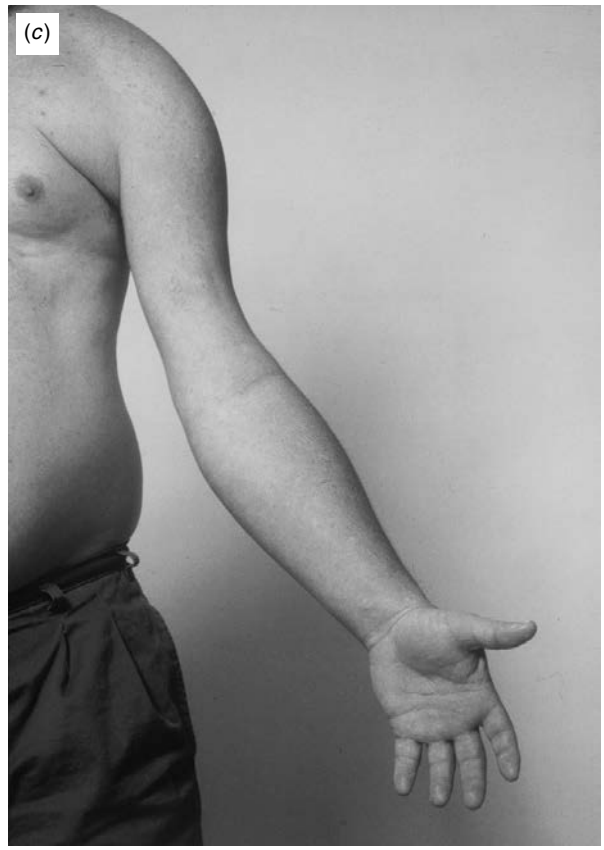


Fig. 70.5. Facioscapulohumeral dystrophy
(*a*) 'Glum' facial appearance and typical shoulder appearance. The scapular winging and descent of the shoulders is evident.
(*b*) Bilateral scapular winging.
(*c*) Atrophy of the elbow flexors and extensors with relative preservation of forearm muscles giving a 'popeye' appearance.

Central core disease

Central core disease is a congenital myopathy, presenting with congenital or early childhood muscle weakness and hypotonia, with developmental delay (Shy & Magee, 1956). There are probably a number of genetic causes, and there is an association with malignant hyperthermia (Denborough et al., 1973). Mutations in the ryanodine receptor gene are identified in central core disease and malignant hyperthermia (Quane et al., 1993). The characteristic morphological feature is the core, which is visible on muscle biopsy as a central, or eccentric, lesion within the muscle fibre. This is probably a result of abnormal maturation and fusion of the myotubes.

Minicore or multicore disease

The cores of minicore or multicore disease are smaller than in central core disease (Paljarvi et al., 1987). The cores are multiple, and the sarcomeres are disrupted. The clinical features are variable, with early childhood onset of slowly progressive muscle weakness. There may be weakness of the extraocular muscles (Fardeau, 1987).

Nemaline myopathy

Nemaline myopathy is a congenital myopathy characterized by formation of rods derived from the Z bands. The term 'nemaline' is derived from the Greek word for thread. The nemaline rods are visible on muscle biopsy (Fig. 70.8, see colour plate section). They are often found in clusters beneath the sarcolemma, but also within the muscle fibre. The ultrastructure of the rods is identical to that of Z bands, containing α actinin (Shy et al., 1963).

Autosomal dominant and recessive forms are

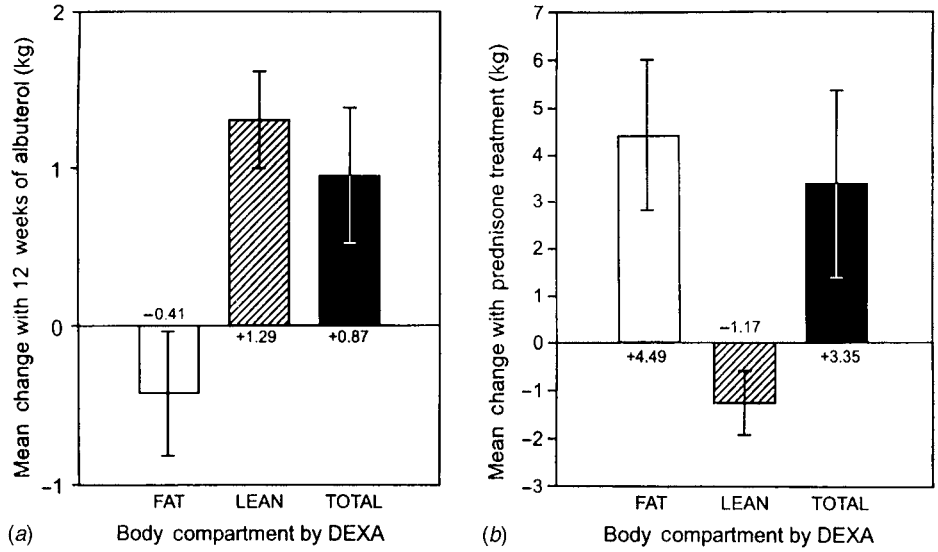


Fig. 70.6. Bar graphs show mean change at 12 weeks in fat, lean, and total body mass compartments for facioscapulohumeral dystrophy patients on albuterol (*a*). The changes contrast with the same determinations made in a prior open-label prednisone trial (*b*). Error bars represent 1 SEM.(From Kissel et al., 1998.)

recognized, as well as sporadic forms. The genes for some forms have been identified: α-tropomyosin (Laing et al., 1995) in autosomal dominant forms, nebulin (Pelin et al., 1999) in autosomal recessive forms, and skeletal muscle α-actin (Nowak et al., 1999) in autosomal dominant and recessive forms. The clinical presentation is most usual in infancy, with hypotonia and proximal or generalized muscle weakness. Facial weakness, and respiratory insufficiency, may be present. More severe neonatal forms, and less severe adult-onset forms occur (Wallgren-Pettersson, 1989; Shimomura & Nonaka, 1989).

Inflammatory myopathies

There are three main groups of inflammatory myopathies: polymyositis, dermatomyositis, and inclusion body myositis, together with some rare conditions such as eosinophilic polymyositis, focal myositis, and myositis associated with other systemic disorders (Dalakas, 1991; Amato & Barohn, 1999).

Polymyositis

Polymyositis is the result of an antigen-specific, cell-mediated immune response directed against skeletal muscle fibres. The specific antigen is not known. On muscle biopsy, there is endomysial inflammation, and mononuclear inflammatory cell invasion of non-necrotic muscle fibres (Fig. 70.9, see colour plate section). These are mainly CD8+ cytotoxic T-cells and macrophages (Arahata & Engel, 1984; Engel & Arahata, 1984). Major histocompatibility complex (MHC) class 1 antigen is expressed on invaded and non-invaded muscle fibres.

Polymyositis most commonly presents in adults, especially women. Initial symptoms are of proximal limb weakness, and neck flexion weakness. Muscle pain and tenderness may be present. Dysphagia may also occur due to oropharyngeal and oesophageal involvement. The myositis may include cardiac muscle, with cardiac failure and conduction abnormalities. Around 10% of patients develop interstitial lung disease, often associated with Jo-1 antibodies (Love et al., 1991). There is a possible mild increased incidence of malignancy in patients with polymyositis (Bohan et al., 1977; Sigurgeirsson et al., 1992; Callen, 1994).

Serum creatine kinase is elevated (5–10×). Jo-1 antibodies are present in around 20% of patients with polymyositis, associated with interstitial lung disease (Hochberg et al., 1984). A more aggressive form of polymyositis may be associated with antibodies to SRP. These patients are resistant to treatment, and have a poor prognosis (Joffe et al., 1993; Miller, 1993). EMG shows features of a myopathy, with additional increased insertional and spontaneous activity.

Polymyositis usually responds to treatment with oral prednisone (Dalakas, 1994). Initial response may take up to 6 months. Prednisone is usually commenced at a high dose, 1mg/kg/day, or higher. Depending on clinical progress, the dose is adjusted, slowly reducing the dose, or converting to alternate day dosing. Azathioprine may be

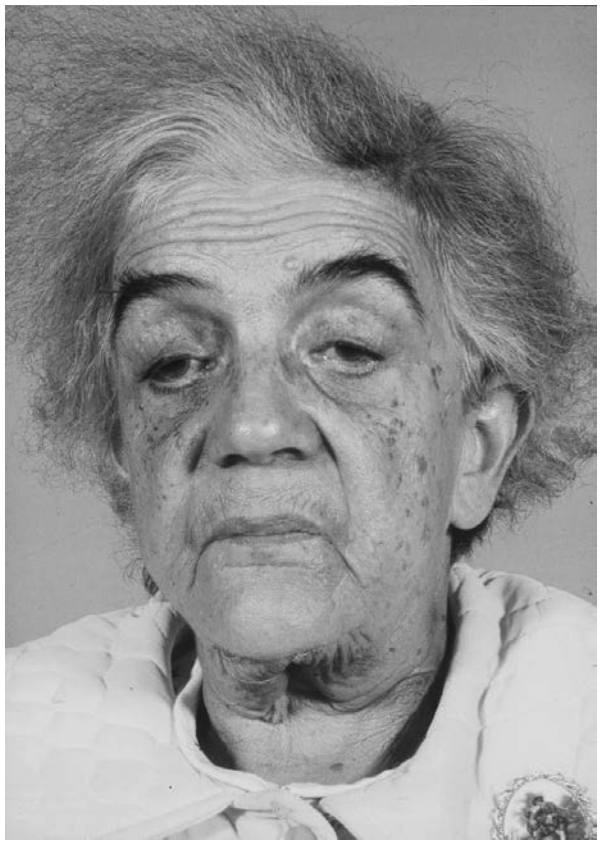


Fig. 70.7. Oculopharyngeal dystrophy: an 84-year-old woman with characteristic appearance. Bilateral ptosis, accompanied by frontalis muscle contraction attempting to elevate the lids. Lower facial weakness is apparent as well.

added if there is inadequate response, or if prednisone is poorly tolerated. The main guide to response is clinical improvement. Serum creatine kinase may be helpful, but may be normal in patients with active disease, or elevated in the absence of disability. If patients become weaker while taking prednisone, a superadded steroid myopathy should be considered. Prophylactic management of steroid-induced osteoporosis is usually indicated, because of the prolonged duration of treatment. In patients refractory to prednisone and azathioprine, other considerations include intravenous immunoglobulin, and rarely other immunosupressants such as methotrexate, cyclophosphamide, chlorambucil, cyclosporine and tacrolimus (Amato & Barohn, 1999).

Dermatomyositis

Dermatomyositis is a humorally mediated microangiopathy, leading to ischemic damage of muscle fibres. Dermatomyositis is an entirely distinct pathological condition from polymyositis, and should not be considered as 'polymyositis with a rash'. Muscle biopsy aids in making the distinction. In dermatomyositis, the muscle biopsy characteristically, although not always, shows perifascicular atrophy (Fig. 70.10, for (*a*) see colour plate section). This has been attributed to a watershed type hypoperfusion of the muscle fascicles, as a result of microangiopathic ischemia. The disease is multifocal. In contrast to polymyositis, invasion of non-necrotic muscle fibres by mononuclear cells is not seen. A perivascular infiltrate may be present in the perimysium. The mononuclear cells are generally macrophages, B-cells, and CD4+ T-helper cells (Arahata & Engel, 1984; Engel & Arahata, 1984).

Dermatomyositis is especially common in childhoood, but may occur at any age, and, as with polymyositis, is more common in women than men. Muscle weakness initially occurs in the proximal limb and neck flexion muscles, but also affects muscles more generally. In children there may be evidence of a more systemic illness with low grade pyrexia and myalgia (Pachman, 1995). Dysphagia may occur in 30% of patients due to involvement of oropharyngeal and esophageal muscles. Involvement of the tongue may rarely cause dysarthria (Tymms & Webb, 1985; Dalakas, 1991).

The characteristic rash of dermatomyositis is called a heliotrope rash, with purplish discoloration of the eyelids, often with some periorbital edema. Papular, scaly, erythematous lesions on the knuckles constitute Grotton's sign. A photosensitive erythematous rash may be present on the face, neck, and other exposed regions. Distal capillary loops may be present in the nail beds, with thrombi or hemorrhage. It is possible for patients to have the characteristic rash, without muscle weakness (Hochberg et al., 1986; Euwer & Sontheimer, 1993).

Subcutaneous calcification is especially common in children with dermatomyositis, but may also occur in adults (Pachman, 1995). This occurs especially on the knees and elbows, but also at other sites, with painful hard nodules, which may ulcerate (Orrell et al., 1998).

The myocardium may be involved, with conduction abnormalities (Haupt & Hutchins, 1982). Around 10% of patients with dermatomyositis develop interstitial lung disease (Dickey & Myers, 1984; Hochberg et al., 1984), often associated with Jo-1 antibodies. The skeletal and smooth muscle of the gastrointestinal tract may be involved, with dysphagia and dysmotility. Vasculitis of the gastrointestinal tract may be a problem, especially in children, with life threatening hemorrhage (Pachman, 1995). The necrotizing vasculitis may affect other tissues including retina, kidney and lungs.

In adults with dermatomyositis there appears to be an increased risk of associated malignancy (Sigurgeisson et

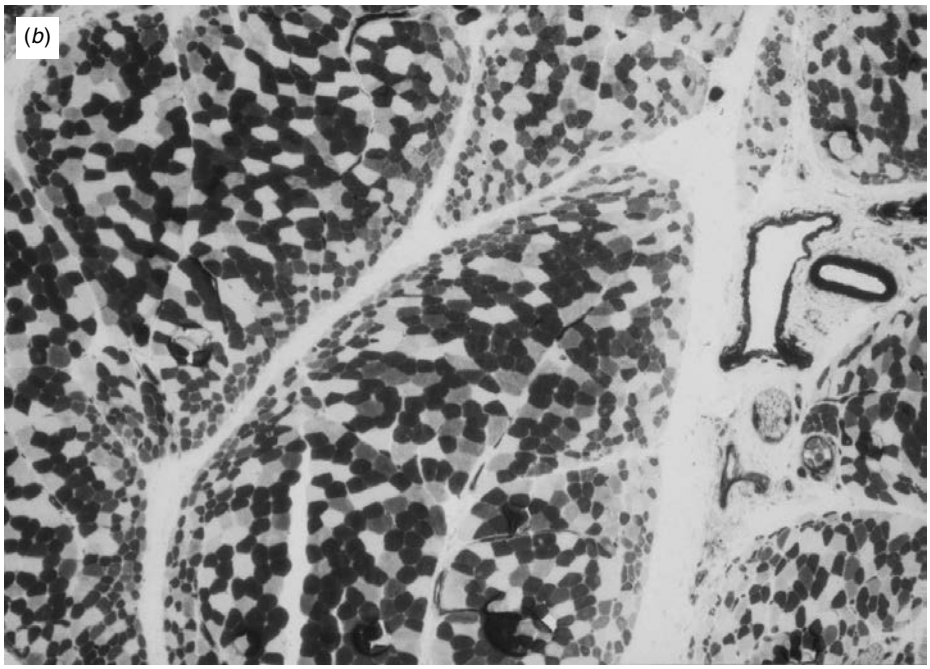


Fig. 70.10. Dermato-myositis muscle biopsy. (*a*) See colour plate section. (*b*) ATPase (pH 9.4) reaction showing that both fibre types are atrophic in a perifascicular distribution.

al., 1992). The extent to which this should be investigated is debatable, but should include full clinical history and clinical examination, with appropriate screening investigations. This examination should be repeated at appropriate intervals. Muscle function may improve after treatment of malignancy.

Serum creatine kinase may be normal or elevated (1–50×). The serum creatine kinase level does not correlate with disease severity. EMG shows features of myopathy, with increased insertional and spontaneous activity.

The treatment of dermatomyositis is similar to that of polymyositis. The rash usually improves with treatment of the myositis. Treatment of subcutaneous calcification is difficult once calcium deposits are found. Oral diltiazem has recently been suggested to be effective (Olizeri et al., 1996).

Overlap syndromes

Myositis may be associated with connective tissue disorders such as scleroderma, and mixed connective tissue disease (mixed clinical features of scleroderma, systemic lupus erythematosus, rheumatoid arthritis, and myositis). This can be either an appearance of polymyositis or dermatomyositis. The diagnostic features are those of the individual connective tissue disease. The myositis is treated as described for polymyositis and dermatomyositis.

Inclusion body myositis

The pathogenesis of inclusion body myositis is unknown. It may be a primary degenerative myopathy, with secondary inflammatory change, or possibly a primary inflammatory myopathy (Griggs et al., 1995). The characteristic findings on muscle biopsy are rimmed vacuoles within the muscle fibres (Fig. 70.11, see colour plate section). Endomysial inflammation may also be present. Amyloid deposition is demonstrated with Congo Red staining. Ragged red fibres may also be present. Electronmicroscopy demonstrates 15–21 nm tubulofilaments in the cytoplasm and intranuclear. An array of proteins including β-amyloid, β-amyloid precursor protein, prion protein, apolipoprotein E, α1-antichymotrypsin, ubiquitin, hyperphosphorylated tau, and neurofilament heavy chain, have been identified within the vacuolated fibres. For diagnostic purposes, the rimmed vacuoles may not always be present on initial biopsy, but may be found on repeated biopsy. The endomysial inflammation is by macrophages and CD8+ cytotoxic T-lymphocytes, invading non-necrotic fibres, and HMC class 1 antigens are expressed on necrotic and non-necrotic fibres. Unlike polymyositis, the T-cell response does not appear to be directed against a muscle specific antigen (Engel & Arahata, 1984).

Inclusion body myositis is the most common inflammatory myopathy in patients over 50 years of age. Patients

exhibit slowly progressive proximal and distal weakness. Unlike polymyositis and dermatomyositis, it is more common in men than women. Muscle weakness and wasting is especially prominent in quadriceps, wrist and finger flexors, and ankle dorsiflexors. Muscle weakness is often asymmetrical. Dysphagia is common, and may be severe. Mild facial weakness may occur. A peripheral neuropathy may be detected. There is no association with cardiac disease or malignancy (Lotz et al., 1989; Amato et al., 1996).

Serum creatine kinase is normal or mildly elevated (1–10×). EMG demonstrates myopathic features, with increased insertional and spontaneous activity, but may also show large polyphasic or 'neurogenic' potentials. Mild axonal sensory neuropathy is present in up to 30% of patients (Amato et al., 1996).

Patients with inclusion body myositis do not respond to treatment with the immunosuppressive agents which are effective in polymyositis and dermatomyositis. It is probable that some patients with steroid-resistant polymyositis have a form of inclusion body myositis. The condition is slowly progressive, and may lead to long term disability, but life expectancy is not usually impaired (Lotz et al., 1989).

Rimmed vacuoles may occur in other myopathies (Table 70.5). The distinction of the hereditary forms is being clarified as the genetic abnormalities are identified. These are termed inclusion body myopathies, as inflammation is not a significant finding.

Table 70.5. Rimmed vacuolar myopathies

Inclusion body myositis
Familial inclusion body myopathy
Distal myopathies
Early adult-onset type II (Nonaka)
Late adult-onset type I (Welander)
Late adult-onset type II (Markesbery–Griggs/Udd)
Oculopharyngeal muscular dystrophy
Miscellaneous myopathies

Eosinophilic polymyositis

The hypereosinophilic syndrome comprises persistent eosinophilia, absence of parasites or other known causes of eosinophilia, and signs and symptoms of organ involvement due to eosinophil infiltration (Moore et al., 1985). Myositis may form part of this syndrome, muscle biopsy showing perivascular and endomysial inflammation, predominantly eosinophils. The cause is unknown, but the muscle necrosis may be related to eosinophilic infiltration.

Clinical features are of slowly progressive muscle pain and proximal weakness, with other systemic features of the hypereosinophilic syndrome. Hypereosinophilia is a diagnostic criterion, and other features include anemia, raised created kinase, and positive rheumatoid factor. Cardiac arrhythmia or conduction block may be present on ECG, chest X-ray may show pulmonary infiltrates, and EMG demonstrates myopathic features with increased insertional and spontaneous activity. Peripheral neuropathy may also be present (Layzer et al., 1977).

Patients may respond to treatment with steroid or other immunosuppressant medication, but for some the multisystem involvement and poor response to treatment may result in a bad prognosis.

Focal myositis

Muscle biopsy demonstrates a mononuclear infiltrate of the endomysium, with macrophages and CD4+ and CD8+ T-cells. The cause is not known, but unlike polymyositis, the cell-mediated response does not appear to be directed against a muscle specific antigen (Caldwell et al., 1995).

The clinical presentation is of a solitary, painful and rapidly expanding skeletal muscle mass, often in the leg. Other diagnostic considerations include soft tissue tumours, and initial focal muscle involvement of sarcoidosis, Behçet's disease, and vasculitis. Serum creatine kinase and ESR are usually normal. The myositis usually resolves spontaneously, without treatment.

Other acquired myopathies

Endocrine myopathies

Abnormalities of muscle have been reported with most forms of endocrine disease, including iatrogenic causes. For many of these conditions, muscle dysfunction resolves on correction of the endocrine abnormality. The commonest causes of muscle dysfunction are thyroid disease (hypothyroid and hyperthyroid), and the corticosteroid disorders (Cushing's disease, Addison's disease, and iatrogenic). Other rarer endocrine causes include growth hormone, insulin, parathormone, and testosterone disturbances (Orrell et al., 1996; Zaidat et al., 1999).

Thyroxine

Hyperthyroid myopathy

Muscle weakness is present in up to 75% of patients with hyperthyroidism, with proximal myopathy being the major manifestation. Cramps, myalgia, fasciculations and

brisk reflexes may resemble amyotrophic lateral sclerosis (Serradell et al., 1990).

Thyrotoxic periodic paralysis
A periodic paralysis clinically resembling hypokalemic periodic paralysis, may be associated with thyrotoxicosis. Proximal limb and truncal weakness may last from hours to a week, and resolves on normalization of thyroid status (Satayoshi et al., 1963).

Exophthalmic Graves' disease
Exophthalmos and ocular myopathy may be associated with autoimmune thyroid disease. Exophthalmic Graves' disease may occur in patients who are biochemically hyperthyroid, but also hypothyroid or euthyroid (Salvi et al., 1990). Enlargement of the extraocular muscles, due to edema, as a result of glycoprotein accumulation and inflammatory changes, may cause optic nerve compression and loss of vision. Treatment of the thyroid disorder should be initiated, but systemic steroids, cyclosporin (Prummel et al., 1989), and rarely surgical decompression of the orbit (Bahn & Gorman, 1987) may be necessary.

Hypothyroid myopathy
Up to 40% of patients with hypothyroidism have evidence of muscle weakness. Hoffmann's syndrome manifests with muscle hypertrophy, weakness, slow movements, painful spasms, and delayed muscle relaxation, in adults (Wilson & Walton, 1959; Klein et al., 1981). In children with congenital hypothyroidism, a similar syndrome, but without cramps, is referred to as Kocher–Debre–Semelaigne syndrome (Debre & Semelaigne, 1935). The muscle symptoms and signs resolve on correction of the hypothyroidism.

Corticosteroids
Glucocorticoid excess
Patients with Cushing's disease, ectopic production of ACTH, and therapeutic corticosteroid administration, may develop a myopathy (Muller & Kugelberg, 1959). Clinical features include a painless, symmetrical, proximal myopathy, affecting the legs more than the arms, together with muscle wasting, and other systemic features of glucocorticoid excess. Recovery of muscle strength may be incomplete following treatment of Cushing's disease (Khaleeli et al., 1983). Treatment of iatrogenic corticosteroid myopathy is often limited by the clinical need for the medication. The lowest dose possible should be given, and alternate day administration may be helpful. A non-fluorinated corticosteroid is less likely to be associated with weakness. Starvation or protein deprivation may exacerbate a corticosteroid myopathy, and adequate nutrition should be given. Physical inactivity may potentiate muscle wasting, and physiotherapy and exercise may be helpful (Falduto et al., 1990).

Critical illness myopathy
A critical illness myopathy has been suggested to be related to steroid administration in critically ill patients (Ramsay et al., 1993). This is an acute, severe myopathy, developing rapidly following administration of high doses of corticosteroids, especially intravenously. This may be an acute necrotizing myopathy in patients with sepsis, and a less severe myopathy in those with uncomplicated asthma (Shee, 1990). The steroids may have a priming effect on the muscle, and other factors such as non-depolarizing blocking agents act as a trigger for the muscle necrosis. Features of critical illness polyneuropathy are usually absent.

Glucocorticoid deficiency
Up to 50% of patients with adrenal insufficiency have symptoms of generalized weakness, muscle cramps and fatigue (Mor et al., 1987). The muscle symptoms recover when the glucocorticoid deficiency is corrected.

Toxic and drug-induced myopathies

Muscle disease or dysfunction is associated with a wide range of toxins and medications (Lane, 1996a,b). An overview is illustrated in Table 70.6. The lists are not exhaustive. The main clinical presentations are of a focal myopathy (related to local administration of toxin or medication), an acute and subacute painful myopathy and a chronic painless proximal myopathy. Medication and toxins should be considered as a cause, and potentially treatable or avoidable cause, of a wide range of muscle symptoms and disorders.

Myopathies associated with systemic disease and infection

Skeletal muscle comprises more than 40% of the body mass, and is vulnerable to involvement in many systemic diseases and infections. Skeletal muscle may be involved in malignant disease, by direct invasion, metastatic spread (Pearson, 1959), carcinomatous neuromyopathy (Brain & Henson, 1958), polymyositis and dermatomyositis (Schulman et al., 1991), and carcinoid syndrome (Swash et al., 1975). Skeletal muscle may be involved in connective tissue disease, including systemic sclerosis (Clements et al., 1978), systemic lupus erythematosus (Tsokos et al., 1981), rheumatoid disease (Haslock et al., 1970), ankylosing spondylitis (Carraba et al., 1984), sarcoidosis (Hewlett

Table 70.6. Drug and toxic myopathies

Type	Drug or toxin	Pathology
Focal myopathy		
Acute	IM injections, e.g. tetracycline, paraldehyde	'Needle myopathy'
Chronic	IM antibiotics or narcotic abuse	Fat, fibrous tissue, loss of muscle cells
Acute and subacute painful myopathy		
Myalgia	anticholinesterases, carbimazole, diuretics, calcium antagonists, β-agonists, danazol, enalapril, topical minoxidil, dipyridamole	
Necrotizing	Alcohol, opiates, lipid-lowering drugs (clofibrate, bezafibrate, fenofibrate, gemfibrozil, lovastatin, pravastatin, memvastatin, simvastatin), ipecac alkaloids, IV steroids, venoms, vitamin A, vitamin E, organophosphates, ε-aminocaproic acid, labetalol, sotalol	Multifocal necrosis, phagocytosis, regeneration
Vacuolar	Drugs or toxins causing hypokalemia, e.g. diuretics, purgatives, amphotericin B, liquorice, carbenoxolone	Cytoplasmic vacuoles
Inflammatory	D-penicillamine, procainamide, and occasionally with many other drugs	Lymphocytic infiltration, necrosis
Mitochondrial	Zidovudine, germanium	Ragged red fibres, abnormal mitochondria on EM
Chronic painless proximal myopathy		
Type 2 atrophy	Alcohol, steroids	Type 2 atrophy
vacuolar	Choroquine, amiodarone, perhexilene, colchicine, vincristine	Lysosomes with myeloid bodies
Drug-induced rhabdomyolysis		
	drug abuse – alchohol, opiates, amphetamines, phencyclidine, ketamine	

Notes:
From Lane (1996), p. 380. By courtesy of Marcel Dekker Inc.

& Brownell, 1975), and other granulomatous disease. Other rare causes of myopathy include vascular and blood disorders (polyarteritis, atherosclerosis, and sickle cell disease), and systemic metabolic disease (hypokalemia, hypomagnesemia, hypophosphatemia, uremic and dialysis myopathy and hypermetabolism of trauma) (Orrell & Lane, 1996).

Muscle may be affected by most infectious agents, including bacteria, viruses, fungi, spirochetes, protozoa, cestodes and nematodes (Orrell & Lane, 1996; Wadia & Katrak, 1999). Of particular importance worldwide are cysticercosis, trichinosis, and human immunodeficiency virus.

Cysticercosis

Human cysticercosis is due to infection with the cestode *Cysticercus cellulosa,* the larval form of *Taenia solium* (the pork tapeworm). The eggs are ingested through human feces. In skeletal muscle, the encysted parasites cause single or multiple nodules, or a pseudohypertrophic myopathy (Jacob & Mathew, 1968). Treatment is with praziquantel. There is a possibility of complications during treatment if large numbers of larvae are rapidly destroyed.

Trichinosis

Trichinosis is due to infection with the larvae of the nematode *Trichinella spiralis*, which is ingested through poorly cooked, infested pork. The larva penetrates the sarcolemma of the skeletal muscle, and encysts within the muscle fibre (Ochoa & Pallis, 1980). The infection may be asymptomatic, or may cause marked myalgia, with tenderness, weakness, and swelling of the muscles. Rapid weakness may cause tetraparesis. Treatment is with thiabendazole, but has the risk of a Herxheimer-like reaction.

Human immunodeficiency virus-associated myopathy

There is an increased incidence of myopathy in patients with human immunodeficiency virus (HIV) infection, although generally not as prominent as the associated neuropathic diseases (Lane, 1996a,b; Wadia & Katrak,

1999). A polymyositis-like inflammatory myopathy is recognized in relation to HIV infection (Dalakas et al., 1986). Also a similar myopathy, but with necrotizing rather than inflammatory features (Simpson & Bender, 1988). HIV-associated myopathy is one of the causes of the relatively common HIV wasting syndrome (Simpson et al., 1990). Myopathy or myositis due to opportunistic infection is relatively uncommon, although staphylococcal pyomyositis (Watts et al., 1987), and muscle infection with, for example, *Mycobacterium intracellulare* (Wrzolek et al., 1989) or microsporidosis (Ledford et al., 1985) may be related to immunosuppression. A myopathy may be associated with treatment of HIV infection. In particular, treatment with zidovudine (AZT) is associated with myalgia and fatiguablity (Simpson et al., 1997). Muscle biopsy in these patients usually demonstrates mitochondrial abnormalities, including ragged red fibres (Dalakas et al., 1990).

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Pathophysiology of myotonia and periodic paralysis

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The electrical excitability of skeletal muscle enables action potentials to be generated at the motor end plate and propagated along the sarcolemma and into the transverse-tubule (T-tubule) membranes of muscle fibres. This spread of electrical activity is critical for coupling the local synaptic depolarization at the neuromuscular junction to the release of intracellular calcium from the sarcoplasmic reticulum. Several primary and secondary disorders of skeletal muscle are associated with abnormal excitability. An increase in sarcolemmal excitability manifests as a tendency for the autonomous generation of repetitive action potentials, persistent contraction and delayed relaxation, the hallmarks of myotonia. By contrast, intermittent failure of muscle membrane excitability causes paroxysmal weakness or paralysis that is characteristic of periodic paralysis. These alterations in muscle excitability produce a spectrum of clinical syndromes in which a patient may have myotonia, periodic paralysis, or a combination of both (Fig. 71.1).

The physiological basis for the generation of muscle action potentials is now well understood at the cellular and molecular levels. The rapid opening of voltage-gated sodium channels is responsible for the initial upstroke in the muscle action potential and for its propagation along sarcolemmal membranes. The somewhat slower activation of potassium channels contributes to repolarization, while chloride conducting ion channels help stabilize the membrane potential at the resting level to guard against spurious action potential triggering. Many of the ion channel molecules that participate directly in generating muscle action potentials have been defined at the primary nucleotide sequence level, and this work has enabled investigation into the genetic basis of disorders of sarcolemmal excitability. In parallel, advances in cellular electrophysiology coupled with the use of recombinant ion channels have contributed greatly to advancing our knowledge of the molecular pathophysiology of such disorders.

This chapter focuses upon the clinical characteristics and pathophysiology of two categories of abnormal sarcolemmal excitability: myotonia and periodic paralysis. In the past decade, the discovery of the underlying molecular defects responsible for many of the inherited myotonias and periodic paralyses has led to a revised classification of these disorders. The functional consequences of the genetic defects on the physiology of voltage-gated sodium and chloride channels serves as a framework from which to understand the mechanistic basis of these disorders at the molecular level. Finally, the symptomatic treatment of myotonia and periodic paralysis is discussed in relation to the therapeutic principles of compensating for the biophysical defects of mutant ion channels.

Non-dystrophic myotonias

Myotonia is clinically characterized by an abnormal delay in relaxation following voluntary or induced muscle contraction (Streib, 1987; Gutmann & Phillips, 1991). Myotonia is associated with a variety of inherited and acquired disorders (Table 71.1) and certain clinical features may aid in establishing the diagnosis (Table 71.2). Patients with myotonia experience muscular stiffness upon initiating movement that typically resolves within several seconds. The resolution of stiffness associated with continued activity is referred to as the 'warm-up' phenomenon and is most typical of the disorder myotonia congenita which is caused by dysfunction of muscle chloride channels. By contrast, muscular stiffness that is accentuated by continued activity (paradoxical myotonia) is characteristic of the disorder paramyotonia congenita which is caused by mutations in the muscle sodium channel gene. In paramyotonia congenita, myotonic

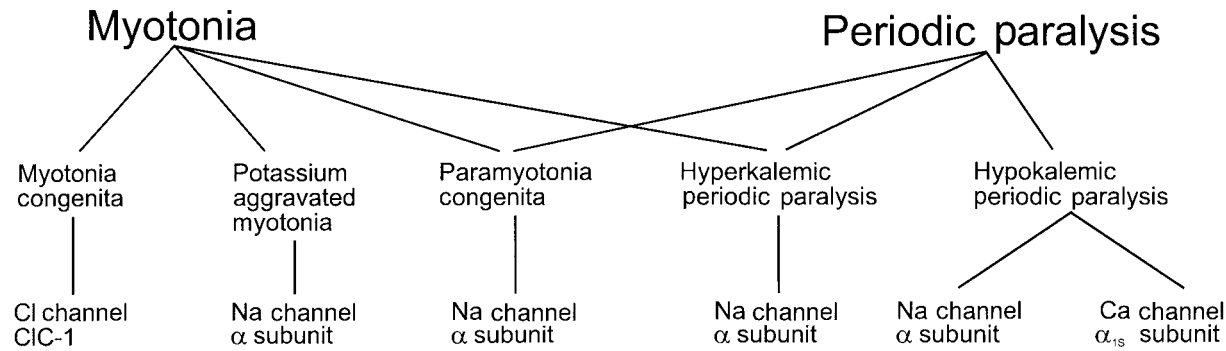

Fig. 71.1. Spectrum of altered skeletal muscle excitability in the hereditary nondystrophic myotonias and periodic paralyses. Enhanced excitability produces myotonia (left side), whereas intermittent loss of excitability results in periodic paralysis (right side). Chloride channel defects cause myotonia, calcium channel mutations give rise to periodic paralysis without myotonia, whereas sodium channel mutations may result in myotonia only, periodic paralysis only, or a combination of both.

Table 71.1. Inherited and acquired myotonias

Non-dystrophic myotonias
Autosomal dominant myotonia congenita (Thomsen's disease)
Recessive generalized myotonia (Becker's myotonia)
Hyperkalemic periodic paralysis
Paramyotonia congenita
Potassium-aggravated myotonia
Other sodium channel myotonias
Chondrodystrophic myotonia (Schwartz–Jampel syndrome)
Dystrophic myotonias
Myotonic dystrophy (DM1)
Proximal myotonic myopathy (PROMM or DM2)
Acquired and drug-induced myotonias
Hypochloremia
Hypothyroidism (unmasks latent PROMM or Thomsen's disease)
Cholesterol lowering drugs (clofibrate, HMG-CoA reductase inhibitors)
2,4-dichlorophenoxyacetic acid (2,4-D)
Anthacene-9-carboxylic acid (9-AC)
20,25-diazacholesterol
Propranolol (unmasks latent myotonic dystrophy)
Vincristine (unmasks latent myotonic dystrophy)

muscular stiffness is usually brought on by exposure to cold temperatures. In other cases, myotonia is exacerbated by ingestion of foods rich in potassium (potassium-aggravated myotonia) or rarely may be associated with pain or cramping in contracting muscles. The term 'sodium channel myotonia' has been introduced to describe inherited forms of myotonia associated with mutations in the muscle sodium channel gene that are difficult to categorize clinically.

Physical examination may reveal a myotonic delay in muscle relaxation after voluntary contraction or percussion myotonia, a persistent dimpling of prominent muscles (e.g. thenar eminence, tongue) following a sudden blunt impact such as the blow from a reflex hammer. The electromyogram in myotonic muscle shows increased insertional activity and high frequency repetitive discharges of motor unit potentials that typically last several seconds following muscle percussion, needle movement or muscle contraction. These repetitive discharges correlate well with the perceived delayed relaxation of muscle and represent the electrophysiological hallmark of the disorder.

Myotonia congenita

Congenital myotonia in the absence of muscular weakness or dystrophy is characteristic of myotonia congenita. Myotonia congenita may be inherited as either an autosomal dominant (Thomsen's disease) or recessive (recessive generalized myotonia (RGM), Becker's myotonia) trait. The clinical features of both conditions are similar except that the recessive form is generally more severe. In addition to myotonic muscular stiffness, patients with RGM may sometimes experience transient (<1 minute) weakness upon initiating movement especially after a period of prolonged rest (Rüdel et al., 1988). In both conditions, myotonia may be manifest soon after birth, although in Thomsen's disease, myotonia is usually not recognized until later in childhood. Mild to moderate muscular hypertrophy is often associated with these conditions and may be the first clinical sign during infancy. Muscular hypertrophy associated with congenital myotonia is presumably caused by chronically increased muscular activity.

Table 71.2. Clinical features of the non-dystrophic myotonias and periodic paralyses

Disorder	Myotonia congenita		Potassium-aggravated myotonia[a]	Paramyotonia congenita	Hyperkalemic periodic paralysis	Hypokalemic periodic paralysis
Inheritance	Dominant	Recessive	Dominant	Dominant	Dominant	Dominant
Penetrance	High	High	High	High	High	↓ females
Age of onset	Congenital	First decade	First decade	First decade	First decade	Second decade (puberty)
Myotonia						
Stiffness	Moderate	Severe	Mild to severe	Moderate	Mild	None
Distribution	Generalized	Generalized, legs	Variable	Hands, face	Hands, face	–
Special features	Improves with warm-up	Improves with warm-up	Fluctuates, aggravated by K^+, Pain with stiffness	Paramyotonia, aggravated by cold	Aggravated by K^+	–
EMG	3+	3+	2+ to 3+	2+ to 3+	0 to 2+	0
Episodic weakness						
Severity	None	Mild	None	Mild to severe	Moderate to severe	Severe (when present)
Distribution	–	Legs or arms	–	Regional or generalized	Regional or generalized	Generalized
Duration	–	Transient (s)	–	Minutes to a day	Minutes to a day	Hours to days
Provocation	–	Forceful effort after rest	–	Cold, rest after exercise	K^+, rest after exercise, fasting	Rest after exercise, carbohydrates
Permanent weakness	None	None	None	None	Variable late-onset proximal weakness	Prominent late-onset proximal weakness

Note:
[a] Includes myotonia fluctuans, myotonia permanens, and acetazolamide-responsive myotonia.

Myotonia may be mild or even subclinical in patients with dominant myotonia congenita but electromyographic evidence of myotonia will usually be evident in these patients (so-called latent myotonia). Electromyographic evidence of myotonia may also be present in asymptomatic carriers of recessive myotonia alleles especially in males (Mailander et al., 1995).

Reduced skeletal muscle membrane chloride conductance in myotonia congenita

Our current understanding of the pathogenesis of myotonia caused by defects in chloride channel function originated with the investigations of Bryant and colleagues that elucidated the membrane abnormalities in the myotonic goat (Bryant, 1979). These animals have been referred to as 'fainting goats' because of their tendency to develop severe acute muscular stiffness and fall when attempting to make sudden forceful movements or when startled. Anecdotal evidence suggests that the myotonic goat phenotype is transmitted as an autosomal dominant trait although most herds have been inbred resulting in a severe condition resembling RGM. The clinical behaviour and electrophysiologic properties of muscle in this animal are remarkably similar to human myotonia congenita. Also similar to the human disease, myotonia in goats is associated with a missense mutation in the muscle chloride channel gene (Beck et al., 1996).

Bryant and colleagues observed that skeletal muscle fibres from myotonic goats have a severe decrease in resting membrane chloride conductance and that this was directly associated with myotonic discharges (Adrian & Bryant, 1974). The link between reduced chloride conductance and myotonia was further supported by their observation that normal muscle fibres became myotonic when bathed in an extracellular solution lacking chloride ions. The importance of the reduced sarcolemmal chloride conductance in the pathophysiology of myotonia has also been supported by the finding of a reduced chloride conductance in myotonia

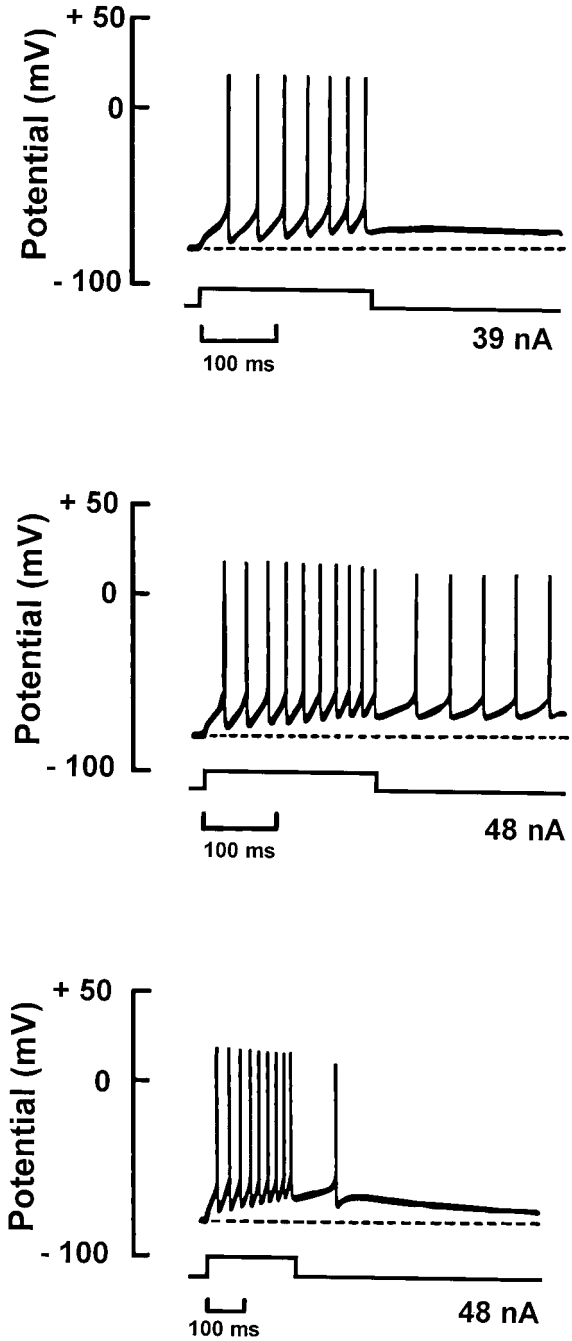

Fig. 71.2. Action potential recordings from myotonic goat muscle in response to graded electrical stimulation (modified after Adrian & Bryant, 1974). In the top tracings, stimulation of muscle fibres (39 nA) produces multiple action potential spikes and a small afterdepolarization visible as the elevated membrane potential above the horizontal dotted line (representing the resting potential). With a stronger stimulus (48 nA, centre tracings) the afterdepolarization reaches threshold voltage and triggers spontaneous action potentials that fire after termination of the electrical stimulus. The lower tracings illustrate the development of the after-depolarization on a compressed time scale.

induced with aromatic carboxylic acids (Furman & Barchi, 1978) and by using computer simulations of muscle action potentials (Barchi, 1975).

Unlike other excitable membranes, skeletal muscle has a high chloride conductance accounting for approximately 70% of the total resting membrane ion conductance (Palade & Barchi, 1977a). To a first approximation, chloride ions are distributed passively across the sarcolemma. This means that on a slow timescale of minutes, chloride moves in or out of the cell until the intracellular concentration is adjusted to set the chloride equilibrium potential equal to the resting potential. Chloride ions do not actively set the resting potential. However, in response to any change in the membrane potential, a large chloride current will flow that tends to return the membrane potential to its previously established resting value. In skeletal muscle the high resting chloride conductance acts like an electrical buffer that is important for stabilization of the resting potential and repolarization after an action potential.

A reduced chloride conductance has two effects on sarcolemmal excitability. First, a smaller electrical stimulus is sufficient to elicit action potentials with a diminished or absent chloride conductance thereby directly demonstrating enhanced excitability (Adrian & Bryant, 1974). Furthermore, with the propagation of action potentials along T-tubule membranes, the local concentration of extracellular potassium rises due to efflux through activated potassium channels. During a sufficiently long train of action potentials, extracellular potassium in the T-tubules rises substantially and exerts a depolarizing effect on the resting membrane potential. Normally, this rise in extracellular potassium has little effect on membrane voltage because of the electrical dampening effect of sarcolemmal chloride conductance. However, in the case of myotonic muscle with a diminished or absent chloride conductance, potassium accumulation in the T-tubule has a substantial impact on membrane voltage. Following each action potential, the membrane potential fails to repolarize to its resting level, producing an afterdepolarization that dissipates slowly over several hundred milliseconds (Fig. 71.2). When sufficient numbers of impulses are propagated rapidly in a myotonic muscle fibre, this afterdepolarization can achieve threshold voltage and trigger spontaneous action potentials in the adjacent surface membranes independent of neuromuscular transmission.

These autonomous action potentials will cause persistent muscle contraction and delayed relaxation after a voluntary movement and thus result in clinical myotonia.

Molecular defects of *CLCN1* in myotonia congenita

The observations of Bryant and colleagues were made in the early 1970s, and a central hypothesis to explain the pathogenesis of myotonia congenita was the existence of defects in the formation of sarcolemmal chloride channels or abnormalities in their regulation. Approximately 20 years later, the first candidate gene encoding a muscle membrane chloride channel was discovered. A new gene family encoding voltage-sensitive chloride channels (the ClC family) was described by Jentsch, and colleagues, with identification of complementary DNA (cDNA) sequences encoding ClC-0 from the electric ray, *Torpedo marmarota* (Jentsch et al., 1990). The first mammalian isoform was identified in rat skeletal muscle (ClC-1) (Steinmeyer et al., 1991a).

Human ClC-1 is a protein of 988 amino acids and is encoded by the 23 exons of the *CLCN1* gene located on chromosome 7q35 (Lorenz et al., 1994). Recombinant human ClC-1 exhibits many of the physiological and biophysical properties of native sarcolemmal chloride channels when reconstituted in heterologous expression systems such as *Xenopus* oocytes or cultured mammalian cells (Pusch et al., 1994; Fahlke et al., 1996). The channel has an ionic selectivity sequence of $Cl^- > Br^- > I^-$, and a current–voltage relationship exhibiting inward rectification (Fahlke et al., 1997a). Human ClC-1 channels have a significant open probability at voltages near the resting membrane potential of skeletal muscle. The ClC-1 channel protein probably has a complex three-dimensional structure consisting of multiple variable length membrane-spanning segments as observed for purified bacterial CIC channels analysed by X-ray crystallography (Dutzler et al., 2002). Two identical ClC-1 subunits are required to form a functional chloride channel (Steinmeyer et al., 1994; Fahlke et al., 1997b) and there is evidence that the channel complex forms two independent ion conduction pathways or ion pores (Saviane et al., 1999) although this is controversial (Fahlke et al., 1998).

Several lines of evidence have indicated that ClC-1 is the principal skeletal muscle chloride channel, an appropriate candidate for genetic abnormalities associated with myotonia congenita. Steinmeyer and colleagues identified mutations in ClC-1 associated with congenital myotonia in the homozygous *adr* (arrested development of righting) myotonic mouse (Steinmeyer et al., 1991b). This work was soon followed by demonstration of linkage of genetic loci near *CLCN1* with myotonia congenita (Abdalla et al., 1992), and the identification of *CLCN1* mutations in both RGM and autosomal dominant myotonia congenita (Koch et al., 1992; George et al., 1993a).

Figure 71.3 illustrates the location and type of most known mutations associated with these two disorders. The majority of mutations associated with autosomal dominant myotonia congenita cause single amino acid substitutions throughout the chloride channel protein (missense mutations). The one exception is a nonsense mutation (R894X) that results in a truncating premature stop codon near the carboxyl terminus of the protein (George et al., 1994). The most common Thomsen's disease mutation found in North America causes the non-conservative substitution of glycine-230 with glutamic acid (G230E) (George et al., 1993a). A missense mutation (P480L) associated with myotonia congenita has also been defined in an extended German pedigree traced back to Dr Julius Thomsen who originally described the syndrome in himself and other family members (Thomsen, 1876; Steinmeyer et al., 1994). A mild form of autosomal dominant myotonia termed myotonia levior has also been associated with mutations in *CLCN1* (Lehmann-Horn et al., 1995). Chloride channel mutations have also been discovered in the myotonic goat (Beck et al., 1996) and myotonic dog (Rhodes et al., 1999).

Most reported *CLCN1* mutations occur in association with RGM or sporadic cases of myotonia congenita, however there are very few common alleles. Perhaps the two most frequently discovered alleles in patients with recessive myotonia are the missense mutation F413C and a 14 base pair deletion inducing a frameshift (Koch et al., 1992; Meyer-Kleine et al., 1994). The majority of mutations have been reported in either single families or isolated cases, and there is a high frequency of compound heterozygosity (inheritance of a different mutant allele from each parent) among RGM patients. In exceptional cases, families have been identified in which more than the two mutations segregate with the disease. This results in the occurrence of different compound genotypes in members of the same family and potentially gives rise to variable myotonia severity within a single family (Sloan-Brown & George, 1997). There are few reliable estimates of the carrier frequency of *CLCN1* mutations, but these disorders are generally considered uncommon.

A few mutations have been associated with either dominant or recessive forms myotonia congenita. In some cases, this may be explained by pseudodominant inheritance whereby an RGM parent having two *CLCN1* mutations mates with a heterozygous carrier to produce offspring with a 50% likelihood of inheriting one disease allele from each parent (Fig. 71.4). Another explanation for this observation is incomplete penetrance (lack of phenotype expression in mutation carriers) of certain dominant mutations.

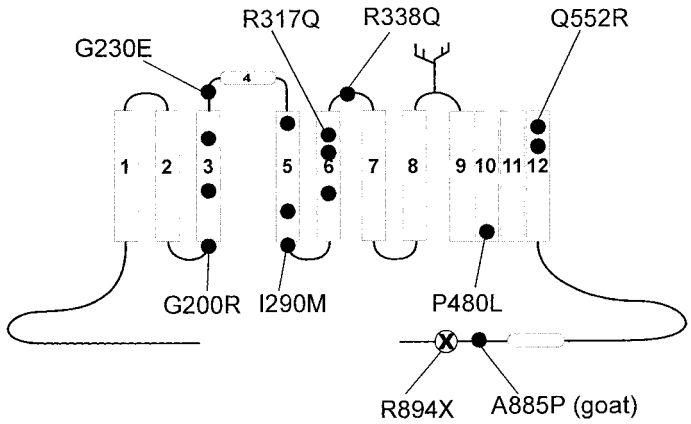

Fig. 71.3. Location and type of mutations in the ClC-1 chloride channel associated with dominant myotonia congenita and recessive generalized myotonia illustrated on a transmembrane topology model of ClC-1. Each symbol represents the approximate position of a single mutation within the channel protein and the type of mutation is coded as indicated by the inset.

Variable phenotype severity and incomplete penetrance associated with certain dominant alleles have not been adequately explained. Current hypotheses include intrinsic differences in the severity of chloride channel dysfunction associated with specific mutations or the existence of modifier genes that affect chloride channel function.

The allelic heterogeneity associated with myotonia congenita indicates that many *CLCN1* mutations arise spontaneously. This creates difficulty for performing molecular genetic analyses because a comprehensive survey of the entire gene sequence is necessary to detect mutations in an individual. In the case of large or consanguineous families with dominant or recessive myotonia, it is conceivable to use linkage analysis with polymorphic markers in and around the chloride channel gene on chromosome 7q35 to help establish a genetic diagnosis. However, most patients with myotonia congenita appear sporadic or are associated with small kindreds. In the future, new methods for mutation detection may facilitate the systematic and comprehensive search for mutations in this gene.

Functional consequences of *CLCN1* mutations

Based on experiments with animal models of myotonia congenita and computer simulations of muscle action

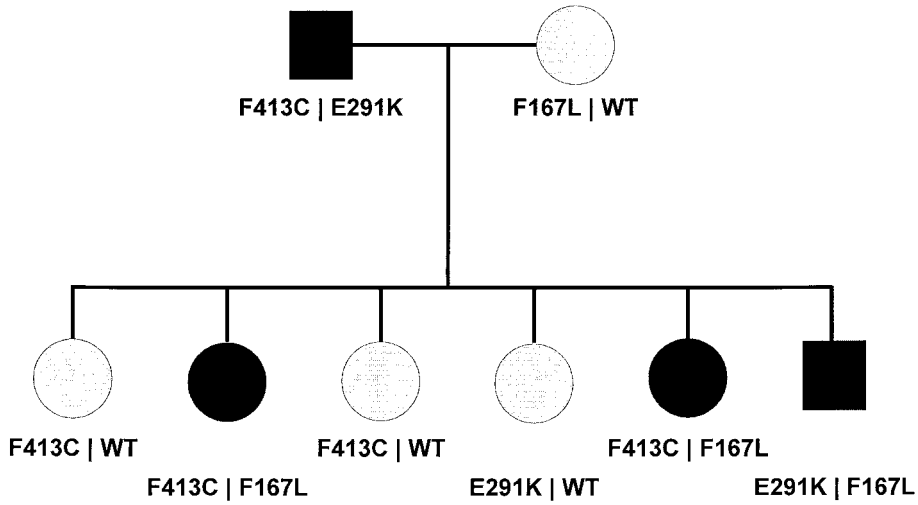

Fig. 71.4. An illustration of pseudodominant inheritance of *CLCN1* mutations in a family with recessive generalized myotonia (RGM). Black symbols indicate affected individuals and grey symbols represent unaffected mutation carriers. Although the mutations F413C, E291K, and F167L have all been associated with RGM, 50% of offspring in this family are affected because of the likelihood that both parents transmit disease-producing alleles.

potentials, it has been deduced that a reduction in sarcolemmal chloride conductance to 20% of normal is required for the occurrence of myotonia (Barchi, 1975). In RGM, this small level of residual chloride conductance is most readily explained by mutations which cause a complete or near complete loss of function of the ClC-1 chloride channel (Heine et al., 1994). As illustrated in Fig. 71.3, approximately half of the *CLCN1* mutations associated with recessive myotonia disrupt the coding sequence of the gene by introducing stop codons, causing defective exon splicing or introducing frameshifts by insertions or deletions. In the case of missense mutations, experiments have been performed with recombinant human ClC-1 chloride channels expressed in heterologous systems including *Xenopus oocytes* and cultured mammalian cells to elucidate their functional effects.

Using electrophysiologic recording techniques, several investigators have ascertained that many missense mutations cause non-function or altered gating behaviour of ClC-1. The most common gating defect caused by a variety of recessive and dominant alleles is a shift in the voltage-dependence of chloride channel activation (Pusch et al., 1995). The open probability of chloride channels is controlled by intrinsic voltage sensitive gating mechanisms such that their activity increases with more depolarized membrane potentials (Fig. 71.5). At the resting membrane potential in skeletal muscle (−85 mV), the probability that chloride channels reside in an active or open state is approximately 30–40%. This open probability increases in a sigmoidal relationship with voltage such that maximal channel opening occurs at positive potentials. Several mutations associated with myotonia congenita shift the relationship between membrane voltage and open probability to more depolarized potentials such that, at the resting membrane potential, the activity of the mutant chloride channels is low.

In heterozygous carriers of mutations, both wild-type and mutant chloride channels will coexist in the same cell. In vitro experiments replicating the combination of wild-type and mutant alleles have illustrated that the presence of a single wild-type allele can overcome the defect associated with recessive mutations but is unable to compensate for dominant mutations (Kubisch et al., 1998). This apparent interaction between alleles most likely occurs at the protein level and is best explained by experimental evidence indicating that the muscle chloride channel is a dimer composed of two identical ClC-1 subunits (Steinmeyer et al., 1994; Fahlke et al., 1997b). In this context, assembly of mutant and wild-type chloride channel proteins results in a dominant-negative reduction in chloride channel activity in the case of mutations in Thomsen's disease. By contrast, recessive alleles may be rescued by assembly with the wild-type allele. A variable degree of rescue of this voltage dependent shift in activation has been observed with certain dominant alleles that exhibit incomplete penetrance in Thomsen's disease families (Kubisch et al., 1998). This has led to the hypothesis that the biophysical mechanism of incomplete penetrance

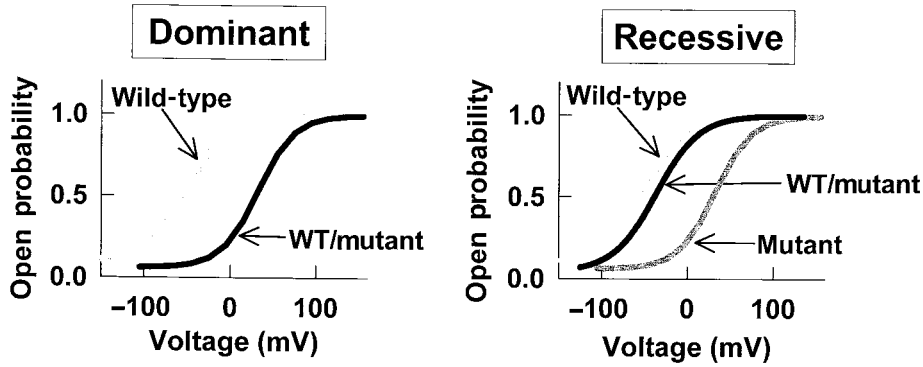

Fig. 71.5. Voltage-dependence of ClC-1 open probability is illustrated for wildtype and mutant channels. Wildtype ClC-1 exhibits a sigmoidal voltage-dependent open probability such that 30–40% of channels will be active at the resting membrane potential of skeletal muscle (−85 mV). A variety of mutations that cause autosomal dominant myotonia congenita and RGM shift the voltage-dependence of ClC-1 open probability to more depolarized potentials thus reducing the proportion of channels that are active at the resting membrane potential. Dominant mutations exert this effect more strongly than recessive alleles and cannot be rescued by coexpression with the wildtype channel.

may relate to a milder degree of dominant-negative effects of the mutant allele on the dimeric channel complex.

A second type of gating disturbance observed in chloride channels with recessive mutations is an inversion of the voltage sensitivity of channel activation. This was first reported in association with the recessive mutation D136G (Fahlke et al., 1995) but has since been reported associated with other alleles (Zhang et al., 2000). Finally, a distinct mechanism of chloride channel dysfunction associated with the common dominant allele G230E has been elucidated (Fahlke et al., 1997c). This mutation causes a dramatic alteration in the ion selectivity of the mutant chloride channel such that there is a reversal in the normal halide ion selectivity sequence and an increase in cation permeability. Disruption of ion selectivity in this context is believed to occur because of a major disruption in the structure of protein segments near the pathway for permeant ions (Fahlke et al., 1997d).

There are two major unanswered questions relevant to the pathophysiology of myotonia congenita. First, there is continued investigation into the explanation for variable penetrance as discussed above. The leading hypotheses include intrinsic variability of the biophysical nature of the channel dysfunction and the variable impact that mutant alleles have on the wild-type channel protein. The second major unanswered question is the etiology of the warm-up phenomenon observed most commonly in myotonias associated with chloride channel dysfunction. There have been suggestions that an activity dependent increase in ClC-1 chloride channel activity may underlie the warm-up phenomenon in some cases (Pusch et al., 1995), although this is difficult to reconcile with myotonia caused by the complete absence of chloride channel protein. It is conceivable that other types of chloride channels contribute to the sarcolemmal chloride conductance in an activity-dependent fashion although there is little evidence to support this presently. The same potassium accumulation that depolarizes the fibre to initiate myotonic discharges may also inactivate a fraction of sodium channels and thereby reduce excitability. Finally, activation of Na^+/K^+-ATPase (sodium pump) during repetitive action potential generation may enable the cell to compensate for after-depolarizations by increasing potassium uptake in the T-tubule membranes and by an increased hyperpolarizing contribution of the sodium pump to the membrane potential.

Acquired myotonia from disruption of skeletal muscle chloride conductance

A small number of drugs and toxins may cause myotonia by reducing sarcolemmal chloride conductance (Kwiecinski, 1981; Mastaglia, 1982). The most well-studied agents are aromatic carboxylic acids including the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) (Bradberry et al., 2000) and the cholesterol-lowering drug clofibrate (2-(*p*-chlorophenoxy) propionic acid) (Conte-Camerino et al., 1984). These agents produce their clinical effects through two distinct mechanisms. Reduction of sarcolemmal chloride conductance by 2,4-D and several other aromatic carboxylic acid compounds is caused by altered ion selectivity of the muscle chloride channel (Palade & Barchi, 1977b). By contrast, clofibrate modulates chloride channel gating (accelerates deactivation) and shifts the voltage dependence of channel activation to more depolarized

potentials (Pusch et al., 2000) similar to many myotonia-producing *CLCN1* mutations. The effects of clofibrate, a racemic mixture, are caused entirely by its negative enantiomer (De Luca et al., 1992; Aromataris et al., 1999). The HMG-CoA reductase inhibitors, simvastatin and pravastatin, can induce myotonia in rabbits by reducing sarcolemmal chloride conductance (Sonoda et al., 1994; Pierno et al., 1995) but there have been no reports of myotonia in humans associated with these agents.

Potassium-aggravated myotonia

Potassium-aggravated myotonia (PAM) is the most recently recognized form of familial non-dystrophic myotonia (Lerche et al., 1993; Mitrovic et al., 1994). PAM presents as dominantly inherited generalized myotonia that often fluctuates over the course of days or in relation to activity or diet. Before the advent of molecular genetic testing, these cases were usually classified as dominant myotonia congenita. Defects in *CLCN1* are not found in PAM, however, and the molecular basis of PAM is missense mutations in the adult skeletal muscle sodium channel gene, *SCN4A* (Fig. 71.6). Functional studies of expressed sodium channels have shown that the mutations associated with PAM partially disrupt fast inactivation (Lerche et al., 1993; Mitrovic et al., 1994; Hayward et al., 1996). This gain-of-function defect increases excitability of the sarcolemma, and predisposes the muscle fibre to runs of myotonic discharges (see further discussion below under HyperPP/PMC). In contrast to other forms of myotonia caused by mutations in *SCN4A*, by definition episodic weakness does not occur in PAM.

After the molecular genetic distinction had been established between PAM and dominant myotonia congenita, several clinical differences between these myotonic syndromes have been recognized. Unlike myotonia congenita, the myotonic stiffness in PAM fluctuates from day to day and may be aggravated by rest several minutes after exercise or by potassium ingestion. Despite the emphasis of potassium sensitivity in the term PAM, exacerbation of myotonia by potassium challenge is not required to establish a diagnosis of PAM. Provocative testing is generally not advisable because this may trigger severe myotonia and muscle pain for hours to a day or more. Cooling does not aggravate myotonia in myotonia congenita, but often worsens the stiffness in PAM. The absence of paramyotonia distinguishes PAM from cases of paramyotonia congenita (PMC, see below) without weakness. Several clinically described variants of dominant myotonia are now considered to be forms of PAM: myotonia fluctuans (Ricker et al., 1994a), myotonia permanens (Lerche et al., 1993), acetazolamide-responsive myotonia (Ptacek et al., 1994a), and painful congenital myotonia (Rosenfeld et al., 1997).

Periodic paralysis

The periodic paralyses are inherited disorders of skeletal muscle that present as recurrent episodes of muscle weakness, without altered consciousness or sensory abnormalities, followed by spontaneous recovery (see Lehmann-Horn & Engel, 1994; Cannon, 1998 for recent reviews). Attacks are episodic, rather than having any regular periodicity, and may range from mild weakness to flaccid quadriparesis. During an attack, affected fibres are depolarized which renders them electrically inexcitable and therefore incapable of generating force. The loss of excitability is caused by the normal voltage-dependent inactivation of sodium channels. Interictally, muscle strength is usually normal. The inheritance pattern is autosomal dominant, with a high degree of penetrance.

Historically, the periodic paralyses were classified according to changes in blood potassium levels that occurred concomitantly with the attacks of weakness. Patients with hypokalemic periodic paralysis (HypoPP) invariably have low serum potassium levels during a spontaneous attack and do not have myotonia. In hyperkalemic periodic paralysis (HyperPP), the serum potassium during an episode of weakness is often high, but may be normal. The changes in serum potassium concentration are primarily due to transient shifts of potassium from the myoplasm to the extracellular space (HyperPP) or from the extracellular space into muscle (HypoPP). HyperPP and related myotonic syndromes (paramyotonia congenita and potassium-aggravated myotonia) are caused by missense mutations in the skeletal muscle voltage-gated sodium channel (for reveiw see Lehmann-Horn & Jurkat-Rott, 1999). HypoPP is genetically heterogeneous. In most families with HypoPP, the molecular defect is a missense mutation in the L-type skeletal muscle calcium channel (Jurkat-Rott et al., 1994; Ptacek et al., 1994b). For a small subset of HypoPP families, missense mutations have been found in the skeletal muscle sodium channel whereas the L-type calcium channel is normal (Bulman et al., 1999; Jurkat-Rott et al., 2000).

Hyperkalemic periodic paralysis and paramyotonia congenita

Periodic paralysis in association with elevated serum potassium was first recognized by Hellweg-Larsen and colleagues (Hellweg-Larsen et al., 1955) and later

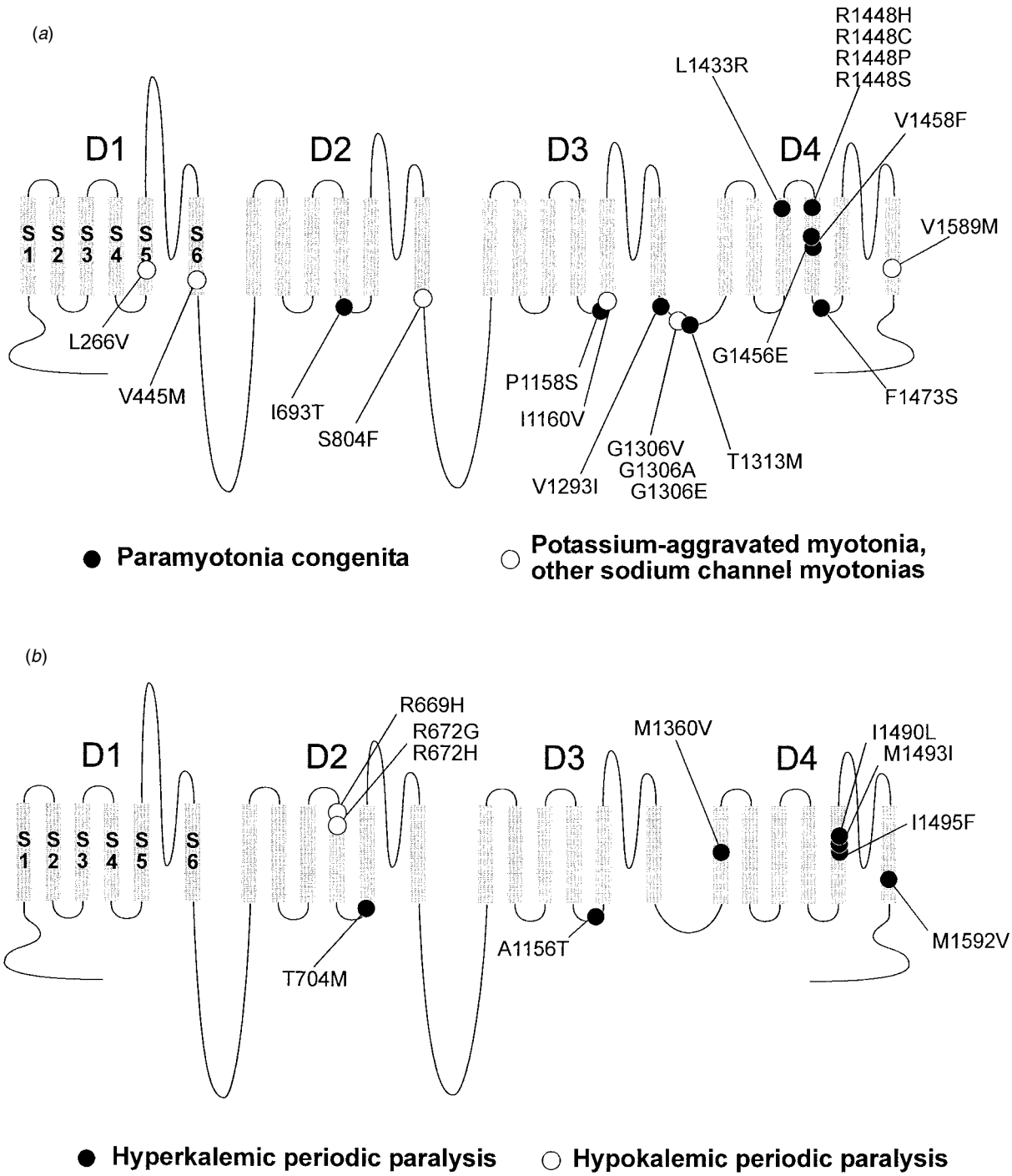

Fig. 71.6. Transmembrane folding diagram of the human adult skeletal muscle sodium channel and locations of missense mutations found in (*a*) myotonia and (*b*) periodic paralysis. (See Lehmann-Horn & Jurkat-Rott, 1999 for references to the original reports of specific mutations.)

described in greater detail by Gamstorp (Gamstorp, 1956), who coined the name adynamia episodica hereditaria. Intermittent attacks of weakness begin during the first decade of life and are often associated with an elevated serum potassium level (5.0 to 8.0 meq/l). A normal serum potassium level does not exclude the diagnosis of HyperPP. A more consistent finding is provocation of an attack by potassium salt administration. Weakness is mild to severe and recovery usually begins within a few hours, although full strength may not return for days. In addition to ingesting potassium-rich foods, several other manoeuvres may elicit an attack: rest after exercise, fasting, cold temperatures, or emotional stress. An incipient attack may be aborted by exercise or a carbohydrate-rich meal. Myotonia or paramyotonia may be present interictally in HyperPP, but intermittent weakness is always the predominant symptom. After the fourth or fifth decade, patients with HyperPP may develop a slowly progressive proximal myopathy. Muscle biopsy may be normal or show only mild non-specific changes (variation in fibre size, central nuclei, vacuolar changes, and proliferation of the sarcoplasmic reticulum).

Paramyotonia congenita (PMC) was first described by Eulenburg (1886), well before HyperPP was recognized as a clinical syndrome. The overlapping signs and symptoms in these two disorders led many clinicians to propose they were allelic disorders with a common molecular defect (de Silva et al., 1990). The pathognomonic feature of PMC is dominantly inherited paramyotonia, especially of the hands and face, that is usually aggravated by cooling. Paramyotonia is the predominant symptom in PMC, but patients may also have severe attacks of generalized weakness, either spontaneous or cold induced, that are indistinguishable from the episodic weakness in HyperPP.

Abnormal sodium currents in skeletal muscle

The membrane defect in HyperPP and PMC was initially identified from microelectrode studies of intercostal fibres biopsied from patients. In a series of landmark studies, Lehmann-Horn and colleagues explored the electrophysiological basis of myotonia that occurred in association with periodic paralysis (Lehmann-Horn et al., 1981, 1983, 1987). Unlike muscle in myotonia congenita or the myotonic goat, the resting chloride conductance was normal. Instead, diseased fibres depolarized excessively in response to raising the extracellular potassium concentration or cooling and had an aberrant inward current not seen in matched controls. Both abnormalities were prevented by tetrodotoxin, a potent and specific sodium channel blocker. These data implicated a defect in the voltage-gated sodium channel.

Molecular defects in hyperkalemic periodic paralysis and paramyotonia congenita

In 1990 genetic linkage was established between HyperPP and *SCN4A* (Fontaine et al., 1990), the gene for the α subunit of the skeletal muscle sodium channel on chromosome 17q23–25 (George et al., 1991). Several months later, PMC was also linked to 17q23–25 (Ebers et al., 1991; Ptacek et al., 1991a). Subsequently, seven different missense mutations in *SCN4A* have been identified in families with HyperPP (Fig. 71.6). The most commonly occurring mutations are T704M and M1592V (Rojas et al., 1991; Ptacek et al., 1991b), which account for about 60% and 30%, respectively, of genotyped HyperPP families. Haplotype analysis did not identify a founder effect, suggesting the same missense mutation has arisen independently in unrelated families (Plassart et al., 1994). Several distinct *SCN4A* mutations have been discovered in patients with PMC (Ptacek et al., 1992; McClatchey et al., 1992a).

The voltage-gated sodium channel in skeletal muscle is a heterodimer of a pore-forming α subunit and non-covalently linked accessory β_1 subunit. The human skeletal muscle α-subunit gene, *SCN4A*, codes for a 1836 amino acid protein (George et al., 1992), contains 24 exons (McClatchey et al., 1992b; George et al., 1993b) and is selectively expressed in skeletal muscle. All of the defects in *SCN4A* that have been associated with periodic paralysis or myotonia result in missense mutations of the α subunit that change conserved amino acid residues (Fig. 71.6). Several structural motifs, with associated functional roles, have been identified in voltage-gated sodium channels (for review see Catterall, 2000). The α subunit contains four internal homologous domains, each of which is composed of six membrane spanning segments (S1–S6). The S4 segment in each domain contains a cluster of positively charged residues (arginine or lysine) that form an integral part of the voltage-sensing mechanism of the channel. Several disease-associated mutations occur in these voltage-sensing S4 segments (Fig. 71.6). The ion-conducting pore is thought to be formed by the four short loops between S5 and S6 segments. The cytoplasmic loop between the third and fourth homologous domains of the sodium channel is critical for the fast inactivation that terminates the action potential and gives rise to the refractory period (West et al., 1992). Five myotonia-associated mutations are located in the fast inactivation gate (Fig. 71.6). Ten other mutations (3 causing HyperPP and 7 causing PMC or PAM) are found in the cytoplasmic ends of S5 or S6 segments, which may form the docking site for the inactivation gate at the intracellular mouth of the pore. The human β_1 subunit is expressed in skeletal muscle, heart, and brain (Makita et al., 1994). No mutations in the β_1 subunit gene have been identified in

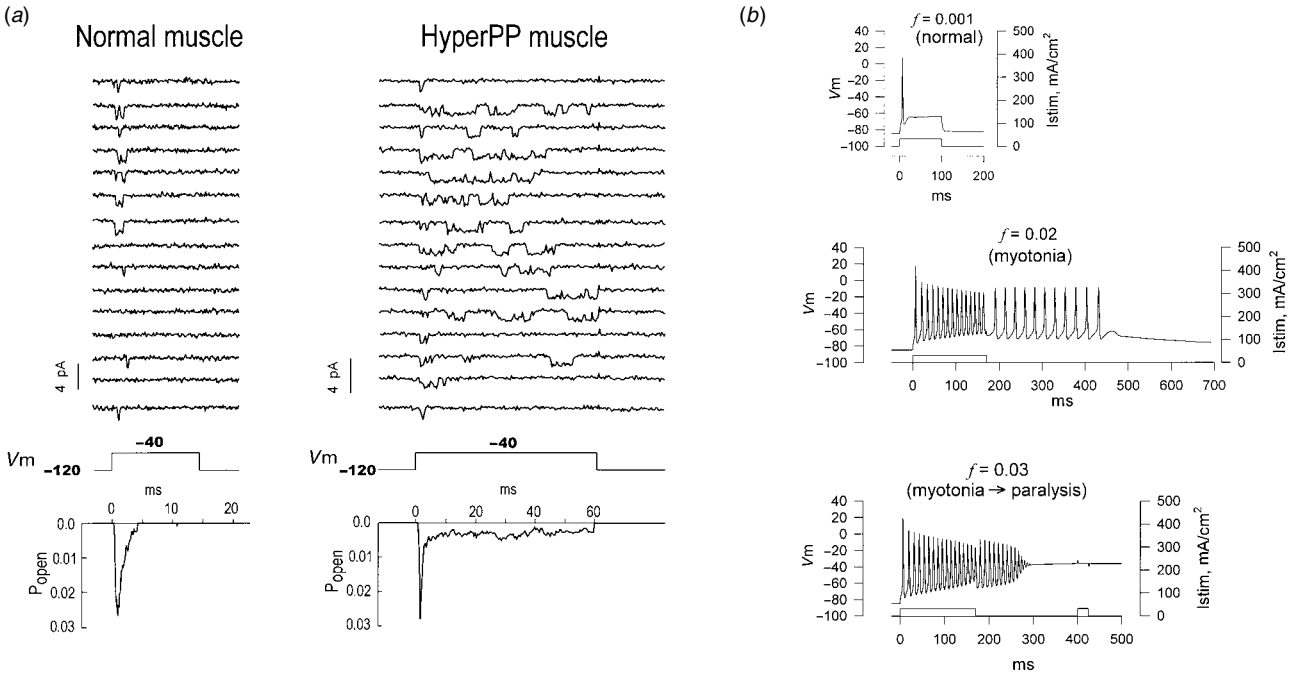

Fig. 71.7. Functional consequences of missense mutations on sodium channel behaviour and muscle membrane excitability. (*a*) Sodium currents were measured in cultured human myotubes from normal (left) and HyperPP (right) muscle using cell-attached patch clamp recording. In response to membrane depolarization, sodium channels quickly open to allow inward net sodium current (brief downward deflections) and then shut to an inactivated state from which further openings normally do not occur. In HyperPP myotubes, mutant sodium channels open and shut repetitively during the depolarization and the duration of individual openings is abnormally prolonged. Both changes are indicative of disrupted fast inactivation. (Figure adapted from Cannon et al., 1991) (*b*) Computer simulations of a model muscle fibre demonstrate that even a subtle disruption of fast inactivation is sufficient to produce myotonia, and slightly more pronounced defects cause depolarization-induced paralysis. Tracings show simulated membrane potential response to injection of a prolonged stimulating current. Normally, only a single action potential is elicited after which the fibre is refractory and repolarizes at the termination of the stimulus (top trace). If fast inactivation is disabled for 2% of the sodium current ($f = 0.02$), then myotonia ensues with repetitive discharges that persist beyond the duration of the stimulus (middle trace). When the fraction of non-inactivating sodium channels is increased to 3% ($f = 0.03$, bottom), then the same stimulus elicits a burst of myotonic discharges, after which the membrane potential settles to an aberrantly depolarized potential. Depolarization inactivates the majority of sodium channels (both wild-type and mutant) and renders the fibre inexcitable, as occurs during episodes of periodic paralysis.

neuromuscular disorders, but a missense mutation has been found to be a rare cause of generalized epilepsy with febrile seizures (Wallace et al., 1998).

Functional defects in mutant sodium channels

Functional studies of sodium channel mutations identified in families with myotonia or HyperPP have revealed gain-of-function defects. Mutant channels pass more inward Na current than normal because the voltage-dependent opening and closing are altered. The ability of sodium ions to pass through the pore is not affected. At the resting potential of −85 mV, sodium channels are in a closed, resting state. In response to membrane depolarization, sodium channels normally open within a fraction of a millisecond and then after about 1 millisecond spontaneously shut to a fast-inactivated state. Channels remain inactivated and unavailable for subsequent opening until they are reprimed by hyperpolarizing the membrane potential.

A defect in sodium channel behaviour was first identified from patch-clamp recordings of sodium currents in myotubes cultured from a patient with HyperPP (Cannon et al., 1991). Mutant channels opened normally in response to depolarization, but occasionally failed to inactivate, as evidenced by bursts of openings and closings during a maintained test depolarization and an increased duration of the open times (Fig. 71.7). On average, 2–5 % of mutant channels were open during a maintained depolarization, whereas for wild-type channels about 0.1% or less remain open. Subsequently, the gating behaviour of 25

different sodium channel mutations associated with myotonia or HyperPP have been characterized in heterologous expression systems. Impaired fast inactivation has been observed as a common feature for all cases (for review see Cannon, 2000). Some mutations disrupt the completeness of fast inactivation, as shown in Fig. 71.7. Others slow the rate of inactivation, shift its voltage dependence, or accelerate the rate of recovery (Chahine et al., 1994; Yang et al., 1994; Hayward et al., 1996). For a few mutants (notably, the most common cause of HyperPP, T704M) activation is enhanced such that channels open at more hyperpolarized potentials (Cummins et al., 1993). Both the inactivation and the activation defects result in more inward sodium current being conducted by mutant channels as compared to wild-type. This aberrant inward current may either trigger myotonic afterdischarges or depolarize the resting potential and render the fibre electrically inexcitable.

Sodium channels in skeletal muscle, heart and brain exhibit more than one form of inactivation. Fast inactivation, as discussed above, occurs on a timescale of milliseconds. This rapid gating behaviour initiates repolarization at the peak of the action potential and produces the refractory behaviour that limits the maximal firing rate. In response to prolonged depolarization lasting seconds to minutes or to high-frequency trains of discharges, sodium channels enter a slow-inactivated state, from which recovery at the resting potential occurs over seconds to minutes. Fast and slow inactivation are not only temporally distinct, they also arise from different functional domains of the channel. Ruff proposed that slow inactivation, as well as fast, must be disrupted if an anomalous persistent sodium current is to cause the prolonged episodes of depolarization-induced inexcitability in periodic paralysis (Ruff, 1994). Otherwise, within seconds, slow inactivation would shut off the persistent current arising from the fast-inactivation defect, and the muscle fibre would repolarize. Expression studies of mutant channels showed that slow inactivation is partially disrupted for the two most commonly occurring mutations in HyperPP (T704M and M1592V) (Cummins & Sigworth, 1996; Hayward et al., 1997) and for another mutation associated with cold-induced attacks of weakness (I693T) (Hayward et al., 1999). On the other hand, slow inactivation was normal for several other sodium channel mutations that are associated with HyperPP (A1156T, M1360V), or PMC with weakness (T1313M, R1448C) (Hayward et al., 1999). Impaired slow inactivation was not detected in any of the nine myotonia-associated mutants (PAM and PMC) tested to date. One interpretation is that disrupted slow inactivation always predisposes the fibre to prolonged episodes of depolarization-induced weakness, but that defective slow inactivation is not a necessary condition for periodic paralysis.

Pathophysiological basis of myotonia and depolarization-induced paralysis from sodium channel defects

The gain-of-function defect in mutant sodium channels is predicted to alter the excitability of the sarcolemma. The anomalous inward current may enhance excitability by depolarizing the fibre and triggering the afterdischarges of the myotonic burst. Alternatively, a persistent inward current could depolarize the resting potential and produce flaccid weakness from a loss of excitability due to chronic inactivation of sodium channels. Two model systems have been used to test these hypotheses and to explore why some mutations in *SCN4A* lead to myotonia only, while others primarily cause episodic weakness, and still others cause both.

In an in vitro toxin-based model, Cannon and Corey simulated the inactivation defect observed for mutant channels by applying sea anemone toxin (ATXII) to normal rat fast-twitch muscle (Cannon & Corey, 1993). In patch clamp recordings, 10 micromolar ATXII partially disrupted fast inactivation so that about 2% of sodium channels remained open in depolarized membranes. Muscle bathed in 10 μM ATXII exhibited myotonia, with trains of repetitive discharges elicited by a single shock and a 20-fold slowing in the relaxation phase of the isometric twitch response. These observations firmly established that even a subtle defect in sodium channel inactivation (2%) is sufficient to produce myotonia.

The toxin-based model also demonstrated a pathomechanism in common between chloride- and sodium-channel based myotonia. In skeletal muscle, each propagated action potential causes an egress of potassium from the myoplasm into the T-tubules. These long narrow invaginations of the surface membrane effectively communicate depolarization to the core of the fibre to elicit contraction, but they also present a substantial barrier to diffusion. This results in activity-dependent accumulation of potassium in the T-tubules (an extracellular space), which will depolarize the fibre. Adrian and Bryant (Adrian & Bryant, 1974) showed that disruption of the T-tubules by osmotic shock prevents the afterdepolarization and afterdischarges recorded after termination of the stimulating current in goat myotonic muscle (chloride channel defect). Similarly, detubulation by osmotic shock abolishes the after-depolarization and the afterdischarges of rat muscle exposed to ATXII (sodium channel defect) (Cannon & Corey, 1993). For both channel defects, the activity-dependent accumulation of T-tubule potassium is the

depolarizing trigger that elicits myotonic discharges. The chloride channel defect attenuates a shunt current, so that an equivalent increase in potassium concentration results in a larger depolarization and afterdischarges. The sodium channel inactivation defect increases the availability of sodium channels at the end of one action potential, so that the mild depolarization from potassium accumulation now triggers an afterdischarge.

In these experiments, muscle weakness was not consistently observed in rat muscle treated with 10 μM ATXII. The interpretation was that the toxin-induced changes in sodium channel inactivation were comparable to the more subtle defects observed for mutations associated with myotonia (PAM), and that if more pronounced gating defects could be produced then paralysis would ensue. Moreover, slow inactivation is not disrupted by ATXII.

Computer simulation has been used as another approach to explore how altered behaviour of mutant sodium channels affects the excitability of skeletal muscle (Cannon et al., 1993). A major advantage of this theoretical approach is that the type of channel defect and the relative proportion of wildtype and mutant channels can be explicitly specified. The model muscle cell consists of two electrically coupled membrane compartments to simulate the surface and T-tubule membranes, each of which contains sodium, potassium, and leakage (chloride) channels.

Figure 71.7 shows the model behaviour in response to a prolonged stimulus current, as the fraction of fast-inactivation defective sodium channels (f) was increased. With normal values for the model parameters ($f = 0.001$ to account for imperfect fast inactivation in wild-type channels), the suprathreshold stimulus elicits a single action potential, and the simulated cell repolarizes at the end of the current injection. This model response is identical to the behaviour observed in wild-type muscle fibres. In agreement with the ATXII toxin studies in rat muscle, even a subtle disruption of fast inactivation ($f = 0.005$ to 0.025) is sufficient to produce myotonic afterdischarges in the computer model (Fig. 71.7(*b*), middle trace). The small pool of inactivation-defective sodium channels that remain available to open at the end of one action potential (in combination with a mild depolarization from activity-dependent potassium trapping in the T-tubules) leads to the generation of a myotonic burst. A slightly larger defect of fast inactivation ($f = 0.03$) results in a myotonic burst of discharges that dissipates to an aberrantly depolarized stable membrane potential. The anomalous persistent sodium current keeps the fibre depolarized. From this depolarized potential of −40 mV, the majority of sodium channels (both mutant and wild-type) are inactivated. Consequently, the fibre is refractory from generating additional action potentials. This model state corresponds to the flaccid weakness, depolarized resting potential, and electrical inexcitability observed in skeletal muscle during an attack of periodic paralysis. This model demonstrates how mutant sodium channels exert a dominant-negative effect via the membrane potential. The gain-of-function channel defect gives rise to a small persistent sodium current that depolarizes the membrane, which in turn inactivates the normally functioning sodium channels. In support of this theoretical analysis, expression studies of sodium channel mutants have shown that paralysis-associated mutations tend to cause more severe defects in gating than those associated with myotonia only (for review see Cannon, 2000).

Computer simulation also provides insights into why some sodium channel mutations cause myotonia only (PAM), others cause depolarization-induced paralysis (HyperPP) and still others may cause both (PMC). Although all of the sodium channel mutations in Fig. 71.6 produce gain-of-function defects, differences in the severity or the type of gating defect presumably determine the clinical phenotype. Expression studies of mutant channels and computer modelling both support this hypothesis. In principle, any gating defect that increases the steady-state open probability of mutant channels could produce prolonged episodes (hours) of depolarization-induced paralysis. Model simulations show that aberrant chronic depolarization and inexcitability are induced most easily by impaired slow inactivation in combination with partially disrupted fast inactivation (as detailed in the above example) or a shift of channel activation to more negative potentials. In contrast, model simulations show that impeding fast inactivation by shifting its voltage dependence to more positive potentials does not readily lead to stable depolarization. Expression studies have shown mutations associated with HyperPP or PMC with weakness usually cause some combination of (i) disrupted fast inactivation (persistent sodium current >1.5% of the peak transient), (ii) hyperpolarized shift of activation (>5 mV), or (iii) impaired slow inactivation. In contrast, expression studies of mutations associated with myotonia only (PAM) have revealed: (i) defects in the rate of fast inactivation (two- to fivefold too slow) but only very small persistent sodium currents (<1% of peak), (ii) only small shifts in activation (<5 mV), and (iii) no impairment of slow inactivation. Slowing the rate of fast inactivation is a common defect observed in many mutations associated with myotonia (PAM or PMC). Model simulations show that the major consequence for this type of inactivation defect is a broadening of the action potential duration, which in turn greatly increases the potassium egress into the T-tubule with each action potential and thereby promotes myotonia.

Although the foundations of the pathogenesis of myotonia and periodic paralysis due to sodium channel defects are now well established, the basis of many clinical phenomena remain to be elucidated. For example, current models predict that raised extracellular potassium and sodium channel gating defects act synergistically to alter membrane excitability. Why, then are attacks precipitated by potassium loading for some disorders (HyperPP, PAM) but not others (PMC)? What is the basis for the cold sensitivity of myotonia in PMC? Expression studies have not identified an aberrant temperature sensitivity in the gating behaviour of channel mutations associated with PMC. How does muscular activity produce paradoxical myotonia or the warm-up phenomena? And, why does rest after exercise provoke attacks of periodic paralysis? Answers to these questions will likely await the development of transgenic animals as model systems to explore these phenomena at the whole-animal level.

Hypokalemic periodic paralysis

Hypokalemic periodic paralysis is the most commonly occurring form of periodic paralysis in humans, but it is still a rare disorder with a prevalence estimated to be about 1:100 000. Familial periodic paralysis was described late in the nineteenth century, but it was not until 1934 that Biemond and Daniels observed that attacks of weakness occurred in association with hypokalemia for some families (Biemond & Daniels, 1934). The clinical hallmarks of HypoPP are episodes of moderate to severe generalized weakness, hypokalemia (often $<$3.0 meq/l) during an attack, and the absence of myotonia. Attacks of weakness typically begin around puberty, but may present any time during the first three decades of life. In comparison to HyperPP, episodic weakness in HypoPP is usually more severe and of longer duration. Acute attacks typically resolve in hours to days, but a more protracted course of mild weakness may persist for weeks or longer. Precipitants of acute attacks include rest after exercise and carbohydrate-rich meals. Many patients with HypoPP develop a mildly progressive late-onset proximal myopathy. HypoPP is inherited as an autosomal dominant trait, and the clinical expression in females is reduced (male-to-female prevalence is about 3:1). For some females, the only manifestation of HypoPP is the late-onset proximal myopathy, without any clinically evident acute attacks of weakness (Links et al., 1990).

During an attack of weakness in HypoPP, affected muscle fibres are depolarized and electrically inexcitable due to inactivation of sodium channels. Hypokalemia results from a shift of potassium from the extracellular space into muscle, but the mechanistic basis for this shift and of the membrane depolarization remains unknown. Under basal conditions, the resting potential of HypoPP muscle is depolarized by 5 to 10 mV compared to normal muscle (Rüdel et al., 1984; Ruff, 1999), and the fibre conduction velocity is reduced (van der Hoeven et al., 1994). In vitro studies on biopsied fibres have shown that reducing the extracellular potassium concentration to 1 mM causes HypoPP fibres to depolarize by 20 mV, whereas normal muscle hyperpolarizes by 10 mV under the same conditions (Rüdel et al., 1984). The paradoxical hypokalemia-induced depolarization is not prevented by sodium channel blockers (tetrodotoxin) (Rüdel et al., 1984) or calcium channel antagonists (nitrendipine) (Ruff, 1999). In patients with HypoPP, insulin administration often provokes an attack of weakness. In part, this effect is due to the ability of insulin to promote a shift of extracellular potassium into muscle. In vitro studies on biopsied HypoPP fibres suggest insulin also promotes depolarization by reducing an inwardly rectifying potassium conductance in diseased, but not normal, fibres (Ruff, 1999).

Molecular defects in hypokalemic periodic paralysis

Electrophysiological studies of HypoPP muscle revealed aberrant depolarization of the resting potential, but did not identify a candidate ion channel or pump as the underlying molecular defect. The molecular defect was discovered by genetic linkage analysis. Fontaine and colleagues mapped the HypoPP locus to chromosome 1q21–31 (Fontaine et al., 1994). The gene encoding the α_1-subunit of the skeletal muscle L-type calcium channel, *CACNL1A3*, had previously been mapped to this region. The calcium channel of skeletal muscle is a heteromeric complex of the pore-forming α_{1S} subunit and four accessory subunits: β_1, α_2 δ, and γ. Subsequent screening of the α_{1S} gene led to the identification of three missense mutations in HypoPP families. Interestingly, all three mutations occur at positively charged arginines in voltage-sensing regions of the channel (Fig. 71.8). The R528H mutation occurs in about 50% of HypoPP families linked to the chromosome 1 locus, and the incomplete penetrance of acute attacks in females is unique to this mutation (Elbaz et al., 1995). The R1239H mutation, in a homologous voltage-sensing region, is the molecular defect in most of the remaining chromosome 1 linked HypoPP families (Ptacek et al., 1994b; Elbaz et al., 1995). A third missense mutation, R1239G, is much rarer.

Hypokalemic periodic paralysis is genetically heterogeneous. Linkage to chromosome 1q21–31 has been excluded in several families with autosomal dominant HypoPP that is indistinguishable clinically from HypoPP in

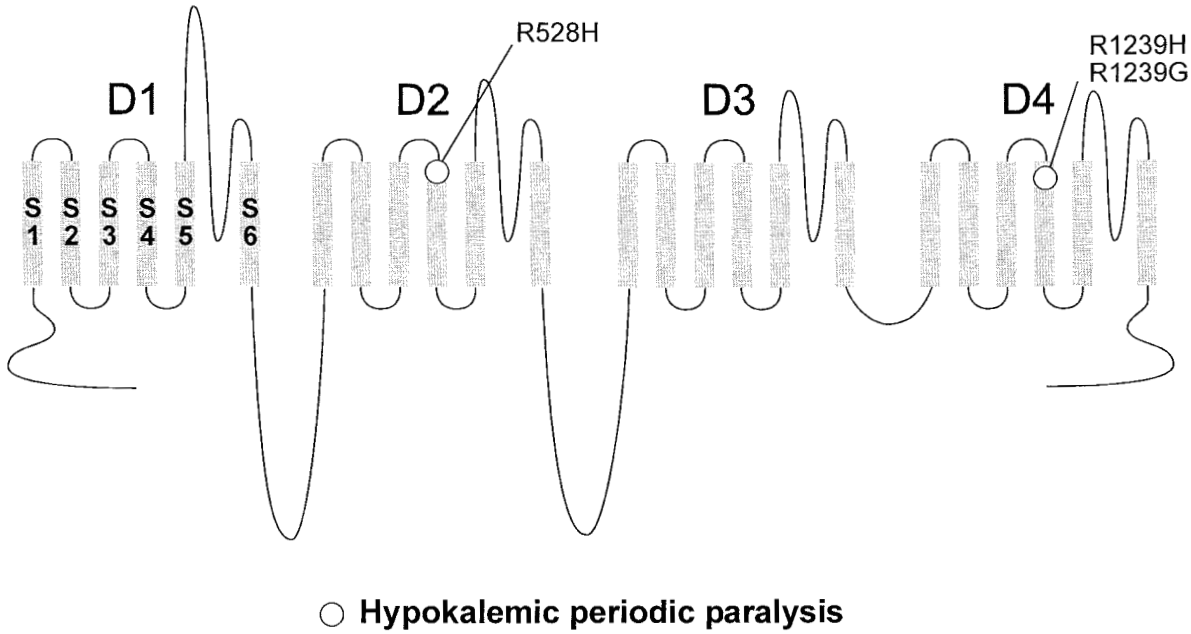

Fig. 71.8. Transmembrane folding diagram for the α subunit of the skeletal muscle L-type calcium channel and location of missense mutations identified in patients with hypokalemic periodic paralysis. HypoPP mutations occur at positively charged arginine residues in the voltage-sensing S4 segments of domains II and IV.

families with a confirmed mutation in the calcium channel α_{1S} subunit gene. Further molecular genetic testing has identified three different mutations in the sodium channel α subunit gene (*SCN4A*) in six families with clinical syndromes typical for HypoPP (Bulman et al., 1999; Jurkat-Rott et al., 2000). Intriguingly, all three mutations occur at positively charged arginine residues in voltage sensing domains of the sodium channel (Fig. 71.6). The R669H mutation in the sodium channel is located at a position that correlates exactly to that of the HypoPP associated R528H mutation in the calcium channel. The other two sodium channel mutations in HypoPP are located at the adjacent arginine within the same voltage sensing region, R672H and R672G.

Functional defects of mutant channels and other skeletal muscle conductances in HypoPP

The functional consequences of the HypoPP missense mutations in the calcium channel and the sodium channel have been characterized by recording ionic currents from biopsied muscle and from heterologously expressed mutant channels. Because all six mutations are substitutions at arginine residues in voltage-sensor domains, it was predicted that the voltage dependence of channel gating would be altered.

The L-type calcium channel has two functional roles in skeletal muscle: (i) voltage-activated calcium channel and (ii) voltage sensor for coupling depolarization of the T-tubule to release calcium from the sarcoplasmic reticulum (excitation–contraction coupling). The defect in maintaining the resting potential for HypoPP muscle implies the channel-forming role has been altered, but both functions could be defective. Excitation–contraction coupling appears to be grossly normal in HypoPP fibres, based on fluorometric measurements of myoplasmic Ca^{2+} transients elicited by depolarization (Jurkat-Rott et al., 1998). Most studies have focused primarily on the calcium-channel properties of α_{1S} mutants. The most consistent change observed in common for all three mutations has been a reduction in the calcium current density by about 50%. This decrease has been found for endogenous mutant channels expressed in cultured HypoPP myotubes (R588H and R1239H) (Sipos et al., 1995; Morrill et al., 1998) and for mutant channels heterologously expressed in mammalian cells (Lapie et al., 1996; Jurkat-Rott et al., 1998) or frog oocytes (Morrill & Cannon, 1998). In addition, the rate of activation at depolarized voltages is slowed by all three mutations (Morrill & Cannon, 1998). The net result of these changes is that in HypoPP muscle less Ca^{2+} entry occurs during a single action potential, and especially in response to a high-frequency burst of discharges. The mechanism by which altered Ca^{2+} entry results in episodic depolarization-

induced paralysis, hypokalemia, and permanent proximal myopathy remains to be elucidated.

Functional studies of mutant sodium channels found in HypoPP suggest that loss-of-function defects are responsible for the attacks of periodic paralysis. Expression studies in mammalian cells showed a two- to fourfold reduction in sodium current density for R672H and R672G mutants, as compared to wild-type channels (Jurkat-Rott et al., 2000). Moreover, the rate of rise of the action potential was decreased in acutely dissected muscle carrying the R672G mutation, which is consistent with a reduced sodium current density for channels endogenously expressed in human muscle. In addition, fast inactivation was enhanced by both mutations at R672 (Jurkat-Rott et al., 2000). For the R669H mutation, fast inactivation was normal, but slow inactivation was augmented, as evidenced by a hyperpolarized shift in its voltage dependence and a slowed time course of recovery (Struyk et al., 2000). In sum, these changes reduce the maximal available sodium current and also cause a greater attenuation of sodium current in response to even mild depolarization of the resting potential. A reduction in sodium current would contribute to the loss of excitability during an attack of HypoPP, but it does not explain the aberrant depolarization of the resting potential or the trapping of potassium in muscle.

Because the behaviour of HypoPP mutant channels studied in isolation has not provided a pathophysiological explanation for clinical features of an attack, attempts to identify functional defects by recording directly from diseased muscle have continued. At present there are no animal models for an inherited HypoPP-like syndrome. The chronically potassium-depleted rat does have insulin-induced attacks of paralysis with muscle depolarization and hypokalemia (Kao & Gordon, 1975), but these animals do not have spontaneous attacks, nor can they be triggered by exercise or carbohydrate ingestion. Consequently, the most informative data comes from experiments on acutely dissociated human HypoPP fibres. Two separate laboratories have reported abnormalities in the potassium conductance of human HypoPP fibers heterozygous for the R528H mutation in the L-type calcium channel gene. Tricarico and colleagues (Tricarico et al., 1999) observed a tenfold reduction in the ATP-sensitive potassium current in excised patch recordings from HypoPP fibres. This decrease was primarily due to a reduction in the open probability of the channel in low ATP, and also partially due to a diminished ability of potassium to flow through the open channel (subconductance states). Ruff reported an insulin-induced reduction in membrane current for HypoPP fibres under conditions that isolated potassium currents (Ruff, 1999). Although not directly proven, this may also reflect a defect in the ATP-sensitive potassium current. Ruff's data also suggested the presence of an anomalous inward current in HypoPP fibres that was not blocked by tetrodotoxin or nitrendipine. The blocker experiments exclude voltage-gated sodium and calcium channels, but the identity of the anomalous current remains unknown. It is not yet known if similar alterations in membrane conductance are present in HypoPP fibres with calcium channel mutations at R1239 or with mutations in the sodium channel.

One intriguing hypothesis for the pathogenesis of HypoPP is that a disruption of Ca^{2+} homeostasis caused by a reduced entry through mutant calcium channels alters the transcription or regulation (e.g. phosphorylation) of other ion channels. This mechanism could account for the reduced ATP-sensitive potassium current. A reduced potassium current would in turn depolarize the resting potential and may trap potassium in the myoplasm.

Thyrotoxic periodic paralysis

A sporadic form of periodic paralysis occasionally occurs in association with thyrotoxicosis. Like familial HypoPP, thyrotoxic periodic paralysis (TPP) presents with profound episodic weakness and hypokalemia, without myotonia (for review see Ober, 1992). Rest after exercise, ingestion of carbohydrates, or administration of insulin may provoke an attack. This disorder is especially prevalent in Asian populations, where it has been estimated that periodic paralysis occurs in 2% of patients with thyrotoxicosis (Okinaka et al., 1957). TPP is much rarer in other ethnic groups, but has been reported in Caucasians and Blacks. There is also a strong gender bias with a male : female ratio of 10–20 : 1. Many patients with TPP do not have overt clinical signs of thyrotoxicosis. Perhaps the acute and dramatic nature of periodic paralysis greatly overshadows the more insidious manifestations of the thyrotoxic state in these patients. Moreover, TPP may occur with either T4- or T3-thyrotoxicosis, and therefore the TSH level is the most sensitive test for distinguishing TPP from HypoPP. Attacks of weakness are abolished by treatments that attain a euthyroid state. Recurrent hyperthyroidism due to relapse or exogenous thyroid hormone may provoke additional attacks of paralysis.

The pathophysiological basis for the attacks of weakness and hypokalemia in TPP remains unknown. The heavily skewed ethnic distribution suggests a genetic component. However, HLA typing has not identified a consistent genetic marker for TPP. A few exceptional cases of familial clustering have been reported, but the mode of inheritance is not clear

and a TPP locus has not been identified by linkage analysis. One hypothesis is that TPP is caused by increased activity of the Na^+–K^+ATPase pump. Thyroid hormone increases the activity and number of the Na^+–K^+ ATPase sites in muscle. Thyrotoxicosis would result in an increased uptake of potassium into muscle. This hypothesis was supported by the finding that platelet Na^+–K^+ATPase activity is higher in hyperthyroid patients with TPP than those with hyperthyroidism without TPP (Chan et al., 1991). The Na^+–K^+ ATPase pump is also stimulated by insulin, which may explain why attacks of weakness are provoked by carbohydrate loading or insulin challenge. The male predominance in TPP may be related to increases in pump activity by androgens and inhibition by estrogen and progesterone.

Diagnosis and treatment of non-dystrophic myotonias and periodic paralysis

Diagnostic approach in the non-dystrophic myotonias

In the differential diagnosis of myotonic syndromes, it is imperative to distinguish those associated with dystrophy from the more benign non-dystrophic forms discussed in this chapter. In most cases this distinction is easily made on clinical grounds. Myotonic dystrophy (DM1) is a multisystem disorder in which late-onset progressive wasting of bulbar and distal muscles usually predominates over a relatively mild degree of myotonia. Additional organ system involvement includes brain (mental retardation), eyes (cataract, retinal degeneration, developmental defects), heart (conduction defects, cardiomyopathy), smooth muscle (dysphagia, megacolon), endocrine (testicular atrophy), and skin (frontal baldness). Inheritance is dominant with high penetrance and progressive worsening in successive generations (genetic anticipation). The molecular defect is an expanded trinucleotide repeat (CTG) in the 3′-untranslated region of the myotonic protein kinase gene (*DMPK*) on chromosome 19 (Brook et al., 1992). Normal individuals have 5 to 40 repeats, whereas patients with myotonic dystrophy have 50 to >2000. Molecular genetic screening for the CTG expansion on chromosome 19 is a sensitive and specific test of myotonic dystrophy. Proximal myotonic myopathy (PROMM or DM2) is a dominantly inherited disorder with several similarities to myotonic dystrophy (Ricker et al., 1994b), but there is no expansion of the CTG repeat in the *DMPK* gene. Unlike myotonic dystrophy, muscle wasting in PROMM is proximal. Most patients with PROMM have mild myotonic stiffness of the legs or hands. Associated features include cataracts, hypogonadism, intermittent muscle pain not associated with myotonia, and in some patients cerebral white matter abnormalities on MRI. Mental retardation and genetic anticipation do not occur in PROMM. The genetic defect in PROMM is a CCTG expanded repeat in intron 1 of the zinc finger protein 9 on chromosome 3q (Liquori et al., 2001).

The non-dystrophic myotonias can usually be distinguished on the basis of clinical features listed in Table 71.2. A true autosomal dominant inheritance pattern excludes a diagnosis of recessive generalized myotonia. On the other hand, the absence of myotonia in both parents is less informative because the disorder could either be recessive or the result of a *de novo* mutation. Paramyotonia of the hands, face and tongue that is aggravated by cooling is pathognomonic for paramyotonia congenita. Cooling may also enhance the myotonia in PAM, but in this latter syndrome the myotonia exhibits warm-up behaviour, rather than paradoxical worsening with repeated muscular activity. In contrast, cooling does not acutely aggravate the myotonia in the chloride channel disorders. Another typical feature of PAM is slow fluctuations in the severity of myotonia over a course of days or in relation to prior exercise. Electromyography is useful in documenting myotonia in clinically ambiguous cases or for detecting latent myotonia. It is not possible to distinguish between the chloride channel and sodium channel based myotonias from the appearance of the EMG. The muscle biopsy often shows fibre hypertrophy, central nuclei, and reduced number of type 2 fibres, but these are non-specific changes that do not distinguish between the different types of non-dystrophic myotonia. At present, a comprehensive molecular genetic screen for all of the mutations in the chloride and sodium channel genes is not available. A few laboratories will screen for a limited number of the more prevalent mutations. The presence of a mutation is highly informative, but the failure to detect a molecular defect does not exclude the diagnosis.

Treatment strategies for myotonia

Many patients with myotonia do not require any pharmacological intervention. Most patients prefer to minimize their symptoms by regulating their level of exercise, dietary potassium intake, or avoidance of cold environments. When these manoeuvres are insufficient, drugs that reduce the excitability of the sarcolemma can be used. The most effective agents for suppressing myotonia due to either a chloride or a sodium channel defect are use-dependent blockers of voltage-gated sodium channels. Mexiletine, starting at 200 mg three times a day is the preferred drug (Ricker et al., 1994a). Elderly patients or those with known cardiac conduction abnormalities should consult a cardiologist before beginning mexiletine. The antiepileptic drugs

phenytoin and carbamazepine may also produce improvement. These agents are anecdotally thought to be less effective than mexiletine, but a controlled comparison has never been performed. A rational approach for ameliorating myotonia due to chloride channel defects (myotonia congenita or RGM) would be to pharmacologically increase the chloride conductance of skeletal muscle. Taurine and the R-(+) isomer of clofibric acid produce measurable increases in the resting chloride conductance of skeletal muscle. The effect is modest, however, and is not sufficient to prevent myotonia (Bryant & Conte-Camerino, 1991).

Diagnostic approach in the periodic paralyses

A diagnosis of periodic paralysis is easily made in the setting of prototypical attacks of weakness and a positive family history of dominant inheritance. The clinical distinction between HyperPP and HypoPP or the recognition of a *de novo* case in the absence of a family history can be more challenging. When ascertaining the family history, the clinician must take into consideration the reduced penetrance for episodic weakness in women with HypoPP. The diagnosis of thyrotoxic periodic paralysis should always be excluded by measuring the TSH, especially for males in whom there is no family history of weakness.

Provocative testing may be used to confirm a suspected diagnosis of periodic paralysis. Exercise-induced changes in the amplitude of the compound muscle action potential provide objective evidence of periodic paralysis (McManis et al., 1986), but the sensitivity of the test is only about 70% and it does not distinguish between HyperPP, HypoPP, and thyrotoxic periodic paralysis. A more specific test is to monitor the patient's serum potassium and strength before and after exercise (Lehmann-Horn & Engel, 1994). After measuring baseline performance, the patient exercises on a treadmill for 30 minutes with the heart rate >120 beats/min. Then the patient is instructed to lay motionless in bed. In normal individuals, serum potassium rises during exercise and then falls to the basal level within minutes. In HyperPP there is a secondary rise in serum potassium 15 to 30 minutes after exercise, often in association with weakness. However, the lack of a secondary rise in serum potassium does not exclude a diagnosis of HyperPP. Patients with HypoPP will have a fall in serum potassium coincident with the onset of weakness. If the exercise test does not elicit weakness or the serum potassium levels are ambiguous, then a more strenuous challenge can be performed in which the serum potassium level is manipulated. In-patient monitoring is required for this more invasive level of testing. In suspected HyperPP, the exercise test is performed after fasting overnight and administration of 40 to 120 meq of a potassium salt orally in an unsweetened solution. An attack usually occurs within one or two hours as evidenced by weakness or a reduction in the amplitude of the compound muscle action potential. To test for HypoPP, an oral glucose load of 2 gm/kg body weight is given in the morning. Weakness and hypokalemia often ensue within 1 hour. If an attack is not elicited, the test can be repeated with coadministration of insulin (10 units subcutaneously) and glucose. In some patients with HypoPP, attacks cannot be reliably induced. Therefore, a positive test is more informative than the lack of a response. The presence of myotonia, either clinically or electromyographically, excludes a diagnosis of HypoPP.

In patients with myotonia and periodic paralysis, the diagnosis could be either HyperPP or PMC. In exemplary cases, the distinction is easily made on the basis of the clinical features listed in Table 71.2. However, there are many clinical variants within the PMC-HyperPP complex that have overlapping signs and symptoms. These intermediate cases have been called normokalemic periodic paralysis, paralysis periodica paramyotonia, and other terms. We favour a simpler scheme in which the criteria for HyperPP and PMC are broadened to include these variants. For example, if the primary symptom is weakness, then the diagnosis should be HyperPP, even if the weakness is cold induced and the serum potassium remains normal.

Treatment strategies for periodic paralysis

A combination of changes in lifestyle and pharmacological intervention is often required to reduce the severity and frequency of attacks in periodic paralysis. Patients with any form of periodic paralysis should avoid excessively strenuous exercise and gradually 'warm down' with progressively decreasing levels of activity to avoid postexercise-induced attacks.

For patients with HyperPP, attacks may be prevented or foreshortened by eating carbohydrate-rich snacks, and avoiding intake of high-potassium containing foods. Judicious use of a diuretic may help (hydrochlorothiazide 25 to 50 mg/day). The most effective prophylactic drug is the carbonic anhydrase inhibitor acetazolamide (McArdle, 1962). The dosage should be started at 125 mg/day and gradually increased until a satisfactory response is obtained or the dose reaches 1500 mg/day. Most patients taking acetazolamide develop distal paresthesias and distaste for carbonated beverages. Chronic use is associated with a high incidence of renal stones (10–20% of patients) (Tawil et al., 1993). The mechanism of acetazolamide's therapeutic effect is not fully understood. One possibility is that the mild metabolic acidosis produced by chronic use results in proton-mediated screening of the fixed negative charges on the outer surface of cell membranes (Lehmann-Horn et al., 1987). Charge screening will cause an apparent depolarized shift in the voltage dependence of

channel gating, and thereby reduce the degree of sodium channel inactivation produced by modest depolarization of the resting potential.

Patients with HypoPP can reduce the frequency and severity of attacks by avoiding strenuous exercise, eating foods rich in potassium, and limiting carbohydrate intake (Lehmann-Horn & Engel, 1994). Oral potassium supplements (20 to 40 meq) may hasten the recovery from an acute attack, but patients should be warned against using escalating dosages of potassium *ad libitum*. For prophylactic management of HypoPP, carbonic anhydrase inhibitors are the preferred drug. Chronic administration of acetazolamide usually reduces the frequency and severity of attacks and improves the interictal low-grade weakness (Griggs et al., 1970). Patients refractory to acetazolamide may respond to a more potent carbonic anhydrase inhibitor, dichlorphenamide 50 to 300 mg/day (Tawil et al., 2000). Agents that reduce urinary potassium loss such as triamterene (150 mg/day) or the aldosterone antagonist spironolactone (100 mg/day) may also reduce symptoms. However, potassium supplements should not be used in conjunction with these drugs. Alternative prophylactic therapies are still being sought because some patients with HypoPP fail to respond to acetazolamide or cannot tolerate its side effects. A placebo-controlled trial of the calcium channel antagonist verapamil did not show significant improvement in nine patients with HypoPP (Links et al., 1998). Another approach has been to search for agents that open potassium channels and thereby repolarize the membrane. In vitro studies in human HypoPP fibres showed that cromakalim, an opener of ATP-sensitive potassium channels, is able to repolarize the muscle membrane and restore twitch force (Grafe et al., 1990). Another K-ATP channel agonist, diazoxide was initially effective in preventing attacks of weakness in patients with HypoPP, but after a few months of continuous use the attacks of weakness returned (Johnsen, 1977). Clinical use of K-ATP channel openers has been limited by side effects of hypotension and hyperglycemia. Different isoforms of the K-ATP channel are present in skeletal muscle, smooth muscle, and pancreatic β cells. If drugs could be found that selectively open K-ATP channels of skeletal muscle, then these agents may be beneficial in preventing attacks of episodic weakness in HyperPP and HypoPP, and in suppressing myotonic discharges.

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Pathophysiology of metabolic myopathies

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The term metabolic myopathy refers to disorders that impair the metabolism of carbohydrates, lipids or both within skeletal muscle. Many of these disorders are associated with abnormal storage of glycogen (glycogen storage diseases) or triglyceride (lipid myopathies) but others, such as distal glycolytic defects and carnitine palmitoyltransferase II deficiency, usually do not result in excess muscle stores of glycogen or lipid. Some metabolic myopathies, notably acid maltase deficiency, affect non-energy yielding pathways, but the majority of metabolic myopathies are inborn errors of muscle energy metabolism. The pathophysiology of these muscle energy defects relates directly to the role of the affected energy pathway in muscle function.

Muscle fuel at rest and during exercise

The fundamental source of energy for muscle contraction and ion transport is the hydrolysis of adenosine triphosphate (ATP) to ADP and inorganic phosphate (Pi). ADP and Pi in turn activate energy-producing reactions that regenerate ATP via anaerobic or oxidative means. The major anaerobic sources of ADP phosphorylation are the hydrolysis of phosphocreatine (PCr) via the creatine kinase reaction, and anaerobic glycogenolysis in which glycogen is metabolized to lactic acid. Anaerobic energy pathways are the major or sole source of ATP production when muscle blood flow is compromised as in ischemic or isometric exercise, e.g. weight lifting, or when energy demand exceeds the limits of oxidative power output, e.g. maximal effort running. Anaerobic sources of energy have several advantageous features: (i) they are intrinsic to muscle and independent of blood flow or oxygen supply; (ii) they enable muscle to work for brief periods at rates of ATP production (power output) that are two- to threefold higher than those available through oxidative metabolism; and (iii) they can reach these high rates of energy turnover in seconds, whereas acceleration to maximal oxidative power output takes 3–30 minutes (Sahlin, 1986). On the negative side, anaerobic sources of energy are rapidly depleted and/or lead to the accumulation of metabolic end products, e.g. protons, inorganic phosphate, and ADP, that are associated with muscle fatigue (see below) (Fitts, 1994). No human defects in PCr metabolism attributable to inborn errors of creatine kinase have been recognized, although genetic 'knockout' animal models of both cytoplasmic and mitochondrial forms of creatine kinase have been produced. In contrast, many inborn errors of muscle glycogen and glucose metabolism have been identified, most of which share common symptoms of exertional fatigue, cramping, and muscle injury under exercise conditions that normally require anaerobic energy production.

Oxidative phosphorylation is required to supply energy for muscle work that has to be sustained for more than a few minutes. The high yield of ATP per mole of substrate and the fact that the end products of oxidative phosphorylation, water and carbon dioxide, are readily removed from working muscle and do not themselves promote muscle fatigue make oxidative metabolism ideal for powering sustained exercise. The major endogenous oxidative fuel of skeletal muscle is glycogen, while free fatty acids (FFA) and blood glucose are the primary exogenous oxidative fuels. The oxidation of glycogen is critically important for rapid (within about 3 minutes) acceleration to oxidative steady-state in the transition from rest to exercise (Sahlin, 1986). In addition, glycogen is required for maximal rates of oxidative ATP production (Haller & Bertocci, 1994). Blood glucose is the most important exogenous carbohydrate fuel. As exercise is continued, muscle glucose uptake increases and blood glucose is replenished by increasing rates of hepatic glycogenolysis. Also, blood glucose represents an important

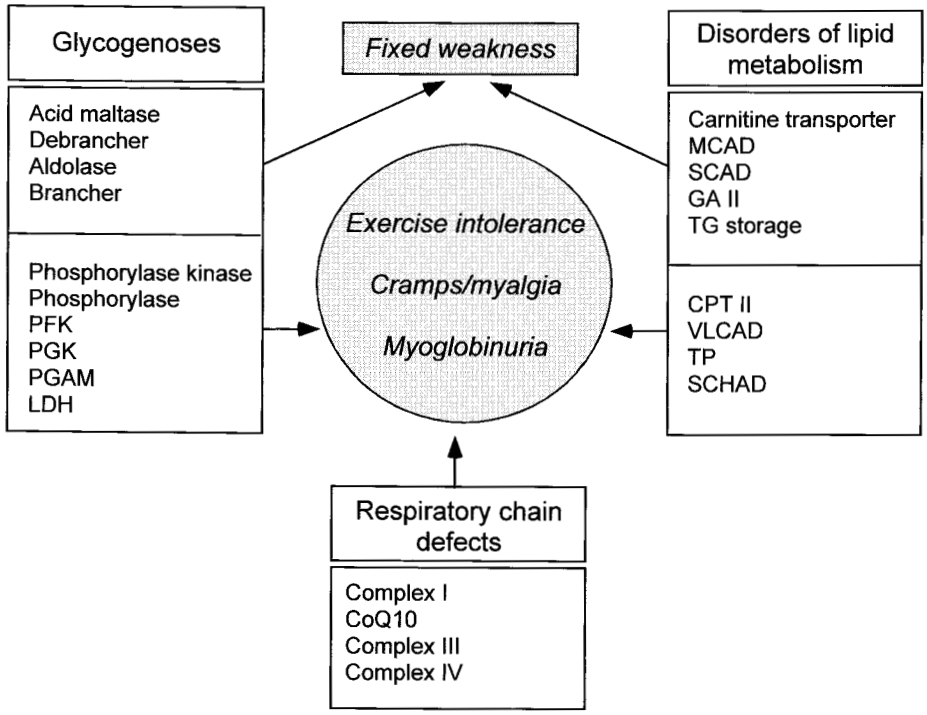

Fig. 72.1. The two major clinical syndromes associated with defects of muscle substrate utilization. Abbreviations: PFK, phosphofructokinase; PGK, phosphoglycerate kinase; PGAM, phosphoglycerate mutase; LDH, lactate dehydrogenase; CPT, carnitine palmitoyltransferase; VLCAD, very long chain acyl-CoA dehydrogenase; TP, trifunctional protein; SCHAD, short chain 3-hydroxyacyl-CoA dehydrogenase; MCAD, medium chain acyl-CoA dehydrogenase; SCAD, short chain acyl-CoA dehydrogenase; GA II, glutaric aciduria type II; TG, triglyceride; CoQ10, coenzyme Q10 (ubiquinone). (Modified from DiMauro & Haller (1999).)

substitute for muscle glycogen, which becomes depleted in prolonged exercise. The most abundant oxidative fuel is lipid, and exercise fueled by fat oxidation can be sustained virtually indefinitely. Peak levels of fat oxidation depend upon the concentration of FFA in blood, which in turn is a function of the rate of mobilization of free fatty acids from triglyceride stores in adipose tissue. Acceleration to peak levels of fat oxidation requires approximately 30 minutes of sustained exercise (Sahlin, 1986), and with prolonged submaximal exercise, lipid is the dominant fuel source for working muscle. Disorders of muscle oxidative metabolism, including mitochondrial myopathies, complete blocks in glycogenolysis/glycolysis and defects of lipid utilization typically impair exercise endurance.

Symptoms in metabolic myopathies

Symptoms in metabolic myopathies may be classified as static or dynamic (Fig. 72.1). The former consist of fixed and often progressive weakness. Dynamic symptoms are provoked by exercise and are the direct result of impaired muscle energy availability within working muscle. These symptoms include abnormal fatigability, cramps, and rhabdomyolysis with myoglobinuria. Muscle pain (myalgia) accompanies cramps and muscle injury and may be a prominent component of exercise intolerance in some of these disorders.

Weakness

Fixed or static weakness is defined as an inability to generate normal muscle force when fully rested. Such weakness generally is attributed to a reduction in functional muscle mass and in the size of functional motor units, and is the dominant feature of some metabolic myopathies, which, in this respect, mimic non-metabolic myopathies. Weakness is typical of acid maltase deficiency. It is also common in some energy defects, such as mitochondrial myopathies and lipid disorders associated with carnitine deficiency. The distribution of weakness is generally symmetrical, affecting predominantly the proximal hip and shoulder girdles, similar to most non-metabolic myopathies. A predilection for extraocular and lid muscles is

typical of mitochondrial myopathies, particularly those attributable to large-scale mitochondrial DNA deletions. Bulbar symptoms also may be a component of myopathic weakness in some mitochondrial and lipid myopathies. Weakness is the most typical neuromuscular presentation of glycogen debrancher deficiency and may complicate other glycolytic defects such as muscle phosphorylase deficiency (McArdle disease) and muscle phosphofructokinase deficiency (Tarui disease). The pathophysiology of weakness in muscle energy defects is poorly understood, but is unlikely to result from disruption of contractile elements due to excess storage of glycogen or lipid, or reduced energy availability. Patients with glycolytic defects and recurrent exertional muscle necrosis may gradually lose muscle mass, potentially exhausting the reserve of satellite cells necessary for muscle regeneration. Energy defects may also play a role in the balance of protein synthesis/catabolism.

Exercise intolerance: abnormal exertional fatigue

Fatigue is defined as an inability to maintain contractile force or power output with repeated muscle contractions. It is a normal phenomenon that is experienced by healthy individuals during intense or prolonged exercise. A hallmark of muscle energy defects is abnormal exertional fatigue in which a decline in muscle force generation occurs prematurely or is provoked by activities that are easily tolerated by healthy individuals.

Normal exertional fatigue

Although the cellular basis of fatigue in healthy individuals is incompletely understood, it must affect one or more steps in the sequence of events involved in normal muscle contraction and relaxation. The mechanism of fatigue and the contribution of various metabolic factors relative to changes in cation levels probably vary depending upon conditions of exercise or experimental paradigms.

Experimentally, the pattern of fatigue in normal muscle is highly dependent upon the rate of stimulation. High-frequency fatigue (HFF) occurs with rates of stimulation around 50 Hz, and has been linked to high levels of extracellular potassium and to increased intracellular sodium/decreased intracellular potassium that accompanies repetitive trains of membrane action potentials (Jones, 1996). These ion shifts tend to lower the transmembrane potential, alter the configuration of the action potential, and ultimately may inactivate sodium channels rendering the sarcolemma inexcitable (Sejersted & Sjøgaard, 2000). Type II muscle fibres (high glycolytic, low oxidative capacity, fast twitch) may be more susceptible to such fatigue (Ruff & Whittlesey, 1992). The activity of Na^+K^+ ATPase (sodium pumps) plays a critical role in the maintenance of membrane excitability under these circumstances, and experimental evidence indicates that reduced pump activity or low pump numbers promote such fatigue, whereas increased pump activity or greater pump numbers are protective (Clausen, 1996). Low frequency fatigue (LFF) accompanies prolonged low rates of muscle stimulation (20Hz). In contrast to HFF where recovery from fatigue is rapid, LFF is associated with a delay of hours or longer before full recovery of muscle force occurs. Impaired release of calcium from the SR with lower levels of intracellular calcium relative to the rate of muscle stimulation has been implicated in LFF, but the cellular mechanisms responsible remain unclear (Favero, 1999).

The major circumstances associated with muscle fatigue are intense and prolonged exercise. As ATP is the ultimate source of energy for muscle contraction, it might be expected that ATP depletion would accompany levels of energy expenditure that outstrip energy supply. In fact, muscle ATP levels change little under conditions of maximal effort exercise (Sahlin et al., 1998). Instead, it appears that the metabolic basis of fatigue in these circumstances involves the accumulation of the end products of ATP hydrolysis and related energy pathways (Fitts, 1994; McLester, 1997). These include inorganic phosphate and diprotonated phosphate and ADP. The accumulation of lactic acid in active muscle during intense exercise has long been linked to fatigue, and experimental studies suggest that acidosis inhibits both force and velocity of muscle contraction (Fitts, 1994). These pH effects may not occur at physiologic temperatures (Pate et al., 1995). These intracellular end products may promote fatigue through inhibitory effects on myosin ATPase. The cross-bridge cycling that underlies muscle contraction depends upon the hydrolysis of ATP to ADP + Pi followed by the sequential release of Pi and ADP from acto-myosin. High levels of Pi and ADP are believed to inhibit the force and/or velocity of contraction by feedback inhibition of this process (McLester, 1997), and may modulate the activity of other ATPases.

A major metabolic mechanism in the development of fatigue with prolonged exercise is glycogen depletion. The necessity for glycogen under these circumstances relates to the fact that the maximal rate of ATP generated from the oxidation of fats is approximately 50% of that achievable from the oxidation of glycogen (Sahlin et al., 1998). This explains the importance of 'glycogen loading' as a prerequisite for prolonged high-level aerobic exercise such as marathon running. The high rates of oxidative phosphorylation obtained with glycogen apparently relate to the fact

that glycogen-derived pyruvate is required to support maximal rates of acetyl CoA production and pyruvate-dependent anaplerosis, thus achieving levels of intramitochondrial malate and related tricarboxylic acid (TCA) cycle intermediates necessary to crank up maximally the TCA cycle flux (Sahlin et al., 1990, 1995). The cellular mechanism of fatigue when glycogen is depleted has been linked to increased levels of ADP, AMP, IMP and ammonia (Sahlin, 1992). High ADP levels result from glycogen depletion which impairs ADP phosphorylation both by oxidative and anaerobic mechanisms. In addition, the kinetics of the proton-dependent creatine kinase reaction are shifted because muscle acidosis is attenuated by the lack of glycogen for lactate production (Radda, 1986). Studies by Sahlin and coworkers have identified two phases of recovery from prolonged, fatiguing exercise in human volunteers: (i) a rapid partial recovery correlates with restoration of metabolic perturbations; (ii) a delayed, non-metabolic recovery phase may correspond to impaired calcium release, as demonstrated in experimental studies of low frequency fatigue (Sahlin et al., 1998).

An important variable for normal fatigue is an individual's level of aerobic or cardiovascular fitness. Aerobic conditioning promotes endurance by increasing peak rates of muscle oxidative phosphorylation, as indicated by higher maximal levels of oxygen consumption (VO_2max). As a result, a given absolute level of exercise represents a lower percentage of maximal aerobic capacity in fit than in less fit persons. Since the duration that aerobic exercise can be sustained rapidly decreases as one approaches VO_2max, a fit person is able to tolerate higher levels of exercise and more prolonged exercise at a given submaximal workload (Sahlin, 1992). An important element in the tolerance of prolonged, submaximal exercise is the ability to utilize fat as an oxidative fuel. A more aerobically fit person covers a greater percentage of the oxidative cost of a given level of exercise by metabolizing fat compared to an individual who is less fit. This person is thus able to sustain such exercise for a longer period of time by preserving limited stores of carbohydrate fuels (Gollnick, 1985).

Mechanisms of abnormal fatigability in metabolic myopathies: oxidative defects

The classical example of impaired oxidative metabolism is mitochondrial myopathy, in which the function of the respiratory chain is impaired. Affected patients have low peak rates of muscle oxidative phosphorylation and low VO_2max with standardized exercise testing (Elliot et al., 1989; Haller & Bertocci, 1994). As a result, even trivial physical activity commonly overtaxes oxidative capacity and engages anaerobic metabolism to meet muscle energy needs. Thus, minor degrees of exercise cause rapid depletion of PCr and increases of lactic acid, inorganic phosphate and ADP, i.e. metabolites that have been linked to fatigue in healthy individuals. These patients resemble, and often are mistaken for, individuals who are severely deconditioned. However, unlike merely deconditioned subjects, patients with severe muscle oxidative defects exhibit a characteristic mismatch between oxygen utilization and oxygen delivery during exercise (Haller & Bertocci, 1994; Haller et al., 1989, 1991).

Oxidative metabolism requires highly regulated cardiopulmonary responses to precisely match O_2 delivery to muscle O_2 utilization in exercise, via neural reflexes activated by metabolites within working muscle that somehow sense the adequacy of O_2 availability relative to muscle oxidative requirements (Haller & Vissing, 1999). In primary muscle oxidative defects this normal relationship is disrupted, resulting in exaggerated O_2 delivery relative to utilization. In severe muscle oxidative defects, increases in cardiac output maybe three – tenfold greater than those accompanying similar levels of exercise in healthy individuals (Taivassalo et al., 2001). Ventilation may also be exaggerated by similar mechanisms. Thus, trivial exercise may cause both muscle fatigue and prominent dyspnea and tachycardia. In fact, exercise limitations in such patients may be incorrectly attributed to primary cardiopulmonary disease (Haller et al., 2000).

Abnormal fatigue with defects in muscle glycolysis/glycogenolysis

Impaired glycogenolysis or glycolysis slows the maximal rate of glycolytic, substrate-level phosphorylation. A characteristic consequence is an abnormally rapid decline in muscle force generation with ischemic or isometric exercise (Dyken et al., 1967; Wiles et al., 1981). Discovery of the exact cellular mechanism or mechanisms responsible for histochemical pattern of fatigue has been elusive. ^{31}P magnetic resonance spectroscopy and needle biopsies indicate that fatigue is not a result of frank depletion of ATP. However, this observation does not exclude the possibility that inadequate availability of discrete pools of ATP may play a role. Experimental studies indicate that ATP generated by substrate-level phosphorylation in glycolysis is tightly coupled to the function of Na^+ K^+ ATPase (sodium pumps) and to Ca^{2+} ATPase, suggesting that impaired glycogenolysis/glycolysis may impair ion transport by limiting the production of this critical source of ATP (James et al., 1996; Xu et al., 1995). Furthermore, patients with muscle phosphorylase deficiency have low levels of sodium pumps, which would exacerbate energy-limited

pump function and could explain the exaggerated increases in extracellular potassium and membrane inexcitability that are typical of this condition (Haller et al., 1998). The mechanism leading to reduced sodium pumps in muscle phosphorylase deficiency is not known, nor is it known whether sodium pumps are decreased in other muscle glycolytic defects. Sodium pump numbers measured in a single case of muscle phosphoglycerate mutase deficiency were normal (Vissing et al., 1999).

A characteristic feature of muscle glycolytic defects is an exaggerated rise in muscle ADP with resulting increases in AMP and in IMP, ammonia and related adenine nucleotide degradation products. Impaired substrate level phosphorylation may contribute to this exaggerated increase in ADP, but a critical mechanism involves the creatine kinase (CK) reaction. The hydrolysis of PCr and phosphorylation of ADP via CK is a proton consuming reaction (i.e. PCr + ADP + H+ ⇋ ATP + Cr). The block in lactate and H+ production that causes muscle to remain at neutral or slightly alkalotic pH during exercise shifts the equilibrium of this reaction to the left, effectively inhibiting the ADP buffering function of CK (Radda, 1986). High ADP levels slow the velocity of cross bridge cycling of acto-myosin by inhibiting myosin ATPase, impair sarcoplasmic reticulum calcium uptake by presumed effects on Ca^{2+} ATPase, and may impair the function of Na^{+}–K^{+} ATPase (McLester, 1997; Ruff, 1996).

Complete blocks of glycogen breakdown in myophosphorylase deficiency (McArdle disease), and of both glycogen and glucose metabolism in muscle phosphofructokinase (PFK) deficiency impair oxidative metabolism primarily by blocking the production of glycogen-derived pyruvate. This results in significant oxidative limitation and intolerance of moderate exercise (Haller & Lewis, 1991; Haller et al., 1985). In addition, such patients experience large swings in exercise capacity, illustrated in McArdle disease by the 'second wind' phenomenon (Pearson et al., 1961). When an activity that initially causes fatigue, breathlessness and tachycardia, is continued beyond 5–10 minutes, exercise suddenly becomes much easier, as increased blood-borne fuels become available to support muscle oxidative metabolism (Pearson et al., 1961; Porte et al., 1966). For reasons that are incompletely understood, patients with PFK deficiency are less able to achieve a second wind, and tend to experience major fluctuations in exercise capacity related to dietary factors that influence the availability of free fatty acids (Haller & Lewis, 1991). Since both glucose and glycogen metabolism are blocked as a result of PFK deficiency, fats represent the major oxidative fuel available to working muscle. When the concentration of free fatty acids falls after glucose infusion or a high carbohydrate meal, exercise capacity plummets, and an activity that was easily tolerated before eating now causes fatigue, tachycardia and breathlessness, the 'out of wind' phenomenon (Haller & Lewis, 1991).

Abnormal fatigue with defects in muscle lipids

The consequences of defects of long chain fatty acid metabolism on fatigability are little studied, and those studies that have been performed have focused primarily upon adult carnitine palmitoyltransferase II (CPT II) deficiency. In CPT II deficiency, tolerance for short-term high-intensity exercise is normal (Lewis et al., 1991). The primary clinical observation is that such patients have reduced tolerance for prolonged, submaximal exercise, particularly under conditions of relative fasting, i.e. exercise that normally depends upon the combustion of fats to meet muscle energy requirements. Patients clearly have reduced endurance to such exercise, and muscle pain and injury are commonly triggered under these circumstances. However, the metabolic mediators of these symptoms are not known. Possible mechanisms include accelerated glycogen depletion and an increase to toxic levels of long chain fatty acids due to the block in fatty acid metabolism.

Chronic fatigue syndrome and related disorders

Subjective complaints of fatigue and fatigability are common in clinical medicine but only rarely attributable to an underlying disorder of muscle metabolism. The relationship of fatigue to exercise is an important clinical clue which can differentiate the abnormal fatigue of metabolic myopathies (brought on by exercise, relieved by rest) from that of psychological disorders or systemic illness. In addition to fatigue that is worsened by exercise, patients with chronic fatigue syndrome and kindred disorders typically have a global loss of energy, which is independent from activity but interferes with their ability to initiate activity. Such patients complain of an unrelenting tiredness that permeates their lives, commonly affecting mental as well as motor functions.

Exercise intolerance: muscle cramps

Cramp refers to an involuntary, typically painful shortening of skeletal muscle. Cramp-like, electrically silent muscle contractures are a hallmark of muscle glycolytic defects, but are not features of other metabolic myopathies (Rowland et al., 1999). They are triggered by brief intense exertion that normally engages anaerobic glycogenolysis to meet energy demands such as maximal effort sprinting,

performing push-ups or pull-ups, or carrying luggage or furniture. The muscle 'locks up' immediately with such exercise and cannot be extended for minutes to as long as an hour. Patients may cautiously and intermittently stretch the affected muscle but sudden lengthening such as that performed to terminate common cramps is not possible and attempts to do so cause extreme pain. Elegant experimental studies by Ruff and coworkers utilizing iodoacetate inhibition of glycolysis have clarified the metabolic basis of these contractures. Contractures were not associated with depletion of muscle ATP, but rather correlated with high intracellular calcium and with increased Ca^{2+} sensitivity of contractile proteins due to combination of high intracellular [ADP] and relative alkalosis (Ruff, 1996; Ruff & Weissman, 1991). These results are compatible with ADP-mediated inhibition of Ca^{2+} ATPase.

Contractures should be differentiated from common cramps, which are mediated by repetitive firing of motor nerve terminals within muscle and are related to neural hyperexcitability, accumulation of metabolites that promote the firing of neural action potentials, or both. In contrast to contractures in muscle glycolytic defects, common cramps usually occur at rest or with non-forceful muscle contractions. They often are heralded by repetitive non-painful muscle twitches. Cramps also may occur after prolonged exercise in otherwise healthy individuals, especially by dehydration and heat stress. Patients sometimes use the term 'cramps' as synonymous with localized muscle pain or with fasciculations. Muscle pain in patients with CPT II deficiency is sometimes referred to as 'cramp-like' but frank muscle cramps are not a feature of this disorder.

Exercise intolerance: exertional muscle injury, rhabdomyolysis, myoglobinuria

Recurrent myoglobinuria is a clinical feature of several metabolic myopathies, especially disorders of glycogenolysis/glycolysis and adult carnitine palmitoyltransferase II deficiency (Tonin et al., 1990). Increasingly, myoglobinuria has been noted in mitochondrial myopathies as well (see below). In muscle glycolytic disorders, rhabdomyolysis is triggered by brief intense exercise. It invariably accompanies muscle contractures. This fact suggests that the same metabolic abnormalities that have been linked to the development of contractures: high intracellular calcium levels, alkalosis, and high concentrations of ADP, may be responsible. In CPT II deficiency, rhabdomyolysis typically is triggered by prolonged, submaximal exercise, particularly when such exercise has been undertaken under fasting conditions. The cellular basis of muscle injury clearly relates to deficient fat oxidation, and the fact that dietary carbohydrate is protective implies that a decline in available carbohydrate plays a role. The basis of rhabdomyolysis in mitochondrial myopathies also is poorly understood. Exercise is often, but not invariably involved, and some patients develop rhabdomyolysis under conditions of fasting, similar to CPT II deficiency.

Although the occurrence of exercise-induced rhabdomyolysis and myoglobinuria always should raise the possibility of an underlying metabolic myopathy, exertional rhabdomyolysis may occur in non-metabolic myopathies and in otherwise healthy individuals. For example, dystrophin deficiency sometimes is associated with exertional rhabdomyolysis and myoglobinuria without frank weakness (Hoffman et al., 1989). Also healthy individuals who engage in unaccustomed heavy exercise, particularly exercise that involves lengthening muscle contractions (eccentric exercise), are prone to exertional muscle injury and pain (Armstrong et al., 1991; Morgan & Allen, 1999). The time course of muscle symptoms differs from metabolic myopathies, however. In contrast to metabolic myopathies, symptoms of muscle pain and pigmenturia do not occur immediately with exercise but rather are delayed in onset 24–48 hours. Such muscle injury is responsible for the syndrome of delayed onset muscle soreness.

Exercise intolerance: muscle pain

Muscle pain routinely accompanies contractures in muscle glycolytic defects and is a feature of rhabdomyolysis attributable to various metabolic myopathies. If patients have developed severe muscle injury, their muscles may be sore for days following the acute insult. Patients with muscle glycolytic defects, who develop focal muscle injury and pain with exercise, may experience a second wave of excruciating pain some hours later due to 'compartment syndrome' (Haller, 1999). Some metabolic myopathy patients experience pain in association with fatigue during exercise, but in many instances myalgia is not an important component of fatiguing exercise in these disorders. Muscle fatigue is commonly experienced as a bland sense of weakness, e.g. 'spaghetti legs', with no particular discomfort. Thus, in general, muscle pain is not the major symptom of metabolic myopathies and the presence of sustained muscle pain or pain as the dominant symptom should suggest a diagnosis other than a metabolic myopathy.

Biochemical and molecular approaches to the diagnosis of metabolic myopathies

Some metabolic myopathies, true to their name, affect only muscle, while others involve one or more non-muscle

tissues. This is explained by various factors, including tissue-specific isozymes or enzyme subunits or, in the case of mtDNA-related diseases, by different degrees of heteroplasmy or by the existence of 'somatic mutations'.

Tissue-specific isozymes

The best example of a muscle-specific isozyme is phosphorylase (myophosphorylase), which is defective in glycogenosis type V (McArdle disease). There are three distinct isozymes of phosphorylase: myophosphorylase, encoded by a gene on chromosome 11 (Lebo et al., 1984); a brain/heart isozyme, encoded by a gene on chromosome 10 or 20 (Newgard et al., 1988), and a liver isozyme, whose gene is on chromosome 14 (Newgard et al., 1986). A variety of mutations in the myophosphorylase gene have been identified in McArdle disease. However, one of them, a nonsense mutation in the first exon of the gene (Arg49Stop) predominates among Caucasian, and especially Anglo-Saxon patients, having been found in 81% of the alleles in British patients (Bartram et al., 1993) and in 63% of the alleles in US patients (El-Schahawi et al., 1996). It is noteworthy, however, that muscle cultures or regenerating muscle from patients with McArdle disease express the brain isozyme (Roelofs et al., 1967; DiMauro et al., 1978), suggesting that muscle phosphorylase undergoes a developmentally regulated transition in isozyme patterns. This has practical implications because the histochemical stain for phosphorylase may be deceivingly positive in biopsies from patients taken too soon after an episode of myoglobinuria and containing regenerating muscle fibres (Mitsumoto, 1979).

Tissue-specific enzyme subunits

Here, examples abound, as many enzymes are multimeric, but one subunit is expressed exclusively or predominantly in skeletal muscle.

Phosphofructokinase (PFK) is a tetrameric enzyme under the control of three autosomal loci. A locus on chromosome 1 encodes the muscle (M) subunit; a locus on chromosome 21 encodes the liver (L) subunit, and a locus on chromosome 10 encodes the platelet (P) isozyme (Vora, 1982). Mature human muscle expresses only the M subunit and contains only the homotetramer M4, while erythrocytes, which express both the M and L subunits, contain five isozymes, the two homotetramers M4 and L4, and three hybrid isoforms. In patients with typical PFK deficiency, genetic defects of the M subunit cause total lack of activity in muscle but only partial PFK deficiency in red blood cells, where the residual activity approximates 50% of normal and is accounted for by the L4 isozyme. Hence, patients with PFK deficiency often have signs of compensated hemolytic anemia (hyperbilirubinemia, increased reticulocyte count), and this can help in the differential diagnosis from McArdle disease.

Two other multimeric glycolytic enzymes are phosphoglycerate mutase (PGAM) and lactate dehydrogenase (LDH). PGAM is a dimeric enzyme composed of a muscle-specific (M) and a brain-specific (B) subunit, and normal muscle contains predominantly the MM homodimer, which accounts for 95% of the total activity. The only other tissues containing substantial amounts of the M subunit are heart and sperm, but there is no evidence of cardiopathy or male infertility in PGAM deficiency (Tsujino et al., 1993).

LDH is a tetrameric enzyme composed of various proportions of a muscle-specific subunit (LDH-A) and a cardiac subunit (LDH-B). LDH-A is encoded by a gene on chromosome 11 and LDH-B by a gene on chromosome 12 (Kanno & Maekawa, 1995).

Heteroplasmy of mitochondrial DNA

One of the distinctive concepts of mitochondrial genetics (as opposed to mendelian genetics) is that each cell contains hundreds or thousands of mitochondria and many more copies of mitochondrial DNA (mtDNA) reviewed in Chapter 119. In most mtDNA-related diseases, some but not all mtDNA molecules harbour a pathogenic mutation (heteroplasmy). The functional consequences of a deleterious mtDNA mutation depend on the relative abundance of mutant mtDNAs in that particular tissue, and a critical minimal degree of heteroplasmy will be needed before oxidative dysfunction becomes manifest (threshold effect). In this respect, skeletal muscle, together with cardiac muscle and brain, is very vulnerable to any impairment of oxidative metabolism.

While mutations in tRNA genes are usually associated with multisystem disorders, in rare cases there is involvement of a single tissue, most commonly skeletal muscle (DiMauro, 2000). It is noteworthy, and a useful diagnostic clue, that four such patients with mutations in the $tRNA^{Leu(UUR)}$ showed preferential involvement of respiratory muscles (Goto et al., 1992; Ogle et al., 1997; Bindoff et al., 1993; Hadjigeorgiou et al., 1999b). In most of the patients, the mutation was also present in blood or cultured skin fibroblasts, implying that the selective muscle involvement was due to 'skewed heteroplasmy', with preferential accumulation of the pathogenic mutation in skeletal muscle.

Only recently we came to realize that mutations in mtDNA protein-coding genes are often tissue specific,

many of them muscle specific. These true mitochondrial myopathies are usually characterized by exercise intolerance, myalgia, and myoglobinuria and can affect subunits of complex I, complex III, or complex IV (DiMauro, 1999), although they seem to be more commonly associated with complex III deficiency (Andreu et al., 1999a). Not only were all of these patients sporadic, but skeletal muscle was the only tissue affected and harbouring the mtDNA mutation. Therefore, these mutations are likely to be 'somatic', that is, spontaneous events that arose in myoblasts or myoblast precursors after germ-layer differentiation and did not affect germline cells.

Is muscle biopsy always necessary?

In those metabolic myopathies in which the enzyme defect is not confined to muscle but involves some or all non-muscle tissues, the biochemical diagnosis can be established in more easily accessible tissues, such as blood cells or cultured skin fibroblasts. For example, debrancher deficiency (glycogenosis type III) and phosphoglycerate kinase (PGK) deficiency (glycogenosis type IX) affect virtually all tissues. Carnitine palmitoyltransferase II (CPT II) deficiency is expressed in lymphocytes and fibroblasts.

Mitochondrial encephalomyopathies due to mutations in mtDNA present a special problem. Even in multisystemic disorders, such as MELAS, MERRF, and NARP/MILS, due to the heteroplasmic nature of these mutations, respiratory chain enzyme defects are invariably partial, and may be difficult to detect in tissues less rich in mitochondria than muscle, such as fibroblasts. In patients with somatic mutations in protein-coding mtDNA genes, muscle biopsy is generally needed for diagnosis, and will show a specific defect of complex I, complex III, or complex IV.

Enzyme defect hunters have been followed by molecular defect hunters, and our molecular knowledge of metabolic myopathies has advanced so rapidly that it is sometimes possible to bypass biochemistry (and muscle biopsy) and go directly to molecular analysis of blood or other accessible cells. To be successful, however, this approach requires at least two conditions: (i) the clinical diagnosis has to be convincing; and (ii) the disease in question must be caused by one, or a few, common mutations. Thus, a Caucasian patient with suspected myophosphorylase deficiency can be tested for the Arg49Stop mutation in genomic DNA extracted from blood with good probability of success. Similarly, European or American patients with suspected CPT deficiency can be tested for the common Ser113Leu mutation (Taroni et al., 1993; Kaufmann et al., 1997). However, negative results do not exclude the diagnosis in either condition and make biochemical studies of muscle the next logical step.

Again, the situation is different in mitochondrial encephalomyopathies due to point mutations in mtDNA, such as MELAS, MERRF, and NARP. In patients with typical clinical phenotypes and evidence of maternal inheritance, looking for the common mutations (A3243G for MELAS; A8344G for MERRF; T8993G for NARP) in blood cells, hair follicles, or urinary sediment is the logical first diagnostic step. However, these mutations may not always be detectable in blood of atypical patients (Sue et al., 1999) or in oligosymptomatic maternal relatives of typical patients (DiMauro et al., 1999). Obviously, this approach does not apply to patients with pure myopathy and somatic mutations in mtDNA protein-coding genes.

Disorders of glycogen metabolism

Eleven hereditary enzyme defects of glycogen metabolism or glycolysis affect skeletal muscle (Fig. 72.2). Of these, one (branching enzyme deficiency, glycogenosis type IV) affects glycogen synthesis, and another (acid maltase deficiency, glycogenosis type II) affects lysosomal glycogen degradation. Presumably, neither of these two pathways is directly involved in energy provision during exercise. Of the remaining seven glycogenoses, three affect glycogen breakdown: phosphorylase b kinase deficiency (type VIII), myophosphorylase deficiency (type V), and debrancher deficiency (type III). Four glycogenoses affect terminal glycolysis: phosphofructokinase (PFK) deficiency (type VII), phosphoglycerate kinase (PGK) deficiency (type IX), phosphoglycerate mutase (PGAM) deficiency (type X), and lactate dehydrogenase (LDH) deficiency (type XI). To these, we should now add two new enzyme defects of terminal glycolysis, each described in a single patient: aldolase A deficiency (glycogenosis type XII) (Kreuder et al., 1996), and β-enolase deficiency (Comi et al., 2001). For each of these disorders, we will provide bullet-like information. Physiopathology and diagnostic approaches have been discussed in previous sections. For detailed clinical and pathological descriptions, the reader is referred to specialized textbooks (DiMauro et al., 1997).

Glycogenoses causing exercise intolerance and myoglobinuria

Glycogenosis type V (myophosphorylase deficiency; McArdle disease)

This is characterized by exercise intolerance with premature fatigue, myalgia, and cramps in exercising muscles, relieved by rest. Symptoms are more likely to occur with intense isometric exercise, such as lifting weights, or with

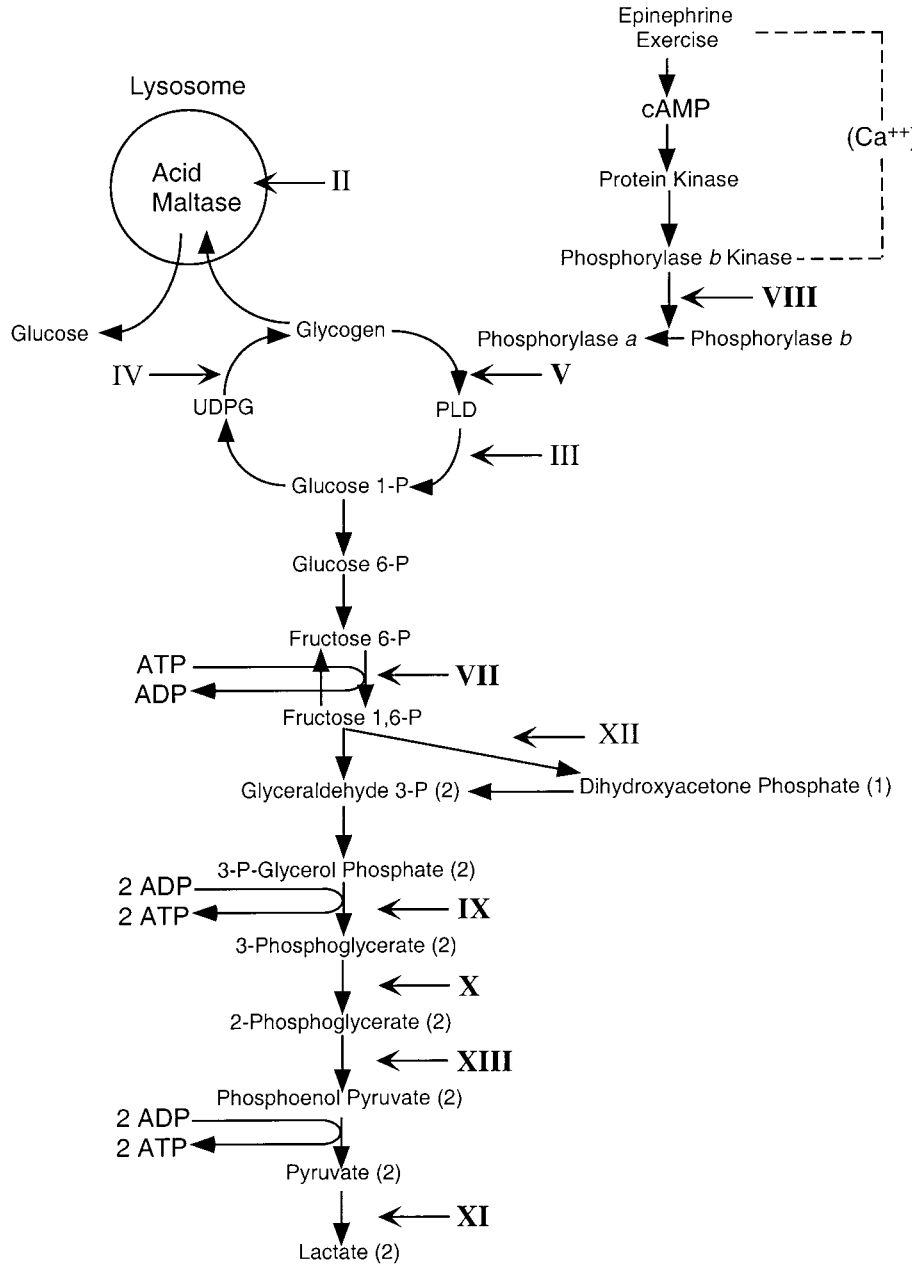

Fig. 72.2. Scheme of glycogen metabolism and glycolysis. Roman numerals indicate enzymes whose deficiencies are associated with muscle glycogenoses: II, acid maltase; III, debrancher; IV, brancher; V, myophosphorylase; VII, phosphofructokinase (PFK); VIII, phosphorylase kinase (PhK); IX, phosphoglycerate kinase (PGK); X, phosphoglycerate mutase (PGAM); XI, lactate dehydrogenase (LDH); XII, aldolase A; XIII, β-enolase. Bold roman numerals indicate glycogenoses causing exercise intolerance, cramps, and myoglobinuria; standard roman numerals indicate glycogenoses causing fixed weakness. Abbreviations: UDPG, uridine diphosphate glucose; PLD, phosphorylase limit dextrion; AMP, adenosine monophosphate; ADP, adenosine diphosphate; ATP, adenosine triphosphate. (Modified from DiMauro & Haller, 1999.)

less intense but sustained dynamic exercise, such as walking uphill. About half of the patients have acute muscle necrosis and myoglobinuria after exercise. The severity of symptoms varies considerably, from 'poor stamina' to frequent and almost incapacitating cramps. Patients with typical symptoms may develop fixed weakness later in life.

Laboratory tests show increased serum CK levels even at rest. EMG is usually normal or compatible with mild myopathy. During cramps, however, shortened muscles are electrically silent, true 'contractures'. The forearm ischemic exercise shows no rise of venous lactate, but is not specific for McArdle disease, and is less commonly employed nowadays. Molecular genetic analysis of blood cells may secure a diagnosis, thus avoiding both forearm ischemic exercise and muscle biopsy (El-Schahawi et al., 1996). Muscle biopsy typically shows subsarcolemmal and intermyofibrillar vacuoles filled with glycogen, which are PAS-positive and digested by diastase.

Phosphorylase catalyses the phosphorylytic stepwise removal of α-1,4-glucosyl residues from the outer branches of glycogen with liberation of G-1-P. This reaction goes on until the peripheral chains have been shortened to 4-glucosyl units, and the resulting 'phosphorylase-limit dextrin' (PLD) can be acted upon by the debranching enzyme.

About 30 mutations have been reported, but by far the most frequent among Anglo-Saxon patients is Arg49Stop. The frequency of this nonsense mutation in the very first exon of the gene explains why the enzyme protein is commonly absent in muscle (Servidei et al., 1988; McConchie et al., 1991).

Glycogenosis type VII (PFK deficiency; Tarui disease)

This is clinically indistinguishable from myophosphorylase deficiency, although myoglobinuria may be less frequent than in McArdle disease. Helpful laboratory signs include reticulocytosis, and increased serum bilirubin and uric acid. As in McArdle disease, resting serum CK values are variably increased, and the forearm ischemic exercise causes no increase in venous lactate. Clinical variants include: (i) late-onset weakness; and (ii) fatal infantile myopathy, often accompanied by brain involvement.

Muscle biopsy shows excessive subsarcolemmal and intermyofibrillar normal-looking glycogen. However, a distinctive morphological feature is the additional presence of polyglucosan deposits in many, especially older patients (Agamanolis et al., 1980; Hays et al., 1981; Danon et al., 1988).

PFK catalyses the phosphorylation of fructose-6-P to fructose-1,6-P, and PFK deficiency results in a marked accumulation of both fructose-6-P and its immediate glycolytic precursor, glucose-6-P (G-6-P). As G-6-P is a physiological activator of glycogen synthetase, we proposed that an abnormally increased ratio of glycogen synthetase relative to branching enzyme activity could be responsible for the deposit of polyglucosan (Agamanolis et al., 1980; Hays et al., 1981).

Glycogenosis type VIII (phosphorylase b kinase [PhK] deficiency)

In its myopathic form, PhK deficiency appears like a milder version of myophosphorylase deficiency, with exercise intolerance, cramps, and occasional myoglobinuria (Wilkinson et al., 1994). Some patients, however, have fixed weakness, and others have combined muscle and liver involvement, with static myopathy. Serum CK is variably increased and the lactate response to ischemic exercise is often normal or blunted.

Muscle biopsy shows mild-to-moderate subsarcolemmal accumulation of glycogen, predominantly in type IIb fibres.

PhK is a decahexamer of four different subunits, α, β, γ, and δ: $(\alpha\beta\gamma\delta)_4$. The γ-subunit is catalytic, the α- and β-subunits are regulatory, and the δ-subunit is identical to calmodulin and confers calcium sensitivity to the enzyme. There are two α-subunits, one specific for muscle (α_M), the other specific for liver (α_L), encoded by two distinct genes on the X-chromosome.

The prevalence of affected men is probably explained by the existence of an X-linked muscle-specific α-gene: in fact, both mutations documented thus far in myopathic patients have been in the α_M gene (Wehner et al., 1994; Bruno et al., 1998).

Glycogenosis type IX (PGK deficiency)

This usually causes hemolytic anemia, seizures, and mental retardation. However, isolated myopathy has been reported in half a dozen patients with exercise intolerance, cramps, and myoglobinuria. Resting serum CK levels are inconsistently elevated, and the rise of venous lactate after ischemic exercise is absent or blunted. Muscle biopsy may or may not show diffuse glycogen storage. PGK is a single polypeptide encoded by a gene on the X-chromosome and expressed in all tissues except the testis. A few mutations have been identified in patients with isolated myopathy (Tsujino et al., 1995).

Glycogenosis type X (phosphoglycerate mutase [PGAM] deficiency)

This causes exercise intolerance, cramps, and recurrent myoglobinuria. With the forearm ischemic exercise, there is abnormally low increase of venous lactate. An unusual

number of heterozygous patients can be symptomatic (Tsujino et al., 1993; Hadjigeorgiou et al., 1999a).

Muscle biopsy shows mild glycogen storage, which may be difficult to detect in some patients.

PGAM is a dimeric enzyme containing various proportions of a muscle (M) subunit and a brain (B) subunit. In normal mature human muscle, about 95% of total PGAM activity is accounted for by the MM homodimer. The small amount of residual PGAM activity found in muscle from patients is due to the BB homodimer.

The M subunit of PGAM is encoded by a gene on chromosome 7, and mutations have been identified in all patients with myopathy (Tsujino et al., 1993).

Glycogenosis type XI (lactate dehydrogenase [LDH] deficiency)

This is also characterized by exercise intolerance, cramps, and myoglobinuria. The forearm ischemic exercise causes very little or no increase of lactate but a large increase in pyruvate. LDH is a tetrameric enzyme composed of two subunits, one of which (LDH-M) predominates in skeletal muscle while the other (LDH-H) predominates in cardiac muscle. Random tetramerization results in the formation of five isozymes, the two homotetramers M4 and H4, and three heterotetramers. Muscle from patients contains only the H4 isoform. Mutations in the gene encoding LDH-M (which is on chromosome 11) have been identified in all patients with myopathy (Kanno & Maekawa, 1995).

Glycogenosis type XII (Aldolase A [ALD] deficiency)

This has been reported in a single patient with myopathy, characterized by episodic exercise intolerance and weakness triggered by febrile illnesses (Kreuder et al., 1996). ALD-A is composed of four identical subunits encoded by a gene on chromosome 16. A mutation (Glu206Lys) has been identified in the patient.

Glycogenosis type XIII (β-enolase deficiency)

This has been described in one man with adult-onset exercise intolerance and chronically elevated serum CK (Comi et al., 2001). Enolase is a dimeric enzyme, and the muscle-specific isoform β-enolase is a homodimer of the β subunit, which is encoded by a gene on chromosome 17. The patient was a compound heterozygote harbouring two missense mutations: Gly156Asp and Gly374Arg.

Glycogenoses causing fixed weakness

Glycogenosis type II (acid maltase [AM] deficiency)

This has two major clinical presentations, a generalized form (Pompe disease), and a myopathic form. Pompe disease starts at or around birth, and is characterized by floppiness, massive cardiomegaly, lesser hepatomegaly, sometimes macroglossia. These children rarely survive more than 1 year. The myopathic form of AMD comes in three varieties, depending on time at onset: infantile, childhood, and adult. Patients with infantile AMD resemble children with Pompe disease, but have no cardiopathy and tend to live longer (Slonim et al., 2000). Childhood AMD may mimic Duchenne or other forms of muscular dystrophy: these patients die in the second or third decade of respiratory insufficiency. Adult-onset AMD mimics limb–girdle dystrophy or polymyositis; truncal and respiratory muscles are especially affected. Serum CK is markedly elevated in all forms of AMD, and electromyography shows myopathic features together with fibrillation potentials, bizarre, high frequency, and myotonic discharges.

In Pompe disease and in the infantile and childhood variants of myopathic AMD, muscle biopsy shows massive accumulation of both intralysosomal and free glycogen, which distorts the contractile system. In adult AMD, glycogen accumulation is milder and may be difficult to detect in some muscles. There is no histochemical stain for acid maltase, but intense staining for acid phosphatase, another lysosomal enzyme, provides an indirect clue to the diagnosis.

Acid maltase is an acid α-1,4- and α-1,6-glucosidase, capable of digesting glycogen all the way to glucose. This lysosomal enzyme is a single polypeptide encoded by a gene on chromosome 17 and expressed in all tissues.

An X-linked disorder characterized by cardiomyopathy, mental retardation, and autophagic vacuolar myopathy, can mimick AMD (Hart et al., 1987). This is due to mutations in LAMP-2, a lysosome associated membrane protein not directly involved in glycogen metabolism (Nishino et al., 2000).

Over 50 mutations have been identified in the gene encoding α-glucosidase, and this has simplified prenatal diagnosis.

Glycogenosis type III (debrancher deficiency)

This typically presents as a benign hepatopathy of infancy or childhood, with hepatomegaly, growth retardation, and fasting hypoglycemia. Clinical myopathy is uncommon and often manifests in adult life, with weakness and wasting of distal leg and intrinsic hand muscles, sometimes suggesting motor neuron disease or peripheral neuropathy (DiMauro et al., 1979). Subclinical cardiac involvement is revealed by laboratory tests in most patients. Serum CK is variably increased, and EMG shows myopathic features associated with fibrillations, positive sharp waves, and myotonic discharges. Nerve conduction studies may reflect peripheral nerve involvement.

Muscle biopsy shows severe vacuolar myopathy with deposits of PAS-positive material under the sarcolemma and between myofibrils. Ultrastructurally, the vacuoles correspond to large pools of free, normal-looking glycogen β-particles.

The debranching enzyme is a single polypeptide encoded by a gene on chromosome 1, which possesses two distinct catalytic functions, oligo-1,4-1,4-glucantransferase and amylo-1,6-glucosidase. Patients with debrancher deficiency are classified into three groups: IIIa, lacking both enzymatic activities in both liver and muscle; IIIb, also lacking both activities in liver, while heart and muscle are spared; IIIc, lacking only the transferase activity in both liver and muscle (Chen et al., 1987; Ding et al., 1990). Most patients belong to group IIIa. Because the enzyme defect is generalized, at least in patients belonging to the IIIa group, biochemical assays can be performed in erythrocytes, white blood cells, or cultured fibroblasts.

Several mutations have been identified in both type IIIa and IIIb patients, and can be used for prenatal diagnosis.

Glycogenosis type IV (branching enzyme deficiency)

This is typically considered a rapidly progressive disease of early childhood, with hepatosplenomegaly, cirrhosis, hepatic failure, and death before 4 years of age. However, clinical presentations vary widely, with predominant involvement of muscle, heart, or brain in different patients. Brain involvement ('adult polyglucosan body disease', APBD) is manifested by late-onset progressive upper and lower motor neuron disease, sensory loss, sphincter dysfunction and dementia.

Muscle biopsy shows basophilic, intensely PAS-positive polysaccharide deposits, which are partially resistant to diastase digestion and which, ultrastructurally, consist of filamentous and finely granular material. The abnormal polysaccharide, called polyglucosan, has been documented in skin, liver, muscle, heart, and brain, but the amount varies widely in different tissues from different patients. In APBD, polyglucosan bodies are seen in processes (but not in perikarya) of neurons and astrocytes in both grey and white matter (Robitaille et al., 1980).

The branching enzyme catalyses the last step in glycogen biosynthesis by adding short glucosyl chains (about 7 glucosyl units long) to linear peripheral chains of glycogen in α-1,6-glucosidic bonds. The newly added stubs are then elongated by glycogen synthetase. The enzyme is a monomeric protein encoded by a gene on chromosome 3 and expressed in all tissues, and thus tissues other than muscle, e.g. leukocytes, can be used for diagnosis (Lossos et al., 1991).

The polysaccharide stored in brancher deficiency (polyglucosan) has longer than normal peripheral linear chains and fewer branching points, thus resembling amylopectin. Mutations have been identified in patients with different clinical phenotypes, including myopathy (Bruno et al., 1999) and APBD (Lossos et al., 1998).

Disorders of lipid metabolism

Two major metabolic pathways are needed for long-chain fatty acid utilization: (i) transport and activation of fatty acids (the carnitine cycle); and (ii) mitochondrial fatty acyl-CoA oxidation (β-oxidation) (Fig. 72.3). In this section, we will review briefly only those disorders that cause neuromuscular disease.

Disorders causing exercise intolerance and myoglobinuria

A disorder of the carnitine cycle, CPT II deficiency, is an important cause of exercise intolerance and myoglobinuria, but its clinical presentation can be mimicked by defects of some β-oxidation enzymes.

Carnitine palmitoyltransferase II (CPT II) deficiency

This causes two distinct phenotypes, myopathic and hepatocardiomuscular. The more common, myopathic form, usually presents in adolescents or young adults, predominantly males, with recurrent myoglobinuria following prolonged, though not necessarily strenuous exercise, prolonged fasting, or a combination of the two conditions. Other precipitating factors include cold exposure, lack of sleep, and, especially in children, intercurrent illnesses with high fever. Between attacks, these patients have normal physical and neurological exams. Unlike what happens in the glycogenoses, the attacks of myoglobinuria are not heralded by painful cramps. In addition, exercising muscles are not necessarily the only ones undergoing acute necrosis and a few patients have been admitted to the hospital in respiratory distress (Bertorini et al., 1980). Another distinguishing feature from the glycogenoses is the normal level of serum CK between attacks of myoglobinuria. Plasma carnitine levels are usually normal. CPT II deficiency, first described in 1973 (DiMauro & DiMauro-Melis, 1973), appears to be the most common cause of hereditary myoglobinuria (Tonin et al., 1990).

When muscle biopsy is taken remote from an episode of myoglobinuria, it can be completely normal. When present, lipid storage is much milder than in the primary or myopathic forms of carnitine deficiency.

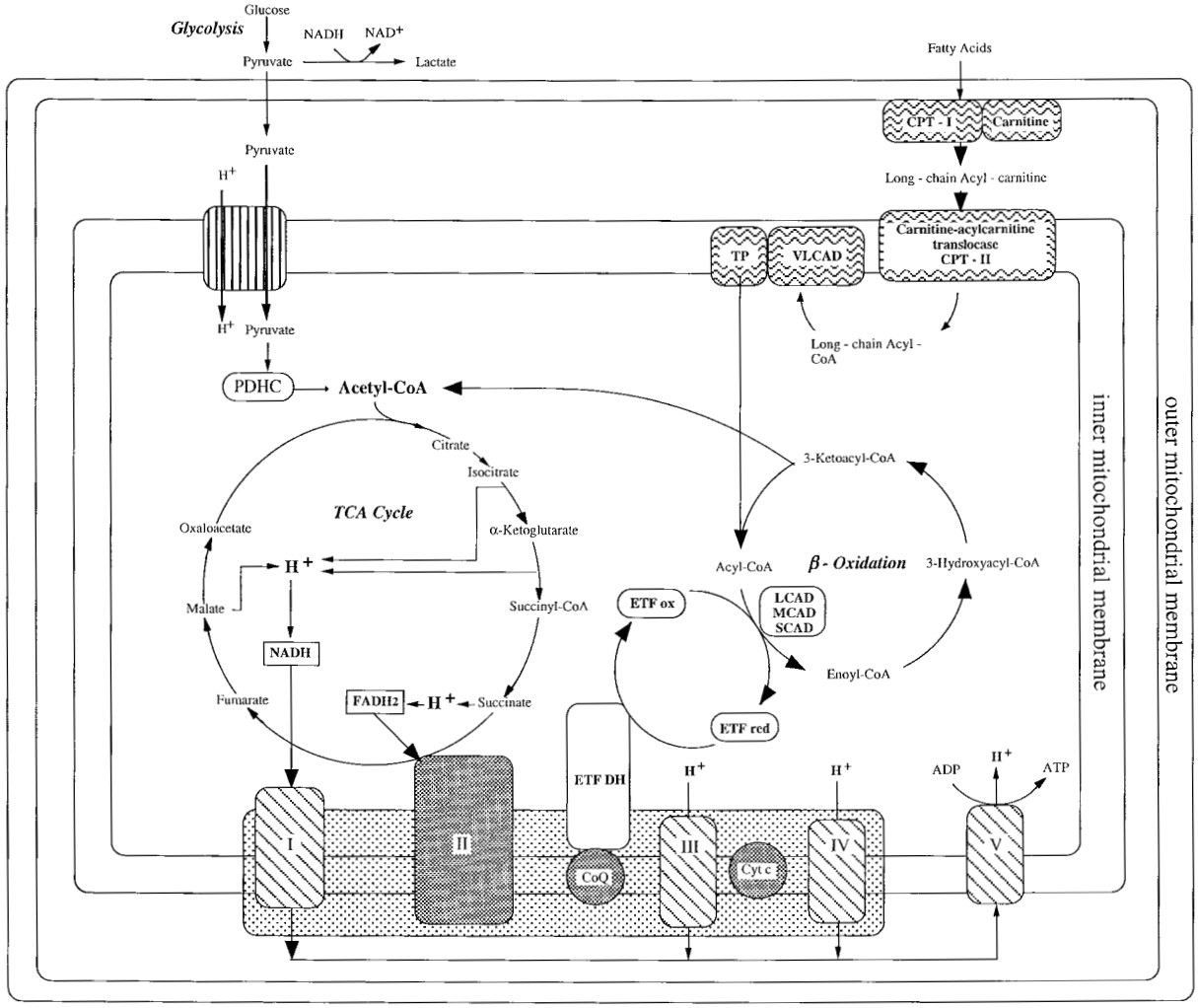

Fig. 72.3. Schematic representation of mitochondrial metabolism. For details, see text. Respiratory chain components or complexes encoded exclusively by the nuclear DNA are solid; complexes containing some subunits encoded by the nuclear genome and others encoded by mtDNA are crosshatched. Abbreviations: PDHC, pyruvate dehydrogenase complex; CPT, carnitine palmitoyltransferase; VLCAD, very long chain acyl-CoA dehydrogenase; TP, trifunctional protein; LCAD, long chain acyl-CoA dehydrogenase; MCAD, medium chain acyl-CoA dehydrogenase; SCAD, short chain acyl-CoA dehydrogenase; HAD, 3-hydroxyacyl-CoA dehydrogenase; KT, 3-ketothiolase; ETFox, oxidized form of electron transfer flavoprotein; ETFred, reduced form of electron transfer flavoprotein; ETF-DH, ETF-coenzyme Q oxidoreductase. (Modified from DiMauro & Haller, 1999.)

Once long-chain acylcarnitines are inside the inner mitochondrial membrane, they have to be reconverted to acyl-CoA esters to enter the β-oxidation spiral. This is catalyzed by CPT II, a single enzyme without tissue-specific isoforms, which is loosely bound to the inner mitochondrial membrane and is encoded by a gene on chromosome 1p32. Numerous mutations have been described, but one of them (Ser113Leu) is commonly encountered in both European and American patients (Taroni et al., 1993; Kaufmann et al., 1997). The relative frequency of this disease and the special circumstances triggering myoglobinuria often suggest the diagnosis. In these cases, the more common mutations can be looked for in blood cells, thus potentially avoiding the need for a muscle biopsy.

The rarer and much more severe hepatocardiomuscular form can affect infants or children. Patients with the infantile form die within weeks, after presenting with hepatopathy, encephalopathy, cardiomegaly, and cardiac arrhythmia. Children with later onset have fasting hypoketotic hypoglycemia, hepatopathy, cardiomyopathy and mild myopathy,

and are at risk for sudden death. In contrast to the myopathic form, plasma carnitine levels are severely decreased in the generalized form.

Very-long chain Acyl-CoA dehydrogenase (VLCAD) deficiency

This causes three major clinical phenotypes: (i) a severe infantile form with hypertrophic cardiomyopathy and early death; (ii) a less severe form with recurrent episodes of hypoketotic hypoglycemia; (iii) a myopathic form closely resembling CPT II deficiency and characterized by recurrent episodes of muscle breakdown and myoglobinuria following prolonged exercise, prolonged fasting, or both together (Straussberg et al., 1997; Minetti et al., 1998; Smelt et al., 1998).

Trifunctional protein (TP) deficiency

This usually presents in infancy, with cardiomyopathy, which is sometimes preceded by episodes of hypoketotic hypoglycemia. However, three patients had a milder presentation, with recurrent myoglobinuria resembling CPT II deficiency and chronic progressive polyneuropathy (Schaefer et al., 1996).

Short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD) deficiency

This was described in a 16-year-old girl with hypoketotic hypoglycemic encephalopathy, cardiomyopathy, and recurrent myoglobinuria (Tein et al., 1991). As SCHAD activity was normal in fibroblasts, it was suggested that the defect involved a muscle-specific isoform, but this remains to be proven.

Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency

This is a special case of the mitochondrial trifunctional protein (TP) deficiency described above, because LCHAD is one of the functions of TP. However, while in TP deficiency all three enzymatic functions are affected, in this case only the long-chain hydroxyacyl-CoA dehydrogenase activity is impaired. This disorder can present in infancy with episodic hypoketotic hypoglycemia after prolonged fasting due to intercurrent infections. Some infants succumb to rapidly progressive cardiomyopathy. Milder and later onset presentations include a myopathic form with exercise-induced episodic muscle breakdown and myoglobinuria, resembling CPT II deficiency (Dionisi-Vici et al., 1991; Tein et al., 1995). However, these patients often have additional features not seen in CPT II deficiency, including peripheral neuropathy and hepatomegaly with liver dysfunction. A 13-year-old boy with neuropathy, limb–girdle myopathy, and recurrent myoglobinuria responded dramatically to oral supplementation with cod liver oil extract, a rich source of docosahexaenoic acid (DHA), which is deficient in children with LCHAD deficiency (Tein et al., 1999b).

Disorders causing weakness

The main disorders of lipid metabolism causing weakness relate to carnitine deficiency, be it primary, myopathic, or secondary. More rarely, defects of enzymes in the carnitine cycle, such as the carnitine–acylcarnitine translocase, or in the β-oxidation spiral, such as short-chain acyl-CoA dehydrogenase (SCAD) or electron transfer flavoprotein (ETF) dehydrogenase are accompanied by weakness.

Primary systemic carnitine deficiency

This has been described in about 30 patients, of whom almost half had a sibling who had died of cardiomyopathy. Mean age at onset is 2 years, and the most common clinical presentation is progressive cardiomyopathy: echocardiography and ECG show dilated cardiomyopathy, peaked T waves, and signs of ventricular hypertrophy. Myopathy is usually associated with cardiomyopathy and is manifested by mild motor delay, hypotonia, or slowly progressive proximal weakness. Both cardiac dysfunction and muscle weakness respond dramatically to carnitine supplementation, and these patients can live normal lives with continued replacement therapy.

Muscle biopsy shows severe lipid storage. Endomyocardial biopsies or postmortem studies also show massive lipid storage in the heart.

Both total and free carnitine concentrations are extremely low (usually below 10% of normal) in skeletal muscle and in the myocardium.

This autosomal recessive disorder involves a genetic defect of the plasma membrane carnitine transporter in kidney, intestine, muscle, heart, and fibroblasts, but not in liver. The combination of defective renal and intestinal carnitine handling causes carnitine levels to fall in blood. Hence the importance of measuring blood carnitine concentrations in all infants and young children with unexplained cardiomyopathy. Linkage analysis has localized the gene responsible for primary carnitine deficiency to chromosome 5q. The gene, which encodes one member of a family of organic cation transporters, has been isolated and several pathogenic mutations have been identified in patients and their asymptomatic parents (Lamhonwah & Tein, 1998; Tang et al., 1999).

Primary myopathic carnitine deficiency

This is characterized by decreased muscle carnitine but normal serum carnitine (Engel & Angelini, 1973). The existence of this entity, however, is controversial because there

is no definitive documentation of an isolated defect of carnitine uptake in muscle. It is possible that patients with the diagnosis of carnitine deficiency myopathy may have other fatty acid oxidation defects, either generalized or muscle specific. In some of the patients described, symptoms appeared in the first years of life, but in most, onset was between the second and third decade. There was progressive and sometimes fluctuating weakness of proximal limb and axial muscles of variable severity. A few of these patients had associated cardiomyopathy.

In all patients, muscle biopsy showed severe lipid storage, especially in type I fibres.

Muscle carnitine levels were 20% of normal or less, while plasma carnitine levels were normal or slightly reduced. Some of the patients improved with carnitine administration.

Secondary carnitine deficiency

This is characterized by decreased levels of carnitine in blood and, often, in tissues, and it can accompany diverse disorders, including inborn errors of metabolism, acquired medical conditions, and iatrogenic states (Pons & DeVivo, 1995).

Examples of inborn errors of metabolism include numerous defects of fatty acid metabolism affecting both the carnitine cycle and β-oxidation (see below), disorders of branched-chain amino acid metabolism and defects of the mitochondrial respiratory chain.

Examples of acquired medical conditions include those causing decreased carnitine biosynthesis, e.g. hepatic cirrhosis or extreme prematurity, those causing decreased carnitine intake, e.g. malnutrition, chronic total parenteral nutrition, strict vegetarian diet, soy protein infant formula, malabsorption, those causing decreased body stores of carnitine in the face of increased requirements, e.g. pregnancy and lactation, extreme prematurity, infant of carnitine-deficient mother, and those causing increased carnitine loss, such as Fanconi syndrome.

Examples of iatrogenic factors include valproate therapy, hemodialysis, and zidovudine administration.

It is important to keep in mind these diverse causes of carnitine deficiency because carnitine replacement often results in marked improvement.

Carnitine–acylcarnitine translocase deficiency

This causes life-threatening episodes in the neonatal period, with generalized weakness, cardiac arrhythmia, hyperammonemia, and inconsistent hypoglycemia. This inner mitochondrial membrane translocase, encoded by a gene on chromosome 3, is needed to shuttle the acylcarnitines formed by CPT I across the inner membrane in exchange for carnitine.

Short-chain acyl-CoA dehydrogenase (SCAD) deficiency

This usually presents in infancy with poor feeding, vomiting, failure to thrive, lethargy, and hypotonia. Psychomotor retardation, seizures and hyperactivity have also been described.

A single adult case of lipid storage myopathy with SCAD deficiency confined to skeletal muscle (Turnbull et al., 1984) was probably due to a different primary metabolic defect because there are no tissue-specific isoforms of SCAD. Myopathy was also prominent in a 13-year-old girl with congenital facial and neck weakness, which spread to limb, axial, and respiratory muscle (Tein et al., 1999a). She also had ptosis, progressive external ophthalmoplegia, and cataracts. Muscle biopsy showed type I fibre predominance and hypotrophy and multicores.

Electron-transfer flavoprotein (ETF) deficiency; ETF:CoQ10 oxidoreductase (ETFDH) deficiency

Both defects result in multiple acyl-Coa dehydrogenase deficiency (glutaric aciduria type II), and give rise to three major clinical phenotypes: (i) a severe neonatal disorder, with hypotonia, hepatomegaly, hypoglycemia, multiple congenital anomalies, and early death; (ii) a milder disorder, without congenital anomalies and with longer survival, but frequently accompanied by cardiomyopathy; and (iii) a later-onset form with vomiting, hypoglycemia, hepatomegaly, and weakness with lipid storage myopathy. An 8-year-old boy with ETFDH had a limb–girdle syndrome in addition to hepatomegaly and episodic hypoketotic hypoglycemia (DiDonato et al., 1986). Postmortem examination showed severe lipid storage myopathy and muscle carnitine deficiency. Of considerable practical importance is the riboflavin-responsive form of glutaric aciduria type II, which has been seen in adults with lipid-storage myopathy. In these patients, riboflavin administration improved wasting and weakness within weeks (DiDonato et al., 1989).

Defects of the mitochondrial respiratory chain

The respiratory chain, which includes five multimeric complexes and catalyses both electron transport and oxidative phosphorylation, is the 'business end' of mitochondrial metabolism, where the energy generated by carbohydrate and lipid oxidation is released as ATP. A unique characteristic of the respiratory chain is that this is the only metabolic pathway in the cell under dual genetic control. Of the approximately 80 proteins that make up the respiratory chain, 13 are encoded by mitochondrial DNA (mtDNA) and all the others are encoded by nuclear DNA

(nDNA). As indicated by the different shadings in Fig. 72.2, complex II, coenzyme Q, and cytochrome c are entirely encoded by nDNA. In contrast, complexes I, III, IV, and V contain some subunits encoded by mtDNA: seven for complex I; one for complex III; three for complex IV; and two for complex V. Both inheritance and clinical expression of mutations in mtDNA are governed by the distinctive rules of mitochondrial genetics (reviewed in Chapter 120).

From the genetic point of view, defects of the respiratory chain can be divided into two major groups: those due to mutations in mtDNA, and those due to mutations in nuclear DNA (nDNA).

Respiratory chain defects with exercise intolerance and myoglobinuria

While exercise intolerance is common in mitochondrial encephalomyopathies, it is often overshadowed by other symptoms and signs (DiMauro & Schon, 1998). Exercise intolerance, myalgia, and myoglobinuria can be the sole presentation of respiratory chain defects.

Exercise intolerance (without myoglobinuria) was the predominant clinical feature in two sporadic patients with complex I deficiency and COX-positive RRF in their muscle biopsies. One had a nonsense mutation (G11832A) in the ND4 gene (Andreu et al., 1999b), the other had an intragenic inversion of seven nucleotides within the ND1 gene, resulting in the alteration of three amino acids (Musumeci et al., 2000).

Nine patients with isolated complex III deficiency in muscle complained of exercise intolerance, but only two had myoglobinuria (Andreu et al., 1999a; DiMauro, 1999). All patients in whom muscle histochemistry was performed showed COX-positive RRF. The nine mutations in the cytochrome *b* gene were different from one another although, except for a single deletion, they were all G-to-A transitions.

The first mtDNA molecular defect identified in complex IV (COX) deficiency was a 15-bp microdeletion in the COX III gene. The patient was a 16-year-old woman with recurrent myoglobinuria triggered by prolonged exercise or viral illness (Keightley et al., 1996). Between attacks, both physical and neurological exams were normal, as were routine laboratory tests, including serum creatine kinase (CK) and lactate. No tissue other than muscle was affected, and family history was entirely negative. Muscle biopsy showed many SDH-positive, COX-negative RRF and marked isolated COX deficiency. A nonsense mutation (G5920A) has been identified in the COX I gene of muscle mtDNA in a 34-year-old man with life-long exercise intolerance and recurrent myoglobinuria induced by intense or repetitive exercise (Karadimas et al., 2000). Muscle biopsy showed scattered COX-negative RRF and numerous COX-negative non-RRF, and isolated COX deficiency. The mutation was not present in blood or fibroblasts from the patient, nor in blood from his asymptomatic mother and sister.

Isolated, presumably primary coenzyme Q10 (CoQ10) deficiency in muscle has been identified in three clinical conditions: (i) a predominantly myopathic disorder, with exercise intolerance and myoglobinuria (Ogasahara et al., 1989; Servidei et al., 1996; Sobreira et al., 1997); (ii) a severe infantile syndrome dominated by encephalopathy and nephropathy (Rotig et al., 2000); and (iii) a heterogeneous syndrome characterized by cerebellar ataxia, weakness, and cerebellar atrophy (Boitier et al., 1998; Musumeci et al., 2001). It is noteworthy that all patients responded to oral CoQ10 supplementation, although the degree of improvement varied from patient to patient.

In the myopathic variant, muscle biopsy shows both RRF and lipid storage. In the other variants, muscle biopsy shows rather non-specific myopathic changes.

CoQ10 concentration is markedly but variably decreased in muscle (4–35% of normal). CoQ10, or ubiquinone, is a lipophilic component of the electron-transport chain, which transfers to complex III electrons derived from complex I and complex II (Fig. 72.3). CoQ10 also plays a role as a membrane stabilizer and an oxygen radical scavenger.

All three clinical variants appear to be inherited as autosomal recessive traits. Given the complexity of the CoQ10 biosynthetic pathway and the heterogeneity of the clinical presentations, it is likely that different steps may be involved, but this remains to be documented.

Respiratory chain defects causing weakness

As implied by the term, virtually all mitochondrial encephalomyopathies cause some degree of weakness, although this is often overshadowed by the involvement of other tissues. However, isolated myopathies can occur in three circumstances: (i) skewed heteroplasmy of ubiquitous mtDNA mutations; (ii) somatic mtDNA mutations; and (iii) mutations in tissue-specific nuclear genes. We will describe only two conditions presumably belonging to the last group and affecting complex IV of the respiratory chain.

There are two main myopathic presentations of Complex IV (COX deficiency), both with onset at or soon after birth, but with very different outcomes. The first (fatal infantile COX-deficient myopathy), is characterized by generalized and progressive weakness, causing respiratory insufficiency and death before age one year (DiMauro et al., 1980). The second (benign infantile COX-deficient myopathy) has very similar onset, with profound, life-

threatening weakness often requiring assisted ventilation. However, with appropriate support, these infants improve spontaneously and are usually completely normal by three years of age (DiMauro et al., 1981). There is lactic acidosis in both conditions, but blood lactate decreases gradually to normal levels in the benign form.

Initially, muscle biopsy shows RRF and generalized histochemical COX deficiency in both fatal and benign myopathies. However, in the benign form, increasing numbers of fibres reacquire normal COX reactivity while RRF gradually disappear, and later biopsies appear normal.

In both conditions, there is isolated, severe COX deficiency in early biopsies, but COX activity returns to normal within about one year in the benign form.

There is no evidence of maternal inheritance in either condition, both sexes are equally affected, and there have been affected siblings, suggesting autosomal recessive inheritance. The molecular defects remain unknown in both fatal and benign COX-deficient myopathies.

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Part IX

Epilepsy

73

The cellular basis of epilepsy

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Epilepsy is the most prevalent serious neurological illness able to affect people of all ages. Treatment of epilepsy is primarily symptomatic, with use of medications to suppress abnormal electrical activity in the brain, or surgical procedures designed to disrupt epileptogenic circuits. Far more satisfactory for the patients and clinician would be a treatment for epilepsy itself, rather than suppression of seizures, with no direct rectification of the underlying disorder. Recent explosive advances in neuroscience and molecular biology have brought such an understanding of epilepsy mechanisms potentially within range. As of mid-year 2000, the key word 'epilepsy' brings forth 57 599 articles in *Medline*, many of them on the subject of epilepsy research. Different dominant themes have transferred from neuroscience to epilepsy research over the decades, as portrayed in Table 73.1.

Recent decades have been characterized by interdisciplinary work that cannot be characterized by any one theme: for example, histological–physiological correlations or genes coding for ion channels. This merging of disciplines is likely to be of great benefit for our understanding of epilepsy, since mechanisms for seizures fail to lie neatly within the traditional disciplines of anatomy, physiology and chemistry. A brief overview such as this one can only touch selected themes. Reference may also be made to prior reviews (Dichter, 1997; Delgado-Escueta et al., 1999; Fisher, 1995; McNamara, 1999).

Table 73.1. Dominant themes in epilepsy research

Pre-1930	Clinical descriptions
1930–1950	EEG findings, anatomic descriptions
1950–1960	Action potentials, resting potentials, potassium and sodium channels
1960–1970	Synaptic potentials: glutamate and GABA
1970–1980	Neurotransmitters and receptors
1980–1990	Ion channels, neurodevelopment
1990–2000	Genes interdisciplinary studies

Table 73.2. Key physiological processes in balancing excitation and inhibition

Excitation
Neuronal depolarization
Excitatory postsynaptic potentials
Action potentials
Inward ionic currents
Long-term excitatory plastic changes
Inhibition
Neuronal hyperpolarization
Inhibitory postsynaptic potentials
Calcium-activated potassium potentials
Outward currents
Metabolic pump potentials
Spike frequency accommodation

Imbalance of excitation and inhibition

Partial and secondarily generalized seizures reflect an imbalance between excitation and inhibition in the brain (Meldrum, 1984). This principle is an extension of the observation made over a century ago by John Hughlings Jackson that epilepsy reflects an excessive and disordered discharge in the highest centres of the brain. Excessive excitation results in rapid neuronal firing during seizures. Output signals from rapidly firing neurons recruit synaptically connected neuronal systems into the excessive discharge. Inhibitory systems also are activated powerfully during seizures, but may be insufficient to control the excessive excitation. Table 73.2 lists several key physiological processes involved in the balance of excitation and inhibition.

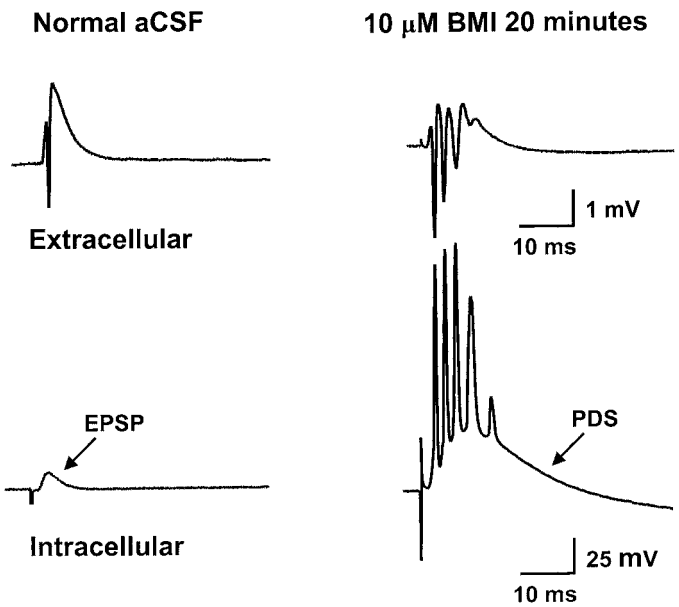

Fig. 73.1. An EPSP (left column) and PDS (right column), shown with extracellular (upper row) and intracellular (lower row) recording from a region CA1 hippocampal pyramidal neuron in a rat hippocampal slice. Abbreviations: EPSP, excitatory postsynaptic potential; PDS, paroxysmal depolarizing shifts; aCSF, artificial cerebrospinal fluid; BMI bicuculline methiodide (an epileptogenic GABA antagonist); mV, millivolts; ms, milliseconds.

Figure 73.1 illustrates an intracellular recording from a hippocampal pyramidal neuron stimulated with an afferent shock in the baseline condition. An EPSP results, giving rise to an action potential. The second part of the figure shows the results of a similar shock given in the presence of bicuculline methiodide. A much larger depolarization, referred to as a paroxysmal depolarization shift (PDS) results, and generates several action potentials, producing a greater degree of excitation. Block of inhibitory interneurons, or the GABA-A receptor-related neurotransmission utilized by such inhibitory interneurons, unleashes excitation.

Excitation and epilepsy

Excessive excitation is a plausible component of some seizures. Excitation is mediated by dozens of known neurotransmitters and neuromodulators, but glutamate receptors are the most important and best studied prototypes for the locus of excitation in epilepsy (Chapman, 1998). The glutamate receptor is a complex macromolecular entity (Meldrum et al., 1999) with many points for possible manipulation, including the cation channel, AMPA, kainate, NMDA receptor sites, three families of metabotropic receptors, two families of neuronal and glial glutamate transporters, and a large variety of modulatory sites.

Much effort has focused on inhibition of the NMDA subtype of the glutamate receptor, because this receptor subtype is activated primarily during times of excess excitation and neuronal depolarization. Blockade of the NMDA channel should, in theory, only interfere with amplification of excitation, and not normal synaptic excitatory transmission mediated by the AMPA and kainate subtypes of the glutamate receptor. Unfortunately, NMDA antagonists so far tested have been excessively toxic. NMDA is involved both in learning and in psychological homeostasis of the human brain. Blockade produces considerable cognitive and psychiatric effects. Work continues in an attempt to isolate the excitatory effects from the psychotomimetic effects of the NMDA receptor. So far, no human seizure disorder has been attributed to mutations directly affecting glutamate (Meldrum et al., 1999).

Inhibition and epilepsy

Inhibition in the brain is arrayed in a hierarchy (Fig. 73.2). At the base of this hierarchy is the all-important fast IPSP mediated by GABA-A receptors. Some neurons also possess a GABA-B receptor, that generates deeper and more prolonged hyperpolarizations, called slow-IPSPs or late hyperpolarizing potentials (LHPs) (Alger & Nicoll, 1979). At the next level of the inhibitory hierarchy is a nonsynaptic potential called calcium-activated potassium (Alger & Nicoll, 1979). Currents underlying this potential are produced by calcium entry into the neuron, resulting in activation of an outward potassium flow. Hyperpolarization from calcium-activated potassium can be profound and last several hundreds of milliseconds. Metabolic pump potentials utilize energy provided by ATP to transport sodium ions out of the neuron and potassium ions back into the neuron after times of neuronal activity. Since the pump transports three sodium ions out for each two potassium ions in, hyperpolarization results (Thompson & Prince, 1986). This hyperpolarization may last for several minutes, and maintain the neuron far away from its action potential firing threshold. It is interesting to speculate as to whether such pump-related hyperpolarizations might be responsible in part for so-called Todd's paralysis after some seizures. Enhancement of response at the GABA-B receptor, or of calcium-activated potassium might be a useful strategy for inhibiting seizures.

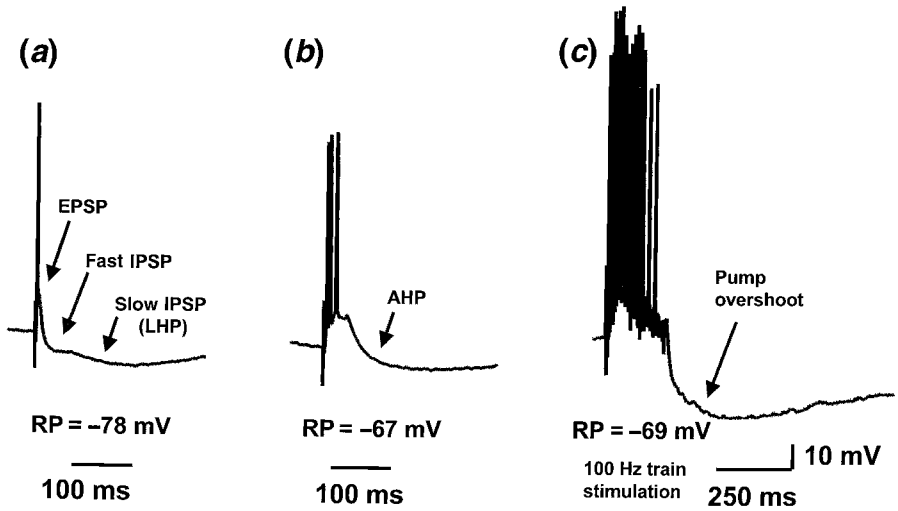

Fig. 73.2. Hierarchy of inhibition in the brain, showing the fast and slow IPSP, the AHP and the pump overshoot hyperpolarizing potential. Recordings were done in a region CA1 hippocampal pyramidal cell in the rat hippocampal slice. Abbreviations: IPSP, inhibitory postsynaptic potential; LHP, late hyperpolarizing potential; AHP, after-hyperpolarizing potential; RP, resting potential.

No single topic has been more explored in epilepsy than the role of GABA and inhibition. The interested reader can refer to several articles devoted to GABA for greater depth (Meldrum, 1989; Roberts, 1986; Tasker & Dudek, 1991). Descriptions have been provided, at the time of this writing, for 16 GABA-A receptors, three GABA-B receptors, and two GABA-C receptors (Chebib & Johnston, 1999). GABA-related targets for AEDs include the postsynaptic GABA-A receptor, the GABA-B autoreceptor and the GABA transporter (Mohler, 1992).

After GABA is released from the presynaptic terminal, it diffuses across the synaptic cleft and binds with the postsynaptic receptor. The GABA-A receptor is a complex macromolecular system, constructed from a family of more than 15 subunits, with different affinities and efficacies of benzodiazepines applying to different subunit assemblies (Mohler, 1992). Subunits available for assembly into a one–five chain complex (probably usually four chains), include 6 alpha, 4 beta, 4 gamma, 1 delta, 1 theta, 1 episilon and 1 pi subchain (Macdonald & Kapur, 1999; Mehta & Ticku, 1999; Whiting et al., 1999). Numbers of subchains found in various systems (for example, chick retina) continue to increase with investigation. Typical native adult GABA-A receptor complexes are composed of two alpha and two beta chains. However, alternative assemblies confer regional and functional specificity of brain inhibition. Mutations in the various chains can lead to a wide variety of dysfunctional GABA-A receptors. It is easy to speculate that such mutations can lead to predispositions to seizures.

The GABA-A recognition site is situated on the beta subunit and the benzodiazepine modulatory site on the alpha subunit (Bormann, 2000), but BDZ sensitivity also can depend upon the gamma chain. Binding of GABA to the GABA-A receptor opens a chloride ionophore on the beta chain. Influx of chloride ion hyperpolarizes the neuron, and further provides inhibition by reducing membrane resistance. The GABA-A receptor GABA recognition site and the chloride ionophore are linked closely with modulatory sites responsive to benzodiazepines and barbiturates. Representatives from each of these categories greatly enhance the inhibitory efficacy of GABA. Barbiturates do so by prolonging mean open time of the chloride channel (Study & Barker, 1981). Benzodiazepines increase the probability of chloride channel opening (Study & Barker, 1981). Endogenous compounds formulated from steroids and related to the hormone progesterone, called neurosteroids, recently have been shown to have various positive and negative actions on GABA systems (Compagnone & Mellon, 2000). Examples include pregnenolone, dehydroepiandrosterone, progesterone itself and their derivatives (Baulieu, 1998). One derivative neurosteroid, ganaxolone, has completed a clinical trial for seizures, with mild efficacy (Monaghan et al., 1997).

Epileptogenic insults selectively can injure GABAergic inhibitory interneurons. A prototype experiment for this hypothesis was performed by counting GAD-positive neurons in a seizure focus produced in a monkey by aluminium hydroxide gel (Ribak et al., 1986). GAD-positive neuronal somata were reduced by about 25–50% in the

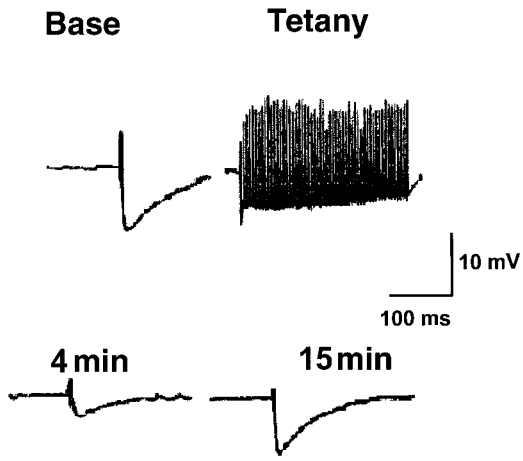

Fig. 73.3. Fade of the IPSP with tetanic stimulation. The intracellularly recorded potentials are from a region CA1 hippocampal pyramidal cell in the rat hippocampal slice. After 15 minutes, the attenuation of the IPSP has reversed.

focus. Acute processes also can decrease GABAergic function. For example, hypoxia depresses the GABAergic inhibitory currents in hippocampal cells before it depresses excitatory currents (Katchman et al., 1994). During this interval of time, brain is hyperexcitable and susceptible to seizures. Nuclear magnetic resonance spectroscopy suggests a significant occipital lobe decline of GABA in brains of patients with uncontrolled seizures (Petroff et al., 1999; Sherwin, 1999).

Decreases in GABA function can be dynamic, and not dependent upon death of GABAergic neurons. Figure 73.3 illustrates a reversible fade of the evoked IPSP in response to tetanic stimulation. Such a dynamic decline of GABAergic transmission could participate in the interictal–ictal transition.

Sloviter has hypothesized that inhibitory basket cells become 'dormant' in chronic temporal lobe epilepsy (Sloviter, 1991). Dormant interneurons also have been documented in the tetanus toxin model (Jefferys & Traub, 1998). The dormant cells are alive and present, but presumably are inactive because of isolation from their usual excitatory afferents. The net result is disinhibition. The dormant basket cell hypothesis has generated considerable controversy. Direct recordings from inhibitory interneurons do not necessarily support the hypothesis (Bernard et al., 1998).

Just as GABA receptors can influence propensity to seizures, so seizures may have an influence on GABA receptors. Status epilepticus produced by pilocarpine in rats led to decreased sensitivity to benzodiazepines, because of alteration in balance of subchains in the receptor (Kapur & Macdonald, 1979). This type of dynamic change in receptor composition provides an opportunity for adaptive plasticity.

Enhancement of inhibition has been a fertile method for antiepileptic drug therapy. A primary target has been the inhibitory postsynaptic potential (IPSP) mediated by the GABA-A receptor. GABA-related inhibition can be augmented in several ways: (i) By increasing synthesis through availability of more precursor by administration of progabide (de Pasquet et al., 1991); (ii) Allosteric modulation of the GABA receptor, for example, barbiturates and benzodiazepines (Study & Barker, 1981); (iii) Inhibition of GABA uptake with tiagabine (Schachter, 1999); and (iv) Inhibition of GABA metabolism by vigabatrin (French, 1999).

GABA has often appeared to be the 'key to epilepsy' (Snodgrass, 1992), but several counterexamples exist to GABA's antiepileptic effects. GABA agonists worsen some cases of absence epilepsy (Snead & Hosey, 1985). The GABA uptake inhibitor, tiagabine, occasionally can precipitate nonconvulsive seizures (Ettinger et al., 1999). GABA agonists injected into the pedunculopontine nucleus increase seizures produced by convulsant chemicals (Snodgrass, 1992). Pilocarpine-induced seizures preferentially injure inhibitory interneurons (Mello & Covolan, 1996). Histochemical markers for GABA-containing neurons show that GABA cells are decreased as expected in models of focal cortical epilepsy, but they are unchanged in certain models of temporal lobe epilepsy, and actually increased in models of absence epilepsy (Houser, 1991). Enhanced GABA transmission can be either anticonvulsant or proconvulsant depending upon the affected system of the brain (Gale, 1992). In acute circumstances, reduction of inhibition can be expected to lower the seizure threshold. The role of inhibition may, however, be different in chronic seizure disorders.

The mass of information on GABA accrued over the past 50 years allows several conclusions pertaining to mechanisms of the epilepsies. First, GABA plays a pivotal role in epilepsy. Acute reduction of GABAergic function is highly likely to reduce threshold for partial and generalized tonic–clonic seizures. Drugs that enhance GABA neurotransmission by a variety of mechanisms serve as useful remedies for partial and generalized tonic–clonic seizures. Secondly, effects of GABA are mediated by actions of at least three types of GABA receptors: A, B and C. The role of the latter in epilepsy is unknown. The GABA-B receptor appears to be involved in spike-wave generation, a subject discussed below. The GABA-A receptor is the most important receptor, but it displays a bewildering array of subchains, heterogeneities and genetic variants. Thirdly,

GABAergic neurons may be selectively vulnerable to injuries, examples including hypoxia, heavy metal deposition models and freeze foci. However, several experimental epilepsy models show no decrease in GABAergic neurons, or in functional inhibition. Epilepsy is diverse. One mechanism does not explain all types of epilepsy.

Other transmitters and epilepsy

Parallel to efforts in the epilepsy research community, the above discussion emphasized glutamate and GABA as neurotransmitters. However, such an emphasis admittedly is myopic, since investigation has disclosed over 200 neurotransmitters and neuromodulators, all of which might be involved in epilepsy (Fisher & Coyle, 1991). Data pertaining to epilepsy is available for aspartate, acetylcholine, norepinephrine, dopamine, serotonin, opiates, adenosine, substance P, neuropeptide Y (NPY), somatostatin, and a variety of other neuromodulators. Future epilepsy research should profitably capitalize on the ability of so many substances to inhibit neuronal activity during particular circumstances.

Rarely, if ever, is it possible to declare a neurotransmitter 'convulsant' or 'anticonvulsant'. All neurotransmitters, even GABA, have multiple synaptic mechanisms in different brain systems. Excitation by a transmitter in one location or circumstance may transform to inhibition in another. As one of many possible examples, GABA is depolarizing when applied to dendrites of hippocampal pyramidal cells, probably because of a dendritic chloride pump that reverses the chloride gradient (Staley et al., 1995).

Cellular and network properties

For many years epilepsy researchers engaged in discussion about whether epileptic activity resulted from disordered neurons, or normal neurons operating within disordered circuitry (Prince, 1985). Both possibilities could theoretically lead to excessive excitation, and both mechanisms now are known to operate in most conditions of epilepsy. Membrane properties of hippocampal neurons from human seizure foci show no obvious change, but bursting is easier to elicit and functional inhibition is decreased (Schwartzkroin, 1994). A few dysfunctioning neurons can serve as pacemakers for recruitment of widely dispersed normal neuronal elements. Normal inhibitory mechanisms restrict development and spread of seizures. Temporal lobe epilepsy correlates with a loss of cells in layer III of the medial entorhinal cortex (Gloveli et al., 1998). Such loss of inhibition allows epileptiform activity induced by low magnesium to propagate from entorhinal cortex to hippocampus (Gloveli et al., 1998).

A physiological hallmark of the disordered epileptiform neuron is the paroxysmal depolarization shift (PDS, Fig. 73.1). The PDS is a giant EPSP (Johnston & Brown, 1984), but also involves the additional elements of voltage-dependent calcium influx into the neuron, triggered by opening calcium channels that normally are closed at or near the resting membrane potential. In normal synaptic circuitry, feed-forward and feed-back inhibitory interneurons truncate the excitatory potential. When these are deficient, excess excitation can result. As will be discussed below, other mechanisms also may play a role in generation of prolonged potentials, for example, genetic alterations in potassium channels.

Computer modelling of circuitry in hippocampus suggests that a decrease in inhibition, or an increase in direct recurrent excitatory connections can throw electrical activity into a positive feedback excitatory mode. Hippocampal slices begin epileptiform bursting when monosynaptic IPSPs are reduced by bicuculline to 17% of their control amplitude (Jeffreys & Whittington, 1996). The brain strikes a delicate balance between synaptic plasticity, useful for enhancing neurotransmission in circuits of importance, and the need to prevent circuits from becoming epileptogenic, in which excitation has crossed some critical threshold.

A characteristic feature of essentially all types of epileptiform activity is increased neuronal synchrony (Wong et al., 1986). During seizures, brain cells fire in mutually linked patterns. Synchrony during seizures may grow out of physiological forms of synchrony, such as that of the alpha rhythm, or thalamo-cortical sleep spindles (Steriade, 1999). In an alumina cream-induced seizure focus in monkeys, interneuronal synchrony was not increased significantly among neurons in the focus (Wyler, 1986). However, in clinical seizures, inter-regional EEG synchrony increases during seizures (Towle et al., 1999) and persists for up to 2 hours after a seizure (Franaszczuk & Bergey, 1999). Inhibition is of major importance in producing intraneuronal synchrony. Recordings of unit (neuron) firing in the region of a temporal seizure focus and contralateral temporal lobe (Colder et al., 1996) show correlation patterns consistent with strong inhibition at the start of a seizure.

Recent discussions of neuronal excitability during seizures have moved beyond synaptic potentials to the underlying ionic currents generating these potentials (Steinlein & Noebels, 2000). In general, sodium and calcium channels mediate neuronal excitation; whereas, a

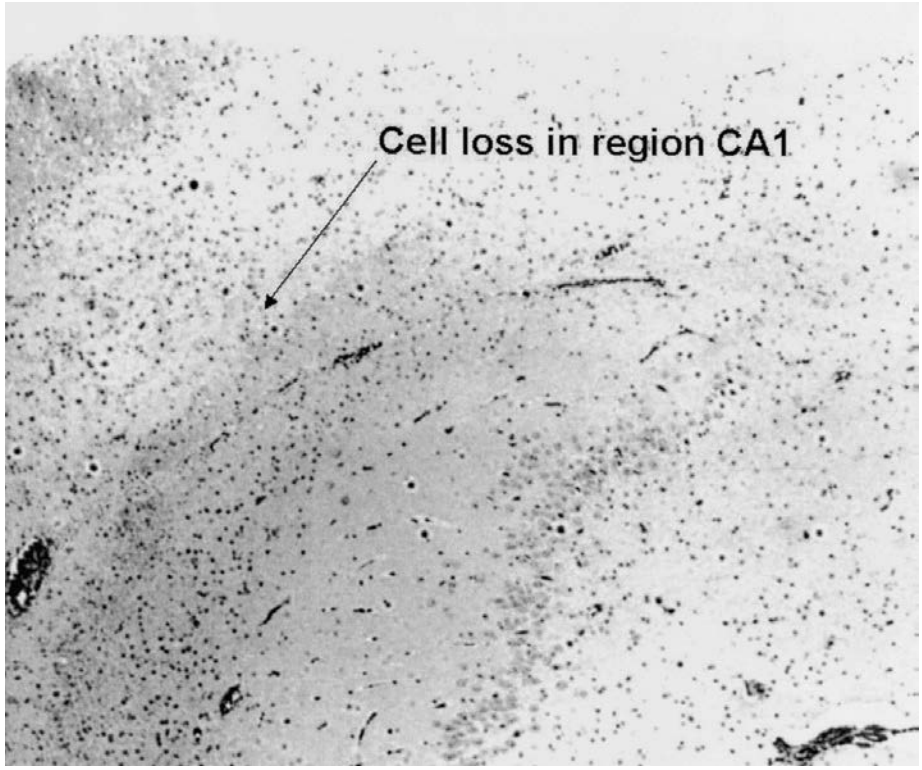

Fig. 73.4. Pyramidal cell loss in region CA1 of hippocampus from a mesial temporal lobectomy surgical specimen from a patient with intractable complex partial seizures. (Courtesy of Dr Allen Wyler, adapted from Fisher, 1998.)

variety of potassium and chloride channels stabilize neuronal firing (Wheal, 1990). Some ion channels increase brain excitability and others may protect brain tissue from effects of seizures (Mody, 1998). Investigators now are looking at channel properties in chronic models of epilepsies. For example, calcium current properties do not change significantly in dentate granule cells from kainate-treated rats, but densities of calcium currents are higher (Beck et al., 1998). In the section below on genes, two clinical epileptic syndromes, benign familial neonatal convulsions and generalized epilepsy with febrile seizures plus, will be seen to be consequent respectively to a sodium and a potassium channel disorder. Channel disorders are starting to explain a variety of previously idiopathic neurological disorders (Davies & Hanna, 1999), and will be of undoubted significance in explaining certain forms of epilepsy.

Epileptogenesis

Brain injury may lead to epilepsy after a latency interval free from seizures. What is the mechanism of such delay in the onset of seizures? Recent research suggests considerable ability for remodeling of injured circuits, although in age-dependent fashion, with young brain better able to remodel and recover. Anoxia–ischemia, trauma, exposure to neurotoxins, and other injuries selectively may affect certain cell subpopulations. When these cells die, axons from surviving neurons sprout additional processes to connect with the partially deafferented neurons (Sutula et al., 1992). For reasons that are unclear, but may relate to selective vulnerability of inhibitory interneurons, the recovered circuit tends to be hyperexcitable. The clinical manifestation of regenerated circuitry in hippocampus is mesial temporal sclerosis, showing an atrophic hippocampus bright on T2 MRI images. Histological views of surgically removed mesial temporal sclerosis tissue demonstrate loss of neurons and replacement with gliotic tissue (Fig. 73.4).

Stains for zinc, which serves as a marker for one type of terminal in region CA3 of hippocampus, show that extra bands of zinc are found in chronic epileptogenic tissue, indicating excessive growth of the zinc-containing terminals (Sutula et al., 1992). Sprouting may be a result of certain patterns of excitation, since it can occur in the

absence of cell death (Stringer et al., 1997). Is mossy fibre sprouting a cause, consequence or epiphenomenon in temporal lobe epilepsy? Longo and Mello (1999) argue that it is an epiphenomenon, since protein synthesis inhibition with cycloheximide inhibits mossy fibre sprouting, but not seizures. Conversely, animals show mossy fibre sprouting with no obvious seizures. Neuropathological analysis of epileptic human temporal tissue is becoming more and more sophisticated (Blumcke et al., 1999), but still suffers from the lack of suitable control tissue.

Recent animal research discloses a small population of primitive neurons available in hippocampus and olfactory cortex able to differentiate into neurons in suitable circumstances, even well into adult life. This novel finding provides another avenue for pathway regeneration after injury. The sprouting of axons and formation of functional connections is governed by a complex system of genes and messengers (Lowenstein, 1996). Epileptogenesis depends not only upon formation of new connections, but upon 'programmed death' or apoptosis of selected cell populations.

Theories of temporal lobe epilepsy have focused upon the hippocampus, but the importance of the hippocampus may be overemphasized because of the popularity of the hippocampal slice. Several other limbic structures, including entorhinal cortex, amygdala and pyriform cortex may be important in TLE (Bertram et al., 1998; Gale, 1992). Medial thalamus may be a pacemaker for limbic structures (Bertram et al., 1998). In experimental models, posterior hypothalamus appears to mediate the zone of hypometabolism around a cortical seizure focus (Bruehl et al., 1998).

Extrasynaptic mechanisms of epilepsy

Most of the business of the brain takes place at synapses, but extrasynaptic processes can influence seizures. Among these are release of extracellular ions and neuronal interactions via non-synaptic field effects. Actions that take place in the extracellular space have been termed 'volume transmission', as opposed to the one-to-one cell-to-cell communication (by chemical synapses or gap junctions) that is termed 'wiring synapses' (Zoli et al., 1999).

Discharging neurons release potassium into the extracellular space. During a seizure extracellular potassium activity can rise from baseline of 3 mM to up to 12–15 mM (Fisher et al., 1976). Increased extracellular potassium depolarizes neurons and brings them closer to their firing threshold, therefore more likely to participate in epileptiform bursting. The resulting cell firing releases more potassium into the extracellular space and produces a positive feedback situation. Counter to this excitation is the glial syncytium, linked by gap junctions and able to serve as a potassium 'sponge' (Lux et al., 1986). In chronic epilepsies, the glial network may function abnormally. Seizures produce a proliferation of astrocytes and a change in the astrocyte cytoskeleton (Khurgel & Ivy, 1996). Astrocytes from human seizure foci show several atypical properties, including highly branched processes, presence of voltage-activated, tetrodotoxin-sensitive channels, and decreased inward-rectifying potassium currents (Bordey & Sontheimer, 1998). These properties conceivably impair the glial syncytium's ability to buffer increases of intracellular potassium.

Other ions than potassium change their extracellular concentrations during a seizure. Sodium, calcium and magnesium all decrease extracellular activity during a seizure (Heinemann & Jones, 1990). Hydrogen ion concentrations increase in the extracellular space during seizures, rendering the ECS more acidic. Since the hydrogen ion competes with the NMDA associated channel, the acidic shift thereby reduces excessive excitation (Tang et al., 1990). Acidification may be part of the mechanism of action of AEDs, such as acetazolamide (Diamox), that block carbonic anhydrase (Reiss & Oles, 1996).

The great debate of the 1940s about electrical vs. chemical synapses was resolved in favour of brain chemical synapses. However, recent times have seen a swing back toward the electrical theory in the form of neuronal and glial gap junctions (Rozental et al., 2000). Gap junctions utilize a protein, connexin, which may regulate cell–cell communication at the junction (Nagy & Rash, 2000). Connexin comes in several forms, connexin26 (Cx26; beta 2), Cx32 (beta 1) and Cx43 (alpha 1), with the balance of these determined by brain region and maturity of development. Gap junctions among neurons have been argued to play a role in neuronal synchrony (Perez-Velazquez & Carlen, 2000), and in the linking of hippocampal inhibitory interneurons (Fukuda & Kosaka, 2000). Pharmacological block of gap junctions decreases seizures in animal models (Carlen et al., 2000). Additionally, gap junctions among hippocampal neurons may play a role in 100–200 Hz oscillatory fast activity (Draguhn et al., 1998) that occurs at the start of some seizures (Fisher et al., 1992).

Another means for non-synaptic spread of epileptiform activity is through the mechanism of axonal backfiring (Hablitz, 1984; Schwartzkroin et al., 1975). With this phenomenon, axon terminals are depolarized distally and fire retrograde to excite their cell soma. The soma then fire all

terminals propagating excitation. Relevance of backfiring to clinical epilepsy remains unknown.

Electric and magnetic fields generated by neuronal activity can influence adjacent neurons directly, without mediation by synapses or gap junctions. Epileptiform activity produced in a hippocampal slice by removing calcium from the bath is eliminated by an applied DC electric field with a gradient of 1–5 mV/mm (Ghai et al., 2000). Similar inhibition can be obtained in hippocampal slices made epileptiform by the GABA antagonist, penicillin (Kayyali & Durand, 1991). Recently, similar inhibition of epileptiform activity is being reported in open-label studies for magnetic field gradients, which have the advantage of being non-invasive and painless (Dobson et al., 2000).

Ictal transition

Clinicians distinguish the EEG finding of an interictal spike, which is a marker for epileptiform activity, from rhythmical ictal discharges, a correlate of clinical partial seizures. Not all patients with partial seizures demonstrate interictal discharges in a given EEG (Salinsky et al., 1987), and not all EEGs with spikes come from people with a seizure history (Gregory et al., 1993). What then are the mechanisms by which the EEG and clinical pattern make the transition from the interictal to the ictal state? This has been a difficult question to address in patients, so investigators have focused upon hippocampal slice model systems.

Epileptiform activity produced in a hippocampal slice by high potassium starts with bursts of 5–7 action potentials, then transforms to large tonic depolarizations (Jensen & Yaari, 1997). Pyramidal cell bursters fire early in the interictal-ictal transition, and eventually recruit non-bursting neurons. Similar findings were observed in slices bathed by high potassium and low calcium (Schweitzer & Williamson, 1995), and these bursts survive blockade of excitatory amino acid synaptic transmission. Interictal–ictal transitions in the pilocarpine-perfused hippocampal slice were influenced by extracellular potassium, GABA-A blockers and NMDA blockers (Rutecki & Yang, 1998). A transition to ictal-like behaviour can be provoked by removing chloride from the perfusion media (Ogata, 1978).

One school of thought argues that interictal activity provides inhibitory control to prevent transition to the ictal state. In the 4-aminopyridine model of seizures in the hippocampal–entorhinal slice, lesion of Schaffer collateral afferents to region CA1 facilitates greater propagation of seizure-like discharges through the slice (Avoli & Barbarosie, 1999).

Mechanisms of absence (spike-wave) epilepsy

Absence epilepsy, formerly called petit mal epilepsy, differs in several ways from partial (focal) seizures. Onset tends to be younger for absence, and a familial component more prominent. Some medications useful for absence, such as ethosuximide, have no value in treatment for partial or tonic–clonic seizures. GABAergic drugs usually improve partial seizures, but may make absence seizures worse (Snead & Hosey, 1985). The EEG patterns of partial seizures present interictal spikes (Fig. 73.5) and rhythmical evolving local ictal events (Fig. 73.6), whereas, EEG of petit mal shows 3–4/s bilateral spike-waves (Fig. 73.7). Some genetic absence models show increased, rather than decreased, GABAergic terminals (Houser, 1991).

These differences lead to a view that absence seizures derive from different mechanisms than do partial seizures. Recent research (Snead, 1995) has contributed significantly to our understanding of these mechanisms. Key in generation of genetic models of spike-waves are outputs of the nucleus reticularis thalami (nRt). If the thalamus can be considered a pacemaker of cortex, then nRt can be considered a pacemaker of the thalamus (de Curtis & Avanzini, 1994). Efferent fibres from nRt release GABA onto GABA-B, and also GABA-A, postsynaptic receptors on thalamic relay nuclei neurons.

In animal models SWs can be shown to depend upon a 'three-legged stool': (i) activation of thalamic neurons by gluatamatergic synapses (McCormick, 1992); (ii) GABAeric outputs from nucleus reticularis thalami (nRt), thalamic relay nuclei (Caddick & Hosford, 1996); and (iii) nRt T-calcium currents generate pacemaking currents (Coulter et al., 1989). GABA-B feed-forward impulses to relay neurons and GABA-A recurrent feedback upon the nRt neurons result in periodic pacing of spike-waves to cortex. Figure 73.8 depicts the cycle of events generating SWs.

First, a variety of cortical, subcortical and thalamic afferents excite nRt neurons via NMDA and non-NMDA glutamatergic receptors. Firing of the nRt neurons generates GABA-B-mediated late hyperpolarizing potentials (slow IPSPs) in thalamic relay nuclei, such as the ventrobasal complex. At the same time, recurrent inhibition in nRt, largely mediated by GABA-A receptors, causes hyperpolarization of nRt neurons. This hyperpolarization 'cocks the trigger' for activation of the so-called low-threshold calcium current (Coulter et al., 1989), which causes calcium entry and cell firing upon movement of the hyperpolarized resting membrane potential to normal resting membrane potential. The resulting firing of nRt cells initiates another cycle of spike and wave. Since the GABA-B mediated hyperpolarization lasts about 300 ms, then SWs cycle at 3–4 per second.

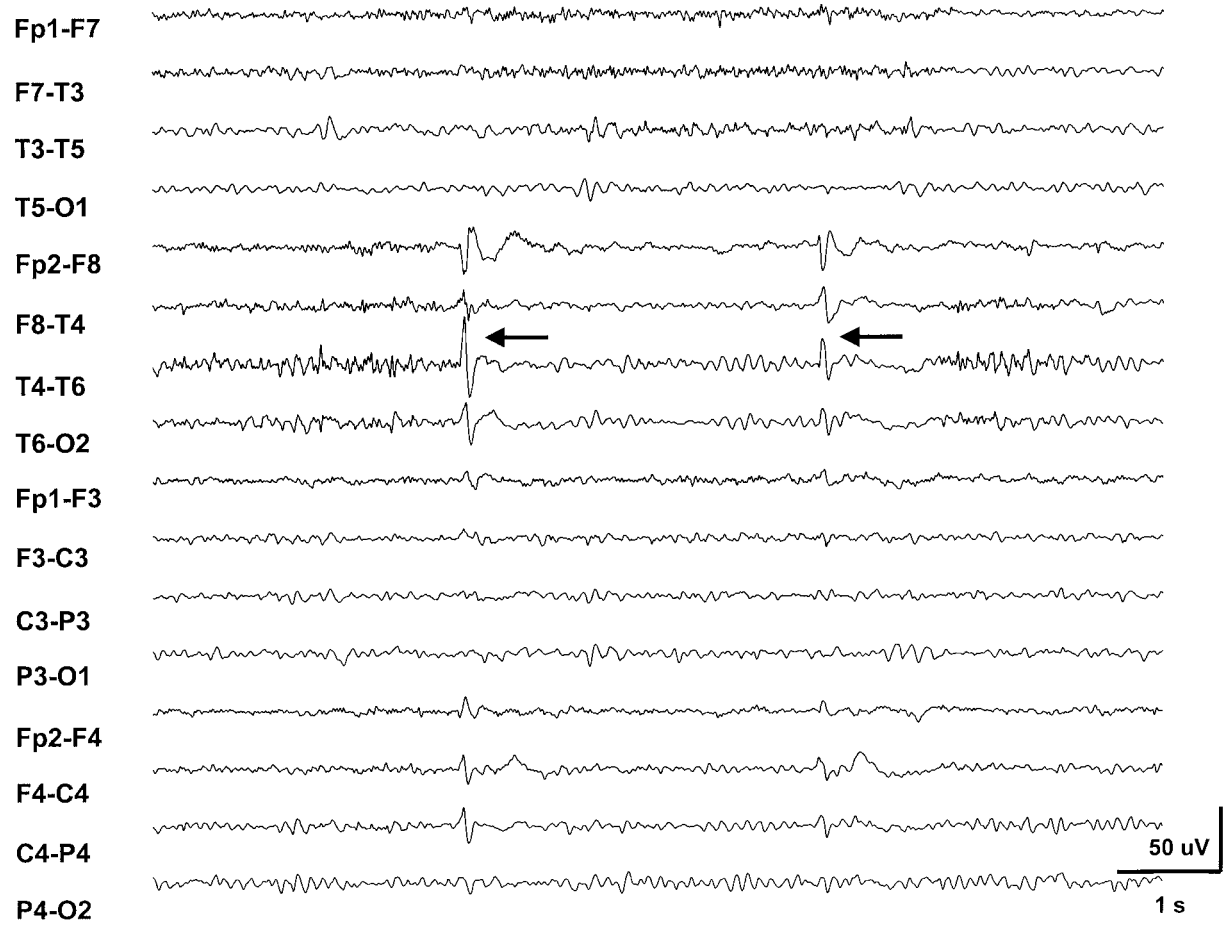

Fig. 73.5. Patient EEG showing an interictal spike with phase reversal (arrow) in the right mid-temporal electrode (T4). Electrode nomenclature is in accordance with the International 10–20 electrode system.

Clinical EEG records, not the thalamic potentials, but the cortical potentials driven by periodic afferent input from thalamic relay nuclei. Intracellular in vivo recordings from laver V cortical neurons of the GAER rat show an EPSP followed by 2–6 IPSPs during spontaneous spike-waves (Charpier et al., 1999). Cortical neurons experience, in addition, a long-lasting hyperpolarization and a tonic increase in input resistance, both of which are of uncertain origin.

SW mechanisms have been studied in rats bred to have spontaneously recurrent SWs and absence seizures, a model called the genetic absence epilepsy rat from Strasbourg (GAERS) (Marescaux et al., 1992). These animals have episodes of activity arrest and staring about 1–2 per minute. EEG recordings show concurrent 7–11 cps spike-wave discharges. Clinically useful antiabsence drugs, including ethosuximide, trimethadione, valproate and benzodiazepines, reduce seizures and spike-waves in this model; while phenytoin and carbamazepine do not (Marescaux et al., 1992). Allopregnanolone, a GABA-A positive allosteric modulator, enhances spike-waves in genetic absence WAG/Rij rats (Budziszewska et al., 1999).

A series of physiological studies of the GAERS (Avanzini et al., 1996) suggests that increased amplitude of the voltage-dependent, low-threshold calcium pacemaker current in nRt is the primary genetic deficit. Impairment of cortical GABA-mediated inhibition and AMPA receptor-mediated excitation also are detectable in this model, but may represent secondary changes. Oscillations can be seen in nRt of GAERS, and these oscillations are not due to any loss of neurons compared to controls (Sabers et al., 1996). Studies of c-fos activation in GAERS (Vergnes et al., 2000) in response to kainic acid and strychnine showed fronto-parietal cortex, rather than limbic or thalamic increases. This emphasizes that spike-wave generation is a task for a system including both thalamus and cortex, as was suggested by Gloor (1978).

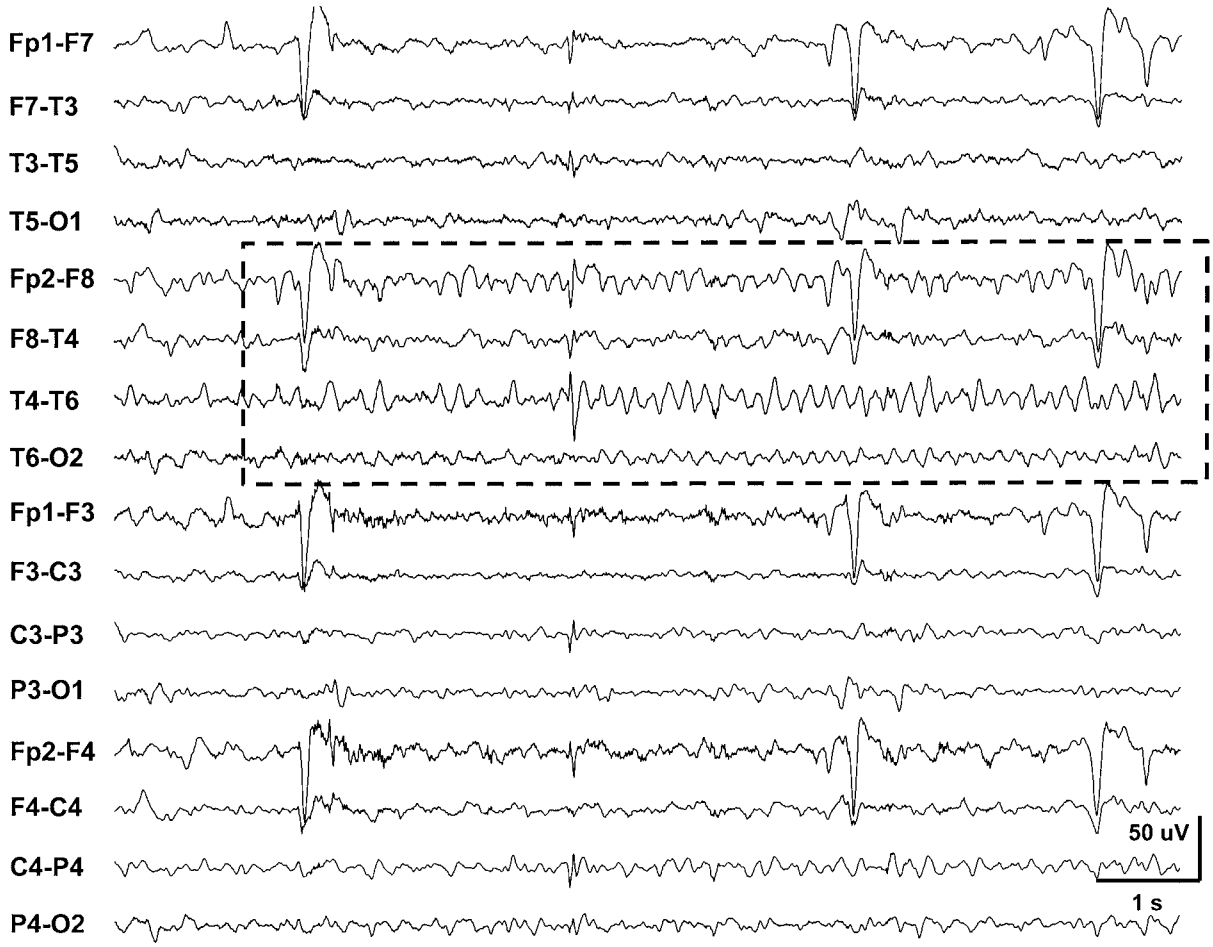

Fig. 73.6. Patient EEG showing the start of a right temporal electroencephographic ictal (seizure) event, enclosed by boxed dotted lines.

Basal ganglia also may have a previously neglected role in absence seizures. Inhibition of GABAergic neurons in the substantia nigra pars reticulata (SNPR) suppresses seizures in various animal models (Deransart et al., 1998). Striatum generates a direct GABAergic projection to SNPR, and an indirect projection via the globus pallidus and the subthalamic nucleus. Activation of either pathway, probably via dopaminergic mechanisms, suppresses spike-waves (Deransart et al., 1998). High-frequency electrical stimulation of the subthalamic nucleus has a suppressant action on absence seizures, independent of motor actions of STN (Vercueil et al., 1998). Infusion of both GABA-A and GABA-B agonists into posterior nucleus of thalamus, which links to basal ganglia and substantia nigra, facilitates fluorothyl seizures (Garant et al., 1993). Infusion into ventromedial thalamus has little effect.

Systemic convulsant drugs, such as penicillin (Fisher & Prince, 1977) and bicuculline methiodide (Neckelmann et al., 1998) produce spike-waves with greater synchrony between cortical regions than thalamo-cortical regions. Whether this represents a fundamentally different mechanism or a variation on a continuum remains to be determined.

In the clinical arena, presence of spike-wave patterns on an EEG does not equate with petit mal (absence) epilepsy. SWs can appears in the evolution of tonic–clonic seizures, with a minority of partial seizures, and with syndromes such as the Lennox–Gastaut syndrome of tonic–atonic seizures, cognitive impairment and 2–3/s SWs. Our group (Smith & Fisher, 1996) and others (Bierkamper & Cenedella, 1978) have developed a model of acquired epilepsy produced by inhibition of cholesterol synthesis, using either AY-9944 or U18666A, blockers of conversion of 25-hydroxycholesterol to cholesterol. As little as one injection of the blocker in the first week of a rat's life can lead to apparently lifelong SW discharges and absence seizures.

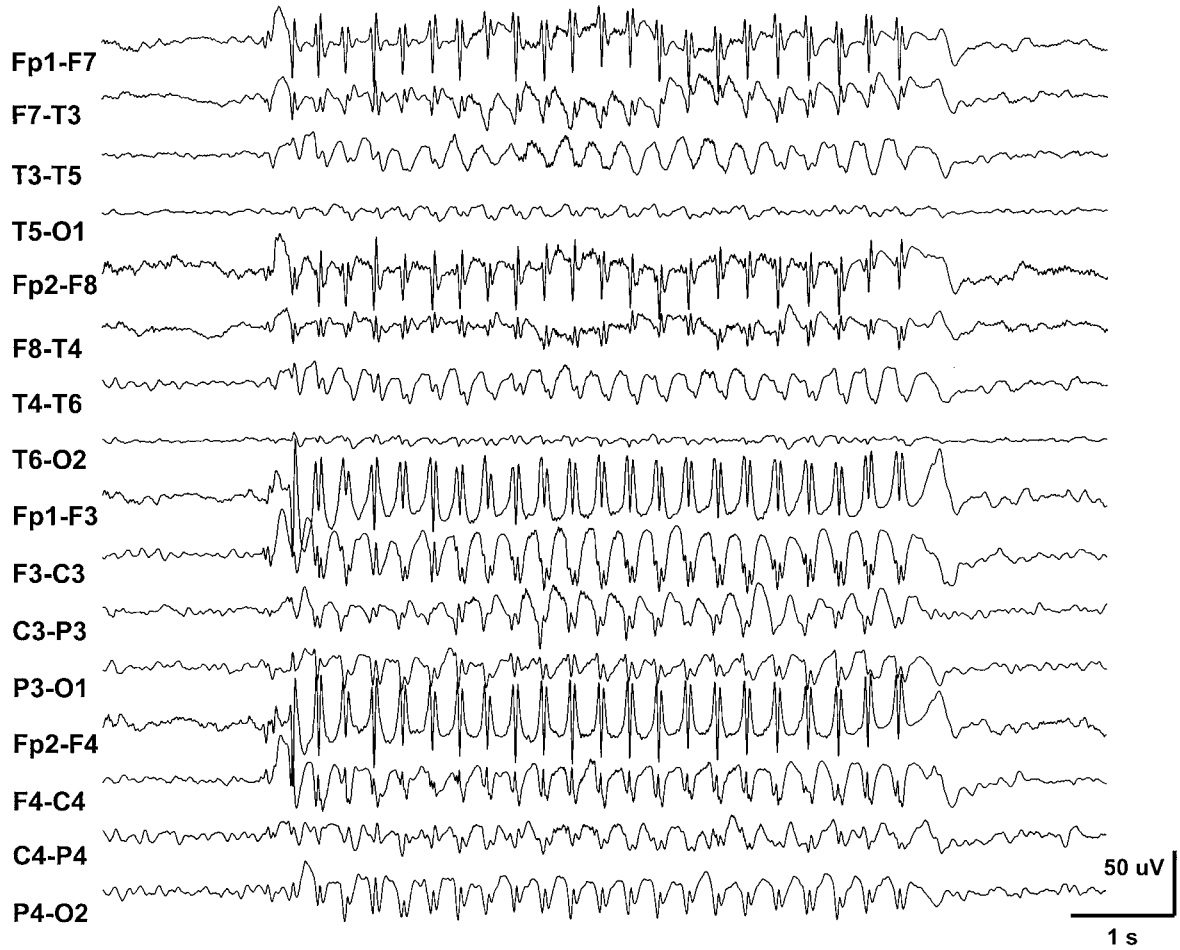

Fig. 73.7. EEG showing 3–4/second spike-waves in a patient with absence (petit mal) epilepsy.

Studies of this phenomenon may give insight into the mechanisms of the acquired, as opposed to inherited, SW epilepsies.

Possible immune mechanisms of seizures

For decades, occasional studies have emphasized a role for the immune system in seizures, although the link between epilepsy and immunology only recently has achieved substantial attention (Aarli, 1993). Disturbed humoral immunity is more likely in people with epilepsy (Schwartz et al., 1989). People with epilepsy and their relatives have been known for years to have decreased IgA levels and altered T4 helper vs. T8 cytotoxic lymphocyte counts (Eeg-Olofsson et al., 1988). Some of these changes could be due to effects of AEDs (Garzon et al., 1996), but similar abnormalities are found in seizure patients on no AEDs (Bostantjopoulou et

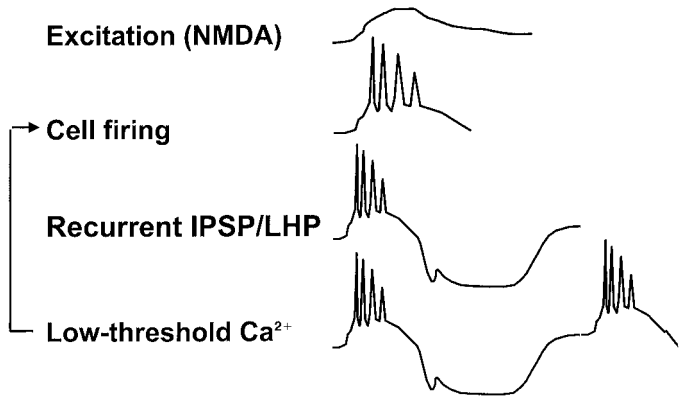

Fig. 73.8. A cartoon portraying the hypothesized sequence of development of spike-waves. See text for explanation. Abbreviations: NMDA, *N*-methyl-*D*-aspartate; IPSP, inhibitory postsynaptic potential; LHP, late hyperpolarizing potential.

al., 1994). After brain injuries, brain-specific antigens and antibodies appear in CSF and in serum (Schwartz et al., 1989).

Systemic lupus erythematosus (SLE) is associated with seizures in from 7% (Sibley et al., 1992) to 18% (Wong et al., 1991) of people with SLE. Some patients with lupus express a circulating anticardiolipin antibody. Years ago (Karpiak et al., 1981), anti-GM1 ganglioside antibodies were demonstrated to produce epileptiform spiking in rats. Anti-GM1 IgG or IgM antibodies were found in 4 in a series of 64 patients with various types of epilepsy (Bartolomei et al., 1996). Some children with seizures (3 of 23) demonstrated antiphospholipid antibody positivity with no clinical nor serological evidence of systemic lupus (Angelini et al., 1998). This antibody can decrease GABA currents in snail neurons (Liou et al., 1994). The Landau–Kleffner syndrome variant, epileptic aphasia, was associated with antibodies to brain cell nuclei or endothelial cells in 5 of 11 patients, but none of two with classical Landau–Kleffner syndrome (Connolly et al., 1999).

Occasional surgical cases of epilepsy show immune attacks on neurons (Andrews et al., 1990). Brain tissue from 16 patients undergoing epilepsy surgery were analysed for presence of viral DNA (Eeg-Olofsson et al., 1995). PCR techniques disclosed cytomegalovirus antigen in 50%, herpes simplex Type I antigen in 44%, and human herpes virus type 6 in 25%. However, only a small control series was available, so it is not possible to interpret the meaning of these associations.

Immunological theories of epilepsy received a boost from the observation that the intractable focal seizures of Rasmussen's encephalitis may derive from antibodies to brain tissue (Rogers et al., 1996). Andrews and McNamara (1996) proposed that Rasmussen's encephalitis might result from antibodies against the GluR3 subtype of the glutamate receptor. Patch–clamp recordings from neurons resected from Rasmussen's encephalitis patients show current and pharmacological sensitivities consistent with disinhibition (Gibbs et al., 1998). The link between immune attack on a glutamate receptor, disinhibition and focal seizures has not yet been forged, but it is possible to speculate that excitatory afferents to inhibitory interneurons might be disabled by the immunological attack.

If some forms of seizures are caused by autoimmune disorders, then it is worth considering immunosuppressive therapy for seizures. Several dozen studies have evaluated efficacy of immune globulin, given intravenously or intramuscularly, for seizures. A meta-analysis (van Engelen et al., 1994) collated data on 368 patients in 24 studies using immune globulin as treatment for intractable seizures. All studies were uncontrolled. Dose of globulin ranged from 0.3–6.8 g/kg, administered over periods of days to a year. Remission was said to occur in 23%. The review could not draw a conclusion about efficacy. A second review, with patient population overlapping that of the prior review, of 373 patients in 29 uncontrolled studies (Duse et al., 1996) concluded that 174 patients with intractable childhood epilepsy benefitted from immune globulin. A single controlled trial of patients with West syndrome or Lennox–Gastaut syndrome showed a trend in favour of immune globulin, but not to the point of statistical significance (Duse et al., 1996). Therefore, immune globulin remains an intriguing, but unproven therapy for seizures. Further work will be required to document efficacy, safety and to define the types of seizures to which immunotherapy might apply.

Very recently, animal studies raise the possibility of providing a vaccine against seizures. An adenovirus vaccine generated antibodies against the NR1 subunit of the NMDA receptor in rats (During et al., 2000). Oral administration of the vaccine conferred protection against kainate-induced seizures. Other intriguing, but anecdotal, immune therapies for seizures have included plasmapheresis for Rassmussen's encephalitis (Andrews et al., 1996), ACTH for infantile spasms (Baram et al., 1996), and corticosteroids for Landau–Kleffner epileptic aphasia (Lerman et al., 1991).

Genes and epilepsy

As the full sequencing of the human genome accelerates rapidly toward the first complete map, the importance of genetics in human disease in general and epilepsy in particular becomes increasingly apparent. Studies of over 20 mouse knockout models for epilepsy suggest that more than 1000 genes can be mutated to influence the presentation of seizures (Frankel, 1999). Over 100 Mendelian single gene disorders include seizures as one component of a syndrome (Gardiner, 1999). Seven regions of the genome, 6p, 8q, 10q, 15q, 16p, 19q, 20q, are now known to contain genes involved in clinical epilepsy (Szepetowski & Monaco, 1998). Unfortunately, the forms of epilepsy for which genetics are relatively simple, such as familial nocturnal frontal lobe epilepsy (Berkovic, 1997) or Baltic myoclonic epilepsy (Alakurtti et al., 2000), are rare. The common forms of epilepsy, such as temporal lobe epilepsy or posttraumatic epilepsy, demonstrate very complex and multigenic patterns of inheritance (Leppert & Singh, 1999). To further increase complexity of genetic analysis in epilepsy, variation in phenotypy can generate two very different appearing types of seizures in two different individuals with the same gene.

Table 73.3. Genetic epilepsy syndromes

Syndrome	Mode	Location	Gene
Benign familial neonatal convulsions	AD	20q, 8q24	KCNQ2, 3
Benign familial infantile convulsions	AD	19q13	?
Absence (pyknoepilepsy)	Complex	8q24	?
Baltic myoclonic epilepsy	–	–	Cystatin B
Juvenile myoclonic epilepsy	Complex	6p, 15q14	?
Benign rolandic epilepsy	Complex	15q14	?
Partial epilepsy with auditory symptoms	AD	10q	?
Nocturnal familial frontal lobe epilepsy	AD	20q, 15q24	CHRNA4
Febrile seizures 1	Complex	8q	?
Febrile seizures 2	AD	19p	?
Generalized epilepsy with febrile Sz plus	AD	19q13	SCN1B

Studies of mouse and rat genetic seizure models have been useful for framing questions about clinical epilepsy. Physiological changes in the genetically epilepsy prone rat (GEPR) include increased membrane resistance, reduced spike frequency adaptation, decreased thresholds for EPSP generation, and reduced GABA-A-mediated inhibition (Verma-Ahuja & Pencek, 1994).

Calcium-controlling genes are of key importance for genetic mouse models of epilepsy (Burgess & Noebels, 1999). The P/Q-type calcium channel regulates neurotransmitter release via the alpha-1A subchain of the pore-forming unit (Plomp et al., 2000). Tottering mutants with ataxia and epilepsy show abnormal acetylcholine release at the neuromuscular junction: more ACh is released initially in response to calcium, magnesium or potassium; but release runs down more quickly and exhausts synaptic transmission (Plomp et al., 2000). The tottering (tg) locus encodes the alpha1 subunit called Cacna1a (Burgess & Noebels, 1999). The lethargic (lh) locus encodes Cacnb4 for the beta subunit. The stargazer (stg) locus encodes the Cacng2 subunit for the gamma chain. Unfortunately, calcium is involved in many biological processes, including synaptic transmission, membrane stabilization, cell survival, cell differentiation, growth and migration and gene expression. This will make it difficult to isolate the mechanisms by which calcium-controlling genes lead to epilepsy.

Table 73.3 summarizes a dozen epilepsy syndromes for which a gene has been positionally cloned, and three for which a function of the defective gene has been identified.

Benign familial neonatal convulsions (Schroeder et al., 1998) is an autosomally dominantly inherited disorder that presents with convulsions on days 2–4 of life. It resolves by 4 months, but 15% develop late seizures. The involved sites, 20q KCNQ2 and 8q24 KCNQ3 code for potassium channels. Related disorders can affect potassium channels in heart muscle and lead to the long Q-T syndrome. Effects of impairing potassium channels can be investigated in laboratory animals. Knockout of the Kv1.1 alpha subunit of the potassium channel produces mice with seizures (Rho et al., 1999). The human homologue is KCNA1, and loss of this locus leads to episodic ataxia and myokymia.

Baltic myoclonic epilepsy of Unverricht and Lundborg (Lehesjoki & Koskiniemi, 1999) is an epileptic disorder with usual onset at age 6–15 years, presenting with stimulus and light sensitive myoclonus. The syndrome results from cystatin B, a cysteine protease inhibitor, gene mutations, in the form of unstable dodecamer repeat expansions (Alakurtti et al., 2000). These satellite repeats disrupt translation and ultimately concentration of cystatin B in neural tissues. Why this leads to seizures is unknown, but loss of cystatin B in mice produces deterioration of cerebellar granule cells (Pennacchio et al., 1998).

Autosomal dominant nocturnal familial frontal lobe epilepsy (Bertrand et al., 1998) is an autosomal dominant syndrome that presents with partial seizures in sleep. Onset typically is from 4–12 years of age. The involved gene site 20q13.2 encodes synthesis of the alpha-4 nicotinic acetylcholine receptor. Impairment of this receptor affects calcium ion flux through the receptor and leads to hyperexcitability of the tissue.

In conclusion, despite major advances in understanding of epilepsy mechanisms, no grand unifying theme yet ties together the means by which genetic predisposition, brain injury, or disturbance of brain metabolism lead to seizures. Investigators have identified only a tiny fraction of the genes that can predispose to or cause epilepsy. We still do

not know why some individuals have seizures, and others do not, nor why a particular seizure happens at a particular time. We are more knowledgeable about properties of ion channels, synaptic potentials, and neuronal circuits, but we still cannot identify the circuitry necessary for clinical seizures, particularly in the case of generalized tonic-clonic (grand mal) seizures.

Much of our current understanding has derived from studies on animal models of the epilepsies (Fisher, 1989). These models are, however, imperfect. The importance of human clinical research in epilepsy cannot be overemphasized (Engel, 1998), despite substantial difficulties inherent in human research.

Epilepsy research has experienced different themes and era, from clinical observation (which continues to this day), through EEG analysis, studies of membrane and synaptic potentials, studies on structural abnormalities in seizure foci, and work on neurotransmitters and neuromodulators, neuroimaging, ion channels and now genes. Future advances will derive from interdisciplinary links among these subjects and from new insights and technologies, not yet imagined.

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74

The clinical spectrum of epilepsy

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Historical note

An epileptic seizure is a paroxysmal event due to an excessive, usually self-limited, abnormal activity in the cerebral cortex. Epilepsy is defined by the recurrence of seizures and derives its name from the Greek verb $\varepsilon\pi\iota\lambda\alpha\mu\beta\alpha\nu\varepsilon\iota\nu$ which means 'to be seized'. In the past it has been alternatively known as the falling sickness as falling down is a common symptom during a seizure, or the sacred disease because seizures were interpreted as an indication of demonic possession.

For centuries the study of epilepsy was mainly identified with the description of seizures. We know now that the clinical spectrum of epilepsy is extremely wide. It ranges from benign, age-related, isolated idiopathic seizures in normal individuals, to malignant symptomatic epileptic encephalopathies with major disability and cognitive impairment. Although for practical clinical purposes, epilepsy may still be a useful diagnostic category, it would be too simplistic to consider it as a single nosologic entity. Epileptic seizures represent a common response of the brain to different etiologic substrates, which can comprise conditions such as age-related ion channel dysfunction and brain tumours.

Epidemiology

Epilepsy is one of the most frequently occurring neurological diseases. However, epidemiological studies have encountered difficulties due to methodological limitations. These are related to clinical and etiological heterogeneity as well as to the criteria used in order to define the disorder (isolated vs. repetitive seizures) and data collection (population-based studies vs. hospital-based studies or national general practice surveys).

Prevalence of active epilepsy in Rochester, Minnesota (Hauser et al., 1991) was estimated at 0.68% when either spontaneous recurring seizures had occurred or an antiepileptic drug treatment had been taken during the last 5 years. Prevalence rates at 0.5–0.8% appeared in other studies in different parts of the world. The incidence of epilepsy has been estimated to range between 17.3 and 136 per 100 000 individuals. The incidence curve for epilepsy with respect to age, has a peculiar bimodal distribution (Fig. 74.1; Hauser et al., 1993). Although the incidence of various seizure types has not been clearly determined, focal seizures seem to be the more frequent. (Fig. 74.2) The incidence of the various epilepsy syndromes is still under evaluation (Commission, 1993).

Mortality

Mortality rates in patients with epilepsy are two to three times higher than in the general population. Increased mortality risk can be directly related to the etiology of epilepsy (i.e. alcoholism, brain tumours, degenerative neurological disorders), or it can be the accidental consequence of seizures or status epilepticus. The sudden unexplained death syndrome in epilepsy (SUDS) (Earnest et al., 1992), is thought to account for about 10% of deaths related to epilepsy. Patients with nocturnal convulsive seizures are at higher risk. Postulated mechanisms include seizure-related cardiac arrhythmia, respiratory arrest and mechanical asphyxia. No specific anatomopathological features are known.

Natural history

The risk of seizure recurrence without treatment after a first unprovoked episode is close to 80% within 3 years

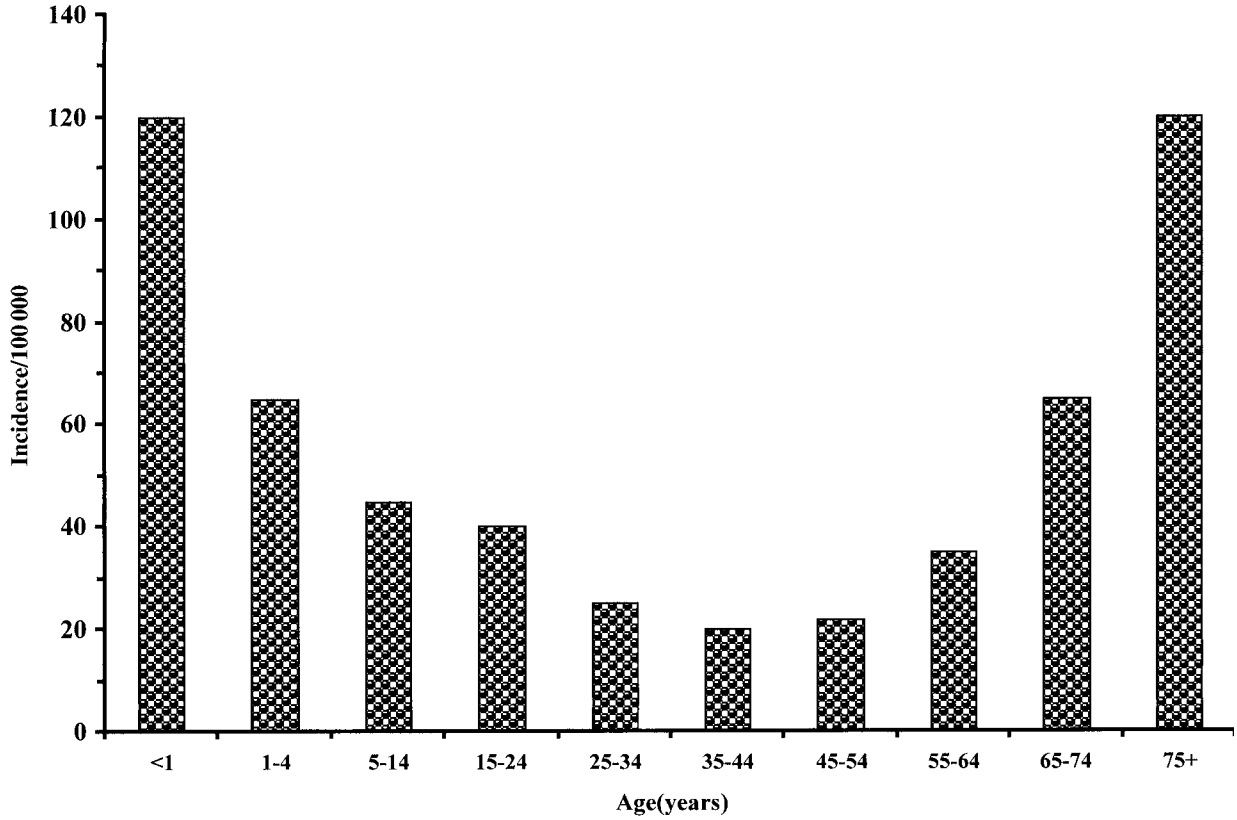

Fig. 74.1. Schematic drawing of incidence of epilepsy per 100 000 people in relation to different ages. There is a clear bimodal distribution with a peak incidence below age 1 year and a second peak above age 75. A lower plateau is present between age 25 and age 54. (From Hauser et al., 1993, modified.)

(Hart et al., 1990). The practical implication of these figures is very limited because the specific epileptic syndrome and etiology have not been considered. On the whole, 70–80% of patients reach remission on AED treatment but subsequent attempts at drug withdrawal after 3 years of complete seizure control, are followed by relapse in about 25% of children and 50% of adults (Schmidt & Graham, 1996). Relapse rate is highly variable, considered as a function of the specific epileptic syndrome: 0% for benign epilepsy with centro-temporal spikes (BECTS), 12% for childhood absence epilepsy, 23% for epilepsy with generalized tonic–clonic seizures (GTCs), 29% for partial epilepsy with secondary GTCs and 80% for juvenile myoclonic epilepsy (Baruzzi et al., 1988).

Prognosis

Patients recently diagnosed with epilepsy may be divided into four, major prognostic groups (Sander, 1993).

The first group includes the spontaneously benign epilepsies with excellent prognosis. Seizures are very rare and may either be precipitated by external factors (alcohol, sleep deprivation), or by the expression of a specific syndrome with good prognosis, i.e. BECTS. If treatment is needed, low doses will suffice to achieve remission. About 20–30% of patients belong to this category.

The second group includes the pharmacosensitive epilepsies, with a similarly good prognosis. Seizure control may be easily achieved by medication and is followed by spontaneous remission after a few years. Childhood absence epilepsy and some forms of partial epilepsy of the adult belong to this category, which accounts for 30–40% of patients.

The third group is defined as pharmacodependant epilepsies in that drug treatment will control seizures but no spontaneous remission seems to occur. Since drug withdrawal is followed by relapse, treatment will be lifelong. This group which includes juvenile myoclonic epilepsy and most non-idiopathic partial epilepsies, accounts for about 10–20% of patients.

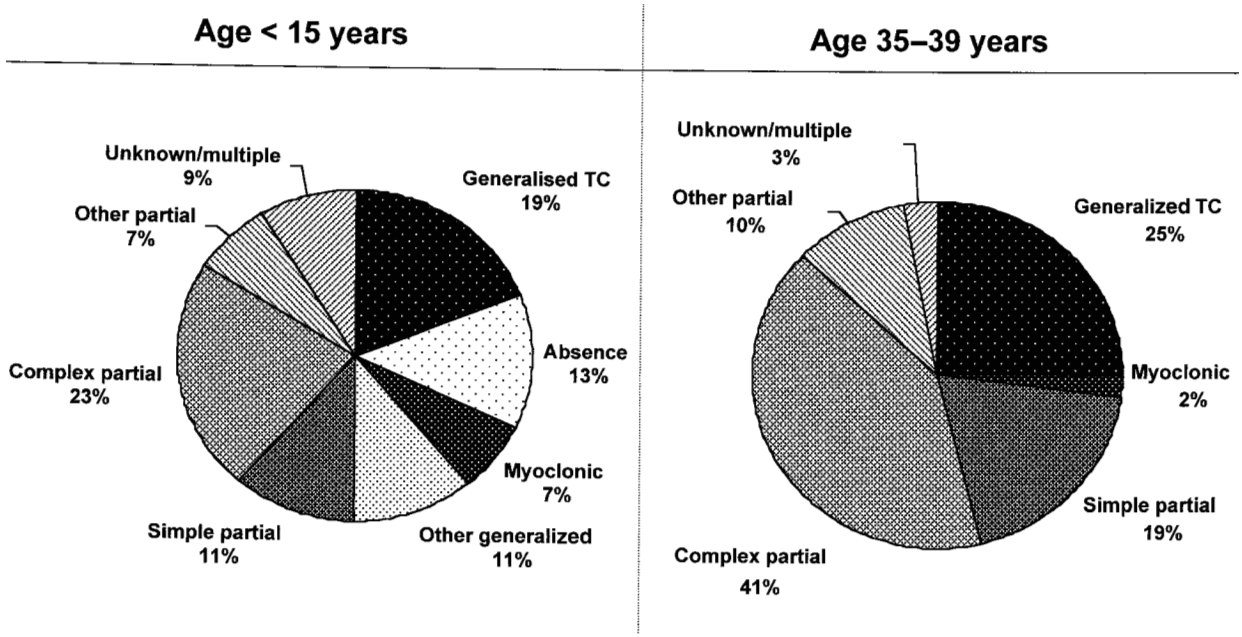

Fig. 74.2. Pie graph showing seizure type distribution in children and adults. Note that generalized seizures (generalized tonic clonic (TC), absence, myoclonic, other generalized seizures) account for 50% of all seizure types below age 15, while they represent only 27% of seizures occurring between age 35 and 39. In the latter age group absence seizures are not frequent enough to reach any measurable percentage. (From Hauser, 1992, modified.)

The fourth group includes the pharmacoresistant epilepsies, with poor prognosis. Pharmacoresistance is defined as the persistence of frequent or disabling epileptic seizures after 2 years of treatment with appropriate antiepileptic drugs. This group accounts for about 20% of patients, most receiving multiple drugs.

Etiology of epilepsy

The etiology of epilepsy is heterogeneous and results from the combination of genetic and acquired factors. In different circumstances, one or the other of these factors will prevail.

Genetic factors

Genetic factors are responsible for around 40% of epilepsies. Multifactorial inheritance is the most frequent. There are different groups of genetically determined epilepsies. They rarely result from chromosomal abnormalities or appear in the context of mendelian inherited syndromes. Most frequent are the idiopathic epilepsies, polygenic or monogenic. The different genetic epilepsies are summarized in Table 74.1. The following section will deal with the most important forms.

Single gene epilepsies

During the last 10 years, some forms of familial epilepsies that are inherited with a mendelian transmission, have been mapped to different loci and for some the genes have been cloned. So far, all identified genes are coding for ion channels responsible for neuronal excitability.

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)

ADNFLE has been described in several families (Scheffer, 2000). Seizures usually start during childhood and are mainly simple/complex partial motor seizures presenting as dystonic/tonic posturing or hyperkinetic behaviour misdiagnosed as parosomnia or nocturnal paroxysmal dystonia (Fig. 74.3). They are often clustered during sleep, but can also present during wakefulness. Carbamazepine treatment is effective in most patients. ADNFLE is genetically heterogeneous, with two subunits of the neuronal nicotinic acetylcholine receptor ($\alpha 4$ and $\beta 2$), responsible for the syndrome in different families (Steinlein et al., 1995; Fusco et al., 2000). A third locus has been mapped on

Table 74.1. Main genetic disorders associated with epilepsy and genetic epilepsies

Chromosomal abnormalities	Chromosomal location/ abnormality	Gene	Epilepsy (%)
Trisomy 21 (Down syndrome)	21	–	12–40
Fragile X syndrome	Xq27.3	FMR1	28–45
Angelman syndrome	15q11–13	UBE3A	80–100
Wolf–Hirschlorn syndrome (4p monosomy)	4p–	–	100
Miller–Dieker syndrome (17p)	17p13.3	LIS1	100
Ring chromosome 20	20 ring	–	100
Autosomal dominant transmission			
Type 1 neurofibromatosis	17q11	NF1	20
Tuberous sclerosis	9q24, 16p13.3	TS1, TS2	60–100
Familial cavernous angiomatosis	7q	CCM1	70
Ceroid lipofuscinosis (dominant)	–	–	100
Benign familial neonatal convulsions	20q13.3, 8q24	KCNQ2, KCNQ3	100
Benign familial infantile convulsions	19q12	–	100
Infantile convulsions and paroxysmal coreoathetosis	16p12–p11	–	80
Autosomal dominant nocturnal frontal lobe epilepsy	20q13.3, 1p21–q24, 15q24	CHRNA4, CHRNAB2	100
Familial lateral temporal lobe epilepsy	10q24	–	100
Familial mesial temporal lobe epilepsy	–	–	100
Autosomal dominant rolandic epilepsy with speech dyspraxia	–	–	100
Generalized epilepsy with febrile seizures plus	19q13, 2q21–q33	SCN1A, SCN1B	60
Familial adult myoclonic epilepsy	8q23.3–24.1	–	100
Familial partial epilepsy with variable foci	22q11–q12	–	70
Autosomal recessive transmission			
Lafora disease	6q23.25	EPM2A	100
Unverricht–Lundborg disease	21q22.3	EPM1	100
Ceroid lipofuscinosis (recessive)	1p32, 1p15.5, 16p12.1, 13q21.1–q32	CLN1, CLN2, CLN3, CLN5	100
Galactosialidosis	20q13.1	GLB2	100
Gangliosidosis GM1 type 1	3p21.33	GLB1	100
Type III Gaucher disease	1q21	–	100
Familial idiopthic myoclonic epilepsy	16p13	–	100
Rolandic epilepsy–exercise-induced dystonia–writer's cramp	16p12–11.2	–	100
X-linked transmission			
Band heterotopia, X-linked lissencephaly	Xq22.3	DCX	90
Bilteral periventricular nodular heterotopia	Xq28	FLMN1	80–90
Aicardi syndrome	Xp22	–	100
X-linked infantile spasms	Xp11.4–Xpter	–	100
Mitochondrial disorders			
MERRF (Myclonus epilepsy and ragged red fibres	Mitochondrial DNA	–	100
MELAS (Mitocondrial myopathy, encephalopathy, lactic acidosis and stroke)	Mitochondrial DNA	–	100

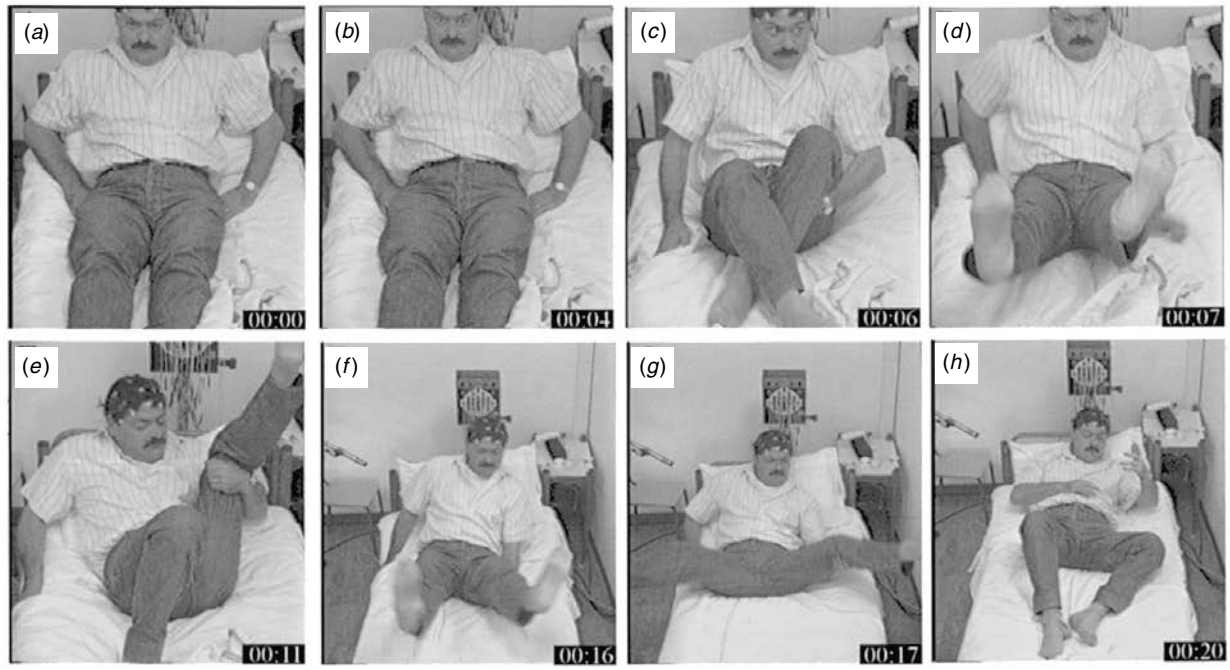

Fig. 74.3. Video recording of a typical hypermotor seizure of frontal lobe origin. In (*a*) the patient has just woken up from sleep. Seizure starts in (*b*) with changing of facial expression. In (*c*)–(*g*) the characteristic motor behaviour appears suddenly with lower limb kicking and thrashing movements. The patient is conscious throughout the episode and tries to hold his legs to prevent involuntary movements (as evident in picture (*e*)). The seizure is over in picture (*h*) and the patient expresses his relief. Numbers on the right bottom corner of each picture indicate time from picture (*a*) in minutes:seconds format.

chromosome 15q24 (Phillips et al., 1998). *De novo* mutations of these genes could be responsible for sporadic cases (Phillips et al., 2001).

Generalized epilepsy with febrile seizures plus (GEFS+)
This syndrome is characterized by heterogeneous phenotypes including febrile seizures (FS) and mild to severe generalized epilepsies (Scheffer & Berkovic, 1997). FS are present in most patients. FS+ are considered fever-related seizures continuing over the age of 6 or associated with afebrile GTCs. FS+ may be associated with absence, myoclonic or atonic seizures. Inheritance is autosomal dominant with 60% penetrance. Mutations of two different genes coding for α1 and for β1 subunit of a voltage-gated sodium channel have been found in different families (Wallace et al., 1998; Escayg et al., 2000).

Familial temporal lobe epilepsy (FTLE)
Two different varieties are described: mesial and lateral FTLE. Onset is during adolescence or adulthood and the course is usually benign. Mesial FTLE is characterized by rising epigastric sensation, psychic symptoms and autonomic phenomena. No loci have been identified (Berkovic et al., 1996). Autosomal dominant lateral TLE is associated with auditory (ringing or humming sounds) or complex visual hallucination and maps to chromosome 10q24 (Ottman et al., 1995).

Benign familial neonatal convulsions (BFNC)
Transmitted with autosomal dominant inheritance, this syndrome manifests on day 2–3 of life with partial seizures that usually disappear within a week. Later seizures are observed in 10% of patients. Two mutations in voltage-gated potassium channel genes (*KCNQ2* and *3*) have been described (Singh et al., 1998; Charlier et al., 1998).

Benign familial infantile convulsions (BFIC)
This autosomal dominant syndrome is characterized by clusters of partial seizures appearing between the ages of 4 and 8 months. Prognosis is good. Two different loci have been identified: one on chromosome 19q and a second on chromosome 16 in patients with associated paroxysmal choreoathetosis (Guipponi et al., 1997; Szepetowski et al., 1997).

Autosomal recessive rolandic epilepsy with paroxysmal exercise-induced dystonia and writer's cramp

The syndrome is characterized by infrequent orobrachial motor seizures during wakefulness, associated with interictal rolandic spikes on EEG, paroxysmal exercise-induced dystonia in childhood, and writer's cramp beginning in childhood and persisting until adolescence (Guerrini et al., 1999a). Linkage analysis points to chromosome 16p within the critical region for benign familial infantile convulsion and choreoathetosis.

Epilepsies with multifactorial inheritance

Most of the idiopathic epilepsies have multifactorial inheritance. Phenotypes in these syndromes derive from the interaction of multiple genes and environmental factors. Penetrance is variable and there is usually an age-dependent expression. A gene for generalized idiopathic epilepsies has been linked to chromosome 8q24 (Zara et al., 1995), and two possible genes for juvenile myoclonic epilepsy have been linked to chromosome 6p (Liu et al., 1995) and 15q24 (Elmsie et al., 1997).

Acquired factors

Pre- and perinatal factors

Multiple perinatal factors can be responsible for epilepsy (Holden et al., 1982). Prenatal causes include cortical malformations, and CNS infections such as toxoplasmosis and cytomegalovirus. The main perinatal factors include hypoxic–ischemic encephalopathy.

Pyridoxine dependency should be suspected in neonates and infants with intractable seizures and excluded by i.v. injection of 50 to 200 mg vitamin B6 during EEG monitoring (Bankier et al., 1983).

Cortical malformations

Cortical malformations are a frequent cause of drug-resistant epilepsies. The use of MRI may permit an early diagnosis (Guerrini et al., 1999b). However, small or microscopic abnormalities escape MRI recognition. Epilepsy can start at any age and progress with variable severity. Mental retardation, focal or bilateral neurological deficit and a positive family history can be observed. Diffuse abnormalities are associated with early onset epileptogenic encephalopathy, usually with infantile spasms. Focal malformations typically induce a focal, drug-resistant epilepsy (Guerrini et al., 1999b). A list of the most common malformations is presented in Table 74.2.

Hippocampal sclerosis

Hippocampal sclerosis is the most frequent lesion observed in human epilepsy. It represents the substrate of the mesial temporal lobe epilepsy syndrome, that accounts for a number of drug-resistant partial epilepsies of adulthood (Baulac et al., 1994). MRI scans can now reliably detect hippocampal sclerosis in most patients (Duncan, 1997). It remains unclear if the lesion is responsible for, or is the consequence of, early-onset prolonged febrile convulsions.

Infections

Febrile illness due to extracerebral causes (upper airway infections, exanthematous diseases) can be responsible for febrile seizures in children below the age of 5. Complicated, prolonged febrile seizures can be both the expression or the cause of CNS structural lesions such as hippocampal sclerosis or HHE syndrome (hemiconvulsion–hemiparesis–epilepsy) (Mahler & McLachlan, 1995), following a fever-related lateralized convulsive status in early infancy (Chauvel et al., 1991). The frequency of HHE syndrome has been reduced since the systematic use of benzodiazepines to treat prolonged febrile seizures. Viral encephalitis, bacterial meningo-encephalitis and cerebral abscess are highly epileptogenic. In children, herpes encephalitis can present as febrile seizures. HIV infection can manifest with epileptic seizures due to direct viral neurotropism or to opportunistic infections.

Cerebral tumours

Epilepsies due to cerebral tumours represent 10–15% of adult-onset epilepsies. On the other hand, epileptic seizures are observed in 20–70% of supratentorial neoplasms (Cascino, 1990). Simple somato-sensory, somato-motor or sensory seizures as well as GTCs are frequent. A brain tumour should be suspected in cases of *de novo* status epilepticus or when there is a gradual changing of clinical characteristics in the course of chronic epilepsy.

Slowly evolving tumours, involving frontal or central cortices are highly epileptogenic. According to pathology, a decreasing epileptogenicity is found in oligodendrogliomas, low-grade astrocytomas, meningiomas, metastases, and glioblastomas. Dermoid, epidermoid and arachnoid cysts have a variable epileptogencity.

Dysembrioplastic neuroepithelial tumours, ganglioglioma, and hamartomas are highly epileptogenic lesions with a low tendency to growth (Cascino, 1990).

Head injury

Post-traumatic epilepsy is fairly common in war-related head injuries (25–50% of cases), but is rare following head

Table 74.2. Main cortical malformations

Malformation type	Epilepsy	Associated signs	MRI
Diffuse malformation			
Agyria (classic lissencephaly)	IS, SGE	Severe mental retardation, quadriparesis	Absent gyral pattern, thickened cortex, vertical sylvian fissure
Pachygyria	IS, SGE	Severe mental retardation	Reduced gyral pattern with thick cortex
Band heterotopia	SPE (variable)	Mental retardation (variable severity)	Double cortex: symmetrical, subcortical grey matter bands, separated from cortex by a white matter band
Periventricular nodular heterotopia	SPE	No signs ⇒ female Severe mental retardation ⇒ male	Periventricular nodules of grey matter
Bilateral regional malformations			
→ Bilateral perisylvian polymicrogyria (congenital, bilateral, perisylvian syndrome)	SGE (variable severity)	Mild to severe mental retardation Oro-facial apraxia	Bilateral perisylvian polymicrogyria with pachigyric appearance of grey matter
Hemispheric malformations			
→ Hemimegalencephaly	IS, SGE, SPE	Mental retardation hemiparesis	Enlarged hemisphere with unilateral gyral malformation; white matter signal abnormalities
Polymicrogyria	SPE, AA, CSWS	Mental retardation hemiparesis	Smaller, polymicrogyric hemisphere
Focal malformations			
Focal cortical dysplasia	Drug-resistant SPE	Related to location and extension	Focal cortical thickening, signal abnormalities in underlying white matter
Focal subcortical heterotopia	SPE (variable severity)	Related to location and extension	Focal grey matter heterotopia within normal looking white matter
Focal polymicrogyria	Variable	Related to location and extension	Focal polymicrogyria, sometimes resembling pseudo-pachigyria
→ Type 1 and 2 schizencephaly	Drug-resistant SPE	No signs ⇒ type 1 Mental retardation, focal deficit ⇒ type 2	Subarachnoid-ventricular fissure, grey matter surrounding the fissure Type 1 ⇒ closed lip schizencephaly Type 2 ⇒ open lip schizencephaly
Complex malformations			
→ Aicardi syndrome	IS, SGE	Mental retardation	Corpus callosum agenesis Corio-retinic alteration Female patients, neuronal migration disorder

Notes:
AA = atypical absences: CSWS = epilepsy with continuous spike-and-wave discharges during slow wave sleep; IS = infantile spasms; SGE = symptomatic generalized epilepsy; SPE = symptomatic partial epilepsy.

injuries in civil life (0.5–5% of cases) (Annegers et al., 1998).

The frequency of early-onset seizures in the first week after a head injury is commensurate with the severity of that injury. These seizures do not always relapse and any treatment started at an early stage can eventually be suspended. Relapsing seizures which onset after the first week can be designated as post-traumatic epilepsy. Penetrating open traumas are more frequently responsible for post-traumatic epilepsy than closed head injuries. Post-traumatic epilepsy appears in around 30–50% of patients with penetrating head injuries. In 70% of patients, epilepsy occurs within 2 years of the injury. Fifty per cent of patients who develop post-traumatic epilepsy will achieve remission.

The presence of neurologic deficit due to cortical damage or intracerebral hemorrhage supports a diagnosis of post-traumatic epilepsy. The presence of at least two of the following: a post-traumatic coma/amnesia longer than 24 hours, a depressed skull fracture or early-onset seizures can support the diagnosis.

Cerebrovascular disease

Cerebrovascular accidents (CVA) are the most frequent cause of epilepsy in the elderly. Simple partial seizures can sometimes precede the onset of a CVA. Acute seizures during a CVA are mostly observed in intracerebral hemorrhages (5–25% of cases) and cerebral venous thrombosis. After a CVA, seizures appear within two years and are more frequently associated with ischemic (10% of cases) than with hemorrhagic lesions (5% of cases). Arterio-venous malformations are associated with epilepsy in 60% of patients (Crawford et al., 1986). If epilepsy proves drug resistant, surgical excision or endovascular embolization should be performed. Small aneurysms can produce seizures in the acute phase following rupture. Cavernous angiomas are always associated with partial, drug-resistant epilepsy (Turjman et al., 1995). Cerebral vasculitis in systemic lupus erythematosus or eclampsia is associated with epileptic seizures.

Toxic, pharmacologic and metabolic factors

Toxic factors

Alcohol can typically induce seizures in patients with epilepsy and excessive intake can precipitate isolated seizures. Abstinence from alcohol by an alcoholic can be linked to GTCs which manifest within a few hours or days after the last intake of alcohol. Alcohol-related epilepsy is characterized by relapsing partial or generalized seizures, appearing in a chronic alcohol-abuser, which occur independently from acute alcohol toxicity or abstinence. Antiepileptic drug treatment is often necessary.

Use of cocaine, codeine, amphetamines and phencyclidine can be associated with GTCs.

Pharmacologic factors

Psychotropic drugs may precipitate seizures following chronic use (antipsychotic drugs: limipramine, fluoxetine), intoxication (antidepressants: lithium), or abstinence (benzodiazepines, barbituarates) (Table 74.3).

Metabolic factors

Hyponatremia and hypocalcemia are highly epileptogenic. Hypoglycemia is associated with isolated GTC seizures, while hyperglycemia with hyperosmolarity can present with recurrent focal seizures.

Myoclonic seizures evolving to myoclonic status are common in uremic encephalopathy. Massive myoclonus is typically observed in postanoxic encephalopathy that can sometimes present with action-intention myoclonus, typical of Lance–Adams syndrome.

Neurological diseases

Some infantile syndromes such as Rett's syndrome and autism are frequently associated with epilepsy. Rarely, epileptic seizures can be observed in the evolution of multiple sclerosis (1.3–10.8% of patients). Epilepsy can be observed in around 10% of patients with Alzheimer's disease and in some patients with Huntington's disease.

Classification of the epileptic syndromes (Table 74.4)

A classification of the epilepsies should allow us to characterize them as different conditions and diseases responsible for seizure recurrence. However, since our knowledge of the mechanisms of epileptogenesis is limited and does not allow us to draw up a classification based upon pathogenesis, a simpler approach is to adopt a syndromic classification. A syndrome is characterized by a group of signs and symptoms that occur in constant association. They include seizure types, characteristic clinical history, clinical signs associated with the epilepsy and neurophysiological/neuroradiological findings. The classification is based on two axes: symptoms and etiology (Commission, 1989).

According to symptoms, epilepsies can be classified as:

(i) *Generalized*: if all seizures are generalized. If motor manifestations are present, they are bilateral. Interictal and ictal EEG show generalized spike, spike-and-wave, polyspike-and-wave discharges.

(ii) *Partial* or *focal*: if seizures originate from a circumscribed cortical region, the epileptogenic zone. Clinical manifestations support a focal onset of the

Table 74.3. Proconvulsant drugs (from Garcia and Alldredge, 1994 modified)

Psychotropic drugs
Antidepressant
Fluoxetine[e]
Maprotiline[e]
Amitryptiline[d]
Imipramine[d]
Nortryptiline[d]
Desipramine[d]
Doxepin[d]
Protriptyline[d]
MAOI[c]

Lithium[c]

Antipsychotic drugs
Clozapine[e]
Phenothiazines[d] (chlorpromazine and derivatives)
Haloperidol and other butyrophenones[c]

Hypnotics
Benzodiazepines (withdrawal)[e]
Barbiturites (withdrawal)[e]
Meprobamate (withdrawal)[c]

Flumazenil[a]
(in case of benzodiazepine intoxication)

Antiepileptic drugs
Phenytoin[a] (absence seizures)
Carbamazepine[a] (absence seizures)
Vigabatrin[a] (absence seizures)

Anesthetic and analgesic
Meperidine[e]
Propofol[d]
Lidocaine[c]
Etomidate[b]
Enflurane[b]
Naloxone[b]

Iodine contrast media[e]

Antibiotics
Pencillins[e]
Isoniazid[e]
Mefloquine[d]
Nalidixic acid[c]
Norfloxacin[c]
Ciprofloxacin[c]

Antiviral drugs
Zidovudine[d]
Aciclovir[c]
Ganciclovir[e]

Antineoplastics and immunosuppresants
Cyclosporin[e]
Ifosfamide[d]
Chlorambucil[d]
Busulfan[d]

Respiratory system drugs
Theophylline and derivates[e]
Topical nasal decongestants, containing phenylpropanolamine[d]

Cardiovascular drugs
Beta-blockers[b]
Mexiletine[b]

Alcohol
Alcohol withdrawal[e]
Alcohol intoxication[d]

Recreational drugs
Cocaine[e]
Amphetamines[e]
Codeine (very high doses)[d]
Phencyclidine[d]
Heroin[c]

Notes:
[a] Epileptogenic only in particular situations.
[b] Rarely epileptogenic.
[c] Low epileptogenic activity.
[d] Moderate epileptogenic activity.
[e] High epileptogenic activity.

epileptic discharge with or without subsequent spread. Ictal and/or interictal EEG show focal abnormalities.

Etiologic classification differentiates:

(i) *Idiopathic epilepsies*: that are not associated with any brain lesions. Background EEG activity is normal. They are considered to be due to a genetic predisposition or to a specific mode of inheritance.

(ii) *Symptomatic epilepsies*: in which focal or diffuse lesions in CNS are present. Structural neuroimaging or biological tests can detect the abnormality.

(iii) *Cryptogenic epilepsies*: are considered as symptomatic forms whose causes remains undetectable. They are not associated with an obvious CNS lesion but lack clinical and neurophysiological characteristics of the idiopathic forms.

Table 74.4. International classification of epileptic seizures

Partial (Focal, local) seizures
Simple partial seizure (without impairment of consciousness)
With motor signs
With sensory symptoms
With autonomic symptoms or signs
With psychic symptoms
Complex partial seizures (with impairment of consciousness)
Simple partial onset followed by impairment of consciousness
With simple partial features followed by impaired consciousness
With automatisms
With impairment of consciousness at onset
With impairment of consciousness only
With automatisms
Partial seizures evolving to secondarily generalized seizures
Simple partial seizures evolving to generalized seizures
Complex partial seizures evolving to generalized seizures
Simple partial seizures evolving to complex partial seizures evolving to generalized seizures
Generalized seizures
Absence seizures
Absences
Atypical absences
Myoclonic seizures
Tonic seizures
Atonic seizures
Clonic seizures
Tonic–clonic seizures
Unclassified epileptic seizures (lack of information)

Source: From Epilepsia (1981), **22**, 489–501.

Combining both symptoms and etiology it is possible to identify the clinical entities (Table 74.4). Seizure classification is indicated in Table 74.5 (Commission, 1981).

Focal epilepsies and epileptic syndromes

Idiopathic partial epilepsies (IPEs)

IPEs are the most frequent epileptic syndromes in children and adolescents. They have an age-dependent course and idiopathic epilepsies may frequently occur in other family members. Seizures are usually brief and can be clustered at the onset. Focal EEG abnormalities have a characteristic morphology, which increase during sleep. Response to antiepileptic drugs (AEDs) is usually satisfactory and the

Table 74.5. International classification of epilepsies and epileptic syndromes

Focal epilepsies/epileptic syndromes:
Idiopathic:
Benign childhood epilepsy with centrotemporal spikes
Childhood epilepsy with occipital paroxysms
Primary reading epilepsy
Symptomatic
Chronic progressive epilepsia partialis continua of childhood
Epilepsy characterized by seizures with specific modes of precipitation
Cryptogenic
The symptomatic and cryptogenic categories comprise syndromes of great individual variability that are based mainly on:
Seizure types (according to International Classification of Epileptic Seizures)
Anatomic localization:
Temporal lobe epilepsies
Frontal lobe epilepsies
Parietal lobe epilepsies
Occipital lobe epilepsies
Bi- and multilobar epilepsies
Etiology (for symptomatic epilepsies)
Specific modes of precipitation
Generalized Epilepsies/Epileptic syndromes
Idiopathic:
Benign familial neonatal convulsions
Benign neonatal convulsions
Benign myoclonic epilepsies of infancy
Childhood absence epilepsy (pyknolepsy)
Juvenile absence epilepsy
Juvenile myoclonic epilepsy
Epilepsy with grand mal (GTC) seizures on awaking
Other idiopathic generalized epilepsies not defined above
Epilepsy with seizures precipitated by specific modes of activation
Cryptogenic or symptomatic
West syndrome
Lennox–Gastaut syndrome
Epilepsy with myoclonic–astatic seizures
Epilepsy with myoclonic absences
Symptomatic
Non-specific etiology
Early myoclonic encephalopathy
Early infantile encephalopathy with suppression–bursts
Other symptomatic generalized epilepsies not defined above
Specific syndrome
Neonate
Non-ketotic hyperglycinemia
D-glyceridacidemia

Table 74.5. (*cont.*)

Infant
Phenylketonuria
Phenylketonuria with biopterin deficiency
Tay–Sachs and Sandhoff disease
Early infantile ceroid lipofuscinosis (Santavouri–Haltia–Hagberg)
Pyridoxine dependency
Child
Late infantile ceroid lipofuscinosis (Jansky–Bielschowski)
Infantile Huntington's disease
Child and adolescent
Gaucher's disease, juvenile form
Juvenile ceroid lipofuscinosis (Spielmeyer–Vogt–Sjögren)
Lafora disease
Progressive myoclonus epilepsy
Cherry red spot myoclonus
Mitochondrial myopathy with abnormal lactate–pyruvate metabolism
Adult
Adult ceroid lipofuscinosis (Kuf's disease)
Epilepsies/epileptic syndromes undetermined as to whether focal or generalized
With both partial and generalized seizures
Neonatal seizures
Severe myoclonic epilepsy in infancy
Epilepsy with continuous spike-waves during sleep
Acquired epileptic aphasia (Landau–Kleffner syndrome)
Other undetermined epilepsies not defined above
Without unequivocal generalized or focal features
Special syndromes
Situation-related seizures
Febrile convulsions
Isolated seizure/status epilepticus
Seizures due to acute metabolic or toxic factors

prognosis is good with remission by late adolescence. It is unclear whether AED treatment influences the outcome (Ambrosetto & Tassinari, 1990).

Benign epilepsy of childhood with centro-temporal spikes (BECTS)

BECTS is the most frequent epileptic syndrome in childhood. Age at seizure onset ranges between 3 and 13 years. Prognosis is excellent with remission by adolescence (Lerman, 1992). Seizures are typically hemifacial, involving mainly the lips, tongue and pharyngeal–laryngeal muscles (Lerman, 1992). Sensory symptoms can involve the same body parts that later present motor phenomena (Lerman, 1992). Sometimes the homolateral upper limb is involved. Attacks are typically sleep related and can determine arousal with ictal anarthria without loss of consciousness. Secondary generalization can supervene. Typically parents are awakened by a grunting sound. They find the child dribbling profusely and unable to speak. Interictal EEG shows typical high amplitude, slow biphasic centro-temporal spikes, with a characteristic tangential dipolar distribution. Spikes greatly increase in frequency and often become bilateral during sleep.

AED treatment can be avoided if seizures are brief and appear only during sleep. If the treatment is necessary carbamazepine or valproate are preferred (Lerman, 1992).

Benign epilepsy of childhood with occipital paroxysms (BEOP)

BEOP was originally described by Gastaut in 1982 as an IPE with age of onset between 15 months and 17 years and with visual seizures (illusions, elementary hallucinations, ictal blindness) evolving either to hemiclonic or complex partial seizures with or without secondary generalization. In around 25% of Gastaut's patients, a migraine-type postictal headache was reported (Gastaut, 1992). Evolution was generally favourable with remission by adulthood. Interictal EEG showed high amplitude, unilateral or bilateral, synchronous or asynchronous, occipital spike-and-wave facilitated by eye closure.

A subset of children with BEOP present brief or prolonged sleep-related partial seizures characterized by tonic eye and head deviation, vomiting and eventually hemiclonic or secondary generalization (Ferrie et al., 1997). The age at seizure onset is between 2 and 8 years. Prognosis is excellent with remission by the age of 12 and with most children having suffered only one seizure (Ferrie et al., 1997).

The EEG abnormalities in this syndrome are not as specific as those of BECTS, in fact similar abnormalities can be observed in cryptogenic or symptomatic focal epilepsies with a less favourable prognosis (Guerrini et al., 2000).

Primary reading epilepsy (PRE)

This type of epilepsy is classified as an IPE, with age-related onset and a specific mode of precipitation (Commission, 1989) but it appears to be not as homogenous as previously considered (Koutroumanidis et al., 1998). Most patients present orofacial/jaw myoclonus induced by prolonged reading aloud. Consciousness is preserved but jerks can progress to a GTCs if reading is not interrupted. In a minority of patients prolonged reading induces partial seizures manifesting as alexia (Koutroumanidis et al., 1998). The average age at onset is 17.7 years. Treatment is not always

necessary, in that seizures are rare and strictly related to reading. Valproate is the most effective AED.

Several other idiopathic partial epilepsy syndromes have been described over the last 15 years (Genton & Guerrini, 1994). While some of these syndromes have been confirmed with several reports, others appear simply to be a variant of the main syndrome groups. It is important to recognize them in that their idiopathic context, EEG characteristics and prognosis are usually benign.

Symptomatic partial epilepsies (SPEs)

Epilepsia partialis continua (EPC) or Kojewnikow syndrome

Two different variants of Kojewnikow syndrome are known.

Type 1

This is observed in children and adults (Bancaud, 1992). An epileptogenic lesion (vascular abnormality, tumour and inflammatory or post-traumatic lesion) involves the motor cortex. Partial motor seizures are usually followed by semi-continuous focal myoclonic jerks involving the same body segment and resistant to AEDs. Epilepsy does not evolve and surgery can be effective at the cost of major motor impairment.

Type 2

This is a progressive neurological disorder known as Rasmussen encephalitis (Hart & Andermann, 2000). It is a chronic encephalitis that can be associated with antibodies against the glutamate receptor 3 in some patients (Andrews et al., 1997). Children present progressive hemiparesis, dystonic movements and cognitive deterioration. MRI shows progressive atrophy of one hemisphere. Medical treatment relies on steroids, antiviral agents and immunoglobulins, but it is usually of little help. Functional hemispherectomy can stop disease progression but it is associated with a variable degree of residual disability.

Epilepsies characterized by seizures with specific modes of precipitation

Different epilepsy syndromes are included in this group usually classified according to the stimulus that provokes them. As an example, we shall discuss startle and hearing-induced epilepsy.

Startle-induced epilepsy

This affects infants, children or young adults with static or progressive encephalopathy. It is rarely observed in neurologically intact individuals. An unexpected noise or a sudden movement can induce a focal or generalized tonic seizure that lasts for 1 to 60 seconds (Rosenow & Lüders, 2000a). Spontaneous seizures are reported by 40 to 95% of patients.

Hearing-induced epilepsy

Complex partial or secondarily generalized seizures can be induced by hearing sounds or music. Age at epilepsy onset varies between 10 and 50 years (Rosenow & Lüders, 2000b). Avoiding the provocative stimulus can reduce seizure frequency but it can be responsible for social isolation.

Lobar epilepsies

These represent the majority of partial epilepsies and are defined according to seizure semiology pointing to an anatomic location. Epileptic discharges can spread and it is therefore important to identify the very first sign or symptom of a seizure to correctly localize its onset. Site definition regarding the onset of focal seizures, when based on clinical and surface EEG findings alone may be very difficult when neuroimaging is normal. Attribution to a definite lobar origin may be misleading in the absence of a highly characteristic clustering of symptoms, in that the epileptogenic area may not respect the anatomic limits of the cerebral lobes. In addition, seizure spread from clinically silent areas may be rapid producing unresponsiveness before subjective symptoms may be reported or memorized.

Temporal lobe epilepsies

These are the most frequent type of partial epilepsies (Bancaud, 1987). Onset is during childhood or early adulthood. Seizures are simple or complex partial and are of relatively long duration (1–2 min). Their onset is characterized by visceral symptoms (rising epigastric sensation, thoracic constriction, hot or cold sensation, olfactory hallucinations) or by psychic or affective symptoms (dreamy state, *déjà-vu*, *déjà-vecu*), usually accompanied or followed by vegetative manifestations (pallor, flushing, tachycardia, poly- or bradypnea, piloerection, midriasis, or sweating). Disruption of consciousness or 'unresponsiveness' appears later and can fluctuate. Sometimes it is not present at all even during automatisms that consist of oro-alimentary behaviour (lip-smacking, swallowing) or gestural automatisms that begin later (Munari et al., 1980). Late somato-motor manifestations such as dystonic posturing of the upper limb, contralateral to the epileptic discharge, represent the propagation to extratemporal cortical regions or activation of subcortical efferent systems. The postictal phase is characterized by prolonged confusion occasionally accompanied by walking.

Aphasia is observed when the dominant hemisphere is involved.

Lateral or neocortical temporal lobe epilepsy
This is characterized by auditory hallucinations or pseudo-vertigo and by aphasic speech arrest.

Mesial temporal lobe epilepsy
This is manifested by a highly characteristic ictal pattern, including epigastric sensation, psychomotor arrest and staring, associated with mastication, lip smacking (oro-alimentary automatisms) and later gestural automatisms in the upper limb, homolateral to the epileptic discharges. Hippocampal sclerosis is frequently found on MRI scans.

Interictal EEGs can be normal or show unilateral or bilateral temporal abnormalities.

Frontal lobe epilepsies
These are frequent (Bancaud & Talairach, 1992). Seizures are usually brief (seconds to tens of seconds) and sleep related. They are often collected in clusters and are highly stereotyped in the same patient. Clinical onset is marked by tonic or postural manifestations causing disabling drop attacks. Disruption of consciousness is highly variable but postictal recovery is very fast. The attack can consist of cephalic, thoracic or abdominal sensation. Other patients can describe psychic symptoms such as forced thought. Secondarily generalized or partial status epilepticus are common. Subjective symptoms are usually ill defined.

Posterior frontal lobe seizures
Seizures emanating from the supplementary motor area are characterized by speech arrest or palialia (involuntary repetition of the same words or sentences) when the dominant hemisphere is involved. This is followed by abduction and elevation of the upper limb, contralateral to epileptic discharge and version of head and eyes to the same side (fencing posture). Secondary generalization is rare.

When the dorsolateral convexity is involved, a contralateral tonic posturing is observed. Frequently, the discharge becomes bilateral with secondary generalization. The involvement of Brodmann's area 4 produces contralateral focal clonic movements. Finally, speech arrest without loss of consciousness is observed when epileptic activity spreads to the *pes* of the third frontal gyrus.

Intermediate frontal lobe seizures
These are associated with a very fast spread of epileptic discharge to other frontal lobe areas. Bilateral tonic manifestations appear suddenly, and can be responsible for a patient's falling. Axial tonic seizures with flexion of head and trunk associated with facial grimace, are typical. The patient can continuously moan and present apnea, due to tonic contraction of the diaphragm.

Anterior frontal lobe seizures
These have a longer duration than other frontal seizures. Secondary generalization is rare. An automatic motor activity appears at seizure onset and involves either upper limbs (fingers snapping, arms windmilling), lower limbs (cycling, rhythmic flexion–extension) or girdles (rocking of pelvis, sexual automatisms). Verbal stereotypes are sometimes observed.

Involvement of specific frontal areas can be suspected when clustering of characteristic symptoms occurs. Forced thought or isolated alteration of awareness (*frontal pseudo-absences*) points to the fronto-polar area. Olfactory hallucination with intense fear, bradycardia and micturition suggests the involvement of fronto-orbital regions. Complex and frantic motor behaviour with screaming and facial expression suggesting terror or rage are typical of anterior *girus cinguli* involvement. Interictal EEG can be normal, but it is sometimes characterized by widespread abnormalities that enable neither lateralization nor localization.

Central region epilepsies
These emanate from the perirolandic cortex (Chauvel et al., 1992). Typical signs include clonic motor or elementary sensory phenomena involving the contralateral hemibody with or without march. Secondary generalization is rare. Some of the seizures originating from this region can be precipitated by sensory or proprioceptive stimulation.

Seizures emanating from the opercular–insular region present with oro-alimentary manifestations such as mastication, swallowing, and salivation. Gustative hallucinations or illusions can be associated. Interictal or ictal abnormalities can be very mild.

Parietal lobe epilepsies
These are rare (Salanova et al., 1995). Fast spreading of epileptic discharges to contiguous lobes (frontal, temporal or occipital) can mask the initial signs or symptoms. Alteration of higher cortical function such as limb movement sensation, and autoscopia (seeing of one's own body image) can be the manifestation of non-dominant hemisphere involvement. In some patients unilateral spatial agnosia can only be recognized because they tend to look preferentially to one side that is homolateral to the epileptic discharge. Visual illusions (macropsia, micropsia, metamorphopsia) are present when posterior parietal

cortex or parietal–occipital junction are involved. Clear rotatory vertigo is associated to epileptic discharge in the inferior parietal region or temporo-parietal junction. Slow rotation of the body directed ipsilaterally to the epileptic discharge and dystonic posturing of the contralateral upper limb are usually due to an involvement of inferior parietal cortex. Interictal and ictal EEG abnormalities may be widespread involving central, parietal, temporal and occipital regions.

Occipital lobe epilepsies

These are rare and difficult to identify correctly because rapid spreading of epileptic discharge to contiguous lobes may mask initial symptoms (Guerrini et al., 2000). Elementary visual hallucinations (coloured blobs, flashes of light) associated with peri-ictal peripheral visual field deficit (hemianopia) are typical and testify to the involvement of the contralateral pericalcarine region. Ictal or postictal headache are frequent, sometimes mimicking migraine attacks. Eye movements are frequent in the course of the seizure. They can be phasic (oculo-clonic movement or epileptic nystagmus) or tonic (slow version of eyes contraleral to the epileptic discharge). Occipital lobe seizures can rapidly propagate to the frontal region, being responsible for the patient's falling, or to the mesial temporal lobe. Interictal EEG abnormalities involve the posterior regions and are usually increased during eye closure.

Cryptogenic partial epilepsies (CPEs)

CPEs do not substantially differ, in terms of their clinical presentation, from SPEs. This nosologic category is intended to include patients suffering from SPEs whose cause cannot be identified with the available diagnostic tools. Since high-resolution MRI scans have become available the number of patients with CPEs has dropped remarkably. The definition of CPEs has apparently been misinterpreted and some authors have lumped CPEs and IPEs together. CPEs do not fulfil the clinical and EEG characteristics of IPEs, although their prognosis is in general better than SPEs.

Generalized epilepsies and epileptic syndromes

Generalized epilepsies are a heterogeneous group of syndromes including benign and frequent forms on one side of the spectrum and rare and severe forms on the other. Seizures are generalized and EEG abnormalities bilateral and synchronous.

Idiopathic generalized epilepsies (IGEs)

IGEs are frequent and usually benign syndromes. Their onset is in infancy or adolescence. A family history of epilepsy is frequent. IGEs seem to be genetically determined even if the exact mechanism of inheritance is known only in a minority of them. Common characteristics to all IGEs syndromes are as follows.

(i) Primary generalized seizures are *Generalized tonic–clonic seizures (GTCs)* absence, and myoclonic seizures. Myoclonic and GTCs usually appear during wakefulness or upon awakening. GTCs have a sudden onset with immediate loss of consciousness. There is a brief tonic phase (10–30 s) with a whole body tonic contraction associated with a loud scream and vegetative symptoms such as tachycardia, midriasis, increased blood pressure, and apnea. Tongue biting if present, is produced at this stage. The clonic phase lasts around 30 s–1 minute and is characterized by bilateral clonic jerks that gradually reduce in intensity and frequency. The postictal phase which can last for several minutes up to hours, is characterized by body relaxation, hypotonia, and sleep. Urination, if present, takes place at this stage. Finally the patient gradually recovers and appears confused, presenting sometimes automatisms, headache, and muscle pain. *Typical absence seizures* are brief (5–20 s). They appear mostly in children and are clinically characterized by sudden interruption of ongoing activity and staring straight ahead or drifting upwards. There is complete loss of awareness during the seizure. The onset and offset is sharp. Possible associated manifestations include slight rhythmic (3 Hz) eyelid myoclonus, slight decrement or increment of postural tone, simple gestural automatisms (if the absence is of long duration) and vegetative symptoms (urinary incontinence, pupil dilatation, pallor, flushing, tachycardia, change in blood pressure). Absence seizures can be easily produced if the child is asked to hyperventilate. Concomitant EEG abnormalities are typical generalized spike-and wave discharge at 3 Hz.

Myoclonic seizures are present with brief symmetrical muscular jerks of different intensity. Proximal muscles such as girdle muscles are mostly involved. During stronger attacks, there is possibility of the patient falling over. The patient is usually fully conscious during the seizure. Myoclonic seizures may often be triggered by photic stimulation.

(ii) Interictal EEG shows generalized spike-and-wave discharges at a frequency higher than 3 Hz.

(iii) Drug treatment (especially valproic acid) is highly effective.

Benign familial neonatal convulsions (BFNC)
See Etiology of epilepsy section (p. 1250).

Benign neonatal convulsions (BNC)
BNC are manifested as hemiclonic seizures migrating from one side to the other, or frequent apnea spells usually taking place on day 5 of life. Tonic seizures are never observed. Evolution is benign with permanent remission.

Benign myoclonic epilepsy in infants (BMEI)
This is a rare syndrome characterized by brief generalized myoclonic seizures with onset during the first or second year of life in otherwise normal children (Dravet et al., 1992a). Valproic acid is effective in controlling jerks. Rare cases are reported with behavioural problems or GTCs appearing during adolescence. Ictal EEG shows generalized polyspike-and-wave discharges, which are time locked with the myoclonic jerks. Interictal abnormalities are very rare.

Childhood absence epilepsy (CAE)
This is a frequent form of IGE with onset in school-aged normal children. Children present very frequent typical absence seizures (up to 200–300 per day). Interictal EEG shows normal background activity and generalized 3 Hz, spike-and-wave discharges that translate into a clinical seizure, if their duration outlasts 4–5 seconds.

Evolution is quite, though not uniformly benign. Treatment with AEDs (valproic acid, ethosuximide or lamotrigine) controls absence seizures, which tend to disappear in adolescence. Phenobarbitone and carbamazepine are not effective and can even increase seizure frequency (Guerrini et al., 1998). GTC seizures can appear from adolescence in one-third of cases. Late onset (above age 8), initial drug resistance and photosensitivity are associated with a less benign prognosis (see Juvenile absence epilepsy).

Typical absence seizures are also part of other rare syndromes, which are not included in the classification, such as eyelid myoclonus with absences and perioral myoclonus with absences.

Juvenile absence epilepsy (JAE)
JAE has its onset around puberty and is characterized by rare typical absence seizures which cluster upon awakening (Wolf, 1992a). In 80% of patients, GTC seizures are also present. Valproic acid is effective. Ictal EEG can show either a typical 3 Hz or a faster (4–5 Hz) spike-and-wave discharge.

Juvenile myoclonic epilepsy (JME)
JME affects around 4% of all patients with epilepsy referred to different epilepsy centres in Europe (Wolf, 1992b). Its onset is between age 6 and 25 years with a peak incidence between 12 and 17 years. Myoclonic seizures are always present. They usually involve the face and the upper limbs. Consciousness is retained and the patient may fall to the ground if the lower limbs are involved. Seizures are typically experienced on awakening when they interfere with fine motor tasks.

GTCs are observed in 90% of patients. They are preceded by a crescendo of bilateral jerks and bring the patient to medical attention, while myoclonic seizures can go unnoticed for months or even years. Ten to 15% of patients can present brief absence seizures. Clinical or EEG photosensitivity is present in 30–40% patients. Sleep deprivation and alcohol intake can be triggering factors, especially for GTCs. Interictal EEG shows generalized or asymmetric polyspike-and-wave discharges at 3 Hz or faster. Myoclonic jerks are time-locked to polyspike-and-wave complexes. A characteristic increase in polyspike-and-wave discharges is observed upon awakening (Fittipaldi et al., 2001).

JME is genetically determined, possibly through a polygenic inheritance (see Etiology of epilepsy section (p. 1250) for details).

Response to treatment (valproic acid, primidone, benzodiazepines) is usually good but JME is a pharmacodependent epilepsy. Withdrawal of AEDs is associated with relapse in 90% of patients, even late in life. Carbamazepine use in patients with JME is associated with seizure worsening, rarely escalating to status epilepticus.

Epilepsy with grand mal seizure on awakening (GMA)
GMA develops during adolescence and it is more frequent in female patients. GTC seizures take place mostly or exclusively within 2 hours of awakening or during evening relaxation. Sleep deprivation, high alcohol intake and induced arousals from sleep are all triggering factors. Interictal EEG can be completely normal or can show generalized spike/polyspike-and-wave discharges that are increased upon awakening. They tend to cluster in the early minutes after arousal from sleep (Fittipaldi et al., 2001).

JAE, JME, and GMA create a syndrome spectrum partially overlapping in age at onset and seizure characterization. It is possible that some patients diagnosed with GMA have JME (Delgado-Escueta et al., 2001).

Epilepsy with seizures precipitated by specific modes of activation
This group is mainly constituted by photosensitive or visual sensitive epilepsy. Visual sensitive epilepsy is a

common manifestation among IGEs, but it can also be found in other generalized as well as partial epilepsies. In pure photosensitive IGEs, seizures are exclusively triggered by photic stimuli such as sunlight through tree foliage, sunlight reflected from water surfaces, stroboscopic light in discos and TV or computer screens. Seizure types are GTC (84% of patients), absence (6%), partial (2.5%), and myoclonic (1.5%) (Binnie & Jeavons, 1992). EEG shows characteristics overlapping IGEs. The photosensitive range should carefully be defined, finding the lowest and highest IPS frequency capable of generating a photoparoxysmal response. AED treatment can have incomplete efficacy because patients may be very sensitive to light or compulsively self-induce seizures. It is essential to teach patients to avoid causative stimuli and/or to occlude one eye in front of them. Dark lenses can sometimes be beneficial.

Some patients are exclusively sensitive to high contrast patterns (blinds, wallpaper). In *photosensitive occipital lobe epilepsy* partial seizures can be induced by photic stimluation (video-games, TV) (Guerrini et al., 1995). They can last several minutes and are characterized by visual symptoms (colourful blobs, flashing light, followed by amaurosis), followed by vegetative symptoms and headache (Guerrini et al., 1995). Clinical characteristics and age at onset around adolescence, partially overlap with those of migraine from which the disorder should be differentiated.

Cryptogenic or symptomatic generalized epilepsies (CGE or SGE)

Four syndromes are included among CGE or SGE. All of them usually have a guarded prognosis.

West syndrome (WS)

WS is characterized by the triad, which is sometimes incomplete, of infantile spasms, developmental arrest, and hypsarrhythmia from the Greek word 'hypsarrhythmia': its own rhythm, appearing during the first year of life (Dulac et al., 1993). Incidence is around 1 in every 5000 children. Infantile spasms usually occur in clusters upon awakening or falling asleep. Each cluster can consist of several spasms whose intensity and frequency follow an increasing-plateau-decreasing pattern. Thus the first spasms in a cluster may be barely visible, presenting a forced opening of the eyes or slight nodding of the head. Gradually, they become more evident and consist of a brief (0.5–2 s) tonic contraction of the neck and trunk in flexion, extension or in a mixed flexed–extended posture. Upper limbs are fast abducted or adducted. Other partial or generalized seizures can be present in some children before, during or after the spasm cluster. Development regression usually accompanies spasm onset but it can precede it. The interictal EEG is highly disorganized. It features high amplitude slow waves, spikes or sharp waves, whose spatio-temporal distribution is anarchic. The ictal EEG is characterized by pseudo-periodic slow polyphasic EEG discharges that are concomitant with the spasms. Occasionally, EEG activity related to spasms is a diffuse electrodecremental pattern. Electromyographic activity from deltoids and neck muscles shows a characteristic rhomboid pattern during the spasm, usually lasting 0.5–2 seconds.

The etiology is divided between symptomatic forms (around 65–70% of cases), bearing a severe prognosis, and a cryptogenic form (30–35% of cases) with a variable evolution. Different cerebral lesions can be associated with WS, in particular anoxic encephalopathies, cytomegalovirus infections, postischemic porencephaly and cerebral malformations (agyria–pachygyria spectrum, focal cortical dysplasia, Down's syndrome). Tuberous sclerosis is the single most frequent specific etiology. Defined metabolic disorders such as phenylketonuria, non-ketotic hyperglycinemia, and mitochondrial encephalopathies, are rarely responsible for WS. Major AEDs are of little help in treating infantile spasms. ACTH and steroids can be immediately effective in suppressing spasms but the long-term effects on cognitive regression are still debated. Some children respond to valproic acid or benzodiazepines. Spasms in children with tuberous sclerosis, or other brain malformations, respond to vigabatrin (Chiron et al., 1990).

Lennox–Gastaut syndrome (LGS)

LGS is a severe form of childhood epilepsy (Genton et al., 2000). Its definition is based on clinical and EEG characteristics. Seizure types associated to LGS include atonic seizures, tonic seizures and atypical absences. Generalized 1–2.5 Hz spike-and-wave discharges are the characteristic interictal EEG pattern. LGS is usually drug resistant from early stages and it is accompanied by mental retardation and behavioural problems.

Onset is before 8 years of age with a peak incidence between 3 and 5.

Tonic seizures are the most characteristic type of seizure. They consist of a sustained, symmetric or asymmetric body contraction lasting usually between 5 and 20 seconds and involving the whole body or just the neck and upper girdle muscles (axo-rhizomielic seizures) (Fig. 74.4). Unresponsiveness is constantly present during the attacks. Sleep facilitates their appearance but they can also manifest during wakefulness, being responsible for traumatic drop attacks. They may cluster, sometimes evolving to status epilepticus. The ictal EEG shows a characteristic

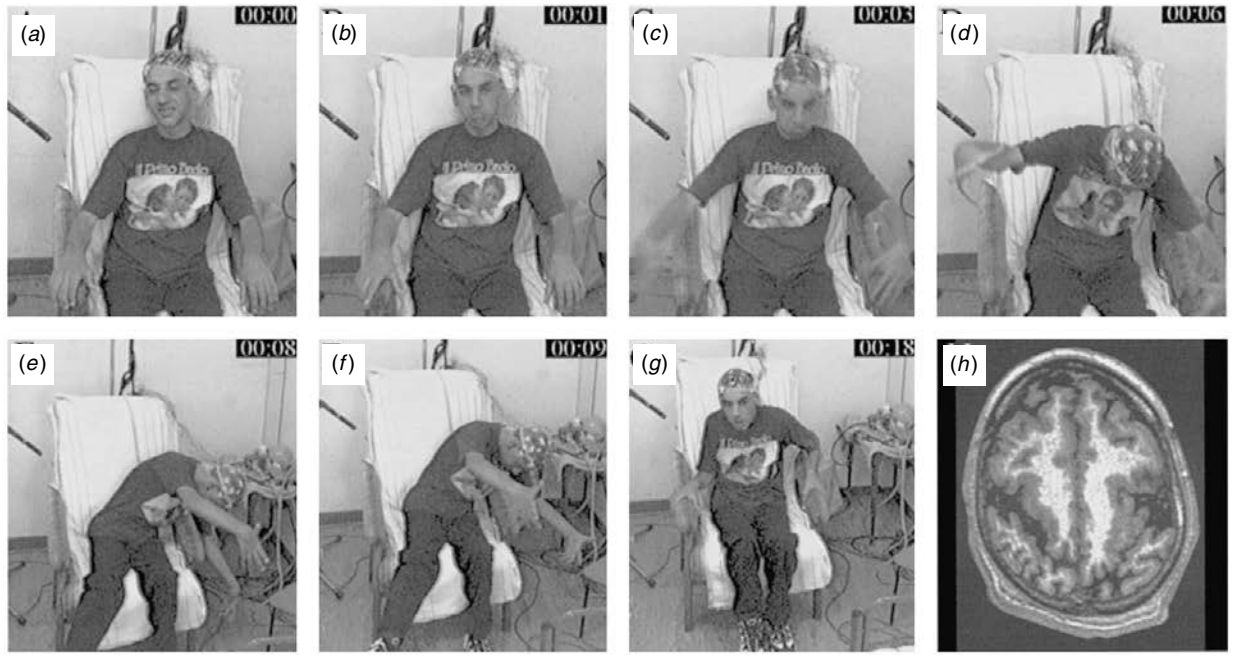

Fig. 74.4. Video recording of a tonic seizure in a patient with symptomatic Lennox–Gastaut syndrome due to bilateral perisylvian polymicrogyria. In (*a*) the patient is talking with the EEG technician and laughing. Seizure starts in (*b*) with change of facial expression (pouting). A contraction involves the upper limbs and the axial muscles, producing a relatively slow flexion of the trunk and abduction and extension of both upper limbs (pictures (*c*)–(*f*)). In (*g*) the tonic seizure has ended and the patient regains the original posture. Numbers on the right top corner of each picture indicate time from the picture (*a*) in minutes:seconds format. An axial T_1-weighted MRI scan from the same patient is presented in picture (*h*). The Silvian fissures appear open and surrounded by a thick cortex.

10 Hz polyspike generalized discharge, lasting as long as the tonic contraction (Fig. 74.5).

Atonic seizures are characterized by decrease or complete inhibition of postural tone. They manifest as head nodding, dropping of the jaw or of a limb or falls, leaving the patient motionless on the ground. Pure atonic seizures are, however, exceedingly rare. The ictal EEG usually is characterized by generalized slow spike-and-wave discharges.

Atypical absences are characterized by incomplete loss of consciousness appearing as a slight confusion and by a progressive onset and offset. Frequently associated manifestations are postural tone, decrement or increment. Ictal EEG shows a 1–2.5 Hz spike-and-wave discharge lasting several seconds. Non-convulsive status epilepticus can easily supervene in children with LGS.

Generalized myoclonic jerks, GTC or partial seizures are observed in some patients. Interictal EEG shows slow background activity associated with frequent generalized 1–2.5 Hz spike-and-wave discharges. Very frequent polyspike discharges occur during sleep, sometimes accompanied by tonic seizures.

A wide range of congenital or acquired cerebral lesions is observed in LGS. However, some children present a cryptogenic form. Prognosis is usually poor both in terms of seizure control and cognitive outcome. Polypharmacy is necessary in order to produce a reduction in seizure frequency. Lack of response to AED can produce a pharmacological escalation that in turn increases sleepiness and tonic seizures.

Myoclonic–astatic epilepsy (MAE)

MAE has its onset between 6 months and 6 years of age with a prominence in boys (Doose, 1992). A genetic predisposition is observed in this syndrome whose nosological boundaries are not well defined. Overlap with other severe childhood epilepsies (LGS and severe myoclonic epilepsy) is possible. Children present atonic or myoclonic-atonic seizures and absence seizures with a clonic or tonic component, and GTCs. Tonic seizures can appear late in the course in particular in drug-resistant children. Non-convulsive myoclonic status with prolonged unresponsiveness can be observed in around 30–35% of children. The interictal EEG, normal at the onset, shows generalized spike/polyspike-and-wave discharges later during the course. Prognosis is variable but it is usually less severe than in LGS.

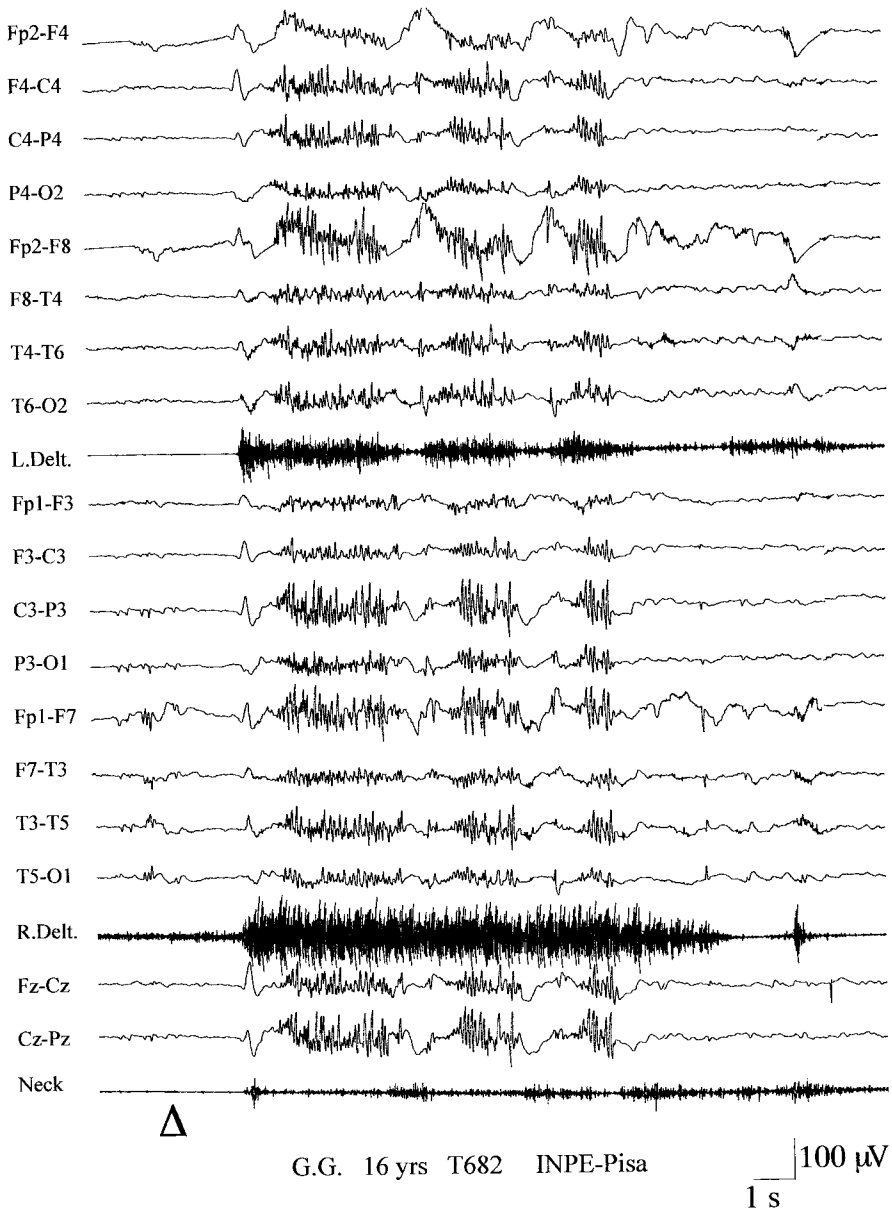

Fig. 74.5. Polygraphic recording of the same seizure as was shown in Fig. 74.4. EEG at seizure onset is characterized by high amplitude, diffuse slow spike complex, that is followed by a diffuse, high amplitude, fast, rhythmic activity, that lasts for around 10 seconds and ends abruptly. EMG from right and left deltoids (R. and L. Delt.) shows an interferential pattern that starts in concomitance with the sharp wave onset and outlasts the fast (recruiting rhythm) polyspike discharge by around 1–2 seconds. The triangle on the left bottom part indicates when picture (*a*) in Fig. 74.4 was shot.

Epilepsy with myoclonic absences (EMA)
EMA is a rare disorder (around 0.5–1% of all patients with epilepsy) with onset around age 7 (Tassinari et al., 1992a). Children present myoclonic absences that appear several times per day, as episodes of interruption of ongoing activity associated to rhythmic jerks in axial muscles causing a rhythmic movement of shoulders, head and arms. Ictal EEG shows generalized 3 Hz spike-and-wave discharges resembling those of CAE, synchronous with myoclonic jerks. Prognosis is variable ranging from poor, with evolution to different seizure types and mental retardation, to very good with remission. A combination of different AEDs (valproic acid + ethosuximide or lamotrigine) is the most effective treatment.

Symptomatic generalized epilepsies (SGE)

SGE have their onset during childhood when different seizure types (myoclonic, tonic, atonic, atypical absence seizures) occur in the same patient. The interictal EEG abnormalities are diffuse. Neurological examination, neuropsychological or neuroadiological investigations, support the presence of a diffuse encephalopathy.

SGE without a specific etiology

Two syndromes are included in this group (Ohtahara et al., 1992).

Early myoclonic encephalopathy
This has its onset by the third month of life with multifocal myoclonic jerks. The course is later characterized by the appearance of partial seizures, tonic seizures, and generalized myoclonic jerks. EEG shows a characteristic pattern with periods of electrical silence separated by generalized polymorphic abnormalities (*suppression bursts*). The etiology is usually metabolic and prognosis is very poor.

Early infantile epileptic encephalopathy with suppression-burst

Early-infantile epileptic encephalopathy with suppression–burst similarly, has its onset early in life. Children show tonic spasms, eventually associated with partial seizures, and a suppression–burst EEG pattern. The etiology is a cerebral malformation or lesion but metabolic screening is necessary. Prognosis is poor with evolution to WS or LGS.

SGE with specific etiology

This can be considered as neurological disorders in which epilepsy is a prominent symptom. They include progressive myoclonus epilepsies, neurocutaneous and other rare disorders such as Aicardi syndrome or disorders due to inborn errors of metabolism.

Progressive myoclonus epilepsies (PMEs)
PMEs are a group of epileptic syndromes including Lafora disease. Unverricht–Lundborg disease, myoclonus epilepsy with red ragged fibres (MERRF), early infantile, late infantile, juvenile and adult ceroid-lipofuscinosis, and sialidosis (Roger et al., 1992).

The clinical picture is rather homogeneous and includes multifocal and generalized myoclonic jerks, GTC or clonic–tonic–clonic seizures, progressive cognitive deterioration, and cerebellar and extrapyramidal signs.

Lafora disease is an autosomal recessive disorder and is produced by cerebral storage of polyglucosane, an abnormal glycoprotein. Patients, frequently originating from Mediterranean countries, develop myoclonic epilepsy around puberty. A diagnosis of JME can sometimes be erroneously suspected at an early stage. Some patients present occipital lobe seizures. The later course is characterized by worsening of the myoclonic syndrome and cognitive deterioration. Death supervenes a few years from onset.

Skin biopsy including sweat glands can allow a diagnosis, based on the presence of storage material in the secretory channel of the glands. The EPM2A gene on chromosome 6p23.25, coding a tyrosine–phosphatase synthesis (Minassian et al., 1998) is responsible for the disease in some families (Table 74.1).

Unverricht–Lundborg disease (ULD) is an autosomal recessive disorder. A progressive myoclonic syndrome is associated with GTC seizures, slight mental deterioration, and a cerebellar syndrome. A highly variable expression of the disorder is typical. The gene (EPM1) responsible for ULD is located on chromosome 21q22.3 and synthesizes B cystatin, an inhibitor of lysosomial proteases.

Mitochondrial encephalopthy such as MERRF or mitochondrial myopathy, encephalopathy with lactic acidosis and stroke (MELAS) can be present as PME. The diagnosis is supported by the determination of enzyme activity in the mitochondrial respiratory chain on biopsed muscles.

Neurocutaneous disorders

Neurocutaneous disorders are characterized by the association of neurological and skin lesions (neuroectodermosis).

Tuberous sclerosis is an autosomal dominant disorder with variable penetrance (Table 74.1). The dermatologic syndrome includes adenoma sebaceum on the face (Pringle adenoma), periungual fibromas (Koenen tumours), and hypomelanotic maculae. Patients may have epilepsy, cognitive impairment and behavioural problems combined or none of these. Severity of epilepsy, the age at seizure onset,

number, size, and location of cortical tubers are correlated with mental outcome. Therefore, children with early onset infantile spasms usually have a prominent cognitive deterioration. A possible visceral syndrome with renal and cardiac involvement can be associated. Magnetic resonance imaging and CT scan show periventricular calcifications, cortical tubers and sometimes, giant cells tumours.

Sturge–Weber syndrome is a sporadic disorder characterized by pial angioma, overlying the parieto-occipital cortex. Unilateral facial angioma of variable distribution and extension is usually associated. Patients may have epilepsy (70–90%), episodes of transitory hemiparesis, which can be postictal or vascular, acquired hemiplegia subsequent to early status epilepticus (26–31%), hemianopia (25%) and a variable degree of mental retardation (54%).

Epilepsies and epileptic syndromes undetermined as to whether focal or generalized

Epilepsies with both partial and generalized seizures

Neonatal seizures

These have a peculiar clinical presentation. Partial seizures are polymorphous and they can sometimes remain undiagnosed because of discrete clinical expression. Generalized tonic seizures observed in intraventricular hemorrhage and myoclonic seizures typical of early onset myoclonic encephalopathy, bear a poor prognosis.

Severe myoclonic epilepsy of infancy (SME)

This has its onset during the first year of life in seemingly normal children with prolonged unilateral clonic or GTC seizures, frequently fever related (Dravet et al., 1992b). Subsequently, partial seizures, atypical absences and a myoclonic syndrome with distal multifocal and generalized jerks, appear. Tonic seizures are never observed. EEG, normal at onset, is later characterized by generalized spike-and-wave discharges, and multifocal abnormalities. Twenty per cent of patients are photosensitive. Developmental delay becomes progressively apparent and the prognosis is poor.

Epilepsy with continuous spike-and-waves during slow wave sleep (CSWS)

CSWS onset is during the school age period (Tassinari et al., 1992b). Three different periods are observed in its evolution:

(i) Age at onset is usually around 4. Children initially present rare nocturnal partial motor or GTC seizures.
(ii) Around 8 years old intractable atypical or atonic absences appear and are associated with mental stagnation or deterioration. Focal atonic events in the form of epileptic negative myoclonus can also be observed (Guerrini et al., 1993). Sleep EEG recordings contain continuous spike-and-wave discharges that cover most of the slow-wave sleep.
(iii) Finally, around 12 years old epilepsy and CSWS remit and cognitive performances improve, although some children can continue to manifest cognitive deficit according to the duration of the disorder.

CSWS bears some similarity with Landau–Kleffner syndrome, BECTS and atypical benign rolandic epilepsy. AEDs are not constantly effective against CSWS. Benzodiazepines, valproic acid and ethosuximide can sometimes be beneficial. Carbamazepine should be avoided in that it can make seizures worse. Steroid treatment is the most effective. Children with CSWS should be carefully evaluated with serial sleep EEG recordings and neuropsychological tests.

Landau-Kleffner syndrome (LKS)

LKS is characterized by acquired aphasia and multifocal spike or spike-and-wave prominent in the temporo-parietal regions (Gordon et al., 1997). Seizures of variable semiology are present in 75–85% of patients, usually remitting by puberty. Aphasia starts as verbal auditory agnosia frequently associated with hyperkinetic behaviour. LSK can be misdiagnosed as acquired hypoacusia or autistic disorder at this stage. A cause–effect correlation between EEG abnormalities and aphasic disorder is difficult to assess fully and remains open to debate. Aphasia can have a variable course. Although AEDs (valproic acid, ethosuximide, benzodiazepines) or steroids may suppress EEG abnormalities, subsequent language recovery can be delayed or incomplete.

Epilepsy without unequivocal generalized or focal features

This diagnostic category includes all syndromes for which clinical and neurophysiological data are insufficient to establish whether the epilepsy is focal or generalized. A typical example is provided by GTC seizures occurring during sleep.

Special syndromes

These syndromes are due to a transient and reversible epileptogenic conditions also known as situation-related

seizures. They are not epilepsies *stricto sensu*, but seizures can relapse when the patient is re-exposed to the provoking factor.

Febrile convulsions (FC)

FCs are convulsive epileptic seizures that appear during a febrile illness, not associated to intracranial infection or other defined causes of seizures, in a normal child between age 3 months and 5 years. FCs are common and affect between 2 and 5% of children below age 5. Epilepsy will develop in only 5% of children who had FC (O'Donohoe, 1992).

Simple FCs

These appear after the first year of life and bear an excellent prognosis. They are characterized by bilateral clonic or tonic–clonic movements, lasting less than 15 minutes, not relapsing during the same febrile illness and not followed by postictal deficit. Seizures take place within 24 hours from fever onset at peak temperature or during defervescence. EEG is not useful in evaluating children with simple FCs. Temperature control is the best prophylaxis. Chronic AED treatment (valproic acid) should be reserved for children with more than three relapses. Subsequent epilepsy is observed in less than 2.4% of cases.

Complicated FCs

These appear within the first year of life in children who frequently have a family history of epilepsy. They represent a febrile status epilepticus characterized by lateralized, prolonged (>15 min), clonic seizures, often relapsing during the same febrile illness and followed by postictal paresis lasting less than 48 hours. An acute treatment with intrarectal (i.r.) diazepam should be used to stop the seizures. A complete neurologic work-up including EEG lumbar puncture and neuroradiologic tests, should be considered if an intracerebral infection is suspected. Prophylactic AEDs should be started and continued for at least 2 years after the last FC. Epilepsy can develop in up to 50% of children particularly if prolonged relapsing seizures followed by postictal paresis are observed. The risk of developing mesial temporal lobe epilepsy with hippocampal sclerosis is proportional to FC duration.

Isolated seizures/isolated status epilepticus

These can appear in a patient without a family history of epilepsy and can remain an isolated event, not developing into an epilepsy syndrome. Isolated simple partial seizures can frequently be observed in adolescents.

Seizures due to acute metabolic or toxic factors

They are very frequent and do not need chronic AED treatment. A list of different metabolic and toxic factors responsible for occasional seizures is supplied in Table 74.5.

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Status epilepticus

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Status epilepticus (SE) is defined traditionally as a condition in which a seizure continues for 30 minutes or more, or in which repeated seizures recur within 30 minutes without the patient regaining consciousness (Dodson et al., 1993). There has been recent debate concerning the proposition that this time interval be shorted to 20 minutes or even 5 minutes, in view of the physiological changes in prolonged seizures, but in normal clinical practice, 30 minutes is considered a useful guide. Any type of seizure can evolve into SE, but classification has been controversial, needing to encompass not only seizure type, but also the observed variations with age, underlying etiology and pathophysiology. A classification proposed by Shorvon (1994), and revised in 2000 is given in Table 75.1. This chapter will concentrate on the syndromes that cross all ages and a detailed discussion of specific neonatal/childhood syndromes will not be included here.

Epidemiological observations about SE have been complicated by inconsistent definitions and different classifications. Furthermore until recently most published data was restricted to tonic–clonic SE, and even here incidence and prevalence figures are of doubtful accuracy. Up to 10% of all epilepsy patients may experience status epilepticus at some point (Lennox, 1960), with a higher incidence in children, those with mental retardation and patients with structural pathology, especially in the frontal lobes. Typical estimates of the annual incidence of convulsive SE range between 18 and 28 cases/100 000 population, (Walker, 1998), with peaks in childhood and old age. However the number of cases of non-convulsive status, often unrecognized particularly in the mentally handicapped population, is probably far higher (Shorvon, 1994).

Table 75.1. Classification of status epilepticus

Status epilepticus confined to early childhood
Neonatal SE
SE in specific neonatal epilepsy syndromes
Infantile spasms
Status epilepticus confined to later childhood
Febrile SE
SE in the partial epilepsy syndromes
SE in myoclonic–astatic epilepsy
Electrical SE in slow wave sleep
Landau–Kleffner Syndrome
Status epilepticus occurring in childhood and adult life
Tonic–clonic SE
Absence SE
Epilepsia partialis continua
SE in coma
Specific forms of SE in mental retardation
Syndromes of myoclonic SE
Simple partial SE
Complex partial SE
Status epilepticus confined to adult life
De novo absence SE of late onset

Note:
Key: SE = Status epilepticus
Source: From Shorvon (2000).

Mechanisms/pathology

The neurophysiological processes which initiate status have been extensively studied in animal models of both focal and generalized epilepsies, and are similar to those producing isolated seizures. They have been reviewed elsewhere (Shorvon, 1994, pp. 139–51), and will not be covered here.

The consequences of status epilepticus, particularly with respect to neuronal damage, have also been much studied, both in man and animal. The hippocampus seems to be especially susceptible to even focal seizure activity, with a characteristic pattern of cell death involving pyramidal cell loss (mainly in the CA1 and CA3 regions), and relative sparing of the CA2 interneurons and dentate granule cells. This is the same pattern of cell death seen in patients with chronic temporal lobe epilepsy and hippocampal sclerosis. Furthermore, both in humans and animal models, status epilepticus can be followed by the development of chronic epilepsy. Such observations have fuelled a debate on whether such changes are the cause or effect of seizures. In addition to hippocampal changes, damage has also been observed in other regions including certain regions of the cerebral neocortex, specific nuclei of the thalamus, and in the cerebellum. These findings are not specific, and have also been documented following, for example, global ischemia or hypoxia, but as in animal models at least they occur in the absence of systemic metabolic upset, or extrinsic toxins (Sloviter, 1983; Tuunanen et al., 1999), and there seems little doubt that they can result from seizure activity *per se*. The mechanism of cell death is probably excitotoxic, involving excessive glutamatergic postsynaptic stimulation and consequent activation of cytoplasmic and mitochondrial pathways including those involved in calcium homeostatis, free radical production and apoptosis (for general reviews on excitotoxic cell death see Sattler & Tymianski, 2000; Kroemer & Reed, 2000). In the epilepsy field there is much work currently under way attempting to unravel the intricate mechanisms of cell death, but those already published support this principle (Cock et al., 2002).

To what extent this cell death and consequent altered circuitry contributes to epileptogensis remains uncertain, but it presumably does contribute to the morbidity observed in some cases following prolonged convulsive status which is further discussed below. In this context alone an increased understanding of the mechanisms of damage following status, and clearer indications as to which forms carry most risk, with the potential to develop neuroprotective strategies, would be of clinical benefit.

Other well-documented changes following status include altered neurotransmitter levels and receptor properties, including both the major inhibitory (GABA) and excitatory (glutamate) pathways, as well as numerous other systems. Again, to what extent such changes are cause or consequence in status is uncertain. Interested readers are referred to the review by Shorvon (1994), pp. 139–74 and Alldredge and Lowenstein (1999).

Diagnosis and management

Some general principles apply to all types of SE, although it is in tonic–clonic SE that complications and significant morbidity/mortality are most often seen. As for any medical emergency for all patients presenting with SE the assessment and protection of cardiorespiratory function takes first priority. Particularly in convulsive status, hypoxia may be much worse than expected and oxygen should always be given. In tonic–clonic SE regular neurological observations, pulse, blood pressure and temperature reading should be taken, accompanied by ECG monitoring, oximetry, and regular measurements of glucose, electrolytes, creatine kinase, blood gases and pH. In all cases if there is any suspicion of hypoglycemia this should be treated, and baseline renal and liver function, calcium and magnesium, hematology and anticonvulsant levels should be recorded. Severe electrolyte disturbances may contribute to the SE and should be rectified where possible. Serum and urine and samples for toxicology screening, including alcohol, should also be taken for future analysis if the cause of the status is not apparent.

Where possible, the diagnosis of SE should be secure before commencing treatment as the drugs used are not without risks. Ideally this should include EEG, but in practice this is often not available in the acute setting and the diagnosis must be made solely on clinical grounds. The clinical and EEG features of the major SE types will be discussed separately in the following sections, but diagnostic difficulty most often arises in cases of non-epileptic attack disorder (NEAD), presenting with what appears to be tonic–clonic SE. Normal blood gases despite prolonged convulsions, irregular flailing limbs, opistothonus and pelvic thursting may alert the treating clinician to the possibility of NEAD, but none are reliable indicators and if there is doubt and EEG is not available cases should be treated as for SE.

In all cases, concurrent with the emergency management, investigations as to the cause of the SE should be initiated. Most cases of tonic–clonic SE occur *de novo*, without a prior history of epilepsy, in which case an acute cerebral event is usually responsible. Common causes include cerebrovascular events, cerebral tumours and cerebral infection, as well as acute toxic or metabolic disturbances. In people with known epilepsy, drug changes or intercurrent illness may be precipitors, or progression of the underlying neurological disease and SE is more common in symptomatic than idiopathic epilepsies. In patients with focal status epilepticus, either convulsive (epilepsia partialis continua) or non-convulsive (complex partial status), the incidence of underlying focal cerebral

abnormalities is high. Thus all patients not known to have epilepsy should have a full biochemical/toxicology screen, structural imaging (CT or if possible MRI), and if this is non-contributory CSF analysis. The latter should also be considered in known epileptics in the absence of any other clear precipitator. As well as potentially needing treatment in its own right, identification of the cause of SE will guide the clinician in decisions about long-term antiepileptic drug (AED) management. In people with known epilepsy, every effort to maintain therapeutic levels of regular AEDs should be made, with parenteral administration if necessary, and increased doses or the addition of new AEDs where indicated. In patients presenting *de novo* with SE this is generally accepted as an indication for long-term AED therapy, unless a clearly identified remediable cause has been identified, and maintenance AEDs should be commenced.

Tonic–clonic status epilepticus

This is the most commonly recognized form of status epilepticus. Many cases will be preceded by a premonitory stage of some hours during which seizure activity increases from its usual level. In patients with generalized epilepsies this may include progressive myoclonic jerking, or more subtle mental changes/confusion representing subclinical seizure activity, as well as an increase in the frequency/severity of the patient's usual seizure type. Other patients may have an abrupt onset. Most cases present with repeated discrete tonic–clonic seizures lasting 2–3 minutes without regaining consciousness in between seizures, but continuous convulsions can also occur. As the status develops, typically the tonic phase becomes prolonged, and the clonic jerking tends to become less pronounced, and finally ceases altogether. At this stage, designated subtle status epilepticus, the patient will be deeply unconscious and the diagnosis less clinically obvious unless a clear history of prior convulsions is obtained. Thus this diagnosis should be considered in patients found unconscious, even if no overt clinical seizure activity is seen, and EEG will usually be diagnostic.

Depending on the cause of the status, there may be additional focal neurological signs, or a focal onset to the seizures. Plantar responses are often but not always extensor, either unilaterally or bilaterally.

Associated with the seizure activity are a number of physiological changes, usually divided into Stage 1 (compensatory) and 2 (decompensated) (Walton, 1993), with transition into the second stage said to occur after about 30 minutes of continuous seizure activity, athough in clinical practice there is great variation. Early on, the seizure activity results in a greatly increased cerebral metabolic demand, which is met by physiological mechanisms to increase blood flow, oxygen and glucose supply. These include increased levels of circulating catecholamines, causing a rise in systemic, left atrial and pulmonary blood pressures, hypertension, and tachycardia. There may also be hypersalivation, hyperpyrexia, hyperglycemia, acidosis, cardiac arrythmias and incontinence at this stage, reflecting the profound autonomic changes. As the status progresses, however, the increased cerebral demands cannot be met, and cardiorespiratory functions may become overwhelmed and unable to maintain the homeostasis. Cerebral autoregulation fails and thus becomes dependent on systemic blood pressure. At the same time, cardiac pressures and blood pressure fall, confounded by increasing acidosis, endocrine changes, and often by drug therapy. Hypoxia is almost universal, and may be more significant than clinically suspected, with both brain and muscle creating huge demand at a time when spontaneous respiration may be compromised for many reasons including ventilatory muscle spasm, excess tracheobronchial secretions, respiratory obstruction or pulmonary edema. Other reported metabolic changes include rhabdomyolysis and myoglobulinuria, sometime severe enough to cause renal failure, disseminated intravascular coagulation, hypo- or hyperkalemia, hyponatremia, and hepatic failure. A leukocytosis in blood is usual, and may also be apparent in CSF, with cell counts of up to 100/mm^3 reported (Shorvon, 1994).

Any combination of complications may/may not be present in individual patients, but with such widespread physiological disturbance it is not surprising that tonic–clonic status epilepticus has a significant mortality and morbidity. Historical series report mortalities of up to 50% (Clark & Prout, 1903). However, even with modern treatments the mortality is probably still in the region of 5–10% based on a review of all published series in 1994 (Shorvon, 1994). Large clinical series often report higher figures (e.g. 35% in the 282 adult cases admitted to an ITU reported by Goulon & Lévy-Alcover (1985)) but as in this case often reflects a bias in the study population. In all series it is difficult to separate the contributions of the status itself from those of the underlying cause, and certainly the prognosis is better in idiopathic cases than those with known cerebral insults. In survivors, formal studies of long-term neurological and psychometric outcome are lacking. In children new motor deficits and mental impairments following status have been well documented, but again are difficult to separate from underlying causes. In adults, clinical experience is that permanent mental and personality deterioration, and/or motor deficits such as

ataxia or psychomotor slowing can certainly occur, but the extent or significance of the problem, and to what extent it reflects the status *per se* is hard to define.

The EEG in tonic–clonic status epilepticus usually starts with the classic EEG pattern of the discrete seizures, including flattening (desynchronization) at the onset, followed by a recruiting rhythm of about 10 Hz interrupted by bursts of high voltage slow activity in the clonic phase, and then ending with post-ictal slowing. As the status evolves however, the discrete seizures may merge, with waxing and waning of the amplitude and frequency of EEG rhythms, eventually resulting in continuous seizure activity. Later still, this may be punctuated with low voltage 'flat' periods, and in extremis no typical seizure activity may be seen with only periodic lateralized epileptiform discharges (PLEDS) visible on a flat background (Treiman et al., 1990). However, individual cases vary in their progression through these stages, and the underlying cause, systemic physiological changes and drug treatment may modify the EEG considerably.

Treatment of tonic–clonic SE is a medical emergency, and as outlined previously must include general measures and the prompt recognition and appropriate management of systemic complications. A treatment protocol is recommended in order to facilitate prompt treatment, as suggested in Fig. 75.1. Parenteral drug treatment during the premonitory or early stages of status epilepticus, usually with a benzodiazepine, will often abort the seizures, and should be given as early as possible. Commonly used drugs include rectal or intravenous diazepam, intravenous lorazepam, or rectal, buccal or intramuscular midazolam. All are highly effective, although lorazepam has the advantage of a longer duration of action and less cardiorespiratory depression (Appleton et al., 1995).

Once seizures have continued for more than 30 minutes, or if initial treatment fails, the patient should be regarded as having entered the stage of established SE. First-line treatment alternatives in these circumstances include subanesthetic doses of barbituates, phenytoin or fos-phenytoin as outlined in Figure 75.1. All require intravenous loading, followed by repeated oral or i.v. supplementation. Benzodiazepine infusions have previously been used in established status, but with the possible exception of midazolam, should be avoided as they can result in dangerous cardiorespiratory depression.

Experience with midazolam, and with valproate which has also been proposed as a suitable treatment, is currently limited. In most patients, if these measures fail, or if seizures have continued for more than 60–90 minutes, full anesthesia and intensive care admission is indicated. Ventilatory support is also indicated at this stage to avoid dangerous hypoxia as previously discussed. The choice of anesthetic agent is controversial. Barbituates are potent antiepileptics and there is much experience with their use in SE, but have poor pharmacokinetic and pharmacodynamic profiles, often associated with hypotension and prolonged recovery. Newer agents such as propofol have received recent favour (Stecker et al., 1998), but there is as yet no good large comparative trial. Ideally, patients in refractory status should have EEG or cerebral function monitoring, to confirm abolition of seizure activity. Outside regional neuroscience centres, however, intermittent EEG recordings should be used as the minimum acceptable standard. Concomitant with the emergency treatment, once initial treatment is successful, in patients presenting *de novo*, chronic antiepileptic drug therapy should be introduced, and in existing patients medication must be reviewed to minimize the risk of recurrence. In patients who fail to respond to the above measures, which is unusual, a search for complicating factors must be made. These may include inadequate maintenance antiepileptic drug treatment, additional medical complications, failure to recognize or treat the underlying cause, or misdiagnosis (e.g. non-epileptic status)

Absence status

Traditionally, absence status has been divided in to typical and atypical cases, although each have considerable clinical and electrographic overlap. Nonetheless, this distinction is probably still valid as each has a different response to treatment and prognosis. More confusing is that much of the literature has addressed 'non-convulsive status', including cases of non-convulsive complex partial status which certainly is a different condition which will be covered in the next section.

Typical absence ('petit mal') status occurs in the setting of primary generalized epilepsy, and is probably relatively common occurring in up to 10% of patients in this group, especially children. Clinical features may range from only a slight clouding of consciousness or loss of concentration, through more marked impairment with a trance-like state, to profound obtundation or an 'epileptic stupor' (Roger et al., 1974). Motor features occur in about 50% of patients, including myoclonus, especially facial or eyelid, hippus, and atonia. Relative preservation of speech, in contrast to complex partial status, is not uncommon. Episodes may last hours or even days, and termination of the status with a tonic–clonic convulsion is very characteristic, but not universal. There may be precipitating factors such as menstruation, flashing lights, sleep deprivation, or medication

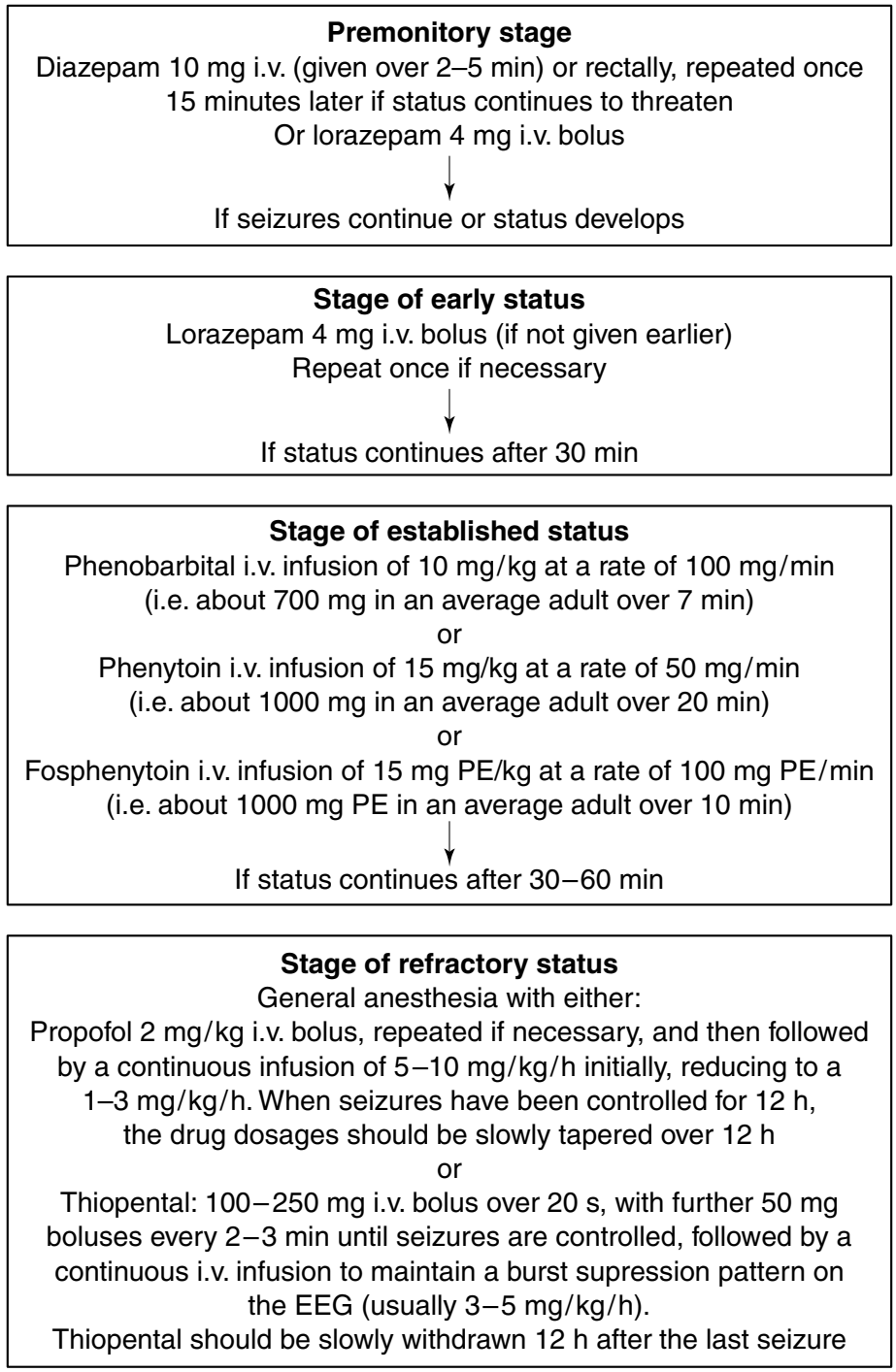

Fig. 75.1. Management of tonic–clonic status epilepticus.

changes (carbamazepine and tiagabine seem to be particular provokers), or the status may be spontaneous anytime in the course of the epilepsy. There are also case reports of occurrence *de novo* during benzodiazepine withdrawal (Thomas et al., 1993). This seems to be particularly common in the elderly, and is often misdiagnosed as a stroke, dementia, or psychosis. Other precipitants include toxins such as radiographic contrast media (Obeid et al., 1988).

Atypical absence status occurs largely in patients with secondarily generalized epilepsy such as the Lennox–Gastaut type, but may be clinically indistinguishable from that described above. However automatisms including facial grimacing, and even ambulatory fugues may occur, together with incontinence, pseudoataxia and pseudodementia. In this population of patients, who are often also significantly learning disabled, diagnosis in subtle cases, and differentiation from non-convulsive complex partial status, can be difficult. Confusion with psychotic, behavioural or affective changes are more suggestive of the latter, contrasting with the fluctuating confusional state with myoclonus characteristic of absence status (Rohr-Le Floch et al., 1988).

The diagnostic EEG pattern is continuous or almost continuous bilateral synchronous symmetrical spike-wave activity, classically at 3 Hz, with little or no reactivity to sensory stimuli. In atypical cases, other frequencies from 1.5–6 Hz have been described, and sometimes prolonged bursts of spikes, generalized periodic triphasic sharp waves or polyspike and wave may be seen. However, overall there is a poor correlation between clinical features and the EEG pattern.

Both forms of absence status are usually rapidly terminated by intravenous benzodiazepines such as diazepam or lorazepam. Rarely additional valproate or phenytoin may be needed, but all cases should have maintenance therapy (usually valproate or ethosuximde in primary generalized cases) optimized, unless a clear precipitating reversible cause has been identified. The prognosis for patients, even with repeated prolonged episodes of typical absence status prior to the advent of modern therapies, appears to be very good, with no deaths of long-term morbidity reported (Krumholz, 1999). The prognosis for atypical cases is less clear, particularly given the potential confusion with complex partial status which certainly has a worse prognosis, and because many atypical cases occur in association with refractory seizures of other types confusing the picture. In syndromes such as Lennox–Gastaut, whether episodes of atypical absence status cause cerebral damage, or whether both are due to the underlying encephalopathy is undetermined.

Non-convulsive simple partial status

Non-convulsive simple partial status is less common than the convulsive form (epilepsia partialis continua p. 1278), and very varied in clinical form depending on the focus. Clinical features in reported cases with electrographic confirmation include oculoclonic status epilepticus (nystagmoid status), prolonged ictal paralysis, complex visual hallucinations, prolonged sensory symptoms, or specific cognitive defects (for review, see Shorvon, 1994, pp. 110–16). Prominent psychic symptoms such as fear may also occur, but are rare in isolation. The ictal EEG changes, usually include spikes or spike-wave paroxysms in the appropriate neocortial or mesial temporal sites, with considerable individual variability in the frequency and degree of spread. Attacks of simple partial status are usually self limiting, or may occur as prolonged auras terminating in a convulsive or complex partial seizure. This form of status rarely requires intravenous therapy, and should be managed as with any partial epilepsy. Attacks may be recurrent, however, and relatively resistant to conventional treatment, particularly in the presence of an underlying focal structural abnormality. There is uncertainty about whether simple partial status results in secondary cerebral damage, but none the less in such cases with structural pathology and distressing symptoms, or additional more severe seizure types, surgical treatment should be considered and may be very effective (Manford & Shorvon, 1992).

Complex partial status

Complex partial status has suffered from problems of definition and classification perhaps more than any other type, is most likely much underdiagnosed, yet arguably the commonest form of status encountered in clinical practice. The most encompassing definition is probably that suggested by Shorvon in 1994: ‘a prolonged epileptic episode in which fluctuating or frequently recurring focal electrographic epileptic discharges, arising in temporal or extratemporal regions, result in a confusional state with variable clinical symptoms’. Others have tried to be more prescriptive, for instance requiring a clear cyclical clinical evolution or specific EEG changes (Delgado Escueta & Treiman, 1987). Although such cycling between unresponsive and partially responsive states is characteristic, and contrasts with absence status, numerous case reports and clinical observations suggest it may only be present for part of the episode, or indeed not at all, and any definition must reflect this.

Confusion is the cardinal and essential clinical feature of complex partial status, of variable severity, but can be

associated with a huge variety of other signs. There may be alterations in posture, convulsive movements or tonic spasms, particularly adversion of the head and eyes, and occasionally adversion of such significance that the patient walks in circles, occurring intermittently throughout the episode. Some degree of expressive language difficulty is usual, and a motor aphasia is not uncommon. There may also be autonomic disturbances such as pupillary dilatation or even fever. Behavioural changes, ranging from agitation or excitation through to severe psychomotor retardation, and psychotic or autistic symptoms such as delusions, hallucinations, paranoia or perseveration may also occur. Motor features, however, are rarely as marked as they are in individual seizures, and in cases with prominent psychic phenomena this may lead to a psychiatric misdiagnosis. The possibility of complex partial status should always be considered in confused patients where other medical causes have been excluded, particularly if there are psychiatric/motor features, however subtle.

The EEG findings in complex partial status are extremely varied. Treiman and Delgado-Escueta (1983) suggest diagnostic features should include bimedial temporal or lateralized temporal 8–20 Hz spikes, alternating with one of three patterns: low voltage fast activity with bursts of diffuse slow, rhythmical bilateral diffuse spike or slow waves, or anterior temporal spikes on a normal background. This cycling EEG pattern may certainly be seen in some patients, particularly those with clear clinical cycling, but equally other widespread or focal spikes or spike slow-wave paroxysms and episodes of desynchronization may be observed. In some patients the ictal scalp EEG may differ little from the interictal pattern. Furthermore, although a clinical and EEG response to intravenous benzodiazepines may be demonstrable, this is non-specific and can also be seen in the other non-epileptic confusional states. SEEG has provided more consistent information, with a mixture of discrete and continuous focal activity, but is not practical from a diagnostic perspective. Such studies have however counteracted the prior supposition that most cases of complex partial status were temporal in origin, with most documented reports demonstrating an extratemporal onset, e.g. Williamson et al. (1985).

To what extent complex partial status contributes to cerebral damage is controversial. On the one hand, animal models of focal limbic status epilepticus (Sloviter, 1983), without the metabolic and systemic features associated with convulsive status, show considerable neuronal death after even brief periods of seizure activity (Tuunanen et al., 1999). In keeping with this, markers of neuronal damage such as neuronal specific enolase are elevated in patients after non-convulsive status (DeGiorgio et al., 1996), and postmortem studies have documented neuronal damage (Fujikawa et al., 2000), although in reality it is difficult to ascribe this to seizure activity and not the underlying cause with any certainty. In contrast, death does not occur, and clinical studies have rarely reported significant neurological deterioration, sometimes even following months of continuous seizure activity. Further work is required to resolve this issue, which also has important implications for management. Thus the urgency with which complex partial status should be treated remains uncertain. In most cases intravenous benzodiazepines will be effective, followed by oral maintenance therapy, although high doses of both may be needed. Carbamazepine, phenytoin or phenobarbitone are the drugs of choice for oral therapy, although any of the newer drugs may also tried. In truly intractable cases, despite high doses of multiple anticonvulsant drugs, whether general anesthesia is justified in the hope of 'switching off' the seizure activity and regaining control is controversial. In clinical practice this may be effective, but only temporarily so with seizure activity recurring as anesthesia is withdrawn. As for other focal status syndromes, the search for a possible treatable or resectable underlying cause should be intensified in such cases and offers the best prognosis.

Myoclonic status

The clinical features and management of myoclonic status vary according to etiology, and are best considered separately as follows.

Myoclonic status in coma

This is undoubtedly the most frequently encountered form, most commonly occurring with anoxic encephalopathy such as following cardiorespiratory arrest (Young et al., 1990). By definition the patients are unconscious, and typically the myoclonus starts within hours of the insult and consists of irregular asynchronous small amplitude jerking of the facial muscles, and to a lesser extent the limbs. Stimulus sensitivity to touch or sound is not uncommon. Other seizure types including generalized tonic–clonic seizures also occur. It is important to distinguish myoclonic status in coma from the postanoxic action myoclonus (Lance & Adams, 1963). The EEG most commonly reveals a burst–suppression pattern, although generalized periodic complexes, and spike-wave discharges have also been observed. The myoclonus is usually treatment resistant, and aggressive management does not alter the eventual outcome. The presence of myoclonic status in this setting is

a universally poor prognostic indicator (Wijdicks et al., 1994), and management decisions should reflect this.

Myoclonic status in primary generalized epilepsy

This is rare, and may reflect changes in therapy. The jerks are synchronous and bilateral, predominantly proximal and occur in preserved consciousness at a rate of 3–6 Hz, usually in a patient known to have PGE. EEG shows bilateral diffuse spike discharges preceding each jerk, often with an anterior predominance. The status usually responds to intravenous benzodiazepines (e.g. diazepam 10 mg or lorazepam 4 mg), and the prognosis is very good. Increases in maintenance therapy (usually valproate or lamotrigine), or the addition of clobazam should be considered if there is no clear precipitant.

Myoclonic status in the progressive myoclonic epilepsies

Myoclonic status is not uncommon, particularly in the later stages, in patients with PME. This rare heterogeneous group of disorders typically present in childhood or young adult life with a combination of seizures (including myoclonus) and ataxia on a background of general cognitive and motor decline (Berkovic et al., 1986). There are numerous mainly genetic causes, and all are relentlessly progressive with only symptomatic treatment available. All such patients should be investigated in a neuroscience centre and a diagnosis made where possible, allowing appropriate genetic counselling. The myoclonus may be generalized or focal, and usually occurs with preserved consciousness except in the very late stages of the disease. EEGs are always abnormal, with diffuse background abnormalities in addition to frequent spike-wave discharges. As with other forms of status, benzodiazepine therapy is the first choice in patients presenting acutely, and for recurrences either valproate, clonazepam or clobazam may help. Zonisamide (not yet licensed in the UK) has also been reported to be of benefit in these notoriously resistant patients (Kyllerman & Ben-Menachem, 1998), although further experience is awaited. The long-term prognosis in this group of disorders is poor, but every effort to control seizures should be made in order to improve quality of life.

Epilesia partialis continua

EPC is a form of simple partial status epilepticus, usually arising from a focus in the prefrontal motor cortex. It may develop at any age and has a broad spectrum of underlying causes. The definition of Obeso et al. (1985) is the most widely accepted: 'spontaneous regular or irregular clonic muscle twitching of cerebral cortical origin, sometimes aggravated by sensory stimuli, confined to one part of the body and continuing for hours, days or weeks.' Any muscle group can be affected, though distal involvement is more common than proximal. Typically, there would be persistent jerking of a hand or foot, with cocontraction of antagonist and agonist muscle groups, with preserved consciousness. The jerking usually persists through sleep, although it may lessen in amplitude.

Up to 50% of cases, particularly in children, are caused by Rasmussen's encephalitis, a chronic inflammatory process of unknown etiology affecting one hemisphere and presenting with a progressive hemiplegia, seizures including EPC, and sometimes cognitive decline. However any pathology affecting the rolandic cortex can be associated with EPC including stroke, structural lesions, infections and in some cases metabolic disorders including not-ketotic hyperglycemia, hepatic encephalopathy, and rare disorders including the mitochondrial diseases. Despite the broad range of potential causes, EPC is rare with an estimated prevalence of less than 1 in a million in the UK (Cockerell et al., 1996).

All patients with EPC should have routine metabolic screening, and modern imaging, preferably by MRI to look for structural pathology. Routine EEG recordings may be normal or reveal only non-specific abnormalities, although if the focus is superficial spike discharges may be visible. More commonly specialized investigation is required to confirm a cortical origin, such as jerk-locked (using concomitant EMG) back-averaging of EEG recordings. Abnormally enlarged SSEPs from the affected limb help to confirm cortical pathology, and more recently functional imaging studies have sometimes demonstrated focal abnormalities where other investigations have been normal, though these are still largely research tools.

EPC is notoriously pharmacoresistant, and single case reports in the literature of successful treatments are difficult to interpret as a proportion of cases spontaneously remit after variable time periods. However EPC is not a medical emergency, and depending on the location, frequency and amplitude of the jerking, EPC may continue unabated for years in individual patients, apparently causing more inconvenience than harm. In acute onset cases parenteral therapy with benzodiazepines, e.g. i.v. diazepam, lorazepam, phenytoin, or phenobarbitone, may abort the episode, but it often recurs on cessation of treatment. The same applies to the use of general anesthesia although this may sometimes be required in very intractable cases where the patient is getting exhausted. Most of the conventional antiepileptics have also been tried, with carbamazepine, clonazepam, valproate and phenytoin

reported to be of limited benefit (Cockerell et al., 1996). Focal resection of the underlying lesion, or in cases of Rasmussen's hemispherectomy (Anderssen, 1991), carries the best prognosis in terms of seizure control, but given the location of the focus often leaves permanent neurological deficit. Patients should be referred to specialist centres for evaluation.

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76

Assessment of the patient with epilepsy

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Is epilepsy the diagnosis?

Differential diagnosis

Of patients referred to 'first seizure clinics' generally less than 30% are considered to have had an epileptic seizure. Further, 15–20% of patients referred to specialist clinics with refractory epilepsy have another condition as the cause of their episodes (Smith et al., 1999). The history from the patient and any witnesses to the attack is most crucial. The patient will have only a limited recall of events and can only summarize what witnesses related. A videotape record often provides invaluable objective data on the nature and sequence of events in a seizure (Samuel & Duncan, 1994; Rugg-Gunn et al., 2001).

The differential diagnosis of seizures varies with the predominant clinical features of the presenting symptoms (Table 76.1). Often, however, these occur in combination, with one or other being the differentiating feature (e.g. loss of awareness with either drop attacks or psychic phenomena).

Table 76.1. Main categories of episodic symptoms that may be caused by epilepsy

Loss of awareness
Generalized convulsive movements
Drop attacks
Transient focal motor attacks
Transient focal sensory attacks
Facial muscle and eye movements
Psychic experiences
Aggressive or vocal outbursts
Episodic phenomena in sleep
Prolonged confusional or fugue states

Table 76.2. Key features of syncopal attacks

Evidence of precipitant factors
Lightheadedness, dizziness, nausea
Pallor
Ringing in the ears
Bilateral loss of vision
Collapse
Some twitching movements may occur
Rapid recovery when supine
Sweating, subsequent flushing

Loss of awareness

The three main causes of loss of awareness are: syncope, epilepsy and cardiac arrhythmias. Microsleeps (very short daytime naps) may occur with any cause of severe sleep deprivation or disruption. Other causes of diagnostic confusion are much rarer and include: hypoglycemia or other intermittent metabolic disorders, transient cerebral ischemia, or lesions affecting the brainstem, or CSF circulation. Syncope (Table 76.2) is considered in more detail in Chapter 52.

Epilepsy

Seizures that may present with loss of awareness include absences, complex partial, tonic or atonic seizures. Typical absences involve arrest of activity, reduced or lost awareness, eyelid blinking or twitching, and sometimes small myoclonic facial or limb jerks, or brief facial automatisms. Typical absences are usually brief but frequent, often occurring many times per day. There may be other associated seizure types, such as myoclonic jerks on waking. The EEG changes are characteristic. 'Atypical absences' are usually associated with mental retardation and other

seizure types, and are often more prolonged. Atonic seizures usually give rise to drop attacks but may appear to cause blank spells if the patient is sat or laying down and so cannot fall. Complex partial seizures may cause loss of awareness with few other features. Enquiry must be made for associated psychic or motor phenomena that may raise the possibility of a seizure disorder.

Transient cardiac arrhythmias may cause episodes of abrupt loss of awareness. There are often prodromal features similar to those seen with simple syncope, as well as palpitations, chest pain, shortness of breath. Stokes Adams attacks due to transient complete heart block are abrupt and short with rapid loss of consciousness. Apparently syncopal features are followed by rapid collapse and sometimes secondary anoxic seizures. Usually the attacks last for less than 1 minute. Sometimes the lack of cardiac output is due to short episodes of ventricular tachycardia or fibrillation. Prolongation of the QT interval may lead to such events (Pacia et al., 1994). There is a high risk of sudden death. The resting ECG often shows some evidence of heart block or bundle branch block. Cardiac valve disease, especially mitral valve prolapse and aortic stenosis may also present with episodic loss of awareness due to fluctuating cardiac output or associated arrhythmias. Aortic stenosis and hypertrophic cardiomyopathy is especially prone to present with episodes of sudden collapse with loss of awareness during exercise. Patients with unexplained blackouts require cardiac evaluation, with ECG, 24-hour ECG tape, chest radiograph, echocardigram and if events are infrequent an implantable ECG loop recorder.

Microsleeps

Sleep deprivation may lead to brief day-time naps, or microsleeps, sometimes lasting for only a few seconds. The most important cause is obstructive sleep apnea. This results in chronic daytime hypersomnolence that may be manifest as daytime naps. Rarely narcolepsy can present with short periods of suddenly falling asleep during the day-time that are misinterpreted as brief epileptic attacks of loss of awareness.

Panic attacks

Panic attacks usually present with feelings of fear and anxiety, associated with autonomic changes and hyperventilation, with lightheadedness, paresthesia, carpopedal spasm, twitching, blurred vision, and nausea. Occasionally these preludes may be forgotten, and attacks present with loss of awareness. Often there is a clear precipitant, such as a particular situation, or the recall of a previous distressing experience. None of these features is consistent, however, and differentiation from epilepsy can sometimes be difficult.

Hypoglycemia

Hypoglycemic attacks causing loss of consciousness are extremely rare except in patients with treated diabetes mellitus. Occasional cases are due to insulin secreting tumours. In these there may be a history of a missed meal prior to the attack and previous weight gain due to increased appetite. The attacks are usually preceded by autonomic features (tachycardia, sweating) and light headedness and may include features such as mood change, irrational behaviour, or involuntary movements (Winer et al., 1990).

Non-epileptic attack disorder

The diagnosis of non-epileptic attack disorder (NEAD), involves both the exclusion of organic causes, and identifying positive phenomena of this entity (Meierkord et al., 1991). Typically episodes of NEAD fall into two broad types:

(i) attacks involving motor phenomena
(ii) attacks of lying motionless.

The latter are often prolonged, continuing for several minutes or sometimes hours. Such behaviour is very rare in epileptic seizures: there will nearly always be other positive phenomena in epileptic attacks that last for more than a few minutes. The sequence of events of NEAD is usually different to that of epileptic attacks (Table 76.3). They may slowly wax and wane. There is often excess salivation but cyanosis is extremely rare. During attacks patients may resist examination, and screw up their eyes if attempts are made to open them and if their own hand is held above their face and then released, the hand deviates to one side, missing the face. If the patients are examined they may show directed violence. Urinary incontinence is uncommon, but may occur, as can self-injury. Recovery is variable and may be much quicker than expected from the duration of the attack. Patients may respond, often claiming to have some recall of things that were said to them during the attacks, and may become tearful after the attacks. The longer the duration of such episodes the less likely they are to be epileptic.

Patients with NEAD often have a history of abnormal illness behaviour. Non-epileptic attack disorder is commoner in females than males, and usually commences in adolescence or early adulthood. Occasionally, there is an obvious secondary gain, but usually the psychological basis is more complex. A history of sexual abuse is common, but this may be coincidental and is not that rare in patients with epileptic seizures. Similarly there may be previous overt psychiatric illness. Attacks are usually resistant to antiepi-

Table 76.3. Differentiation of epileptic seizures and non-epileptic attack disorder (NEAD)

	Epileptic attack	NEAD
Precipitating cause	Rare	Common, emotional and stress related
When alone or asleep	Common	May be reported
Onset	Usually short	May be short or over several minutes
Aura	Various, usually stereotyped	Fear, panic, altered mental state
Speech	Cry, grunt at onset; muttering, words in automatisms	Semi-voluntary, often unintelligible
Movement	Atonic, tonic; if clonic synchronous small amplitude jerks	Asynchronous flailing of limbs; pelvic thrusting; opisthotonous
Injury	Tongue biting, fall; directed violence rare	May bite tongue, cheeks, lip, hands, throw self to ground. Directed violence not uncommon
Consciousness	Complete loss in generalized tonic–clonic; may be incomplete in complex partial	Variable, often inconsistent with seizure type
Response to stimulation	None in generalized tonic–clonic; may respond in complex partial and postictally	Often reacts and this may terminate episode
Incontinence	Common	Sometimes
Duration	Few minutes	Few minutes, may be prolonged
Recovery	Depends on seizure type. Few minutes and more prolonged confusion	May be rapid or very prolonged

leptic drug treatment and this may lead to escalating dosages and iatrogenic complications. The diagnosis should be considered in anyone with prolonged drug resistant attacks. The most useful test is to record an attack with simultaneous EEG and video, but the feasibility of this depends upon their frequency and reproducibility. Videotapes of seizures may provide useful diagnostic data, and can be combined with 24-hour ambulatory EEG recordings (Samuel & Duncan, 1994). Some patients have both epileptic and non-epileptic attacks, but usually one of these types clearly predominates.

Generalized convulsive movements

Epilepsy

The convulsive movements usually last for a minute or so, and as the attack proceeds the jerking slows in frequency and increases in amplitude. There is often cyanosis, and irregular breathing followed by confusion, headache and sleepiness. When all or most of these features are present, there is little room for diagnostic confusion.

Syncope with secondary jerking movements.

People who faint often have small, myoclonic twitches of the extremities (Lempert et al., 1994). With prolonged cerebral hypoperfusion (e.g. due to preventing the subject lying flat) these may be more prominent, and become reported as 'a convulsion'. The myoclonic jerking is usually irregular, short lived and does not have a pattern which evolves in the same way as do the convulsive movements of a tonic–clonic seizure.

Primary cardiac or respiratory abnormalities presenting with secondary anoxic seizures.

In any patient presenting with a convulsion, the possibility of primary cardiorespiratory disease and secondary anoxic seizures should be considered. Stokes–Adams attacks are especially prone to cause confusion. Occasionally, syncopal features are followed by rapid collapse and sometimes secondary anoxic seizures.

Non-epileptic attack disorder

Non-epileptic attacks with prominent motor phenomena are commoner than those with arrest of activity. Movements are varied but often involve semi purposeful thrashing of all four limbs, waxing and waning over many minutes, distractibility or interaction with the environment, prominent pelvic movements and back arching (Table 76.3). Non-epileptic attacks may be difficult to differentiate from frontal lobe complex partial seizures, with bizarre motor attacks, some retained awareness and with quick recovery and no scalp EEG changes.

Table 76.4. Causes of drop attacks

Epilepsies
Secondary generalized tonic or atonic seizures (including startle-induced seizures and Lennox–Gastaut syndrome)
Cardiovascular
Syncope
Stokes–Adams attacks
Transient brainstem ischemia (vertebro-basilar insufficiency)
Movement disorders
Hyperekplexia
Steele–Richardson–Olzweski syndrome
Parkinson's disease
Multisystem atrophy
Paroxysmal kinesogenic choreoathetosis
Subcortical myoclonus
Other
Brainstem, spinal or lower limb abnormalities (e.g. Arnold–Chiari malformation, cervical disc disease, spinal angioma, cauda equina disease)
Third ventricle tumours
Vestibular
Cataplexy
Metabolic (e.g. periodic hypokalemia)
Non-epileptic attack disorder

Drop attacks

Any cause of loss of awareness may proceed to a sudden collapse or drop attack. Epilepsy, syncope and other cardiovascular disorders are the most common causes (Table 76.4).

Transient focal motor and sensory attacks

The commonest cause of transient focal motor and sensory attacks is epilepsy. In children and adolescents consideration should be given to tics and associated syndromes. Paroxysmal movement disorders are rare. Transient cerebral ischemia usually presents with negative phenomena. Tonic spasms of multiple sclerosis are usually seen once other features of the illness have become apparent, but may be a presenting feature.

Tics usually present with stereotyped movements in childhood or adolescence, sometimes restricted to one particular action but may be multiple. They can be suppressed voluntarily, although to do so leads to a rise in psychological tension and anxiety that is then relieved by the patient allowing the tics to occur. Repetitive tics and stereotypies are particularly common in the mentally retarded.

Transient ischemic attacks (TIAs) usually present with negative phenomena, although positive phenomena such as paresthesiae may occur. Involuntary movements can be seen with basal ganglia ischemia. Transient ischemic attacks may last for a few minutes, but may persist for up to 24 hours. TIAs are not usually stereotyped or repeated with the frequency of epileptic seizures, and are usually associated with features of vascular disease.

Benign rolandic epilepsy usually presents with seizures in childhood affecting the face, often with unilateral grimacing, hemicorporeal sensory and motor phenomena, or secondarily generalized seizures occurring in sleep. Focal motor seizures may cause twitching of one side of the face, although this may be bilateral due to the bilateral representation of the face in the primary motor cortex, that may be restricted to specific areas. Eye deviation may be seen with frontal, parietal or occipital seizures. Complex partial seizures may cause automatisms with lip smacking, chewing, swallowing, sniffing or grimacing, with amnesia and impaired awareness.

Psychic experiences

Intermittent psychic phenomena can be seen in partial seizures (especially of temporal lobe origin), migraine, panic attacks, transient cerebral ischemia, drug induced flashbacks, or with illusions associated with loss of a sensory modality as well as psychotic illnesses.

Aggressive or vocal outbursts

These are rarely epileptic in nature if they occur in isolation. They are especially common in adults and children with mental retardation (Donat & Wright, 1990). In this setting there is organic brain disease which could lower the overall seizure threshold. Care should be given to attempting to elicit other clinical features of epilepsy. EEGs are often abnormal because of the underlying brain disorder and, unless unequivocal, interictal changes are not in themselves strong support for a diagnosis of epilepsy in this setting. A forensic issue is the occurrence of violent, or other, crimes in patients with epilepsy, and the defence claim that the crime was committed in a state of automatism. Certain features are strong evidence against an epileptic basis to the attack (Table 76.5).

Episodic phenomena in sleep

Attacks occurring during sleep (Table 76.6) present particular diagnostic difficulties because they are often poorly witnessed, and the patient may have little, if any, recall of the event or the preceding circumstances.

Table 76.5. Features against there being epileptic basis to an aggressive attack

Absence of a prior history of epilepsy with automatisms
Premeditation and evidence of planning or preparation
Directed violence
Evidence of complicated and organized activity during the episode
Recall of events during the episode
Witness accounts not indicative of a disturbance of consciousness
Subsequent attempts at escape or concealment of evidence.

Prolonged confusional or fugue states

Epileptic seizures usually last for seconds or minutes. There may be confusion for many minutes, after generalised convulsions or complex partial seizures, but rarely more than an hour. Such episodes only present diagnostic difficulty if the initial seizure is unwitnessed or forgotten. The differential diagnosis of prolonged epileptic confusional states (non-convulsive status) includes: acute encephalopathy, non-convulsive status epilepticus, transient global amnesia, intermittent psychosis, hysterical fugue (NEAD).

Investigations to assess patients with epilepsy

The principal objectives of investigating new and chronic patients referred for evaluation are: (i) to clarify the diagnosis of epilepsy or non-epileptic attacks; (ii) to determine the nature of the seizure types and epilepsy syndrome; (iii) to identify the laterality and localization of partial seizure onset; (iv) to identify the etiology of the epilepsy; (v) to identify concomitant neurological, psychological, psychiatric and medical problems; (vi) to monitor the progression of the condition and the consequences of the epilepsy and its treatment.

Answers to these questions allow the formulation of a rational treatment plan, and the provision to the patient and their family of accurate information regarding their diagnosis, treatment and prognosis.

Electroencephalogram

Use and misuse of the electroencephalogram (EEG)

In the assessment of a patient with a seizure disorder the EEG is a useful test to address the following questions: Are there epileptiform changes to support the clinical diagnosis of epilepsy? Is the seizure disorder likely to be partial or generalized? Does the patient have photosensitivity? Is there evidence of an encephalopathy?

Table 76.6. Episodic phenomena in sleep

Normal physiological activity
Whole body jerks (hypnic jerks)
Fragmentary myoclonus
Periodic movements of sleep
Epilepsies
Frontal lobe seizures
Other partial epilepsies
Generalized convulsions
Sleep disorders
Pathological fragmentary myoclonus
Restless leg syndrome
Non-REM parasomnias
REM parasomnias
Sleep apnea

An EEG also helps to classify the type of epileptic syndrome, especially in childhood and adolescence, and virtually all such patients require an EEG to answer these questions.

In clinical practice it must be remembered that: a normal interictal EEG does not exclude epilepsy; the EEG is not specific or sensitive at diagnosing the presence or absence of underlying structural cerebral lesions; normal EEG variants may mimic epileptiform activity; all EEG changes need to be considered in the clinical context; with the exception of patients with idiopathic generalized epilepsy and 3 Hz spike-wave activity, the interictal EEG is a poor guide to seizure control or to the likelihood of seizure relapse in a patient who has become seizure free and in whom withdrawal of antiepileptic drugs is being contemplated.

EEG recording techniques

The routine EEG comprises 20–30 minutes recording during the awake state including overbreathing for 3 minutes and photic stimulation. Only 30–40% of patients with epilepsy show epileptiform discharges on a single wake record (Ajmone Marsan & Zivin, 1970).

A sleep EEG should be requested when the routine EEG is normal or borderline abnormal and further confirmation of the diagnosis or syndromic classification is required. Epileptiform changes are seen on a sleep EEG in 70–80% of patients with clinical epilepsy. About 50% of patients with unhelpful wake records show definite interictal epileptiform activity during a sleep record (Gastaut et al., 1991). Most of the additional yield occurs during drowsiness or light sleep rather than deep sleep.

Overnight sleep deprivation only marginally improves the yield, and there is the risk that significant sleep deprivation may trigger additional seizures. It may occasionally be helpful in suspected idiopathic generalized epilepsy if EEG confirmation is essential.

Ambulatory EEG

This allows the detection of generalized spike and slow wave discharges, infrequent interictal localized epileptiform discharges, and diagnostic screening of ictal events in patients with frequent paroxysmal attacks of unknown nature. Sixteen channels may be recorded digitally and the data reformatted and remontaged after acquisition. A push button marker may be used to identify the timing of events, but artefacts may be difficult to detect without simultaneous documentation of motor behaviour. Simultaneous videotape recording is useful, but precise electro-clinical correlation is not possible unless the EEG recorder and video recorder are time locked. Only definite EEG patterns should be considered to be of diagnostic importance.

Video–EEG telemetry

Video–EEG telemetry provides long-term monitoring of the EEG and time locked video of the patient. It is the most definitive method for the diagnosis of paroxysmal attacks and is feasible if episodes are occurring more than once per week or can be provoked. It is much easier to identify artefact than with ambulatory records, and the technology is more flexible and appropriate for presurgical assessment.

Normal EEG findings

The normal EEG evolves with age and varies between subjects. Posterior rhythms are relatively slow in infancy (typically 4 Hz at 6 months of age), increasing to 8 Hz by age 2–4 years and thereafter increasing further to the normal mature pattern of 8–12 Hz (alpha activity). These posterior rhythms are usually symmetric, and attenuate with eye opening or alerting. Posterior delta waves (2–4 Hz) may occur intermittently in adolescence or early adulthood (posterior slow waves of youth). Theta activity (5–8 Hz) is often seen in the central regions particularly with drowsiness. Low amplitude beta (15–22 Hz) activity is best seen anteriorly.

Important normal EEG variants may mimic epileptiform discharges (Klass & Westmoreland, 1985) and lead to erroneous support being given to a diagnosis of epilepsy.

Abnormal EEG findings

These are of three types: interictal epileptiform discharges, ictal electrographic activity, non-epileptiform changes.

Interictal epileptiform discharges

Interictal epileptiform discharges consist of spikes (duration 20–70 ms) or sharp waves (duration 70–200 ms), with or without associated slow waves. These may be localized, multifocal or generalized. Epileptiform abnormalities are seen in less than 1% of apparently healthy subjects without a history of epilepsy (Gregory et al., 1993). The false-positive rate is higher in patients with other neurological abnormalities. Lesions such as strokes and tumours may be associated with sharp waves or spikes without any clinical seizures. Skull defects may cause 'breach rhythms' (Cobb et al., 1979), sometimes producing apparent spikes or runs of rhythmic sharp activity mimicking a seizure, but are of no clinical significance.

Ictal electrographic patterns

An EEG recording taken during an epileptic seizure can take many forms, depending upon the seizure type and pathways of spread. They are usually sustained, rhythmic, clearly different from the interictal record and, at least in partial epilepsies, evolve in frequency and/or amplitude, sometimes being followed by flattening of the trace and/or slow activity. Simple partial seizures are often not associated with any change in the scalp EEG. Frontal lobe attacks often have prominent motor components that obscure the EEG, and there may be few evident changes.

Non-epileptiform EEG abnormalities

Non-epileptiform EEG abnormalities include asymmetry of amplitude or frequency, localized and generalized slow waves. Asymmetries of the background EEG activity may reflect areas of localized damage. Widespread or generalized slow waves suggest an encephalopathic process, including antiepileptic drug toxicity, and may also occur postictally.

EEG findings characteristic of epilepsy syndromes

Idiopathic generalized epilepsy

The key features are: generalized epileptiform discharges, often at 3 Hz, normal background and, often, photosensitivity. In contrast, EEGs of partial epilepsy commonly have focal or multifocal epileptiform discharges, abnormal background activity and rarely photosensitivity. Confusion can occur. Focal spikes may propagate to produce bilaterally synchronous discharges mimicking generalized epilepsy. This is most likely to occur with extratemporal epilepsy, especially if due to parasagittal lesions or cortical dysgenesis. EEGs in patients with idiopathic generalized epilepsy may contain focal discharges or show asymmetries (Grunewald & Panayiotopoulos, 1993). Occasional patients have both idiopathic generalized and partial epilepsy.

Photosensitivity is age dependent. In the peak age group of 7–19 years 10% of patients with newly presenting seizures show unequivocal photosensitivity on the EEG, with a female: male ratio of 3: 2, while it rarely presents at other ages (Fish et al., 1993). Photosensitive EEG responses have been classified by Waltz et al. (1992) into four categories: (i) occipital spikes; (ii) occipital spike and slow waves with spread to the parieto-occipital regions; (iii) occipital spike and slow waves with frontal spread; (iv) generalized spike and slow wave discharges.

Type 4 responses are the most common in patients with idiopathic generalized epilepsy, but may occur in progressive myoclonic epilepsies, metabolic disorders, and occasionally in occipital partial epilepsies.

EEG findings in partial epilepsies

EEG findings in partial seizure disorders reflect the site of onset and the etiology of the epilepsy. Foreign tissue lesions are likely to be associated with localized slow activity, while neocortical atrophic processes may be associated with a relative paucity of normal rhythms.

In temporal lobe epilepsy interictal spikes are usually maximum over the temporal or fronto-temporal regions. Even in patients with unilateral temporal lobe lesions or hippocampal sclerosis who are good surgical candidates the interictal spikes are often bilateral and independent, especially during sleep. The ictal scalp EEG often shows rhythmic theta at the onset that may be localized to the affected temporal lobe or be bilateral. In frontal lobe epilepsy there is much variability between patients in the scalp EEG, reflecting the heterogeneity of syndromes and the difficulties in recording from the frontal cortex. The interictal EEG often shows no epileptiform activity, bilaterally synchronous spikes or widespread spiking. Localized unifocal spikes are relatively uncommon. The ictal scalp EEG is often obscured by muscle and movement artefact, and because of rapid seizure propagation, localized changes are rare. Even when movement artefact does not obscure the trace, the scalp EEG may remain unchanged or only show poorly formed postictal slowing.

In parieto-occipital lobe epilepsy interictal spikes may be posterior, but there are often more anterior discharges, over the temporal regions or bilateral, synchronous widespread discharges. The latter may be the most apparent feature. Similarly, ictal scalp recordings may show more anterior changes than would have been expected.

Infantile spasms

The resting EEG shows a characteristic disorganized high voltage pattern, with generalized attenuation during the spasms. Hypsarrythmia may be seen bilaterally or, in some cases, unilaterally.

Benign rolandic epilepsy

This condition is characterized by unilateral or bilateral, triphasic, large-amplitude spikes that are maximum in the central or centro-temporal areas, without background abnormalities (Loiseau & Beaussart, 1973).

Benign occipital epilepsy

Posterior 1.5–3 Hz spike and slow wave discharges may occur singly or in long runs, may be lateralized, and usually attenuate with eye opening. Spread of activity may occur to produce a picture of generalized epileptiform discharges (Newton & Aicardi, 1983).

Lennox–Gastaut syndrome

The background EEG is usually slow and disorganized, with 1–2.5 Hz generalized, anteriorly predominant spike and slow wave discharges. During sleep there are often bursts of fast generalized spikes.

Electrical status epilepticus in slow wave sleep

More than 85% of slow wave sleep shows spike and wave activity, which is usually generalized.

Non-epileptic seizures

In non-epileptic seizures, rhythmic head movements can produce EEG artefacts that may mimic cerebral ictal activity, and this may lead to erroneous conclusions. In non-epileptic attack disorder, however, the record abruptly returns to normal in-between the movements and alpha activity may then be seen which attenuates with alerting stimuli such as calling the patient's name or forced eye opening (Meierkord et al., 1991).

Assessment of possible encephalopathy

Herpes simplex encephalitis has a characteristic appearance with disorganized and slow background rhythm with periodic lateralized epileptiform complexes at 2–4 second intervals, which are often particularly evident over the fronto-temporal areas. These features may, however, be lacking or only evolve over several days. In a metabolic encephalopathy, background rhythms are slowed and there is widespread excessive theta and delta activity. These appearances however are non-specific and the EEG appearances are not a good guide to the cause of an encephalopathy.

Magnetic resonance imaging (MRI)

The investigation and treatment of patients with epilepsy has been revolutionized by MRI. The superiority of MRI over X-ray computed tomography (CT) scanning in terms

of sensitivity and specificity for identifying the etiology of epilepsy in both adults and children is clear (Kuzniecky et al., 1993). The most common abnormalities are hippocampal sclerosis (HS), malformations of cortical development (MCD), vascular malformations, tumours, and acquired cortical damage. X-ray CT, however, may be preferred to MRI if a patient is disturbed or acutely unwell, as the patient is more accessible during the procedure. An X-ray CT scan is also valuable for the investigation of possible acute intracranial hematomas and skull fractures, and as a supplement to MRI for clarification of possible intracranial calcification.

MRI epilepsy protocol

Indications for neuroimaging of patients with epilepsy

The Neuroimaging Commission of the International League against Epilepsy has produced consensus statements of recommendations. The rationale for imaging the brains of patients developing epilepsy is first to identify underlying pathologies such as vascular lesions and tumours that require specific therapy; and second to assist the formulation of syndromic and etological diagnoses (Berkovic et al., 1997). Further recommendations have been made for patients with refractory seizures (Berkovic et al., 1998) and for functional imaging techniques (Duncan et al., 2000).

MRI should include T_1- and T_2-weighted sequences to cover the whole brain in at least two orthogonal planes, with the minimum slice thickness possible on the scanner used. Gadolinium contrast enhancement is not indicated routinely, but may clarify findings in occasional patients (Cascino et al., 1989). Sequences should include a volume acquisition with a partition size of 1.5 mm or less to permit reformatting in any orientation and three-dimensional reconstruction of the data set. In the first two years of life, incomplete myelination results in poor grey–white matter contrast, making identification of cortical abnormalities difficult, and in these cases MRI may need to be repeated after 1 to 2 years.

In an acute situation when seizures occur in the context of a neurological insult, X-ray CT is an appropriate initial investigation if MRI is not readily available or not possible for technical reasons, for instance if the patient has a cardiac pacemaker or requires attention during the scan.

The best practice is to obtain MRI in all patients with epilepsy, with the exception of those with a definite diagnosis of idiopathic generalized epilepsy or benign rolandic epilepsy of childhood with centrotemporal spikes. MRI is particularly indicated in patients with: onset of partial seizures, at any age; onset of generalized or unclassified seizures in the first year of life, or adulthood; evidence of a fixed deficit on neurological or neuropsychological examination; difficulty obtaining seizure control with first-line antiepileptic drugs; loss of seizure control, or a change in the pattern of seizures.

Patients who are candidates for surgical treatment of epilepsy require detailed brain imaging (see chapter 78).

In situations in which access to MRI is limited, essential indications for MRI are: patients with partial or secondary generalized seizures, and apparently generalized seizures, that are not controlled with AEDs; patients who develop progressive neurological or neuropsychological deficits.

A typical presurgical MRI protocol would be: volume acquisition T_1-weighted data set that is acquired in an oblique coronal orientation, orthogonal to the long axis of the hippocampi, and covers the whole brain in 0.9 mm partitions. This sequence produces approximately cubic voxels, allowing for reformatting in any orientation, subsequent measurement of hippocampal morphology and volumes, and for three-dimensional reconstruction and surface rendering of the brain; oblique coronal spin-echo sequence, with proton density (TE = 30) heavily T_2-weighted (TE = 90 or 120) and FLAIR acquisitions that are orientated perpendicularly to the long axis of the hippocampus, to demonstrate any increase in T_2-weighted signal intensity.

Structural cerebral abnormalities underlying epilepsy identified with MRI

Hippocampal sclerosis

This is the single most common pathology underlying refractory partial seizure disorders. Two-thirds of patients with HS become seizure free after an anterior temporal lobe resection (Berkovic et al., 1995). The hippocampus is best visualized in two planes: along its long axis and orthogonal to this. These imaging planes may be readily determined on a sagittal scout image: the axial plane being in the line joining the base of the splenium of the corpus callosum to the inferior, posterior border of the frontal lobe and the coronal plane being perpendicular to this, parallel to the anterior border of the brainstem.

The features of HS identified by MRI are hippocampal atrophy, demonstrated with coronal T_1-weighted images, and increased signal intensity within the hippocampus on T_2-weighted spin-echo images (Jackson et al., 1990), decreased T_1-weighted signal intensity and disruption of the internal structure of the hippocampus (Jackson et al.,

1993a). Atrophy of temporal lobe white matter and cortex, dilatation of the temporal horn and a blurring of the grey–white matter margin in the temporal neocortex (Meiners et al., 1994) variably accompany HS.

Quantitative MRI assessment of the hippocampus

Assessment of atrophy can be improved by measurement of the hippocampal volumes (Cascino et al., 1991). However, a satisfactory operative outcome is possible in patients with bilaterally symmetric mesial temporal sclerosis (Jack et al., 1995), underlining the fact that factors other than MRI need to be taken into account in presurgical decision-making. Identification of a structural lesion does not always indicate the site of seizure origin. Clinical, EEG and other data all need to be considered (Holmes et al., 1999).

The severity of hippocampal atrophy on the side of the language-dominant hemisphere is an important determinant of impairment of verbal memory following hippocampal resection. The more severe the atrophy preoperatively, the less likely it is that there will be a significant decline of verbal memory after surgery (Trenerry et al., 1993).

Hippocampal volumetry is demanding and time consuming, requiring a skilled operator and a postprocessing computer (Cook et al., 1992). In clinical practice, hippocampal asymmetry of 20% or more is reliably visually apparent to skilled neuroimaging specialists, but lesser degrees of asymmetry require quantification (Van Paesschen et al., 1995).

Hippocampal T2 signal may be quantified by measurement of hippocampal T2 relaxation time (HT2). T2 relaxation time measurements are a useful identifier of hippocampal pathology, with marked elevations being associated with HS and intermediate values being seen in patients without qualitative MRI evidence of HS, contralateral to HS, and some patients with extratemporal seizures (Jackson et al., 1993b). There is an inverse correlation between HT2 and the ratio of glial to neuronal density in the hippocampus and a close correlation between HT2 and severity of hippocampal volume loss, allowing delineation in vivo of a spectrum of the severity of HS, using quantitative MRI (Van Paesschen et al., 1995, 1997a,b). This may be used in the evaluation of patients and also in longitudinal studies to determine whether there is any evidence of progression of the condition.

HS may be of varying severity along the length of the hippocampus. Hippocampal atrophy and increase in T2 may be confined to the anterior centimetre (Duncan et al., 1996; Woermann et al., 1998). Hippocampal T2 measurements and hippocampal volumes, corrected for the intracranial volume, are useful methods for identifying bilateral hippocampal sclerosis (Van Paesschen et al., 1997a; Free et al., 1995).

Although MRI has made a considerable difference to the evaluation of patients with refractory seizures who are candidates for surgical treatment, the technique does not make other investigations redundant. Clinical and functional data (neurophysiological, psychological and, in some cases, functional imaging) all need consideration in reaching a consensus for individual patients (Spencer, 1995). Some patients with seizure onset outside of the temporal lobe may have MRI features of HS (Cascino et al., 1993).

Malformations of cortical development

Malformations of cortical development (MCD) are common causes of epilepsy and neurodevelopmental deficits. The range of MCD identified with MRI include schizencephaly, agyria, diffuse and focal macrogyria, focal polymicrogyria, minor gyral abnormalities, subependymal grey matter heterotopias, bilateral subcortical laminar heterotopia, tuberous sclerosis, focal cortical dysplasia and dysembryoplastic neuroepithelial tumours (DNTs). The best results are obtained using T_2-weighted and high resolution T_1-weighted volumetric techniques with thin partitions, covering the whole brain and allowing viewing of the structures in two orthogonal planes. Analysis of MRIs of young children needs to take into account the normal development of myelination and the indistinct grey–white matter boundary on T_2-weighted images in children aged less than two years.

Dysembryoplastic neuroepithelial tumours are regarded as benign developmental tumours and not infrequently underlie refractory partial seizures. A circumscribed cortical mass may indent the overlying skull and extend subcortically, with low signal intensity on T_1-weighted images, high signal on T_2-weighted images that is similar to CSF, and slightly higher signal intensity in the lesion than CSF on proton density images. Cyst formation and enhancement with gadolinium–DTPA may occur. Calcification is present in some cases and may be more readily demonstrated with X-ray CT. Confident differentiation from low-grade astrocytomas and ganglioglioma is not possible by MRI (Koeller & Dillon., 1992; Raymond et al., 1994, 1995).

Granulomas

Tuberculomas and cysticercosis are the most common identified causes of epilepsy in developing countries. Epilepsy is the most common manifestation of neurocysticercosis (Aubry et al., 1995; Gulati et al., 1991). MRI is more sensitive than X-ray CT in demonstrating various stages in

the development of non-calcified cerebral cysticercosis lesions (Sanchetee et al., 1991).

Cavernomas

Cavernomas are often not identified on X-ray CT, but have a characteristic appearance on MRI (Requena et al., 1991). Cavernomas have the characteristic appearance of a range of blood products. The central part contains areas of high signal on T_1- and T_2-weighted images, reflecting oxidized hemoglobin, with darker areas on T_1-weighted images due to deoxyhemoglobin. The ring of surrounding hemosiderin appears dark on a T_2-weighted image. There may be calcification, which usually appears dark on T_1- and T_2-weighted images. There is no evidence of arteriovenous shunting. Arteriovenous malformations with high blood flow have a different and distinctive appearance.

Other pathologies

Focal and generalized atrophy, tumours, scars, cysts, ischemic and traumatic lesions underlying and associated with epilepsy are all well demonstrated with MRI. Ischemic lesions associated with epilepsy are particularly common in the older age group and are well demonstrated with MRI (Kilpatrick et al., 1991).

Indolent gliomas are clearly identified using MRI. These lesions are commonly ill defined, non-cystic, do not enhance, and appear to arise from deep white matter. Intracranial epidermoid cysts may give rise to refractory partial seizures and a fixed neurological deficit that is stable over many years.

MRI in evaluation for surgical treatment of epilepsy

MRI has had a marked impact on presurgical evaluation (Berkovic et al., 1998; Spencer, 1995; Cascino, 1994; Zentner et al., 1995). While MRI may identify lesions underlying refractory epilepsy, such as HS, MCD and cavernomas, clinical and functional data (neurophysiological, psychological and, in some cases, functional imaging) also need consideration to reach a consensus for individual patients. Refer to Chapter 78 for more details.

Functional MRI

Ictal and interictal epileptiform activity

Functional MRI (fMRI) can detect ictal changes in cerebral blood flow (Jackson et al., 1994; Detre et al., 1995; Warach et al., 1996). Limitations of the method include movement artefact, and the fact that it is impracticable for a patient to lie for hours in an MRI scanner awaiting the onset of a seizure.

The development of safe and reliable EEG recording from subjects having fMRI studies has been a major step forward in the fMRI of interictal epileptiform activity (Ives et al., 1993; Allen et al., 1998). Focal increases in cerebral blood delivery have been identified in patients with frequent interictal spikes (Krakow et al., 1999). These methods will aid EEG interpretation and understanding of the pathophysiological basis of epileptic activity. Their application, utility and limitations in defining the irritative zone of the cortex and its relationship with the epileptogenic zone in patients in whom surgical treatment is being considered will need careful evaluation.

Localization and lateralization of cognitive function

An important use of fMRI is to delineate areas of brain that are responsible for specific functions, such as the primary sensory and motor cortex, and to identify their anatomical relation to areas of planned neurosurgical resection (Puce et al., 1995; Rao et al., 1995). In patients with cerebral lesions, the localization of cognitive activation may differ from the pattern in normal subjects (Alsop et al., 1996).

Language function may be lateralized using fMRI (Binder et al., 1996) and fMRI language studies have generally concurred with carotid amytal testing (Desmond et al., 1995; Benson et al., 1999). fMRI results, however, do not always accord with the carotid amytal data (Worthington et al., 1997). Further, identification of the areas of brain involved in language is not the same as determining if someone can speak when half of the brain is anesthetized. Studies in which word generation is compared with the rest state usually show activation of anterior language areas. Comparisons of semantic tasks with non-linguistic control tasks show more widespread activation in the dominant hemisphere (Binder et al., 1997).

At present, many candidates for anterior temporal lobe resection require carotid amytal tests in order to determine whether they would be at risk of severe memory impairment following the surgery. The test is crude and indicates whether the contralateral temporal lobe is able to subserve basic short-term memory functions. Several fMRI studies have shown activation of bilateral posterior medial temporal lobe during encoding of novel verbal and spatial material (Gabrieli et al., 1997). A complex visual scene encoding task that activates mesial temporal structures has been used during fMRI. Activation patterns were nearly symmetric in normal subjects, but asymmetries were noted in patients with temporal lobe epilepsy (Detre et al., 1998). The development of appropriate fMRI visual and verbal memory tasks is an area of intense research (Otten et al., 2001; Maguire et al., 1998). fMRI may have a

role in preoperative assessment of memory function, but the integration of cognitive activation data into surgical decision-making needs to be cautious. There are two principal caveats: first, if a cerebral area does not activate on a specific task this does not imply that it may be removed with impunity; secondly, the activation of a particular cerebral area with a specific task does not necessarily imply that surgery to that area would cause a clinically significant fixed deficit.

Proton magnetic resonance spectroscopy

In epilepsy studies in vivo, the principal signals of interest have been those from *N*-acetyl aspartate (NAA), creatine + phosphocreatine (Cr), choline-containing compounds (Cho), and lactate (Lac). NAA is located primarily within neurons and precursor cells and a reduction of NAA signal is usually regarded as indicating loss or dysfunction of neurons. Cr and Cho are found both in neurons and in glial cells. In temporal lobe epilepsy caused by HS, reduction of NAA and increases of choline-containing compounds and creatine + phosphocreatine, reflecting neuronal loss or dysfunction and astrocytosis are commonly found (Connelly et al., 1994; Cross et al., 1996; Woermann et al., 1999). The implication from these data was that there is neuronal loss or dysfunction and astrocytosis in the temporal lobes of patients with temporal lobe epilepsy. Abnormalities of metabolite profiles may be found in temporal lobes with normal MRI (Knowlton et al., 1997; Connelly et al., 1998; Woermann et al., 1999). At present, ^{1}H MRS appears to be a sensitive method for detecting regional neuronal integrity and may identify areas of gliosis. The rapid developments now being made in MR hardware and software may enable parametric imaging of the cerebral concentrations of these compounds, and this may have important consequences for the non-invasive investigation and the medical and surgical treatment of patients with epilepsy.

Single photon emission computerized tomography (SPECT)

Single photon emission computerized tomography is principally used to image the distribution of cerebral blood flow (CBF). In addition, there have been a few studies of specific receptors in the brain.

Interictal SPECT studies

The marker of an epileptic focus studied interictally is a region of reduced CBF, but the results are not always reliable (Stefan et al., 1987; Ryvlin et al., 1992). In one large representative series, there was correct localization in 38% in interictal studies of patients with unilateral temporal lobe EEG foci (Rowe et al., 1991). Localization with interictal SPECT is more difficult in patients with extratemporal epilepsy. In a blinded comparative study, interictal SPECT was less effective at lateralizing the focus of temporal lobe epilepsy than MRI, with correct lateralization in 45% compared to 86%. Furthermore, agreement of MRI and EEG data was a good predictor of a satisfactory result from surgical treatment, whereas SPECT was not and was prone to give an incorrect result in patients whose MRI was not lateralizing (Jack et al., 1994). In consequence, interictal SPECT has little place in the routine investigation of patients with epilepsy.

Ictal and postictal SPECT studies

The increase in CBF associated with a seizure may be detected using SPECT (Bonte et al., 1983). This may provide useful localizing information in patients with partial seizures. An injection of ^{99m}Tc-HMPAO at the time of a seizure results in an image of the distribution of CBF 1 to 2 minutes after tracer administration, which is then stable for several hours so that the patient may be imaged when the seizure is over. The general pattern is of localized ictal hyperperfusion, with surrounding hypoperfusion, that is followed by accentuated hypoperfusion in the region of the focus, which gradually returns to the interictal state. Combined data from interictal and ictal SPECT scans give a lot more data than interictal scans alone. A meta-analysis showed that in patients with temporal lobe seizures, the sensitivities of SPECT relative to diagnostic evaluation were 0.44 (interictal), 0.75 (postictal) and 0.97 (ictal) (Devous et al., 1998).

Ictal SPECT investigations may be carried out in children (Cross et al., 1995; O'Brien et al., 1998a). In one large series, ictal SPECT achieved 97% correct localization in unilateral temporal lobe epilepsy, compared with 71% for postictal SPECT and 48% for interictal scans. In extratemporal seizures ictal SPECT studies localized the focus in 92%, compared to 46% for postictal studies, and interictal SPECT was of little value (Newton et al., 1995). The coregistration of interictal with ictal or postictal SPECT images, to result in an 'ictal difference image' that may be coregistered with an individual's MRI enhances objectivity and the accuracy of data interpretation (Zubal et al., 1995; O'Brien et al., 1998b, 1999). In conclusion, SPECT gives the ability to obtain images representative of CBF at the time of seizures. These data need careful and cautious interpretation and are non-quantitative.

Positron emission tomography (PET) studies

An epileptogenic focus, studied interictally, is associated with an area of reduced glucose metabolism, and reduced blood flow, that is usually considerably larger than the pathological abnormality (Engel et al., 1982). ^{18}FDG-PET scans provide superior resolution and greater reliability for identifying a focal deficit than do PET scans using ^{15}O-water or SPECT scans of cerebral blood flow (Ryvlin et al., 1992). Partial seizures are associated with an increase in regional cerebral glucose metabolism and blood flow in the region of the epileptogenic focus, and often a suppression elsewhere (Engel et al., 1983). In general, ictal PET scans can only be obtained fortuitously, because of the two minute half-life of ^{15}O and the fact that cerebral uptake of ^{18}FDG occurs over 40 minutes after injection, so that cerebral glucose utilization data will reflect an amalgam of the ictal and post-ictal conditions. The place of this technique has been re-evaluated in the light of developments in MRI as the finding of a definite focal abnormality with the latter technique, such as HS, may render an ^{18}FDG–PET scan superfluous (Heinz et al., 1994; Gaillard et al., 1995).

There is a 60–90% incidence of hypometabolism interictally in temporal lobe epilepsy (Engel et al., 1982; Ryvlin et al., 1992), and in about 60% of patients with frontal lobe epilepsy. In 90% of those with a hypometabolic area, structural imaging shows a relevant underlying abnormality. In common with temporal lobe epilepsy, the area of reduced metabolism in frontal lobe epilepsy may be much larger than the pathological abnormality. In contrast, however, the hypometabolic area may be restricted to the underlying lesion (Engel et al., 1995). Overall, ^{18}FDG–PET does not appear to provide additional clinically useful information in the majority of patients with frontal lobe epilepsy.

Studies with ^{18}FDG-PET have defined the major cerebral metabolic associations and consequences of epilepsy but the data are non-specific with regard to etiology and abnormalities are more widespread than the pathological lesions. The role of ^{18}FDG–PET in the clinical evaluation of patients has been reduced by the advances made in MRI over the last 5 years. Activation studies may be performed with $H_2{}^{15}O$ but these studies are now increasingly performed with functional MRI.

Specific ligands

Positron emission tomography may be used to demonstrate the binding of specific ligands, for example, ^{11}C-flumazenil to the central benzodiazepine–$GABA_A$ receptor complex and abnormalities of binding may identify functional abnormalities that are more widespread than structural abnormalities identified by MRI (Duncan & Koepp, 2000).

Neuropsychological assessment

A minority of patients with epilepsy, particularly those with poorly controlled seizures, are at risk of disorders of cognitive function and benefit from a detailed neuropsychological assessment.

Assessment of newly diagnosed and chronic patients

Testing may reveal a specific cognitive deficit. Subsequent assessments can determine whether there is progressive impairment of focal or widespread cerebral dysfunction, which requires further evaluation and treatment.

Monitoring of the effects of AEDs

All AEDs, at high doses, may impair cognitive function. The predominant effects of AEDs are slowing on tasks with a motor component and impairment of mental speed, attention and concentration. Neuropsychological assessment can identify deficits in these areas and repeat testing after changes in AED therapy may be used as an indicator as to whether function has improved or not. Computerized psychological tests add precision to assessments, particularly in recording the speed of processing (Thompson, 1991). It may be difficult to ascertain the effects of continued seizures, AEDs and fixed cerebral deficit on motor and mental speed, attention and concentration.

Assessment of individual potential

People with intractable epilepsy frequently may have their abilities under- or overestimated because a global IQ figure may mask an uneven cognitive profile. Identifying an individual's strengths and weaknesses helps realistic goals to be set regarding independent living and employment and to identify whether they have untapped potential that may respond to a period of rehabilitation. This knowledge can avoid misunderstandings, particularly when there are hidden deficits. Assessment may also determine whether there is evidence of progressive decline of cognitive functions. Identification of deterioration has important implications for investigations of the cause and for the making of care plans.

Neuropsychological test schedules

There is no one cognitive deficit that is characteristic of patients with epilepsy and a broad range of functions needs to be assessed. A basic neuropsychological schedule for patients with epilepsy would comprise the subtests of the WAIS-R, tests of language, memory, perception and spatial functioning. The Nelson Adult Reading Test provides an estimate of an individual's premorbid intellectual function. Measures considered sensitive to frontal lobe

function are also employed. Additional more detailed testing of functions is undertaken if specific difficulties are uncovered during the routine neuropsychological screen.

Interpretation of data in patients with epilepsy

The neuropsychological assessment of patients with epilepsy needs to take into account the possible effects of AED therapy, recent seizures and ongoing seizure activity. Sometimes this is obvious, for example the patient who has had a generalized tonic–clonic seizure two hours previously and who is still drowsy, or the child in whom absences are occurring every few minutes throughout the test session. The possibility of occult disturbance by seizures needs to be considered if performance is less good than expected, and can be assessed by simultaneous video–EEG recording.

The relevance of performance on neuropsychological tests to day-to-day functioning is not always evident. Measures of general intelligence can be linked to educational attainment and potential to live independently. The finding of frontal lobe deficits can help explain why an apparently able individual is functioning poorly in daily living situations, for example being dependent on others to structure activities. Language difficulties may have been covert for many years and contribute to disturbed behaviour.

Memory

Patients with epilepsy frequently complain of memory difficulties, but on neuropsychological assessment of memory may perform at an average level. Memory is an umbrella term and formal neuropsychological assessment generally focuses on the ability to learn new information. Important areas that current tests do not adequately evaluate include prospective memory functions, such as the ability to take medication or attend an appointment (Corcoran & Thompson, 1993; Blake et al., 2000).

Assessment of patients with mental handicap

There is only a limited range of assessment measures suitable for patients with moderate to severe learning difficulties. The general approach is to employ measures that have been developed for use with children, which may not be appropriate for use with adults. Instruments such as The British Ability Scale however, allow consideration of relative strengths and weaknesses of different cognitive functions (Elliott et al., 1983).

Assessment of mood, wellbeing and behaviour

At present, such measures have little use in the day to day management of patients, but are used in research protocols that attempt to evaluate the effect of medical and surgical treatment on broader aspects than suppression of seizures. Data are usually gathered from patient compiled questionnaires that result in a single score or a profile of scores (Hermann et al., 1992; Vickery et al., 1992; O'Donoghue et al., 1998). Behavioural disturbance sometimes accompanies epilepsy, often in the setting of mental handicap, and may be compounded by some medications. It can be useful to quantify the extent of this disturbance in order to monitor the effects of changes in medication, environment and behavioural management programmes, with the use of questionnaires and rating scales compiled by relatives, carers and teachers.

Presurgical neuropsychological evaluation

Detailed neuropsychological evaluation is fundamental to the consideration of patients for epilepsy surgery (see Chapter 78), particularly when a temporal lobe resection is contemplated.

Other investigations at initial assessment

This should include a biochemical screen and full blood count. HIV and other serological tests should be considered. There is usually a rise in serum prolactin concentration for up to 20 minutes after a generalized tonic–clonic seizure to above 1000 mU/l. It is important to compare postictal prolactin levels with a baseline value, to differentiate between a postictal rise and a persistent elevation of prolactin concentration. Serum prolactin does not generally elevate after non-epileptic convulsive seizures. These data may be diagnostically useful, in conjunction with video and EEG data (Rao et al., 1989). Prolactin may rise however after a severe syncopal event. Serum prolactin does not rise as far or as consistently following complex partial seizures. Seizures arising from a temporal lobe are more likely to be associated with a rise than those from the frontal lobes (Meierkord et al., 1992). No consistent rise is seen after simple partial seizures (Pritchard et al., 1983).

Cardiac investigations are indicated if there is a suspicion of arrhythmias or other cardiac disease.

Inborn errors of metabolism only rarely give rise to epilepsy but need to be considered, particularly if there is evidence of other neurological disease. The more common include: pyridoxine dependency, that presents in the neonatal period and responds rapidly to intravenous pyridoxine; adrenoleukodystrophy, diagnosed by finding increased very long chain fatty acids in plasma; non-ketotic hyperglycinemia; D-glyceric acidemia; phenylketonuria; porphyria; biopterin deficiency; GABA transaminase deficiency with 4-hydroxybutyric aciduria; urea cycle defects; mitochondrial

cytopathy; neuronal ceroid lipofuscinosis; GM2 gangliosidosis; Gaucher's disease; sialidosis I & II; Lafora body disease; globoid cell leukodystrophy.

Examination of the cerebrospinal fluid (CSF) is not routinely indicated in the evaluation of patients developing epileptic seizures.

Assessment of neurological and cognitive decline in patients with epilepsy

Approach to investigation

As epilepsy often occurs in the context of mental handicap and fixed neurological deficit, it is necessary to determine whether a patient with mental and/or neurological dysfunction has a static or progressive deficit and to establish the etiology. A static deficit may result from an acquired brain insult or congenital malformation (Table 76.7). Investigation should be pursued more aggressively if there is evidence of progressive deterioration, to determine whether there may be a remediable pathology, to give an estimation of prognosis so that appropriate care may be arranged, and to ascertain whether there is an inherited condition that may carry genetic implications for the patient's relatives.

Clinical features

It is not always straightforward to determine whether or not a patient is showing progressive decline. A careful history and clinical examination are essential as are knowledge of the behaviour and development of normal children. Important aspects of the history are to determine from relatives and carers what social, motor, language and self-care skills a patient had at best, and whether further skills are being acquired, whether the situation is static, or whether once-held skills are being lost. This assessment needs to take into account the normal processes of acquisition of skills through the first two decades of life. Normal development may mask the occurrence of gradually progressive dysfunction until the late teens. Further, if a patient is functioning at a low level, it may be difficult to detect a progressive deterioration. A careful family history, including enquiries about consanguinity and of more distant relatives than the immediate family, is essential if there is any suggestion that the patient has a genetically determined disorder. In the history and examination particular attention should be paid to identifying any cognitive decline, pyramidal signs, dystonia, myoclonus, other movement disorders, cerebellar ataxia, visual deficit, peripheral neuropathy or myopathy.

Table 76.7. Causes of epilepsy and static cognitive and neurological deficit

Inherited
Tuberous sclerosis
Neurofibromatosis
Incontinentia pigmenti
Hypomelanosis of Ito
Angelman's (Happy puppet) syndrome
Non-inherited congenital malformations
Chromosomal abnormalities: trisomy, deletions, fragile X
Neuronal migration defects, cortical dysplasia (may also result from prenatal, postnatal insult).
Aicardi syndrome
Sturge–Weber syndrome
Other cerebral malformations
Acquired
Prenatal
Antepartum hemorrhage
Toxemia
Brain infection (encephalitis, meningitis): especially CMV, toxoplasmosis, herpes, rubella, Epstein–Barr, influenza, syphilis
Perinatal
Anoxia
Hypoglycemia
Hypocalcemia
Postnatal
Brain infection (encephalitis, meningitis)
Hydrocephalus
Cerebral trauma
Cerebral ischemia, infarction
Cerebral hemorrhage
Postimmunization encephalopathy
Malignancy
Radiation
Status epilepticus

Iatrogenic causes

It is essential to consider whether apparent cognitive and neurological decline may be iatrogenic, as a result of AEDs or other medication. In patients with pre-existing cognitive and motor impairment, the expected features of dose-related intoxication may not be apparent and serum AED concentrations should be checked. Further, some patients, particularly those with mental handicap, may be intoxicated with AEDs at serum concentrations that are not above the widely quoted 'therapeutic ranges'. If there is a possibility that AEDs may be contributory the appropriate course is to reduce the dose and to then reassess the patient.

Table 76.8. Conditions in which epilepsy is the only evident disorder causing progressive impairment

Iatrogenic: Intoxication with medication
Cryptogenic infantile spasms (West syndrome)
Non-convulsive epileptic status epilepticus (including some patients with the Lennox–Gastaut syndrome)
Focal epileptic encephalopathies (e.g. Landau–Kleffner syndrome)
Electrical status epilepticus in slow wave sleep
Epileptic encephalopathy: frequent seizures, episodes of status

Although most frequent with barbiturates and phenytoin, this situation may also arise with more modern AEDs, and a 'pseudodementia' in association with sodium valproate is well recognized (Pakalnis et al., 1989, Jones et al., 1990).

Conditions in which progressive neurological impairment is secondary to the epilepsy

These are summarized in Table 76.8.

Investigation of progressive neurological diseases

It is difficult to lay down criteria for when a patient's cognitive deterioration is disproportionate to the severity of their epilepsy and a neurodegenerative condition of which epilepsy is just one manifestation should be sought. The possibility should be considered if a patient is deteriorating, particularly if evidence of other fixed neurological dysfunction becomes apparent.

Identified conditions that give rise to a progressive impairment of higher mental function and epilepsy are mostly genetically determined (Table 76.9). There are many common clinical features to diseases causing progressive neurological and cognitive decline and there is a considerable overlap between syndromic groupings and identified etiologies. It is, however, possible to identify clinical syndromes which have a limited range of etiologies and necessary investigation can be restricted. The investigations that may be useful in the assessment of progressive neurological conditions of which epilepsy is a part are summarized in Table 76.10.

Progressive myoclonus epilepsy (PME)

The progressive myoclonus epilepsies form a recognizable syndrome, with several identified etiologies. The key features of this syndrome are progressive myoclonic seizures, occasional tonic–clonic seizures, ataxia and cognitive impairment (Berkovic & Andermann, 1986). This syndrome

Table 76.9. Progressive neurological conditions of which epilepsy may be part

Structural lesions
Hydrocephalus
Progressive structural lesions, e.g. glioma
Cerebrovascular disease
Storage disorders
GM2 and GM1 gangliosidosis
Neuronal ceroid lipofuscinosis
Niemann–Pick Disease
Gaucher's disease
Sialidosis
Lafora body disease
Leukodystrophies
Metachromatic
Globoid cell (Krabbe's)
Adrenoleukodystrophy
Spongiform leukodystrophy (Canavan's)
Alexander's disease
Pelizaeus–Merzbacher disease
Defined neurometabolic disturbance
Amino acidurias
Urea cycle disorders
Organic acidemias
Non-ketotic hyperglycinemia
Progressive neuronal degeneration of childhood with liver disease
Mitochondrial cytopathy (MERRF and MELAS)
Menkes' disease
Wilson's disease
Porphyria
Disorders of folate and cobalamin metabolism
Lesch–Nyhan disease (and other disorders of purine and pyrimidine metabolism)
Biochemical defect uncertain
Rett's syndrome
Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy
Neuroacanthocytosis
Juvenile Huntington's disease
Infective causes
Human immunodeficiency virus
Creutzfeldt–Jakob disease
Subacute sclerosing panencephalitis
Syphilis
Uncertain etiology
Rasmussen's encephalitis
Alzheimer's disease

Table 76.10. Investigations of progressive neurological conditions of which epilepsy may be part

1	Careful history, including a detailed family history
2	Examination, including skin with UV light, slit lamp examination of eyes
3	Serum AED concentrations
4	Neurophysiology
	EEG: waking, sleep, prolonged monitoring
	electroretinogram (ERG)
	Visual evoked response (VER)
	Somatosensory evoked response (SER)
5	Imaging: brain MRI, X-ray CT scans
6	Hematological indices
	Full blood count and film
	B12 and folate
	Lymphocyte vacuolation in peripheral blood
7	Blood chemistry
	Immunoglobulins
	Electrolytes, glucose, liver function
	Amino acids
	Serum acid phosphatase
	Porphyrins, porphobilinogen
	Leukocyte lysosomal enzymes
	Ammonia: fasting and after protein-containing meal
	Plasma copper, ceruloplasmin
	Very long chain fatty acids
8	Serology
	Viral: HIV, measles, rubella,
	Syphilis
9	Urine
	Amino acids and organic acids
	Porphyrins, porphobilinogen
	Bile salts
	Dolichols (urine sediment)
	Sialyloligosaccharides
10	Genetic analysis
	Karyotype
	Analysis of DNA in lymphocytes
	Mitochondrial cytopathy
	Prion mutation
	Huntington's disease
11	CSF examination
	Lactate and amino acids
12	Biopsy
	skin
	muscle
	bone marrow
	liver
	brain

needs to be differentiated from conditions which result in a progressive encephalopathy, but in which myoclonic seizures are not usually a prominent feature.

Causes of progressive myoclonus epilepsy (PME)

Unverricht–Lundborg disease; Lafora body disease; sialidosis type I and type II; neuronal ceroid lipofuscinosis; mitochondrial cytopathy (MERRF: myoclonus epilepsy ragged red fibres); Gaucher's disease; neuroaxonal dystrophy; dentatorubral–pallidoluysian atrophy; biotin responsive encephalopathy.

The most common etiology is Unverricht–Lundborg disease, which is autosomal recessive and is due to a deficiency of cystatin B (Alakurtti et al., 2000).

Neurophysiology

The EEG in PME usually shows generalized spike or polyspike and slow wave discharges and photosensitivity is often present. There is slowing of the background activity, reflecting the underlying progressive disorder. The EEG patterns do not help to distinguish the different etiologies.

In neuronal ceroid lipofuscinosis, the electroretinogram is usually undetectable. The visual evoked response (VER) is enlarged in the late infantile form and the EEG may show a low frequency photic stimulation response. The VER is reduced in the juvenile form and in sialidosis. Giant cortical responses to somatosensory stimulation are common in PME, but are not specific to the etiology. Peripheral neuropathy may occur with sialidosis I and mitochondrial cytopathy.

Neuroimaging

Variable degrees of atrophy may occur, but the appearances are not specific for the subtypes of PME.

Urine

Sedimentary dolichol is often increased in neuronal ceroid lipofuscinosis. Sialyloligosaccharides are increased in sialidoses. Organic acids are increased in biotin-responsive encephalopathy.

Blood

Lymphocyte vacuolation may be seen in neuronal ceroid lipofuscinosis and sialidosis. Gaucher's disease is commonly associated with a pancytopenia. Assays of leukocyte enzymes can diagnose the sialidoses (α-*N*-acetylneuraminidase, alpha-galactosidases) and Gaucher's disease (beta-glucocerebrosidase). In sialidosis type 1 alpha-*N*-acetylneuraminidase is reduced, in sialidosis type 2, activities of both alpha-*N*-acetylneuraminidase and beta-galactosidase are deficient. Analysis of mito-

chondrial DNA may reveal mutations that underly mitochondrial cytopathy.

Biopsies

Pathological examination of eccrine sweat glands in a skin biopsy for polysaccharide-containing inclusion bodies, using PAS, is a reliable method for diagnosing Lafora body disease. Lafora bodies may also be identified on a liver biopsy. Electron microscopy examination of eccrine secretory cells and other tissues reveals fingerprint profiles, deposits and curvilinear bodies in neuronal ceroid lipofuscinosis. The axon spheroids found in neuroaxonal dystrophy may not be seen in sections of peripheral nerve, but have been reported in autonomic nerve terminals.

A muscle biopsy is currently needed to diagnose mitochondrial cytopathy causing MERRF, but in the future may be obviated by advances in analysis of leukocyte DNA. Gaucher's disease may be diagnosed by finding characteristic foam cells on bone marrow examination. Brain biopsy is only very rarely indicated, when less invasive investigations have not yielded an answer, and when there is rapid progression, the possibility of a remediable etiology, when the patient and family wish to have as precise an explanation as possible, and when the diagnosis has profound implications for genetic counselling. Currently, neuroaxonal dystrophy and atypical inclusion body diseases may only be diagnosed in this way.

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Principles of pharmacotherapy of the epilepsies

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With a prevalence of 0.5 to 1% and over 50 million people affected worldwide, the epilepsies as a group represent the most common serious neurological disorder. In recent years, major advances have been made in characterizing their clinical and prognostic features and in clarifying their etiologies and pathophysiological mechanisms. Contrary to common belief, many epilepsies are potentially life threatening, with significant mortality being ascribed not only to the underlying disease but also to the seizures and their consequences (Nilsson et al., 1999). Moreover, seizures carry an important risk of morbidity, including traumatic injuries, psychiatric disturbances and impaired quality of life (Baker et al., 1997; Spitz, 1998). Even in educated societies, epilepsy is associated with significant stigma, and affected people may suffer more from prejudice and discrimination than from the actual manifestations of the disease (The Rest1 Group, 2000).

Fortunately, most epilepsy syndromes are fully treatable, and up to 70% of patients may achieve complete seizure control and live a normal life, mainly thanks to the availability of effective drugs. Appropriate management requires knowledge of the characteristics of the disease, its associated risks, its natural prognosis and, not least, the clinical pharmacology of antiepileptic drugs (AEDs). It is the purpose of this chapter to discuss the basic principles underlying rational drug selection and optimization of therapy.

Objectives of treatment

The treatment of epilepsy should fullfil at least two primary objectives.

Prevention of seizure recurrence

If exception is made for the control of ongoing seizures and status epilepticus, AEDs are prescribed to prevent seizure recurrence. The ultimate goal should be complete seizure control, but in severe epilepsies this may not be achievable, and a reduction in seizure frequency becomes a more realistic objective.

Minimization of side effects

Most AEDs have a narrow therapeutic index, i.e. the dosage required to achieve seizure control is close to that which produces significant toxicity. Skillful management rests with the ability to select the drug whose side effect profile is least likely to interfere with the patient's wellbeing, and to optimize its dosage to reduce the risk of side effects. Seizure control should not be achieved at any cost. Physicians should avoid the situation whereby patients are made to suffer more from the side effects of treatment than from the manifestations of the disease.

Additional goals to be actively pursued whenever feasible or relevant include the following.

Reduction of mortality and morbidity

When seizures are triggered by an identified treatable cause, e.g., a brain tumour, etiological therapy is essential to reduce morbidity and mortality and, in some cases, to cure the epilepsy. Even when no etiological treatment is available, improved seizure control would be expected to have a positive impact on seizure-related mortality and morbidity, including injuries and impaired quality of life (Perucca et al., 2000).

Control of subclinical epileptic activity

Although therapy should be aimed primarily at controlling seizures and not at normalizing interictal EEG activity, there may be situations, especially in children with generalized epilepsies, where frequent paroxysmal discharges

lead to subclinical functional impairment, detectable at cognitive testing. In these patients, suppression of EEG discharges may become an objective of treatment, provided that this can be shown to result in significant functional improvement.

Reduction of seizure severity

When seizures cannot be controlled completely, there may be advantages in a treatment that reduces seizure severity. Although this is a poorly explored area, preliminary evidence suggests that some AEDs may modify ictal manifestations and reduce the severity of seizures or associated subjective distress (Smith et al., 1993).

Avoidance of adverse drug interactions

Since AEDs are administered for prolonged periods, often for a lifetime, adverse drug interactions may be troublesome (Perucca, 1995). Drugs with a low interaction potential offer distinct advantages.

No obstruction to patient's life

The ideal treatment should interfere as little as possible which the patient's lifestyle. AEDs which can be given twice daily or, preferably, once daily are less likely to obstruct daily activities and to cause psychosocial embarassment, and they are associated with a better compliance.

Prevention of epileptogenesis

Although, theoretically, suppression of epileptogenesis (i.e. the mechanism by which an epileptic condition becomes established) should be top priority, there is no evidence that this is achievable with current pharmacological tools. Some animal experiments do suggest that uncontrolled seizure activity leads, with time, to structural brain damage and establishment of a self-sustained epileptic condition, and some AEDs exert a putative antiepileptogenic effect in these models (Löscher, 1998). However, whether repeated seizures also lead to chronicity in some forms of human epilepsies is debated (Chadwick, 1995; Reynolds, 1995), as shown by the controversy on whether hippocampal sclerosis is a cause or a consequence of temporal lobe seizures (Jefferys, 1999; Perucca et al., 2000). If uncontrolled ictal activity leads to chronicization of the disorder, there would be a strong case for early and aggressive treatment, and for preferential use of drugs which antagonize putative epileptogenic processes. Available evidence, however, suggests that in most epilepsy syndromes AEDs exert merely a symptomatic effect and do not affect the natural course of the disease (Camfield et al., 1996; Shinnar & Berg, 1996). This does not deny that some conditions may exist in which early effective treatment does improve the ultimate prognosis, possible examples being West syndrome and other early childhood myoclonic encephalopathies associated with progressive cognitive decline. In these conditions, early seizure control seems to be important for prognosis, even though its ultimate benefits may relate to cognitive outcome rather than seizures (Shinnar & Berg, 1996).

Indications for treatment

As a general rule, a correct diagnosis should be formulated before treatment is instituted, and special care should be taken in differentiating epileptic from non-epileptic attacks such as psychogenic or syncopal episodes. Every effort should also be made to identify seizure type and syndromic form, because these are essential in determining drug selection and prognosis. Basically, pharmacological treatment is indicated whenever the expected benefits outweigh potential risks. The risk/benefit equation is determined by the stage of the epilepsy, its type and severity, the age of the patient, associated medical conditions, the characteristics of the drug(s) being considered and the presumed influence of treatment on the patient's wellbeing and aspirations (Perucca et al., 2000). In certain situations, indications are clearly defined, but grey areas exist where the optimal therapeutic strategy is uncertain. The reasons for starting or for deferring treatment, together with corresponding implications, should be discussed with the patient, whose own views should be considered in the decisional process. Most cases will fall into one of the following categories.

Patients with a single seizure

A common situation generating therapeutic uncertainty is that of a patient with a single tonic–clonic seizure whose nature is considered to be probably epileptic. Because many such patients will not have a recurrence (Berg & Shinnar, 1991), and because treatment after a first seizure does not improve long-term prognosis (Musicco et al., 1997), drug therapy should generally be deferred in these patients until a second seizure occurs. Treatment after a first seizure, however, may be considered when specific prognostic factors (in particular, interictal epileptiform EEG abnormalities and/or an identified persisting cause for the seizures) indicate a high risk of recurrence, or when it is felt that the physical or psychosocial consequences of

a recurrence outweigh the risks associated with AED treatment (Beghi & Perucca, 1995).

Patients with infrequent seizures or seizures precipitated by specific triggers

In patients with rare seizures, e.g. every 12 months or longer, especially when these occur at night or cause little psychosocial inconvenience, treatment may be witheld. Individual considerations, such as patient's age, attitude towards seizures and need for a driving license, play a key role in determining whether treatment is indicated. When seizures are precipitated by specific triggers, avoidance of the latter may be sufficient. Some forms of photosensitive epilepsy for example, can be managed by instruction on how to avoid exposure to offending light frequencies.

Patients with benign self-remitting seizure disorders

In these patients, treatment should be given only when the frequency, timing or severity of seizures cause significant psychosocial or functional impairment, as in childhood absence epilepsy. Children with benign partial epilepsy with centrotemporal spikes (rolandic epilepsy) generally do not require treatment, unless seizures are frequent and occur during daytime. Continuous pharmacological prophylaxis is also unwarranted in children older than 1 year with febrile seizures (American Academy of Pediatrics, 1999).

Patients with epilepsies not having a clearly self-remitting course

These patients generally require drug therapy.

In exceptional cases, AED treatment may be indicated even in the absence of any previous seizure. For example, it has been argued that in infants with tuberous sclerosis early therapy may be considered to prevent the occurrence of infantile spasms and, possibly, associated neurological worsening (Perucca et al., 2000). Many physicians, particularly neurosurgeons, recommend long-term anticonvulsant prophylaxis in seizure-free patients considered to be at risk for epilepsy after severe head trauma, or in patients undergoing supratentorial surgery. This practice would be justified if prophylactic treatment reduces the incidence of epilepsy in these patients, but there is no evidence that this is the case. While long-term prophylaxis cannot be justified in this situation, an argument could be made for the short-term use of intravenous phenytoin in selected cases to prevent acute seizures in the immediate postoperative period, e.g. in the first week after supratentorial surgery.

Table 77.1. Advantages of monotherapy

Complete seizure control in most patients (up to 70–80%)
Minimization of side effects
Easier management (effects of individual drugs can be evaluated separately)
Improved compliance
Avoidance of adverse drug interactions
Lower treatment costs

Factors affecting drug selection

Treatment should be started with a single drug (Table 77.1), whose dosage should be adjusted gradually to produce the optimal response (Reynolds & Shorvon, 1981). Up to 60–70% of patients with partial seizures and up to 80% of those with primarily generalized tonic–clonic seizures achieve complete seizure control on the initially prescribed drug (Mattson et al., 1985, 1992; Richens et al., 1994; Heller et al., 1995; Verity et al., 1995; De Silva et al., 1996). Even better response rates are achieved in children with absence epilepsy, whereas most symptomatic generalized epilepsies are often resistant to treatment (Beghi & Perucca, 1995).

Following the introduction of several new AEDs in the last decade, physicians are faced with a complex pharmacological armamentarium (Gatti et al., 2000). No single drug can be proposed as being optimal for all patients, and a number of factors need to be taken into account when selecting an AED for an individual patient.

Efficacy spectrum

Since AEDs differ in their spectrum of activity (Table 77.2), a drug should be chosen whose spectrum extends to the seizure type(s) affecting the individual patient. If a syndromic diagnosis has been formulated, drug choice may be also influenced by prediction of additional seizure types which might occur as part of the natural history of the disorder. For example, the fact that tonic–clonic seizures develop later in life in some children with absence epilepsy can be an argument for prescription of a drug effective against both these seizure types (valproate) instead of one effective against absences only (ethosuximide).

In recent years, evidence has accumulated that certain AEDs paradoxically worsen or precipitate specific seizure types, particularly in children with generalized epilepsies (Perucca et al., 1998). Carbamazepine, tiagabine and vigabatrin may trigger or worsen myoclonic and absence seizures, gabapentin may precipitate or worsen myoclonus,

Table 77.2. Efficacy spectrum of antiepileptic drugs in different seizure types

Effective or possibly effective against all seizure types	Effective against all seizure types except absences	Effective against partial and generalized tonic–clonic seizures	Effective against absence seizures
Valproic acid	Phenobarbital	Carbamazepine[f]	Ethosuximide[h]
Lamotrigine[a]	Primidone	Phenytoin[f]	
Benzodiazepines[b]		Oxcarbazepine[f]	
Topiramate[c]		Gabapentin[f]	
Zonisamide[d]		Tiagabine[f]	
Levetiracetam[e](?)		Vigabatrin[f,g]	
Felbamate[d]			

Notes:

[a] Lamotrigine may aggravate severe myoclonic epilepsy. Efficacy is best documented for partial and secondarily generalized tonic–clonic seizures, primarily generalized tonic–clonic seizures, absence seizures, and drop attacks.

[b] Benzodiazepines occasionally precipitate tonic seizures, particularly after intravenous use in patients with Lennox–Gastaut syndrome.

[c] Efficacy against absence seizures has not been documented. Topiramate efficacy is best documented for partial and secondarily generalized tonic–clonic seizures, primarily generalized tonic–clonic seizures, and drop attacks.

[d] Evidence of efficacy against some generalized seizure types is preliminary. Efficacy is best documented for partial and secondarily generalized tonic–clonic seizures. With felbamate, efficacy is also well documented in drop attacks associated with the Lennox–Gastaut syndrome.

[e] Tentative classification. Broad-spectrum efficacy is suggested by findings in animal models but adequately controlled clinical studies have been completed only in partial and secondarily generalized seizure types.

[f] Carbamazepine, phenytoin, vigabatrin, tiagabine and oxcarbazepine may exacerbate myoclonic and absence seizures. Gabapentin may exacerbate myoclonic seizures. Carbamazepine may be effective against tonic seizures associated with the Lennox–Gastaut syndrome.

[g] Vigabatrin is also effective against infantile spasms.

[h] Ethosuximide may also be effective against myoclonic seizures.

Source: Modified from Gatti et al. (2000).

barbiturates may aggravate absence seizures, and lamotrigine may aggravate severe myoclonic epilepsy of infancy (Guerrini et al., 1998). These observations reinforce the importance of a correct syndromic diagnosis. The difficulties in early differentiation between syndromic forms led some authors to stress the advantages of broad spectrum drugs (Richens & Perucca, 1993).

Mechanisms of action of AEDs

For a pharmacological treatment to be rational, two conditions must be met: (i) the pathophysiological mechanisms of the disease should be known and (ii) a drug must be available which counteracts specifically these mechanisms. Unfortunately, our understanding of the epilepsies and the modes of AED action is too fragmentary to allow mechanism-driven rational drug selection. Although a number of primary modes of actions have been identified for most AEDs (Table 77.3), additional actions have been described for virtually all of these agents: for example, phenytoin also acts on GABAergic transmission and calcium channel conductance, carbamazepine and oxcarbazepine modulate potassium channels, lamotrigine, felbamate and MHD (the active metabolite of oxcarbazepine) inhibit voltage-activated calcium channels, and lamotrigine may act as an antagonist or negative modulator of 5-HT1A receptors (Gatti et al., 2000). Although the precise contribution of these actions to antiepileptic efficacy remains to be determined, this represents an important area for research: some day, for example, we might be able to identify a putative subgroup of patients in whom seizure susceptibility is related to impaired GABAergic transmission, and to demonstrate a superior response to GABAergic drugs in this subgroup.

Recent evidence suggests that knowledge of modes of drug action will become increasingly important for prescribing. For example, a consistent pattern is emerging whereby drugs which act by increasing GABA levels in the synaptic space (e.g. vigabatrin, tiagabine and possibly, gabapentin) can be useful in controlling partial seizures but can be aggravating on absence and/or myoclonic seizures. Mechanistic considerations are also important in selecting drug combinations in refractory patients (Brodie et al., 1997).

Table 77.3. Main mechanisms of action of available antiepileptic drugs. For most drugs, additional mechanisms have been described

Benzodiazepines	Potentiation of GABAergic transmission through amplification of $GABA_A$ responses at benzodiazepine receptors
Carbamazepine	Blockade of voltage-dependent sodium channels
Ethosuximide	Blockade of T-type calcium channels in thalamic neurons
Felbamate	Blockade of voltage-dependent sodium channels Attenuation of excitatory neurotransmission by an action at the glycine modulatory site of the NMDA receptor Potentiation of postsynaptic GABA responses
Fosphenytoin	Phenytoin prodrug
Gabapentin	Potentiation of GABAergic transmission through increased brain GABA synthesis Modulation of voltage-sensitive calcium channels Inhibition of release of several monoamine neurotransmitters
Lamotrigine	Blockade of voltage-dependent sodium channels Blockade of voltage-activated calcium channels
Levetiracetam	Unknown
Oxcarbazepine	Prodrug for MHD, which acts primarily by blocking voltage-dependent sodium channels
Phenobarbital	Potentiation of GABAergic transmission, partly through increased chloride conductance
Phenytoin	Blockade of voltage-dependent sodium channels
Primidone	Main effects mediated by conversion to phenobarbital
Tiagabine	Potentiation of GABAergic transmission through inhibition of synaptic GABA reuptake
Topiramate	Blockade of voltage-dependent sodium channels Potentiation of GABAergic transmission Attenuation of excitatory neurotransmission through antagonism at kainate/AMPA receptor sites Inhibition of high voltage-activated calcium channels Inhibition of carbonic anhydrase
Valproic acid	Blockade of voltage-dependent sodium channels Potentiation of GABAergic transmission Inhibition of gamma-hydroxybutyrate release
Vigabatrin	Potentiation of GABAergic transmission through irreversible inhibition of GABA transaminase
Zonisamide	Blockade of voltage-dependent sodium channels Blockade of T-type calcium channels Inhibition of carbonic anhydrase

Source: Modified from Gatti et al. (2000).

Etiology of epilepsy

As discussed above, the relation between etiology of the disease and modes of drug action is still poorly understood. There are reports, however, suggesting that, within a syndromic form, response to treatment may vary depending on underlying etiology. For example, infantile spasms associated with tuberous sclerosis respond to vigabutrin better than infantile spasms associated with other etiologies (Chiron et al., 1997; Vigevano & Cilio, 1997). In preliminary studies, seizures associated with glial tumours responded well to tiagabine (Dean et al., 1998).

Adverse effect profile

In newly diagnosed patients, no major differences in efficacy exist among those AEDs which are effective in a given seizure type (Mattson et al., 1985, 1992; Richens & Perucca, 1993; Richens et al., 1994; Heller et al., 1995; Verity et al., 1995; De Silva et al., 1996; Perucca & Tomson, 1999). There are, however, important differences in side effects produced by individual drugs and tolerability profile is a major factor influencing the treatment algorithm (Beghi & Perucca, 1995; Perucca, 1996a).

An overall evaluation of comparative side effect profiles (Table 77.4) usually leads to choosing preferentially

Table 77.4. Most common adverse effects and interactions with antiepileptic drugs

Drug	Adverse effects	Adverse drug interactions
Benzodiazepines	Sedation, cognitive dysfunction, dizziness, incoordination, withdrawal seizures, and, in children, hyperactivity, behaviour disturbances and hypersalivation. *Respiratory depression (i.v. use)*	Benzodiazeines may occasionally increase the levels of other anticonvulsants
Carbamazepine	Dizziness, fatigue, somnolence, diplopia, headache, incoordination, mild skin rashes, *serious hypersensitivity reactions*	As an enzyme inducer, carbamazepine decreases the levels of many drugs, including valproate, lamotrigine, tiagabine, steroids, cyclosporine and many cardiovascular agents Carbamazepine levels are decreased by barbiturates and phenytoin, and increased by macrolide antibiotics, verapamil, diltiazem, propoxyphene and many other drugs
Ethosuximide	Nausea, vomiting, anorexia, sedation, headache, hiccups, behavioural disturbances, *hypersensitivity reactions*	Ethosuximide levels are decreased by phenytoin, carbamazepine and barbiturates
Felbamate	Nausea, vomiting, headache, dizziness, insomnia, behaviour disturbances, weight loss, *aplastic anemia (1:4000), hepatotoxicity (1:30 000), other serious hypersensitivity reactions*	Felbamate increases the levels of phenytoin, phenobarbital, valproic acid, carbamazepine-10,11-epoxide and decreases the levels of carbamazepine and oral contraceptives Felbamate levels are decreased by carbamazepine, phenytoin and barbiturates and increased by valproic acid
Gabapentin	Dizziness, fatigue, somnolence, ataxia, tremor, weight gain. Behaviour disturbances (children)	None significant
Lamotrigine	Dizziness, blurred vision, diplopia, somnolence, ataxia, headache, fatigue, nausea, mild skin rashes, *serious hypersensitivity reactions*	Lamotrigine levels are decreased by carbamazepine, phenytoin, barbiturates, oxcarbazepine and methsuximide, and increased by valproic acid
Levetiracetam	Somnolence, fatigue, headache, behaviour disturbances	None significant
Oxcarbazepine	Fatigue, headache, dizziness, sedation, incoordination, hyponatremia, mild skin rashes, *serious hypersensitivity reactions*	Oxcarbazepine decreases the levels of lamotrigine, oral contraceptives and felodipine The levels of the active hydroxymetabolite of oxcarbazepine are decreased by carbamazepine, phenytoin and barbiturates
Phenobarbital	Sedation, cognitive dysfunction, incoordination, dizziness, withdrawal seizures and, in children, hyperactivity and behaviour disorders. Mild skin rashes, *shoulder-hand syndrome, serious hypersensitivity reactions*	As an enzyme inducer, phenobarbital decreases the levels of many drugs, including valproate, lamotrigine, tiagabine, steroids, cyclosporine and many cardiovascular agents Phenobarbital levels are increased by valproate, felbamate, phenytoin, propoxyphene and other drugs
Phenytoin	Dizziness, tremor, ataxia, dysarthria, diplopia, nystagmus, cognitive dysfunction, headache, mild skin rashes, *serious hypersensitivity reactions*	As an enzyme inducer, phenytoin decreases the levels of many drugs, including valproate, lamotrigine, tiagabine, steroids, cyclosporine and many cardiovascular agents Many drugs, including valproate, displace phenytoin from plasma albumin leading to altered relation between plasma phenytoin levels and response Phenytoin levels are increased by felbamate, isoniazid, diltiazem and many other drugs
Primidone	Similar to phenobarbital. In addition, primidone may initially produce an acute intolerance syndrome (nausea, vomiting, dizziness, malaise)	Since primidone is converted to phenobarbital, the same interactions described for phenobarbital apply

Table 77.4 (*cont.*)

Drug	Adverse effects	Adverse drug interactions
Tiagabine	Dizziness, fatigue, headache, tremor, nervousness, impaired concentration, *abdominal pain, depression*	Tiagabine levels are decreased by carbamazepine, phenytoin and barbiturates
Topiramate	Dizziness, somnolence, mental slowing, dysnomia, anorexia, fatigue, ataxia, weight loss, paresthesias, *nephrolithiasis (1–2%)*	Topiramate occasionally increases phenytoin levels Topiramate reduces the levels of oral contraceptives Topiramate levels are decreased by carbamazepine, phenytoin and barbiturates
Valproic acid	Nausea, vomiting, weight gain, tremor, dizziness, sedation, *encephalopathy, hyperammonemia, thrombocytopenia, liver toxicity (1:800 in infants). Spina bifida on fetal exposure*	Valproate increases the levels of phenobarbital, lamotrigine and carbamazepine-10,11-epoxide Valproate displaces phenytoin from albumin (see phenytoin) Valproate levels are increased by felbamate and isoniazid and decreased by phenytoin, carbamazepine and barbiturates
Vigabatrin	Irreversible visual field constriction (30%, symptomatic in 1–3%), somnolence, fatigue, dizziness, weight gain, behaviour disturbances, *psychosis, depression*	Vigabatrin occasionally reduces the levels of phenytoin
Zonisamide	Fatigue, dizziness, somnolence, anorexia, mental slowing, confusion, ataxia, gastrointestinal symptoms, paresthesias, *nephrolithiasis*	Zonisamide affects inconsistently the levels of carbamazepine and phenytoin Zonisamide levels are decreased by carbamazepine, phenytoin and barbiturates

Notes:
Some adverse effects not common but clinically relevant are listed in italics. The risk of fetal malformations following prenatal exposure to older generation anticonvulsants is about 4–6% compared to 2% in the general population. Teratogenic risks associated with newer drugs are unknown.

carbamazepine for partial epilepsies and valproate for generalized epilepsies. Although some newer AEDs may be better tolerated compared to older agents, they are rarely used as first-line therapy due to limited clinical experience and cost considerations (Perucca & Tomson, 1999). In practice, the process of drug selection should be flexible and take into consideration how side effects could impact on the physical and functional characteristics of the individual patient. For example, the cosmetic side effects of phenytoin, particularly hirsutism, are of far greater concern in a young girl than in an elderly male. Carbamazepine has a relatively high allergenic potential and may not be the best choice for a patient with a history of severe immune-mediated drug reactions. Valproate tends to cause weight gain, and it may be poorly tolerated in a patient who is already struggling to keep her weight under control. Associated diseases may represent specific contraindications: most AEDs, for example, are best avoided in acute intermittent porphyria, whereas vigabatrin should be preferably avoided when there is a history of psychiatric disturbances.

Interaction potential

Carbamazepine, phenytoin and barbiturates are inducers of certain cytochrome P450 enzymes and they stimulate the elimination of several drugs, including other anticonvulsants, steroid oral contraceptives, glucocorticoids, cyclosporine and several cardioactive agents. Among newer AEDs, topiramate, oxcarbazepine and felbamate also induce the metabolism of oral contraceptives (Perucca, 1996b). Interactions by which non-epilepsy medications affect the kinetics or response to AEDs also need to be considered: for example, erythromycin, verapamil and diltiazem may cause carbamazepine intoxication by inhibiting its metabolism.

Available AEDs differ markedly in their interaction potential (Table 77.4).

Ease of use

Ease of use encompasses some of the properties discussed above: for example, a broad spectrum of efficacy, an excellent tolerability and a low interaction potential all contribute to ease of use. Additional favourable properties include:

Easy titration
Some AEDs, e.g. levetiracetam, gabapentin, can be titrated rapidly to maintenance dosage, whereas others require a slower dose escalation to minimize central nervous system intolerance, e.g. topiramate, primidone, or idiosyncratic reactions, e.g. lamotrigine.

Wide therapeutic index
Ease of use is enhanced when the therapeutic dose range is much smaller than that associated with toxicity

Easy individualization of dosage
A small variability in dosage requirements across patients facilitates clinical use. Within-patient dosage adjustments are easier for drugs which have linear kinetics. Saturation kinetics leading to a curvilinear relationship between dosage and steady-state serum concentration makes phenytoin a difficult drug to use (Perucca, 1996a). Similarly, dose-dependent autoinduction may complicate the use of carbamazepine.

No tolerance and no withdrawal seizures
Loss of response and seizure exacerbation after drug withdrawal, as seen most commonly with benzodiazepines, complicates clinical management.

Once or twice daily dosing
The need for more frequent dosing is inconvenient and adversely affects compliance.

Availability of a parenteral formulation
This is important when an intercurrent condition, e.g. abdominal surgery or prolonged vomiting, prevents oral treatment.

Drug availability and cost
In 28 countries, which are host to 40% of the world population, the per capita annual gross national product barely suffices to buy a year's supply of carbamazepine or valproate for one or two patients (Meinardi, 1993). As cost containment is a priority even in affluent societies, the price of medications and reimbursability considerations affect prescribing patterns.

Route of administration

When a rapid effect is required, as in status epilepticus or ongoing convulsive seizures, the intravenous route is usually preferred. Intramuscular injection of phenytoin, phenobarbitone and diazepam is not recommended, because absorption after injection of these drugs into muscle tissue may be slow and poorly predictable (Perucca, 1996a). By contrast, rectal administration of diazepam in the form of solution, gel or rectal capsules ensures rapid and efficient absorption and may be especially valuable for non-medical personnel, for example to prevent or terminate febrile seizures (American Academy of Pediatrics, 1999). Recently, interest has also focussed on intranasal midazolam as a potentially useful alternative to obtain rapid control of recurrent seizures.

Whenever AEDs are used long term to prevent seizure recurrence, the oral route is preferred, although a parenteral administration may be required when a patient is temporarily unable to take a drug orally. Regrettably, an injectable formulation is available for only few drugs, and for none of the newer drugs.

Dosing optimization and therapeutic monitoring

Due to marked interindividual differences in pharmacokinetics and pharmacodynamics, the dosage required to produce an optimal response varies considerably across patients. Therefore, identifying the best individual dosage is as important as selecting the correct drug. The need to follow closely the prescribed dosing schedule and the danger of status epilepticus associated with abrupt discontinuation of therapy should be discussed carefully with the patient.

Dose escalation and initial target maintenance dosage

In recently diagnosed patients, an aggressive approach aimed at achieving rapidly a relatively large maintenance dosage is seldom indicated. In most cases, it is desirable to aim initially at a target maintenance dosage at the lower end of the effective range and, if necessary, to make further adjustments based on clinical response (Beghi & Perucca, 1995). For most drugs, optimal dose escalation schedules have been identified to minimize the incidence and severity of side effects. To fully assess the effect of the initial maintenance dosage (and any subsequent dosage adjustment), an appropriate interval must elapse which should take into account both the half-life of the drug (four half-

Table 77.5. Main pharmacokinetic parameters of antiepileptic drugs in adults

Drug	Oral bioavailability	Plasma protein binding	Apparent volume of distribution[a] (l/kg)	Half-life (h)		Main routes of elimination
				Patients not taking enzyme inducers[b]	Patients taking enzyme inducers[b]	
Clobazam[c]	Nearly complete	90%	1.4	10–30	8–16	Oxidation[c]
Clonazepam	Nearly complete	85%	3	20–60	10–30	Reduction and oxidation
Carbamazepine[d]	About 80%	70%	1.2	15–25	5–15	Oxidation[d]
Ethosuximide	Nearly complete	nil	0.6	40–60	20–40	Oxidation
Felbamate	Nearly complete	30%	0.8	14–23	10–18	Oxidation, renal excretion
Fosphenytoin[e]	Prodrug	90%	0.7[f]	10–80[g]	10–80[g]	Oxidation
Gabapentin	35–60%[h]	nil	0.8[f]	5–7	5–7	Renal excretion
Lamotrigine	Nearly complete	55%	1.2	15–30[i]	8–20[i]	Glucuronidation
Levetiracetam	Nearly complete	nil	0.6	6–8	4–8	Renal excretion, hydrolysis
Oxcarbazepine[j]	Pro-drug	40%	–	8–15	7–12	Glucuronidation
Phenobarbital	Nearly complete	55%	0.6[f]	50–170	50–170	Renal excretion, oxidation
Phenytoin	Nearly complete	90%	0.7[f]	10–80[g]	10–80[g]	Oxidation
Primidone[k]	Nearly complete	20%	0.6	10–20	5–10	Renal excretion, oxidation[k]
Tiagabine	Nearly complete	96%	1.2[f]	4–13	2–4	Oxidation
Topiramate	Nearly complete	13%	0.7	20–30	10–15	Renal excretion, oxidation
Valproic acid	Nearly complete	90%	0.2	12–18	6–12	Oxidation, glucuronidation
Vigabatrin	60–70%	nil	0.8	5–8	5–8	Renal excretion
Zonisamide	≥ 50%	50%	1.5	50–70	23–35	Glucuronidation acetylation, oxidation

Notes:

[a] Calculated assuming complete bioavailability after oral dosing.

[b] Enzyme inducers include carbamazepine, phenytoin, phenobarbital and primidone.

[c] The active metabolite *N*-desmethylclobazam (half-life 35–45 h) contributes to pharmacological effects.

[d] The active metabolite carbamazepine-10,11-epoxide may contribute to carbamazepine effects.

[e] Kinetic parameters refer to phenytoin, for which fosphenytoin is a pro-drug. The half-life of fosphenytoin conversion to phenytoin is about 8–15 min. Phenytoin half-life is dose dependent.

[f] Calculated after intravenous doses.

[g] The half-life of phenytoin is dose-dependent and increases with increasing serum phenytoin concentration.

[h] Bioavailability decreases with increasing oral dosages.

[i] Lamotrigine half-life is 30 to 90 hours in patients comedicated with valproic acid without enzyme inducers and 15 to 30 hours in patients comedicated with valproic acid and enzyme inducers.

[j] Kinetic parameters refer to the monohydroxyderivative (MHD), for which oxcarbazepine is a pro-drug

[k] Primidone is partly converted to phenobarbital, which is primarily responsible for its pharmacological effects.

lives are required to reach steady-state serum drug concentrations) and the baseline seizure frequency.

Number of daily administrations

For drugs possessing a long half-life (e.g. phenobarbitone) or an irreversible mode of action (e.g. vigabatrin), once or twice daily dosing is preferred to maximize convenience and compliance. Drugs with a short half-life such as carbamazepine, gabapentin and tiagabine usually require more frequent administrations to minimize side effects or the risk of breakthrough seizures related to excessive fluctuations in serum drug concentration. Half-lives of AEDs are given in Table 77.5. For some drugs, most notably carbamazepine and valproate, sustained release formulations allow prolongation of the dosing interval.

Need for dosage adjustments

If seizures persist in a compliant patient without significant side effects, an increase in dosage is usually appropriate. Failure to increase dosage, if necessary up to the

highest tolerated level, is a common cause of therapeutic failure (Perucca, 1998). With phenytoin, adjustments should be made carefully because small increments in dosage can result in disproportionate changes in the serum concentration, with the attendant risk of toxicity.

Monitoring serum drug concentrations

For a number of AEDs, serum drug concentration ranges have been identified at which the majority of patients exhibit an optimal response. Measuring drug concentrations can be useful in selected cases, for example when seizures are not controlled despite intake of a large dosage, when toxicity or a drug interaction are suspected, or when compliance is in doubt (Eadie, 1995). Monitoring serum drug concentrations, however, is no substitute for clinical observation, and the golden rule is to treat the patient and not the serum level (Jannuzzi et al., 2000). Intraindividual variability in optimal serum drug concentrations is considerable. When a patient is well controlled at serum drug levels below the usually quoted optimal range, there is no justification for adjusting dosage. Likewise, there are patients who require and tolerate concentrations in the 'toxic' range.

Adequate studies to determine the potential value of serum drug concentration measurements have not been conducted with the new AEDs, partly because measuring drug concentrations is seen as unfavourable for the marketing of a new drug. This view, however, has been questioned and while at present there is no justification for routine measurements of concentrations of new AEDs, there are reasons for considering some of these drugs as potential candidates for monitoring (Perucca, 2000).

Strategies in patients not responding to treatment

Lack of response to the initially prescribed drug should prompt diagnostic re-assessment and consideration of possible causes, such as inappropriate drug choice, inadequate dosing schedule, and poor compliance. If seizures persist at a maximally tolerated dosage, the best strategy initially is to switch to monotherapy with an alternative drug (Perucca, 1997). Up to 40% of patients with partial and/or generalized tonic–clonic seizures failing on the initially prescribed drug become seizure free on alternative monotherapy, which is usually better tolerated than polypharmacy. Switching to the alternative drug may be accomplished by discontinuing gradually the initial medication while increasing simultaneously the dosage of the second agent. Many neurologists, however, prefer to titrate the dosage of the second agent up to the maintenance level and to discontinue gradually the initial agent thereafter. This offers the advantage of minimizing withdrawal seizures, but potentially adverse drug interactions may occur while escalating the dosage of the second agent.

In patients refractory to two or more sequential monotherapies, a trial with combination therapy is generally warranted, and early consideration should be given to the possibility of epilepsy surgery. While the probability of achieving seizure control with pharmacotherapy in these cases is comparatively small, there are patients in whom seizure control can only be achieved by using a combination of two or, rarely, three drugs, even though this entails a higher risk of side effects and drug interactions (Krämer, 1997). When opting for combination therapy, it makes sense to associate drugs with different (or possibly, even antagonistic) side effects, and to avoid drugs associated with adverse interactions. Theoretically, it might also be appropriate to combine agents with a different mechanism of action, although it is as yet unclear what combined actions (if any) would be expected to be particularly beneficial. Clinical experience does suggest that certain combinations may offer greater benefits than others: examples include valproate plus ethosuximide in refractory absence seizures (Rowan et al., 1983) and valproate plus lamotrigine in a variety of refractory seizure types (Panayiotopoulos et al., 1993; Brodie et al., 1997; Pisani et al., 1999). The latter combination is also advantageous in pharmacoeconomic terms, because valproic acid inhibits lamotrigine metabolism and reduces the dosage requirements (and associated cost) of lamotrigine.

The natural history of epilepsy entails spontaneous fluctuations in seizure frequency. Because patients seek medical help more frequently at the time of exacerbation, it is difficult to determine whether any improvement in seizure frequency seen after adding another drug is due to a real effect or, rather, to spontaneous amelioration of the disorder (the so-called 'regression to the mean'). For this reason, pharmacological treatment should be reviewed regularly and the need for combination or high dosage therapy reassessed critically (Perucca, 1995). Patients should never be made to suffer more from the toxic effects of drugs than from the manifestations of the disease, and in refractory epilepsies the aim is the best compromise between maximal seizure control and need to keep side effects within acceptable limits. In many patients who fail to achieve sustained benefit from an added drug, restoration of monotherapy often leads to relief of side effects without deterioration, and sometimes even with improvement in seizure control.

How long should treatment be continued?

In patients who have been free from seizures for a prolonged period (usually at least two years), the possibility of discontinuation should be considered, especially in children who show a higher prevalence of self-remitting epileptic syndromes and in whom the psychosocial consequences of seizure relapse are less severe than in adults (Chadwick, 1994). Drug discontinuation should be carried out gradually, to allow assessment of response at each dose level and to minimize the risk of withdrawal seizures. The proportion of patients whose seizures recur within 2 years following discontinuation of therapy is on average about 30% (Berg & Shinnar, 1994), but this figure in itself has little meaning because relapse rates range from close to zero to over 90% depending on the characteristics of the population. Risk of relapse increases with increasing age, presence of an underlying neurological condition (symptomatic epilepsy), an abnormal EEG and a longer duration of active disease prior to seizure control (Beghi & Perucca, 1995). The most important predictor is, however, the syndromic form: relapse rates are very rare in rolandic epilepsy, relatively rare (5–25%) in childhood absence epilepsy, intermediate (25–75%) in cryptogenic or symptomatic partial epilepsies and high (85–95%) in juvenile myoclonic epilepsy (Perucca & Beghi, 1995).

The option of discontinuing treatment should be discussed with the patient taking into consideration not only the probability of relapse, but also any side effects of treatment, the patient's psychological attitude to continuation of treatment and to the possibility of relapse, and legal implications with special reference to driving regulations.

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Epilepsy surgery: disease treatment and investigative opportunity

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Epilepsy surgery has long been and remains one of the areas of clinical neuroscience that best lends itself to a combination of disease treatment and scientific investigation. The surgical treatment of various forms of epilepsy is highly effective in rendering patients seizure-free or markedly improved. At the same time, investigations in the intraoperative and extraoperative setting allow for detailed study of both mechanisms of cerebral organization and cognition, as well as the opportunity to study epilepsy pathophysiology at the single cell, brain tissue slice, and systems levels. This brief overview of epilepsy surgery will outline the history of epilepsy surgery, goals of surgery, criteria used to determine patient suitability, the various types of epilepsy surgery, and anticipated outcomes of these approaches. Research opportunities that are currently being applied during the surgical management of epilepsy patients to study both normal and abnormal brain function, will be highlighted.

Historical background

Prior to the mid- to late nineteenth century, epileptic patients were treated with a variety of surgical treatments including trephination, cauterization, castration and circumcision. Advances in epilepsy surgery were made possible by the parallel discovery of the localization of cerebral functions and the development of tools to map these functions. Stimulation mapping of the mammalian cerebral cortex evolved in the late nineteenth century as a means to experimentally test two opposing theories of cortical localization: the theory of cerebral equipotentiality and the theory of precise localization of different brain functions. Following novel focal stimulation and resection experiments in animals, Flourens concluded in 1824 that the cerebrum was inexcitable and that, although function was located in various parts of the brain, intellectual and perceptual functions were diffusely represented. He was thus the first to propose a theory of cerebral equipotentiality (Flourens, 1824; Tizard, 1959).

Subsequently, on the basis of clinical and pathological data, the opposing view of precise cortical representation of function was hypothesized for language by a group of French scientists including Bouillaud, Broca, and Aubertin and for sensorimotor function by the English neurologist, Jackson. Jackson carried out clinical observations of patients' ictal symptoms and subsequent postmortem examination of their cerebral lesions in the mid-nineteenth century. Based on his clinicoanatomical investigations, he recognized that partial seizures may have a focal pathological substrate in the brain. His pioneering work provided evidence both for the localization of cerebral function and the focal nature of partial epilepsy.

Jackson believed that an anatomically distinct sensorimotor cortex existed that was responsible for contralateral movements following neuronal excitation (Clarke & Dewhurst, 1996). The first experimental confirmation of this notion was provided by the work of Fritsch and Hitzig in Berlin in 1870. They demonstrated the electrical excitability and localized motor functions of the cerebral cortex by stimulating dog cortex and eliciting contralateral limb movements (Fritsch & Hitzig, 1870). Soon thereafter, the British school of cortical stimulation and ablation emerged. Ferrier carried out experiments in dogs and monkeys, confirming Jackson's views of cortical localization and further defining mammalian motor cortex (Ferrier, 1876). Other British investigators extended Ferrier's monkey observations including Horsley (Paget, 1919) and Sherrington, the latter in collaboration with Grunbaum (Grunbaum & Sherrington, 1902). Although many early investigators transposed their monkey results onto outlines of the human brain, mapping of the human

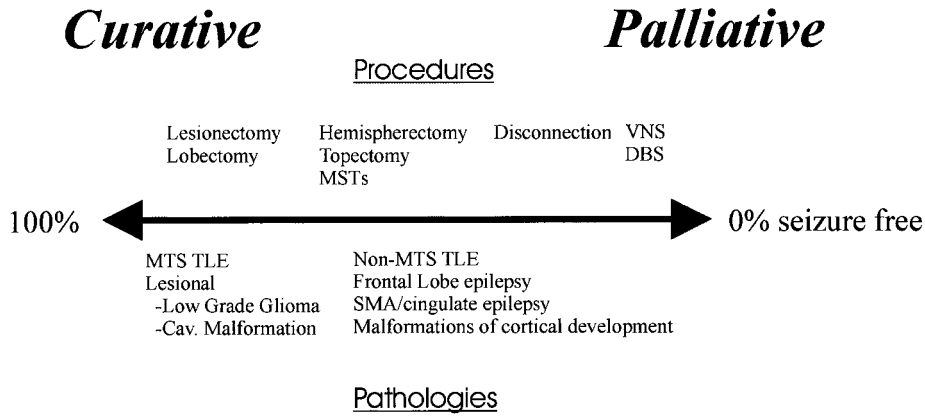

Fig. 78.1. Schematic diagram outlining the continuum of epilepsy surgical procedures from curative to palliative.

motor cortex was not performed until neurosurgeons Mills and Frazier in Philadelphia (Mills & Frazier 1905–1906), Cushing in Baltimore (Cushing, 1909), and Krause in Berlin (Krause, 1911; Foerster, 1936; Walker, 1951) sequentially produced stimulation derived drawings of the primary motor area between 1905 and 1911. In Berlin, Foerster subsequently began extensive stimulation experiments in man in 1924 in an attempt to corroborate the comparative stimulation and cytoarchitectonic experiments that had been carried out in the long-tailed monkey by the Vogts during the previous decade. His cortical localization studies confirmed the Vogts' monkey results and were used to form a 'synthetic' map of cytoarchitectonic and stimulation-induced cortical localization (Foerster, 1936). Because of Foerster's expertise in resection of epileptogenic cortex and cerebral localization, Penfield studied under him during 1928 and then subsequently returned to Montreal and devoted his professional life to these areas of study.

Based on the principles of functional localization established by Jackson, Broca, and others, Macewen in 1879 and Horsley in 1886 removed epileptogenic lesions to treat focal seizures. Horsley's initial surgery was carried out with the intraoperative assistance of both Jackson, a neurologist, and Ferrier, a neurophysiologist. This multidisciplinary team approach was subsequently adopted by Penfield, following his epilepsy surgery training with Foerster. In collaboration with Boldrey, Rasmussen, Jasper, and Milner, Penfield established the Montreal Neurological Institute (MNI), forming the predominant epilepsy clinical and research centre for much of the twentieth century. Much of our early knowledge regarding the utility of electroencephalography (EEG) to detect temporal lobe seizure onsets; the neocortical organization of human language, sensation, and movement; and the material specific functions of the left and right temporal lobes was obtained by this team. The collaborative team approach remains the optimal way to combine clinical care with scientific investigation in the management of epilepsy.

Surgical epidemiology and goals

Epilepsy is a very common disorder, with a cumulative lifetime incidence of 3%. Based on a point prevalence of ~0.5%, there are over one million people suffering from epilepsy in the United States. Approximately 40% of these individuals have complex partial seizures and 20% have other secondary epilepsies; 50–65% of these 600 000 patients can become seizure free with antiepileptic medications. Of the 250 000–300 000 remaining epileptics, at least one-third are potential candidates for epilepsy surgery. Thus, by conservative estimates, there are at least 100 000 epilepsy surgery candidates in the United States, with an estimated 5,000 new patients who may benefit from surgery each year (Engel & Shewmon, 1993).

Epilepsy surgery can be divided based on the goals of the operation into palliative and curative procedures (Fig. 78.1). Examples of curative procedures include lesional resection, lobectomy, corticectomy, and most cases of hemispheric surgery and multiple subpial transections. There is preliminary evidence that gamma knife radiosurgery may be curative in temporal lobe epilepsy and for cavernous malformation-associated epilepsy (see below). The primary goal of a curative surgery is for the patient to be able to lead a normal life, preferably off all antiepileptic medications. There is gathering evidence that early surgical intervention is favourable for a variety of reasons. Becoming seizure free at a younger age may lessen the cognitive, behavioural, and psychosocial problems experi-

enced by epilepsy patients, potentially improving societal integration. Additionally, because continued seizures may result in progressive neurological damage over time, surgery has the potential to be neuroprotective in comparison to continued medically refractory seizures. If a hemispheric procedure is required or if 'eloquent' areas of brain are within the epileptogenic zone, the potential for recovery of language and sensorimotor functions is better when patients are younger.

Palliative procedures by definition only very rarely result in cessation of seizures; rather these surgeries may prevent the occurrence of a particularly morbid type of seizure such as drop attacks or lessen the frequency or severity of seizures. Palliation may be a desirable result in patients with seizure-related injuries or with a predominance of one seizure type that can be eliminated with surgery. Examples of palliative surgery include some cases of hemispheric surgery, multiple subpial transections, disconnection procedures including callosotomy, and stimulation procedures including vagal nerve stimulation, and deep brain stimulation. There is a continuum between likely curative and likely palliative, and patient and family expectations must be adjusted accordingly. For example, the procedure of choice for a patient with invasive monitoring documented mesial temporal lobe epilepsy (TLE) who has no magnetic resonance imaging evidence of mesial temporal sclerosis (MTS) is resection of the anteromesial temporal lobe through one of a variety of surgical options (see below). The likelihood of seizure freedom in this patient is ~60%, in contrast to at least 80–90% seizure freedom if MTS is present. Although the goal of this surgery is curative, there is a significant likelihood that the outcome will be palliative.

The ultimate decision making in epilepsy surgery will depend on the type of seizures, location of the epileptogenic zone, presence or absence of a lesion, the patient's clinical and developmental status, and the natural history of the epilepsy syndrome. Complete discussion of all epilepsy syndromes amenable to surgical treatment is beyond the scope of this chapter; however, many of the commonly treated surgically remediable syndromes are described below under types of surgery.

Surgical patient evaluation

Medical intractability

In order for patients to be considered for epilepsy surgery, they must first be deemed to be medically intractable such that they are unable to achieve seizure control despite adequate trials with a sufficient number of drugs at doses that are associated with acceptable side effects (Bourgeois, 2000). However, there are no standardized definitions of what constitutes adequate seizure control, acceptable side effects, adequate trials, or a sufficient number of drugs. For example, the spectrum of sufficient number of drug trials ranges from two major drugs at maximal tolerated dose to four major drugs and six combinations, totalling ten trial periods. This variation is because there remains a small chance of seizure freedom with subsequent antiepileptic medications after failing a first-line major drug. In a recent examination of 470 untreated epilepsy patients, just 47% became seizure free with one drug, with improvement to 64% with 3 medications or combinations of medications. However, the probability of controlling seizures after failure with 2 drugs was less than 10% (Kwan & Brodie, 2000). Despite the recent introduction of a number of new antiepileptic medications (gabapentin, lamotrigine, topiramate, vigabitrin) and the vagal nerve stimulator (discussed in more detail below), less than 5% of medically intractable patients achieve seizure freedom with the addition of one of these therapies (Lhatoo et al., 2000).

Not all epilepsy syndromes have the same degree of intractability, raising the possibility that medical intractability may be able to be documented after two to three adequate medication trials in many surgically amenable conditions. Patients with temporal lobe epilepsy, malformations of cortical development, dual pathology, and head injury are some of the groups least likely to have their seizures effectively controlled with antiepileptic medications. In a recent study of 2200 adult outpatients in France, of whom 62% had partial epilepsy, only 20% of temporal lobe epilepsy patients achieved seizure control, defined as more than 1 year without seizures (Semah et al., 1998). In addition, previous analysis of 74 adult surgery candidates who had not received the maximal tolerated dose for three major drugs revealed that no patients became seizure free with further antiepileptic therapy and less than 10% had marked (>80%) seizure reduction (Hermanns et al., 1996).

Taken together, the low likelihood of achieving adequate seizure control in patients with many of the surgically remediable epilepsy syndromes combined with the detrimental social, developmental, and possibly neurobiological consequences of persistent seizures makes early surgical intervention a logical treatment course. However, even for the best understood surgically remediable syndrome, temporal lobe epilepsy with MTS, early surgery is not yet the standard of care. A recent prospective randomized trial in London, Ontario confirmed what has long been known by epilepsy surgery centres caring for patients with temporal

lobe epilepsy. In this study, 65% of patients who underwent surgery were seizure free at 1 year follow-up in comparison to 8% of patients randomized to best medical therapy. Operated patients also had improved quality of life (Wiebe et al., 2001). A multicentre prospective trial is currently being organized to investigate the potential benefits of early surgery in MTS TLE.

Presurgical evaluation

Once a patient has been determined to be medically intractable, extensive preoperative evaluation is necessary to classify that patient's epilepsy and determine whether it can be treated with surgery. The goals of the preoperative evaluation are to determine: (i) to which side of the brain the patient's seizures are lateralized; (ii) to which specific area of the brain these seizures are localized; and (iii) the extent of the epileptogenic zone, the region that is necessary and sufficient for initiating seizures and whose removal or disconnection is 'necessary for abolition of seizures'. Unfortunately, no currently identifiable imaging, EEG, clinical evaluation, or other examination methods fully elucidate the epileptogenic zone. A number of other zones have been defined in epilepsy evaluation: (i) the irritative zone, which is the cortical area capable of generating interictal discharges; (ii) the ictal onset zone, as defined by EEG recording; (iii) the epileptogenic lesion, as defined by MR imaging or histopathological examination; (iv) the functional deficit zone, which refers to the area of interictal non-epileptic dysfunction identified during neurological examination; neuropsychological testing; or perfusion or metabolism studies, such as PET or SPECT scanning; and (v) the symptomatogenic zone, the area of the brain that produces the initial ictal symptoms (Luders et al., 1993).

The overall strategy of presurgical evaluation is to use a combination of testing modalities to identify structural abnormalities, deficits in non-epileptiform function, and areas of ictal and interictal EEG abnormality; and to then identify the surgical removal area where the testing results are concordant. The exact methodologies that are used vary somewhat from epilepsy centre to centre, particularly the utilization of PET, SPECT, MR spectroscopy, and other specialized neuroimaging techniques. It is possible that in the future, advances in MR technology will simplify presurgical evaluation by eliminating the need for many adjunctive components. MR is already used on sporadic basis in select centres to capture ictal activation zones, as well as interictal patterns of MR activation. In addition, MR localization of cerebral language and memory function will likely eventually replace the intracarotid amobarbital (Wada) investigation for determination of hemisphere dominance and memory function.

The exact preoperative evaluation is determined by the location of EEG seizure onsets, whether a structural abnormality is present, and which procedure is being considered. For example, the standard evaluation of temporal lobe epilepsy patients usually includes multiple interictal EEG recordings, MRI examination for the detection of structural abnormalities, sodium amobarbital (Wada) intracarotid perfusion testing, and neuropsychological testing, resulting in lateralization of the seizure process to one anterior temporal lobe. The majority of patients have video EEG telemetry monitoring of ictal events. Several seizures are analyzed for ictal onset. Brain MRI includes coronal images of the temporal lobes in all patients, using both T_1-weighted, T_2-weighted, and inversion recovery (STIR) images to assess the degree of hippocampal atrophy and increased hippocampal signal (Fig. 78.2). Many centres employ either high-resolution phase arrayed surface coils to allow better definition of local hippocampal pathology, or hippocampal volumetric calculations that are compared to a normalized control database. Adjunctive interictal neuroimaging tests applied in selected tertiary centres include ^{18}F-fluorodeoxyglucose positron emission tomography (PET) scanning to detect localized areas of decreased brain metabolism, single photon emission computed tomography (SPECT) scanning to show areas of decreased perfusion; and magnetic resonance spectroscopy to look for localized alterations in brain chemical spectra. SPECT scanning is particularly useful when interictal images are computer subtracted from ictal images, delineating areas of ictal hyperperfusion (SISCOM scanning) (O'Brien et al., 1999, 2000).

Wada testing is applied to lateralize language and memory function between the two hemispheres, while neuropsychological testing strengthens localization by providing information regarding temporal lobe dysfunction. If all of these studies are concordant, implicating the same temporal lobe in a patient's seizure pathogenesis, an anteromesial temporal lobe resection is performed. In those patients with discordant test results, non-localizing EEG, or bilateral temporal seizure onset by scalp EEG, intracranial monitoring with subdural strip and/or grid electrodes is performed to confirm a unilateral side of onset. In some centres, a minority of patients do not undergo either video EEG monitoring or invasive recording prior to surgery. These individuals have strictly unilateral interictal epileptiform abnormalities on multiple preoperative EEGs and no discordance on any of the other preoperative studies (Holmes et al., 1996).

Types of surgery

Anesthesia/intraoperative recording

The majority of epilepsy surgery procedures are carried out at specialized centres where a multidisciplinary group of epilepsy neurologists, clinical physiologists and neurosurgeons employ a systematic approach to surgical planning. Though there is typically consistency in surgical strategies within an institution, approaches vary considerably across centres. One fundamental point of departure relates to the use of general anesthesia. In some centres all cortical resections are carried out in awake patients under local anesthesia, while at other centres resections are usually done under general anesthesia. These different anesthetic strategies reflect differences of opinion regarding the utility of intraoperative monitoring of neurological function and EEG recordings from awake patients during surgery. Surgeons who perform 'tailored' resections rely on the results of intraoperative EEG recordings obtained directly from the brain surface to guide certain stages of their surgical planning. The quality of these recordings, and ability to detect interictal discharges, is optimal in an unanesthetized brain. These surgeons also use stimulation mapping to identify cortical locations that are essential for language function, and tailor their resection to avoid these sites. The disadvantage of an awake craniotomy is that surgeon and anesthesiologist must keep the awake patient comfortable and cooperative throughout the procedure. In centres where this approach is used routinely, experienced operating room teams rarely encounter significant difficulties with this approach. Proponents of general anesthesia prefer the control and familiarity of this approach and believe that in properly selected patients the impact of intraoperative EEG and functional mapping is not significant. This issue continues to be a point of debate and is unlikely to be resolved in the near future.

Temporal lobe resections

The temporal lobe is the most common seizure focus site targeted for resection surgery; specifically the mesial structures (i.e. amygdala and hippocampus). Patients with a temporal lobe seizure focus have a high incidence of refractoriness to medical management, and conversely have the best overall results from seizure surgery. Properly selected temporal lobe epilepsy patients have an up to 80–90% probability of being seizure free following resection surgery. A variety of technical approaches have evolved, all of which are directed at the common goal of eliminating temporal lobe seizures. The differences

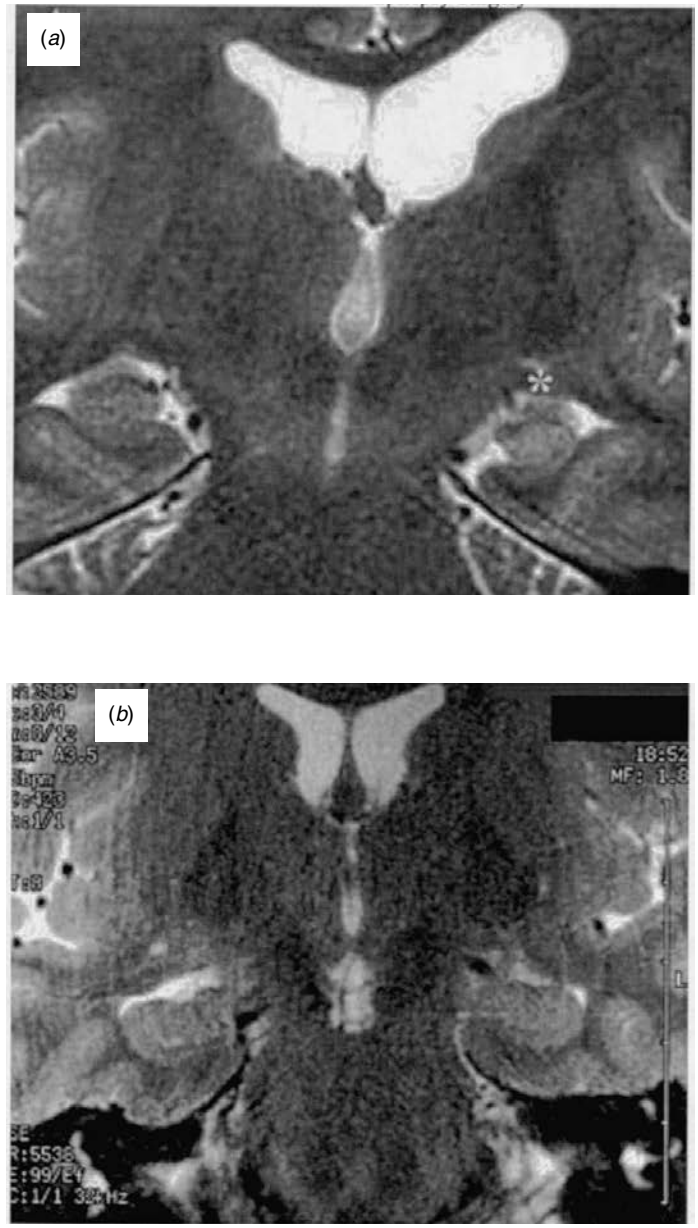

Fig. 78.2. Representative coronal MR image from a patient with mesial temporal sclerosis (*a*) and a patient with MR symmetric hippocampi (*b*). The hippocampus with the atrophy and increased signal is marked with an asterisk. Both of these patients presented with mesial temporal lobe epilepsy. The preoperative prediction of seizure freedom following surgery is 80–90% for patient (*a*) and 50–60% for patient (*b*).

between techniques stem from varying opinions regarding what temporal lobe regions should be resected, and how the extent of resection should be planned. One area where different surgeons vary their technique is in their approach to the anterior lateral temporal neocortex. Based on the rationale that the temporal lobe seizure focus is typically confined to mesial structures, Yasargil and colleagues developed and described the selective amygdalohippocampectomy (Yasargil et al., 1993). With this procedure, the surgeon gains access to the mesial structures via a trans-Sylvian route, an approach that spares the lateral temporal lobe neocortex. The approach is technically more challenging and is dependent on the use of fine microdissection techniques that evolved from aneurysm surgery. Despite excellent results reported by proponents of the selective amygdalohippocampectomy, the procedure has not been widely adopted by epilepsy surgeons elsewhere. The Yasargil technique has been modified to avoid the need to microdissect the Sylvian fissure. In these approaches, an MRI frameless stereotactic image guidance system is used to facilitate dissection through the superior temporal sulcus, middle temporal sulcus, or middle temporal gyrus down to the temporal horn of the lateral ventricle, from which selective amygdalohippocampectomy is performed (Roberts, 2000).

The more common, and classical approach to temporal lobe resections involves removal of some portion of the anterior lateral temporal neocortex. There are two reasons for using this strategy; (i) the lateral neocortex may serve as a seizure focus in some patients; and (ii) removal of a portion of the lateral cortex affords optimal surgical access to mesial structures. As was described in the section on anesthesia, surgeons employ varying strategies when deciding what portion of the lateral temporal lobe should be resected. Proponents of tailored resections will carry out EEG recordings directly from the exposed brain surface in order to identify interictal discharges. If a clear discharge focus is identified, that region of neocortex will be incorporated into the lateral resection. If no lateral discharges are noted, only a small region of the temporal tip will be removed in order to gain access to mesial structures. In the dominant hemisphere, proponents of tailored resections identify temporal lobe sites that are essential to language function using electrical stimulation disruption methods in the awake patient. Cortical sites that subserve critical language functions are spared from resection. Epilepsy surgeons who do not subscribe to the need for intraoperative EEG recordings and language mapping carryout standardized lateral resections that typically incorporate the most anterior 3–4 cm of lateral temporal lobe on the language dominant side, and 4–5 cm in non-dominant cases. There is no compelling evidence in the literature indicating superior seizure control efficacy for the tailored vs. standard resection technique. The majority of epilepsy centres do not use intraoperative ECoG to guide the extent of lateral neocortical resection in patients with mesial temporal lobe epilepsy.

All successful surgical techniques designed to treat complex partial seizures of temporal lobe origin emphasize the importance of resecting the hippocampus. From the seizure control perspective, it is preferable to remove as much hippocampus as is technically feasible, particularly if intraoperative hippocampal ECoG is not utilized to guide hippocampal resection. The surgical technique developed and popularized by Spencer at Yale results in nearly complete resection of the hippocampal formation (Spencer et al., 1984). Support for a more radical hippocampal resection was provided by a randomized prospective study by Wyler et al. (1995). All patients who were candidates for a mesial temporal resection were randomized to an anatomical hippocampal resection that was either 'partial' (to the anterior peduncle) or 'total' (to the collicular cistern), regardless of any differences in regional electrophysiological abnormalities as detected during preoperative evaluation. The authors found that patients with a 'total' hippocampal resection were more likely to be seizure free and had a greater average time to first postoperative seizure. However, 38% of the patients with 'partial' resections were seizure free, raising the issue of whether this subgroup of patients can potentially be identified and spared a larger hippocampal resection.

One of the problems with performing an extended hippocampal resection in all patients is the possibility that it may increase the rate of postoperative memory deficits. Patients with a larger hippocampal resection have been found to have a greater impairment in verbal memory following dominant temporal resection or non-verbal memory following non-dominant temporal resection, respectively (Milner, 1971; Katz et al., 1989; Helmstaedter & Elger 1998; Nunn et al., 1999). However, other studies found no correlation between memory outcome and extent of hippocampal resection (Wolf et al., 1993; Wyler et al., 1995; Hermann et al., 1999). Some investigations show that postoperative memory decline correlates most closely with a lack of pathologically demonstrated hippocampal neuronal loss (Sass et al., 1990, 1992, 1994; Baxendale et al., 1998; Bell & Davies 1998; Davies et al., 1998; Martin et al., 1998).

Some surgeons use EEG recordings to determine the extent of hippocampal resection. The rationale for using recording data to plan the hippocampal resection is based on the assumption that it is desirable to spare more poste-

rior regions of the hippocampus if these areas are not epileptogenic. This is of particular concern in patients who have an normal hippocampus MR imaging that is being resected or in rare patients with dysfunctional contralateral hippocampus. These patients are at increased risk of neurocognitive deficits following hippocampal resection, particular on the dominant side. Recent analysis of 140 consecutive TLE patients operated at the University of Washington utilizing an ECoG tailored resective strategy provides evidence that the seizure outcome is the same for all sizes of hippocampal resection if the amount of hippocampectomy is determined by hippocampal electrophysiology (McKhann et al., 2000). Whether preserving a portion of hippocampus during surgery provides any functional benefit remains to be determined.

In contrast to the hippocampus, it is less clear how important the amygdala is as a target for resection. Surgical cases of amygdalar sclerosis without hippocampal sclerosis have been documented (Miller et al., 1994; Zentner et al., 1999). The ventrobasal amygdala is almost always incorporated into any form of mesial resection due to its immediate proximity to the hippocampus and safety of resection. In order to perform a nearly complete amygdala resection, however, the surgeon must extend the mesial resection dorsally into the region of the temporal stem and caudal basal ganglia. This introduces additional surgical risks, and the seizure control benefit of this approach is unclear.

In patients with medically refractory temporal lobe epilepsy there are no new medications that can be offered that would even approximate the high rates of seizure free outcomes that can be expected from epilepsy surgery (Wiebe et al., 2001). Despite this fact, surgical treatment is underutilized because of fear of complications. Modern surgical techniques have improved considerably compared to the early days of epilepsy surgery, and the vast majority of patients have uncomplicated procedures, but significant risks still exist. Untoward results can be attributed to removal of brain tissue intentionally resected, or be a consequence of unexpected surgical complications. Resection of any brain tissue to treat epilepsy risks damaging the neurologic functions mediated by the brain regions that were removed. Following dominant temporal lobe epilepsy surgery, patients may experience a significant decline in verbal memory function, particularly if their MRI does not demonstrate MTS or their preoperative verbal memory function is not already compromised (Hermann et al., 1999). If the neocortical resection abuts or includes a cortical area that is essential for language function, a patient is likely to have at least transient worsening of postoperative language (Ojemann & Dodrill, 1987; Ojemann et al., 1989).

The most feared complications of temporal lobe epilepsy surgery result from inadvertent injury of vascular structures abutting the medial temporal lobe, or mechanical disruption of the optic tract or brain tissue deep to the temporal stem (Behrens et al., 1997). Approximately 1–2% of patients will develop a permanent hemiparesis, presumably as a consequence of damage to the anterior choroidal artery or branches of the posterior communicating artery. The optic tract is immediately adjacent to the hippocampal formation and can be injured mechanically or from a vascular insult, resulting in visual field deficits of varying density. In the worst case, a patient can develop a disabling homonymous hemianopsia.

Extratemporal resections

Patients with intractable epilepsy referable to a cortical seizure focus outside of the temporal lobe represent a difficult surgical treatment challenge. This is a heterogeneous group of patients who have developed a neocortical seizure focus, the pathophysiology of which is usually poorly understood. Unlike temporal lobe epilepsy patients who present with characteristic and clearly recognizable complex partial seizures, the anatomical site of seizure onsets cannot be as readily characterized based solely on clinical criteria in patients with extratemporal lobe epilepsy (Olivier, 1995; Olivier & Boling, 2000). Often the earliest stage abnormal electrical activity develops in a functionally silent region of the brain, then spreads rapidly into multiple distant brain regions causing convulsive clinical features that do not reflect the true anatomical site of seizure onsets. The spatial resolution of scalp EEG monitoring is frequently inadequate to resolve the location of these seizure onsets. Brain MRI and metabolic imaging studies are utilized in the hopes of identifying an anatomical or metabolic abnormality that can help localize what regions of the brain should be targeted for further investigation. Ictal scalp video–EEG clinical information, combined with these anatomical studies, is used to guide the placement of intracranial electrodes. Customized arrays of surface grids, strip electrodes, and depth electrodes are implanted to cover and 'bracket' the brain regions thought most likely to harbour the focus of seizure onsets.

In addition to determining the site of seizure onsets, intracranial electrodes are used to functionally map the location of eloquent brain regions that may abut or represent a portion of the seizure focus. When consistent evidence has been gathered that clearly defines a seizure focus and surrounding eloquent brain regions, an effective resection strategy must be formulated balancing the needs to carry out a comprehensive resection of all tissue

constituting the seizure focus, while avoiding neurological morbidity. Certain functional regions can be resected with minimal long-term morbidity, such as non-dominant face motor and sensory cortex, and certain regions of extrastriate visual cortex (Nawrot et al., 2000). Other functionally defined regions, such as hand, arm and leg regions within the pre- and postcentral gyri, and language critical sites in the frontal and parietal lobes, cannot be safely resected. Morrell and colleagues have described a technique of multiple subpial transections (MST) to address seizure foci within such eloquent regions of cortex (Morrell et al., 1989). The MST method is based on the hypothesis that abnormal propagation of epileptic activity is dependent on horizontal spread of cortical activity whereas the normal functions of the cortex are largely mediated by activity within vertical columns. A fine dissecting tool is introduced into the neocortex along the width of a gyrus at 4–5 mm intervals to disrupt local horizontal fibre tracts while preserving the structural integrity of vertical columns of neurons. In experienced hands, this technique can substantially improve seizure control without causing significant neurological morbidity. However, recent concerns have been raised over the durability of seizure control following MSTs (Orbach et al., 2001).

Patients who have little functional use of the contralateral limb represent a distinct population of epilepsy surgery patients. In these patients with congenital hemiplegia or chronic encephalitis, hemispherectemy is a viable treatment option. Careful attention must be paid to the functional status of the patient's affected hand and foot, in that no useful fine motor control of hand or foot will be preserved following this procedure. Initially, hemispherectemies were performed by surgically ablating all neocortical tissue and underlying white matter external to the deep grey matter structures (Rasmussen, 1983). This approach has subsequently undergone several modifications to achieve a 'functional' hemispherectemy or hemispherotomy (Tinuper et al., 1988; Behrens et al., 1997; Schramm & Behrens 1997; Yoshioka et al., 1999). In these procedures, varying degrees of peri-Sylvian, insular and temporal lobe structures are initially resected. The lateral ventricle is then entered and a complete corpus callosotomy is carried out. In the final steps, frontal and parieto occipital white matter disconnections complete the isolation of the involved hemisphere. The modified approaches have been sequentially designed to avoid the development of superficial hemosiderosis or hydrocephalus, either of which can develop in a delayed fashion following anatomical hemispherectemy. In addition, modified procedures result in less operative blood loss, decreasing the need for transfusion in this young patient population.

Difficulties related to localizing seizure onsets, the need to avoid damaging eloquent brain regions, and the wide variability in clinical–pathological features among patients with extratemporal epilepsy all contribute to suboptimal seizure control results following surgery. Although many more patients experience some degree of improvement in seizure control, long-term seizure free outcomes are achieved in only 40–60% of patients who undergo extratemporal neocortical resections. In properly selected children who undergo hemispherectomy, the seizure free outcome can be better than 50% (Edwards et al., 2000).

Corpus callosotomy

The normal role of the corpus callosum is to transmit action potentials between the two hemispheres, and this electrophysiological conduit allows certain forms of seizure activity to synchronously engage both hemispheres with adverse clinical consequences. A wide range of disconnection procedures have been used in the past with the intent of disrupting the propagation of seizure activity, including sectioning the corpus callosum, interhemispheric commissures, the mass intermedia, and the fornix. In more recent years it has become increasing clear that the only midline disconnection procedure that should be considered as an epilepsy surgery treatment option is callosotomy; there are no clear benefits to resecting additional midline structures (Luessenhop et al., 1970; Wilson et al., 1978; Gates et al., 1987; Sass et al., 1988).

Sectioning the corpus callosum does not eliminate seizure activity, it simply inhibits synchronization between the hemispheres. If the patient has a focal seizure disorder, it is preferable to identify the epileptic focus and carry out a neocortical resection procedure as described above. Patients whose seizures cannot be localized to a specific brain locus, and who suffer from abrupt synchronous, bilateral loss of motor tone and posture control may benefit from callosal sectioning. These are patients with falling spells and atonic (akinetic) seizures. Greater than 65% of patients who undergo callosotomy experience a diminution in the frequency of these drop attacks. In the past, the entire corpus callosum was resected, often in a staged procedure. More recent reports suggest that near equal efficacy can be achieved by simply sectioning the anterior two thirds of the callosum. Clinically significant disconnection syndromes are rare, particularly if the posterior one third of the callosum is spared (Sass et al., 1988).

Stimulation techniques: vagal nerve stimulation, deep brain stimulation

Some of the most exciting and rapidly advancing areas of modern neurosurgery involve chronically delivering electrical stimuli to the nervous system. Because of technical advances in material sciences and microelectronics it is now feasible to implant stimulating devices that can deliver precisely controlled currents to targeted structures throughout the peripheral and central nervous system for a period of years. These developments have had a significant impact on the surgical treatment of epilepsy, most notably with the wide spread adoption of the vagal nerve stimulator (VNS). The exact mechanisms by which vagal nerve stimulation affects seizure activity are unclear, although vagal afferent projections via the nucleus of the tractus solitarius to more rostral structures such as the hypothalamus, thalamus, amygdala, locus ceruleus, and raphe nuclei have been implicated (Woodbury & Woodbury, 1990). However, the positive impact of VNS on seizure frequency has been consistently demonstrated in clinical studies. One attractive attribute of this treatment approach is ease of surgery and patient safety. The stimulator leads are placed around the left vagus nerve in the neck and the stimulator housing is implanted in the soft tissue of the chest wall. In some institutions this is done as an outpatient procedure. Unlike brain resection techniques, there is almost no risk of serious neurological injury. The drawback to VNS relates to its limited efficacy compared to brain resection procedures. Although approximately half of patients implanted with a VNS will experience a 50% decrease in seizure frequency, less than 5% of patients are seizure free long term (Woodbury & Woodbury, 1990; Amar et al., 1998; Patwardhan et al., 2000). For these reasons, VNS is recommended for patients with intractable epilepsy who cannot benefit from traditional resection treatments.

Another electrical stimulation strategy being pursued on an experimental basis involves activating deep brain structures with the intent of disrupting generalized seizure activity (Velasco et al., 1993). This strategy is based on the understanding that certain targets such as the anterior nucleus of the thalamus and the subthalamic nucleus are critical relay stations in the network of seizure propagation. High frequency deep brain stimulation has the potential to (i) functionally inactivate the neurons in the area of stimulation, inhibiting downstream projections and (ii) exert a desynchronizing effect on on-going EEG activity. The safety of long-term subcortical stimulation has been clearly demonstrated in extensive studies of patients treated with deep brain stimulation for Parkinson's disease. Whether thalamic or subthalamic stimulation for the control of epilepsy will be similarly effective is unclear at this time. This novel treatment approach, along with efforts to directly infuse inhibitory compounds into targeted brain structures, appears to have considerable potential. Separate multicentre trials are beginning to investigate the safety and efficacy of bilateral DBS of the anterior thalamus and subthalamic nucleus in the management of epilepsy.

In addition to their utility as therapeutic devices, both VNS and DBS are being studied to better understand the pathways and mechanisms of neuronal network synchronization in the brain.

Gamma knife radiosurgery

The ability of radiosurgery to control seizures has been extensively documented in patients with intracerebral arteriovenous malformations (AVMs), who most commonly present with either hemorrhage or seizures. Following radiosurgical treatment of AVMs using a variety of techniques including proton beam, linear accelator, and gamma knife radiotherapies, 55–80% of patients with pretreatment seizures have achieved seizure freedom following treatment. The chance of becoming seizure free inversely correlates with the duration of epilepsy; while complete AVM obliteration is not required for seizure freedom. Radiosurgery does have the potential to induce seizures in a minority of patients ($<5\%$) (Heikkinen et al., 1989; Kurita et al., 1998; Kida et al., 2000; Ghossoub et al., 2001).

Because radiosurgery delivers focused radiation to selective targets within the brain using stereotaxic guidance, it has been used to treat other 'lesional' epilepsies including cavernous malformations, mesial temporal sclerosis temporal lobe epilepsy (MTS TLE), and hypothalamic hamartomas. In the largest reported series of epilepsy associated with cavernous malformations managed with gamma knife radiosurgery, 26/49 patients were seizure free beginning one year after treatment. However, in the subgroup with mesial temporal lesions, only 2/12 were seizure free (Regis et al., 2000a,b,c). Eight patients from seven centres were recently reported following gamma knife radiosurgical treatment of their hypothalamic hamartoma-associated epilepsy. Four patients were rendered seizure free, two of whom required second treatments (Regis et al., 2000a,b,c).

Experience has been gathering using gamma knife radiosurgery for MTS TLE. Animal research using both electrical stimulation and kainic acid models of limbic epilepsy demonstrates marked reduction of seizures following

radiosurgery, even at doses that do not induce necrosis (Maesawa et al., 2000; Regis et al., 2000a,b,c; Chen et al., 2001; Kurita et al., 2001). Based on initial promising results in humans, with 13/16 patients seizure free at 2 year follow-up (Regis et al., 2000a,b,c), there are ongoing European and NIH supported American multicentre trials applying gamma knife radiosurgery to patients with MTS TLE.

Whether radiosurgery offers any neuropsychological benefit over open surgical resection of the mesial temporal structures remains to be determined. There are risks of radiosurgery including radiation necrosis or edema, neurological deficits referable to the targeted area, radiation damage to structures outside targeted zone, and a possible increase in auras prior to reduction in seizures. In general, the effects of radiosurgery are not maximal until up to 1 year following treatment. In addition, there are rare (four as of summer 2001) reports of radiation-induced neoplasms following over 135 000 cases of gamma knife treatment worldwide. The potential benefit of using 'subnecrotic' dosing of radiosurgery to treat epilepsy remains intriguing and is being further investigated.

Research opportunities provided by epilepsy surgery

Cerebral localization of function

Intraoperative sensorimotor/language/cognitive/memory paradigms

Despite recent advances in non-invasive functional mapping methods, there remains a compelling need to carry out additional direct cortical mapping procedures during surgery. The rationale for this approach relates to important distinctions between the physiologic mechanisms that are monitored using non-invasive methods and the functional consequences of direct electrical stimulation of cerebral cortex. Non-invasive investigative methods such as scalp EEG, MEG, PET and fMRI are used extensively by investigators seeking to better understand brain physiological events that mediate human sensorimotor, language, cognitive and memory functions. These powerful methods have provided important insights into normal brain function and pathophysiology. By their nature, however, these techniques cannot accurately predict the consequence of creating a localized brain lesion in a given surgical patient. This lack of predictability relates to a distinction between the relatively widespread regions of neocortex that demonstrate changes in electrical, magnetic or metabolic activity during performance of a task, vs. the much more localized area of cortex that is 'essential' to carrying out the task (Ojemann & Dodrill, 1987). Resections of functionally active cortex outside of the essential region result in minimal or no detectable deficits, whereas removal of the 'essential' cortex leads to a profound neurological deficit. To date, the most accurate method available for identifying and sparing these essential regions involves the use of direct electrical stimulation disruption techniques.

This approach has been used for more than a century and in its current form is a key element of the epilepsy surgeon's technical armamentarium. The method involves having the awake patient carry out a series of tasks as the surgeon delivers disruptive currents to localized regions of cortex. The electrical stimuli are delivered via a hand held electrode in the operating room (Fig. 78.3), or through brain surface recording contacts in patients undergoing video–EEG monitoring with intracranial electrodes. EEG recordings are obtained from the brain tissue being electrically stimulated to insure that abnormal electrical activity (e.g. afterdischarges) does not persist or spread after the period of electrical stimulation.

If the patient is unable to perform the task during the stimulation period, the stimulated brain region is identified as essential to that task. The predictive accuracy and interpretability of electrical stimulation functional mapping has been clearly demonstrated in language, motor and sensory systems. Attempts at using disruption techniques to identify memory critical regions have been less successful and are not utilized routinely. Perhaps the most robust example involves the identification of language critical sites. In the simplest form of language mapping, patients are instructed to name objects or count as the surgeon reversibly deactivates regions of the frontal, parietal and temporal lobes. The exact brain sites that will disrupt this function cannot be predicted based on simple anatomical criteria, the pattern of 'language critical' sites varies significantly from one patient to the next (Ojemann et al., 1989). Disruption sites are highly localized in that movement of the stimulation site by a few millimetres frequently results in a complete elimination of the effect.

Electrical stimulation mapping can be combined with pre and postoperative functional MRI investigations to compare fMRI detected areas of activation for a particular task with electrical stimulation based regions of inactivation. These studies are necessary to determine how to use the information gleaned from fMRI to most accurately facilitate operative planning. In addition, the ability to obtain preoperative fMRI images that can then be compared with postoperative studies provides the opportunity

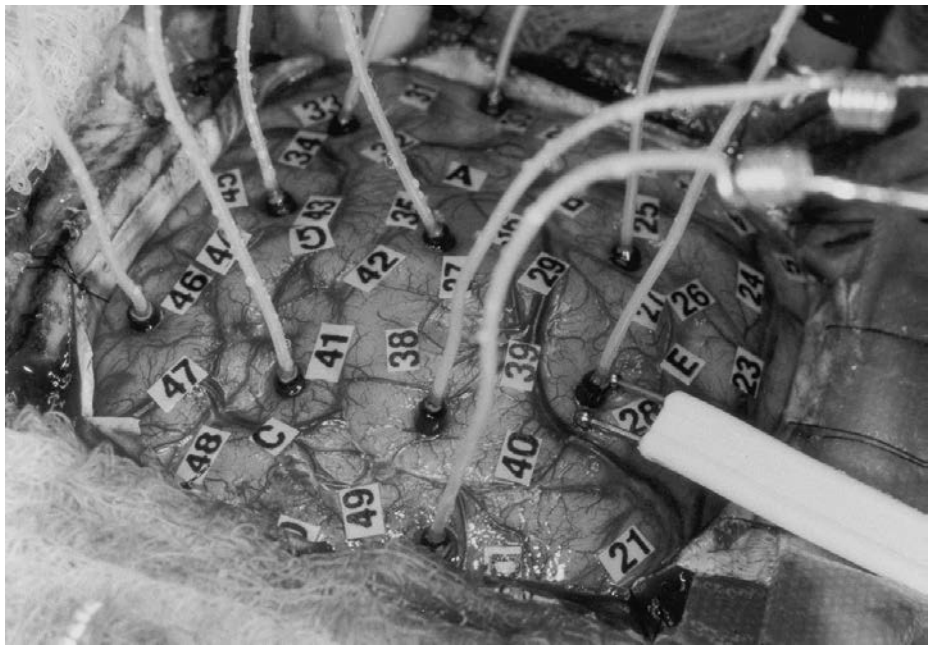

Fig. 78.3. The Ojemann brain stimulator being used for intraoperative stimulation mapping of brain function.

to investigate postoperative recovery of function in patients who develop new deficits following epilepsy surgical resection.

Tract tracing methods

One of the salient characteristics of brain organization is the existence of functional connections between different brain regions. The nature of these functional connections is of great scientific interest and the focus of intensive animal research in experimental laboratories. The most powerful, and highly refined methods for examining connections between brain regions involve injecting compounds into a targeted brain region in a living animal, allowing time to pass, and then processing the brain for histological analysis and observing where these compounds have been transported along axons.

Most of these anatomical tract tracing methods cannot be used to study connections in the human brain, thus necessitating the use of alternative methods. The oldest approach involved bluntly dissecting postmortem brain specimens in an effort to part the tissue along densely packed white matter tracts. The classic descriptions of the major subcortical fibre bundles in humans were compiled using this method. Though valuable in its time, this method is incapable of reliably delineating fine fibre bundles or discerning the manner in which fibre tracts originate and terminate in subcortical or cortical brain regions. Recently, an in vivo MRI anatomical tract tracing method has been described which has advantages over the postmortem blunt dissection method but still lacks the resolving power of histological techniques. The compound DiI has been used to histologically trace connections in postmortem human brain specimens. However, the DiI technique relies on passive diffusion over short distances and thus cannot be used to examine the long-range connections that are of great interest in the human brain.

One technique that can be used to examine long distance functional connections in the human brain involves delivering electrical stimuli to one site, and recording evoked responses from other brain regions that are functionally connected to the brain site that was stimulated. This approach has been used extensively in experimental animals, and carries with it the additional advantage of providing information of the physiologic properties of the connection. By examining the evoked waveforms, it is possible to determine the speed with which signals are conducted between the two sites, and discriminate distinct populations of conduction fibres. This approach is ideally suited for applications in epilepsy surgery patients, in conjunction with the electrophysiologic methods already described in this chapter. There are no known risks associated with the technique, and electrical stimulation functional mapping is used routinely for purely clinical purposes in these patients. Using this method, investigators have identified

and characterized functional connections between primary auditory cortex located within Heschl's gyrus and a secondary auditory field of the posterior superior temporal gyrus (Howard et al., 2000) (Fig. 78.4).

This same group has been systematically investigating the century old hypothesis that a functional connection exists between Wernicke's and Broca's area. Wernicke reasoned that a connection must exist between the auditory receptive region of the posterior superior temporal gyrus and a motor speech centre within the posterior inferior frontal gyrus. Results of blunt dissection postmortem examinations have demonstrated large fibre bundles (e.g. superior longitudinal fasciculus and arcuate fasciculus) that might represent components of the hypothetical connection, but this method is incapable of accurately resolving connections from one cortical site to another. Using the electrical stimulation track tracing method in epilepsy patients, investigators recently demonstrated a robust functional connection between the posterior superior temporal gyrus and the posterior inferior frontal gyrus (Fig. 78.5). The physiological characteristics of this connection indicate that information is being conducted along large calibre axons at velocities that are among the highest known to exist in the central nervous system.

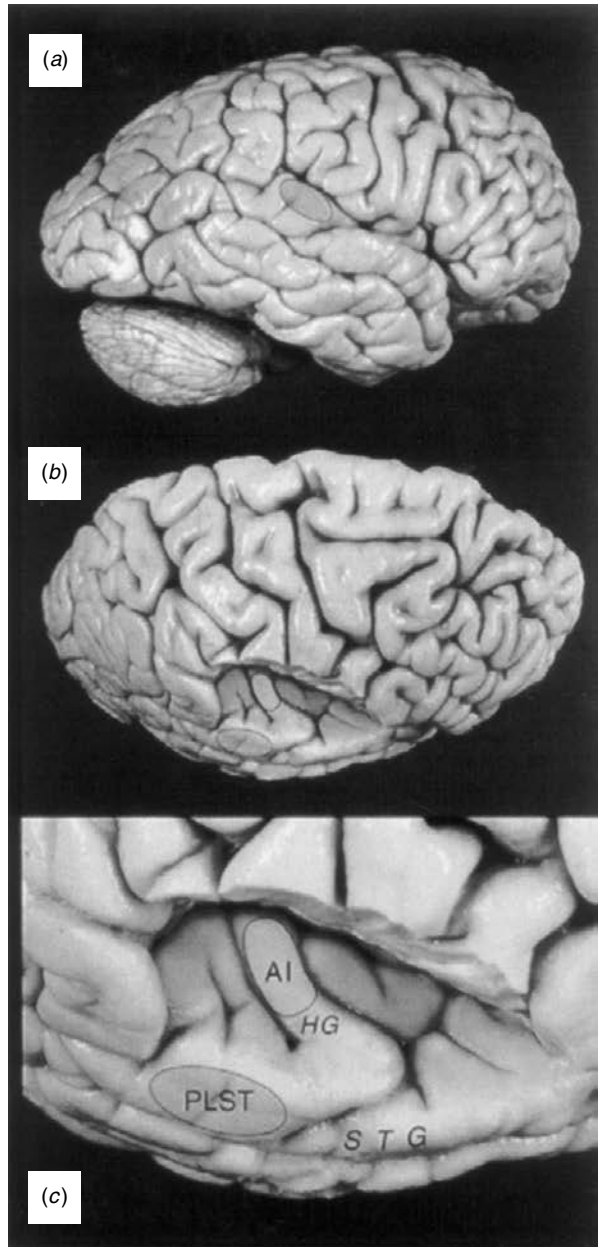

Fig. 78.4. Photographs of the lateral surface (*a*) and superior temporal plane (*b*), (*c*) of a postmortem human brain showing the relative size and location of a discrete auditory cortical field identified on the posterior lateral superior temporal lobe (field PLST). This field was identified and characterized using direct recording and electrical stimulation track-tracing techniques in epilepsy surgery patients. Field PLST is distinct from, but functionally connected to, primary auditory cortex located on the mesial aspect of Heschl's gyrus.

Investigations of higher cortical function

Many advances in brain neurobiology have been catalysed by the development of new research techniques. In the realm of experimental animal research, many of the most powerful and widely used brain research techniques are invasive, i.e. instrumentation is positioned directly within brain tissue. In order to study the electrophysiological characteristics of individual brain neurons, for example, it is necessary to place a small recording electrode within approximately 100 μm of the cell being studied. Microdialysis techniques, whereby the extracellular fluid in a select brain region is extracted and analysed, also require positioning a fine instrument directly into brain tissue.

The brain is the most highly evolved organ of the human species, and many fundamental questions concerning human cognition, speech neurobiology, and our evolution from non-human primates can only be addressed by studying human subjects. Additionally, the ability of humans to follow commands and describe experiences makes them uniquely cooperative research subjects for investigations of even the most basic brain functions. For example, in order to understand how the brain mediates effortless shifts of attention from one environmental stimulus to the next, this can be accomplished in human subjects simply

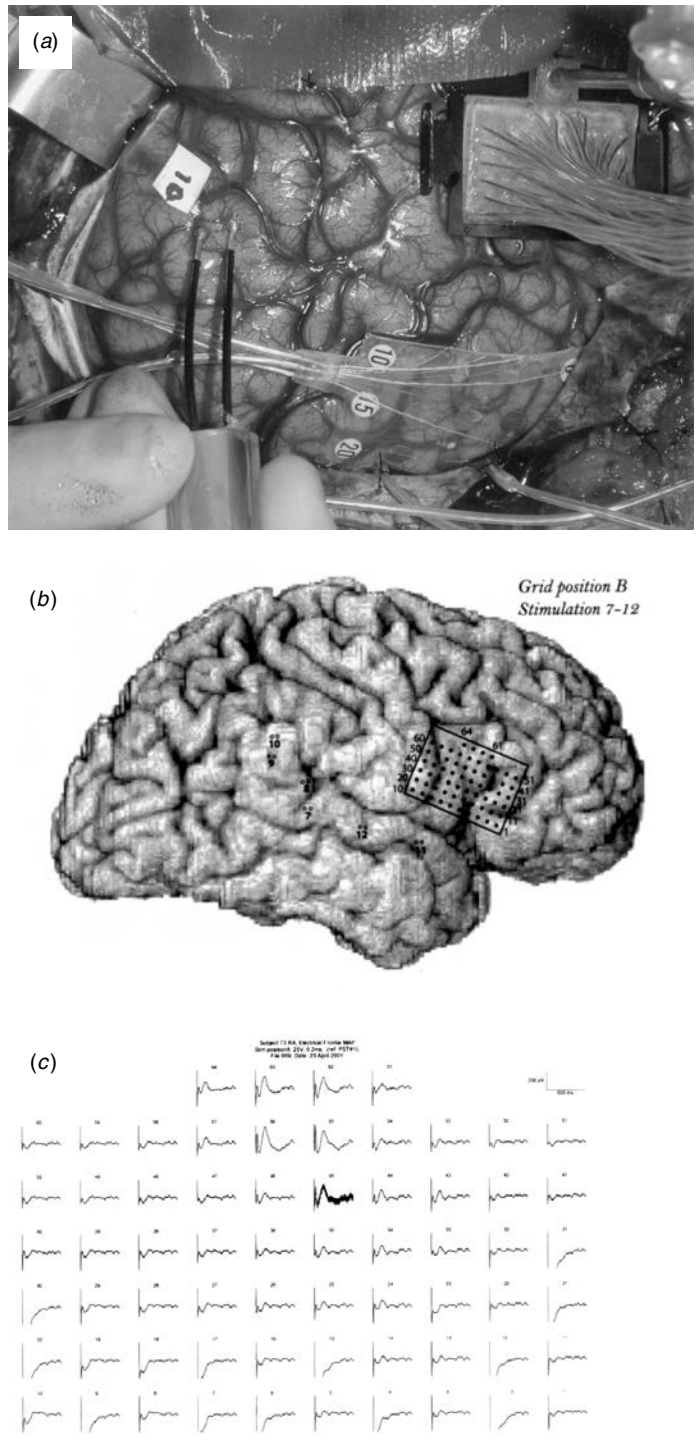

Fig. 78.5. Intraoperative photograph (*a*) during an electrical stimulation tract tracing experiment. A high-density multicontact recording platform is positioned over the right frontal lobe, as sites along the superior temporal gyrus are electrically stimulated with a hand-held probe. The stimulation and recording sites are depicted on the patient's 3D surface-rendered MRI (*b*). A large amplitude electrical stimulation evoked response is observed from recording sites overlying the pars opercularis when the superior temporal gyrus is electrically stimulated at the site labelled 7 (*b*). (*c*) This representative result provides evidence of a robust functional connection between the posterior superior temporal gyrus and inferior frontal gyrus; a pathway that may play an important role in human communication.

by explaining the nature of the experimental task. In contrast, experimental animals must be conditioned over relatively long time periods to display the desired behaviour, and the conditioning process itself may be a confounding variable.

Ideally, investigators studying human brain neurobiology would be able to employ the full range of invasive experimental methods used in the laboratory. Although there is a compelling rationale for direct human brain experimentation, there is always a degree of risk associated with placing devices directly into the human brain. No human subject can be exposed to this risk solely for the purpose of research. It is for this reason that invasive methods, which are indispensable components of experimental animal neuroscience research, are so rarely utilized in humans. Epilepsy surgery patients represent a unique group of human subjects with whom investigators can systematically study normal human brain physiology using powerful invasive research methods.

Patients undergoing epilepsy surgery are presumed to have a localized seizure disorder that can be treated by resecting the focus of seizure onsets. However, as described in an earlier section of the chapter, it is not always apparent from the pre-operative data where the seizure focus is located. In order to detect the site of seizure onsets it is often necessary to place an array of penetrating and surface electrodes over a wide range of brain sites, many of which will subsequently be identified as functionally normal and not the focus of seizure onsets. Additionally, certain normal brain regions must sometimes be resected in order to gain access to a seizure focus. A typical example is the need to resect the lateral neocortex of the anterior temporal lobe in order to gain access to a seizure focus in the amygdala or hippocampus. In essence, in this unique patient population there are opportunities to invasively access normal brain tissue in awake, behaving humans without exposing the subjects to additional surgical risk.

Conventional microelectrode recordings

Investigators at the University of Washington, led by Professor George Ojemann, have compiled the greatest experience in obtaining single neuronal recordings from awake epilepsy surgery patients. In their protocol, standard research microelectrodes are advanced into the exposed lateral temporal neocortex in the brain of awake subjects in the operating room. Recordings are restricted to neocortical regions that will be resected subsequently during the procedure. In this way, damage caused by a microelectrode is irrelevant because the brain region penetrated by the electrode is removed as part of the standard clinical treatment plan.

During these intraoperative experiments, patients are able to visualize an examiner on the opposite side of the surgical drapes and cooperate fully with complex interactive tasks. The period of research recording is typically 30 minutes. Over a period of decades, Professor Ojemann's group has recorded from hundreds of subjects and examined the firing properties of neocortical neurons during memory and language tasks. This work has resulted in a uniquely important body of knowledge concerning human temporal lobe physiology. Using the microelectrode technique these investigators have clearly identified patterns of firing at the single neuron level that demonstrate the distributed nature of temporal lobe neural networks (Ojemann et al., 1988; Creutzfeldt & Ojemann, 1989; Creutzfeldt et al., 1989a,b; Haglund et al., 1994; Ojemann & Schoenfield-McNeill, 1998, 1999). Such high temporal and spatial resolution physiological information cannot be obtained using non-invasive research techniques.

Hybrid depth electrodes

Under optimal conditions, microelectrode recordings obtained in the operating room provide excellent resolution of action potentials from individual neurons. There are, however, three distinct limitations to this technique. First, 'research only' electrodes can only be placed in brain tissue that will subsequently be resected during the epilepsy surgery procedure. For all practical purposes this in effect limits the potential recording sites to the anterior portion of the temporal lobe and a few extratemporal locations. Secondly, the time available for experimentation is limited. Although a moderate prolongation of a standard neurosurgical procedure does not carry with it any known increase in risk, out of consideration for patient comfort the entire research period available for intraoperative experimentation is typically limited to 30 minutes. Finally, because the patient is lying constrained on an operating room table there is a limitation to the types of tasks that can be carried out.

These limitations have been partially circumvented with the development of hybrid depth electrodes (HDE). As described earlier in this chapter, depth electrodes are widely used to detect seizure foci that cannot be resolved using non-invasive diagnostic methods. The typical clinical depth electrode is approximately 2 mm in cross-sectional diameter and has a series of low-impedance contacts positioned along the shaft of the electrode. The electrode is stereotactically implanted into an anatomical target defined on the preoperative MRI or CT scan. Patients are then transferred to the epilepsy ward where continuous video–EEG recordings are obtained from the low impedance contacts. Chronic monitoring is carried out for a period of up to 2 weeks during which time the patient is awake and alert, minimally encumbered by the monitoring equipment, and fully capable of participating in complex neuropsychological and psychophysical testing protocols.

Investigators at the UCLA epilepsy centre were the first group to make use of this clinical depth electrode platform to obtain systematic chronic microelectrode recordings in awake humans. The low impedance contacts on the standard depth electrode have a large surface area and are designed to record field potentials generated by the activity of thousands of neurons located in the general region of the recording site. These low impedance contacts are not capable of resolving individual action potentials. The UCLA team modified the standard depth electrode by advancing fine recordings wires ($< 50\,\mu$m o.d.) through the hollow lumen of the electrode, out the end of the tube and into the brain tissue surrounding the tip of the electrode. This group also described a technique for measuring extracellular neurochemicals by cerebral microdialysis with simultaneous recording of electroencephalographic (EEG) and single-unit (neuron) activity in selected targets in the human brain (Fried et al., 1999). In the course of evaluating large numbers of epilepsy surgery patients with complex seizure disorders these investigators have targeted a broad range of brain locations, all of which could then be investigated at the single neuron level. Using these novel methodologies, the UCLA group has made numerous important and unique contributions to our understanding of human brain physiology, most notably in their studies of the amygdala, hippocampus, and cingulum (Fried et al., 1999, 2001; Kreiman et al., 2000a,b; Cameron et al., 2001).

More recently, investigators at the University of Iowa and Radionics Inc. introduced a further modification of the HDE concept (Fig. 78.6). The Iowa HDE differs from the UCLA prototype in that the fine microelectrode wires are positioned at sites all along the length of the depth electrode, thus enabling investigators to obtain microelectrode recordings from multiple brain regions along the trajectory

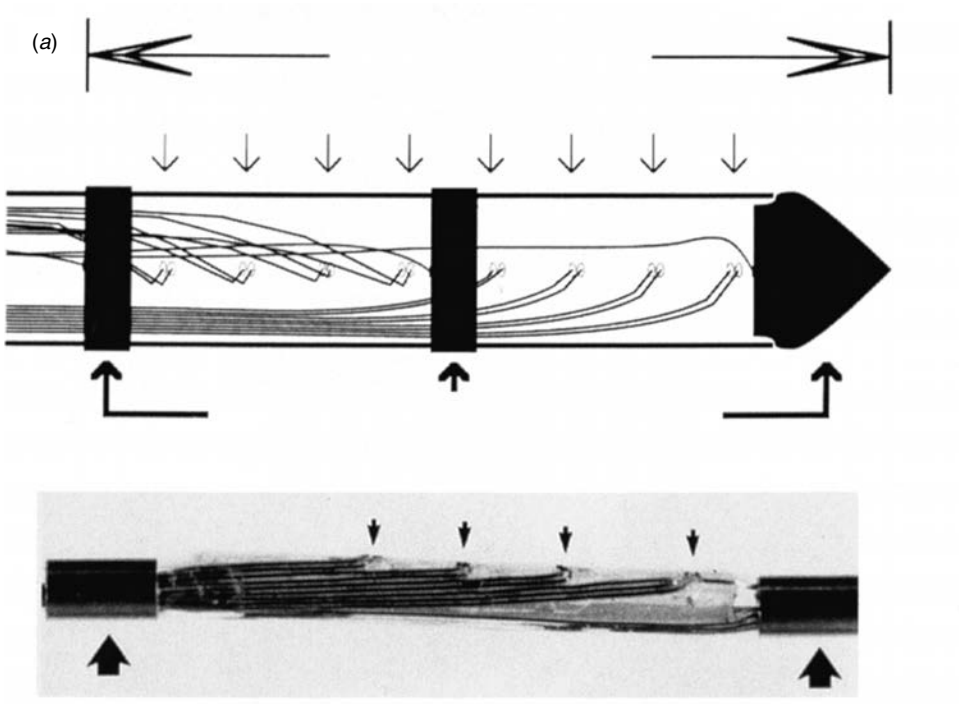

Fig. 78.6. (*a*) Schematic diagram (upper) and photograph (lower) of a hybrid depth electrode (HDE). Clinical EEG data is collected using the low impedance concentric ring recording contacts (large arrows), while microelectrode research recordings are obtained from multiple fine wire high-impedance recording sites (small arrows). (*b*) Representative chronic microelectrode recordings from two epilepsy surgery patients implanted with hybrid depth electrodes (HDE). Action potentials from individual units can be identified and discriminated.

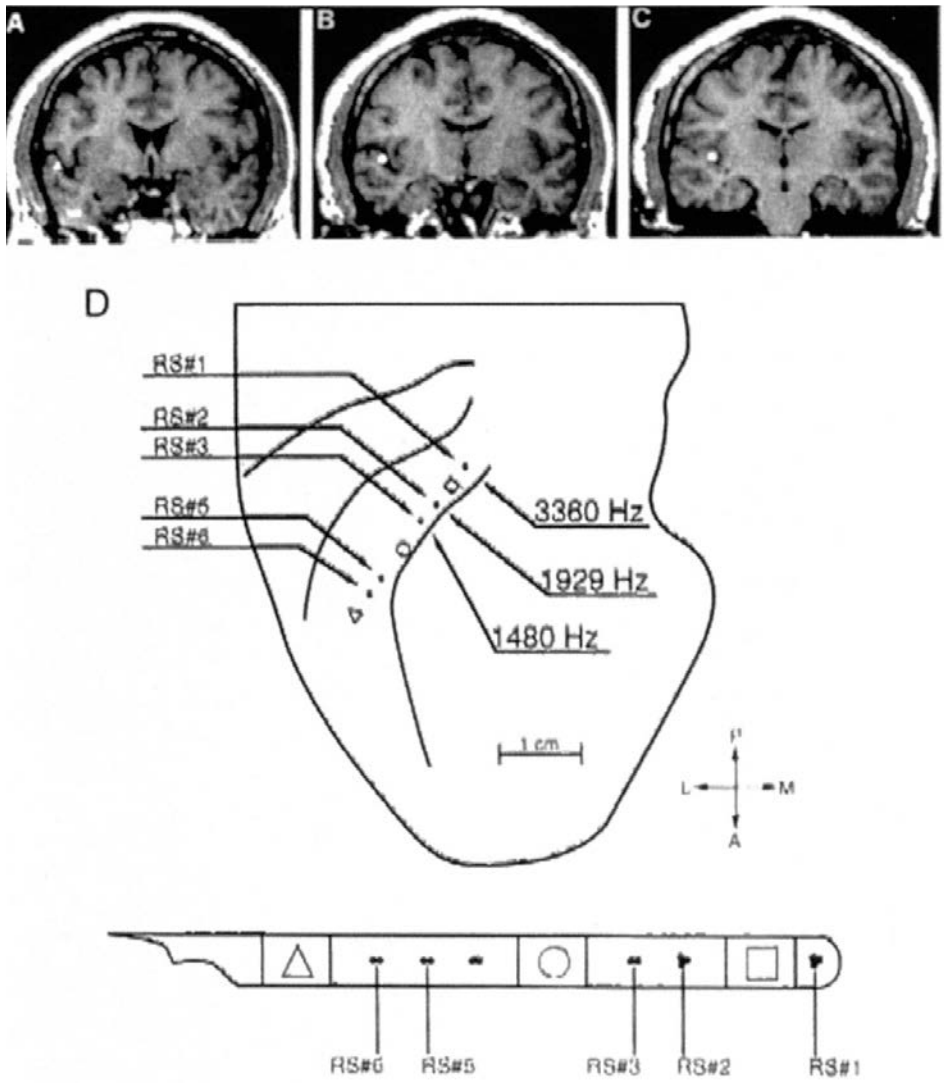

Fig. 78.7. Anatomical and physiologic data demonstrating the tonotopic organization of human auditory cortex in an epilepsy patient. A HDE has been placed along the crest of Heschl's gyrus, as indicated by the coronal MRI images (*a*)–(*c*) and top-down scaled schematic view of the supratemporal plane (*d*). The best frequencies of individual neurons were determined at each high impedance recording site, and the average best frequency for each site is depicted in panel (*d*). This data provided the first evidence at the cellular level of the functional organization of human primary auditory cortex.

of the electrode. By embedding the microelectrode wires in known geometric configurations it is also possible to use advanced single unit isolation techniques based on stereotrode and tetrode principles. This isolation technique was originally developed to enhance the ability of investigators to reliably isolate action potentials from individual neurons during chronic recordings in experimental animal preparations, and is now applied to human recordings using the Iowa HDEs (Howard et al., 1996b). Making use of this capacity to simultaneously record from multiple cortical sites along a linear trajectory, the Iowa group was able to precisely characterize the location, tonotopic organization, and cellular properties of human primary auditory cortex (Howard et al., 1996a) (Fig. 78.7). This knowledge of human auditory neurophysiology could not be obtained prior to the development of this new research tool.

Multidisciplinary research techniques

Another distinct advantage of carrying out chronic human recordings outside the operating room is that the epilepsy

ward setting is well suited to multidisciplinary research collaboration. The well-controlled, spacious environment of the epilepsy ward lends itself to active participation by neuropsychologists, linguists, and neurophysiologists. After an initial period of recovery from the implantation surgery the study patients are typically awake, alert and fully able to participate in complex research protocols. These subjects are confined to the monitoring room for an average period of two weeks while waiting for seizures to occur, and most patients view participation in research studies, and interacting with the investigators, as a welcome diversion.

This multidisciplinary approach has been pursued at the University of Iowa for the purpose of better understanding the neurophysiological properties of human emotion. Over a period of decades, Professors Antonio Damasio, Hanna Damasio, Ralph Adolphs, and colleagues in the Department of Neurology have made seminal contributions to our understanding of the biological basis of human emotion by systematically investigating patients with brain lesions. More recently, these same scientists, in collaboration with neurosurgical investigators, have begun to examine the functional properties of individual neurons within brain regions known to play a role in the representation of emotional states. HDEs are frequently placed in the ventral frontal lobe and amygdala, and the epilepsy research subjects are fully capable of cooperating with carefully controlled experiments designed to evoke a variety of emotional states. Using this approach, these investigators discovered that cells within the human ventral frontal lobe are able to characterize and respond to emotional stimuli with extraordinary speed (Kawasaki et al., 2001). Abrupt changes in firing patterns occurred within 120 ms of the onset of an aversive visual stimulus, providing the first direct evidence that humans carry out high speed emotional categorizations of their environment at a subconscious level.

Optical imaging of intrinsic signal is another technique that is being applied to investigate human physiology as well as pathways of seizure spread. This technique takes advantage of activity-induced changes in the intrinsic optical scattering and absorption properties that accompany neuronal activation of specific brain regions. While the exact mechanisms of these changes (blood flow, neuronal activity, changes in extracellular space size) remain under investigation, the power of these techniques has been well demonstrated. Optical techniques have already been used to image sensory, motor, and language functions in awake patients in the operating room as well as human, primate, and ferret epileptiform activity (Haglund et al., 1992; Haglund, 1997; Schwartz & Bonhoeffer, 2001). Newer optical imaging technology combines submillimetre spatial resolution capabilities with millisecond temporal resolution (Hochman, 1997; Schwartz & Bonhoeffer 2001). In addition, it is likely that transcranial optical imaging of activity-dependent intrinsic signal changes will be possible in the future, allowing these techniques to be implemented extraoperatively.

In addition to the utilization of intracranial electrode arrays for the mapping of primary functional areas and for anatomical tract tracing as described above, subdural implants offer unparallelled opportunites to investigate cognitive tasks and mechanisms of seizure generation in awake functioning humans. For example, in the area of cognition, a recent collaborative effort between the epilepsy surgery team at Children's Hospital in Boston and neuroscientists at Brandeis University has revealed that theta oscillations may play a role in both spatial processing, as is known from rodent investigations, as well as in working memory (Kahana et al., 1999; Raghavachari et al., 2001). Another team of researchers from the University of Pennsylvania and the Georgia Institute of Technology have combined to study the overall signal energy during EEG recordings leading up to temporal lobe seizures (Litt et al., 2001). They found that subclinical bursts of energy became more prevalent in the hours leading up to a seizure, with the accumulated energy increasing in the 50 minutes before a seizure in all five patients studied. These results, together with other efforts using the theory of chaotic dynamics to study non-linear parameters of the EEG (Lehnertz et al., 1999, 2001), raise the possibility of seizure prediction prior to the actual clinical event. Feedback devices are being developed to allow this information to be coupled with electrical stimulation (Litt et al., 2001) or drug delivery (Stein et al., 2000) to potentially abort a developing seizure.

Investigation of resected tissue (in conjunction with appropriate animal models)

Another area of epilepsy research that is fostered by epilepsy surgery is the in vitro investigation of resected tissue. Because of the lack of appropriate human control tissue, particularly in the area of electrophysiological investigation, parallel animal model research into the basic mechanisms of epileptogenesis is required. Nevertheless, resected human tissue is an extremely valuable resource for the investigation of epilepsy pathophysiology. An increasing variety of scientific techniques are being applied to these studies including electrophysiological techniques, single cell genetic amplification combined with genomics, and proteomics. Detailing the many areas of scientific inquiry utilizing resected tissue is beyond the

scope of this chapter. Examples of some of the potentially epileptogenic mechanisms under investigation include synaptic reorganization of temporal lobe and neocortical microcircuits, changes in neurotransmitter transporters and receptors, perturbations of astrocytic functions such as potassium homeostasis and pH regulation, and alterations in glial–neuronal–extracellular space interactions. Combining techniques such as single cell electrophysiological recording followed by genetic amplification of aspirated contents of individual cells promises to provide further insight into the pathophysiology of temporal (Brooks-Kayal et al., 1998; Coulter, 2001) and extratemporal epilepsy, neuronal migration disorders (Crino et al., 2001), Rasmussen's encephalitis and various other pathological conditions.

Human tissue resected during epilepsy surgery is also extremely valuable as a potential source of progenitor cells. Together with the recent realization that neurogenesis is a normal process in the adult mammalian hippocampus (Eriksson et al., 1998; Kempermann et al., 2000), resected temporal lobe tissue can be used to isolate neuronal and glial precursor cells from human dentate gyrus and white matter specimens obtained during epilepsy surgeries. A promoter-based fluorescence activated cell sorting (FACS) technique is used for the neural progenitor isolations (Roy et al., 2000), while glial progenitor cells have cell surface antigens such as A2B5, NG-2, CD-44, AC133, and RC1 that allow them to be sorted by FACS without requiring plasmid transfection. Exciting recent advances have demonstrated that radial glial cells are the likely progenitor cells for migrating neurons during embryonic development (Noctor et al., 2001) and that hippocampal astrocytes may differentiate into granule cells (Seri et al., 2001). It is thus possible that white matter glial progenitor cells or dentate gyrus radial glial cells isolated from resected epilepsy surgery tissue may provide potential pools of stem cells that can be utilized to generate neurons for therapeutic purposes in the future.

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Part X

Cerebrovascular disorders

79

Physiology of the cerebral circulation

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The human cerebral circulation is anatomically unique in its degree of extracranial to intracranial anastamoses and its need to supply a highly developed and metabolically highly dependent cerebral neocortex. The physiology of the cerebral circulation is key to understanding its pathophysiology and thus the management of patients with cerebrovascular disease. It has been covered by a number of monographs (Edvinsson et al., 1993; Mackenzie et al., 1984; Mraovitch & Sercombe, 1996; Purves, 1972; Welch et al., 1997) and particular aspects are routinely and expertly reviewed in specialized journals, such as the *Journal of Cerebral Blood Flow and Metabolism*. The cerebral circulation has certain key physiological features that can be clinically meaningful:

(i) the relationship between brain blood flow and metabolism, vasoneuronal coupling;
(ii) the maintenance of constant flow in the face of variations in perfusion pressure, autoregulation;
(iii) the effect of key respiratory gases, oxygen and carbon dioxide, on cerebral blood flow (CBF); and
(iv) the direct effects of nerves on the cerebral circulation, neurovascular influences on CBF.

Vasoneuronal coupling is a well-established principle (Kuschinsky, 1989), as is the fact that the brain can regulate flow in the face of changes in perfusion pressure. The effect of changes in CO_2 and O_2 on CBF is also an old and established concept. Neural control or neurogenically mediated changes in cerebral blood flow are a relatively recently accepted concept, although the observation that nerves exist on the vessels dates to Thomas Willis in 1664. Some established concepts will be considered here as a backdrop to the clinical discussions that follow. The classical view of the cerebral circulation has been that blood flow and cerebral metabolism are tightly coupled under the influence of substances, such as H^+, adenosine, and K^+ that ensure a rapid and matched supply of blood when required without neural influence. As the role of the neural innervation and its neuromodulators emerges and their functions are clarified opportunities for intervention and understanding will arise and eventually inform the management of patients with cerebrovascular disorders.

Vasoneuronal coupling

The fact that cerebral blood flow tracks closely cerebral metabolic activity remains a tenet of cerebrovascular physiology. It is the basis for many modern functional neuroimaging methods (Frackowiak & Friston, 1994). As early as 1890 Roy and Sherrington (1890) identified hydrogen ions as a byproduct of cellular metabolism, which could effect changes in regional CBF by vasodilatation. However, increases in regional CBF can be shown to precede any interstitial pH changes. Potassium release also follows neuronal activation and is also a potent vasodilator. Interstitially released K^+ is taken up by astrocytes and is associated with their depolarization and further K^+ release at their distal perivascular processes so buffering the perineuronal K^+ changes (spatial buffering) (Paulson & Newman, 1987). Such a mechanism effectively siphons K^+ towards the microvasculature to effect regional vasodilatation. However, as with interstitial pH changes, the functional significance of this model is questioned by the observation that astrocyte K^+ uptake inhibition with Ba^{2+} does not alter the regional increases in CBF accompanying local cortical electrical stimulation (Iadecola, 1993). Furthermore the time course of vasodilatation after topical application of potassium is too slow to account for the rapidity of regional vascular regulation.

Adenosine, a metabolic byproduct of adenosine monophosphate dephosphorylation, has received the most experimental support in rCBF regulation. Adenosine is a

potent vasodilator of cerebral vessels when applied topically in vivo, and marked elevation in levels is observed with hypoxia, epileptic seizure, hypotension and focal cortical stimulation. However, the latter has not been consistently demonstrated, since pretreatment of brain cortices with adenosine deaminase inhibitors does not inhibit sciatic stimulation-induced cortical hyperemia. For adenosine to mediate vasoneuronal coupling its synthesis would have to increase by an order of magnitude before the onset of vasodilatation to overcome washout effects and then switch off equally rapidly at the end of activation, a situation not supported experimentally. It is plausible that adenosine may contribute to the maintenance of regional vasodilatation in the situation of prolonged activation or tissue hypoxia, such as severe hypotension and ischemia (Winn et al., 1981).

Nitric oxide

Considerable excitement has surrounded the prospect that nitric oxide (NO) may link brain blood flow and metabolic activity (Iadecola, 1993). The role of the endothelium, a monocellular cell layer, in the tonic, dynamic regulation of cerebrovascular tone was first demonstrated by the dependence on the endothelium of vascular relaxation in response to topical application of acetylcholine (Furchgott & Zawadzki, 1980). That this EDRF could be NO was demonstrated using chemiluminescence detectors originally designed to monitor atmospheric levels of NO (Moncada et al., 1991). The NO:L-arginine pathway is of early phylogenetic origin present in species as diverse as slime mould and horseshoe crab, and is both highly functionally conserved across the species barriers and ubiquitously distributed within the body as an intercellular messenger and host defence system. NO is a small lipophilic molecule and therefore easily diffuses across cell membranes. As a signal transducer it binds to the haem moiety of guanylate cyclase to effect increases in cyclic-GMP in surrounding cells so producing most of its biological activity, although at higher concentrations it also has some activity as a hyperpolarizing agent by an action on membrane potassium channels. The half-life of NO is 1 second in a blood-free isolated perfused guinea pig heart with a maximum diffusion distance of 100 μm.

The physico-chemical properties of this potent vasodilator, the compartmentalization of the endothelial and neuronal NO synthase isoforms within different neuronal populations, and the demonstration of the physiological and ultrastructural coupling of NO synthase activation to *N*-methy-D-aspartate receptor activation by glutamate, has made a compelling argument for a central role for NO in vasoneuronal coupling. Animal models using NO synthase inhibitors of varying selectivity for the different isoforms have suggested that NO from neuronal NO synthase may have a role, but the fact that mice lacking genes for the different isoforms have relatively normal cerebrovascular physiology indicates that there are other mediators in the absence of NO. Studies in humans are complicated by the difficulties of blood–brain barrier penetration by NO synthase inhibitors and the difficulties of quantification of local NO inhibition, but do suggest that NO derived from the vascular endothelium does not play a significant role (White et al., 1999).

Autoregulation

Autoregulation is that property of a vascular bed maintaining a constant blood flow in the face of changes in perfusion pressure. It is not confined to the brain but the discussion in this section relates to the phenomenon as it affects cerebral blood flow (Fig. 79.1). The perfusion pressure for the brain is the difference between the arterial blood pressure and either the venous or cerebrospinal fluid pressure, dependent on that which is greater. Autoregulation is achieved by alterations in vessel calibre so that when perfusion pressure drops, flow is maintained, and when it elevates there is no excess of flow in comparison to brain requirements. Experimental data suggest that autoregulation is predominantly a function of smaller intracortical resistance vessels. Autoregulation to changes in cerebral perfusion pressure is a rapid homeostatic mechanism with a time constant in seconds, superimposed over and above systemic pressor regulatory mechanisms. Considered to be a property of the vessels the phenomenon is conventionally studied using steady state techniques. Figure 79.1 illustrates the constancy of cerebral blood flow between limits, which are themselves not fixed but dependent upon resting autonomic neurogenic input, particularly from the sympathetic nerves, and regional myogenic or metabolic activity. Beyond the limits of autoregulation flow is passively dependent upon perfusion pressure, although at the lower end flow may fall to zero if the perfusion pressure falls below that critical level required to overcome the elasticity of the vessel, the critical closing pressure.

The most convincing data explain autoregulation as an intrinsic myogenic mechanism, such that stretch-dependent vasoconstriction or vice versa maintains a constant blood flow. Such a mechanism would be responsive to changes in transmural pressure. However both pressure dependent vasoconstiction and flow-dependent vasodila-

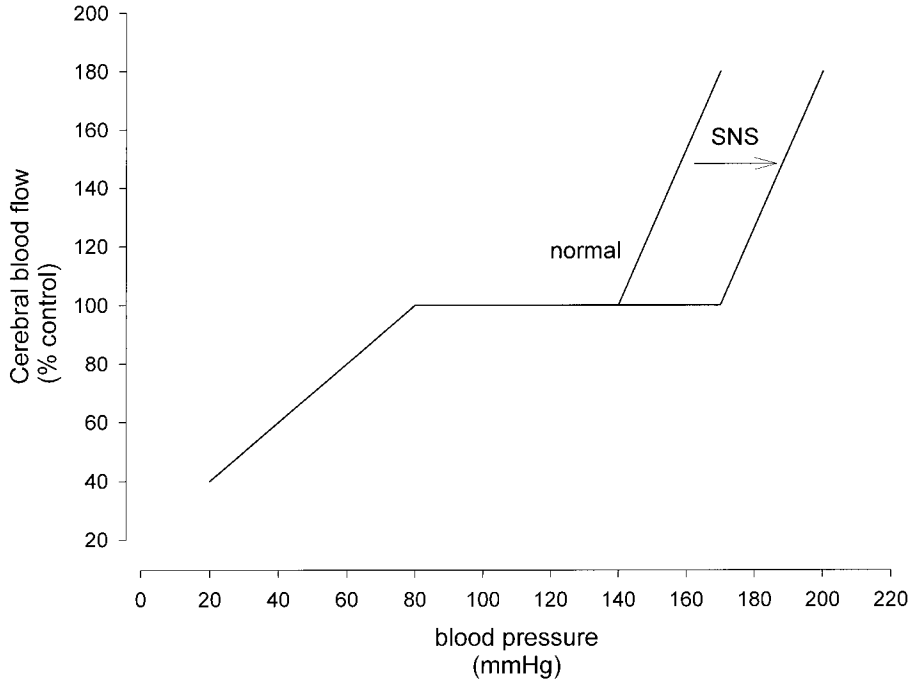

Fig. 79.1. Classical autoregulatory control of the cerebral blood flow with stable flow over a range of perfusion pressures (mmHg abscissa). The sympathetic nervous system (SNS) has been shown to extend the upper limit of cerebral autoregulatory limits.

tation are endothelium dependent, pointing either to an endothelially synthesized factor or ultra structural linkage to myocytes, which probably involves calcium entry into endothelial cells during stretch. Studies of NO inhibition in animals have been conflicting, either suggesting no role for NO or an increase in upper and lower autoregulatory limits as a passive response to changing basal vascular tone and resting blood pressure. However, there is evidence that at lower blood pressures local changes in adenosine may contribute to maintaining cerebral blood flow.

It is perhaps a surprise that, despite the relatively simple nature of the response and its consistency, the precise mechanisms involved in autoregulation remain to be elucidated. Partly, this reflects the lack of temporal resolution of steady-state techniques in studying dynamic phenomena and it is probable that several effectors of varying time constants of action are involved in both initiation and maintenance of altered vascular tone (White et al., 2000).

Autonomic neural influences on cerebral autoregulation

It has been established for some time that stimulation of the sympathetic nerves during hypertension will extend the upper limits of autoregulation. It is considered that the shift in the autoregulatory curve seen with sympathetic activation is a protective phenomenon against cerebral damage that can be caused by excessive pressure. Both noradrenaline and neuropeptide Y (NPY) seem to be involved in this protective process. A similar mechanism may be activated to modulate intracranial pressure. Certainly, sympathetic nerve stimulation can alter intracranial pressure. The regulation of venous capacitance and the dense innervation of the choroid plexus by adrenergic nerves is likely to have an important influence upon intracranial pressure and is the subject of ongoing research.

Influences of carbon dioxide and oxygen

Hypercapnic and hypoxic cerebral vasodilator responses are basic features of normal cerebrovascular physiology. Hypercapnic vasodilatation is a potent effect that is clearly impaired after cortical spreading depression (Lauritzen, 1994) and is otherwise a test of cerebrovascular integrity from a physiological viewpoint. This response has been considered a function of changes in perivascular pH analogous to the proposed interstitial pH changes following cellular metabolism. The vasodilatory response to hypercapnia is notably more marked that that due to metabolic

acidosis; an effect presumed to reflect the ease of diffusion of CO_2 from the circulation to the myocyte, as opposed to the polar H^+ ions. However, there is no direct evidence that alterations in $PaCO_2$ alter myocyte pH *per se*, or an accepted cellular mechanism whereby pH alters myocyte contractility. Furthermore cerebrospinal fluid pH can be shown to remain constant despite plasma pH changes following hypercapnia or intravascular acid/alkali injection. Thus at least part of the response may require other mediators. Noradrenergic effects on vascular tone are pH dependent, and hypercapnic hyperemia is attenuated by indomethacin, although other eicosanoid inhibitors such as diclofenac do not possess this property.

Evidence for a role for NO in modulating the hyperemic response has come from NO synthase inhibitor studies in several animal species including subhuman primates which show attenuation of hyperemia to moderate degrees of hypercapnia only (Iadecola & Zhang, 1996; Wang et al., 1992). As for studies of basal flow the reduction in hypercapnic hyperemia post NOS inhibition occurs independently of any change in metabolic activity. For extreme hypercapnia the hyperemic response is NO independent. Equally it is unclear which compartment of NO activity may be participating: endothelial ablation does not abolish the response to hypercapnia, and sectioning of NO synthase-expressing nerves originating at the sphenopalatine ganglion has no effect on the hyperemic responses. Furthermore, endothelial NOS knockout mice have normal hypercapnic responses. Myocytic NO synthase activity is not constitutively expressed and therefore unlikely to play a significant role.

Furthermore, not all animal studies have shown a role for NO in hypercapnic hyperemia, with appreciable differences in the sensitivity to NO synthase inhibitors reported between models and within species. These differences may partly be explained by the dose and time dependence of total NO synthase inhibition following arginine analogues in different experimental models. Recently, using the putative neuronal NOS inhibitor 7-nitro-indazole (7NI) it has been reported that the effects of NO inhibition in hypercapnic hyperemia are permissive since basal NO replacement with NO donors reversed the reduction observed. Thus the direct extrapolation of data derived in different animal models to humans is potentially misleading and more studies in humans with newer imaging methods may be helpful.

Hypoxia is a potent vasodilatory stimulus for the cerebral vasculature independent of any coincident changes in CO_2 levels. However, its mechanism remains poorly understood and is independent of any changes in underlying cellular metabolic rate. There is evidence that physiological changes in arterial oxygen levels may directly influence myocyte contractility possibly via an interaction with membrane calcium uptake, but further work is needed to clarify the physiology of this fundamental cerebrovascular response.

Table 79.1. Intrinsic neural innervation of the cerebral circulation-implicated structures

Structure	Effect on CBF	Possible neuromodulator
Medulla		
Dorsal medullary reticular formation	↑	
Rostroventrolateral medulla	↑	Adrenaline
Pons		
Locus ceruleus	↓	Noradrenaline
Parabrachial nucleus (medial)	↓	?
Midbrain		
Dorsal raphe nucleus	↑	serotonin acetylcholine nitric oxide
Cerebellum		
Fastigial nucleus (electrical)	↑	acetylcholine nitric oxide
Forebrain		
Basal forebrain	↑	acetylcholine nitric oxide galanin
Centromedian parafasicular thalamus	↑	?

Notes:
↑, increased cerebral blood flow; ↓, decreased cerebral blood flow; when the listed structure is stimulated.

Neurogenic control of the cerebral circulation

The neural innervation can be divided into intrinsic and extrinsic systems. The division is somewhat arbitrary but underlies some common themes. The intrinsic systems consist of nerves that arise from within the brain and pass through brain substance to innervate parenchymal vessels (Table 79.1). The extrinsic systems while arising in the brain pass out of the brain to traverse peripheral nerves returning to innervate large intracranial and pial vessels (Table 79.2). These nerves may have several roles including modulating local vasoneuronal coupling, providing trophic influences on vessels, or as reserve systems in times of physiological threat. They are reviewed in detail elsewhere (Goadsby, 2002). The intrinsic systems are perhaps less clear in their immediate clinical consequences, although will, no doubt,

Table 79.2. Extrinsic innervation of the cerebral circulation

	Ganglia	Effect of stimulation on CBF	Neuromodulators
Sympathetic	superior cervical	–	Noradrenaline Neuropeptide Y (NPY)
Parasympathetic	sphenopalatine otic IC miniganglia	↑	Acetylcholine VIP PHI (M) PACAP Helodermin Helospectin I and II Nitric oxide (NO)
Trigeminal	trigeminal	↑	Substance P CGRP Amylin Neurokinin-A (NKA) Cholecystokinin-8 PACAP NO

Abbreviations:
CGRP, calcitonin gene-related peptide; IC, internal carotid; PACAP, pituitary adenylate cyclase activating polypeptide; PHI (M), peptide histidine isoleucine (methionine); VIP, vasoactive intestinal polypeptide

become more interesting as they are better understood. The extrinsic systems will be dealt with in some greater detail because of their direct potential role in diseases, such as pure autonomic failure syndromes (See also Neurodegeneration Section) and primary neurovascular headaches (See also Headache Section).

Parasympathetic influences on the cerebral circulation

The parasympathetic innervation of the cerebral circulation represents potentially the most powerful of the neural vasodilator influences. Its influence cannot be overlooked in any pathophysiological situation. The parasympathetic system is basically vasodilator in nature and is capable of altering brain blood flow independently of the prevailing metabolic demand and perfusion pressure. It is a potential reserve system that is well characterized in experimental animals but still lacks detailed analysis in humans.

Anatomy

The parasympathetic system is that system arising from the superior salivary nucleus and passing out of the brain in the facial (VIIth cranial) nerve, distributing fibres through the pterygopalatine (sphenopalatine) and otic ganglia and carotid miniganglia to dilate vessels, almost certainly by way of a peptidergic transmitter. The terms pterygopalatine and sphenopalatine imply the same structure, with the former being the preferred term in humans because of its relationship to the pterygopalatine fossa. Pharmacologically the system is characterized by the presence of one or more substances, such as acetylcholine, vasoactive intestinal polypeptide (VIP), and peptide histidine methionine (PHM; isoleucine in the rat, thus PHI).

Transmitters and modulators

The parasympathetic system contains a number of transmitter or neuromodulator substances that are often colocalized in the same neurones. All the substances known to exist in the parasympathetic nerves are vasodilator (Table 79.2) but their precise role and, in particular, relationship to one another remains unclear. Whether these anatomical subgroups with one, two, three or even four colocalized transmitters have functional correlates remains to be established.

Of the localized transmitters, vasoactive intestinal polypeptide (VIP) is particularly potent and, coexistent with it, peptide histidine methionine (PHM). VIP is a 28-amino acid basic polypeptide that was first isolated from the porcine duodenum. It belongs to a structural superfamily of peptides along with glucagon, secretin, and gastrin inhibitory peptide. The family is characterized by helodermin/helospectin-like peptides that are distributed in the central nervous system and in endocrine cells, such as the C cells of the thyroid. It has been shown that each of helodermin and the helospectins I and II are vasodilatory in the cerebral circulation. There are as yet no data that address the inter-relationship of these transmitters, although they can have added effects.

Nitric oxide (NO)

Because of its unique position as a gaseous transmitter NO is worthy of special mention. Whilst the effects of blockage of NO production on non-neural responses, such a hypercapnia and autoregulation, remain somewhat controversial in terms of quantity, and its role in vasoneuronal coupling is still open to debate, its role in parasympathetic responses seems clearer. Blockade of NO synthesis reduces the effect of parasympathetic stimulation in the cerebral circulation. This observation is important because NO can be both deleterious through direct oxidative toxicity in ischemic brain and yet protective by allowing regional vasodilatation, a dichotomy of function partially dependent upon the levels of production and underlying redox state of ischemic tissue. Modulation of parasympathetic tone has potential for protective neurovascular dilatation in the cerebral circulation without fuelling oxidative stress.

Physiological effects

Given that the cranial parasympathetic outflow to the cerebral vessels via the facial nerve is marked by many neurotransmitters or neuromodulators (acetylcholine, VIP, NO, and PHI (M)), what is the effect of blocking this outflow? The responses that characterize normal cerebral blood flow (CBF) are the hypercapnic vasodilator response, the autoregulatory response to changes in blood pressure, and the hypoxic vasodilator response. None of these are affected by parasympathetic blockade.

Direct stimulation of the facial nerve in humans leads to an increase in total cranial blood flow. These responses are mediated through a classical parasympathetic ganglion as they can be blocked by hexamethonium, and probably use vasoactive intestinal polypeptide as the major transmitter of the system. Studies of the peripheral ganglion mediating facial nerve vasodilatation have included peripheral reflex (trigeminal ganglion) and central structure (locus ceruleus) stimulation. It is clear that effects mediated by the facial nerve can be substantially blocked by sphenopalatine ganglion removal and that this same response is VIP mediated.

In summary, the cranial parasympathetic pathway to the cerebral vessels arises in the superior salivatory nucleus in the pons; it traverses the facial nerve, joining the greater superficial petrosal nerve to be distributed to the vessels after synapsing chiefly in the pterygopalatine (sphenopalatine) or otic ganglia. A variable small number of fibres in different species (including humans) have this peripheral synapse located in microganglia on the wall of the internal carotid artery, particularly near the carotid siphon. The transmitters contained in this system are acetylcholine, VIP, PHM(I), nitric oxide, and helospectin-related peptides. A classical parasympathetic nicotinic ganglion mediates the ganglionic transmission in the periphery, while current data would suggest that VIP is the major neuroeffector substance at the nerve–smooth muscle junction. The pathway does not play a role in either hypercapnic or hypoxic vasodilator responses or autoregulatory responses to changes in arterial perfusion pressure. The system can be activated by either direct stimulation or via connections with other important central neural vasoactive nuclei to increase cerebral blood flow independent of cerebral metabolic needs. The parasympathetic system is ideally placed to engage when ordinary metabolic driving factors are impaired.

Sympathetic influences upon the cerebral circulation

The sympathetic nervous innervation of the cerebral circulation is by far the best characterized of the neural modulators of CBF. It is involved in augmenting autoregulation (see above) and has interesting potential trophic roles for cerebral vessels.

Anatomy

The sympathetic nervous innervation of the cerebral circulation arises in the hypothalamus as first-order neurons and projects to the intermediolateral cell column of the spinal cord. Second-order neurons arise from the sympathetic chain and proceed to synapse with third-order neurons in the superior cervical ganglion. The innervation is lateralized and largely respects the midline, with subsequent projection to the cerebral vessels being provided by sympathetic nerves that run rostral with the carotid artery.

There is a dense innervation, particularly of more proximal large arteries, which follows vessels out to the pia and along the brain surface but generally only follows penetrating vessels for a short distance into the cerebral parenchyma. The largest part of the adrenergic supply of the intraparenchymal vessels is supplied by the locus ceruleus (Table 79.1). The sympathetic nerve terminals are often located close to smooth muscle cells in the outer media.

Transmitters and neuromodulators

The main transmitter of the sympathetic innervation is the classical autonomic amine transmitter, noradrenaline. The effect of noradrenaline release is to constrict the vessels through activation of α-adrenoceptors in the vessels. In humans the predominant receptor subtype is the α_1-adrenoceptor, while in some experimental animals α_2-adrenoceptors can be seen. These receptors mediate vasoconstriction.

In addition to the classic constrictor aminergic transmitter, sympathetic nerves release the vasoconstrictor peptide neuropeptide Y (NPY). NPY is widely distributed in the brain and peripheral nervous system. Fibres that contain NPY form a dense network around cerebral arteries and veins and double stain for noradrenaline. Retrograde tracing studies have shown NPY-positive fibres that have cell bodies in the superior cervical ganglion, and these fibres are substantially reduced by sympathectomy. NPY is a potent constrictor of cerebral vessels at the $NPY Y_1$ receptor. This receptor has been identified on cerebral vessels using PCR for the human $NPY Y_1$ receptor.

Physiological effects

Direct stimulation of the cervical sympathetic nerves in experimental animals results in large vessel constriction but no change to small calibre vessels. The effect is more prominent on the cerebral veins and is blocked by α_1-adrenoceptor blockade. The influence of the sympathetic innervation of the cerebral circulation is discussed above under 'Autoregulation' and this is by far its best-described effect. In this context it is probably primarily permissive, setting a background vascular tone upon which autoregulatory mechanisms are superimposed and protecting the brain from hyperperfusion during transient hypertensive systemic responses to stress. There are some data to suggest that hypercapnic vasodilatation is influenced by the sympathetic innervation, such that the response is enhanced, but this requires further study.

There are excellent data that have established a role for the sympathetic nerves in development, particularly of the muscular layer of the wall of cerebral vessels. The trophic effects of the sympathetic nerves deserve further investigation.

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80

Stroke syndromes

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Clinical diagnosis is made by systematic, logical, inductive probablistic reasoning facilitated by pattern matching. We recognize Tom because we know what he looks like especially if we have seen him before. This chapter shares various common patterns of stroke-related symptoms and signs.

Stroke subtypes

Stroke mechanisms are divided into those that cause ischemia and those related to hemorrhage.

Ischemic mechanisms

These can be divided into three main pathophysiological groups.

Thrombosis

This term is used to indicate a local process within an artery or vein that causes a lack of blood to its supply zone. It includes a variety of vascular pathologies: atherosclerotic plaques and stenosis, dissection, arteritis, fibromuscular dysplasia, etc. The vascular disorder can involve large extracranial or intracranial arteries or small penetrating arteries. The disease process narrows the lumen of the artery diminishing distal blood flow. Often, white and red thrombi form and cause occlusion of the vessel. The signature of the local 'thrombotic' process is transient ischemic attacks all in the same vascular territory. If and when a stroke develops, it can occur suddenly or show fluctuations and gradual, stepwise, or stuttering devlopment of neurological signs and symptoms. The local process in the artery ('thrombosis') can also be the source of intra-arterial embolism.

Embolism

In this ischemic mechanism, the material that blocks a recipient artery arises from a different proximal donor site. Donor sites include the heart, aorta, and arteries proximal to the recipient artery. The signature of embolism is the very sudden onset of neurological deficits that are maximal at onset. In some patients there may be a single stepwise worsening within 48 hours. Sudden dramatic improvement in a neurological deficit also can occur when emboli pass or are lysed.

Systemic hypoperfusion

Thrombosis and embolism are characterized by blockage of single vessels that cause focal ischemia in the region of supply of the blocked vessels. In contrast systemic hypoperfusion refers to a general decrease in blood flow to the brain. A number of systemic disorders can be responsible including myocardial infarction, cardiac arrythmia, pulmonary embolism, gastrointestinal or other sites of blood loss, etc. Patients feel light headed and vision can become dimmer and noises sound more distant. They lose the ability to think clearly and feel as if they will pass out and many do lose consciousness. Lateralized motor, sensory, and visual symptoms and signs are not present.

Hemorrhagic stroke syndromes

There are two relatively distinct hemorrhagic stroke syndromes.

Subarachnoid hemorrhage (SAH)

Blood issues rapidly into the space around the brain and spinal cord, usually under systemic arterial pressure because of the rupture of an arterial aneurysm or a vascular malformation. This causes sudden severe headache that is usually generalized but may be more prominent on

the side of the leaking vessel. The headache is often located in the neck and may radiate into the back and even into the buttocks and lower extremities mimicking sciatica. Vomiting is very common near the onset of the headache. The sudden increase in spinal fluid pressure causes a cessation of brain activity that may lead to the knees buckling and the cessation of making of new memories. The increased CSF pressure may lead to decreased consciousness: either restless agitation or stupor. Usually, there are no major focal neurological signs.

Intracerebral hemorrhage (ICH)

Bleeding in this subtype is directly into brain parenchyma. The earliest signs relate to the location of the hemorrhage. Symptoms and signs may gradually increase. If the hemorrhage becomes large, symptoms and signs of increased intracranial pressure develop including headache, decreased alertness, and vomiting. The commonest causes are hypertension, trauma, amyloid angiopathy, bleeding diathesis, drugs and vascular malformations.

Syndromes of occlusive disease and brain ischemia in the anterior–carotid circulation

Internal carotid artery (ICA) stenosis or occlusion in the neck

Atherosclerotic disease

The modern era in ischemic cerebrovascular disease began with the key report of Miller Fisher that called attention to the clinical findings associated with occlusion of the ICA in the neck (Fisher, 1951). The major cause of ICA occlusive disease in the neck is atherosclerotic narrowing. The lesion usually begins in the distal CCA and extends into the first few centimetres of the ICA. Occlusive disease of the coronary, iliac and femoral arteries often accompanies carotid atherosclerosis. Atherosclerotic plaques gradually narrow the ICA lumen. Ulceration, attachment of platelets and clot to crevices in plaques, and hemorrhage into plaques all become more common as the arterial lumen becomes increasingly stenosed. Plugs of platelets and thrombin may detach from the arterial wall and embolize to intracranial arteries causing transient or prolonged neurological dysfunction. The single most important clue to an ICA localization is an attack of transient monocular visual loss. The visual loss is described as a dimming, darkening, or obscuration. An apparent shade or curtain usually falls from above but may move from the side like a theatre curtain. After seconds or a few minutes, the curtain lifts or recedes, usually leaving no permanent visual loss. Transient visual obscurations are caused by decreased blood flow through the ophthalmic artery, the first tributary of the ICA. Transient monocular visual loss occurs when the lesion affects the ICA proximal to the ophthalmic artery (in the neck or proximal carotid siphon) or involves the ophthalmic artery itself. Some patients with severe ICA occlusive disease report unilateral spells of reduced vision after exposure to bright light, a type of retinal claudicaton.

Also common are episodes that reflect hemispheral ischemia. The episodes of hemispheral ischemia are also usually brief. Attacks may be quite varied and include different deficits in different limbs during individual attacks, but sometimes the spells are stereotyped. Numbness and/or weakness of the hand and arm are the most common symptoms, aphasia is also common. In some patients with critical stenosis, the attacks are very frequent and may be precipitated by suddenly standing or by a drop in blood pressure. Embolism of clot from the ICA causes sudden onset strokes which usually cause syndromes of middle cerebral artery dysfunction (described below).

Dissection of the ICA in the neck

After atherosclerosis, dissection is the next most common lesion that affects the carotid artery in the neck. Dissections usually involve the pharyngeal portion of the artery above the origin but below entry into the skull. Dissections cause symptoms primarily by the presence of luminal compromise and luminal clot. Dissections through the adventitia lead to rupture into the surrounding neck muscles and fascia, a process that causes neck pain and formation of a pseudoaneurysm. Thrombus is present within the lumen because of rupture of intramural clot into the lumen, or thrombus formation *in situ* within the lumen. Narrowing of the lumen by the intramural blood alters blood flow and irritates the endothelium causing release of endothelins and tissue factors which activate platelets and the coagulation cascade contributing to formation of intraluminal thrombus. Brain ischemia can result from hypoperfusion usually from acute luminal compromise. Hypoperfusion usually causes transient ischemia. Infarction is more often due to embolization or propagation of luminal thrombus.

The major symptoms of extracranial carotid artery dissection are: neck and head and face pain, Horner's syndrome, pulsatile tinnitus, transient ipsilateral monocular visual loss, transient hemispheral attacks with contralateral limb numbness/weakness, sudden onset strokes, and palsy of the lower cranial nerves (IX–XII). (Caplan, 2000; Bogousslavsky et al., 1987) Some patients have pain and

headache as the only symptom, and do not have neurological findings. Pain is often in the neck, face or jaw. Headaches may be generalized, but are most common on the side of the dissection. Features of Horner's syndrome are caused by involvement of the sympathetic fibres along dilated carotid artery segents. Pulsatile tinnitus is another common symptom since the carotid artery courses near the tympanic membrane. Neurological symptoms related to hypoperfusion are usually multiple brief TIAs. Sudden onset strokes are usually casused by embolism of clot from the region of dissection. The distended dilated carotid artery at the skull base can compress lower cranial nerves (IX to XII) which exit in this region.

Internal carotid artery occlusive disease intracranially

Narrowing and thrombotic occlusion of the ICA occur at the siphon less frequently than at the ICA origin. The ophthalmic artery originates from the ICA within the siphon. TIAs are less frequent and fewer in number in patients with siphon disease, as compared to ICA-origin disease. The ratio of strokes to TIAs and of asymptomatic patients is higher in carotid-siphon disease.

The presence of transient monocular visual loss depends on the level of the siphon lesion; it occurs when the stenotic lesion is proximal to the opthalmic artery origin. Hemispheral attacks are indistinguishable from those that occur in ICA disease in the neck. The symptoms and signs that develop when strokes occur are those related to anterior and middle cerebral artery territory infarcts and are described under those arteries.

Occlusion or severe stenosis of the middle cerebral artery stem or its major upper and lower trunks

Patients with MCA occlusive disease, when compared to patients with ICA disease, are more often black or Asian, young, female, hypertensive and diabetic (Caplan et al., 1986a). Patients of Japanese, Chinese and Thai descent, as well as diabetics and women taking contraceptive pills, have a propensity for MCA pathology. TIAs are less common in patients with MCA disease compared with ICA disease and occur during a shorter timespan.

Patients with MCA disease often develop their deficits more gradually than comparable patients with ICA disease. Patients with MCA disease often note their abnormalities on awakening in the morning or from a nap, and they have a high incidence of subsequent fluctuation or progression during the next 1 to 7 days. This gradual onset and progressive course support a low-flow mechanism of the ischemia (Caplan et al., 1985). In contrast, patients with ICA disease more commonly have sudden-onset deficits while awake and thereafter remain stable, a course better explained by embolism from their ICA lesion than by low flow.

Basal ganglia and internal capsule infarction is usually due to occlusion of the main-stem MCA before its lenticulostriate branches. There is excellent potential for collateral circulation over the convexities, but poor collateral circulation in the deep basal grey nuclei and the internal capsule. For this reason, some patients with MCA occlusion have selective ischemia of the deep lenticulostriate territory ('striatocapsular infarcts'; Adams et al., 1983; Weiller et al., 1990).

Patients with striatocapsular ischemia are invariably hemiparetic, but the distribution of weakness in face, arm and leg is variable. Sensory loss is usually minor because the posterior portion of the internal capsule is spared. When the lesion is in the left hemisphere, after a short period of temporary mutism, speech is sparse and dysarthric, but repetition of spoken language is preserved. Comprehension of spoken and written language depends on both the size and the anteroposterior extent of the lesion. When the right hemisphere is involved, there often is neglect of contralateral visual and tactile stimuli, usually more transient than with parietal cortical infarction.

Superior division of the MCA ischemia

The superior trunk of the MCA supplies the frontal and superior parietal lobes. Ischemia is most often due to embolism to the superior division but *in situ* narrowing does occur. The findings include hemiplegia, more severe in the face and hand and upper extremity, with relative sparing of the lower extremity; hemisensory loss, usually including decreased pinprick and position sense, sometimes sparing the leg; conjugate eye deviation, the eyes resting toward the side of the brain lesion; and neglect of the contralateral side of space, especially to visual stimuli. Visual neglect is usually more severe in patients with right-hemisphere lesions.

When the lesion is in the left, dominant hemisphere, there is invariably an accompanying aphasia. Verbal output is sparse, and patients do not do what they are asked with either hand, although they may follow whole-body commands. They may nod appropriately to yes/no questions asked verbally, but comprehension of written material is poor. With time, a pattern of Broca's aphasia evolves, with sparse effortful speech, poor pronunciation of syllables, and omission of filler words but preserved comprehension of spoken language.

In superior-division right hemisphere MCA infarcts, patients frequently seem unaware of their deficit (anosognosia) and may not admit that they are hemiplegic or

impaired in any way. Some patients are also impersistent, performing requested tasks quickly but they do not persevere, and terminate tasks prematurely.

Inferior divison of the MCA ischemia

Ischemia is almost entirely due to embolism to this arterial territory. In contrast to patients with lesions of the superior division, these patients usually have no elementary motor or sensory signs. They often have visual field defect, either hemianopia or upper-quadrantanopia, affecting the contralateral visual field.

When the left hemisphere is involved, patients have a Wernicke-type aphasia. Speech is fluent and syllables are well pronounced, but patients use wrong or non-existent words, and what is said makes little sense. Comprehension and repetition of spoken language are poor. There may be relative sparing of written comprehension, with the patient preferring that words be written. When the right hemisphere is affected, patients draw and copy poorly and may have difficulty finding their way about or reading maps (Caplan et al., 1986b).

Behavioural abnormalities often accompany temporal lobe infarctions. Patients with Wernicke's aphasia are often irascible, paranoid and may become aggressive. Patients with right temporal infarcts often have an agitated hyperactive state resembling delirium tremens. The key findings in patients with right inferior MCA division infarcts are a left visual-field defect, poor drawing and copying and agitation (Caplan et al., 1986b).

Ischemia in the territory of the anterior cerebral artery

Intrinsic occlusive disease of the ACA is unusual. Most ACA territory infarcts are caused by embolism from the heart or the ICA (Bogousslavsky & Regli, 1990; Gacs et al., 1983). Many patients with intrinsic disease of the ACA also have extensive ICA and MCA disease, often with multiple infarcts. Some ACA-territory infarcts are due to occlusive disease of the ICA, and others are caused by vasospasm-related ischemia in patients with SAH due to anterior communicating artery aneurysms.

The single most important clue to an ACA-territory infarct is the distribution of motor weakness. Paralysis is usually greatest in the foot but is also severe in the proximal thigh. Shoulder shrug is weak on the involved side, but the hand and face are usually normal if the deep ACA territory is spared. Some patients with anterior or large ACA territory infarcts have a hemiplegia. Cortical sensory loss is also present in the weak limbs but is usually slight. A grasp refex is often present in the hand contralateral to the infarct. When the infarct involves the left ACA territory and the supplementary motor cortex, a transcortical motor and sensory aphasia often results.

Occasionally, patients have the sudden development of bilateral ACA territory infarction explained by hypoplasia or absence of the A1 segment of the ACA on one side. In that circumstance, the territories of the ACA on both sides are supplied by one ACA. Occlusion of the ICA or ACA supplying both sides leads to bilateral frontal-lobe infarction. The resulting clinical picture is that of sudden apathy, abulia, and incontinence. When the paracentral lobule is involved, there is weakness on one or both sides, predominantly affecting the lower extremities.

Occlusion of the anterior choroidal artery

Many patients with AChA-territory infarcts are diabetic or hypertensive. Most often infarction in AChA territory is due to occlusion of the AChA. Carotid artery occlusion, vasospasm in patients with carotid artery aneurysms, and cardiac-origin embolism occasionally cause AChA territory infarction, often coupled with MCA territory infarcts. The syndrome of the anterior choroidal artery includes: (i) hemiparesis affecting face, arm, and leg; (ii) prominent hemisensory loss, which is often temporary; (iii) homonymous hemianopia; (iv) when the lateral geniculate body is infarcted, an unusual hemianopia, with sparing of a beak-shaped tongue of vision within the center of the hemianopic visual field; and (v) absence of important persistent neglect, aphasia, or other higher-cortical-function abnormalities (Helgason et al., 1986).

Hemiparesis is the most consistent finding. Dysarthria and hemisensory abnormalities are less often present and usually do not persist. Hemianopia is the least common sign. Some patients with bilateral AChA territory capsular infarcts have severe dysarthria and may even be mute.

Ischemia within the posterior (vertebrobasilar) circulation

The most common occlusive lesion within the posterior circulation is occlusion or severe stenosis of the proximal portion of the vertebral artery in the neck (Caplan, 1996; Wityk et al., 1998). Atherosclerosis of the intracranial vertebral arteries (ICVAs) and of the basilar artery are also very common. Dissection of the extracranial vertebral artery (ECVA) and ICVA are also frequent causes of ischemia within the posterior circulation. Atherostenotic lesions of the innominate and subclavian arteries do cause TIAs but seldom cause strokes. Syndromes relating to disease of

these arteries will be discussed according to localization within the territories supplied by the posterior circulation arteries.

Occlusion or severe stenosis of the subclavian and innominate arteries

The extracranial vertebral arteries (ECVAs) arise from the proximal subclavian arteries, so disease of the subclavian or innominate arteries before the VA origin can diminish VA flow. In the subclavian-steal syndrome, obstruction to the proximal subclavian artery produces a low-pressure system within the ipsilateral VA and in blood vessels of the ipsilateral upper extremity. Blood from a higher-pressure system, the contralateral VA and basilar artery, is diverted and flow retrograde down the ipsilateral VA into the arm.

Most often, subclavian artery disease is detected when patients with coronary or peripheral vascular occlusive disease are referred to ultrasound laboratories for non-invasive testing. Most patients with subclavian artery disease are asymptomatic. Neurological symptoms are uncommon unless there is accompanying carotid artery disease. The most frequent symptoms of subclavian artery disease relate to the ipsilateral arm and hand. Coolness, weakness, and pain on use of the arm are common. Dizziness is by far the commonest neurological symptom of the subclavian-steal syndrome and usually has a spinning or vertiginous character. Diplopia, decreased vision, oscillopsia, and staggering all occur, but less frequently, often accompanying the dizziness. Attacks are brief and occasionally are brought on by exercising the ischemic arm. In most patients exercise of the ischemic limb does not provoke neurological symptoms or signs.

When the lesion affects the innominate artery, signs and symptoms of decreased carotid artery flow also can occur. Innominate artery disease is much less common than subclavian artery disease (Brewster et al., 1985; Caplan, 1996). Ipsilateral monocular visual loss, ipsilateral hemisphere ischemia in ACA and/or MCA territory, ipsilateral arm ischemia, and ischemic symptoms referable to the distal portion of the posterior circulation and/or the cerebellum indicate innominate artery disease.

Atherosclerotic occlusion or severe stenosis of the extracranial vertebral artery

The most frequently reported symptom during TIAs is dizziness. Attacks are indistinguishable from those described by patients with subclavian steal, except that VA TIAs are not precipitated by effort or by arm exertion. Although dizziness is the commonest symptom, it is seldom the only neurological symptom. Usually, in at least some attacks, dizziness is accompanied by other signs of hindbrain ischemia. Diplopia, oscillopsia, weakness of both legs, hemiparesis, or numbness are often reported.

Dissection of the ECVA

Dissections usually involve the distal portion of the ECVA as it winds around the upper cervical vertebrae. Sometimes dissections involve the proximal ECVA between the origin and entry into the vertebral column – usually at C5 or C6. Pain in the neck and/or occiput and TIAs or strokes involving the proximal intracranial posterior circulation territory are the commonest findings. Occasionally cervical root pain and signs, and spinal cord ischemia can develop.

Localization of brain lesions within the posterior circulation

Localization within the posterior circulation is simplified by dividing the vertebrobasilar territory into proximal, middle, and distal territories (Caplan, 1996). The proximal intracranial posterior circulation territory includes regions supplied by the ICVAs: the medulla oblongata and the posterior inferior cerebellar artery (PICA)-supplied region of the cerebellum. The ICVAs join together to form the basilar artery at the medullopontine junction. The middle intracranial posterior circulation territory includes the portion of the brain supplied by the basilar artery and its penetrating artery branches up to its superior cerebellar artery (SCA) branches: the pons and the anterior inferior cerebellar artery (AICA), supplied portions of the cerebellum. The distal intracranial posterior circulation territory includes all of the territory supplied by the rostral basilar artery and the SCA, posterior cerebral artery (PCA) and their penetrating artery branches, midbrain, thalamus, SCA, supplied cerebellum, and PCA territories. This distribution is shown diagrammatically in Fig 80.1.

Lesions within the medulla are most often unilateral and predominantly lateral tegmental. When an infarct is found in the medulla on one side, the ipsilateral ICVA or its branches must have been obstructed at one time. Infarcts in the pons tend to be bilateral and medial-tegmentobasal when the basilar artery is occluded. When a penetrating branch is occluded, the infarcts are unilateral and in the territory of a branch. Infarction in the midbrain, thalamus and posterior portions of the cerebral hemispheres supplied by the PCAs is due to disease within the distal basilar artery or its branches.

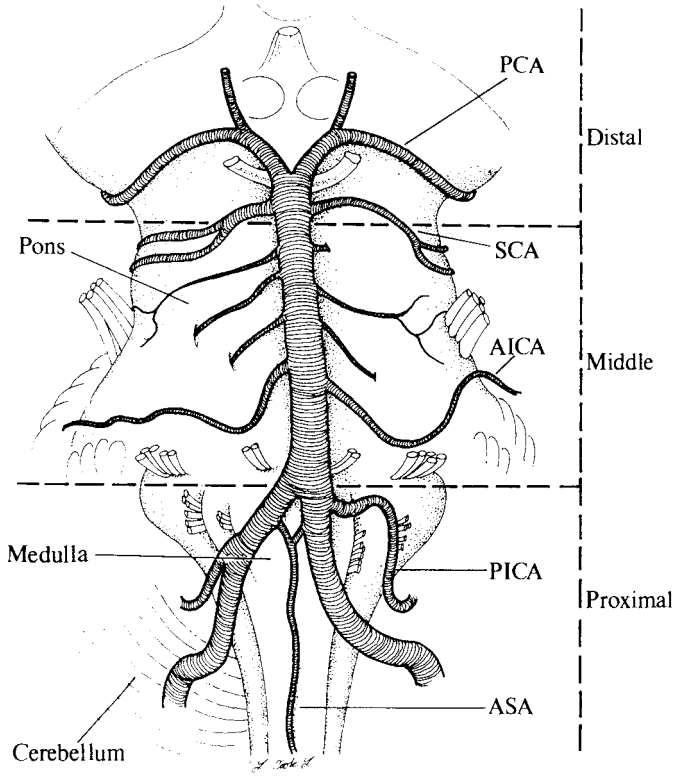

Fig. 80.1. Sketch of the base of the brain showing the intracranial vertebral and basilar arteries and their branches. The section is divided into proximal intracranial territory, middle intracranial territory, and distal intracranial territory. ASA = anterior spinal artery; PICA = posterior inferior cerebellar artery; AICA = anterior inferior cerebellar artery; SCA = superior cerebellar artery; PCA = posterior cerebral artery. (Drawn by Lausel Cook-Lowe from Caplan, 1996, with permission.)

Proximal intracranial territory

Lateral medullary infarction

The symptoms and signs found in patients with lateral medullary ischemia depend on the dorsal–ventral, medial–lateral, and rostro-caudal location of the infarcts.

Vestibulo-cerebellar symptoms and signs are nearly always present in patients with lateral medullary infarcts. Most patients describe feeling dizzy or off-balance. Others report vertigo: turning, rotating, whirling or moving in relation to their environment. Some patients feel as if they are being pulled or are falling towards one side (most often ipsilateral to the lesion); other patients describe a swaying, rolling feeling as if they are moving from side to side. Feelings of tilting or leaning are also frequent.

Patients with vestibular system abnormalities often describe blurred vision or frank diplopia. Some patients report oscillopsia, rhythmic motion or oscillation of objects on which they attempt to focus. Less common is tilting or inversion of the visual environment.

Ataxia is also very common. Some patients cannot feed themselves using the ataxic arm. They overshoot targets and have difficulty pointing accurately to moving targets. Nystagmus is nearly always present in patients with lateral medullary infarcts especially in patients who report dizziness or vertigo. The nystagmus usually has both horizontal and rotational components. The rapid phase of the rotatory nystagmus usually moves the upper border of the iris towards the side of the lesion. Most often, larger amplitude, slower nystagmus is present on gaze to the side of the lesion, while smaller amplitude quick nystagmus is found on gaze directed to the contralateral side. Ocular torsion is also often present; the ipsilateral eye and ear may rest in a down position below the contralateral eye and ear (Morrow & Sharpe, 1988). At times, ocular torsion is accompanied by a head tilt and skew deviation with the ipsilateral eye positioned downward. This combination of findings is referred to as the ocular tilt reaction (Keane, 1992; Brandt & Dieterich, 1994). Deviation of the perception of the visual–vertical axis is more common than the full ocular tilt reaction. A rarer oculomotor abnormality is ocular lateropulsion, a forced conjugate deviation of the eyes to one side.

Patients with lateral medullary infarcts initially often have difficulty sitting upright without support. They topple, lean or veer to the ipsilateral side when they sit or stand. In many patients standing or walking is impossible during the acute period and helpers may need to support patients in the erect position. When they become able to walk, patients often feel as if they are being pulled to the side of the lesion. They veer, list or weave to the side especially on turns. Hypotonia of the ipsilateral arm can be shown by having the patient quickly lower or raise the outstretched hands together, braking the ascent and descent suddenly. The arm on the ipsilateral side often overshoots and is not as quickly braked. In some patients, the ipsilateral arm also makes a slower ascent or descent.

Sensory symptoms and signs are also very common. Pain or dysesthetic feelings in the face are sometimes the earliest and most prominent feature of the lateral medullary syndrome and are diagnostic of a lateral tegmental brainstem localization. The facial pain is usually described as sharp jolts or stabs of pain most often in the ipsilateral eye or face. Sometimes, pain persists and is limited to the forehead and frontal scalp region. At times, the abnormal sensation is described as hot, burning, or scalding. Although contralateral loss of pain and thermal sensation involving the contralateral body and limbs is usually found on examination, most patients with contralateral hypalge-

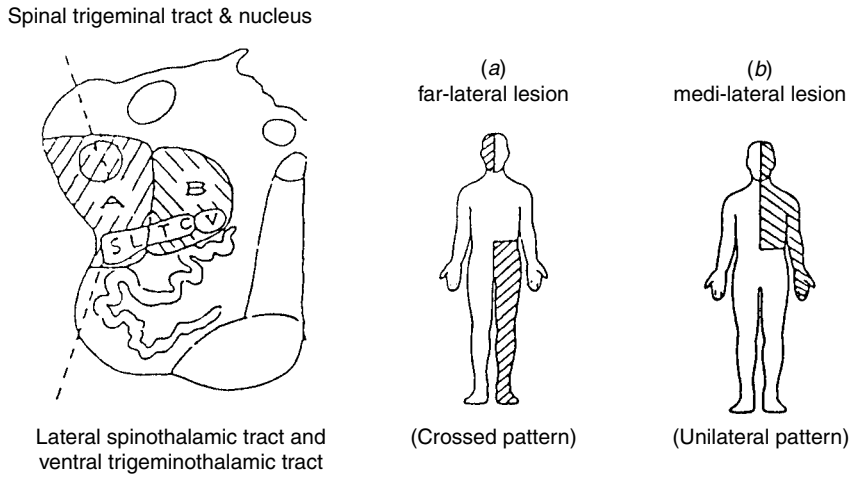

Fig. 80.2. Distribution and localization of pain fibres in the medulla. On the left is a cartoon of half of the medulla. Hashed lines point to the localization of the lateral spinothalamic tract and the spinal trigeminal tract and nucleus. The letters S = sacral, L = lumbar, T = thoracic, C = cervical, V = ventral trigeminothalamic tract show the posited localization of pain and temperature sensation fibres from these body parts. The cartoons on the right show the pattern of loss of pain and temperature sensation due to lesions at A and B in the medulla as shown on the left. (From Matsumoto et al., 1988, with permission.)

sia are unaware of their sensory loss until they are tested. Some notice loss of thermal sensation when they touch hot or cold objects. They then realize that they cannot tell the temperature of objects with their contralateral upper and/or lower limbs. Examination usually shows decreased pain and temperature sensation in the ipsilateral face. The corneal reflex is usually reduced in the ipsilateral eye, and the corneal stimulus also fails to evoke a contralateral blink. Initially, the contralateral hypalgesia can extend to the jaw, but a sensory level may be present on the thorax or abdomen. Pain and temperature sensibility may be normal in the arm. Sensory levels may appear during recovery.

The most common pattern of sensory abnormality is loss of pain and temperature sensation in the ipsilateral face and the contralateral trunk and limbs. The next most frequent combination is hypalgesia in the ipsilateral face and contralateral face, trunk and limbs. Less often, the hypalgesia can be solely contralateral involving the face, arm and leg or sometimes only the face and arm (Matsumoto et al., 1988). The least common pattern of sensory loss is hypalgesia only involving the contralateral trunk, arm and leg or parts thereof. Figure 80.2 from Matsumoto et al., 1988 shows diagrammatically the anatomical basis for the patterns of involvement of the somatosensory tracts in the lateral medulla.

The ipsilateral eye often shows features of Horner's syndrome. Weakness of bulbar muscles innervated by the lower cranial nerves is a very prominent feature in patients whose lateral medullary infarcts extend medially. Involvement of the nucleus ambiguus causes paralysis of the ipsilateral palate, pharynx and larynx resulting in hoarseness and dysphagia. The paralysis of the muscles of the oropharynx results in food being trapped in the piriform recess of the pharynx. Food and secretions have relatively free access into the air passages. Patients try to extricate the food with a cough or throat-clearing manoeuvre which makes a characteristic crowing-like sound. Examination shows paralysis of the ipsilateral vocal cord and a lack of elevation of the ipsilateral palate on phonation. The uvula often deviates to the contralateral side. Dysarthria and dysphonia are common. In some patients dysphagia and aspiration are prominent. Aspiration and pneumonia are very important complications of abnormal pharyngeal function. Usually the abnormality is unilateral. Hiccoughs are also a relatively common and annoying complaint.

Respiratory dysfunction is an important feature of lateral medullary ischemia. Control of inspiration and expiration and their automaticity lies within the ventrolateral medullary tegmentum and the medullary reticular zone. The most common abnormality described in patients with lateral tegmental caudal brainstem lesions is failure of automatic respirations, a phenomenon especially apparent during sleep. This failure to initiate respiration has been referred to as Ondine's curse. Other autonomic functions are also occasionally affected. Abnormalities of sweating, thermal regulation, and vasomotor control are occasionally present. Cardiovascular abnormalities include tachycardia, orthostatic hypotension without cardiac rate acceleration, and

intermittent bradycardia (Caplan, 1996). Gastrointestinal autonomic dysfunction includes decreased esophageal motility, gastroesophageal reflux, and gastric retention. Some patients have labile blood pressures, tachycardia, unusual sweating and arrythmias.

Medial medullary infarction

The most consistent finding in patients with medial medullary ischemia is a contralateral hemiparesis (Tyler et al., 1994; Caplan, 1996). Usually, the hemiparesis is complete and flaccid at onset. Later, increased tone and spasticity develop. Sensory symptoms are related to ischemia of the medial lemniscus. In about one-half of patients, the face is also involved. Facial weakness when it occurs is usually slight and transient and rarely persists. Some patients report paresthesias or less often dysesthesias in the contralateral lower limb and trunk. Less often, sensory symptoms occur in the arm and hand. In many patients with sensory symptoms there are no objective signs of touch, vibration, or position sense loss. Proprioceptive dysfunction with slight loss of position and vibration sense in the contralateral foot are found in some patients. Ipsilateral tongue paralysis is the least common but most topographically localizing sign of medial medullary infarction. Tongue paresis causes slurring of speech especially of lingual consonants.

Hemimedullary infarction

Occasional patients have infarction that involves both the lateral and medial medullary territories on one side. Symptoms are identical to those found in patients with lateral medullary ischemia with the addition of a hemiparesis contralateral to the lesion. The hemiparesis may develop concurrently with lateral medullary symptoms and signs or can occur later.

Cerebellar infarction in PICA distribution

PICA cerebellar infarcts can be divided into: (i) infarction in the territory of the medial branch of PICA (mPICA) affecting mostly the inferior cerebellar vermis, (ii) infarction limited to the lateral branch of PICA (lPICA) affecting mostly the lateral surface of the posterior inferior cerebellar hemisphere, and (iii) full PICA territory infarcts involving both the mPICA and lPICA territories. Full PICA territory infarcts are often accompanied by edema formation and mass effect, so-called pseudotumoral cerebellar infarcts. About one-fifth of PICA territory cerebellar infarcts are accompanied by infarction in the dorsal or dorsolateral medulla (Caplan, 1996). The combination of lateral medullary and PICA cerebellar infarction occurs when the ICVA is occluded and blocks the orifice of both PICA and the lateral medullary penetrators. Most often mPICA territory infarcts are accompanied by dorsal medullary infarcts since the mPICA branch has some supply to the dorsal medulla (Amarenco & Hauw, 1989; Amarenco et al., 1989; Caplan, 1996).

Infarcts limited to the medial vermis in mPICA territory usually cause a vertiginous labyrinthian syndrome that closely mimics a peripheral vestibulopathy (Amarenco et al., 1990). Severe vertigo with prominent nystagmus are the major findings. Some patients also have truncal lateropulsion characterized by feelings of magnetic pulling of the trunk to the ipsilateral side. Ocular lateropulsion may also be present. Lateral cerebellar hemisphere PICA territory infarcts are usually characterized by minor degrees of dizziness and gait incoordination with veering to the side of the lesion. Minor limb hypotonia and incoordination are found. A common syndrome is acute unsteadiness with ataxia but without vertigo or dysarthria. Body sway towards the side of the lesion, ipsilateral limb ataxia, and abnormal rapid alternating movements are also common.

When the full PICA cerebellar territory is involved, headache is usually present in the occiput or high neck on the ipsilateral side. The head may also be tilted with the occiput tending ipsilaterally. Vomiting, gait ataxia, truncal lateropulsion, and limb incoordination are other common findings. The truncal dysfunction is similar to that found in the lateral medullary syndrome; the body is often tilted or pulled ipsilaterally upon sitting or standing. The limb incoordination consists mostly of hypotonia rather than a rhythmic intention tremor.

The syndrome of pseudotumoural cerebellar infarction is most often found after large full PICA territory infarcts. After the first day or so, patients develop increased headache, vomiting, and decreased consciousness. At first, they become drowsy and later stuporous. Bilateral Babinski signs are an early sign of cerebellar mass effect. Most characteristic of large cerebellar space-taking infarcts are the oculomotor abnormalities which develop. Most common are a conjugate gaze paresis to the side of the lesion or a paresis of abduction limited to the ipsilateral eye. Bilateral VIth nerve paresis may occur. Later bilateral horizontal gaze palsies may develop often accompanied by ocular bobbing. These signs are due to compression of the pontine tegmentum by the swollen cerebellar infarct. Stupor is followed by deep coma when the oculomotor abnormalities become bilateral.

Vascular lesions and stroke mechanisms in patients with proximal intracranial territory infarction

Lateral medullary infarcts are most often explained by intrinsic disease, atherosclerotic stenosis often with super-

imposed thrombosis or arterial dissection of the distal ECVA or the ICVA (Caplan, 1996; Mueller-Kuypers et al., 1997; Graf et al., 1997). Less often, cardiogenic or artery-to-artery emboli usually from the ECVA explain lateral medullary infarction.

Most often, ischemia in the medial medullary base has accompanied lateral medullary ischemia (hemimedullary infarction) and is caused by occlusions of the ipsilateral ICVA (Caplan, 1996). Unilateral medial medullary infarction usually results from atheromatous branch disease or the vascular pathology within penetrating ASA branches that underlies lacunar infarction, in which case the infarct is usually limited to one medullary pyramid. The most common cause of PICA territory cerebellar infarction is embolism to the ICVA from the heart or the proximal ECVA (Amarenco et al., 1990, 1994; Graf et al., 1997; Caplan, 1996). Less often, occlusion of the ICVA is due to *in situ* atherosclerosis with superimposed thrombosis. PICA branch territory infarcts are almost always embolic, the source being the heart, aorta, or ECVA (Caplan, 1996).

Middle intracranial territory

Pontine ischemia due to basilar artery occlusive disease

Most patients with symptomatic basilar artery occlusive disease and pontine ischemia have some transient or persistent degree of paresis and corticospinal tract abnormalities (LaBauge et al., 1981; Kubik & Adams, 1944; Caplan, 1996). The initial motor weakness is often lateralized and has been referred to as the 'herald hemiparesis' of basilar artery occlusion. Hemiparetic patients with basilar artery occlusion almost always show some motor or reflex abnormalities on the non-hemiparetic side: slight weakness, hyperreflexia, an extensor plantar reflex or abnormal spontaneous movements such as shivering, twitching, shaking or jerking on the relatively spared side. Asymmetry but bilaterality is the rule. Limb adventitious movements are occasionally seen and can be prominent. Movements are variable and can be small fasciculation-like movements or large shivering, shuddering, jerking or a tremulous intermittent shaking motion. Movements are sometimes intermittent. Movement of the limbs or painful stimuli may precipitate a flurry of abnormal movements. At times, there are large repetitive jerking and twitching movements especially in limbs contralateral to a hemiparesis (Ropper, 1988).

Ataxia or incoordination of limb movements is another common motor finding. Ataxia is invariably combined with some degree of paresis. Incoordination is usually more severe in the legs. Toe-to-object and heel-to-shin testing usually shows a rhythmic 'cerebellar' type component to the dysfunction. The ataxia is invariably bilateral but may be asymetric and more severe on the weaker side. Intention tremor is not common.

Weakness of bulbar muscles is very common and is an important cause of morbidity and mortality. The face, pharynx, larynx and tongue are most often involved. The pattern may be that of crossed motor loss, e.g. one side of the face and the contralateral body but, more often the bulbar muscle weakness is bilateral. Bulbar symptoms include facial weakness, dysphonia, dysarthria, dysphagia and limited jaw movements. Some patients become totally unable to speak, open their mouth, protrude their tongue, swallow or move their face at will or on command. Secretions pool in the pharynx and aspiration is an important and serious complication. Patients with ventral pontine infarcts frequently have exaggerated crying and laughing spells and are hypersensitive to emotional stimulus. Despite the inability to voluntarily move the muscles, the jaw, face and pharyngeal reflexes may be exaggerated and clonic jaw movements or clamping down on a tongue blade may occur as a response to attempts to pry the mouth open and to insert a tongue blade. When all voluntary movement other than the eyes is lost but consciousness is retained, the deficit is referred to as the 'locked-in syndrome'.

Some patients with pontine ischemia develop palatal myoclonus, a rhythmic involuntary jerking movement of the soft palate and pharyngopalatine arch which can involve the diaphragm and larynx (Caplan, 1996). This movement disorder usually begins sometimes after the brainstem infarct. The movements of the palate vary in rate between 40 and 200 beats per minute. The movements are readily seen by watching the palate and pharynx when the mouth is open. The movements involve the eustachian tube and make a click that the patient and doctor can hear.

Oculomotor symptoms and signs are common. Few patients with pontine infarction due to basilar artery occlusive disease have normal eye movements. Abnormalities include: complete horizontal gaze palsy, unilateral horizontal conjugate gaze palsy, unilateral or bilateral internuclear opthalmoplegia (INO) and a one-and-a-half syndrome (conjugate gaze palsy + an INO). Skew deviation of the eyes and ocular bobbing may also be present. Horizontal, gaze paretic nystagmus is common and, when asymmetric, usually is more prominent when gaze is directed to the side of a unilateral pontine tegmental lesion. Dissociated nystagmus, that is nystagmus that is more severe in one eye and not rhythmically concordant in the two eyes, and vertical nystagmus are found in patients with an INO. Ptosis of the upper eyelids is also very frequent. The

pupils may remain normal or become small. In some patients the pupils are bilaterally very small ('pinpoint'). Use of a magnifying glass can show that, despite their very small size, the pupillary response to light is preserved, although the amplitude of the response is slight.

Somatosensory abnormalities are not prominent in patients with basilar artery occlusions. Paresthesias on one side of the body and limbs reflects involvement of the contralateral medial lemniscus in the paramedian dorsal portion of the basis pontis. Bilateral paramedian lesions that include the medial lemnisci on both sides can cause bilateral paresthesias. Usually proprioceptive loss is minimal or absent despite the paresthesias. Some patients with basilar artery occlusive disease have unusual burning pain in the face usually located in the centre of the face near the midline. Tinnitus and hearing loss relate to involvement of the central auditory tracts and nuclei (auditory nuclei, lateral lemnisci, trapezoid bodies, inferior colliculi) or to ischemia of the VIIIth nerves or the cochlea.

Alteration in the level of consciousness is an important sign in patients with basilar artery occlusion.

Anterior inferior cerebellar artery territory infarction

When infarction is limited to unilateral AICA territory, the clinical findings are identical to those found in patients with lateral medullary infarcts except that VIIth and VIIIth nerve findings are present rather than symptoms and signs related to Xth nerve (nucleus ambiguus) dysfunction (Amarenco & Hauw, 1990). The lesion may involve the facial, vestibular and cochlear nuclei, the VIIth nerve fibres within the lateral tegnentum and base, the VIIIth nerve peripheral fibres, or the cochlea and vestibule. Weakness of the contralateral limbs and an extensor plantar sign are found when the infarct extends to the pontine base. The internal auditory artery is most often a branch of AICA. In some patients, especially diabetics, ischemia of the inner ear structures supplied by the internal auditory artery can herald a full AICA territory infarct (Oas & Baloh, 1992). Tinnitus, hearing loss and vertigo are the most common symptoms related to inner ear ischemia.

Vascular lesions and stroke mechanisms in patients with middle intracranial territory ischemia

When pontine ischemia is bilateral, the causative vascular lesion is almost always an intrinsic lesion within the basilar artery: most often atherostenosis with or without superimposed thrombosis. Dissection of the basilar artery can produce a similar syndrome. Sometimes thrombosis begins in one distal ICVA and extends into the basilar artery or the occlusion involves a basilarized ICVA, the contralateral ICVA being hypoplastic, or ends in PICA (Caplan, 1996). When infarction is limited to the territory of one AICA, the cause is almost always atheromatous branch disease (Caplan, 1996). When there is AICA + infarction, then basilar artery or bilateral ICVA occlusions are usually present.

Distal intracranial territory

Rostral brainstem ischemia as part of the 'top of the basilar' syndrome

Occlusion of the rostral portion of the basilar artery can cause ischemia of the midbrain and thalami as well as the temporal and occipital lobe cerebral hemispheral territories supplied by the PCAs. In many patients infarction is limited to either brainstem or hemispheral structures. The major abnormalities associated with rostral brainstem ischemia involve alertness, behaviour, memory and oculomotor and pupillary functions.

The most common abnormalities of eye position and movement involve vertical gaze and convergence (Caplan, 1980, 1996; Mehler, 1988). There is often a disparity between paralysis of voluntary vertical gaze and vertical eye movements induced by vertical oculo-cephalic manoeuvres, simultaneous caloric stimulation of both ear canals or Bell's phenomenon. Some patients have a loss of all voluntary and reflex vertical eye movements. Reflex movements are sometimes preserved despite loss of voluntary vertical eye movements. Either up gaze or down gaze can be selectively involved, but in most patients both directions of vertical gaze are involved. Upgaze and vertical gaze palsies are more common than down gaze palsies (Caplan, 1996). Monocular elevation palsies, ipsilateral or contralateral to the lesion and vertical one-and-a-half syndromes (bilateral upgaze palsy and monocular downgaze palsy or bilateral downgaze palsy and monocular upgaze palsy) also occur. Asymmetric or unilateral lesions in the midbrain tegmentum and posterior thalami can cause contraversive ocular tilt reactions in which the contralateral eye and ear are down. The abnormalities include skew deviation, ocular torsion, and abnormal estimation of the visual vertical (Brandt & Dieterich, 1994).

Convergence abnormalities are also very common. Usually one or both eyes are hyperconverged. One or both eyes may rest inward or down and in at rest. On attempted upgaze, the eyes may show adductor contractions causing convergence movements.

Retraction of the upper eyelid to widen the palpebral fissure has been called Collier's sign when the abnormality is due to a rostral mesencephalic lesion near the level of the posterior commissure. In some patients both lids are retracted but one eye may have normal lid position or

ptosis. Lesions in the rostral brainstem often affect the pupillary light reflex so that the pupils react slowly and incompletely, or not at all to light. The pupils are often small at rest in patients with diencephalic lesions and may be fixed and dilated if the lesions involve the third nerve Edinger–Westphal nuclei. A combination of diencephalic and midbrain lesions cause midposition fixed pupils. In midbrain lesions, the pupil may become eccentric ('corectopia') (Caplan, 1980) or oval.

Abnormalities of alertness and behaviour are common in patients with rostral brainstem infarcts. Hypersomnolence and abulia are common. Abnormal reports and hallucinations probably relate to the altered sleep–wake dreaming cycle present in patients with rostral basilar artery territory infarction (Caplan, 1980). Reports often consist of replies to queries that have no relation to reality. The patient may mislocate themselves in place, giving the names of far distant geographical locations, and in the personal time dimension, saying that they are presently performing activities that they had done only in their childhood, adolescence, or much earlier in their adult life. Peduncular hallucinations are predominantly visual but there may be some minor tactile and auditory components. Visual hallucinations are often quite vivid and contain colours, objects, and scenes. The hallucinations occur predominantly after sunset (Caplan, 1980, 1996).

Some patients with rostral brainstem infarcts that include the thalamus have prominent and sometimes persistent memory deficits. The amnesia involves both anterograde and retrograde memory and usually includes both verbal and non-verbal memory.

Sensory and motor abnormalities are usually absent in patients with top of the basilar infarction unless the proximal PCAs are also occluded. Movement disorders especially hemiballism have been described in some patients with small infarcts and hemorrhages involving the subthalamic nuclei, but hemiballism is rare in patients with well documented top-of-the-basilar infarcts.

Superior cerebellar artery territory infarction

Most often SCA territory infarcts are accompanied by other infarcts in regions supplied by other arteries that arise at the rostral end of the basilar artery. The classic SCA syndrome is said to consist of: ipsilateral limb ataxia; ipsilateral Horner's syndrome; contralateral loss of pain and temperature sensibility of the face, arm, leg, and trunk; and contralateral IVth nerve palsy (Caplan, 1996). Abnormal ipsilateral spontaneous involuntary movements also occur. The classic syndrome is present when the pontine and midbrain tegmentum and superior cerebellar surface are infarcted. The full syndrome is quite rare.

Slight dizziness, vomiting, ipsilateral limb dysmetria, gait ataxia, and dysarthria are common. Vertigo is usually not prominent in patients with isolated SCA territory infarcts. Limb incoordination, limb ataxia, intention tremor and dysarthria are more common in SCA territory cerebellar infarcts than in either AICA or PICA territory cerebellar infarcts (Caplan, 1996). Patients with infarcts in the territory of the lateral branch of the SCA have prominent limc ataxia, varying from slight clumsiness to severe incoordination and dysmetria, and dysarthria. Cerebellar gait ataxia and veering and pulling of the trunk to the ipsilateral side, so-called axial lateropulsion also occur.

Dysarthria and abnormal speech rhythm are common in patients with SCA territory infarcts, no matter whether the lesion involves the full territory or the medial or lateral branches.

Posterior cerebral artery territory infarction

The most common finding in patients with PCA territory infarction is a hemianopia (Pessin et al., 1987b; Caplan, 1996, 2000; Yammamoto et al., 1999). If just the lower bank of the calcarine fissure is involved, the lingual gyrus, a superior-quadrant field defect results. An inferior quadrantanopia results if the lesion affects the cuneus on the upper bank of the calcarine fissure. When infarcts are restricted to the striate cortex and do not extend into adjacent parietal cortex, patients are aware of the visual defect. Usually described as a void, blackness, or a limitation of vision to one side, patients usually recognize that they must focus extra attention to the hemianopic field. When given written material or pictures, patients with hemianopia due to occipital lobe infarction are able to see and interpret stimuli normally, although it may take them a bit longer to explore the hemianopic visual field. In patients with occipital lobe infarcts, physicians can reliably map out the visual fields by confrontation. At times, the central or medial part of the field is spared, so-called macular sparing. Optokinetic nystagmus is preserved. Some patients, although they accurately report motion or the presence of objects in their hemianopic field, cannot identify the nature, location, or colour of those objects. When the full PCA territory is involved, visual neglect can accompany the hemianopia.

In patients with PCA territory infarcts, lateral thalamic ischemia is the major reason for somatosensory symptoms and signs (Caplan et al., 1988). Patients describe paresthesias or numbness in the face, limbs and trunk. On examination, touch, pinprick, and position sense are reduced. The combination of hemisensory loss with hemianopia without paralysis is virtually diagnostic of infarction in the PCA territory. The occlusive lesion is within the PCA before the thalamogeniculate branches to the lateral thalamus.

Rarely, occlusion of the proximal portion of the PCA causes a hemiplegia (Hommel et al., 1990; Caplan, 1996).

When the left PCA territory is infarcted (Caplan, 1996, 2000), alexia without agraphia, anomic or transcortical sensory aphasia (Kertesz et al., 1982) and Gerstmann's syndrome may be found. Defective acquisition of new memories is common when both medial temporal lobes are damaged but also occurs in lesions limited to the left temporal lobe (Caplan, 1996). The memory deficit in patients with unilateral lesions is usually not permanent but may last up to 6 months. Patients cannot recall what has happened recently, and when given new information, they cannot recall it moments later. They often repeat statements and questions spoken only minutes before. Some patients with left-PCA territory infarction have difficulty in understanding the nature and use of objects presented visually (associative visual agnosia) (Caplan & Hedley-White, 1974). They can trace with their fingers and copy objects, demonstrating that visual perception is preserved and can name objects presented in their hand and explored by touch or when verbally described.

Infarcts of the right PCA territory are often accompanied by prosopagnosia, difficulty in recognizing familiar faces (Damasio et al., 1982). Disorientation to place and an inability to recall routes or to read or revisualize the location of places on maps are also common (Fisher, 1982). Patients with right occipito-temporal infarcts also may have difficulty revisualizing what a given object or person look like. Dreams may also be devoid of visual imagery. Visual neglect is much more common after lesions of the right than of the left PCA territory.

When the PCA territory is infarcted bilaterally, the commonest findings are cortical blindness, amnesia, and agitated delirium (Caplan, 1980, 1996). Bilateral PCA territory infarction is most often due to an embolus that blocks the distal basilar bifurcation. Cortically blind patients cannot see or identify objects in either visual field but have preserved pupillary light reflexes (Symonds & McKenzie, 1957). Amnesia due to bilateral medial temporal-lobe infarction may be permanent and closely resembles Korsakoff's syndrome. Infarction of the hippocampus, fusiform, and lingual gyri, usually bilaterally, leads to an agitated hyperactive state that can be confused with delirium tremens (Caplan, 1980, 1996).When infarction is limited to the lower banks of the calcarine fissures bilaterally, the major findings are prosopagnosia and defective colour vision.

Vascular lesions and stroke mechanisms in patients with distal intracranial territory infarcts

Most distal posterior circulation intracranial territory infarcts are caused by embolism from the heart, aorta, and ECVAs and ICVAs (Caplan, 1980, 1996). Rostral brainstem infarcts that are unilateral and are within the territory of single penetrating branches such as the polar artery, thalamic–subthalamic artery, posterior choroidal artery, and midbrain penetrating arteries are caused by disease of those branches, lipohyalinosis or atheromatous branch disease. Most infarcts that are limited to the lateral thalamus in the territory of the thalamogeniculate arterial pedicle are caused by atheromatous branch disease and not disease of the parent PCA (Caplan et al., 1988). Superior cerebellar artery territory infarcts are predominantly embolic especially when infarction is limited to mSCA or lSCA branches. Occasional patients with bilateral SCA territory have a stenosing lesion involving the basilar artery affecting the region of the artery from which the SCAs originate.

Unilateral PCA territory infarcts are also predominantly embolic. Emboli most often have been documented to arise from the heart and the ECVAs and ICVAs but the aorta may also be a frequent source (Pessin et al., 1987b; Caplan, 1993, 1996; Yammamoto et al., 1999). Occasional patients have an intrinsic atherostenotic lesion within the PCA. These patients often have TIAs characterized by visual, sensory, or visual and sensory symptoms before their strokes (Pessin et al., 1987a; Caplan, 1996).

Penetrating artery disease syndromes

Hypertension and aging cause degenerative changes within arteries that arise perpendicularly from the major basal cerebral arteries. Disruption and narrowing of the lumens of these arteries cause small deep infarcts in the basal ganglia, cerebral white matter, thalami and brainstem. Atheromatous branch disease (Caplan, 1989) also causes small deep infarcts. The commonest syndromes of deep (lacunar) infarction are: (i) pure motor stroke: weakness of face, arm, and leg with increased reflexes and a Babinski sign on one side of the body without cognitive, behavioural, sensory, or visual abnormalities (infarct in internal capsule or pons); (ii) pure sensory stroke: numbness or paresthesias in face, arm, leg and often trunk on one side of the body without accompanying motor, visual or cognitive or behavioural abnormalities (small infarct in the ventrolateral thalamus or in sensory tracts within the brainstem); (iii) ataxic hemiparesis: weakness and ataxia of the limbs on one side of the body usually without visual, cognitive or behavioural abnormalities but sometimes with paresthesias (infarct in the pons or posterior portion of the internal capsule); (iv) dysarthria–clumsy hand syndrome: slurred speech usually with facial and tongue

weakness and clumsiness of the hand on the same side, small brainstem infarct).

Intracerebral hemorrhage syndromes

Hemorrhages of the lateral basal ganglia, putamen, and internal capsule

The commonest location of hypertensive ICH is the lateral basal–ganglionic–capsular region. These lesions are usually referred to as *putaminal hemorrhages* because they most often begin in the putamen. The usual findings include contralateral hemiparesis and hemisensory loss, and conjugate deviation of the eyes toward the side of the hematoma. The pupils are generally normal, and gait is hemiparetic. Patients with a left putaminal hemorrhage usually have a non-fluent aphasia with relative preservation of the ability to repeat spoken language. Right-sided lesions are associated with left visual neglect, motor impersistence, and constructional dyspraxia. If the hematoma enlarges and becomes sizable, patients develop increasing stupor; the ipsilateral pupil at first becomes smaller, and later larger than the opposite pupil; the ipsilateral plantar response becomes extensor; and a bilateral horizontal gaze palsy develops.

The findings described above are those found in patients with large hematomas that involve the medial and most anterior portions of the posterior putamen and the anterior two thirds of the posterior limb of the internal capsule (Kase & Caplan, 1994; Chung et al., 2000). This location is the commonest site for putaminal hemorrhage because it is supplied by the largest of the lateral lenticulostriate arteries. Some lesions affect the anterior limb of the internal capsule and anterior putamen and produce a milder, more transient hemiparesis without sensory abnormalities. When hematomas are located in the posterior third of the internal capsule and far posterior extreme of the putamen, sensory abnormalities predominate with little or no hemiparesis. An inferior quadrantanopia or hemianopia may be present. Lesions in the far posterior left putamen may cause fluent Wernicke-like aphasia because of undercutting of the temporal lobe or extension of the lesion into the temporal isthmus, giving the hematoma a hockey-stick-like configuration.

Caudate hemorrhage

Caudate hematomas frequently discharge quickly into the adjacent lateral ventricle or may spread laterally toward the internal capsule or inferiorly toward the hypothalamus (Kase & Caplan, 1994; Stein et al., 1984). Early ventricular dilation by blood probably accounts for the most common symptoms of caudate hemorrhage: headache, vomiting, decreased alertness, and stiff neck. Some patients also are confused, disoriented, and have poor memory. Larger parenchymatous hematomas cause a contralateral hemiparesis, conjugate deviation of the eyes to the side of the lesion, conjugate gaze palsy to the opposite side, and an ipsilateral small pupil or Horner's syndrome. Sensory findings are usually absent or minimal.

Thalamic hemorrhage

Neurologic signs in patients with thalamic hemorrhages differ greatly depending on the size, location within the thalamus of the hematoma, and dissection into and pressure effects on the third ventricle and adjacent brain structures (Kase & Caplan, 1994; Chung et al., 1996). The largest hemorrhages are located in the ventrolateral and posteriomedial thalamus in the territories of the thalamogeniculate and thalamic-subthalamic arteries. Other hemorrhages are located anteriorly in the territory of the tuberothalamic (polar) arteries and dorsally in the territory of the lateral posterior choroidal arteries (Chung et al., 1996). Most thalamic hematomas are posterior to the pyramidal-tract fibres in the internal capsule, so that contralateral sensory abnormalities are usually more prominent than contralateral hemiparesis. Some large thalamic hematomas dissect rostrally and involve the anterior portion of the posterior limb of the internal capsule causing a hemiplegia. Sometimes, the limbs contralateral to the hematomas are ataxic or have choreic movements. The contralateral hand may rest in a fisted or dystonic posture. The key neurological findings that separate thalamic from caudate and putaminal hemorrhages are the eye signs. Patients with caudate or putaminal hemorrhages have conjugate deviation of the eyes toward the side of the lesion and paresis of conjugate gaze to the opposite side. The characteristic oculomotor abnormalities in patients with thalamic hematomas are: (i) *paralysis of upward gaze,* often with one or both eyes resting downward; (ii) *hyperconvergence of one or both eyes,* a combination of these findings giving patients the appearance of peering downward and inward at the tops of their noses; (iii) *ocular skew* in which one eye rests below the other, with this divergence in vertical eye position remaining constant in gaze in all directions; (iv) *eyes gazing the wrong way,* resting toward the opposite side; (v) *disconjugate gaze,* with limited abduction of one or both eyes, so-called pseudo-sixth-nerve paresis. The pupils are usually small and react poorly to light because of interruption of the afferent limb of the pupillary reflex arc.

Patients with large left thalamic hemorrhages often have an unusual aphasia. After beginning a conversation almost normally, patients may lapse into a remarkable fluent aphasia, with many jargon or non-existent words and poor communication of ideas. In contrast to patients with Wernicke's aphasia, comprehension of spoken language is good. Patients with thalamic ICH may repeat and duplicate words or syllables at the ends of words in both spoken and written language. Paraphasic errors and poor naming are also common. Patients with right thalamic hematomas often have left visual neglect, anosognosia, and visuospatial abnormalities. Decreased levels of alertness and consciousness and hypersomnolence are very common at the onset of thalamic hemorrhage.

Lobar hemorrhages

ICH may develop beneath the region of the grey–white junction of the cerebral cortex. These subcortical hemorrhages usually spread in a linear direction along white-matter pathways (Kase & Caplan, 1994). Symptoms and signs depend on the lobes affected, as follows.

Frontal hematomas

Far anterior lesions usually cause abulia. Patients appear apathetic and have reduced spontaneity, prolonged latency in responding and short, terse replies. If the lesions extend deeply or toward the precentral gyrus, conjugate eye deviation toward the side of the hematoma and contralateral hemiparesis are found.

Paracentral hematomas

Lesions near the central sulcus produce contralateral motor and sensory signs, sometimes with aphasia if the lesion is in the left hemisphere.

Parietal hemorrhages

These hematomas cause contralateral hemisensory loss, with neglect of the contralateral visual field. The limbs contralateral to the hemorrhage are often incoordinated. Apahsia and disorders of reading, writing, and arithmetic functions are present when the lesions involve the left inferior parietal lobule. Patients with right inferior parietal hematomas have hemianopia or quadrantanopia and defective drawing and copying and may have difficulty with visual-spatial functions.

Occipital hematomas

These cause a severe contralateral hemianopia, often with slight contralateral hemisensory or motor signs and visual neglect.

Temporal-lobe lesions

These lesions often cause agitation and delirium. Wernicke-type aphasia accompanies left temporal lesions. Temporal-lobe hematomas are particularly likely to swell and may cause herniation without preceding hemiparesis. Brainstem compression may develop insidiously, with deepening stupur and then an ipsilaterally dilated pupil.

Pontine hemorrhage

Primary brainstem hemorrhages are located most often in the pons. Primary pontine hemorrhages usually begin in the centre of the pons at the tegmental–basal junction. These hematomas grow quickly usually destroying the centre of the tegmentum and the base of the pons. The blood may dissect rostrally into the midbrain but rarely extends caudally into the medulla. Hematomas frequently dissect into the fourth ventricle. These large pontine hemorrhages arise from the larger median pontine penetrating vessels that originate from the basilar artery (Kase & Caplan, 1994).

The signs accompanying large medial pontine hematomas are: quadriparesis, often with limb stiffness and rigidity; coma; absent horizontal eye movements; small but reactive pupils; and rapid or irregular respirations. Headache and vomiting occasionally occur. Some pontine hemorrhages develop gradually, and early findings may be asymmetrical. A hemiparesis is common early in the course. Deafness, dysarthria, facial numbness, asymmetsic facial or limb weakness, and dizziness occasionally precede the development of coma. Some patients have shivering, or spasmodic limb movements, usually culminating in decerebrate rigidity. Vertical reflex eye movements are preserved unless the lesion extends rostrally into the midbrain. In some patients, the eyes spontaneously and repeatedly bob downward.

Lateral basal hematomas can cause pure motor hemiparesis, ataxic hemiparesis, or the dysarthria–clumsy hand syndrome mimicking findings in lacunar infarction involving the pons. Lateral basal lesions can spread into the adjacent tegmentum, causing unilateral cranial nerve signs and contralateral hemiparesis. Lateral tegmental hematomas arise from penetrating vessels that course from lateral to medial after branching from the lateral circumferential pontine arteries. These lesions involve the rostral pons, and the findings are those of a predominantly unilateral tegmental lesion. Most distinctive and diagnostic of lateral tegmental pontine hematomas are the oculomotor abnormalities, which include ipsilateral conjugate gaze paresis, ipsilateral INO, or a combination of INO and gaze palsy (a 'one and one-half syndrome') in which the only preserved eye motion is abduction of the contralateral eye. Because

the sensory lemniscus is lateral tegmental, accompanying loss of pinprick, temperature, and position sense on the opposite side of the body is common. Limb and truncal ataxia are usually present and may be bilateral or predominantly ipsilateral. Unilateral facial numbness or weakness, ipsilateral miosis, and transient deafness may also be present.

Cerebellar hemorrhages

The most consistent symptom is inability to walk (Kase & Caplan, 1994). Some patients have difficulty maintaining a sitting or standing position, often leaning or tilting toward the side of the hematoma. Headache is common, usually affecting the occiput or neck or frontal region. Dysarthria, hiccups, and tinnitus occur but are less frequent. Loss of consciousness at onset is unusual, but when these patients reach the hospital, about one-third are obtunded. Neurological signs include an ipsilateral abducens or gaze palsy toward the side of the hematoma; small pupils, with the ipsilateral pupil slightly smaller; rebound overshoot of the rapidly elevated ipsilateral arm; and gait ataxia. Hemiparesis probably does not occur in cerebellar hemorrhage, but cerebellar lesions do produce an apparent asthenia or slowness of the affected limbs. Inferior extremity reflexes are usually symmetrically exaggerated, but plantar responses are flexor. Patients with large cerebellar hematomas often have brainstem compression. They develop increasing stupor, lateral gaze palsy toward the side of the hematoma, and bilateral extensor plantar responses.

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81

The treatment of acute ischemic stroke

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Historically, the treatment of stroke has been viewed with nihilism. With the approval of intravenous tissue plasminogen activator (i.v.-rTPA) (Nat. Inst. Neurol. Disorders, 1995), the past attitudes of helplessness in the face of stroke are changing. Despite the efficacy of thrombolytic therapy, less than 3% of all ischemic stroke patients are actually treated with i.v.-rTPA. The major reason for this lack of treatment appears to be the short time window. Both human and animal studies suggest that the time window for therapy will remain at approximately 3–6 hours even with the development of successful neuroprotection (Fig. 81.1). For this reason, time is a critically important factor in the treatment of acute stroke.

The approach to acute stroke can be separated into five overlapping concepts. The first and, thus far, most successful is restoring flow through the occluded vessel. The second is altering the ischemic cascade. Third is maximizing collateral flow. Fourth is the prevention of complications and the final concept is the use of a multidisciplinary team and designated Stroke Units to maximize patient care. Recovery and its augmentation is a sixth concept that is beyond the scope of this chapter.

Restoration of flow

The normal perfusion to brain grey matter is 60–70 ml for every 100 grams of brain tissue every minute. When perfusion decreases to less than 25 ml/100 mg/min, the neuron is no longer able to maintain aerobic respiration. If perfusion is not restored, the ischemic tissue will reach a point of no return where cell death is inevitable. This process is very time dependent, with irreversibility occurring after 5–6 hours. However, if flow is restored, then the brain tissue can potentially be spared and neurological function preserved (Figs. 81.2 and 81.3) (Jones et al., 1981). This concept has led to the use of pharmacological and mechanical attempts to disrupt the occluding thrombus. To date, this remains the most efficacious treatment of acute stroke and represents the only Food and Drug Administration approved therapy.

Intravenous thrombolysis

There have been multiple recent trials of intravenous thrombolytics in the setting of acute ischemic stroke. Streptokinase was examined in three major trials enrolling 1192 patients (MAST-I, 1995; Donnan et al., 1996; Multicenter Acute Stroke Trial, 1996). An increased rate of intracerebral hemorrhage with significantly worse outcomes in the treatment groups in persons treated with streptokinase negated possible benefit and forced early stoppage of the trials. The use of intravenous streptokinase is discouraged.

Intravenous rTPA was shown to reduce disability at 90 days in the setting of acute stroke. The NINDS trial (1995) was two sequential trials of rTPA vs. placebo in patients treated within 3 hours of symptom onset based on clinical criteria (i.e. angiographic demonstration of obstructing clot was not required prior to treatment). Patients were stratified into half treated within the first 90 minutes, and the other half within 180 minutes of stroke onset. A total of 624 patients were enrolled. In the pivotal second part of the trial, a normal to near normal recovery occurred in 31% of the treatment arm versus 20% in the placebo group (Fig. 81.4). A similar significant benefit was found at 90 days in part 1. This response rate included those 6.4% of patients who suffered a symptomatic ICH. Note in Fig. 81.4 that despite the increased incidence of ICH in treated patients, mortality was no higher and death or severe disability was less in those treated with rTPA.

There have been multiple post-marketing studies confirming the therapeutic effect of i.v. rTPA. The most notable

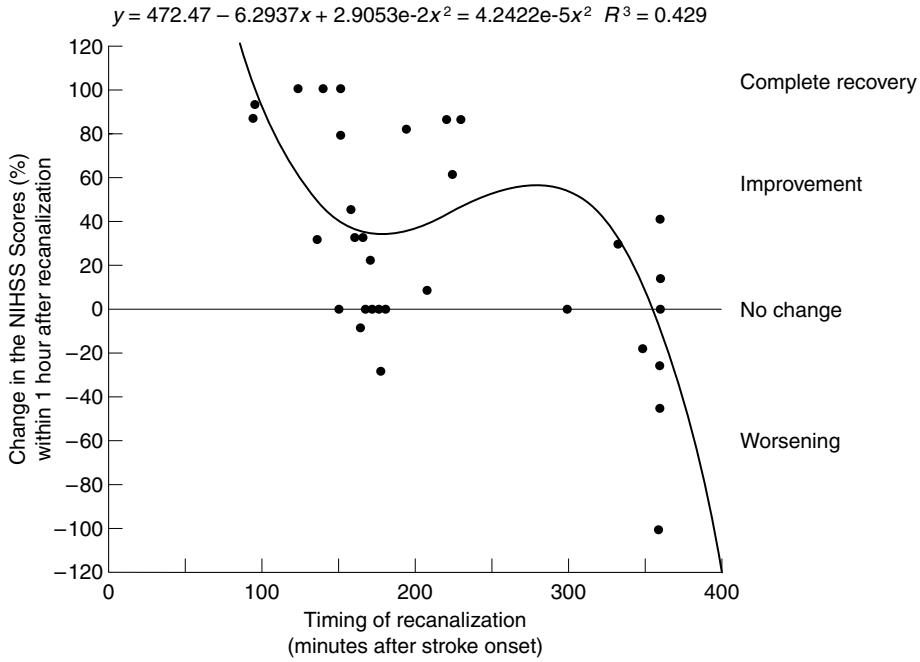

Fig. 81.1. Recovery from acute ischemic stroke correlates with the total time of ischemia. By using Transcranial Doppler to asses time until flow is restored, the link between early restoration of flow and good outcome is shown above. Note the lack of good outcome past 300 minutes of ischemia. (From Christou et al., 2000, with permission.)

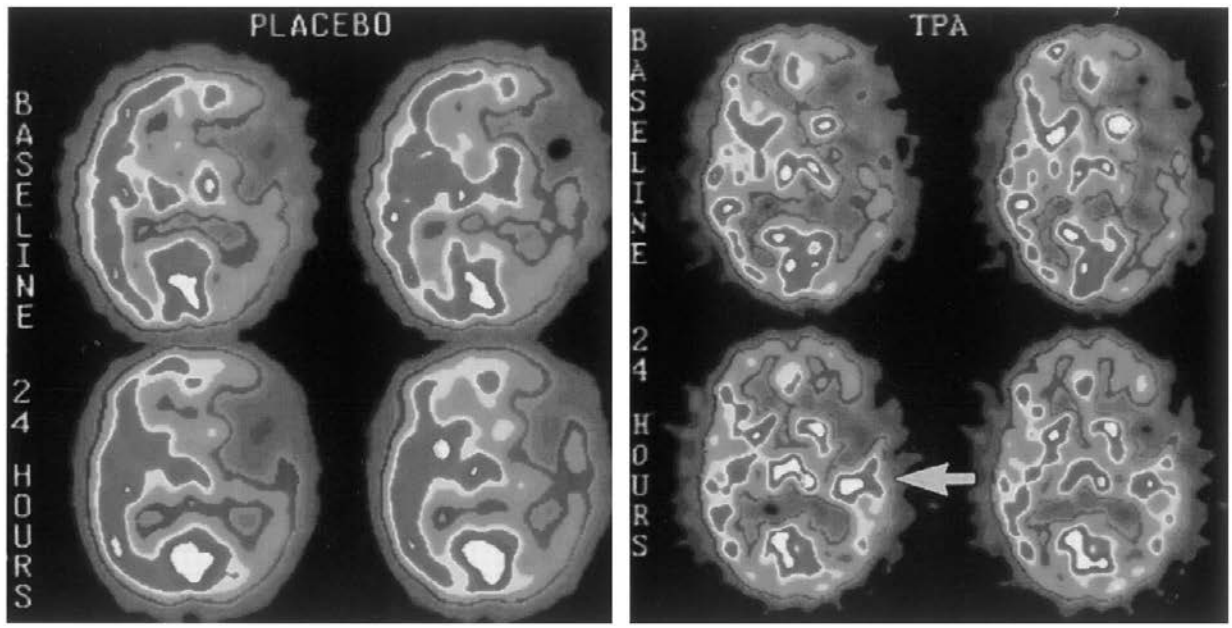

Fig. 81.2. SPECT scan demonstrating restoration of flow following intravenous tissue plasminogen activator. The image on the left is a patient who received placebo. No significant improvement is noted. The image on the right demonstrates a significant flow improvement to the ischemic region (arrow). This patient dramatically improved within 24 hours after treatment. (From Grotta & Alexandrov, 1998, with permission.)

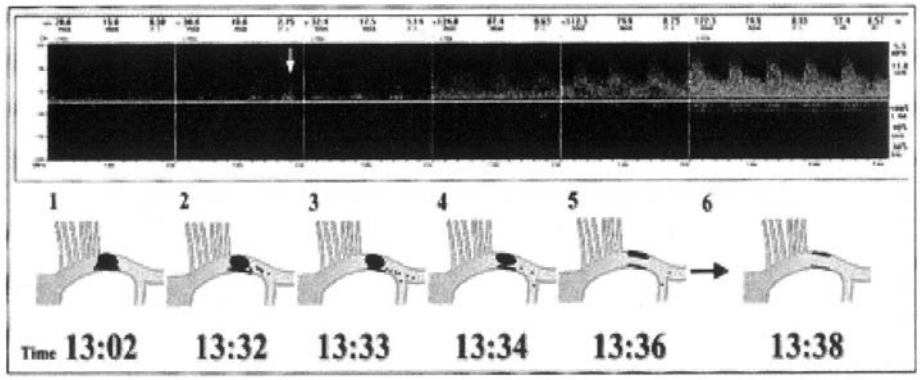

Fig. 81.3. Transcranial Doppler ultrasound representation of restoration of flow. The transcranial Doppler is shown in the upper figures. The bottom image is the interpretation of the transcranial Doppler signal. The occlusion at the M1 middle cerebral artery level begins to recanalize 30 minutes into intravenous thrombolysis with tissue plasminogen activator. As flow restoration occurs, the Doppler signature improves. The patient went on to have a dramatic recovery following restoration of flow. (From Demchuk et al., 1999, with permission.)

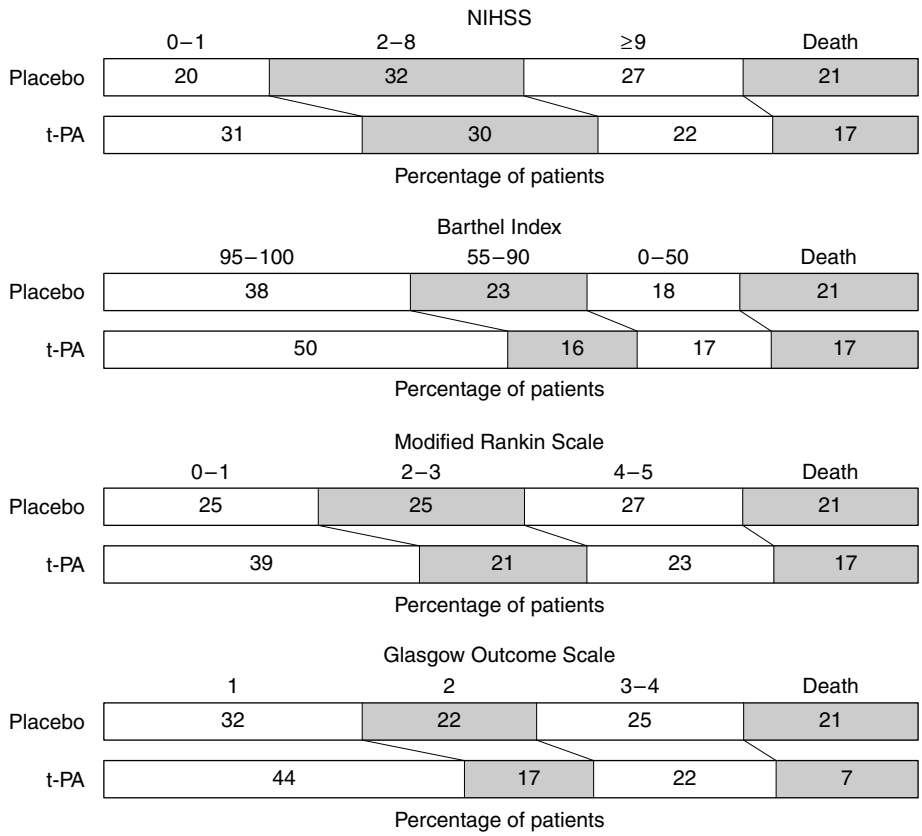

Fig. 81.4. Outcome at 90 days in the NINDS tissue plasminogen activator trial. Note the shift towards decreased disability. Although there was a trend towards lower mortality in the treatment group, this was not statistically significant. (From The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995, with permission.)

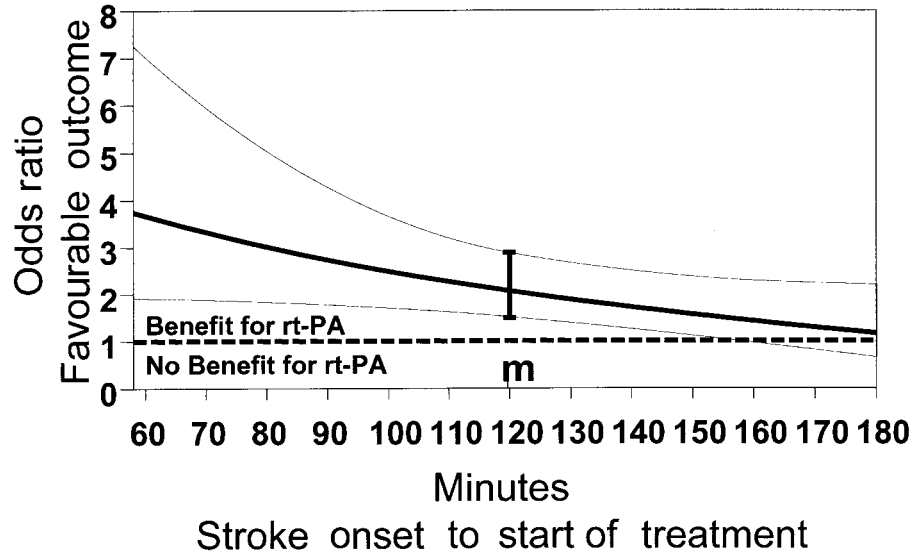

Fig. 81.5. Time to treatment with intravenous rTPA and outcome. Patients treated earliest into the course of their stroke had the best outcome. (From Marler et al., 2001, with permission.)

to date was the Standard Treatment with Alteplase to Reverse Stroke (STARS) (Albers et al., 2000) trial that duplicated the outcome benefit while showing a symptomatic ICH rate of 3.3%. The STARS trial along with other post marketing studies has shown that protocol violations result in a higher ICH rate. For this reason, strict adherence to treatment algorithms is advised.

The time to treatment is the single most important factor in determining outcome from i.v. rTPA therapy. (Fig. 81.5). Patients treated within 90 minutes do significantly better than patients treated closer to the 180-minute time window. Trials looking at the 3–6 hour time window have been negative, although a *post hoc* meta-analysis has suggested a trend towards decreased deficit (Wardlow et al., 2000).

At present, i.v. rTPA is the only FDA approved treatment for acute ischemic stroke. Quickly becoming the standard of care, all qualifying patients should be strongly considered for i.v. rTPA therapy. An outline of rTPA care is included (Fig. 81.6). It is imperative that neurologists work with Emergency Medical Services and Emergency Medical Departments to integrate the care of stroke patients. The Brain Attack Coalition (Alberts et al., 2000) has recommended the formation of Stroke Centres in an attempt to increase access to medical care (Fig. 81.7). We recommend a formal system of acute stroke triage, whereby patients are diverted from non-stroke centres to emergency departments that are capable of thrombolysis and post thrombolysis care.

Intra-arterial thrombolysis

There have been many anecdotal reports and two major trials of intra-arterial (i.a.) thrombolysis. The Prolyse in Acute Cerebral Thromboembolism II (PROACT II) (Furlan et al., 1999) trial showed a benefit for patients with an anterior stroke syndrome and middle cerebral artery occlusion. Patients showed benefit if treatment began up to 6 hours after stroke onset, potentially increasing the time window for that segment of stroke patients eligible for i.a. therapy. Patients were screened with an initial cerebral angiogram before being randomized. For every one patient randomized, four patients received a screening angiogram. Forty per cent of the patients who received i.a. prourokinase recovered to normal or near normal compared to 25% who did not receive i.a. thrombolysis.

The i.a. approach to thrombolysis has certain advantages and disadvantages. Because angiography is performed, it makes possible direct visualization of the thrombus with the ability to confirm the occlusion and determine the etiology in certain cases. Serial examinations can be performed and restoration of flow can be assessed. If thrombolysis is not successful, mechanical techniques such as the use of suction devices might be used to maximize clot dissolution. The greatest advantage of i.a. thrombolysis is the evident increase in the time window of therapy.

The disadvantages of i.a. thrombolysis are mainly related to access and time issues. Few centres have the

Intravenous tissue plasminogen dosing:

- *0.9 mg/kg total dose*
  - *Maximum total dose 90 mg*
- *10% bolus [(0.9 mg/kg) × (0.10)] over 1 minute*
  - *Maximum bolus 9 mg*
- *Remaining infusion dose over 60 minutes*

Eligibility:

- *Clinical diagnosis of stroke causing measurable deficit*
- *Time of onset within 180 minutes of initiating therapy*

Contraindications:

- *Evidence of hemorrhage on CT*
- *Clinical presentation consistent with SAH*
- *Active internal bleeding*
- *Known bleeding diathesis*
- *Within 3 months of intracranial surgery, traumatic brain injury or stroke*
- *History of ICH, AV malformation, or aneurysm*
- *Uncontrollable hypertension*

Warnings:

- *Minor or rapidly improving symptoms*
- *GI or urinary hemorrhage withing 21 days*
- *Major surgery or trauma within 14 days*
- *Recent lumbar puncture or arterial puncture at non-compressible site*
- *Hyper- or hypoglycemia*
- *Seizure at onset of stroke symptoms*
- *Postmyocardial infarction pericarditis*

Fig. 81.6. Overview on intravenous tissue plasminogen activator therapy for acute ischemic stroke. Time of onset is defined by the last time a patient is known to be normal. See package insert for further directions.

Elements of a stroke centre:

- Patient care services
  - Acute stroke teams
  - Written and easily accessible care protocols
  - Emergency medical services and emergency department
  - Stroke unit
    - Only required for those stroke centres that will provide ongoing in-hospital care for patients with stoke
  - Neurological services
    - Available within reasonable time and geographical distance

Support services

- Commitment and support of medical organization
- Designated stroke centre director
- Neuroimaging and laboratory services
  - 24 hour availability
- Outcome and quality of care assessment and improvement
- Medical education activities

Fig. 81.7. Stroke Centre guidelines per the recommendations of the brain attack coalition. (From Alberts et al., 2000, with permission.)

expertise and equipment required to treat all eligible patients on a consistent basis. As time to restoration of flow is critical in determining outcome, the added time of transport, alerting the angiography team, and gaining intravascular access can significantly delay time to restoration of flow. In an attempt to minimize these disadvantages, the combination of an initial i.v. dose of rTPA followed by i.a. thrombolysis is being investigated. The need for a high number of screening angiograms also reduces the attractiveness of i.a. therapy. Transcranial Doppler is a promising screening technique in the ED that might be used for identifying patients who would be likely to have treatable arterial occlusions (Denchuk et al., 2000).

ProUrokinase, the agent used in the PROACT II trial is not currently available in North America. The agent with the most reported use outside of the PROACT trial is Urokinase, but this drug has supply difficulties and is often not available. Tissue plasminogen activator is gaining popularity as an i.a. thrombolytic agent. Intra-arterial thrombolysis is not currently an approved procedure and should

only be attempted at centres with experienced personnel and under investigational conditions.

The role of i.a. thrombolyis in posterior circulation events has been reported in anecdotal reports and case series. Thus far, no randomized trials have investigated safety or effectiveness. Posterior circulation strokes, especially those involving occlusion of the basilar artery, have a dismal prognosis with a high mortality. The posterior circulation may have a relative resistance to ischemia, with reports of recovery following thrombolysis out to 18 hours. For this reason and the overall poor outcome, it is reasonable to consider i.a. thrombolysis in patients with basilar artery occlusion who do not respond to conventional i.v.-rTPA or who are not candidates due to time constraints. The investigational nature of such procedures based on anecdotal and case series evidence must be emphasized and informed consent should be obtained.

Heparin

The use of anticoagulation with heparin and heparin-like products goes back nearly 50 years. Despite the lack of evidence in favour of its use and the significant possibility of hemorrhagic transformation, heparin remains a commonly used agent in the treatment of acute stroke. Heparin theoretically inhibits new thrombus formation or extension of preformed thrombus to prevent recurrent stroke or worsening of prior infarction.

Heparin was evaluated in the International Stroke Trial (1997). A total of 19435 patients within 48 hours of acute stroke onset were enrolled into no treatment, 5000 i.u. of subcutaneous heparin b.i.d., 12500 i.u. of subcutaneous heparin b.i.d., both heparin doses with or without aspirin 300 mg daily, and aspirin alone. No improvement in outcome was found in any of the heparin treatment groups. Most significantly, the benefit seen in the higher heparin dose (0.9% prevention of recurrent stroke) was diminished by an increase in hemorrhagic stroke (0.8% absolute increase). The combination of 300 mg of aspirin daily with 5000 i.u. of Heparin BID was associated with the best outcome (1.2% decrease of death or non-fatal recurrent stroke at 14 days) without a significant increase in hemorrhagic stroke when compared to 300 mg of aspirin alone.

Heparinoids, low molecular weight heparin derivatives formed by enzymatic cleavage, have been evaluated in multiple well-designed trials. Danaparoid was evaluated in the Trial of ORG 10172 in Acute Stroke Treatment trial (TOAST) (1998). Patients treated within 24 hours of acute stroke showed no difference in outcome from the control group. A *post hoc*, subgroup analysis suggested benefit in those patients with stroke due to large vessel atherosclerotic disease (Adams et al., 1999). This finding remains to be confirmed by further prospective study. Another heparinoid, nadroparin was evaluated in two randomized trials (Kay et al., 1995; Bath et al., 2000). The first, smaller trial suggested benefit. This was not confirmed in a larger follow-up study.

Much misinformation and many queries remain concerning heparin and heparinoids. There is belief that heparin is beneficial for 'stroke in progression'. This hypothesis has not been validated by results from controlled trials. There is also a concern that the current trials have not replicated the North American practice of an i.v. bolus followed by an i.v. continuous infusion. However, this argument is also not supported by data since this type of dosing is very similar to the negative TOAST trial protocol, and there was also no evidence of a dose effect suggesting even a marginal benefit in other trials. An important discovery from the heparin and heparinoid trials is the relatively infrequent rate of recurrent stroke (approximately 2–4% in the first 14 days), lessening concern for the need for anticoagulation to prevent recurrent strokes in the first days following an acute stroke.

In conclusion, full dose heparin or heparinoids cannot be recommended in most settings based on the outcome of well-designed trials enrolling nearly 20000 patients. At present, the only clearly effective treatment for acute stroke is thrombolysis and this should be made available to as many patients as possible. In certain acute stroke situations, such as high-grade large vessel stenosis or dissection, or established cardiac conditions likely to cause embolization, i.v. heparin might be used with caution, recognizing the significant risk of hemorrhagic transformation of the stroke. Subcutaneous low dose heparin appears beneficial, likely by preventing deep venous thrombosis, and is recommended for routine use.

Ancrod

By decreasing the availability of fibrinogen, Ancrod decreases the ability to form thrombi. Derived from the Malaysian Pit Viper, ancrod was shown to be beneficial in patients treated within three hours of acute stroke (Sherman et al., 2000). At 90 days, 42% of the treatment arm recovered to normal or near normal when compared to 34% of the placebo group. Ancrod has not yet been approved for the treatment of acute stroke. Although a promising modality, ancrod administration is a rather burdensome procedure that may prevent general acceptance. Its utility compared to thrombolyis, and the role of ancrod

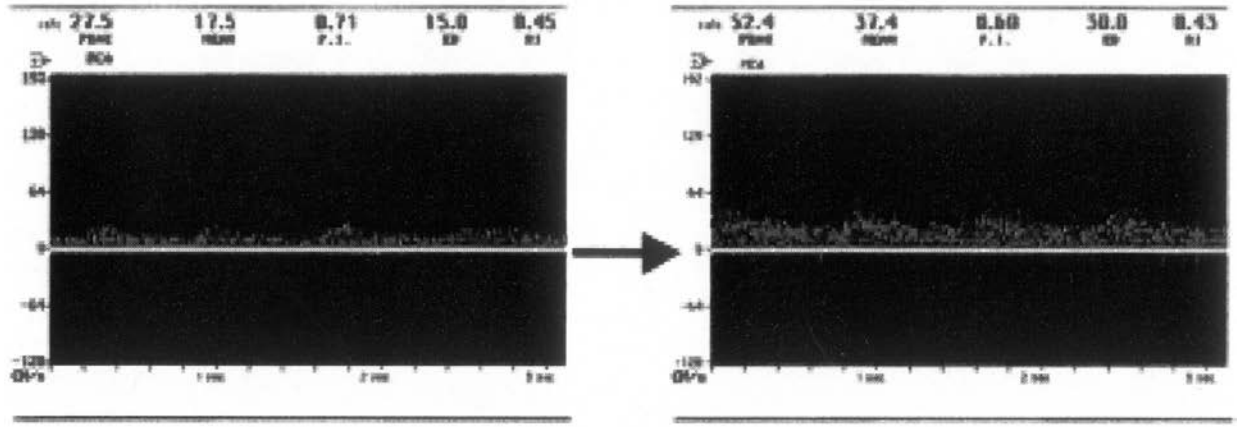

Fig. 81.8. Response to change in head of bed position. Transcranial Doppler images of the right middle cerebral artery. The image on the left shows the wave tracing with the head of bead at 70°. The patient has a moderate left leg paresis. The image on the right shows the response of lowering the head of bed to 0°. The patient had a complete recovery of leg paresis when the head of bed was lowered. (From Alexandrov et al., 2000, with permission.)

combined with thrombolytics and antiplatelet agents remain to be seen.

Aspirin

Aspirin given early in acute stroke was minimally beneficial in a combined analysis (Chen et al., 2000) of the Chinese Acute Stroke Trial (1997) and International Stroke Trial (1997). This trend suggested an overall decrease of further stroke or in-hospital death for 9 per 1000 acute stroke patients treated with aspirin versus placebo.

The mechanism of this benefit is uncertain. Besides preventing recurrent stroke, aspirin prevents hyperthermia, myocardial infarction, and potentially prevents deep venous thrombosis. The role of aspirin in combination with thrombolytics and the role of other antiplatelet agents in acute stroke still needs to be investigated. Aspirin, 81mg to 325 mg, can be recommended for all acute ischemic stroke patients who do not qualify for thrombolysis, and after 24 hours for those who receive rTPA. As there is reason to believe that aspirin could potentially extend an intracerebral hemorrhage, patients or emergency medical personnel should not use aspirin prior to appropriate neuroimaging.

Altering the ischemic cascade

Much attention has been given to the potentially salvageable ischemic penumbra. Neuroprotective strategies and agents have been the subject of multiple clinical trials. Although this concept remains promising, thus far no agents have shown benefit. This topic is covered in greater detail in Chapter 5.

Collateral flow

Along with neuroprotection, attempts to salvage the ischemic penumbra have often focused on collateral flow and 'miserly perfusion'. Miserly perfusion is a concept arising from positron emission tomographic imaging, simultaneously measuring cerebral blood flow and oxygen metabolism in ischemic brain regions (Baron et al., 1981). These studies demonstrated that ischemic brain parenchyma extracts the maximum oxygen available from the blood, much like a 'miser' would take the maximum resources available. The outlaying border zone regions of the ischemic penumbra may receive potentially nutritive perfusion via leptomeningeal collateral flow from adjacent vascular territories. By increasing the quantity and quality of collateral flow to the ischemic penumbra, there is the potential for 'reversing' miserly perfusion resulting in parenchymal rescue.

Multiple reports suggest that decreasing collateral flow is harmful. Since the capacity for autoregulation of cerebral blood flow in ischemic regions is diminished, cerebral perfusion is directly affected by changes in blood pressure. This is the basis for avoiding excessive lowering of blood pressure in the setting of acute stroke, either pharmacologically or by dehydration. Anecdotally, many patients show clinical improvement simply by lowering the head of the bed from upright to $<$30 degrees, presumably decreasing orthostatic hypotension and hypoperfusion (Fig. 81.8).

To date, no trial has conclusively proven that interventions to increase collateral flow are beneficial. The Hypervolemic Hemodilution Treatment of Acute Stroke Trial (1989) used pentastarch, a synthetic albumin-like oncontic agent, in acute stroke patients to increase intravascular volume, cardiac output, and presumably brain perfusion. Although no benefit was seen, a *post hoc* analysis suggested a significant benefit in those patients who received pentastarch and had a 10% increase in cardiac output when compared to those who received either placebo or pentastarch with a $<$10% increase in cardiac output. Conversely, congestive heart failure and low cardiac output is associated with poor outcome in stroke patients.

A particularly interesting approach to increasing perfusion of the ischemic penumbra is the use of transvenous retroperfusion (Frazee et al., 1990). Arterialized blood from the femoral arteries is delivered via a catheter system to the central venous sinuses. There, arterialized blood is perfused in a retrograde fashion to the compromised cortex, circumventing the arterial occlusion. Besides acting as a method to increase oxygenation, transvenous retroperfusion represents a unique method of drug delivery. Despite early encouraging results in a few patients, logistic issues have hindered further evaluation.

To maintain or improve collateral flow to penumbral regions in acute stroke patients, the following are recommended guidelines (Adams et al., 1994).

Excessive lowering of elevated blood pressure should be avoided. In general, the patients' usual antihypertensive agents (if any) should be held. Recommendations are that systolic pressures $\leq$200 mm Hg not be treated, unless there is evidence of end organ damage such as myocardial ischemia or aortic dissection, or the patient is a candidate for thrombolysis. In patients receiving rTPA, systolic and mean arterial pressures can safely be reduced to 180 and 130 mm Hg, respectively (Brott et al., 1998). If blood pressure is lowered, easily titrated drugs should be used, and pressures reduced gradually while monitoring the patient's neurological status. Dehydration, which is common in stroke patients (Grotta et al., 1985), should be avoided. Intravenous normal saline solution up to150 cm^3/h should be given over the first 24 hours after stroke. Patients with unstable blood pressure or fluctuating neurological exam should be kept at bedrest for 24 hours with the head of bed $<$30 degrees. Mobilization is then encouraged, with close monitoring for orthostasis. In some cases, blood pressure support with volume expanders or pressors might reverse clinical deterioration, particularly if mean arterial blood pressure has fallen below 100 mm Hg.

Preventing complications

Poststroke complications are common and can often be avoided. Through standardization of admission orders, a multidisciplinary approach to patient care, and, most importantly, skilled and experienced nursing care, outcome can be improved. This is the paradigm behind the Stroke Unit concept that is discussed below. The importance of monitoring, recognizing, and treating hypotension, hypovolemia, and decreased cardiac output is emphasized above

Nosocomial infections, particularly pneumonia from aspiration and urinary tract infections from indwelling catheters, are a common source of increased morbidity. Before feeding, patients should be screened for aspiration risk, and speech pathology should be consulted in all at-risk patients. Nurses should be trained in recognition of silent aspiration and should be empowered to initiate appropriate measures. We have found that dyspnea, with respiratory rates $>$22/minute is a sensitive early marker of aspiration pneumonia. A rapid and predefined urinary continence protocol should be developed to decrease the exposure to indwelling catheters.

Both hyperglycemia and hypoglycemia have been implicated as harmful to acute stroke patients, most likely through accentuating the ischemic cascade. Serum glucose should be measured on admission in all patients. Known diabetics or those with hyperglycemia should receive an aggressive blood glucose monitoring protocol. Though not proven by prospective studies, serum glucose levels above 150 mg/dl should be lowered pharmacologically. Glucose-containing intravenous solutions should be avoided to minimize iatrogenic hyperglycemia.

Hyperthermia has been shown to worsen outcome in both animal stroke models and human stroke patients (Ginsberg & Busto, 1998). Conversely, hypothermia is neuroprotective in experimental models and associated with better outcome in small case series (Schwab et al., 1998). All stroke patients' temperature should be closely monitored. Hyperthermia should be actively treated through a predefined algorithm with the goal of maintaining normothermia to mild hypothermia.

Any cardiopulmonary condition leading to hypoxemia is problematic in this population. Blood oxygenation should be monitored. Heparin 5000 i.u. b.i.d. is discussed above and should be used to prevent deep venous thrombosis (DVT). The importance of early and aggressive mobilization, and prevention of aspiration, should be emphasized to prevent both DVT and pneumonia.

Stroke units

Specialized geographical units caring only for stroke patients are beneficial in improving outcome, decreasing length of stay, decreasing complications, and decreasing overall mortality up to 10 years after discharge (Indredavik et al., 1999b). Other than i.v. rTPA and aspirin, Stroke Units are the only other proven beneficial intervention in acute stroke.

The benefit of a Stroke Unit seems to result mainly from skilled nurses and the intermediate level of care that they provide. A recent review suggested that the close monitoring and management of blood pressure and body temperature lead to the improved outcome seen in Stroke Units (Indredavik et al., 1999a). A multidisciplinary approach with other medical specialties, rehabilitation services, speech pathology, case management, social work services, and often pastoral services ensures rapid evaluation, fosters a positive attitude in patients and families, and facilitates discharge to appropriate levels of long-term care.

Given the large body of evidence that Stroke Units improve outcome and are more cost effective than general ward or Intensive Care Unit admission, Stroke Unit admission should become the standard of care for appropriate patients.

In conclusion, acute ischemic stroke is a treatable condition. Recovery is a time-dependent process, with a time window of 3–6 hours. Restoration of flow with thrombolysis is the most effective therapy and should become standard treatment for all appropriate patients. By maximizing collateral perfusion, admitting patients to a Stroke Unit, and actively preventing complications, outcome can be maximized.

The neurologist has a responsibility to work closely with emergency medical specialists to increase access to proven interventions. As the therapeutic era of stroke management progresses, the leadership of neurologists in the medical community will become even more important to reduce the significant burden caused by this illness.

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82

Behavioural manifestations of stroke

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Introduction

Recent studies have concluded that neuropsychiatric complications (i.e. emotional, behavioural, and cognitive disorders) may have a negative effect not only on the social functioning and overall quality of life of stroke survivors (King, 1996) but on the recovery of their motor functioning as well (Clark & Smith 1997). This chapter will discuss a number of these neuropsychiatric disorders (Table 82.1), including their effect on recovery and methods of treatment.

Poststroke depression (PSD)

Depression is among the most common neuropsychiatric disorders that occur after stroke. Despite its high frequency and negative influence on the overall recovery of stroke patients, a study by Schubert et al. (1992) reported that poststroke depression (PSD) was under-diagnosed by non-psychiatric physicians in 50% to 80% of cases.

Epidemiology

The frequency of PSD has been examined in numerous studies. The frequency depends upon whether patients are examined in hospital or in community surveys and whether they are studied during the acute poststroke period or many months following stroke (Table 82.2). In addition, the use of cutoff scores to define the existence of PSD, rather than structured interviews and diagnostic criteria have also contributed to reported differences in the prevalence rates of PSD.

The mean prevalence in hospitalized acute stroke patients was 22% for major depression and 17% for minor depression. In outpatient populations, the mean prevalences were 23% for major depression, and 35% for minor depression; while in community samples was 13% for major depression and 10% for minor depression. (Table 82.2)

Diagnosis

The diagnosis of PSD may be difficult or impossible in some groups of patients with stroke. For instance, the presence of language comprehension disorders and/or significant cognitive impairment may prohibit the reliable assessment of symptoms of depression (Gustafson et al, 1991).

While the DSM-IV (American Psychiatric Association, 1994) criteria for 'mood disorders due to a medical condition' are applicable for the diagnosis of PSD (Starkstein & Robinson, 1989), some investigators have suggested that several symptoms used by DSM-IV for the diagnosis of major depression, such as loss of energy and appetite, and insomnia, are also found among euthymic stroke patients secondary to hospital environment, the use of medications, other associated medical conditions or the stroke itself (Harrington & Salloway, 1997). In 1991, a study by Fedoroff et al. (1991) examined the frequency of depressive symptoms among both depressed and non-depressed patients with acute stroke. This study found that, with the exception of early morning awakening, all neurovegetative and psychological symptoms of depression were significantly more frequent among patients with depressed mood compared to patients without depressed mood. Even when the frequency of non-specific symptoms among the non-depressed was taken into account, the frequency of major depression decreased only 2%, from 23% to 21%.

Thus, although PSD cannot be reliably diagnosed in patients with severe comprehension impairments, the

Table 82.1. Neuropsychiatric disorders associated with stroke

Syndrome	Prevalence	Clinical features
Poststroke depression	35%	Depressed mood, appetite or weight loss, insomnia, social withdrawal
Mania	rare	Elevated mood, decreased sleep, flight of ideas, pressured speech, grandiosity
Bipolar disorder	rare	Alternating symptoms of depression and mania
Anxiety disorder	25%	Apprehensive expectation, restlessness, loss of energy, muscle tension
Apathy without depression	20%	Loss of interest and drives
Psychotic disorder	rare	Delusions and halluciations
Pathological affect	20%	Out of proportion emotional outbursts
Catastrophic reaction	20%	Burst of aggressive behaviour, anxiety, crying

Table 82.2. Prevalence studies of poststroke depression

Investigators	Patient population	*n*	Criteria	% major	% minor	Total %
Wade (1987)	Community	379	Cutoff score			30
House (1991)	Community	89	PSE-DSM-III	11	12	23
Burvill (1995)	Community	294	PSE-DSM-III	15	8	23
Robinson (1983)	Acute hosp	103	PSE-DSM-III	27	20	47
Ebrahim (1987)	Acute hosp	149	Cutoff score			23
Fedoroff (1991)	Acute hosp	205	PSE-DSM-III	22	19	41
Castillo (1995)	Acute hosp	291	PSE-DSM-III	20	18	38
Starkstein (1992)	Acute hosp	80	PSE-DSM-III	16	13	29
Aström (1993)	Acute hosp	80	DSM-III	25	NR	25[a]
Hermann (1993)	Acute hosp	21	RDC	24	14	38
Andersen (1994)	Acute hosp or outpatient	285	HDRS cutoff	10	11	21
Folstein (1997)	Rehab hosp	20	PSE and items			45
Finklestein (1982)	Rehab hosp	25	Cutoff score			48
Sinyor (1986)	Rehab hosp	35	Cutoff score			36
Finset (1989)	Rehab hosp	42	Cutoff score			36
Eastwood (1989)	Rehab hosp	87	SADS-RDC	10	40	50
Morris (1990)	Rehab hosp	99	CIDI-DSM-III	14	21	35
Shubert (1992)	Rehab hosp	18	DSM-III-R	28	44	72
Schwartz (1993)	Rehab hosp	91	DSM-III	40		40[a]
Feibel (1982)	Outpatient (6 months)	91	Nursing eval			26
Robinson (1982)	Outpatient (6 months–10 years)	103	Cutoff score			29
Collin (1987)	Outpatient	111	Cutoff score			42
Aström (1993)	Outpatient (3 months)	73	DSM-III	31	NR	31[a]
	(1 year)	73	DSM-III	16	NR	16[a]
	(2 years)	57	DSM-III	19	NR	19[a]
	(3 years)	49	DSM-III	29	NR	29[a]
Castillo (1995)	Outpatient (3 months)	77	PSE-DSM-III	20	13	33
	(6 months)	80	PSE-DSM-III	21	21	42
	(1 year)	70	PSE-DSM-III	11	16	27
	(2 years)	67	PSE-DSM-III	18	17	35
			Mean	20	21	34[a]

Notes:

[a] Since minor depression was not included, these values may be low. PSE = present state examination; SADS = schedule for affective disorders and schizophrenia; RDC = research diagnostic criteria; CIDI = composite international diagnostic interview; HDRS = Hamilton depression rating scale.

Source: Robinson (1998).

DSM-IV diagnostic criteria for 'depression due to stroke with major depressive-like episode' are applicable to patients with PSD and the phenomenology of these depressions was found by Lipsey et al. (1986) to be similar to those found in elderly patients with primary depression. DSM-IV criteria for depression due to stroke with major depressive-like episode requires the presence of either depressed mood or loss of interest during 2 or more weeks following a stroke accompanied by at least four of the following symptoms: decreased or increased appetite or weight; insomnia or hypersomnia; psychomotor agitation or retardation; loss of energy; feelings of worthlessness or inappropriate guilt; loss of concentration; and recurrent suicidal ideation.

Minor depression is a DSM-IV research diagnosis which requires the presence of more than two, but less than five major depressive symptoms including either a depressed mood or loss of interest. Although it excludes depressions 'due to a general medical condition', we have used this diagnosis to identify stroke patients with milder (subsyndromal) forms of depression. Our studies have provided some validation for this diagnosis by identifying differences between major and minor depression in the frequency of past personal history of depression (Morris et al., 1992), the association with cognitive impairment (Downhill & Robinson, 1994) and association with lesion location (Paridiso & Robinson, 1999).

Although most authors have used these standardized criteria for the diagnosis of poststroke depression (Astrom et al., 1993a; House et al., 1990b; Morris et al., 1992; Eastwood et al., 1989), Gainotti et al. (1999), however, have disagreed with the comparability of poststroke depression with primary depression and the distinction of major and minor depression. Using their own Post-stroke Depression Rating Scale (PSDRS), these investigators found that 153 patients with stroke, compared to 30 patients with endogenous (primary) major depression, showed higher scores on catastrophic reactions and hyperemotionalism and were more likely to attribute their depression to handicap or disabilities, while endogenous depression patients were higher on suicide and anhedonia. Gainotti et al. (1999) also asserted that the failure to assess these aspects of depression (included in the PSDRS) demonstrated methodological errors in the assessment of depression by Robinson et al. The inclusion of catastrophic reactions, hyperemotionalism and patients' attribution of their depression to disability are clearly idiosyncratic criteria for the diagnosis of depression added to show differences with primary depression. Validation of a new form of depression should include predictable demonstration of the course of the disorder, specific clinical and pathological correlates, and response to treatment that are not found when the widely accepted and validated criteria for 'standard' depression are used. Furthermore, symptoms such as hyperemotionalism and catastrophic reactions are seen in patients with and without depression (see later sections of this chapter of these disorders) and are not specific to poststroke depression.

Duration

The duration of depression has been examined in several longitudinal studies. In a prospective study of mood disorders in 65 acute stroke patients (Robinson et al., 1987), we found that 9 patients (14%) had an in-hospital symptom cluster of major depression, while 12 patients (18%) had a symptom cluster of minor depression. All of the follow-up patients with major in-hospital depression were improved by 2 years, whereas only 3 patients (30%) with in-hospital minor depression recovered by this time.

Morris et al. (1990) found that the mean duration of poststroke major depression was 34 weeks, while the mean duration of minor depression was only 13 weeks. Aström et al. (1993b) also found that the majority of major depressions remitted by 1-year follow-up. Yet, 30% of patients with in-hospital major depression remained depressed at 1-year follow-up, 25% were depressed at 2-year follow-up, and 20% were still depressed at 3-year follow-up.

Thus, although the mean duration of major depression appears to be about 9 months, there are a significant number of patients with major or minor depression in-hospital who remain depressed for several years following stroke.

Anatomical correlates

Since the 1980s there has been a growing interest in finding a correlation between lesion location and PSD in order to delineate a pathophysiological hypothesis to explain this disorder.

In one of the earliest studies that examined the relationship between PSD and lesion location, we found that 14 of 22 patients with left hemisphere lesions suffered either major or minor depression while these disorders occurred in only 2 of 14 patients with right hemisphere lesions. We later compared 13 PSD patients with predominantly left-sided lesions to a group of stroke patients without depression matched for age, lesion size and location. We found that subcortical atrophy (as evidenced by increased ventricular: brain ratios) was associated with the presence of PSD (Starkstein et al., 1988). In yet a later study of 93 patients with right-sided lesions, both right frontal (i.e. 6 of

17 depressed patients and 1 of 25 non-depressed patients had a frontal lesion) and right parietal lesions (i.e. 11 of 17 depressed and 9 of 25 non-depressed had a parietal lesion) were associated with PSD (Starkstein et al., 1989).

Although some of these findings have been replicated by other authors (Aström et al., 1993a; Morris et al., 1996), numerous studies have not found lateralized effects (House et al., 1990b). We have recently shown that these laterality effects are present only during the acute stroke period, and many studies which examined patients several months or several years after stroke would not be expected to show laterality effects. Some studies done within the first few months poststroke have failed to show this laterality effect. For example, Gainotti et al. (1999) examined lesion location in 53 patients using MRI or CT scans. Among patients who were less than 2 months poststroke, only one of nine patients had major depression while three of seven with right anterior lesions had major depression. This failure to replicate findings was referred to by Gainotti as a 'factual error of Robinson et al.' (Gainotti et al., 1999) Negative findings happen all the time and failure to replicate is far from proving the null hypothesis (Gainotti proposes no clinical pathological correlation). Thus, this area of investigation and whether there is a strategic lesion location which leads to depression is still a matter of controversy.

Mechanism

While the cause of PSD remains unknown, we have hypothesized (Robinson & Starkstein, 1990) that the depletion of monoaminergic amines occurring after lesions in the frontal lobe or basal ganglia of the brain may play a role in PSD. Norepinephrine and serotonin nuclei send ascending projections from their location in the brainstem to the frontal cortex through the median forebrain bundle. These ascending axons then arc posteriorly running through the deep layers of the cortex where they arborize and send terminal projections into the superficial cortical layers.

Lesions of the frontal lobe or basal ganglia have been shown in animal models to disrupt these pathways (Robinson, 1998). Furthermore, we reported higher serotonin receptor binding in ipsilateral, non-injured, temporal, and parietal cortex of patients with right compared to left-sided lesions. Among patients with left hemisphere stroke, we found a significant correlation between severity of depression and the absence (i.e. decreased amount) of serotonin receptor binding (Mayberg et al., 1988). Disruptions of dopaminergic pathways ascending from ventral tegmental area have also been implicated in the pathogenesis of PSD (Herrmann et al., 1993).

Association between physical impairment and PSD:

Stroke survivors often suffer some degree of long-term impairment. The relationship between PSD and functional impairment is complex. The measurement of physical impairment usually involves both the neurological motor and sensory examinations and quantification of deficits in the performance of daily activities (ADL). In one of our earliest studies of PSD (Robinson et al., 1983), we found a significant correlation among 130 patients between the severity of depressive symptoms measured using the Zung depression scale, the HAM-D scale, or the PSE scale and the severity of impairment in ADL including the patient's ability to dress and feed themselves, walk, find their way around, express needs, read and write, keep their room in order, and to maintain sphincter control.

While most stroke patients experience some natural recovery of their neurological functioning and ability to perform activities of daily living, we have reported that, at 2 years follow-up, patients with major or minor depression after acute stroke were significantly more impaired in their ADL than comparably impaired patients without depression. Furthermore, a recent study found that 24 patients with major or minor PSD who had remission of depression were significantly more improved in their ADL scores than 35 comparably depressed patients who were not improved in their depression (Chemerinski et al., 2001). In addition, however, in-hospital impairment in ADL was found to correlate with severity of depression at both 3 and 6 months follow up (Robinson, 1998). These findings suggest that depression influences ADL recovery and that severity of ADL impairment influences the duration and severity of depression.

Association between cognitive impairment and PSD

Deficits in one or more domains of cognitive function are, along with motor impairment, the most common complications of stroke. We first reported a specific association between cognitive impairment and major PSD in 1986 (Robinson et al., 1986). In this study, 38 patients who had single infarcts in the left hemisphere, as documented by either CT scan or clinical history, were grouped according to whether they had major depression ($n=11$), minor depression ($n=10$), or no depression ($n=17$). Although there were no significant differences in terms of background characteristics and neurological findings among groups, patients with major depression had significantly more cognitive impairments measured with the Mini

Mental State Exam (MMSE) than minor depression or non-depressed patients (Folstein et al, 1975).

Using a comprehensive neuropsychological battery, we (Bolla-Wilson et al., 1989) subsequently found that patients with major depression and left-hemisphere infarcts had significantly greater deficits in tasks involving language, temporal orientation, executive motor, and frontal lobe functions than patients with comparable lesions but without depression.

Longitudinal studies of the course of cognitive impairment and PSD found that this association tended to decline with time. House et al. (1990a), for example, found that the high correlation between depression measured with the Beck depression inventory (BDI) and cognitive impairment that was seen in 76 patients at 1 month after stroke failed to reach significance at the 1-year follow-up. In a 2-year longitudinal study of 103 patients, we found that patients with in-hospital diagnosis of major depression following a left hemisphere stroke had significantly greater cognitive impairment at the in-hospital, 6-month ($P=0.03$) and 12-month ($P=0.02$) follow-up but no difference in cognitive function at 2-year follow-up (Downhill & Robinson, 1994).

Treatment

The widespread belief that depression is an understandable psychological reaction to the physical impairments of stroke, and the increased frequency and severity of side effects that psychotropic drugs (e.g. tricyclic antidepressants) might produce in this mostly advanced-age patient population, are factors that probably account for the reluctance by many physicians to use antidepressant medications in PSD.

There are currently at least four double-blind placebo-controlled studies which have examined the efficacy of antidepressant medication in PSD. The first controlled treatment trial of poststroke depression was conducted by our group and reported in 1984 (Lipsey et al., 1984). In this study, 39 patients with stroke who met the diagnostic criteria for major or minor depressive disorder were enrolled in a double-blind placebo-controlled study of the efficacy of nortriptyline among this population. Of the 39 patients entered in the study, five dropped out within 1 week. Of the 34 remaining patients, 14 received nortriptyline and 20 received placebo. Repeated-measures analysis of variance of depression scores and *post hoc* tests demonstrated that the nortriptyline group had significantly greater improvement than the placebo group at 4 and 6 weeks of treatment. All 11 patients who completed the course of nortriptyline treatment responded, while only 5 of the 15 placebo patients responded ($P=<0.001$).

In a controlled study by Reding et al. (1986), 7 PSD patients with an abnormal dexamethasone suppression test (DST) treated with trazodone had a significantly greater improvement in activities of daily living at 2–3 months following stroke measured with the Barthel ADL scale, compared to 9 comparable patients treated with placebo.

Andersen et al. (1994) assessed the efficacy and tolerability of the selective serotonin reuptake inhibitor antidepressant citalopram in a controlled study of 66 patients with stroke. The HAM-D and the Melancholia Scale (MES) scores were significantly better at both 3 and 6 weeks among patients who received citalopram compared to patients given placebo.

We have recently compared the efficacy of nortriptyline and fluoxetine in the treatment of depression and recovery following stroke in an entirely different socioeconomic population (Robinson et al., 2000). A total of 104 patients with acute stroke were randomized to receive either nortriptyline, fluoxetine or placebo over 12 weeks of treatment. Patients treated with nortriptyline (25 mg week 1, 50 mg week 2, 75 mg weeks 3–6 and 100 mg weeks 7–12) had a significantly greater decline in HDRS scores than either fluoxetine (10 mg weeks 1–3, 20 mg weeks 4–6, 30 mg weeks 7–9 and 40 mg weeks 10–12) or placebo-treated patients at 12 weeks of treatment ($F=3.73$, $df=2,53$, $P=<0.031$). (Fig. 82.1). There were no significant differences between fluoxetine and placebo. The successful treatment rate for nortriptyline was 77% for patients who completed the study while the successful treatment rate for fluoxetine was 14% (Fisher Exact Test, $P=<0.0018$). Thus, nortriptyline was superior to fluoxetine in treating poststroke depression. There was no effect of nortriptyline or fluoxetine on cognitive recovery as measured by Mini Mental State Examination (MMSE) scores or psycho-social outcome as measured by Social Functioning Examination (SFE) (Starr et al., 1983) scores. However, at 9 and 12 weeks, nortriptyline-treated patients showed significantly better activities of daily living functioning as measured by Functional Independence Measure (FIM) (Forer & Granger, 1987) scores than the fluoxetine treated patients.

Of the 104 patients enrolled in the study, 25 patients dropped out before completing the protocol (15 of the 40 patients receiving fluoxetine, 5 of the 31 patients receiving nortriptyline and 5 of 33 patients receiving placebo). The dropout rate was significantly greater in the fluoxetine than the nortriptyline or placebo group ($\chi^2=4.1$, $P=0.04$). Gastrointestinal side effects, insomnia and headache were more frequent in the fluoxetine-treated group. In addition, fluoxetine led to an average 14 pound weight loss over 12 weeks that was not seen with other treatments.

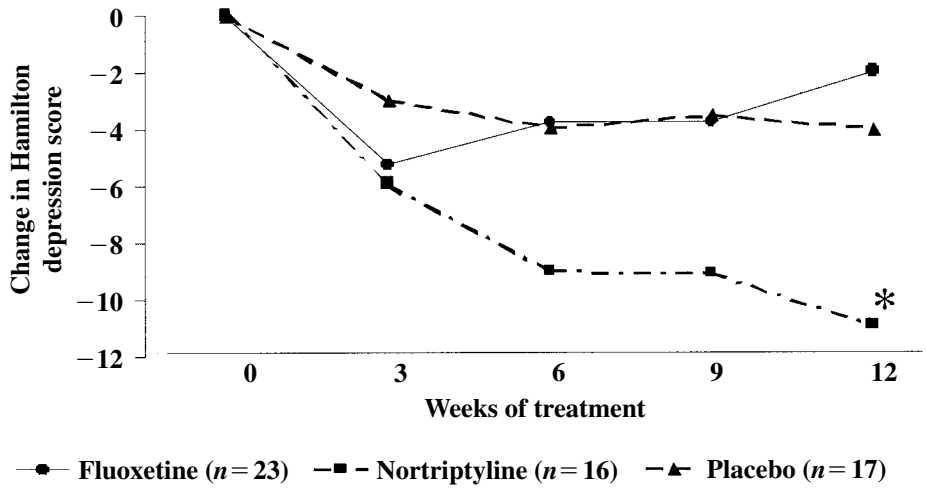

Fig. 82.1. Comparison of Hamilton Depression Rating Scale scores over 12 weeks of double blind treatment with nortriptyline, fluoxetine or placebo. Nortriptyline was superior to placebo or fluoxetine treatment. Fluoxetine was not significantly different from placebo in this population. Hamilton scores were significantly lower in the nortriptyline treated patients comparerd with the fluoxetine or placebo patients at 12 weeks of treatment (reprinted from Robinson et al., 2000 with permission).

There were no cardiovascular side effects attributable to treatment with nortriptyline, although patients with a recent myocardial infarction or cardiac conduction abnormalities were excluded from the study.

We have also studied the effect of antidepressants on the cognitive impairment associated with PSD. Patients whose depression remitted (predominantly associated with nortriptyline treatment) had significantly greater recovery in cognitive function than patients whose mood disorder did not remit (predominantly associated with placebo treatment) (Fig. 82.2) (Kimura et al., 2000). Thus, successful treatment of depression may constitute one of the major strategies of promoting cognitive recovery in victims of strokes.

Although other treatment modalities such as stimulant medication and electroconvulsive therapy have been used for PSD, they have not been evaluated in controlled studies, therefore most clinicians agree that antidepressant drugs constitute the first choice for the treatment of PSD. Since depressive symptoms have a negative influence on functional recovery, medication should be administered as soon as these symptoms are recognized in order to diminish the risk of long-term impairment.

Poststroke anxiety disorder

Epidemiology

A significant comorbidity exists between poststroke anxiety and PSD. In a study of 98 acute stroke patients, we (Starkstein et al. 1990) found that, while only 6 patients met modified DSM-III criteria for GAD (i.e. excluding the 6-month duration criteria) in the absence of any mood disorder, 23 of 47 patients with major depressioin also met criteria for GAD.

In another study (Castillo et al., 1995), we reported that 78 (27%) patients of a population of 288 stroke patients met the modified DSM-III criteria for GAD (i.e. excluding the 6-month duration criteria). Major or minor depression was also present in most of them (i.e. 58 of 78 GAD patients).

Similar results were reported by Aström (1996) in a 3-year longitudinal study of 80 patients with acute stroke. In this study, the prevalence of GAD in the acute stage was 28% with no significant decrease through the 3 years of follow-up. Criteria for major depression were met by 85% of those poststroke GAD patients at some time during the 3-year follow-up period.

Diagnosis

The DSM-IV categorizes poststroke generalized anxiety disorder (GAD) as 'anxiety disorder due to stroke with generalized anxiety'. The criteria for primary GAD requires the presence of sustained worrying state associated with at least three anxiety symptoms including restlessness, decreased energy, difficulties in concentration, irritability, muscle tension and sleep disturbance, for a period of at least 6 months. In order to study patients in the acute poststroke stage, most studies of poststroke GAD have not required the 6-month duration.

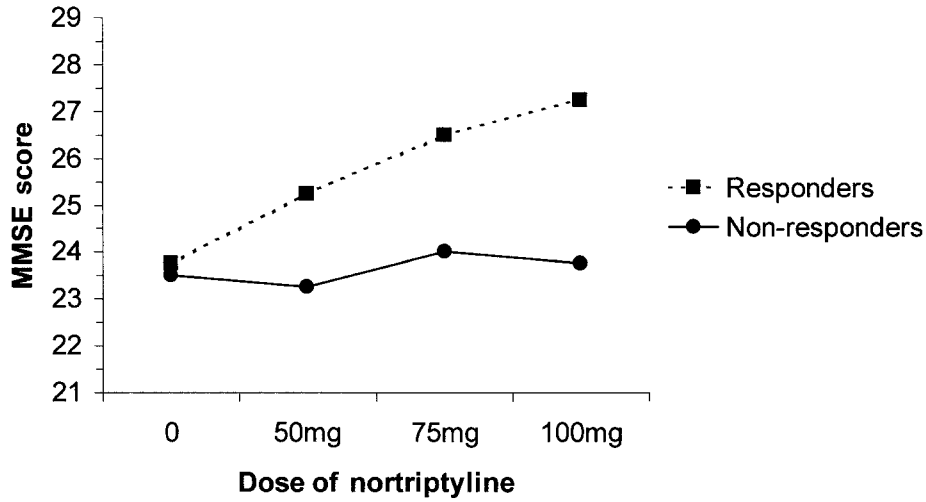

Fig. 82.2. Cognitive function as measured by the Mini-Mental State Exam (MMSE) at varying doses of nortriptyline. Patients who were treated with 75 or 100 mg of nortriptyline and responded to treatment had significantly higher (less impaired) MMSE scores than patients who were given nortriptyline or placebo and failed to respond to treatment. These findings indicate that successful treatment of poststroke major depression leads to significantly better recovery of cognitive function compared to patients who do not respond. (Reprinted from Kimura et al., 2000 with permission.)

Using our overall population of stroke patients, we examined the frequency of symptoms of GAD among patients who acknowledged the symptoms of anxiety or worry. With the exception of decreased energy, all the individual symptoms of GAD were significantly more frequent among patients with anxiety (Robinson, 1998). Thus, since anxiety symptoms are not associated with the stroke itself, poststroke generalized anxiety disorder can be diagnosed using DSM-IV symptom criteria.

Anatomical correlates

Our original population of 98 stroke patients were divided into those with anxiety only, those with anxiety plus depression, those with depression only, and those with no mood disorder (Starkstein et al., 1990). The examination of the CT scans of these patients showed that anxious–depressed patients had a significantly higher frequency of cortical lesions than did either the depression-only group or the control group (Fig. 82.3). Moreover, the depression-only group showed a significantly higher frequency of subcortical lesions than did the anxious–depressed group.

We subsequently reported in our overall group of 288 patients, that depression plus anxiety was associated with left cortical lesions, whereas anxiety alone was associated with right-hemisphere lesions (Castillo et al., 1995).

In the 3-year longitudinal study of stroke patients by Aström (1996), similar findings were reported. In the acute poststroke period, pure GAD was significantly associated with right hemispheric lesions, whereas comorbid anxiety/depression was significantly associated with left-hemipsheric lesions. Another important finding of this study was that, at 3 years after stroke, GAD was significantly associated with both cortical and subcortical atrophy. Aström suggested that this atrophy might play a role in the prolonged maintenance of GAD after stroke.

Risk factors and effect on recovery

Longitudinal studies of poststroke GAD have shown that functional recovery of patients with stroke was negatively affected by the presence of GAD. For example, in her 3-year longitudinal study, Aström (1996) found that ADL impairment was associated with GAD not only in the acute period but at all time periods after discharge from the hospital. Thus, anxiety was more than an immediate reaction to loss of function. In another study of 142 patients, we found that patients with GAD ($n=18$) and depression had significantly greater impairment in ADL at a 2-year follow-up than patients with PSD alone ($n=9$) (Shimoda & Robinson, 1998). We suggested that one possible explanation was that, as the comorbidity of PSD and GAD produced a longer duration of depression than PSD alone, this prolonged depression might lead to more profound adverse physical and social functioning outcomes.

Treatment

Benzodiazepines are the most commonly prescribed medications for the treatment of GAD but tend to accumulate

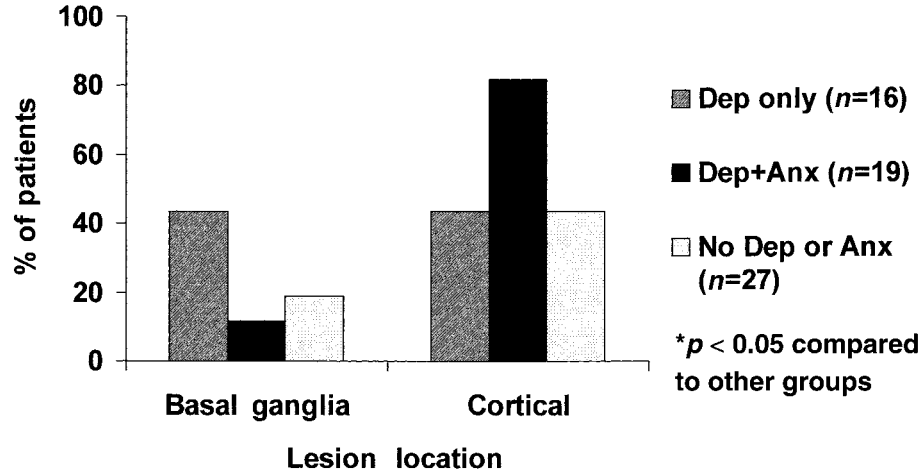

Fig. 82.3. Comparison of the frequency of basal ganglia and cortical lesions among patients with major depression only (Dep only), major depression plus generalized anxiety disorder (Dep + Anx), and no mood or anxiety disorder (No Dep or Anx). Major depression alone was associated with basal ganglia lesions while major depression plus generalized anxiety disorder was associated with cortical lesions. (Reprinted from Robinson, 1998 with permission.)

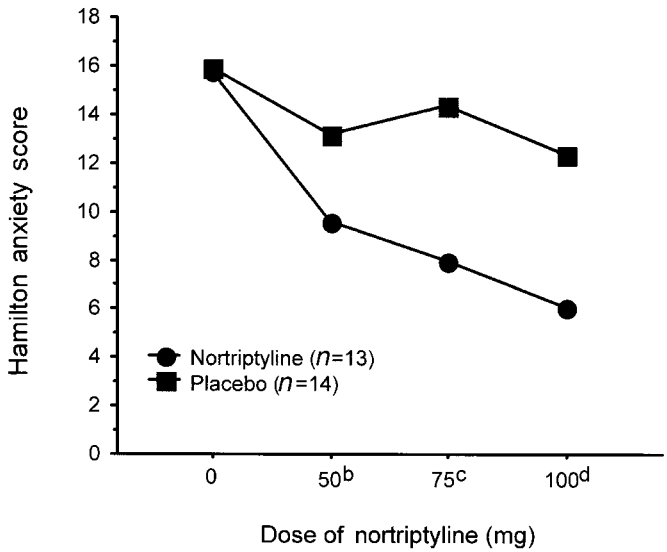

Fig. 82.4. Results of a double-blind study of poststroke anxiety disorder showing Hamilton anxiety score and corresponding dose of nortriptyline. At doses of 50 (*b*) ($P<0.05$), 75 (*c*) ($P=0.01$) and 100 (*d*) ($P=0.02$) mg, the patients who met criteria for both generalized anxiety disorder and post-stroke major or minor depression had significantly lower Ham-A scores than patients given placebo. (Reprinted from Kimura et al., 2000.)

in older people. Given the fact that stroke patients constitute an older population, benzodiazepines should be used as a time-limited treatment. Buspirone, an anxiolytic medication with partial serotonin agonist properties, has been reported (Rickels & Schweizer, 1987) to have a similar efficacy of diazepam in the treatment of GAD but with a more tolerable side effects profile. The utility of buspirone in this population has not been examined.

We have examined the efficacy of nortriptyline treatment for patients with comorbid GAD and depression after stroke (M. Kimura & R.G. Robinson, unpublished data). Patients receiving nortriptyline treatment ($n=13$) showed significantly greater improvement on their Hamilton anxiety symptoms than patients receiving placebo ($n=14$), demonstrating that poststroke GAD can be effectively treated with nortriptyline (Fig 82.4). In addition, the Hamilton anxiety score declined significantly more than the Hamilton depression score during the first 2 weeks of treatment, suggesting that the response of anxiety symptoms is both independent of depression and more rapid than the response of depressive symptoms in poststroke patients.

Other poststroke neuropsychiatric disorders

Apathy

Marin defined apathy as the absence or lack of feeling, emotion, interest, concern and motivation. He has pro-

posed diagnostic criteria for apathy based on the overt behavioural, cognitive and emotional concomitants of goal directed behaviour (Marin, 1991).

Few studies have examined the prevalence of apathy in stroke patients. Starkstein et al. (1993a) found apathy in 18 out of 80 patients (22%) with acute stroke lesions. In nine of these patients apathy coexisted with a depressive syndrome. Among depressed patients, apathy was significantly more frequent in those with major depression compared with those that have minor depression. This suggests that while depression and apathy can occur independently, apathy is significantly associated with major but not minor depression.

Marin et al., studied the prevalence of apathy among patients with chronic stroke lesions. Apathy was diagnosed in 7 out of 40 stroke patients (17.5%). There was no significant comorbidity with depression, suggesting that apathy and depression may be related early after stroke but not in the chronic stage (Marin et al., 1993).

In our experience, apathetic patients tend to be older and have a greater physical and cognitive impairment than stroke patients without apathy. In addition, Okada and associates found that most of their patients with mild dementia were also apathetic (Okada et al., 1997).

Several studies have examined the association between apathy and lesions in specific brain regions. Bogousslavsky et al. (1986) reported apathy in patients with bilateral lesions to ventrolateral and dorosmedial thalamic nucleus. Andersson et al found a higher frequency of apathy in patients with either subcortical or right hemisphere lesions compared with patients with left hemisphere damage (Andersson et al., 1999). Other studies have found a higher frequency of apathy in patients with lesions involving the posterior limb of the internal capsule and adjacent globus pallidus (Helgason et al., 1988). Cummings proposed that apathy in poststroke patients may result from dysfunction of cortico-subcortical circuits involving the prefrontal cortex, basal ganglia and thalamus (Cummings, 1993). To our knowledge, there have not been any controlled treatment studies of poststroke apathy.

Marin et al. (1995) suggested the use of dopamine agonists for patients with basal ganglia and frontal lobe lesions, whereas patients with multiple infarcts or with comorbid depression may obtain benefits from stimulant drugs or antidepressants with a more stimulant profile like bupropion.

Catastrophic reaction

In 1939, Goldstein first used the term 'catastrophic reaction' to describe a series of symptoms (i.e. anxiety, aggressiveness, refusal and renouncement) that may occur in patients with brain injury and appear to be due to the 'inability of the organism to cope with physical or cognitive deficits'.

Starkstein et al. (1993b) developed a scale (i.e. the Catastrophic Reaction Scale) for the assessment of the existence and severity of catastrophic reactions. Using this scale, we reported that a catastrophic reaction was present in 19% ($n=12$) of a consecutive series of 62 patients with acute stroke. Moreover, since catastrophic reactions were significantly associated with both major depression and basal ganglia lesions, we suggested that this phenomenon might represent the release of depressive emotions provoked by anterior subcortical damage.

The preferred treatment for the catastrophic reaction is prophylactic (Benson, 1979). Since this condition appears frequently in patients with non-fluent aphasia, speech therapists and physical therapists should be careful to not stress patients who are known to display catastrophic reactions.

Pathological affect

Pathological affect is characterized by frequent and easily provoked episodes of crying and/or laughing that are not appropriate to the situation or are in excess of the underlying emotion. Several studies (Andersen, 1995; Morris et al., 1993) have reported that approximately 15% of acute stroke patients manifest this condition. We (Robinson et al., 1993) demonstrated the reliability and validity of the Pathological Crying and Laughing Scale (PLACS) for the assessment of emotional lability in 54 patients with acute stroke. Furthermore, in a double-blind drug trial of nortriptyline versus placebo, patients receiving nortriptyline ($n=14$) showed a significantly greater decrease in PLACS scores (i.e. less pathological affective symptoms) at 4 to 6 weeks of treatment compared to patients receiving placebo ($n=14$) (Fig. 82.5). In another double-blind drug trial using a crossover design, Andersen et al. (1993) reported that all 13 patients treated with the selective serotonin reuptake inhibitor (SSRI) citalopram responded to treatment as measured by a reduction in the number of crying episodes by at least 50% as compared to two placebo responders. Although significant improvement in Hamilton depression scores were also seen in our treatment study, analysis of the data to exclude the effect of depression demonstrated that nortriptyline was an effective treatment for pathological emotions.

Poststroke psychosis

Delusions or hallucinations are rare complications of stroke. Rabins et al. (1991) screened all individuals ≥ 60

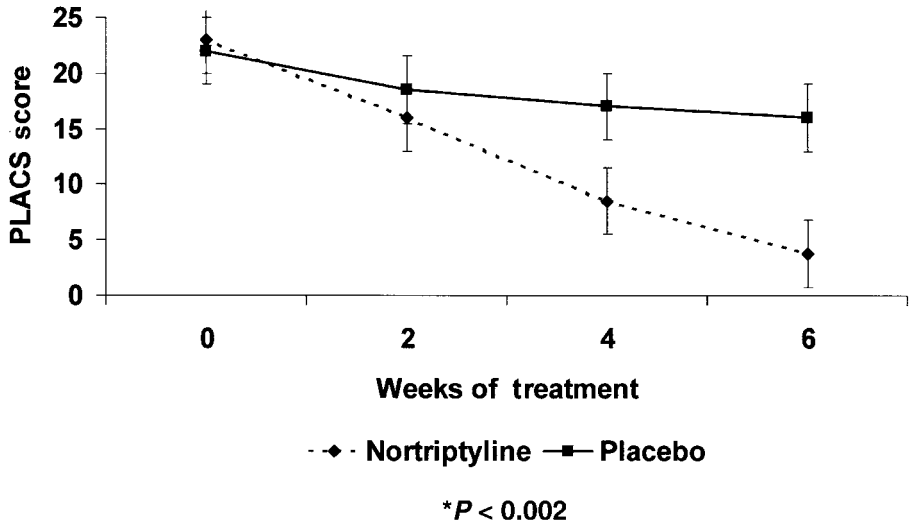

Fig. 82.5. Comparison of pathological laughter and crying scale (PLACS) scores over 6 weeks of double-blind treatment with nortriptyline or placebo. Nortriptyline produced significantly lower PLACS scores than placebo at both 4 and 6 weeks of treatment. (Reprinted from Robinson et al., 1993 with permission.)

years who were admitted to a hospital during a 9-year period and identified five patients with poststroke psychosis. All of them had right frontoparietal lesions and showed a significantly greater degree of subcortical atrophy compared to five stroke patients matched for age, gender and lesion size and location but without psychosis. Moreover, three of the five patients with poststroke psychosis had seizures while no seizures were seen in any of the five nonpsychotic patients.

Generally, patients respond to treatment with neuroleptic medications, although some treatment-resistant cases have been reported (Levin & Finkelstein, 1982). In treatment-resistant cases, anticonvulsant medications have been reported to be useful (Levin & Finkelstein, 1982).

In conclusion, there are numerous neuropsychiatric disorders which may occur following stroke (Table 82.1). The limited space for this review has restricted us to examining only a few of these disorders. Depression and anxiety disorder are two of the most common poststroke neuropsychiatric disorders and they frequently occur as comorbid conditions. In addition to producing a significant degree of psychological distress, both of these disorders have been shown to be associated with particular lesion locations and to adversely affect the physical recovery from stroke.

Similarly, apathy, catastrophic reactions, pathological effect and poststroke psychosis are disorders which may occur following stroke and probably influence the course of recovery as well as quality of life following stroke. Given the frequent occurrence of these disorders and the magnitude of the public health problem produced by stroke, it is remarkable how few treatment studies have been conducted. Apart from the early treatment interventions to prevent new vascular events, treatment of the neuropsychiatric disorders following stroke appears to have the greatest potential to improve the outcome and quality of life for people who have suffered a stroke.

Acknowledgements

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83

Intracerebral hemorrhage

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Approximately 500 000 new strokes occur yearly in the US. Fifteen per cent of these patients are diagnosed with intracerebral hemorrhage (ICH). Despite development of specialized stroke and neurological intensive care units, overall mortality of ICH patients remains high and patients who survive are often left with profound disabilities. However, new treatment avenues seem to be evolving for this disorder.

In addition to its use as thrombolytic therapy for myocardial infarction, the last 3 years have witnessed a more widespread use of rTPA for the treatment of acute ischemic stroke. Since blood pressure was controlled after rTPA or placebo administration during the NINDS Stroke with an improved rate of hemorrhagic complications in relation to other thrombolytic trials, it seems that uncontrolled hypertension may increase the risk of hemorrhagic transformation or hematoma formation in ischemic brain tissue after thrombolysis. For this reason, the American Heart Association and American Academy of Neurology have provided guidelines for blood pressure control when thrombolytic therapy is used in ischemic stroke victims (Guidelines for thrombolytic therapy, 1996). In this chapter, we will review the epidemiology, physiopathology, pertinent clinical features, complications and the available therapies for non-traumatic, supratentorial ICH as well as current and future avenues of research in this field.

Epidemiology

Spontaneous intracerebral hemorrhage comprises approximately 13% of all stroke types (Broderick et al., 1993). Although significant geographical variability in the incidence of ICH exists, Asian countries have a two- to threefold higher incidence of ICH. Whether the reason for this striking difference in incidence rate resides only in genetic factors is unclear, but environmental factors certainly play an important role. In the United States, ICH affects 37 000 persons annually and it has a 30-day mortality rate of 35 to 52%. Only 20% of ICH patients have some degree of functional independence at 6 months (Counsell et al., 1995). Some of the clearly defined risk factors include presence of systemic hypertension, alcohol consumption, hypercholesterolemia, use of anticoagulants, and recreational drug abuse. In the elderly, cerebral amyloid angiopathy (CAA) becomes a prevalent cause of ICH.

Since the 1950s, a consistent fall in mortality due to ICH has been documented worldwide (Broderick et al., 1993). Although better control of risk factors is partly responsible for this phenomenon, widespread advent of CT technology has also helped in the detection of smaller, non-lethal hematomas, thus reducing the apparent fatality rate of the disease. Nevertheless, ICH remains an important cause of morbidity and mortality among stroke victims.

Clinical features

The presence of intraparenchymal hematomas produces different neurologic syndromes in relation to their specific location. These syndromes have, however, high variability due to (i) secondary enlargement of the hematoma and (ii) development of surrounding white matter edema. Furthermore, when the mass effect associated with the hematoma, edema, or both, becomes significant enough to overcome intracranial compliance adaptability, the development of herniation syndromes may further complicate the clinical presentation of an individual patient. The presence of supratentorial ICH can lead to the development of one of the following syndromes according to their location and/or extension.

Putaminal hemorrhage

Several syndromes derive from putaminal hemorrhages (Hier et al., 1997). They can be defined based on their size, ventricular extension and patterns of extension from the putamen. The classic, large putaminal hemorrhage produces the syndrome of dense hemiparesis, hemisensory loss, homonymous hemianopsia, and aphasia or hemiinattention when present in the dominant or non-dominant hemisphere, respectively. These deficits, although abrupt in onset, tend to gradually worsen within the first hours after the stroke. Conjugate eye deviation towards the injured hemisphere can be seen when the frontal eye fields or their output are involved. Presence of intraventricular extension, once associated with poor functional and survival prognosis, is currently believed to be a surrogate marker of large putaminal hematomas.

Caudate hemorrhage

This form of hemorrhage represents 5 to 7% of cases of ICH and its clinical presentation is relatively constant (Stein et al., 1984). Headache of sudden onset followed by vomiting have been described. Nuchal rigidity and behavioural changes such as disorientation, confusion and short-term memory loss are common in patients with this type of hemorrhage. Sometimes horizontal and vertical conjugate gaze abnormalities are found. Intraventricular extension of the hemorrhage is an almost uniform occurrence. Acute obstructive hydrocephalus and meningismus are the result of obstruction of CSF circulation and chemical meningitis respectively. The outcome after caudate hemorrhage is favourable in the vast majority of cases, with only a small percentage of patients requiring external ventricular drainage.

Thalamic hemorrhage

This form of hemorrhage represents 10 to 15% of all cases of ICH. The onset of symptoms is usually abrupt as opposed to putaminal hemorrhages (Walshe et al., 1977). Headache is not a prominent symptom. Hemiparesis and hemisensory loss are uniformly found due to compression or extension of the hemorrhage into the internal capsule. A conspicuous finding on the physical exam is the presence of upward gaze palsy with miotic, unreactive pupils. This is likely the result of extension of the hemorrhage or edema in the mesencephalic tectum. The syndrome of 'wrong-way' eye deviation is sometimes observed after thalamic hematomas. The mechanism of this conjugate gaze deviation contralateral to the lesion remains obscure. Brainstem damage due to extension of the hematoma has been suggested. Nevertheless, oculocephalic and caloric testing can overcome this gaze abnormality, as in supratentorial horizontal gaze abnormalities. The lateral expansion of the hematoma or edema can produce aphasia or hemiinattention when this occurs in the dominant or non-dominant hemisphere, respectively.

Lobar hemorrhage

Lobar hemorrhages are more prevalent in temporal, parietal and occipital locations. This form of ICH does not commonly involve the frontal lobes. Systematic hypertension explains 35% of the lobar hemorrhages. Therefore, AVMs, tumours and CAA should be actively investigated in these patients as cause of the ICH. Headaches and seizures are common after lobar hematomas. The level of consciousness is usually not significantly impaired, likely because of the remote location of the intraparenchymal hematomas in relation to midline structures. The specific neurological deficits are dictated by the location and size of the hemorrhage.

Cerebellar hemorrhage

Most often seen in hypertensive patients, this form of hemorrhage constitutes a potential life-threatening emergency. The evolution of symptoms in these patients follows the described sequence outlined by Heros for posterior fossa mass lesions such as ischemic and hemorrhagic stroke (Heros, 1982). In early stages symptoms such as dizziness, vertigo, vomiting, unsteadiness, are related mainly to destruction of cerebellar tissue and its connections. During the intermediate stages, reduced level of consciousness can develop as a manifestation of obstructive hydrocephalus (due to either compression of the fourth ventricle or associated intraventricular hemorrhage). In later stages, direct compression of the brainstem by the expanding mass can induce coma and cardiorespiratory instability, as a manifestation of lower brainstem injury. Patients with cerebellar hemorrhages larger than 3 cm^3 and with evidence of neurological deterioration are deemed surgical candidates for hematoma evacuation (Broderick et al., 1999). Open suboccipital craniotomy with either paramedian or midline approach with clot evacuation is the standard procedure performed. The use of external ventricular drainage (EVD) can alleviate symptoms derived from hydrocephalus. However, the use of EVD only, in the presence of posterior fossa mass effect, is felt by many to increase the risk of upward cerebellar herniation and therefore to add further neurological damage.

Mechanisms of neurological damage

It seems widely accepted that the initial neurologic deficit after ICH is the product of tissue disruption by the sudden mass of blood, which can be associated with abrupt ICP elevation in cases of large hematomas. As mentioned previously, the presenting neurological syndrome depends fundamentally on the discrete location of the hematoma. However, the subsequent neurological deterioration will depend on a variety of factors, particularly ongoing bleeding and vasogenic edema formation. When combined, these two components can inflict significant mass effect and tissue distortion that, according to the location of the hematoma, could trigger herniation syndromes followed by death or subsequent permanent neurological damage. If the presence of mass effect is not significant or is well tolerated by the cranial vault, another threat, subsequent neuronal 'toxicity' or 'damage', has the potential to modify long-term neurological outcome due to its effects, not only on perihematoma regions, but also remote to it. Thus, the effects of the blood clot on remaining viable brain tissue can be divided into mechanical and biochemical.

Mechanical effects

The immediate effects of the hematoma on neurological function are directly related to the size of the blood clot and its location. If large enough, elevated ICP can induce global reduction in cerebral perfusion pressure and a superimposed global ischemic encephalopathy. Furthermore, several studies have demonstrated ongoing bleeding in ICH patients during the first hours after hemorrhage. Brott and coworkers showed that up to 38% of ICH patients develop enlargement of the hematoma within the first 20 hours of the ictus, and that this enlargement is associated with clinical deterioration (Brott et al., 1997). After reviewing their experience with 627 patients, Fujii and coworkers have shown that admission shortly after the onset of the stroke, heavy alcohol drinkers, irregularly shaped hematoma, decreased level of consciousness, and low levels of fibrinogen, were associated with hematoma enlargement (Fujii et al., 1994).

It is becoming more apparent that early blood pressure reduction does not induce a superimposed ischemic insult in perihematoma regions, since the presence of such a region of ischemic 'penumbra' has not been consistently demonstrated. Closer neurological and hemodynamic monitoring of these higher risk patients may therefore be warranted and blood pressure may perhaps be safely controlled during the early hours after the ictus.

A subject receiving renewed attention is the generation of cerebral edema after ICH. Although recognized for many years as a factor with potential to influence neurological deterioration, our knowledge of its pathophysiology and natural history remains incomplete. There is animal as well as human pathologic data confirming the presence of an intense inflammatory component characterized by the early presence of inflammatory cells surrounding the blood clot during the early hours after the ictus. This is paralleled by the disruption of the blood brain barrier in surrounding capillaries that allows the passage of coagulation proteins to the interstitium furthering the development of white matter edema. The presence of vasogenic edema superimposed on the hematoma mass can produce not only acute neurological deterioration but also delayed worsening as recently demonstrated (Zazulia et al., 1999). Development of perihematoma vasogenic edema is therefore a target at which current basic and clinical research is directed to reduce the risk of neurological worsening after ICH. Although there is no specific therapy directed towards preventing hematoma-induced edema formation, animal research seems to suggest (Xi et al., 1998; Altumbabic et al., 1998) that rapid evacuation of blood products either by surgical removal or infusion of a thrombolytic agent into the clot may prevent the development of this form of edema by reducing the exposure of brain tissue to thrombin and hemoglobin degradation products.

Biochemical effects

Recent interest has centred on secondary neuronal injury after ICH. Early animal models of ICH using inflatable balloons and collagenase injections showed evidence of an ischemic penumbra surrounding the hematoma. However, the more recent available evidence does not support the concept of neuronal ischemia as a predominant mechanism of secondary neuronal injury in this patient population. SPECT, PET, and MRI studies in ICH patients have failed to show cerebral ischemia in surrounding brain tissue (Carhuapoma et al., 2000; Diringer et al., 1998; Mayer et al., 1998; Qureshi et al., 1999). Evidence of decreased cerebral blood flow or blood volume cannot be interpreted as an indicator of ischemia in the absence of an associated reduction of cerebral metabolism (oxygen tissue extraction fraction in PET studies, or reduced diffusion coefficient for water on diffusion-weighted MRI). This is particularly true because non-ischemic forms of neuronal injury can also induce a coupled decrement in regional blood flow (Mayer et al., 1998; Miyasaka et al., 1998).

Lee and coworkers demonstrated that thrombin plays a central role in the development of vasogenic edema, and neuronal toxicity (Lee et al., 1996b) using a rodent ICH model (Lee et al., 1995, 1996b, 1997; Nishino et al., 1994;

Suidan et al., 1992; Vaughan et al., 1995; Zurn et al., 1998). These effects of thrombin appear attenuated after the simultaneous administration of specific thrombin inhibitors. Furthermore, as in other forms of brain injury such as ischemia, controlled pretreatment with thrombin can induce future tolerance to brain edema formation.

The effects of blood and specifically thrombin may not be limited to the induction of vasogenic edema. Since the 1990s, data has been collected that involves thrombin as a direct neurotoxin in several animal models of neuronal injury. In brief, animal studies revealed that injections of thrombin into brain tissue produces inflammatory cell infiltration, proliferation of mesenchymal cells, angiogenesis induction, reactive astrocytosis and spongiosis (Nishino et al., 1993).

Complications

Intraventricular hemorrhage

Extravasation of blood in the ventricular system from a dissecting intraparenchymal hematoma complicates 40% of spontaneous, hypertensive ICH (Naff & Tuhrim, 1997), and independently increases the morbidity and mortality associated with ICH (Tuhrim et al., 1998). Obstructive hydrocephalus resulting from blood in the ventricles is thought to induce an ischemic encephalopathy, however a recent report suggests that use of intraventricular catheters (IVC) to drain CSF has not modified the natural history of this condition (Adams & Diringer, 1998). Intraventricular administration of thrombolytic agents, specifically urokinase (UK) is being studied in some centres as an alternative to CSF drainage alone (Coplin et al., 1997; Findlay et al., 1991, 1993; Findlay & Wong, 1997; Mayfrank et al., 1997; Rohde et al., 1995; Todo et al., 1991). Based initially in animal models, and currently on clinical studies, evidence collected so far seems to suggest that use of intraventricular UK and rTPA may accelerate clot lysis (Findlay et al., 1991, 1993; Rohde et al., 1995; Todo et al., 1991; Pang et al., 1986a,b,c). More rapid clot lysis may reduce the risk of complications associated with prolonged CSF drainage (Kanter et al., 1985; Mayhall et al., 1984). Although the use of intraventricular thrombolytic drugs seems safe, careful monitoring is required since secondary hemorrhages have been reported (Schwartz et al., 1998b).

Vasogenic edema formation

The development of brain edema contributes significantly to subacute neurological deterioration after ICH. There is convincing evidence that thrombin plays an important role in the development of blood–brain barrier disruption and water accumulation in the interstitial space. More recently, Mun-Bryce and Rosenberg have provided evidence that serum metalloproteinases play a central role in the development of this form of edema (Mun-Bryce & Rosenberg, 1998; Rosenberg & Navratil, 1998). Once fully developed, edema volume sometimes exceeds hematoma volume itself, behaving as an additional mass lesion. There is no specific therapy directed to prevent hematoma-induced edema formation. However, animal research seems to suggest (Xi et al., 1998; Altumbabic et al., 1998) that rapid evacuation of blood products either by surgical removal or infusion of a thrombolytic agent into the clot may prevent the development of this form of edema by reducing exposure of brain tissue to thrombin and hemoglobin.

Diagnosis

The combination of appropriate epidemiologic background (e.g. hypertension, coagulopathy, etc.) and the form of onset and progression of the neurologic deficits (progressive rather than fluctuating or resolving) in combination with computerized tomographic (CT) imaging of the brain are required to make the diagnosis of ICH in the acute setting. Computerized tomography provides information about the location of the hemorrhage, its causal relationship to the patient's signs and symptoms and its relation to midline structures as well as the potential to progress towards brain herniation. The presence and extent of surrounding edema predominantly in white matter can also be identified on brain CT as a hypodense halo surrounding the hematoma. It has been observed that hematomas related to thrombolytic therapy for myocardial infarction or ischemic stroke have a conspicuous lack of surrounding edema, develop fluid levels in the core of the clot and tend to be multifocal (Gebel et al., 1998; The NINDS t-PA Stroke Study Group, 1997).

Acute MRI has shown to be very sensitive for the diagnosis of acute ICH based on paramagnetic properties of blood and its products. However, brain CT remains the gold standard for the diagnosis of ICH in the emergency room where patients with acute onset of neurologic deficits are first identified.

The diagnosis of underlying causes of ICH such as vascular malformations or tumours should include brain MRI with gadolinium. Follow-up studies after resolution of the blood and edema allow a better visualization of brain tissue and tissue abnormalities such as AVM malforma-

tions. Similarly, for stable young patients (<45 years) without risk factors for ICH, cerebral angiography should be considered to investigate the presence and define the anatomy and location of vascular malformations (AVMs, cerebral aneurysms, dural fistulas). New, non-invasive diagnostic modalities such as 3D magnetic resonance angiography and CT angiography are being currently tested to help in the non-invasive diagnosis of these patients. When the diagnosis of cerebral amyloid angiopathy (CAA) is entertained, gradient echo MRI can assess the presence of prior lobar petechial hemorrhages, which together with APOE $\varepsilon 2$ and $\varepsilon 4$ genotype testing can add further information towards the diagnosis of probable CAA in normotensive patients 60 years or older without other apparent cause for ICH (Greenberg et al., 1999).

Treatment

There is no disease-specific therapy for ICH to date. Several studies before and after the introduction of CT have been conducted in attempts to determine the best surgical indications for hematoma evacuation, and if one form of therapy is superior to another. However, no consensus has been reached thus far.

Medical

Medical therapy offered to this patient cohort is provided in a monitored setting when uncontrolled hypertension may increase the risk of recurrent bleeding or when vasogenic edema is present early. Although the acute control of blood pressure may contribute to a decreased risk of hemorrhage after administration of rTPA for acute ischemic stroke, as suggested by the rTPA NINDS Stroke Study Group, its contribution in primary, spontaneous ICH enlargement seems more controversial. Given the absence of consistent evidence of an ischemic penumbra, and the positive epidemologic evidence that poor blood pressure control is a risk factor for hematoma enlargement, it seems reasonable to recommend judicious early lowering of blood pressure (Tietjen et al., 1996). The use of beta-blocker agents (e.g. i.v. labetalol, esmolol) is recommended by the American Heart Association Guidelines for the treatment of ICH patients (Broderick et al., 1999) leaving direct vasodilator agents (e.g. i.v. nitroglycerine and sodium nitroprusside) as alternative drugs due to their potential to increase cerebral blood volume and intracranial pressure (Table 83.1). Hypotension of any cause, on the other hand, can produce reflex cerebral vasodilation, elevated CBV and further ICP elevations. Therefore, when it occurs, it should initially be treated aggressively with i.v. fluid administration and with vasoactive agents if required, with cerebral perfusion pressure (CPP) endpoint of 70 mmHg.

Table 83.1. Elevated blood pressure: recommended agents

Labetalol	5–100 mg/h by intermittent bolus doses of 10–40 mg or continuous drip (2–8 mg/min)
Esmolol	500 mg/kg as a load; maintenance use, 50–200 μg/kg min^{-1}
Nitroprusside	0.5–10μg/kg min^{-1}
Hydralazine	10–20 mg Q 4–6 h
Enalapril	0.625–1.2 mg Q 6 h as needed

Because psychomotor agitation, pain and incoordination with the ventilator (when airway artificial protection or ventilation are required) can increase ICP secondary to reduced venous return, sedation is often central to the care of ICH patients. Although concerns regarding clouding clinical neurological monitoring are valid, adequate choice of sedative agent as well as depth of sedation are crucial. Nevertheless, occasionally, ICP monitoring becomes necessary to tailor medical and/or surgical therapies.

The management of brain edema and elevated ICP in ICH patients can be approached using hyperventilation and mannitol in the acute stage. Mannitol, as well as other osmotic agents such as hypertonic saline solutions achieve serum osmolarity capable of promoting shift of free water from the interstitial to the intravascular space. Hypertonic saline, which has received recent attention as alternative therapy for brain edema in several clinical scenarios, should be administered with caution in this setting however, as a form of malignant cerebral edema can be associated with its use in ICH patients (Qureshi et al., 1998).

Surgical hematoma evacuation

Hankey and Hon in a recent meta-analysis did not find either medical or surgical therapies to be superior in the treatment of ICH (Hankey & Hon, 1997). However, the differences in diagnostic modalities available at the time when these studies were conducted, differences in level of medical care provided to these patients, and perhaps more important, differences in the level of involvement of the surgical team in the care of these patients limits this meta-analysis of treatment modalities for ICH. In an attempt to minimize this type of bias, the surgical evacuation of the

hematoma, as any other therapy modality available for a medical condition, should and currently is being investigated following the scientific method routinely applied in medical research to other forms of treatments. More recently, a single-centre randomized clinical trial comparing early surgical clot removal versus medical therapy in patients with ICH concluded that early surgery is feasible and that there seems to exist a modest improvement in early mortality (Zuccarello et al., 1999; Morgenstern et al., 1998). However, these results should be considered preliminary, as Hacke and coworkers have suggested that surgical therapy of ICH did not improve outcome at discharge in their cohort of patients (Schwartz et al., 1998a,b). In the US, the American Heart Association has developed concensus recommendations for the surgical treatment of ICH based on our limited current level of knowledge of the natural history of this disease and the effects of medical and surgical therapies on the outcome of these patients (Table 83.2).

Table 83.2. Recommendations for surgical treatment of ICH

Non-surgical candidates

1. Patients with small hemorrhages ($<10 cm^3$) or minimal neurological deficits (levels of evidence II through V, grade B recommendation).
2. Patients with a GCS Score <4 (levels of evidence II through V, grade B recommendation). However, patients with a GCS score <4 who have a cerebellar hemorrhage with brainstem compression may still be candidates for lifesaving surgery in certain clinical situations.

Surgical candidates

1. Patients with cerebellar hemorrhage >3 cm who are neurologically deteriorating or who have brainstem compression and hydrocephalus from ventricular obstruction should have surgical removal of the hemorrhage as soon as possible (levels of evidence III through V, grade C recommendation).
2. ICH associated with a structural lesion such as an aneurysm, arteriovenous malformation, or cavernous angioma may be removed if the patient has a chance for a good outcome and the structural vascular lesion is surgically accessible (levels of evidence III through V, grade C recommendation).
3. Young patients with a moderate or large lobar hemorrhage who are clinically deteriorating (levels of evidence II through V, grade B recommendation).

Best therapy unclear

1. All other patients.

Notes:

Level of evidence

- Level I: Data from randomized trials with low false-positive (α) and low false-negative (β) errors
- Level II: Data from randomized trials with high false-positive (α) or high false-negative (β) errors
- Level III: Data from non-randomized concurrent cohort studies
- Level IV: Data from non-randomized cohort studies using historical controls
- Level V: Data from anecdotal case series

Strength of recommendation

- Grade A: Supported by Level I evidence
- Grade B: Supported by Level II evidence
- Grade C: Supported by Levels III through V evidence

Use of thrombolytic agents

For a long time concepts such as blood and its degradation products inducing neuronal damage have been entertained as explanations of secondary neuronal damage. However, it is only recently that these concepts have been incorporated as the driving force behind attempts to remove blood from the subarachnoid space and brain parenchyma in intracranial hemorrhage patients. Hondo and coworkers reported their early experience with catheter evacuation of deep hematomas after lysis with a thrombolytic agent (Hondo, 1983). Using a stereotactically placed silicone catheter urokinase (UK) was administered and was followed by aspiration. Further UK was injected every 6 to 12 hours until the clot was totally removed. The hematoma, when treated in this manner, usually disappears 2 or 3 days postprocedure onset. More recently, Andrefsky and Montes independently reported on their experiences using UK in the treatment putaminal ICH patients and concluded that the administration of intraparenchymal thrombolytic agents is safe and able to significantly reduce hematoma size (Andrefsky et al., 1998; Montes et al., 2000).

When ICH extends into the ventricular system, several processes have potential to complicate the management and therefore outcome of these patients. Acute obstructive hydrocephalus, mechanical distention of midline and lateral ventricular structures, neurotoxic effects of blood on surrounding brain tissue and impairment of normal CSF resorption mechanisms impact upon neurologic function in the acute and subacute periods. Furthermore, standard treatment with external ventricular drainage has also the potential to damage viable brain tissue as well as become a source of CSF contamination and infection. The use of thrombolytic drugs administered directly into the ventricular system via intraventricular catheters has evolved from early animal models to more clinically sound evidence obtained from human data. Thus far, this form of therapy appears safe when appropriate patients are care-

fully screened and seems able to significantly reduce mortality after IVH.

If substantiated by larger and controlled prospective studies, these newly attempted therapies could improve upon the observed natural history of patients after ICH.

Prognosis

The role that the volume of blood has in outcome prediction after ICH has been clearly delineated in recent years. Tuhrim and coworkers, after developing an approach to estimate the chances of surviving after ICH, observed a direct correlation with the admission Glasgow Coma Score. ICH can occur in many cerebral locations and has many distinct sizes. However, despite well-known relationships between ICH locations and neurologic deficits, no clear relationship exists between ICH location and mortality. ICH volume does relate to mortality. There is an incremental, direct relationship of volume to mortality for ICH volumes greater than 30 cm^3, with an apparent threshold at 30 cm^3 at which level ICH mortality is a low frequency event (occurring at a rate of approximately 20%). Currently, all available data support the concept that mortality in small (<30 cm^3) ICH with IVH extension is in large part related to the extent or volume of IVH.

Current and future research areas in ICH

Treatment of ICH has remained mainly supportive throughout the years. It is only recently that basic and clinical research is being dedicated to the understanding of the natural history of secondary neuronal damage after human ICH. In particular, the following questions remain unanswered in this field:

What are the underlying mechanism(s) and natural history of ICH-induced brain edema?

Several lines of evidence are pointing towards inflammation and accompanying blood brain barrier disruption as the mechanism of perihematoma cerebral edema. Nevertheless, the actual trigger of the inflammatory cascade remains to be firmly identified. Thrombin and other blood components have been implicated; however, their precise role in this process is yet to be defined.

Although the rate of evolution of brain edema after ischemic stroke has been already delineated, its counterpart, brain edema after ICH, remains poorly defined. Clinical experience demonstrates that this type of edema progresses at a different rate and may reach sufficient magnitude to produce acute and subacute neurologic deterioration after ICH. If better understood, therapies aiming to arrest or decrease the intensity of brain edema may be able to be instituted at a time when the inflammatory cascade has not been irreversibly triggered.

What is the nature of the secondary neuronal injury induced by the contact of blood and brain tissue?

After years of basic and clinical research it has become apparent that cerebral ischemia in perihematoma regions does not add significantly to secondary neuronal damage after ICH. Inflammation and apoptosis may have a role in functional neurologic outcome in these patients due to their effects in perihematoma regions and perhaps in areas remote to the hematoma. Further knowledge will be required before rational criteria are used in the design of enrolment for future ICH clinical trials.

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Aneurysms and arteriovenous malformations

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Intracranial aneurysms and arteriovenous malformations (AVMs) are structural vascular lesions that are life threatening by virtue of their propensity to cause intracranial hemorrhage. The Greek word 'aneurysma' is derived from a combination of 'ana-' (up, through) and 'eurynein' (to widen) (Haubrich, 1984). Peripheral aneurysms were well recognized by Hippocratic times, when physicians were familiar with superficial traumatic vascular lesions (Weir, 1987). The first description of an intracranial aneurysm was probably by Biumi, in 1765 (Biumi, 1778) and the first clinical description differentiating subarachnoid hemorrhage (SAH) from other types of apoplexy was in 1813 (Blackall, 1825). Various surgical attempts were made to treat intracranial aneurysms in the late nineteenth and early twentieth centuries, including proximal ligation by Horsley and others and packing with muscle by Dott (1933), before the first definitive cure by clip application, which was performed by Dandy in 1937 (Dandy, 1938).

Cerebral arteriovenous malformations (AVMs) are some of the more challenging lesions to come under the ambit of neurological surgery. Regarding surgery for AVMs, Cushing considered any attempt at excision 'foolhardy' (Cushing & Bailey, 1928) and Northfield stated, 'The dangers of fatal hemorrhage and the extensive damage to brain forbid any attempt' (Northfield, 1940). It was not until the mid-twentieth century that these lesions were recognized as malformations rather than neoplasms. With the advent of arteriography and its widespread use by the 1940s and 1950s, an understanding of the configuration of feeding arteries and draining veins of AVMs emerged, along with more favourable surgical results (Bergstrand et al., 1936; Olivecrona & Riives, 1948; Pilcher, 1946).

Clinical presentation

Spontaneous disruption of the abnormal walls of AVMs and aneurysms results in intracranial hemorrhage with obvious catastrophic consequences. Most aneurysms and AVMs are not detected until such a rupture occurs. A minority of lesions will come to clinical attention because they cause mass effect on cranial nerves or the brain, obstruction of cerebrospinal fluid pathways, or epilepsy. Aneurysms occasionally present with ischemic deficits caused by thromboemboli originating from the aneurysm sac. Investigation of neurological symptoms with high resolution CT or MRI is leading to an increase in the incidental detection of vascular abnormalities.

The hallmark of intracranial hemorrhage of any cause is the instantaneous onset of headache of unparalleled severity. The clinical features of aneurysmal and AVM hemorrhage differ somewhat by virtue of the location and severity of the bleed. Aneurysms are located in the subarachnoid space and most hemorrhages are therefore subarachnoid or intraventricular. Occasionally the hemorrhage is purely intraparenchymal or subdural. Over 90% of aneurysms present with rupture and approximately 15% of these patients die before reaching hospital (Weir, 1987). Up to 80% of patients have at least a brief loss of consciousness (Rodman & Awad, 1993). Additional clinical features include meningism and vomiting. It is distinctly unusual for patients suffering a SAH, who remain conscious, to *not* vomit (Shaw, 1987). Cranial nerve dysfunction, particularly of the oculomotor, is caused by direct pressure of an aneurysm on the nerve during its subarachnoid course. The majority of aneurysmal ruptures do not cause significant intraparenchymal hemorrhage, so focal neurological deficits other than cranial neuropathies are uncommon. Rupture of a middle cerebral artery aneurysm is an exception; hematomas within the Sylvian fissure

often cause hemiparesis or dysphasia. Intraocular hemorrhage, thought to result from an acute elevation of intracranial pressure transmitted to ocular venous pressure, is more common with severe SAH and correlates with poor outcome (Weir, 1987). Arterial hypertension is a common finding, even in patients without a corresponding history. Electrocardiographic changes, notably ST segment depression, are also common and probably result from release of catecholamines and blood pressure disturbance (Rodman & Awad, 1993). Clinical SAH grading scales have been designed in an attempt to predict outcome (Table 84.1); the worst pre-treatment grade appears to be the best predictor of outcome (Chiang et al., 2000). SAH is frequently preceded by a 'warning' headache that is not caused by rupture (Rodman & Awad, 1993).

Haemorrhage is also the most common presentation of an AVM, occurring in approximately 50–60% of cases (Brock, 1999). Although associated with a mortality of 10–30%, AVM rupture is generally less severe than aneurysmal SAH (Brown, 1999). It is unusual for AVMs to present with pure SAH and clinical features identical to aneurysmal rupture. More commonly the hemorrhage remains intraparenchymal, so that meningism, vomiting, and cranial neuropathies are less common and focal neurological deficits are more likely. AVMs can present with epilepsy (20–40% of cases) (Brock, 1999) or as a mass lesion. The arteriovenous fistula in some lesions is sufficient to cause a low pressure shunt and steal of blood from the surrounding vascular bed, causing chronic ischemic deficits or intermittent focal deficits clinically similar to embolic transient ischemic attacks. Unusual presentations include a bruit, palpable enlarged scalp vessels and heart failure in children. It remains unclear whether migraine headaches are more frequent in patients with AVMs, but such headache is often relieved when the malformation is treated (Steinberg et al., 1990). Spinal vascular malformations present with hemorrhage or the effects of raised venous pressure, which causes a progressive deterioration in lower limb function (Henn et al., 1999).

Aneurysms

Classification

Cerebral aneurysms are classified by pathology (Fig. 84.1), size and location. S*accular* aneurysms are focal outpouchings of the vascular wall that usually occur at arterial branching points. Aneurysm walls do not have an internal elastic lamina, the media contains fibrohyaline tissue and little smooth muscle, and the adventitia is thinner than in normal arteries. There may be luminal thrombus, calcification, and fatty or atherosclerotic plaques (Weir, 1987). *Fusiform* aneurysms, usually a result of atherosclerosis and therefore occurring in older age groups, are dilated and elongated arterial segments. In contrast to saccular aneurysms, the dilatation is circumferential so there is no neck, or orifice, between the vessel and the aneurysm. The internal elastic lamina and media are deficient and atherosclerotic changes are usually prominent. Laminated luminal thrombus is common. Fusiform aneurysms also occur in young patients with diseases affecting the arterial wall such as Marfan's syndrome, homocysteinuria, pseudoxanthoma elasticum, syphilis, and giant cell arteritis (Weir, 1987). Dissecting aneurysms result from an intimal tear and separation of the mural layers by blood that forms a new false channel. The new channel can rupture back into the original lumen or through the adventitia to cause subarachnoid hemorrhage. The original lumen is narrowed irregularly and the angiographic appearances can be of a tapering stenosis (Fig. 84.2), narrow residual lumen (string sign), dilatations, or combinations of dilatations and narrowing (pearl and string sign). Etiological factors include trauma, atherosclerosis, fibromuscular dysplasia, and diseases affecting the arterial media. False aneurysms contain none of the normal layers of the arterial wall. The very fragile aneurysm 'wall' in these cases is composed of thrombus and surrounding connective tissue. Trauma is the usual cause and there is a high risk of rupture. Infectious aneurysms are usually bacterial and occasionally fungal (the term 'mycotic' should be applied only to the latter). Endocarditis is the usual source of emboli that may cause abscesses in addition to aneurysms. Infection of the arterial wall affects predominantly the intima and media, with necrosis of the wall and fusiform dilatation of the vessel. These aneurysms are very fragile and have a high rupture rate. Most of the following discussion relates to saccular aneurysms, which are the most common cause of non-traumatic subarachnoid hemorrhage.

Intracranial aneurysms are classified anatomically as those affecting the internal carotid artery and its branches ('anterior circulation') or those affecting the vertebral and basilar arteries and their branches ('posterior circulation'). Non-saccular aneurysms are classified according to the vessel involved whereas the nomenclature of saccular aneurysms relates to the branch at which the aneurysm occurs (for example, an aneurysm of the internal carotid artery at the origin of the posterior communicating artery is classified as a posterior communicating artery aneurysm).

Saccular aneurysms are categorized as small (<10 mm diameter), large (10 mm–25 mm), and giant (>25 mm).

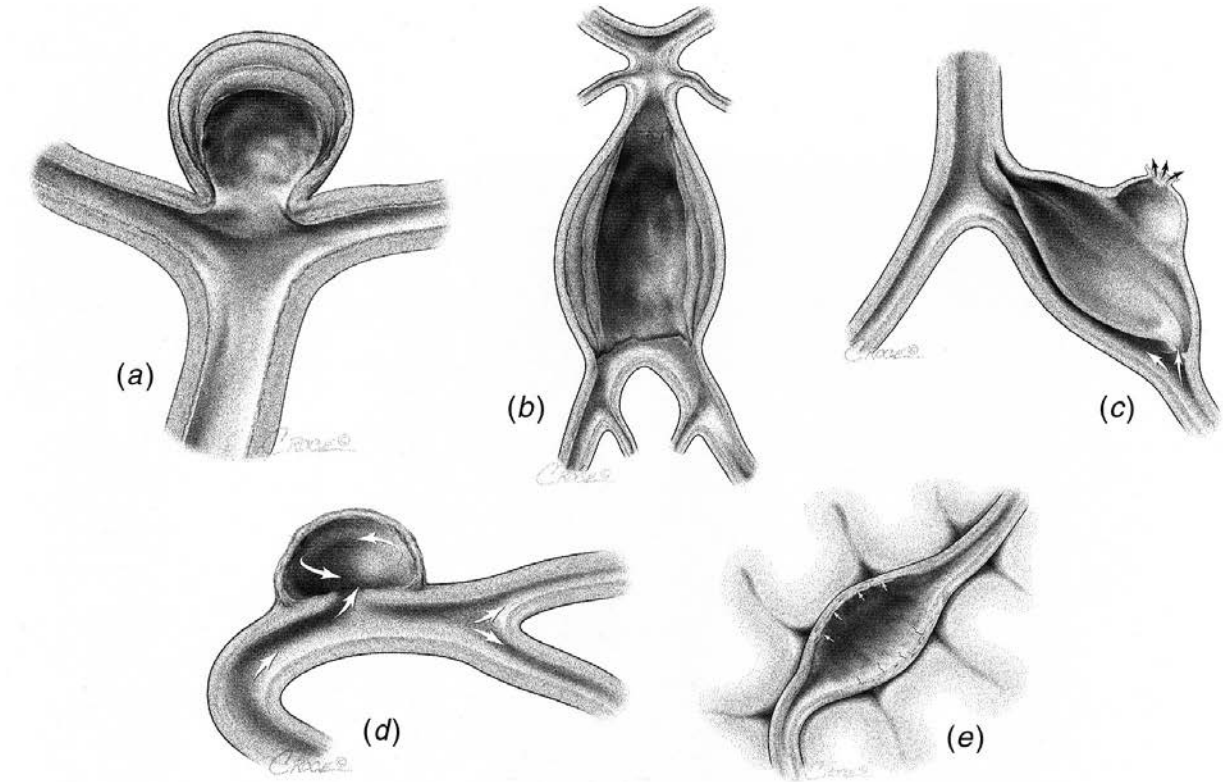

Fig. 84.1. Pathological classification of cerebral aneurysms. The most common aneurysm encountered in clinical practice is of the saccular type (*a*). Other lesions included in the general category of aneurysms include fusiform (*b*), dissecting (*c*), false (*d*), and infectious (*e*).

Epidemiology

Aneurysms affect all racial groups and are found at postmortem in 1–3% of autopsies and incidentally in 2.7% of patients undergoing angiography. The incidence of subarachnoid hemorrhage is approximately 10 per 100 000 population per year; there appears to be a slightly higher incidence in Finland and Japan (Weir, 1987). Men are more frequently affected than women until about the fifth decade, beyond which women predominate. Proximal internal carotid artery aneurysms are more common in women whereas anterior communicating artery aneurysms are more frequent in men. The internal carotid bifurcation and the basilar artery are sites of predilection in children. The average age of patients suffering SAH is approximately 50 years and the incidence of SAH increases with age. In familial cases the average age at the time of SAH is approximately 10 years younger than in other patients. Middle cerebral artery aneurysms are more common in familial cases. Diseases associated with aneurysms include coarctation of the aorta, polycystic kidney disease, fibromuscular dysplasia, moyamoya disease, sickle cell disease, and arteriovenous malformations. Cigarette smoking predisposes to aneurysm formation and rupture.

Risk of rupture and natural history

Based on a prevalence of unruptured aneurysms of 0.5% and an annual incidence of SAH of 10 per 100 000 per year, there might be a 2% annual rupture risk for previously unruptured aneurysms (Weir, 1987). This rate is supported by several clinical studies, but it is unlikely that a nonselective prospective trial will ever determine the true rate (Asari & Ohmoto, 1993; Juvela et al., 1998). Some authors have argued that small aneurysms are unlikely to rupture (International Study, 1998; Wiebers et al., 1987). This is difficult to reconcile with the fact that the majority of ruptured aneurysms are small and the absence of evidence that aneurysms shrink after rupture (Weir, 1987). Unruptured giant aneurysms carry a particularly poor prognosis, with a 5-year survival rate of less than 50%.

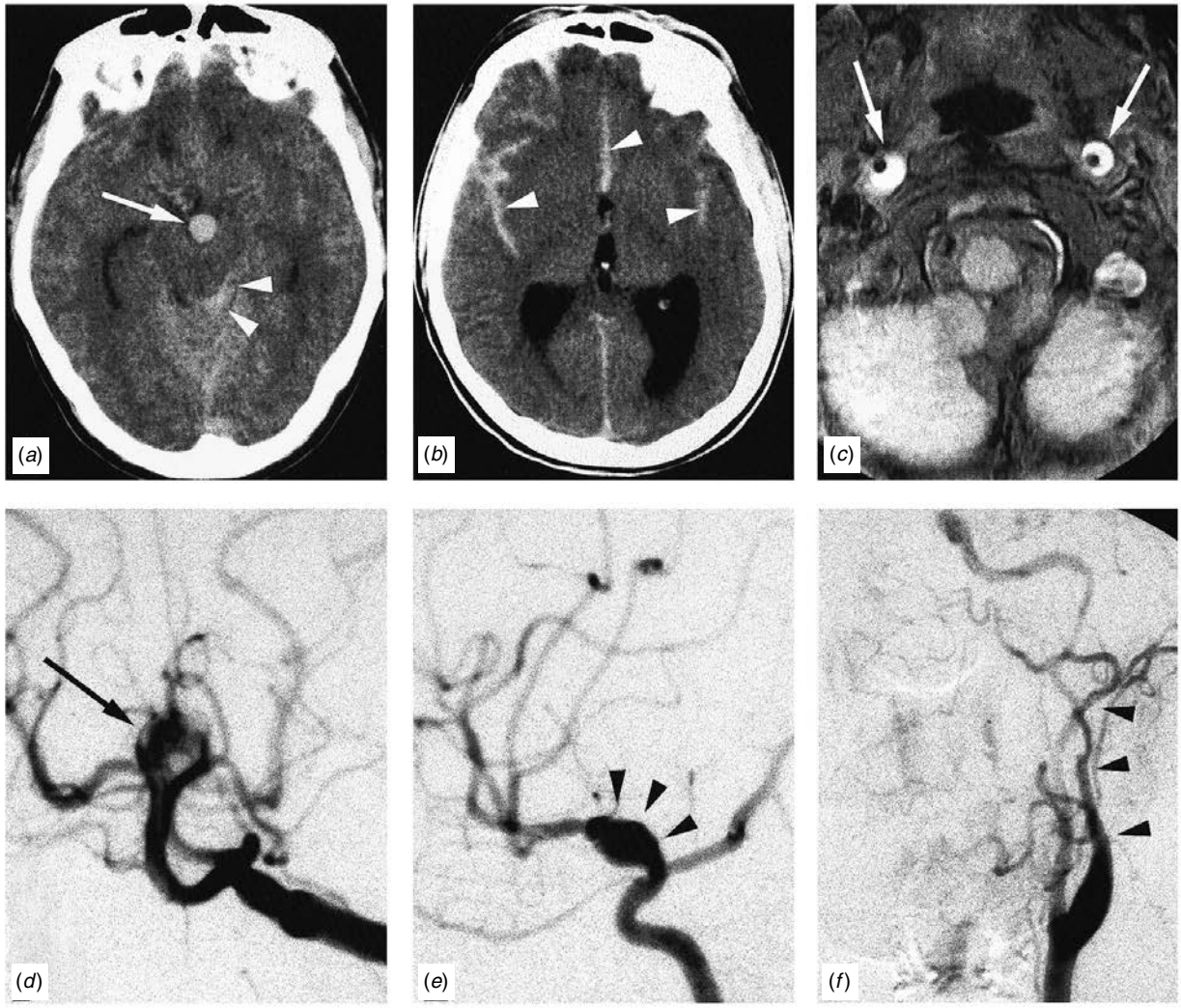

Fig. 84.2. Imaging studies of aneurysms. (*a*) CT scan demonstrating thrombus within a basilar bifurcation saccular aneurysm (arrow) and subarachnoid blood in the left ambient cistern (arrowheads). (*b*) CT demonstrating diffuse subarachnoid hemorrhage from a ruptured mycotic aneurysm with blood in the Sylvian fissures and interhemispheric fissure (arrowheads). (*c*) Bilateral dissecting aneurysms of the cervical internal carotid arteries (arrows). In this axial MR scan, the normal hypointense flow void of each carotid artery is surrounded by the hyperintensity of fresh blood within the wall of the vessel. (*d*) Vertebral angiogram demonstrating a basilar bifurcation saccular aneurysm (arrow) (same case as (*a*)). (*e*) Right internal carotid angiogram demonstrating a mycotic aneurysm of the right intracranial internal carotid artery (arrowheads). There is fusiform enlargement of the artery beyond the posterior communicating artery origin to the carotid bifurcation (same case as (*b*)). (*f*) left internal carotid angiogram revealing a carotid artery dissecting aneurysm, with irregular narrowing of the internal carotid artery beyond the common carotid bifurcation (arrowheads) (same case as (*c*)).

Posterior circulation location and morphological features such as daughter loculi are probably associated with an increased risk of rupture, although this has not been proven.

The natural history of aneurysmal rupture is poor. Approximately 10–20% of patients die immediately after rupture and are not admitted to hospital. The outcome of patients who survive the initial hemorrhage correlates with clinical grade (Table 84.1). Adverse prognostic features include a history of hypertension, smoking, or cocaine use and CT evidence of thick subarachnoid clot, midline shift, intracerebral hemorrhage, or intraventricular hemorrhage. Patients with posterior circulation aneurysms fare worse than their counterparts with anterior circulation

Table 84.1. Clinical grading scales and mortality for patients suffering subarachnoid hemorrhage.

Grade	Hunt and Hess (1968)	World Federation of Neurosurgical Societies (1988)	Approximate mortality (%)
I	Asymptomatic, or minimal headache and slight neck stiffness	GCS 15, no motor deficit	10
II	Moderate to severe headache, no neurological deficit (except cranial nerve palsy)	GCS 13–14, no motor deficit	15
III	Drowsy, confusion, or mild focal deficit	GCS 13–14, motor deficit	20
IV	Stupor, moderate to severe hemiparesis, early decerebrate rigidity and vegetative disturbances	GCS 7–12	40
V	Deep coma, decerebrate rigidity, moribund	GCS 3–6	70

Table 84.2. Correlation between subarachnoid blood assessed with CT scan and risk of vasospasm.

Fisher grade	Blood	Risk of vasospasm
1	Not detectable on CT	Low
2	Diffuse subarachnoid blood with all vertical layers <1 mm thick	Low
3	Localized clots and/or vertical layers of blood ≥ 1 mm thick	High
4	Intracerebral or intraventricular clot with diffuse or no subarachnoid blood	Low

Source: From Fisher et al. (1980).

lesions. Without treatment, the overall mortality from an initial aneurysmal rupture is approximately 50% at 30 days (Le Roux & Winn, 1998; Pakarinen, 1967). The major causes of morbidity and mortality after the initial hemorrhage are rebleeding and vasospasm. Untreated, 50% of patients will suffer a repeat hemorrhage within 6 months. The risk is probably highest within the first few hours, is 25% within 2 weeks, and gradually diminishes thereafter. If a patient survives to 6 months and remains untreated, the annual risk of rupture remains slightly higher than with unruptured aneurysms. Rebleeding has a 70–80% mortality rate. The onset of vasospasm is 3–4 days after the SAH, with a peak severity at 7–10 days. Angiography during this time will demonstrate arterial narrowing in approximately two-thirds of patients and half of these will have symptomatic ischemic deficits. Long-term morbidity from vasospasm occurs in 10–15% of patients and approximately 5% of patients die from vasospasm alone. The effects of vasospasm are more severe in poor grade patients and those with thick subarachnoid blood (Table 84.2) (Weir, 1987).

Investigation and diagnosis

Current generation CT scans have a greater than 95% sensitivity in detecting SAH if the scan is performed on the day of hemorrhage (Fig. 84.2). There is a gradual reduction in sensitivity with time so that by day three a CT will be positive in only 70–80% of cases and in 50% after 1 week. The pattern of blood on CT scan is helpful in determining the location of an aneurysm and in the case of blood confined to perimesencephalic cisterns, can predict a non-aneurysmal cause for the hemorrhage. CT will also detect intraparenchymal and intraventricular hemorrhage, the amount of subarachnoid blood (and hence the risk of vasospasm), and hydrocephalus. MRI is generally not helpful in assessment of acute SAH, but can detect blood in cases where the presentation is delayed and CT is negative.

Lumbar puncture is reserved for those cases where a clinical suspicion of SAH is not confirmed on CT. Hemorrhage caused by the lumbar puncture itself cannot reliably be differentiated from SAH by examining serial specimens from the same tap. Red cells begin lysing within a few hours after SAH so in most cases the supernatant will be xanthochromic to the eye, although it is detected definitively by spectrophotometry. Lumbar puncture is contraindicated in the presence of an intracranial mass lesion, so that at a minimum it should be preceded by fundoscopic examination and a CT scan if it is available.

Detection of a structural vascular cause for SAH is most effectively done with digital subtraction catheter angiography (Fig. 84.2). MR and CT angiography have not yet reached the sensitivity required for detection of small aneurysms. In addition, catheter angiography provides important dynamic information such as collateral and

dominant flow that is not available with other techniques. The risks of modern catheter angiography are extremely low. We therefore have a low threshold for investigating patients where there is a clinical suspicion of a ruptured aneurysm because the consequences of failing to make the diagnosis are potentially disastrous. When SAH has been proven and angiography is initially negative, a delayed repeat study is warranted unless the pattern of SAH is of the benign perimesencephalic type. We also carry out MR angiography and MRI to exclude a freshly thrombosed aneurysm if initial angiography is negative.

Medical management

Initial management of patients with SAH depends on the consciousness level and hemodynamic status. For poor grade patients, priorities in the emergency department are ventilation and oxygenation, hemodynamic stabilization, and control of raised intracranial pressure (Le Roux & Winn, 1998). Stabilization in the emergency department should occur even before the diagnosis is established. Poor grade patients are sedated and ventilated and have the intracranial pressure monitored. Patients who are alert at presentation are kept resting in bed with close neurological monitoring. Avoidance of hypo- or hypertension is critical. Hypertension is exacerbated by pain, which is difficult to control without sedation. An adequate level of analgesia is achieved with morphine. Other pharmacological measures are used as required to control blood pressure; we prefer sodium nitroprusside initially. Maintenance of normal serum sodium and blood volume is important to avoid delayed ischemic deficits. A central line is sometimes used to guide fluid management; dehydration must be strictly avoided. Hyponatremia is especially common after rupture of anterior communicating artery aneurysms and associated hypothalamic dysfunction. Prophylactic anticonvulsants are given only for younger patients with ruptured middle cerebral artery aneurysms and intracerebral hematomas, who are at high risk of seizures.

The mortality and morbidity associated with vasospasm are reduced with the prophylactic administration of the calcium channel blocker nimodipine. The mechanism of action is probably small vessel dilatation or a neuroprotective effect, rather than preventing narrowing of large basal arteries (Le Roux & Winn, 1998). Therapy for established vasospasm includes elevating cerebral perfusion pressure and increasing blood volume. Some authors advocate endovascular therapy such as angioplasty or intra-arterial infusions of papaverine immediately that neurological deficits develop (Eskridge et al., 1998). We have tended to reserve these invasive interventions for those cases that do not respond to fluid and blood pressure management. Intrathecal thrombolytic therapy after aneurysm clipping in highly selected cases probably reduces the incidence of vasospasm (Findlay et al., 1995).

Surgical and endovascular management

Impaired conscious state in many poor grade patients is predominantly a result of hydrocephalus. Judicious ventricular drainage in such patients is valuable in treating intracranial hypertension, although drainage does increase the transmural pressure and slightly increases the risk of rebleeding until the aneurysm is obliterated. We generally keep the opening pressure of such drains at 15–20 cm H_2O to minimize this risk, while avoiding further ischemic deficits from insufficient cerebral perfusion pressure. Raised intracranial pressure from an intracerebral hematoma is an indication for urgent surgery; the aneurysm should be clipped at the same operation.

A central goal in the management of a patient with a ruptured aneurysm is to prevent rebleeding by obliterating the lesion. Results of delayed surgery are good, but the overall management outcome is better with early surgery because this policy prevents more rebleeding episodes (Haley et al., 1992). The current standard method of aneurysm obliteration is with surgical clipping (Fig. 84.3). Endovascular coiling (Fig. 84.3), trapping, and proximal occlusion are alternatives in certain situations. The main advantages of clipping are a high rate of complete occlusion and a proven low rate of aneurysm reformation. Other advantages of direct surgery include the ability to evacuate subarachnoid and intracerebral clot and to control intraprocedure aneurysm rupture. Temporary clipping of parent vessels reduces intra-aneurysmal pressure and improves the safety of neck dissection and clip application. Intraoperative electrophysiological monitoring is sometimes used for the early detection of ischemic changes during temporary clipping and inadvertent major branch or perforator occlusion (Lopez et al., 1999). Intra-operative angiography has also been useful in detecting branch occlusion and incomplete clipping, providing immediate feedback and the opportunity for clip adjustment (Alexander et al., 1996).

Occlusion of major proximal arteries has been an aneurysm treatment method for over a century. Good results are obtained with proximal occlusion for giant aneurysms of the anterior and posterior circulation, making this a viable alternative when the risks of direct surgery are considered excessive (Steinberg et al., 1993). Aneurysm trapping by placing clips proximal and distal to the aneurysm is a curative manoeuvre that can be used in situations where collateral flow to the distal vessel is sufficient and there are no

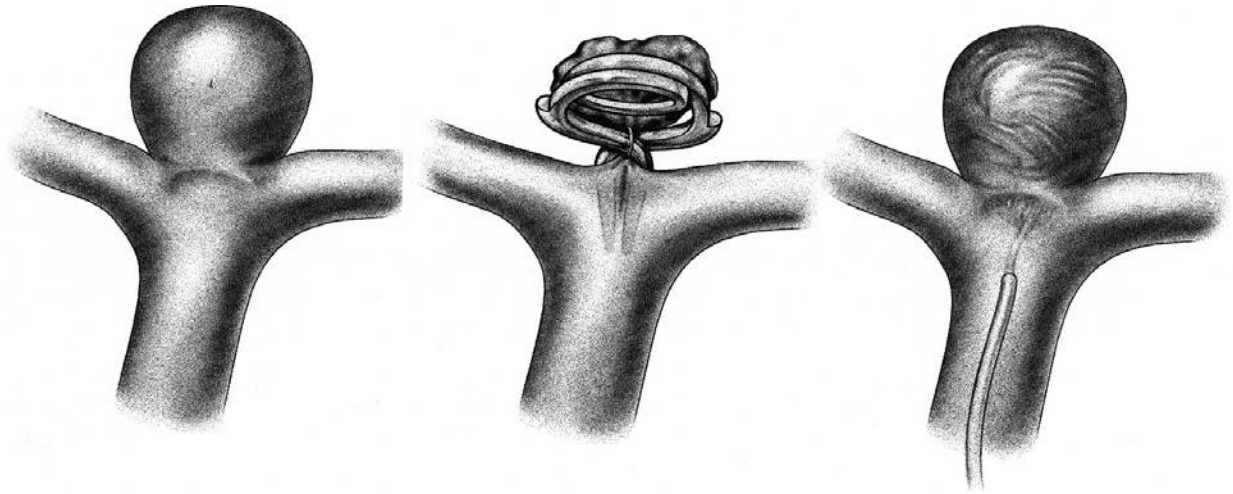

Fig. 84.3. Methods for obliterating aneurysms. Left: aneurysm with neck at an arterial bifurcation. Centre: surgical clipping. The aneurysm neck is occluded and the intimal surface is reconstructed. Right: endoluminal coiling. Complete obliteration of the lesion depends on thrombosis within the aneurysm sac. The intimal surface is not reconstructed.

perforators arising from the trapped segment. In very unusual circumstances a revascularising bypass graft is used to supplement flow distal to a trapped aneurysm.

Endovascular packing of the aneurysm lumen with platinum coils is a relatively new technique that has been increasingly used for cases unsuitable for surgery. In general, coiling is best suited to those aneurysms that are also amenable to surgery. Broad necked, large or giant, or partially thrombosed aneurysms are relatively less suited to endovascular techniques. Coiling does not reconstitute the intimal lining and often leaves residual aneurysm that can enlarge with time (Fig. 84.3). The precise role of coiling in the overall management of aneurysms remains to be determined and technical advances are occurring rapidly.

Arteriovenous malformations

Classification and pathology

The pathological classification of brain vascular malformations (Fig. 84.4) is based on the work of McCormick, who categorized lesions according to their gross and microscopic features (McCormick, 1966). The term 'arteriovenous malformation' has been used ambiguously as a general name for all vascular abnormalities and as a specific subtype of vascular malformation. The subtype arteriovenous malformation, referred to by some authors as 'high flow' AVM, occurs throughout the brain and spinal cord. They are present in 0.5–1% of the population and are presumed congenital in origin (Henn et al., 1999). An AVM is a fistula between an artery or arteries and a draining vein or veins, without an intervening capillary bed. There are arterial feeders, a nidus, which is the location of the fistulous connections, and a venous outflow. Arterial pressure is transmitted directly to the nidus by the feeding arteries. Arterial blood is then shunted to the draining veins, which are described as 'arterialized'. Arterialized veins carry oxygenated blood and are dilated and tortuous. The pressure change across the nidus depends on fistula resistance. In low resistance AVMs, there is steal of blood from surrounding brain, with dilatation of small arteries and arterioles that has been described as 'angiomatous change'. The general configuration of an AVM is a pyramidal-shaped lesion with its base at the surface of the brain and the apex directed towards the ventricle. Any brain parenchyma within the lesion tends to be abnormal, demonstrating gliosis, edema, or necrosis. There is often a gliotic reaction adjacent to the nidus and evidence of previous hemorrhage such as hemosiderin staining, thrombosis, and hyalinization (Henn et al., 1999). Although the vessels within an AVM are identifiably arteries and veins, there are degenerative and reactive changes that are presumed secondary to increased flow through the lesion (Henn et al., 1999). The vessels are generally dilated and the walls tend to be irregularly thickened or thin. Draining veins show evidence of fibrosis and do not have an elastic lamina (Henn et al., 1999). Associated aneurysms can be venous, within the nidus, on feeding arteries, or on unrelated arteries (Steinberg & Stoodley, 2000). A widely used grading scale is used to assess the risks associated with surgical treatment (Spetzler & Martin, 1986). One point is assigned to lesions

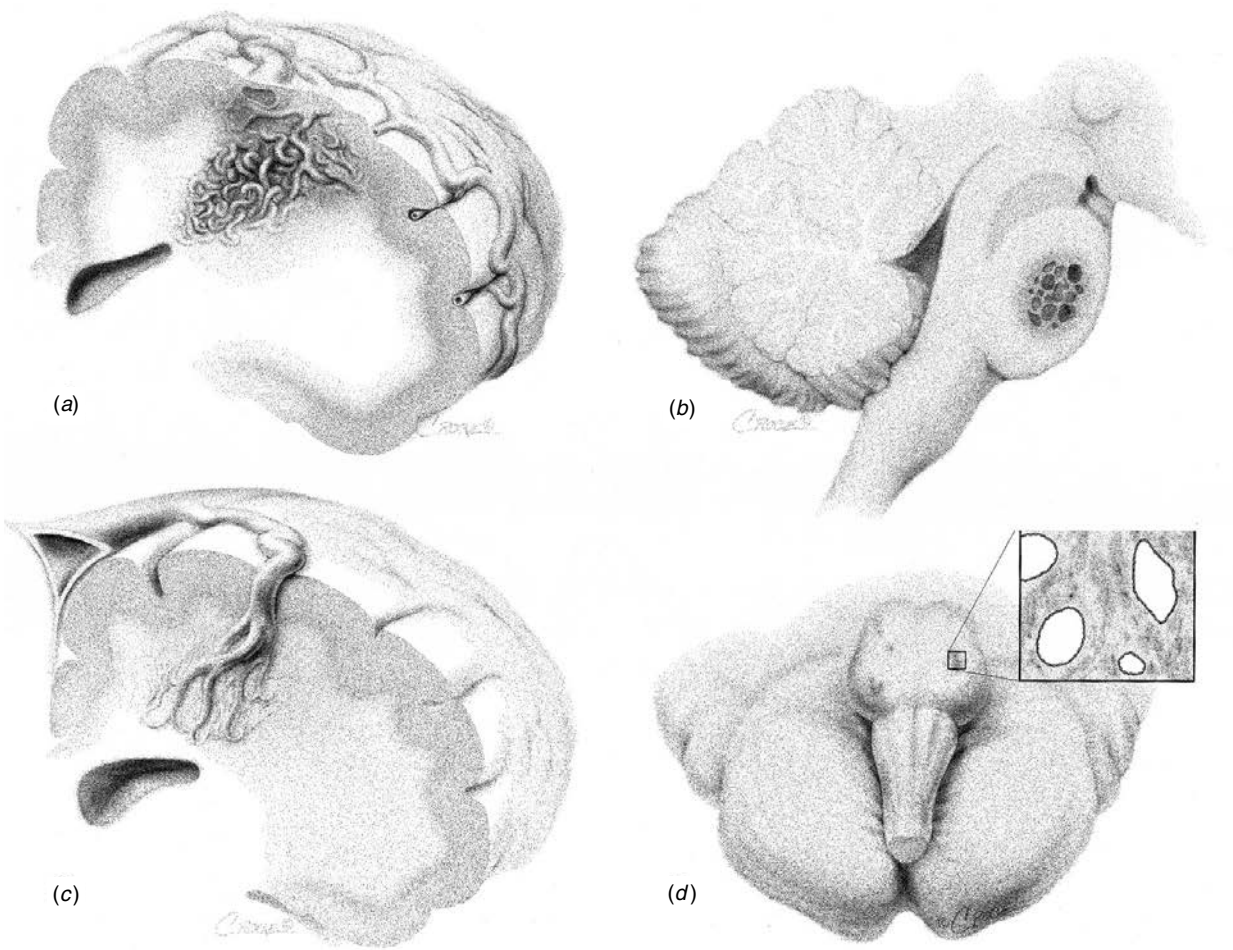

Fig. 84.4. Pathological classification of brain vascular malformations. (*a*) Arteriovenous malformation. (*b*) Cavernous malformation. (*c*) Venous malformation. (*d*) Capillary telangiectasia.

that are less than 3 cm in maximum diameter, 2 points for lesions between 3 cm and 6 cm diameter and 3 points for AVMs larger than 6 cm. Additional points are added for malformations that have drainage to the deep venous system and those located in eloquent regions of the brain. Higher grade lesions are associated with higher surgical risks.

Cavernous malformations, also referred to as cavernomas, cavernous hemangiomas, and cavernous venous angiomas, are compact lesions consisting of abnormal, thin-walled sinusoidal vessels without intervening brain parenchyma (Henn et al., 1999). Approximately 0.5% of the population harbour these malformations, which occur in all parts of the brain and spinal cord. There is a predilection for subcortical white matter, external capsule, and pons (Challa et al., 1995). Gross appearances are of a well-circumscribed, multilobulated lesion resembling a mulberry (Henn et al., 1999). There can be a collagenous capsule. The thin-walled vessels have a single endothelial layer adjacent to a fibrous outer layer, without elastin, smooth muscle, or basement membrane (Henn et al., 1999). Almost all cases show evidence of previous hemorrhage, with hemosiderin, organizing thrombus, and calcification within and around the lesion. The presumed congenital nature of these lesions has recently been questioned. New malformations arise in familial and non-familial cases, regions of brain treated with radiotherapy, and there is laboratory evidence to suggest a possible etiological role of viral infection (Flocks et al., 1965; Henn et al., 1999). The genetic mutation responsible for cavernous malformations has been localized to the long arm of chromosome 7 (Günel et al., 1995).

Venous malformations, or venous angiomas, are composed of a large, morphologically normal, vein that drains

into a deep or superficial venous sinus. Blood enters the large vein from small veins that are arranged radially around the trunk to give the appearance of a 'caput Medusa' (Fig. 84.4). There is no arteriovenous fistula or shunt and normal brain lies between the veins. These malformations are essentially developmental anomalies of normal venous drainage and are present in approximately 3% of the population. As many as 30% of cavernous malformations are associated with venous malformations and if a hemorrhage occurs near a venous malformation it is almost always from an associated cavernous malformation.

Capillary telangiectases are congenital lesions that are thought to result from a focal failure of capillary involution that normally occurs in the second month of gestation (Henn et al., 1999). The pons is a site of predilection, but they can be found anywhere in the central nervous system. They are rarely symptomatic and are usually an incidental finding at autopsy, occurring in 0.1–0.8% of the population.

Mixed or 'transitional' lesions occur. The particular relationship between cavernous malformation and venous malformation has been mentioned, and all possible combinations of lesions have been reported. Mixed histological features have also been noted, for example some lesions combine elements of cavernous malformation and capillary telangiectasia.

Dural arteriovenous fistulae were originally considered malformations, but are now classified separately. There is a fistulous connection between arteries and veins and the nidus is within the dura. Venous drainage is usually by dural venous sinuses or cortical veins. The cavernous, transverse, and sigmoid sinuses and dural veins at spinal nerve root sheaths are most commonly affected (Henn et al., 1999). A congenital origin is likely in some cases; however, most lesions probably follow trauma, surgery, or venous sinus thrombosis. One hypothesis relating to formation of these lesions is that angiogenic activity creates a fistula at the site of thrombosis or trauma. Neurological deficits are caused by raised venous pressure or hemorrhage. Borden and colleagues have classified dural arteriovenous fistulae into those that drain directly into dural venous sinuses (Type I), those that drain into dural sinuses and cortical veins (Type II), and those that drain only into cortical veins (Type III) (Borden et al., 1995). The risk of hemorrhage is highest in types II and III. The carotid cavernous type has been subdivided into direct (from a ruptured aneurysm or traumatic disruption of the intracavernous internal carotid artery) and indirect (from the external carotid artery or meningeal branches of the internal carotid artery) (Barrow et al., 1985).

Epidemiology and natural history

The approximate incidence of intracranial vascular malformations is 2 per 100 000 population per year and the prevalence is 20 per 100 000 population (Brown, 1999). AVMs are the most common type presenting clinically, followed by cavernous malformations and venous malformations. Most AVM ruptures occur in adults under the age of 40. Hereditary hemorrhagic telangiectasia and Wyburn Mason syndrome are associated with a higher incidence of AVMs and in these cases there can be multiple lesions.

The best available data concerning the natural history of AVMs indicates an annual hemorrhage risk of 2–4% per year, regardless of whether a malformation has previously bled (Brown, 1999; Steinberg & Stoodley, 2000). There is an elevation in risk (6%) during the first 6 months after a hemorrhage. Mortality from an initial hemorrhage ranges from 10 to 30% and morbidity is up to 40% (Brown, 1999). Numerous imaging features of AVMs have been associated with an increased risk of hemorrhage. These include the presence of aneurysms, periventricular or intraventricular location, deep venous drainage, absence of angiomatous change, impairment of venous drainage, deep venous drainage, arterial supply by perforators, and high feeding artery pressure (Brown, 1999).

Cavernous malformations account for 5–10% of vascular malformations presenting clinically. The mean age at presentation is approximately 40. Familial forms with near 100% penetrance occur, particularly in the Hispanic population. Multiple lesions are more common in familial cases. The low risk of fatal hemorrhage with this type of lesion is probably related to the low pressure within the abnormal vessels and the small bleeds that occur. Morbidity depends on the location of the lesion; posterior fossa lesions are typically more prone to developing neurological deficits. The overall risk of hemorrhage is approximately 4% per year (Porter et al., 1997). An increased risk is seen with familial cases or if there has been a previous hemorrhage (Wascher & Spetzler, 1999). Females present more commonly with hemorrhage and there appears to be an increased risk during pregnancy (Brown, 1999). The clinical course of brainstem lesions is more malignant, characterized by clinical deterioration associated with recurrent hemorrhage and a less than 50% recovery rate from each hemorrhage (Porter et al., 1997; Wascher & Spetzler, 1999).

Venous malformations and capillary telangiectasia appear to have a very benign natural history and treatment for them is not generally recommended. Hemorrhages occurring in the presence of these lesions are often from an associated cavernous malformation.

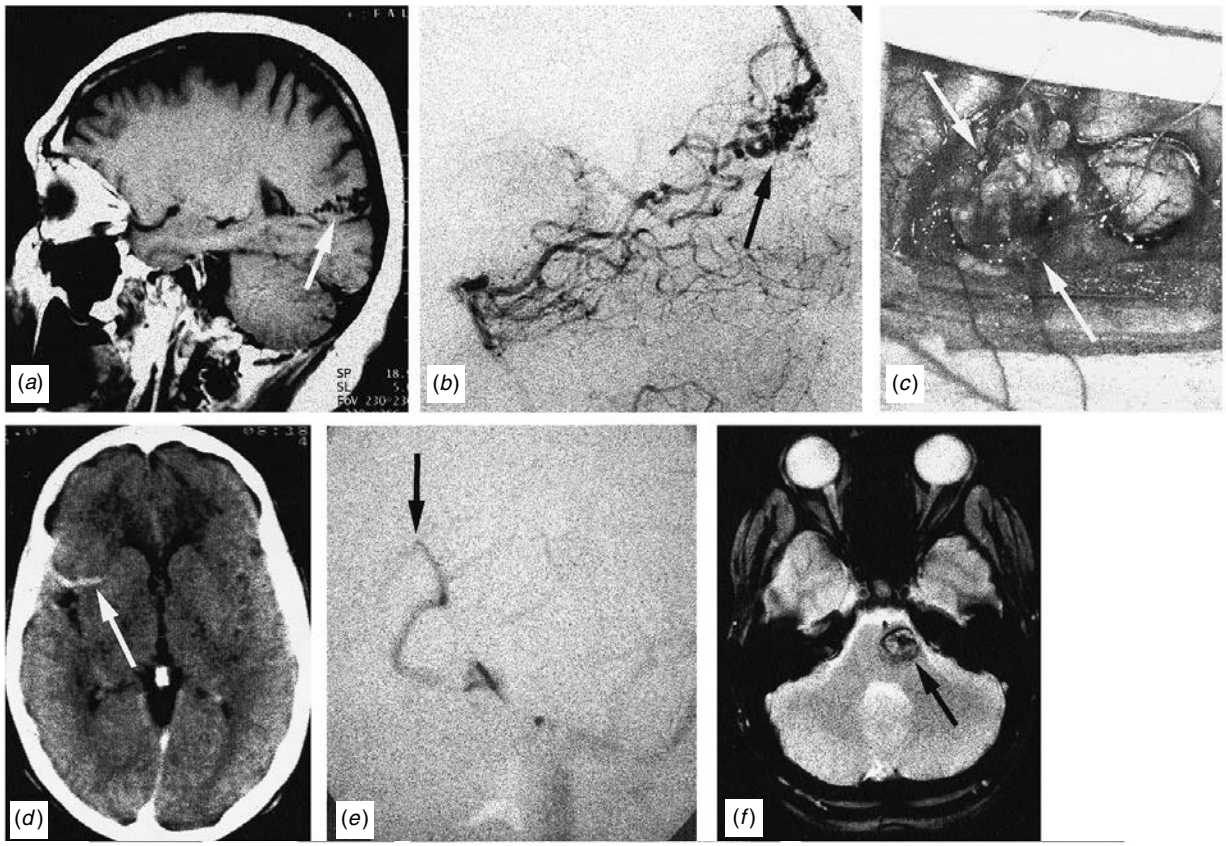

Fig. 84.5. Imaging studies of vascular malformations. (*a*) Sagittal T_1-weighted MRI demonstrating a parieto-occipital arteriovenous malforxmation (arrow) with the apex of the lesion reaching the occipital horn of the lateral ventricle. (*b*) Same case as (*a*). A vertebral angiogram shows filling of the malformation (arrow) and venous drainage to the superficial and deep venous systems. (*c*) Same case as (*a*) and (*b*). The malformation has been dissected from the surrounding brain (arrows) and is about to be detached from its superficial and deep venous attachments, which is the last step in removing the lesion. (*d*) CT scan with contrast demonstrating an enhancing vascular lesion in the right Sylvian fissure (arrow). On venous phase carotid angiography (*e*), this was revealed as a venous malformation with a typical 'Caput Medusa' appearance. (*f*) MR scan revealing a large cavernous malformation in the left side of the pons.

Investigation

Hemorrhage from an AVM is usually detected on CT, but the underlying malformation might not be detected, even with intravenous contrast enhancement. Subtle calcification is the only evidence on CT in some cases. MRI is more sensitive because the feeding arteries, draining veins and nidus will usually produce signal flow voids (Fig. 84.5), but there will still be false negatives. MR angiography is not sensitive enough to replace catheter angiography, which remains the gold standard for the detection of AVMs. Angiography demonstrates collateral vessels, risk factors for hemorrhage and surgery (such as aneurysms and venous drainage patterns), and feeding vessels including basal perforators. MRI is valuable in determining the anatomical location of the lesion and in planning treatment.

In contrast, MRI is the gold standard for the detection of cavernous malformations (Fig. 84.5), which are absent or seen as a faint blush on angiography. Typical MR appearances are of a well-circumscribed lesion with heterogeneous signal characteristics, and a rim of low signal intensity hemosiderin on T_1- and T_2-weighted images. Gradient echo sequences are very sensitive in the detection of cavernous malformations. T_1-weighted axial images are required for brainstem lesions because an assessment of the proximity of the malformation to the surface is crucial for surgical planning.

Venous malformations are seen as a 'caput Medusa' on venous phase angiography (Fig. 84.5). There is no early

venous filling or shunting of blood and the arterial pattern is usually normal. Capillary telangiectases are seen as faint blushes on angiography, if at all. Dural arteriovenous fistulae are generally not detectable on CT or MRI. Often internal carotid and vertebral angiography will also be normal; external carotid branches must be injected for the detection of these lesions. Spinal angiography with catheterization of each radicular branch is necessary to evaluate spinal dural arteriovenous malformations and fistulae.

Management

Acute medical management of ruptured vascular malformations is similar to other causes of intracranial hemorrhage. Nimodipine is generally not used as the risk of vasospasm is small unless there is thick basal subarachnoid hemorrhage. Anticonvulsants are used for patients presenting with seizures and for those with lesions involving cerebral cortex.

Decision making regarding management of vascular malformations is complex and is best made by a multidisciplinary management team of a vascular neurosurgeon, interventional neuroradiologist, and radiosurgeon. The risks of treatment are balanced against the natural history risks and analysed with regard to the patient's age, medical condition, psychological state, and the mode of presentation. A large AVM presenting with a single seizure in an elderly patient is not likely to be treated, whereas a case can be made for treating all but the most formidable lesions in young patients. The risk of hemorrhage from AVMs and cavernous malformations does not diminish until they are completely obliterated. Therefore, partial treatment is not an acceptable goal, with the possible exception of specific treatment of such risk factors as associated aneurysms. The main aim of treating these lesions is to prevent hemorrhage, although easier control of seizures and headaches is a common sequel to obliterating a malformation. Dural arteriovenous fistulae, if treated, must be eradicated completely; any residual arteriovenous connection is likely to enlarge with time.

Treatment options for vascular malformations are surgery, radiosurgery, endovascular embolization, and combinations of these modalities. Surgical excision remains the preferred treatment for most malformations because it provides immediate protection from hemorrhage and has the highest rate of complete obliteration. While having the attraction of being 'less invasive' radiosurgery is effective only for small lesions. Even malformations less than 3 cm diameter have obliteration rates of only 70–80% with this modality, and there is a risk of delayed radiation necrosis that must be considered. Radiosurgery is therefore usually reserved for cases that would have excessive surgical risk, such as those in the brainstem and thalamus. Endovascular embolization is rarely curative, although it is often used as an adjunct to the other modalities. It can be used to reduce a malformation to a size suitable for radiosurgery. Used prior to surgery, it is valuable for lowering intranidal pressure and reducing intraoperative hemorrhage, occluding arterial feeders that would be difficult to access, and possibly effecting more gradual restoration of normal hemodynamics that might lower the incidence of 'breakthrough' postoperative hemorrhage (Steinberg & Stoodley, 2000).

The immediate risk of recurrent hemorrhage from a vascular malformation is not as high as it is with aneurysms and there is consequently usually no urgency in treating the underlying lesion. AVMs with high risk factors identified on angiography are an exception. The precise timing of surgery is individualized to avoid operating in the presence of an edematous, swollen brain, yet early enough to take advantage of dissection produced by a hemorrhage. There is no reason for prolonged delay in cases with minor hemorrhage. Urgent evacuation of the hematoma is indicated for cases with life-threatening hematomas, but in contrast to aneurysm surgery the underlying vascular malformation is usually left for removal at a later time.

Current indications for treating cavernous malformations include recurrent hemorrhage of a superficial lesion and a single hemorrhage from a brainstem malformation. A critical factor in determining suitability for surgery is accessibility. In the brainstem a lesion is generally accessible only if it reaches a pial or ependymal surface. This is best judged preoperatively on T_1-weighted MR images, but some cases deemed suitable by this criterion will be discovered at surgery to be covered by a thin layer of normal parenchyma that should not be transgressed. Deep supratentorial lesions are usually not suitable for surgical excision, unless they also approach a deep pial or ependymal surface. There is some evidence to suggest that control of seizures is easier if superficial cortical lesions are removed early, but this is not a strong indication for surgery. Once access is gained to a cavernous malformation, its removal is less demanding than for AVMs; there are few feeding vessels and usually a gliotic plane. The effectiveness of radiosurgery is not sufficient for it to be a first-line therapy and there is evidence that the complications of such treatment exceed those associated with the treatment of other vascular lesions (Chang et al., 1998). In addition, radiosurgery tends to make subsequent surgical excision more difficult, in contrast to AVM surgery after radiation. We consider using radiosurgery only for lesions that have multiple hemorrhages and remain surgically inaccessible.

Dural arteriovenous fistulae are difficult lesions to manage. Spontaneous thrombosis does occur in a small proportion of cases. Indications for treatment include cortical venous drainage, which corresponds with a high risk of intracranial hemorrhage, and intolerable bruit. Carotid cavernous fistulae generally should be treated because the natural history is of progressive enlargement of the lesion with proptosis and cranial nerve palsies. Embolization is the preferred initial treatment in most cases. A transarterial route is usually used first, although venous catheterization with occlusion of the draining venous sinus is an option in many cases. This does not usually risk causing venous infarction because the sinus is already under high pressure and causing retrograde flow. The goal is complete occlusion of all arterial feeders or the draining venous sinus. If any fistulous connection remains, there is a high likelihood of further feeding artery recruitment and enlargement. Surgical obliteration by skeletonization of the dural venous sinus, division of all feeding arteries, and division of retrograde-flowing subarachnoid veins is a demanding undertaking reserved for cases with angiographic or clinical features of high risk that are not completely embolized. Radiosurgery has been used with some success (Guo et al., 1998). Spinal arteriovenous fistulae are usually located in the nerve root sleeve, even though there are dilated abnormal veins within the subarachnoid space and on the spinal cord. Simply dividing the fistula at the nerve root sleeve or its draining vein immediately that it enters the subarachnoid space, will usually be curative. Endovascular embolization is an option in cases where the general condition is a contraindication to surgery.

In conclusion, central nervous system aneurysms and arteriovenous malformations are a diverse group of conditions that are life threatening in many cases. Treatment is usually indicated for those lesions that have bled, or are considered at high risk of hemorrhage. The preferred method of treatment is surgery in most cases. Endovascular coil embolization is an alternative treatment of aneurysms that is likely to play a more prominent role as there are improvements in the technology and techniques of this method. Embolization of various occlusive substances into AVMs is also becoming more useful, although it is not likely that this will be a frequent curative treatment in the near future. For certain types of AVM, radiosurgery is effective in many cases, although this method is generally reserved for those patients who are unsuitable for surgery. For complex and difficult AVMs, combinations of the three treatment modalities are proving to be safer and more effective than a single approach.

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85

Hereditary causes of stroke

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This chapter focuses on mendelian disorders with stroke as part of the clinical syndrome. Within recent years most of the major gene loci have been mapped. In some instances this has allowed a new nosologic classification. Many of the genes have been cloned, thus allowing a direct diagnosis in the index patient and its relatives. Moreover, the cloning of the genes has provided new insights into the molecular mechanisms underlying these disorders. Thus for example the identification of genes implicated in CADASIL and familial cavernoma revealed cell signalling pathways involved into angiogenesis.

In order to recognize mendelian stroke syndromes it is essential to perform a systematic family inquiry and to search for neurological and non-neurological signs and symptoms in index cases and relatives. The diagnosis may have implications both for therapeutic decisions and genetic counselling. At present, there is no uniform classification for mendelian stroke syndromes. Criteria that may be useful for clinical practice include the type of stroke, the presence or absence of associated symptoms, and the mode of inheritance. The chapter gives a summary of actual data regarding clinical, genetic and physiopathological aspects of these conditions.

Monogenic disorders with stroke as the prevailing manifestation

Conditions causing ischemic stroke

CADASIL

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is an autosomal dominantly inherited small vessel disease causing stroke in young adults. Previous descriptions of families with 'hereditary multi-infarct dementia', 'chronic familial vascular encephalopathy', and 'familial subcortical dementia' represent early reports of the same condition. In 1993, Tournier-Lasserve et al. mapped the gene on chromosome 19 and coined the acronym CADASIL (Tournier-Lasserve et al., 1993). Since then numerous families have been reported from all over the world.

Clinical manifestations include recurrent ischemic episodes (TIAs and strokes; 80%), cognitive deficits (50%), and migraine (40%) mostly with aura, as well as psychiatric disorders (30%) and epileptic seizures (10%) (Dichgans et al., 1998). Onset of ischemic symptoms is usually in mid-adulthood (mean age: 46.1 years). Magnetic resonance imaging reveals a combination of small lacunar lesions and diffuse white matter abnormalities (Fig. 85.1). The latter reflect varying degrees of demyelination, axonal loss, enlargement of the extracellular spaces and gliosis. There is evidence for additional subtle tissue alterations (both cortical and subcortical) outside T_2-visible lesions. Cerebral blood flow is reduced already within asymptomatic individuals. The underlying vascular lesion is a unique non-amyloid angiopathy involving small arteries (100–400 micrometres) and capillaries primarily in the brain but also in other organs. The diagnosis may therefore be established by skin biopsy. Ultrastructural examination reveals granular osmiophilic deposits within the vascular basal lamina (Fig. 85.2). These deposits are often seen in contact with degenerating smooth muscle cells. Yet they have not been characterized biochemically and their origin remains unresolved.

The disease is caused by mutations in *Notch3* (Joutel et al., 1996). *Notch* genes encode evolutionary conserved cell surface receptors that regulate cell fate choices in vertebrates and invertebrates during embryonic development. A constant feature of Notch receptors is a large number of

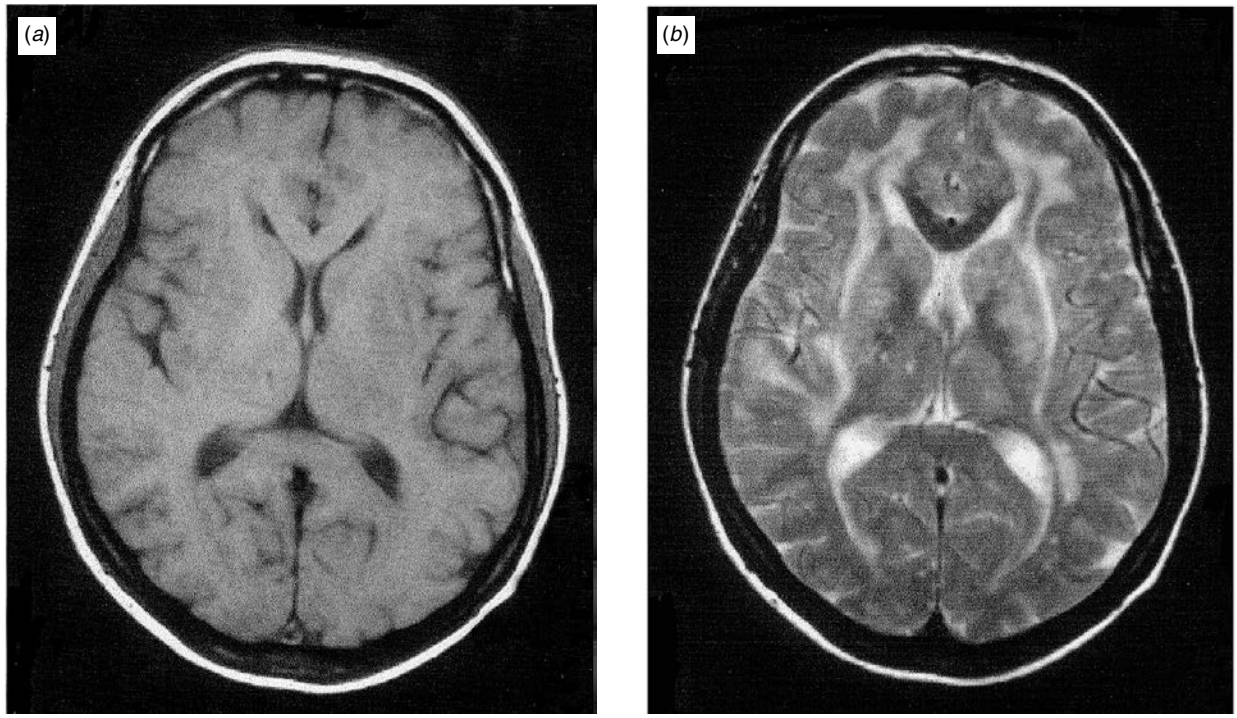

Fig. 85.1. Magnetic resonance images of a 48-year-old patient with CADASIL. (*a*) T_1-weighted image showing a small circumscribed lesion within the right thalamus as well as periventricular signal hypointensities; (*b*) T_2-weighted image showing diffuse signal-hyperintensities in the periventricular white matter and the external capsule.

tandemly arranged epidermal growth factor-like (EGF-like) repeat domains which account for most of the extracellular domains of these proteins. All CADASIL mutations are located in EGF-like domains of the Notch3 receptor with a strong cluster at the N-terminus. Mutations show a striking stereotyped nature: all mutations lead to the creation or loss of one cysteine residue. Since each wtEGF repeat domain contains six cysteines these mutations result in an odd number of cysteine residues within one EGF domain (Dichgans et al., 2000). Notch3 expression is restricted to vascular smooth muscle cells in human adult tissues. In CADASIL there is a dramatic accumulation of the ectodomain of the Notch3 receptor within blood vessels (Joutel et al., 2000). Accumulation takes place at the cytoplasmic membrane of vascular smooth muscle cells and pericytes, in close vicinity to but not within the granular osmiophilic deposits. These findings are in line with recent clinical studies evidencing vascular smooth muscle cell dysfunction in vivo.

There is no causative treatment for the disease. Management should focus on the control of symptoms such as headache, mood disturbances, urinary incontinence and sleep disturbances. Motor disabilities require formal rehabilitation. Forced crying and laughing may respond to selective serotonin reuptake inhibitors. When oral hydration and feeding become insufficient, the patient should receive additional tube feeding.

Conditions causing hemorrhagic stroke

Familial cerebral cavernoma

Cerebral cavernous malformations (CCM) are characterized by collections of large, abnormally dilated sinusoidal vascular spaces without intervening normal vessel wall elements or neural tissue. CCM usually present with seizures, headache, hemorrhagic stroke or focal neurologic deficits. Magnetic resonance imaging (MRI) demonstrates a characteristic lesion of variable signal intensity surrounded by a dark ring attributable to hemosiderin (Fig. 85.3). Gradient-echo sequences are particularly sensitive in displaying small lesions. Multiple lesions have been found in one-third of the sporadic cases and in up to 84% of the familial cases. The prevalence of CCM in the general population is close to 0.5%. A significant proportion of cases remain asymptomatic. CCM lesions are dynamic in time: subjects have been shown to acquire new lesions and lesions may undergo spontaneous involution. The risk of hemorrhage has been estimated at 0.7 to 1.1% per lesion per year.

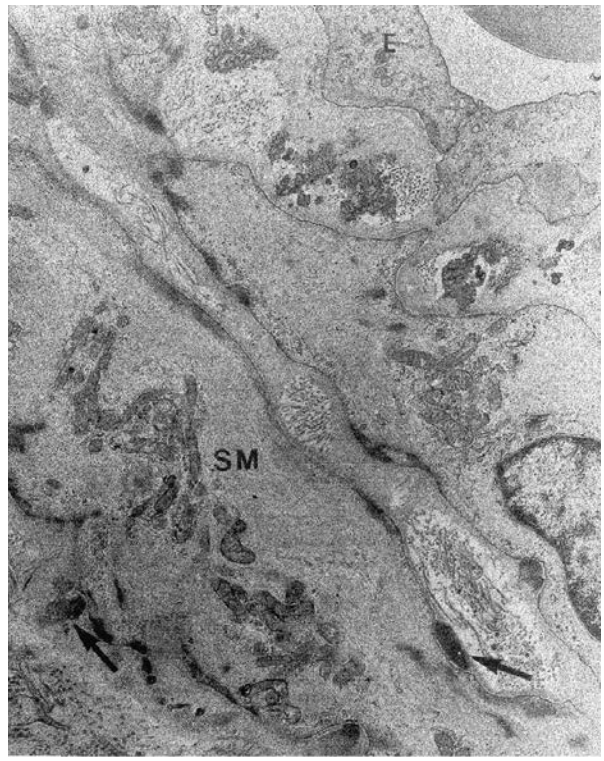

Fig. 85.2. Electron micrograph of a dermal vessel from a CADASIL patient: granular osmiophilic electron-dense material (arrows) within the vascular basal lamina (E = endothelial cell; SM = smooth muscle cell). Magnification ×16500. (Kindly provided by J Müller-Höcker, Munich.)

In a significant proportion of cases CCM are inherited as an autosomal dominant condition (Labauge et al., 1998). In the Hispano-American population this proportion was reported to be close to 50%. Most patients with multiple cavernous lesions have a hereditary form of the disorder. Three chromosomal loci have been identified on 7q, 7p and 3q. A strong founder effect was observed among Hispanic–Americans of Mexican descent, all familial cases being linked to *CCM1* on chromosome 7q. *CCM1* is also a major locus in the non-Hispanic population. The gene has recently been cloned. *CCM1* encodes KRIT1 an ankyrin repeat domain-containing protein. KRIT1 interacts with RAP1A/KREV1, a member of the RAS family of GTPases. RAP1A is involved in cell differentiation and morphogenesis. Moreover, several lines of evidence indicate that RAS signalling is involved in angiogenesis. The *CCM1* mutations identified thus far predict truncated CCM1 proteins

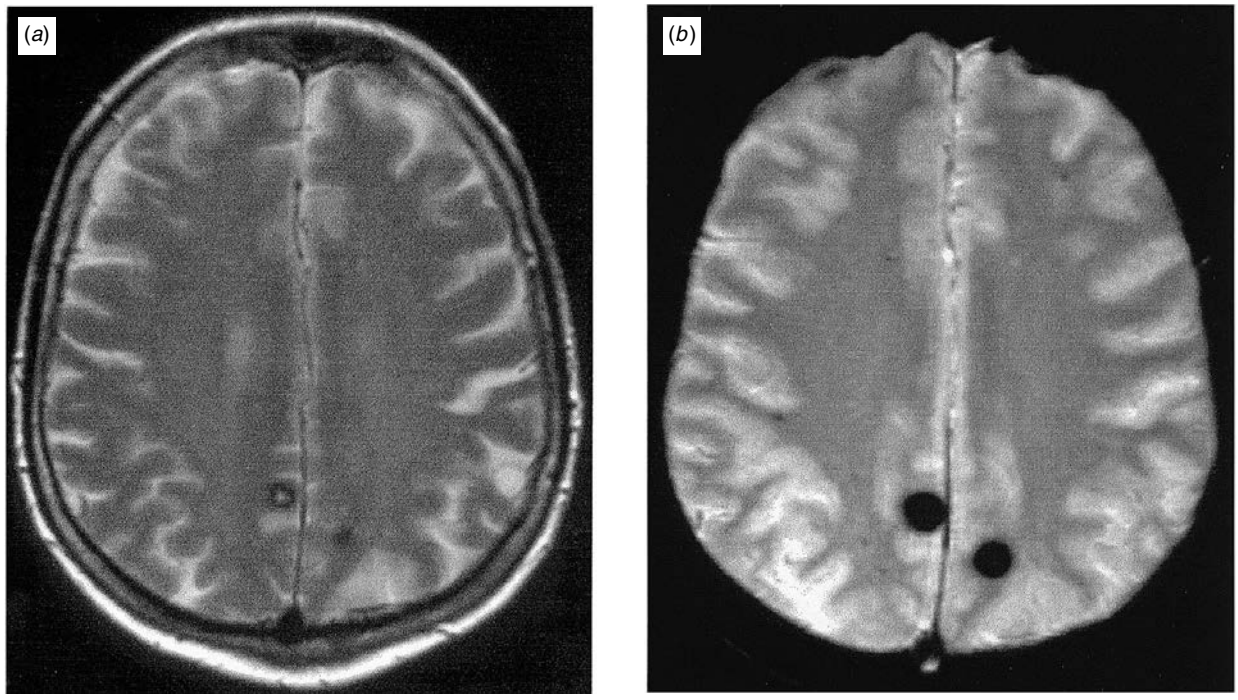

Fig. 85.3. Magnetic resonance images of a 69-year-old patient with multiple cerebral cavernous malformations. (*a*) T_2-weighted image, (*b*) gradient-echo image. For explanation see text.

completely or partially devoid of the putative RAP1A-interacting region. This points towards loss of function as the underlying mechanism. Laberge-le-Couteulx proposed a 'Knudson double hit mechanism' to explain the manifestation of sporadic forms of cavernomas as unique lesions and familial forms as multiple lesions (Laberge-le Couteulx et al., 1999). Following this hypothesis, a complete loss of CCM1 function would be required for the appearance of cavernous angiomas.

The primary therapeutic challenges in cavernous angiomas are: the management of the acute hemorrhage, the prevention of recurrent hemorrhages, and seizure control. Depending on the clinical situation pharmacological or surgical interventions may be necessary.

Conditions causing both ischemic and hemorrhagic stroke

Cerebral amyloid angiopathy

The cerebral amyloid angiopathies (CAA) encompass a heterogeneous group of disorders characterized by the deposition of amyloid in the walls of leptomeningeal and cerebral cortical blood vessels (Coria & Rubio, 1996). They are clinically characterized by recurrent or multiple lobar hemorrhages, cognitive deterioration, and ischemic strokes. MRI displays diffuse white matter abnormalities and focal lesions that can be ischemic or hemorrhagic. Apart from amyloid deposition vessel walls exhibit a number of changes such as cracking between single layers, microaneurysm formation, and fibrinoid necrosis. Rupture of such structurally weakened arteries eventually results in cerebral hemorrhage.

There are two autosomal dominantly inherited forms of CAA which can be differentiated based on clinical, biochemical and pathologic findings. Hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D) has been described in several large families from the Netherlands (Bornebroek et al., 1996). Stroke is usually the first clinical sign and occurs between age 45 and 60. Those who survive may experience multiple recurrences. The disease is biochemically characterized by deposition of β-amyloid in meningocortical blood vessels and cerebrocortical grey matter. β-amyloid refers collectively to a group of peptides, 38–42 amino acids in length, that arise from proteolytic cleavage of β-amyloid precursor protein (βAPP). HCHWA-D is caused by a mutation in the *APP* gene on chromosome 21. This mutation (Glu693Gln) has been shown to increase the aggregation of β-peptides into amyloid fibrils in vitro. Aggregation of normal β-peptide may further be enhanced by the presence of amyloid-binding proteins such as alpha1-antichymotrypsin or apolipoprotein E (apo E). Specific *APOE* alleles have been identified as important risk factors for the by far more common sporadic forms of CAA. The Flemish (A692G), Arctic (E693G), Italian (E693K) and Iowa (O694N) type of familial CAA represent allelic variants of the Dutch type.

Hereditary cerebral hemorrhage with amyloidosis-Iceland type (HCHWA-I) has been described in eight families of the same ethnic origin. Biochemically, this variant is characterized by vascular deposition of cystatin C, a cysteine protease inhibitor. The disease is due to a point mutation at codon 68 of the *CST3* gene. Mean age at onset for cerebral hemorrhage is considerably earlier than in HCHWA-D and most patients die before the age of 50. Genetic testing is feasible both for HCHWA-D and HCHWA-I. Several other hereditary amyloidoses show amyloid deposition within the central nervous system, but stroke has not been described as a major clinical feature of these diseases.

CAA also occurs in the context of Alzheimer's disease, Down's syndrome, and as a sporadic condition. Sporadic CAA may be suspected in patients aged 60 years or older with multiple hemorrhages confined to lobar brain regions and no other cause of hemorrhage. Gradient-echo MRI may be helpful to establish the presence of small previous hemorrhages. Whereas the biology of vascular damage in CAA appears to be distinct from other types of hemorrhage, there is no evidence for differences in the behaviour of the acute hematoma. Acute treatment may necessitate surgical intervention. Preventive treatment is limited to withdrawal of anticoagulant or antiplatelet agents.

Moyamoya disease

Moyamoya is a chronic progressive disease characterized by spontaneous bilateral stenosis or occlusion of the terminal carotid artery associated with telangiectatic vessels at the base of the brain (Ikezaki et al., 1997). Suzuki and Takaku observed that these collateral vessels give the appearance of a puff of smoke on arteriography and coined the name moyamoya (Suzuki & Takaku, 1969). Moyamoya occurs more frequently in females (male-to-female ratio 2:3) and is prevalent among patients $<$10 years of age, particularly of Japanese origin. Hemiplegia of sudden onset and epileptic seizures constitute the prevailing presentation in childhood. They are evoked by cerebral ischemia due to the narrowing or occlusion of the circle of Willis. Progressive narrowing of the carotid fork results in gradual development of collateral circulation. Eventual rupture of these abnormal vessels causes subarachnoid hemorrhage, the predominant manifestation of moyamoya disease in patients older than 30 years.

Most cases appear to be sporadic, but about 10% occur as familial cases. Linkage has been reported to loci on

chromosomes 3p24.2–26 and 17q25 reaching maximum lod scores of 3.46 and 4.58, respectively. Non-invasive diagnostic methods such as magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) have assisted in identifying asymptomatic family members thus increasing the number of familial cases. About 70% of cases of moyamoya disease among family members occur in siblings, whereas 24% occur in a parent and offspring.

Hypotheses concerning additional etiologies of moyamoya disease include infection with subsequent autoimmune response and environmental agents. So far, none of these hypotheses have been definitely confirmed. Instead, there is accumulating evidence that the condition is largely caused by genetic factors with multiple genes involved. Moyamoya-like vascular changes have been described in association with a variety of conditions such as von Recklinghausen disease, tuberous sclerosis, Marfan syndrome and pseudoxanthoma elasticum.

Histologically, there is a cellular fibrous thickening, or eccentric fibrosis, of the intima. The internal elastic lamina shows duplication and tortuosity, whereas the media shows atrophy and thinning. The adventitia is without major changes. The most severely affected site is confined to the carotid fork. However, similar vascular changes have been found in other organs. Recent studies on vascular smooth muscle cells derived from patients with moyamoya disease suggest an increase in elastin synthesis within arterial smooth muscle cells and elastin accumulation.

Patients have been treated with antiplatelet agents, rheologic therapy, corticosteroids and calcium-channel blockers, although the efficacy of these treatments has not been proven. Anticoagulants should be avoided because of the risk of bleeding. Good results have been reported with surgical revascularization such as superficial temporal artery to MCA anastomosis.

Monogenic disorders with stroke as part of a more complex syndrome

Hereditary hemorrhagic telangiectasia

Hereditary hemorrhagic telangiectasia (HHT) or Osler–Weber–Rendu disease is an autosomal dominant vascular dysplasia. The condition is characterized by mucocutaneous telangiectasies, severe recurrent epistaxis, gastrointestinal hemorrhage, and a high incidence of vascular malformations in the lung and brain (Guttmacher et al., 1995). Telangiectasies tend to enlarge and multiply over time. Among patients with neurological deficits, about two-thirds have embolic complications of pulmonary arteriovenous malformations (AVM). The most common mechanism is paradoxical embolism. However, rarely a thrombus may form within the fistula itself. Transient ischemic attacks during hemoptysis may be caused by air embolism from a bleeding pulmonary arteriovenous fistula. Intracranial AVMs may cause intraparenchymal or subarachnoid hemorrhage. About 25% of unselected HHT cases have evidence for cerebrovascular malformations (CVM) on magnetic resonance images of the brain. HHT should always be considered in patients with multiple CVMs.

Most HHT families have mutations in one of two known genes. *HHT1* is the endoglin gene on chromosome 9q33. Endoglin is a homodimeric transmembrane receptor which is highly expressed on endothelial cells. Endoglin binds transforming growth factor-beta (TGFβ) isoforms 1 and 3 in combination with the signalling complex of TGFβ receptors types I and II. Its expression increases during angiogenesis, wound healing, and inflammation, all of which are associated with TGFβ signalling and alterations in vascular structure. Mouse embryos lacking both copies of the endoglin gene die due to defects in vessel and heart development. *HHT2* is the activin receptor-like kinase 1 (ALK1) gene on chromosome 12q13. Like endoglin, ALK1 is a cell-surface receptor for the TGFβ superfamily of ligands that is heavily expressed in endothelial and vascular smooth muscle cells. Mice deficient in ALK1 show severe vascular abnormalities characterized by fusion of capillary plexes into cavernous vessels. Thus both *HHT1* and *HHT2* highlight the role of receptors for TGFβ family members in the regulation of vascular differentiation.

The treatment of HHT is usually limited to the management of complications. In some cases resection or occlusion of pulmonary arteriovenous fistulas may be recommended. In patients with recurrent bleedings chronic iron administration and periodic transfusion may be necessary.

MELAS

Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) is associated with several mutations in mitochondrial DNA (mtDNA). Most cases result from a point mutation (A3243G) in the $tRNA^{leucine\ (UUR)}$ gene which is associated with respiratory chain complex I deficiency. Muscle biopsy reveals ragged-red fibres.

The phenotype of MELAS is highly variable ranging from asymptomatic cases to severe childhood multisystem disease with lactic acidosis. Stroke-like episodes usually occur before age forty. The mechanisms underlying these episodes are incompletely understood. In many cases 'stroke' regions are not limited to vascular territories

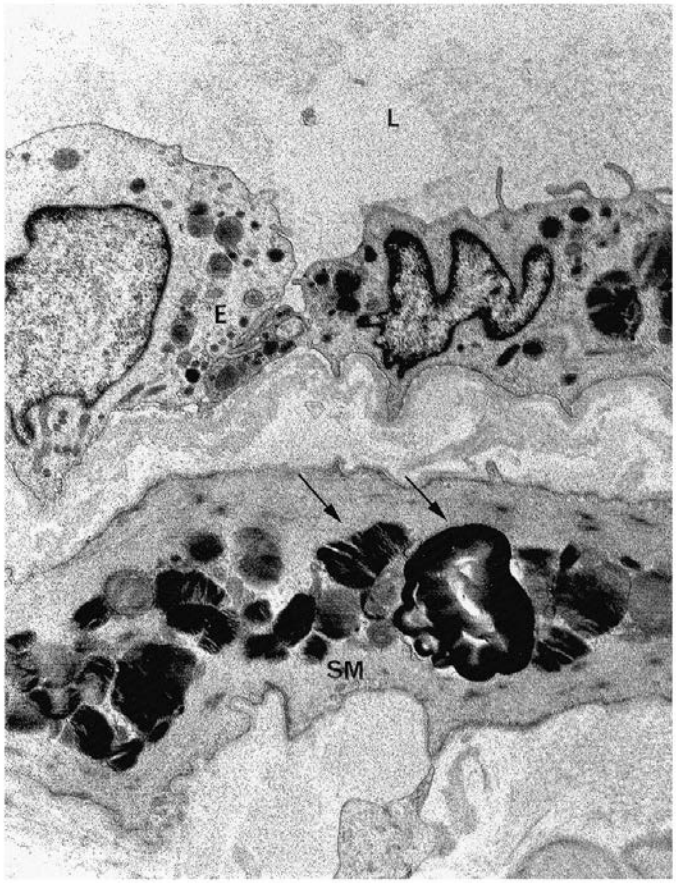

Fig. 85.4. Electron micrograph of a dermal vessel from a Fabry patient: Multilamellated zebra bodies (arrows) within vascular smooth muscle cells (L = vessel lumen; E = endothelial cell; SM = smooth muscle cell). Magnification ×16500. (Kindly provided by J Müller-Höcker, Munich.)

and cerebral angiography does not reveal embolic or stenotic lesions. These observations indicate that a mechanism other than cerebral infarction may be involved. Some authors have suggested a disturbance of the blood–brain barrier, presumably due to mitochondrial respiratory failure in the vascular endothelium (Yoneda et al., 1999). Others suspected an impaired autoregulation of cerebral blood supply secondary to metabolic abnormalities within precapillary sphincters. Both hypotheses are supported by studies that have indicated increased numbers of enlarged and structurally abnormal mitochondria in endothelial cells, pericytes, and vascular smooth muscle cells of capillaries and small arteries. In addition, primary defects in neuronal oxidative metabolism may be involved in the pathogenesis of stroke-like episodes in MELAS.

Several anecdotal reports have advocated the use of coenzyme Q, dichloroacetate, creatine, or vitamins in MELAS. However, in one of very few controlled trials there was no significant effect of coenzyme Q and multiple vitamins in mitochondrial diseases.

Fabry disease

Fabry disease (FD), is an X-linked recessive disorder due to alpha-galactosidase A deficiency. The deficiency of this enzyme results in progressive accumulation of glycosphingolipids in all areas of the body, but predominantly in the lysosomes of endothelial, perithelial and smooth muscle cells of blood vessels. Cerebrovascular symptoms are mediated both by large- and small-artery involvement (Mitsias & Levine, 1996). The latter is characterized by progressive occlusion of blood vessels, secondary to deposition of glycosphingolipid within the vessel wall (Fig. 85.4). The most frequent sign of large artery disease is dolichoectasia of the basilar and vertebral arteries. Large infarcts involving the cortex have been explained by artery-to-artery embolism from ectatic vessels. There is accumulating evidence for a prothrombotic state in Fabry disease. Some patients may develop intracranial hemorrhage (ICH). The latter may be caused by vessel degeneration as well as uncontrolled hypertension from renal failure. In hemizygous patients the penetrance for cerebrovascular involvement on MRI is complete by about age 54. In female heterozygotes the penetrance and expressivity of the phenotype is much lower. The diagnosis of Fabry disease may be suspected based on the typical skin changes that characterize the disease ('angiokeratoma corporis diffusum'): clustered non-blanching angiectases primarily over the lower part of the trunk, buttocks, and scrotum. Another frequent finding are painful paresthesias due to autonomic neuropathy (involvement of the vasa nervorum). The diagnosis is confirmed by skin biopsy (lipid inclusions in the vascular endothelium) (Fig. 85.4) and biochemical studies. Death usually occurs from systemic complications in particular renal failure and cardiac insufficiency. So far, there is no completely effective treatment. However, enzyme replacement therapy is under investigation. Carbamazepine or phenytoin may offer relief from the painful paresthesias.

Cerebroretinal vasculopathy (CRV) and hereditary endotheliopathy with retinopathy, nephropathy and stroke (HERNS)

Cerebroretinal vasculopathy (CRV) is a rare condition characterized by a microangiopathy of the brain and retina

in conjunction with a cerebral pseudotumour typically located within the fronto-parietal white matter. Clinical symptoms include progressive visual loss, headache, seizures, focal neurologic deficits and progressive cognitive worsening. The few families reported so far suggest an autosomal dominant pattern of inheritance. Small intracerebral vessels exhibit amorphous thickening of their walls with adventitial fibrosis. Some of the vessels become necrotic and show thrombosis. Jen et al. (1997) described a large family in which multiple members from three generations had developed a syndrome consisting of retinopathy, nephropathy and stroke. In most cases the disease had started with visual disturbances ('blind spots') followed by focal neurologic deficits within a few years. On brain magnetic resonance images these individuals were shown to have contrast enhancing lesions with surrounding vasogenic edema most commonly in the frontoparietal region. Fluorescein angiograms demonstrated capillary obliteration with telangiectatic microaneurysms. Ultrastructural examination of microvessels from different organs including the brain, kidney and skin revealed multilayered capillary basal membranes. Based on these findings the authors suspected a primary endothelial injury and coined the acronym HERNS. Apparently, CRV and HERNS represent allelic disorders. Both conditions have recently been mapped to chromosome 3p21 (Ophoff et al., 2001). Although renal insufficiency has not been reported as a feature of CRV, evidence exists that CRV and HERNS may represent variants of the same condition (Weil et al., 1999). Corticosteroids have been advocated for the treatment of edema in the acute stage. Surgical resection of the pseudotumour has not helped those who underwent this procedure.

Connective tissue disorders

Ehlers–Danlos syndrome type IV

Vascular complications are the hallmark of Ehlers–Danlos syndrome (EDS) type IV, an autosomal dominant condition due to mutations in *COL3A1*, the gene for collagen type III. The clinical diagnosis is made on the basis of at least two of the following clinical criteria: easy bruising, thin skin with visible veins, characteristic facial features, and rupture of arteries, uterus, or intestines (Pepin et al., 2000). The diagnosis is confirmed by mutational screening or biochemical studies (cultured fibroblasts synthesize abnormal type III procollagen). Hyperextensibility of the skin and hypermobility of large joints are unusual in the vascular type of EDS. Neurovascular complications include intracranial aneurysms (IA), arterial dissection and spontaneous rupture of large- and medium-sized arteries. IAs may be saccular or fusiform, and they are commonly located in the cavernous sinus (Schievink, 1997). Rupture of these aneurysms results in carotid–cavernous fistula. Rupture of any artery into a free space such as the pleural cavity requires immediate intervention, even though the tissues are friable and repair may be difficult. In contrast, rupture into a confined space may be sealed by tamponade, and in such cases, surgery may be deleterious. Arteriography carries special risks and should be avoided if possible. Whether incidental aneurysms should be treated is still unclear. Prompt surgical intervention is crucial in the treatment of bowel rupture. Women with EDS type IV who become pregnant have to be considered at high risk for uterine and vessel rupture and should therefore be followed at specialized centres.

Marfan syndrome

Marfan syndrome (MFS) is an autosomal dominant disorder characterized by abnormalities of the skeleton, cardiovascular system and eye (Pyeritz, 2000). The condition is caused by mutations in the gene encoding fibrillin-1 (*FBN1*). Major diagnostic criteria include pectus carinatum or excavatum, reduced upper to lower segment ratio or arm span to height ratio >0.5 (Fig. 85.5), scoliosis $>20°$, ectopia lentis, and dilation of the ascending aorta with or without regurgitation. Molecular diagnosis is feasible though laborious since the majority of people with MFS have private mutations in a very large gene.

The most common cerebrovascular complication of MFS is extension of aortic dissection into the common carotid arteries. Aortic dissection may further cause spinal cord infarction. Spontaneous dissections limited to the cervical arteries are less frequent. An association between MFS and intracranial aneurysms (IA) has been repeatedly proposed but also challenged (Schievink, 1997). Many of the vascular complications of MFS are due to the changes in elastic arteries, which are age dependent and are localized primarily in the media. They include fragmentation and disarray of elastic fibres, degeneration of smooth muscle cells, and separation of muscle fibres by collagen and pools of mucopolysaccharide. As a result, the ascending aorta becomes less distensible and stiffer than usual.

Individuals with MFS should avoid intense physical or emotional stress. Patients should be considered for β-adrenergic blockade. Annual echocardiographic studies are recommended. In some cases, surgery may become necessary. Individuals with MFS should use routine antibiotic prophylaxis before dental and other procedures that carry a high risk of introducing bacteria into the bloodstream.

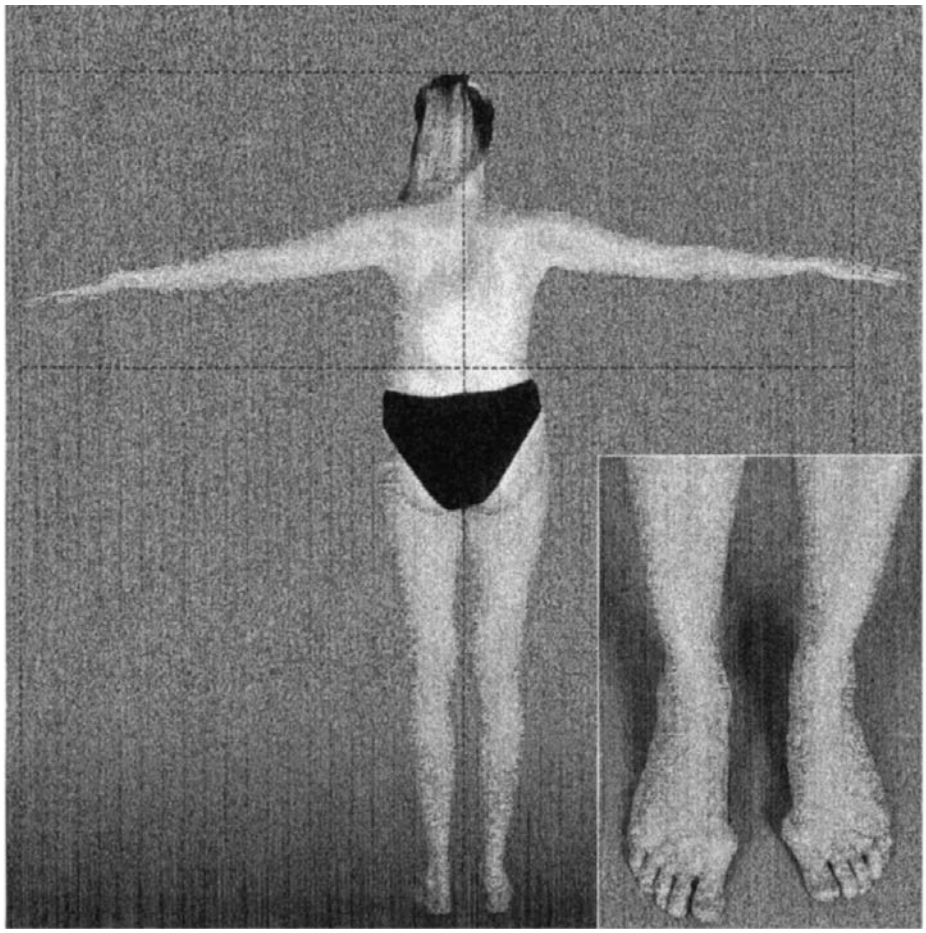

Fig. 85.5. Back view of a 33-year-old patient with Marfan syndrome and cerebrovascular complications. Note the characteristic skeletal abnormalities (reduced upper to lower segment ratio, arm span to height ratio >0.5, scoliosis, pes planus).

Pseudoxanthoma elasticum

Pseudoxanthoma elasticum (PXE) is characterized by calcification of elastic fibres in the skin, eye and cardiovascular system. Typical skin changes consist in yellowish-grouped papules beginning on the lateral aspect of the neck. Ophthalmoscopic examination reveals mottled appearance of the retina as well as angioid streaks which are due to the breakdown of the elastic lamina of Bruch's membrane. The diagnosis may be confirmed by histologic examination of a skin biopsy. Recently, mutations in *ABCC6*, a member of the ATP-binding cassette (ABC) gene subfamily C have been shown to cause autosomal recessive and autosomal dominant variants of the disease (Ringpfeil et al., 2000). However, the mechanisms by which these mutations become pathogenic are still unknown. Cardiovascular complications are common due to calcification of the internal elastic lamina of mostly medium-sized arteries. Patients with PXE are at an increased risk of developing ischemic infarction. There are several case reports on a co-occurrence of PXE with intracranial aneurysms or spontaneous dissection of cervical arteries. However, these observations may be fortuitous. Platelet inhibitors, high systemic blood pressure and contact sports should be avoided because of an increased risk of bleeding. Patients should be followed by an ophthalmologist. Nutritional restrictions (calcium) are controversial.

Neurofibromatosis Type I

Neurofibromatosis Type 1 (NF1) is a progressive systemic disease involving tissues of meso- and ectodermal origin. Inheritance is autosomal dominant with a high rate of new mutations. The *NF1* gene codes for neurofibromin, a large tumour suppressor protein.

Cerebrovascular symptoms are a rare though accepted complication of the disease (Rizzo & Lessell, 1994). Stenosis, and eventually occlusion of the supraclinoid internal carotid artery is the most commonly reported abnormality. Intracranial arterial occlusions are often associated with a moyamoya-like pattern of collateral vessels which indicates that stenosis develops early in life. There have been a number of case reports on intracranial aneurysms (IA) in NF1 (Schievink, 1997). However, an association between IAs and NF1 has not been firmly established. The vascular pathology in NF1 includes concentric growth of the intima, disruption of the elastica, and nodular aggregates of proliferating smooth muscle cells. These findings are in agreement with studies that have demonstrated a vascular expression of NF1 within smooth muscle cells and vascular endothelium. The impact of *NF1* mutations on the vascular pathology is further corroborated by a mouse model of mutations in p120-rasGAP and *NF1* genes. Like p120-rasGAP, neurofibromin has been shown to act as a GTPase activating protein (GAP) on Ras. Disruption of p120-rasGAP in mice affects the ability of endothelial cells to organize into vascularised networks, and mutations in *GAP* and *NF1* genes have a synergistic effect on the observed phenotype which includes thinning and rupture of large and medium-sized arteries during embryonic development. There is no specific therapy for cerebrovascular complications in NF1.

Autosomal dominant polycystic kidney disease (ADPKD)

Patients with ADPKD may develop cysts not only in the kidney but also in other organs including liver, spleen, pancreas and subarachnoid space. The systemic nature of ADPKD is demonstrated by its associated cardiovascular abnormalities. Vascular complications include mitral valve prolapse, aortic root dilatation, aortic dissection, aortic aneurysm and coarctation. The association of intracranial aneurysms (IA) with ADPKD has been firmly established (Schievink, 1997; Chapman et al., 1992). IA (mostly saccular) are found in about one-fourth of autopsy cases of ADPKD and they are responsible for death in up to 20% of the cases. ADPKD is caused by mutations in one of two genes: *PKD1* (Chr 16p13.3) or *PKD2* (Chr 4q13–23). *PKD1* accounts for approximately 85% of pedigrees and is associated with a more severe phenotype. Polycystin-1, (the gene product of *PKD1*) and polycystin-2 (the gene product of *PKD2*) are transmembrane proteins that are coordinately expressed in vascular smooth muscle cells. It has been suggested that polycystin-1 preserves vascular integrity during angiogenesis by stabilizing the adhesion of cells to each other or to the extracellular matrix. This hypothesis is supported by recent animal data. Mice homozygous for targeted mutations in *PKD1* and *PKD2* exhibit focal hemorrhage, particularly in tissues undergoing angiogenesis. Patients with ADPKD may be at higher risk for invasive procedures, presumably because of increased vascular fragility.

Homocystinuria

Of the several autosomal recessive enzyme deficiencies that cause homocystinuria cystathionine beta-synthase deficiency, in which the conversion of homocysteine to cytstathionine is impaired is the most common form (Mudd et al., 1995). Homocystinuria may also result from disturbances in the conversion of homocysteine to methionine by a pathway that requires the formation of methylated derivatives of both folate and vitamin B12.

The disease should be considered in any child with stroke, mental retardation, or atraumatic dislocation of optic lenses. Other features include skeletal abnormalities (marfanoid habitus) and premature atherosclerosis and thrombosis. Cerebrovascular accidents account for about one-third of thromboembolic complications. Damage to the endothelium is suspected to be a critical step of the atherosclerotic process. Homocysteine has been shown to directly damage endothelial cells and increase smooth muscle cell proliferation in vitro. Putative factors whereby homocysteine may induce vascular injury further include extracellular matrix modification, lipoprotein oxidation and effects on platelet survival time and coagulation. Mild to moderate elevations of plasma homocysteine have been established as an independent risk factor for extracranial carotid artery stenosis and cardiovascular complications including stroke.

Early diagnosis of homocystinuria is critical, as the frequency of clinical complications can be minimized by instituting an appropriate diet and, in some forms of the disease, large daily doses of pyridoxine. Betaine, a methyl donor that recycles homocysteine to methionine, is recommended for those who do not tolerate a methionine-restricted diet and do not respond to pyridoxine. Folate is recommended because of a secondary deficiency. Antiplatelet agents are given to prevent thromboembolic complications. Patients with homocystinuria are at increased risk for surgery and need special perioperative care.

Miscellaneous

A large number of heritable hemoglobinopathies, coagulopathies, and platelet disorders are associated with an

increased risk for cerebrovascular complications. This also applies for heritable forms of cardiac arrythmia, cardiomyopathy, mitral valve prolapse, intracardiac myxoma and hypercholesterolemia. A detailed description of these disorders is beyond the scope of this chapter, but is covered by a number of excellent reviews (Natowicz & Kelley, 1987; Weksler, 1995).

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86

Preventive management of stroke

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Stroke is the third most common cause of death worldwide after coronary heart disease and cancer, the most important single cause of severe disability in people living in their own homes in the UK, and consumes almost 5% of health service resources in Scotland. The overall burden of stroke disease could be reduced by improving the outcome of patients with acute stroke, and by preventing both first-ever-in-a-lifetime strokes (primary prevention) and recurrent strokes (secondary prevention).

There are three broad strategies to stroke prevention: reducing the average level of causative risk factors in the whole population (the 'mass strategy' for primary prevention), identifying and treating people at a particularly high risk of stroke (the 'high-risk' approach to primary prevention) and reducing the risk of recurrent stroke in patients with a previous transient ischemic attack (TIA) or stroke (secondary prevention) (Fig. 86.1). The 'mass strategy' will have very little effect on an individual's own risk of stroke, but the overall effect in population terms is large (Figs. 86.2 and 86.3). Conversely, the 'high-risk' and 'secondary prevention' strategies may reduce an individual's risk of stroke by a substantial amount, but will have rather little impact on the frequency of stroke in the population.

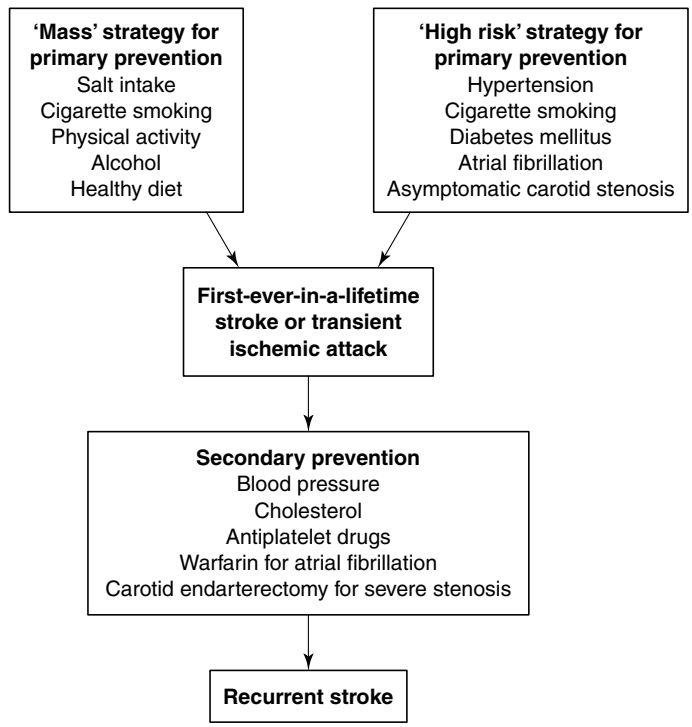


Fig. 86.1. Strategies for reducing the frequency of stroke.

The mass strategy for the primary prevention of stroke

Blood pressure and salt

A modest 5 mmHg reduction in mean population blood pressure could be achieved by reducing the mean daily salt intake in the population by 50 mmol, and this may reduce mortality from stroke by 22% (Law et al., 1991a,b). By reducing salt content of processed foods, a reduction in mean daily intake of 100 mmol could be achieved, which may further reduce the incidence of stroke.

Physical activity

Observational studies suggest that physical activity is associated with a lower risk of stroke, independent of other factors (Wannamethee & Shaper, 1999; Evenson et al., 1999). A systematic review, of largely non-randomized evidence, suggested that exercise programmes for people

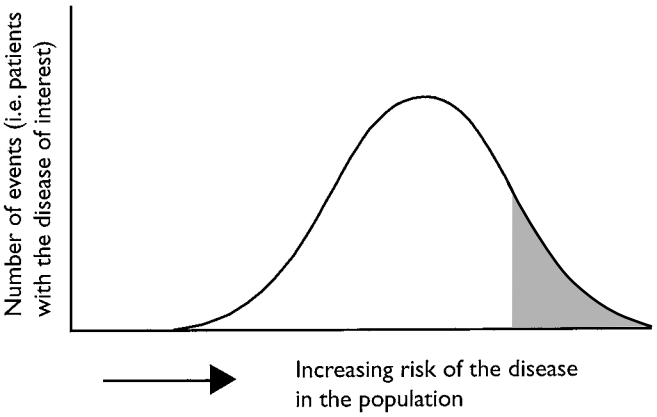


Fig. 86.2. Most cases of a disease occur in people at moderate risk, rather few (shaded) in people at the very highest risk in the right hand tail of a normal distribution.

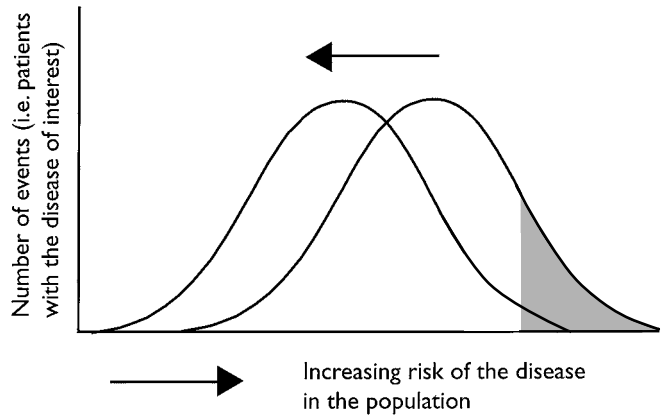


Fig. 86.3. The 'mass' strategy of disease prevention involves a small left shift in the risk distribution, by for example, moving the average blood pressure for the population. This not only reduces the number of people at high risk in the (shaded) tail of the normal distribution but also reduces the number events in the much larger number of people at moderate risk in the middle of the normal distribution.

aged 45 and over might be effective in primary stroke prevention (Nicholl et al., 1994). The benefits are probably mediated by a reduction in blood pressure, weight loss, a change in lipid profile, improved glucose tolerance, and by promoting a lifestyle conducive to other 'healthy' activities (such as reducing cigarette smoking).

Alcohol

High levels of alcohol consumption are associated with high blood pressure, and are also a risk factor for stroke and vascular dementia in a number of observational studies. However, people who drink no alcohol at all are at a slightly higher risk of cardiovascular events (possibly including stroke) than people who drink a modest to a moderate amount of alcohol regularly (Hillbom et al., 1999). Therefore, it is probably sensible to avoid heavy alcohol consumption, but whether this will reduce the risk of stroke or vascular dementia is not known (Hillbom et al., 1999; Mulrow & Jackson, 2000). Complete abstinence may not necessarily be a good idea.

Cigarette smoking

Cigarette smoking increases the risk of stroke by about 50%; and the risk increases with the number of cigarettes smoked per day (Shinton & Beevers, 1989). Cessation of smoking is associated with a reduced risk of stroke, and after five years, the risk of stroke is similar to that of people who have never smoked. Randomized trial evidence of stopping smoking has been impractical to obtain, but the observational studies are reasonably convincing.

Healthy diet and weight reduction

Observational epidemiological studies show that a diet rich in fresh fruit and vegetables is associated with a lower risk of stroke (Ness & Powles, 1999). The average Westerner must make several changes to achieve a healthier diet: reduce the total fat content to no more than 30% of calorie intake; switch from saturated animal fat to unsaturated vegetable fats; increase the intake of vegetables and fresh fruit and dietary fibre; and reduce the consumption of low-residue processed foods. Such a diet is also likely to reduce blood pressure slightly (Mulrow & Jackson, 2000). However, it is unclear whether or not a healthy diet reduces the risk of stroke and other vascular disease; and the role of increased vitamin C and fish consumption is also uncertain.

Long-term aspirin

The risk of stroke and other vascular events in healthy middle-aged people is so low that the risk of serious intra- and extracranial hemorrhage with aspirin may outweigh the potential benefits. Hence, people would get all the (small) risk of treatment and almost no benefit (Sudlow & Baigent, 2000a).

Evaluation and implementation of the 'mass strategy'

The benefits of the 'mass strategy' cannot be evaluated by a randomized controlled trial because it would be impractical to apply the intervention to a random 50% of the population; but the strategy is worth pursuing because it is prob-

ably effective, sensible and presumably safe. Politicians have much more influence than doctors in ensuring that the population adopts a healthy lifestyle (e.g. a ban on tobacco advertising, a reduction in the salt content of processed foods, facilitation of physical exercise, e.g. provision of cycle paths, and a reduction in social deprivation and poverty).

Primary prevention in high-risk individuals

Principles

The 'high-risk' strategy requires the identification and treatment of people at particularly high risk of stroke, e.g. hypertensives, smokers, diabetics, and those in atrial fibrillation or with severe carotid stenosis, by screening everyone in the community or by opportunistic 'case-finding' (for example, by measuring the blood pressure of all adults attending a doctor or nurse for whatever reason). However, even if all 'high-risk' individuals were identified, not all are prescribed treatment, and even if treatment is prescribed, compliance is often poor in people who feel well. A further problem with the 'high-risk' approach is that it is unethical to identify an individual as 'high risk' unless their risk of stroke can be reduced; because the individual will have gained nothing and may even have lost something as a result of being labelled 'sick' (Rose, 1991).

The 'high-risk' strategy is harder to sustain as one attempts to identify and treat people at moderately high risk as well as those at very high risk. The number of people at moderately high risk who would need to be treated to prevent one event is substantially larger than the number of very high-risk individuals who would need to be treated, which means that the treatment becomes less cost-effective. For example, the absolute risk of stroke is higher in elderly hypertensive people than in middle-aged hypertensive people. This means that treatment of elderly hypertensive people saves both strokes and money, whereas it costs several thousand US dollars to avoid one stroke in a middle-aged women with mild hypertension (Asplund et al., 1993).

Blood pressure lowering and primary stroke prevention

Antihypertensive drugs for primary stroke prevention amongst patients with moderate to severe hypertension have been evaluated in trials which have recruited almost 50 000 individuals. Conventional antihypertensive drugs reduced the relative risk of stroke by about 38%, with most of the benefit becoming apparent within a year or two of starting treatment (Collins & MacMahon, 1994; MacMahon & Rodgers, 1994a,b).

However, even if treatment were given to all those people with a systolic blood pressure of 160 mmHg or more, irrespective of their absolute risk of stroke, then stroke incidence would be reduced by only 15%. In practice, the actual effect of blood pressure lowering on stroke incidence will be far less, because of practical difficulties in identifying and treating all hypertensive people in the community and lack of compliance by people who feel well without treatment. It has been suggested that only about half of all people with hypertension in the community are identified; of those identified, only half are treated, and of those who are treated, only half have well-controlled hypertension (Bannan et al., 1991).

Reduction in dietary salt has substantial promise as an effective means of blood pressure control in 'high-risk' individuals as well as populations (Frost et al., 1991; Law et al., 1991a,b). It therefore seems reasonable to advise hypertensive people to reduce their dietary salt intake.

Aspirin for individuals with symptomatic vascular disease

Antiplatelet drugs reduce the relative risk of stroke and other 'vascular events', e.g. myocardial infarction or vascular deaths, by about 25% in patients with a history of symptomatic vascular disease such as myocardial infarction, angina, or intermittent claudication, even if they have not had a previous stroke or TIA (Antiplatelet Trialists' Collaboration, 1994; Antithrombotic Trialists Collaboration (ATT), 2001) (Fig. 86.4) (see p. 1418).

Atrial fibrillation and primary stroke prevention

Non-rheumatic atrial fibrillation (AF) is associated with an increased risk of stroke by a factor of five and is present in about 15% of patients with acute stroke (Wolf et al., 1978, 1991). Its prevalence increases with age, so that almost 9% of people between the ages of 80 and 89 are in AF (Wolf et al., 1991). A meta-analysis of all the available data from five randomized trials demonstrated that, after exclusion of the small number of patients who had suffered a previous stroke or TIA, oral anticoagulation (International Normalised Ratio, INR between 2.0 and 2.6) reduced the risk of ischemic stroke, all stroke, all disabling or fatal stroke and the combined endpoint of all stroke, myocardial infarction and vascular death by between one-half and two-thirds (Benavente et al., 2000a) (Fig. 86.5). The observed rates of intracranial and extracranial hemorrhage were not significantly increased by oral anticoagulants, but confidence intervals were wide.

There are people with AF who are at particularly high risk from stroke, e.g. those with a history of hypertension, diabetes mellitus, coronary heart disease, congestive cardiac

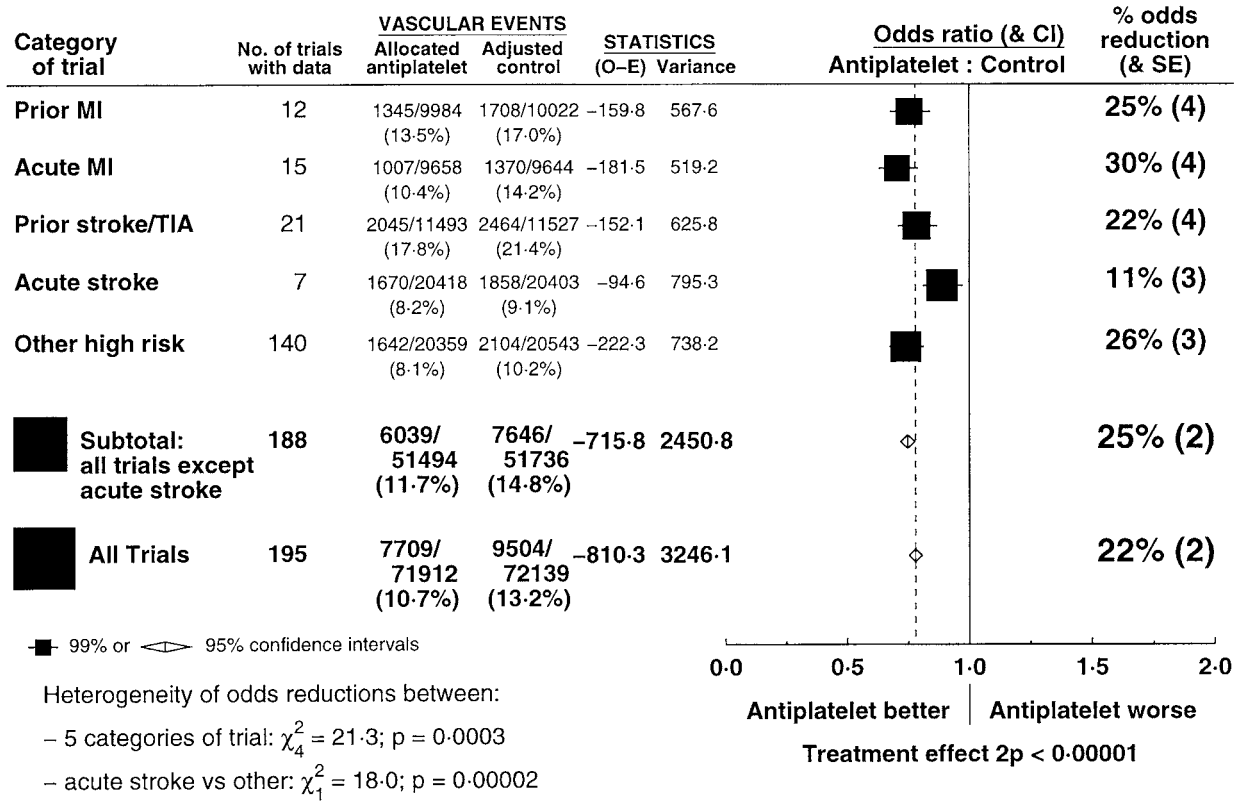


Fig. 86.4. Proportional effects of antiplatelet therapy on serious vascular events in 198 trials of antiplatelet therapy vs. control subdivided by type of patient; MI, myocardial infarction. In most trials, patients were allocated roughly evenly between treatment groups, but in some, more were deliberately allocated to active treatment; to allow direct comparisons between percentages having an event in each treatment group, adjusted totals have been calculated after converting any unevenly randomized trials to even ones by counting control patients more than once. Statistical calculations are, however, based on actual numbers from individual trials. The ratio of the odds of an event in the treatment group compared with that in the control group is plotted for each type of patient (black square: area proportional to amount of statistical information contributed by trials) along with its 99% confidence interval (horizontal line). Stratified overview of results of all trials (and 95% confidence interval) is represented by open diamond, indicating an odds ratio of 0.78 (SD 0.015) or, equivalently, an odds reduction of 22% (SD 1.6%) (With permission from Antithrombotic Trialist's Collaboration, 2000 and the *British Medical Journal*).

failure and age >75 (Hart & Benavente, 1999) (Table 86.1). 'High-risk' patients with AF have more to gain in absolute terms from anticoagulation compared with 'low-risk' patients such as young people with lone AF, i.e. without underlying heart disease. Therefore, the absolute risk of stroke should be taken into account when deciding which individual patients to anticoagulate.

Despite the evidence that anticoagulation reduces stroke risk, not all eligible patients receive it (Bath et al., 1993; Sudlow et al., 1997). The reasons are complex, but include concerns about the applicability of the trial results to patients in the community, the feasibility of monitoring anticoagulation in such a potentially large number of patients, and the long-term safety of warfarin (Sweeney et al., 1995).

The role of aspirin in primary prevention for AF

A systematic review of trials comparing antiplatelet drugs with placebo (1680 patients) in patients with non-rheumatic AF and no previous stroke or TIA found that aspirin resulted in a non-significant reduction of about 20% in the risk of ischemic stroke, all strokes, all disabling/fatal strokes and the combined endpoint of stroke, MI or vascular death. (Benavente et al., 2000b). About 10 strokes would be prevented annually for every 1000 patients given aspirin. Hence,

Table 86.1. Annual risk of stroke in patients with non-valvular atrial fibrillation

Risk group	Untreated (%)	Aspirin (%)	Warfarin (%)	Number-needed-to-treat[a]
Very high				
Previous ischemic stroke or transient ischemic attack	12	10	5	13
High				
Age over 65 and one other risk factor:	5–8	4–6	2–3	22–47
Hypertension				
Diabetes mellitus				
Heart failure				
Left-ventricular dysfunction				
Moderate				
Age over 65, no other risk factors	3–5	2–4	1–2	47–83
Age under 65, other risk factors				
Low				
Age under 65, no other risk factors	1.2	1	*ca.*0.5	200

Notes:
[a] Number-needed-to-treat with warfarin instead of aspirin for one year to prevent one stroke.
Source: Reproduced with permission from Scottish Intercollegiate Guidelines Network, 1999.

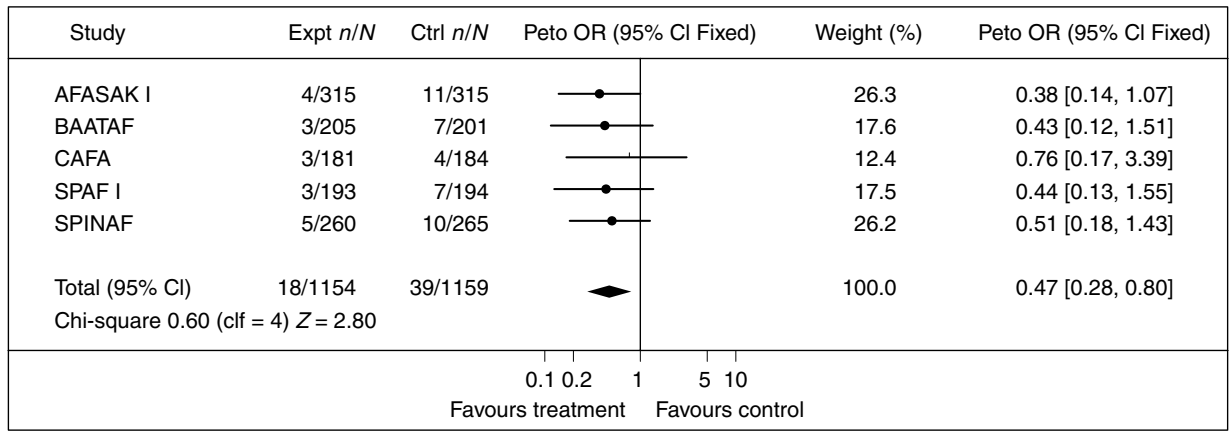


Fig. 86.5. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous stroke or transient ischemic attack. The outcome is all disabling or fatal ischemic stroke or intracranial hemorrhage. Each trial result is illustrated by a horizontal line (95% confidence interval) and a box (estimated relative reduction in odds of disabling or fatal stroke). The pooled odds ratio of 0.47 and its confidence interval are represented by a black diamond. (With permission from Benavente and Update Software 2000a.)

aspirin is less effective than warfarin, but is worth prescribing to patients where warfarin is contraindicated (Table 86.1).

Lowering plasma cholesterol and primary stroke prevention

Prospective observational studies among healthy middle-aged western populations have shown no overall association between blood total cholesterol and stroke risk (Prospective Studies Collaboration, 1995), but the lack of an overall association may conceal a positive relationship with ischemic stroke and a negative relationship with hemorrhagic stroke. Non-statin drugs do not reduce the risk of fatal or non-fatal stroke, but statin drugs (which cause a much larger reduction in plasma cholesterol) do reduce the risk of non-fatal stroke. However, they increase the risk of

fatal stroke by 17% (non-significant), perhaps a surrogate marker that statins increase the risk of hemorrhagic stroke which is more likely to be fatal than ischemic stroke (Hebert et al., 1995, 1997; Sudlow & Baigent, 2000a).

We tend to prescribe statins to patients with symptomatic coronary heart disease who have a total cholesterol of >5 mmol/l, as this will certainly reduce the risk of future cardiovascular events, and will probably reduce the overall risk of stroke as well.

Diabetes mellitus

Diabetes mellitus is associated with an increased risk of stroke. The final results of a multicentre study of over 4000 patients with type II diabetes demonstrated that 'intensive blood–glucose control', with sulphonylureas or insulin therapy to maintain a median HBA_{1C} of 7.0%, reduced the risk of any diabetes-related endpoint, including both microvascular and macrovascular complications (relative risk 0.88 (95% CI 0.79–0.99) compared with 'conventional treatment' (diet only) (UKPDS Group 1998a). However, there was no effect on the incidence of stroke (relative risk 1.11, 95% CI 0.81–1.51). A separate publication described the effect of tight blood pressure control (target level <150/85mmHg) with captopril or atenolol in the 1148 patients with hypertension (UKPDS Group, 1998b). There was a reduction in the risk of diabetes-related endpoints (RR 0.76, 95% CI 0.62–0.92) and the risk of stroke (RR 0.56, 95% CI 0.35–0.89) in patients randomized to 'tight blood pressure control'. Therefore, controlling blood pressure in patients with type II diabetes is probably more important than 'tight glucose control' in the prevention of diabetic complications and stroke.

Endarterectomy for asymptomatic carotid stenosis

Carotid endarterectomy reduces the risk of stroke (plus all perioperative strokes or deaths) in patients with a >50% asymptomatic carotid stenosis by almost two-thirds (Benavente et al., 1998). This relative risk reduction sounds impressive, but the annual risk of stroke without surgery in people with severe stenosis is only around 2% (Warlow, 1995); therefore the absolute risk reduction is only about 2% in 3 years (Benavente et al., 1998). It follows that the cost-effectiveness of surgery for asymptomatic carotid stenosis is highly questionable; about 50 patients must be operated on to prevent one having a stroke in 3 years. Nonetheless, some advocate screening for asymptomatic carotid stenosis and then offering surgery to those fit for surgery (perhaps under the age of 80 years). However, this would be extremely expensive, and even if surgery was done on all those aged 50–79 years, stroke incidence would only be reduced by about 6% in the next year, and maybe by a similar amount in each subsequent year.

Unless subgroups of particularly 'high-risk' patients can be identified, we would not recommend screening for asymptomatic carotid disease, because there is so little benefit of surgery for individual patients, and because surgery will have so little impact on the incidence of stroke in the population. Also, there are not enough resources to operate on everyone with an asymptomatic stenosis.

Other interventions

A systematic review of all epidemiological studies investigating the relationship between homocysteine and the risks of cardiovascular and cerebrovascular disease found that elevated total homocysteine levels were associated with an increased risk of coronary artery and cerebrovascular disease in cross-sectional population and case-control studies, but most prospective studies found a smaller or no association (Christen et al., 2000). Hence, it is uncertain whether or not elevated homocysteine levels cause cardiovascular and cerebrovascular disease. Further studies are required to investigate whether or not a reduction of total homocysteine levels is followed by a reduction in the risk of atherothrombotic vascular disease; and randomized trials of multivitamin therapy (to reduce homocysteine levels) are in progress (Hankey & Eikelboom, 1999).

Secondary prevention of stroke

Principles

Stroke physicians and neurologists regularly see patients in clinics and hospital wards who have already had TIAs and strokes. Their role is to ensure that these patients receive the best possible advice and treatment to minimize their risk of recurrent events.

The risk of recurrent stroke after a TIA or ischemic stroke is about 10% in the first year, and then about 5%/year. The risk of recurrent stroke following primary intracerebral hemorrhage is uncertain as it has not been well studied. There are some patients who are at particularly high risk from further events following their TIA or stroke, so it is important to ask the question 'What is the risk of another important vascular event in this particular patient?' Prognostic models have been developed to identify which particular patients are at highest risk from recurrent stroke and other vascular events, but these models have yet to be properly validated in independent cohorts of patients (Table 86.2).

Table 86.2. Prediction equation for survival free of stroke, myocardial infarction or vascular death in a patient with transient ischemic attacks

Age in years	Minus 60	Multiplied by 6
Female		Subtract 68
Transient ischemic attack of the eye (amaurosis fugax) only		Subtract 56
Number of transient ischemic attacks in the last 3 months (n)		Add $1.5 \times (n-1)$
Carotid and vertebrobasilar transient ischemic attacks		Add 71
Peripheral vascular disease		Add 84
Residual neurological signs		Add 66
Left-ventricular hypertrophy (ECG)		Add 54
		Total score = y

Divide y by 100 and exponentiate ($e^{y/100}$) = x

Probability of survival free of stroke, myocardial infarction or vascular death:

at 1 years = 0.95^x

at 5 years = 0.79^x

Notes:

Example: 65-year-old woman with five episodes of amaurosis fugax only in last 3 months and ECG shows left ventricular hypertrophy.

	Cumulative score
65–60 years = 5 multiplied by 6	30
Female: subtract 68	−38
Transient ischemic attack of the eye (amaurosis fugax) only: subtract 56	−94
Five transient ischemic attacks in the last 3 months: add $(1.5 \times [5-1])$	−88
Left-ventricular hypertrophy (ECG): add 54	−34
	Total score = −34

Divide −34 by 100 and exponentiate ($e^{-0.34}$)

$= 1/(e^{0.34})$

$= 1/1.4$

$= 0.7$

Probability of survival free of stroke, myocardial infarction or vascular death:

at 1 year = $0.95^{0/7} = 0.96$ or 96%

at 5 years = $0.79^{0.7} = 0.85$ or 85%.

The most common cause of death following a TIA is coronary heart disease rather than recurrent stroke; and patients are also at risk of developing cognitive impairment and vascular dementia. Hence, a physician must also consider how to prevent vascular disease in general as well as stroke, although in practice, broadly similar interventions are usually appropriate.

The risk of recurrent stroke is highest early after the initial event, which means that early assessment and intervention are important. This has implications for adequate provision of outpatient services, including prompt access to carotid Doppler studies.

Treat any specific underlying cause

If a treatable cause for cerebral ischemia is identified, e.g. vasculitis, endocarditis, then specific treatment should be given. In practice, though, this only applies to a very small proportion of patients with ischemic stroke.

Strategies for secondary stroke prevention

These can be divided into two broad categories: risk factor modification which applies to patients with both ischemic and hemorrhagic stroke, e.g. control of blood pressure, and specific interventions, e.g. antiplatelet drugs, anticoagulants and vascular surgical procedures, which apply only to patients with ischemic events.

General risk factor modification

The same advice about 'healthy lifestyles' should be given to patients who have had a previous stroke or TIA as to those who have not experienced vascular events. Because

patients who have had a stroke are at much higher risk of another one compared to the risk of a first stroke in the general population, their absolute benefit from risk factor control is considerably higher. The effect of exercise on the risk of recurrent events is uncertain, but it is reasonable to suggest that, after a stroke, patients should be encouraged to return to normal physical activities. Even though the levels of physical activity likely to reduce the risk of further vascular events may not be achievable, exercise may bring other benefits such as reducing the risk of falls (Campbell et al., 1998; Gillespie et al., 2000).

Blood pressure reduction

Although the role of blood pressure reduction in the primary prevention of stroke is well established, its effect on reducing the risk of recurrent stroke is less clear. A systematic review of the data from 2742 patients from the two trials of blood pressure reduction in patients with ischemic stroke, and the two trials where beta-blockers were used to prevent recurrent events, found a relative reduction in the risk of stroke of 19%, which was not statistically significant (MacMahon & Rodgers, 1994a,b, PROGRESS Management Committee, 1996). Since then, a large placebo-controlled trial in China of blood pressure reduction with the diuretic indapamide in 5665 stroke survivors (some of whom were 'normotensive') published a preliminary report suggesting that the treatment achieved a reduction of 2 mmHg in diastolic blood pressure over two years which was associated with a 29% reduction in stroke risk (PATS Collaborating Group, 1995).

Long-term blood pressure reduction after stroke may not be beneficial because in theory this may precipitate a further stroke. A large trial evaluating the balance of risks and benefits of blood pressure reduction in TIA and stroke survivors is attaining completion, the Protection against Recurrent Stroke Study (PROGRESS) trial (PROGRESS Management Committee, 1996). Until the results are available in 2001, we tend not to treat patients unless their blood pressure exceeds about 160/90 mmHg. We usually delay initiation of treatment after stroke for at least one or two weeks as drops in blood pressure shortly after a TIA or stroke may have adverse effects on cerebral blood flow.

Cholesterol

In patients with and without a history of ischemic heart disease, statins reduce the risk of stroke (Hebert et al., 1997). However, it is unclear whether cholesterol reduction in patients following a TIA or ischemic stroke is also beneficial: ongoing trials will provide further information. In the meantime, we prescribe statins to patients with an elevated cholesterol who also have a history of ischemic heart disease.

Antiplatelet drugs

In patients with a history of past ischemic stroke or TIA, antiplatelet drugs reduce the risk of vascular events from about 22% to about 18%, equivalent to the avoidance of 38 serious vascular events per 1000 patients treated over about 3 years (Antiplatelet Trialists' Collaboration, 1994). In an overview of the long-term trials, hemorrhagic strokes occurred in 0.5% of controls and 0.6% of treated patients (Antithrombotic Trialists' Collaboration, 2000), but this small but definite hazard is outweighed by the reduction of recurrent ischemic stroke, both in the acute phase of stroke, and in long-term secondary prevention.

In the Antithrombotic Trialists' (ATT) review, aspirin was the most extensively tested drug. The data suggest that doses of less than 75 mg may not be as effective as doses of between 75 mg and 300 mg. Our preferred dose of aspirin is 75 mg daily, which probably minimizes the risk of adverse effects and is as effective as higher doses. Most of the trials evaluating aspirin in high-risk patients lasted only 2 or 3 years (Antiplatelet Trialists' Collaboration, 1994). The benefits of continuing aspirin beyond this period have not been evaluated formally, but it seems sensible to suggest that individuals who are at continuing high risk because of past stroke or TIA should probably continue aspirin lifelong, provided there are no adverse effects.

If a patient continues to have vascular events while on aspirin, it is worth checking whether the clinical diagnosis is correct, e.g. are these events really TIAs, or could they be focal seizures, whether other vascular risk factors are being optimally managed, and whether the patient is complying. If all these have been checked, some clinicians increase the dose of aspirin, whilst others change to a different antiplatelet drug or add another one. At present, there is no evidence that, for patients in sinus rhythm, anticoagulation is better than aspirin alone, but in patients who are having very frequent TIAs on aspirin, we tend to use heparin, then warfarin, at least for a few weeks.

The thienopyridines, ticlopidine and clopidogrel, inhibit the binding of adenosine diphosphate (ADP) to its receptor on platelets. Forty-five trials comparing ticlopidine with control, recruiting 7600 patients, have been completed. Ticlopidine reduced the relative odds of a serious vascular event by 31% (95% CI, 18%–42%) (Antithrombotic Therapy Trialists' Collaboration, 2000). Although there are no trials comparing clopidogrel with control, the data are consistent with both drugs being effective (Hankey et al., 2000).

Four trials (22 656 high vascular risk patients) have compared ticlopidine or clopidogrel with aspirin. There was an overall reduction in the relative odds of a serious vascular event of 9% (95% CI 2–16%) (Hankey et al., 2000). The *Drug and Therapeutics Bulletin*, an independent UK publication which reviews new treatments, concluded 'clopidogrel appears to offer little or no advantage over aspirin' (Anon, 1999). Furthermore, clopidogrel is very much more expensive than aspirin. The role of adding clopidogrel to aspirin is uncertain, but further trials (if performed) may resolve this issue.

Dipyridamole has been compared with control in 15 trials (over 5700 patients). There was no clear evidence of benefit: the 16% reduction in the odds of vascular events was only marginally significant (95% CI, 3%–28%) (Antithrombotic Trialists' Collaboration, 2000). This suggests that dipyridamole alone may not be an effective antiplatelet agent. The most recent analyses based on 25 trials (10 400 patients) showed that the combination of dipyridamole and aspirin was associated with a non-significant 6% reduction in serious vascular events (95% CI, 6% increase to 17% reduction) compared with aspirin alone and a 24% reduction in the relative odds of non-fatal stroke (99% CI, 2%–42%) (Antithrombotic Trialists' Collaboration, 2000). In a subgroup analysis of patients with a TIA or minor stroke, the addition of dipyridamole produced an 18% reduction in the relative odds of a vascular event ($2P = 0.01$), and a 29% reduction in non-fatal stroke ($2P = 0.002$).

The ESPRIT trial is now comparing aspirin with aspirin plus dipyridamole with oral anticoagulant (INR 2–3), in 4200 patients with TIA and ischemic stroke, so additional data will become available about the combination of dipyridamole and aspirin (de Schryver & Algra, 2000).

The data at present suggest that dipyridamole alone is not particularly effective, and until ESPRIT is completed, it is unclear how much benefit there is from adding dipyridamole to aspirin. Because of the cost and extra adverse effects, e.g. headache, we would not use the combination as first-line therapy. However, if a patient who already takes aspirin has a recurrent vascular event, we tend to add dipyridamole.

Secondary stroke prevention for people in atrial fibrillation

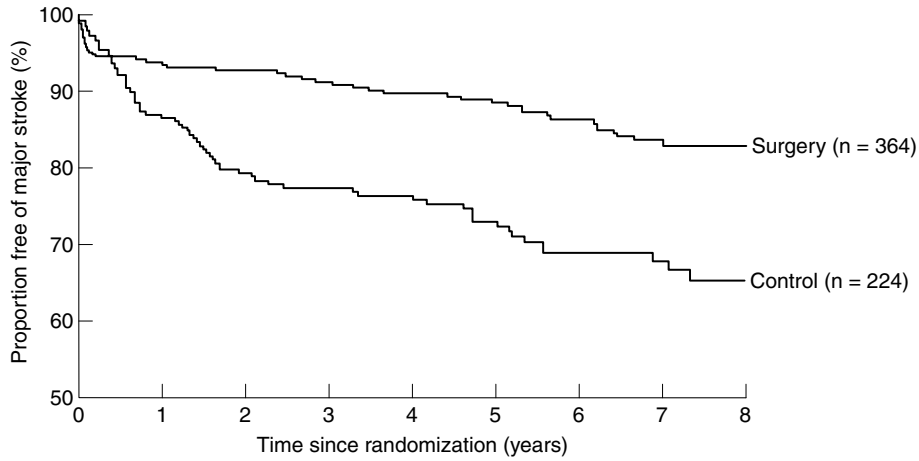
Atrial fibrillation (AF) increases the risk of stroke by about five times, mainly as a consequence of emboli from the fibrillating left atrium. Patients in AF who have had a TIA or minor ischemic stroke are at considerable risk of recurrent stroke. A meta-analysis of data from two trials recruiting 485 people in AF and a previous TIA or minor ischemic stroke found that anticoagulants (INR 2.5–4.0) reduced the risk of recurrent stroke by two-thirds (odds ratio 0.36, 95% CI 0.22–0.58) and also reduced the risk of all vascular events by almost half. No intracranial bleeds were reported among patients given anticoagulants (Koudstaal, 2000).

Fixed minidose warfarin regimens, either alone or in combination with aspirin, have not been adequately evaluated for secondary prevention. Their lack of effect in the primary prevention trials suggests that further randomized trials, to identify the lowest effective anticoagulant intensity for secondary prevention of stroke, would not be worthwhile.

For long-term secondary prevention after TIA or ischemic stroke in patients in AF, we would routinely attempt to use moderate-intensity oral anticoagulants (INR 2–3) rather than antiplatelet drugs. However, there are some patients for whom anticoagulation may be contraindicated, e.g. uncontrolled hypertension, recent gastrointestinal bleeding, liver disease, confusion or dementia, tendency to falls. Clinicians must ensure that the risks of treatment do not outweigh the benefit, and also that patients are prepared to accept the inconvenience of regular blood tests and the increased risk of bleeding. It is unclear how soon after ischemic stroke anticoagulants should be started: we tend to wait for at least 2 weeks, as this may minimize the risk of hemorrhagic transformation of the infarct.

Most of the trials have tested only a few years of anticoagulants, so it is unclear whether the balance of risk and benefit alters with prolonged therapy, although the risk of bleeding does appear to increase with increasing duration of treatment (Levine et al., 1998). Further research is required to determine the optimum duration of anticoagulation. If the patient remains at high risk from stroke, if no bleeding has occurred, and if no new risk factors for bleeding have developed, e.g. falls or dementia, we tend to continue anticoagulants.

If a physician feels that the risks of anticoagulation outweigh the benefits, or if the patient is not prepared to accept the inconvenience and risks of anticoagulation, then aspirin is often prescribed as an alternative. The only trial which has compared aspirin with placebo in patients with AF and a previous ischemic stroke or TIA found a non-significant reduction in the risk of recurrent stroke from 12% per year to 10% per year (odds ratio 0.89, 95% CI 0.64–1.24) (European Atrial Fibrillation Trial Study Group, 1993). Further work is probably required to confirm whether or not aspirin is definitely beneficial, but in the meantime, we prescribe aspirin if anticoagulation is contraindicated.



Number at risk

Surgery	364	335	326	306	286	249	195	143	100
Control	224	189	172	165	158	128	92	63	43

Fig. 86.6. Kaplan–Meier survival curves to show survival free of major stroke (with non-stroke deaths occurring more than 30 days after surgery censored) in surgery and control patients with 80–99% stenosis of the symptomatic carotid artery (With permission from *Lancet* 1998 and European Carotid Surgery Trialist's Collaboration.)

A systematic review of the six trials (3874 patients) with cardio- and cerebsovascular disease found that the addition of aspirin to anticoagulants doubled the risk of intracranial hemorrhage (Hart & Benavente, 1999). For most patients, the combination should be avoided. However, some patients are at particularly high risk of thromboembolism, e.g. those with mechanical prosthetic valves, so the greater antithrombotic benefit of the combination may outweigh the extra bleeding risk (Loewen et al., 1998).

Angiotensin converting enzyme (ACE) inhibitors

The findings of the Heart Outcomes Prevention Evaluation study suggest that the benefits of inhibition of the angiotensin converting enzyme, with ramipiril, are greater than might be expected from its effect on blood pressure reduction (Heart Outcomes Prevention Evaluation Study Investigators, 2000a,b,c). These data suggest that activation of the renin–angiotensin system may be an independent risk factor for cardiovascular disease and that ACE inhibitors might have protective effects on the arterial wall. Further work is required in this area.

Oral contraceptives and hormone replacement therapy (HRT)

Young women who have a stroke of any pathological type whilst on oral contraceptives should stop them, and other vascular risk factors should also be addressed, e.g. smoking.

It is unclear whether HRT should be discontinued in the event of a stroke or TIA. Observational epidemiological data suggest that, amongst women free of vascular disease when they start treatment, HRT is more likely to prevent coronary heart disease events than cause breast or uterine cancer, and may also reduce the risk of limb bone fractures. There are several ongoing randomized trials of HRT in primary and secondary prevention of vascular disease.

Carotid endarterectomy for symptomatic carotid stenosis

Endarterectomy of recently symptomatic severe carotid stenosis almost completely abolishes the high risk of ischemic stroke ipsilateral to the operated artery over the subsequent 2 or 3 years, and this effect probably lasts for at least 8 years (European Carotid Surgery Trialists' Collaborative Group, 1998; Mayberg et al., 1991; Barnett et al., 1998). Even after taking into account the early risk of surgery, the balance of surgical risk and long-term benefit is in favour of surgery (Fig. 86.6).

On average, there is clearly an advantage to surgery when the symptomatic stenosis exceeds about 80% diameter reduction of the arterial lumen using the European Carotid Surgery Trial method, which is equivalent to about 70% using the North American Carotid Surgery Trial method. The risk of surgery is unrelated to the severity of stenosis and because the unoperated risk of stroke in patients with less than 60% (ECST) stenosis is so low, the

Table 86.3. Models to predict ipsilateral ischemic stroke (the medical model) and surgical stroke or death (the surgical model) derived from the European Carotid Surgery Trial

Prognostic variable	Hazard ratio	(95% CI)	*P*	Predictive points
Medical model				
Cerebral vs. ocular events	2.45	(1.09–3.71)	0.02	1
Plaque surface irregularity	2.09	(1.21–3.62)	0.008	1
Any events within the last 2 months	1.82	(1.02–3.18)	0.04	1
Carotid stenosis (per 10% stenosis)	1.30	(1.10–1.40)	0.001	0–2
Surgical model				
Female sex	2.05	(1.29–3.24)	0.002	−0.5
Peripheral vascular disease	3.48	(1.51–4.13)	0.0004	−0.5
Systolic BP > 180 mmHg	2.21	(1.39–3.79)	0.004	−0.5

Notes:
Medical model: a Cox's proportional hazards model for ipsilateral carotid territory major ischemic stroke (i.e. fatal or lasting longer than 7 days) on medical treatment derived from the 857 patients with 0–69% stenosis randomized to no-surgery in the European Carotid Surgery Trial.
Surgical model: a multiple logistic regression model for any major stroke (i.e. fatal or lasting longer than 7 days) or death from other causes within 30 days of carotid endarterectomy derived from the 1203 patients with 0–69% stenosis randomized to surgery in the European Carotid Surgery Trial.
In the risk factor model, which is applied to the 70–99% stenosis group, surgical predictive points are subtracted (i.e. become negative) and their weighting is reduced by 50%.
With permission from European Carotid Surgery Triallist's Collaboration.

risk of surgery outweighs the benefit. For patients with between 60% and 80% (ECST) stenosis there is still some uncertainty because there may be a few patients at high enough risk of stroke who would gain from surgery. At present, it is unclear what these risks are for individuals but we do have an approximate idea of what the risks may be in groups of individuals. By adding risk 'points' from a 'medical' model predicting stroke without surgery, and subtracting the 'risk' points from a 'surgical' model predicting the risk of surgery, a score can be calculated which may be clinically useful (Table 86.3). In the 16% of patients in the ECST, with recently symptomatic and severe carotid stenosis and a score above 3.5, there was an advantage to surgery. In patients with a lower score, there was no clear advantage to surgery and even net harm. This approach must be validated in other data sets before it can be widely recommended, but it may reduce the 'numbers-needed-to-treat' to avoid a stroke from 10 to about three (Rothwell et al., 1999b).

It is important to remember that the risk of stroke declines with time after a TIA or ischemic stroke. If the diagnosis is delayed for several months, then the risk of surgery may no longer be justifiable. Ideally, patients should be investigated quickly and efficiently to minimize the problem.

A few patients with a lacunar ischemic stroke or lacunar TIA have an ipsilateral severe carotid stenosis. The question then arises whether the stenosis is 'asymptomatic' (i.e. the stenosis is a coincidental bystander and the infarct was really due to intracranial small vessel disease). There are so few patients in the randomized trials that it is unclear whether or not surgery is beneficial (Boiten et al., 1996). Observational studies show that severe stenosis is about equally rare in the symptomatic and contralateral carotid arteries, which supports the idea of the ipsilateral stenosis being coincidental, but the numbers are too small to be sure (Mead et al., 2001). We would probably recommend surgery, particularly if the stenosis is very severe (>90%), because even if the artery was 'asymptomatic' the risk of stroke without surgery is probably high enough to justify the risk of surgery. The same arguments probably apply if there is also a major coexisting source of embolism from the heart (such as non-rheumatic atrial fibrillation), in which case the patient may reasonably be offered surgery as well as anticoagulation.

It is uncertain whether carotid endarterectomy should precede, follow or be combined with coronary artery bypass surgery in patients who have both cerebrovascular and cardiac symptoms severe enough to require surgery.

Carotid angioplasty and stenting

The one reasonably large randomized trial of carotid angioplasty so far available suggests that the procedural stroke complication rate is similar to carotid endarterectomy (albeit with wide confidence intervals) and that there are few strokes in the long term (with even wider confidence intervals), although the risk of minor morbidity, e.g. neck hematomas and cranial nerve palsies, was lower in patients randomized to angioplasty (CAVATAS, 2000). Larger trials are now being planned to establish both the safety and durability of angioplasty and stenting compared with surgery (Crawley et al., 2000a).

If the benefits do turn out to be greater than the risks, angioplasty, with or without stenting, may be applicable not just to patients presently eligible for carotid endarterectomy but also to those who are unfit for surgery, for stenoses too distal for direct surgery, and for other causes of arterial stenosis such as irradiation and fibromuscular dysplasia.

Surgery and angioplasty for vertebrobasilar ischemia

There are no large randomized trials of surgery or angioplasty for patients with vertebrobasilar ischemia (Crawley et al., 2000b), so at present, we cannot recommend such treatments.

In conclusion, our role as doctors is to ensure that individuals at high risk of stroke and those who have already had TIAs and stroke receive optimal treatment and advice to reduce their risk of serious cerebrovascular and cardiovascular events. Also, whenever possible, we should put pressure on politicians to facilitate healthy changes in the lifestyle of the whole population, which will, ultimately, have a much bigger impact on the burden of stroke disease in the population.

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Part XI

Neoplastic disorders

87

Primary brain tumours in adults

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Approximately 29 000 primary benign and malignant central nervous system tumours are diagnosed in the United States each year (CBTRUS, 1998). Histological diagnosis, location, biological tendency to infiltrate into surrounding brain, surgical resectability, and patient age at diagnosis are strong determinants of their associated morbidity and mortality. Although primary brain tumours are generally resistant to cytotoxic therapies, recent advances in chemotherapy, radiation therapy, and drug delivery in conjunction with more novel therapeutics based upon molecular and cellular biological mechanisms have created new opportunities for prolonging life and preserving the quality of life for brain tumour patients. Even though primary tumours occur infrequently (less than 2%) relative to more common systemic neoplasms such as breast, lung and prostate, they contribute substantially to cancer morbidity because they present at early- to mid-adult life and can rapidly cause neurological disability.

The World Health Organization (WHO) has established a histopathological classification system that divides primary brain tumours into nine separate categories on the basis of routine histochemical and immunohistochemical criteria intended to identify the cell of tumour origin (Table 87.1) (Kleihues et al., 1993). This classification scheme is a standard for pathological diagnosis and clinical decision making. It is generally recognized that all classification schemes available to date have many limitations and need to incorporate molecular and genetic criteria that reflect cellular origins and distinct pathways of transformation. The WHO category of Tumours derived from neuroepithelial tissue consists of nine subcategories that include the most common glial tumours: astrocytoma, oligodendroglioma, ependymoma, and mixed glioma. In adults, gliomas represent the largest proportion of primary brain tumours, accounting for approximately 50% of the total. Meningiomas are the next most common comprising approximately 20–25%, followed by pituitary adenomas, nerve sheath tumours and primary CNS lymphoma that each represent less than 10% of all primary brain tumours (CBTRUS, 1998). A brief summary of the most common gliomas and meningiomas follows. A more comprehensive and detailed description of primary brain tumours can be found in *Tumors of the Central Nervous System* (Burger & Scheithauer, 1994).

Astrocytomas

Astrocytomas are the most common of the gliomas. These tumours have a predilection for the cerebral hemispheres and occur in a range of aggressiveness or tumour 'grade' that, along with patient age at diagnosis, strongly predicts the tumour's biological behaviour and patient survival (Figs. 87.1 and 87.2). The World Heath Organization established a system that divides the infiltrative astrocytomas into three grades (II–IV) of increasing malignancy on the basis of the presence or absence of nuclear atypia, cellular mitoses, micovascular proliferation, and necrosis (Table 87.2) (Kleihues et al., 1993). Low grade astrocytomas (grade II) contain nuclear atypia without other features; anaplastic astrocytomas (grade III) display nuclear atypia and mitoses; and glioblastomas (grade IV) display the additional features of endothelial proliferation and/or necrosis. WHO grade I designates a distinct type of well-demarcated resectable and surgically treatable astrocytoma that includes pilocytic astrocytoma, which is more common in children than in adults, and the subependymal giant cell astrocytoma associated with tuberous sclerosis. The St. Anne-Mayo system uses three histologic features similar to those in the WHO system, but combined in a non-hierachical fashion to generate four tumour grades that are similar, although not always identical, to those defined by the WHO system (Daumas-Duport et al., 1988). Low grade

Table 87.1. World Health Organization classification of CNS tumours

I	Tumours of neuroepithelial tissue
	A. Astrocytic tumours
	1. Astrocytoma
	2. Anaplastic astrocytoma
	3. Glioblastoma
	4. Pilocytic astrocytoma
	5. Pleomorphic xanthoastrocytoma
	6. Subependymal giant cell astrocytoma
	B. Oligodendroglial tumours
	1. Oligodendroglioma
	2. Anaplastic oligodendroglioma
	C. Ependymal tumours
	1. Ependymoma
	2. Anaplastic ependymoma
	3. Myxopapillary ependymoma
	4. Subependymoma
	D. Mixed gliomas
	1. Mixed oligo-astrocytoma
	2. Anaplastic oligo-astrocytoma
	E. Choroid plexus tumours
	1. Choroid plexus papilloma
	2. Choroid plexus carcinoma
	F. Neuroepithelial tumours of uncertain origin
	G. Neuronal and mixed neuronal–glial tumours
	H. Pineal tumours
	I. Embryonal tumours
II	Tumours of cranial and spinal nerves
	A. Schwannoma
	B. Neurofibroma
	C. Malignant peripheral nerve sheath tumour
III	Tumours of the meninges
	A. Tumours of meningothelial cells
	1. Meningioma
	2. Atypical meningioma
	3. Anaplastic (malignant) meningioma
	B. Mesenchymal, non-meningothelial tumours (benign and malignant)
	C. Primary melanocytic lesions
	D. Tumours of uncertain origin
	1. Hemangiopericytoma
	2. Capillary hemangioblastoma
IV	Hemopoietic neoplasms
V	Germ cell tumours
VI	Cysts and tumour-like lesions
VII	Tumours of the anterior pituitary
VIII	Local extensions from regional tumours
IX	Metastatic tumours

Table 87.2. Histologic grading of astrocytic tumours

Features used for grading	
atypia	
mitoses	
endothelial proliferation	
necrosis	
World Health Organization (WHO) system	
Grade II	nuclear atypia only
Grade III	nuclear atypia and mitoses
Grade IV	nuclear atypia, mitoses and either endothelial proliferation or necrosis
St Anne–Mayo (Daumas–Duport) system	
Grade 2	any single feature
Grade 3	any two features
Grade 4	any three or all four features

astrocytoma (WHO grade II) is often referred to as 'benign', which is somewhat of a misnomer since low grade astrocytomas are generally not surgically resectable and frequently progress to higher 'malignant' grade tumours (WHO grades III and IV) over time.

Oligodendroglioma

Oligodendrogliomas are very cellular infiltrative gliomas composed of predominantly oligodendroglial cell types. These tumours are best recognized by the classic appearance of uniform collections of cells with round nuclei and a distinctive perinuclear halo that occurs as an artefact of tissue handling. Like astrocytomas, oligodendrogliomas arise most frequently in the cerebral hemispheres, but they differ from astrocytomas in their predilection for cortical grey matter, a high frequency of calcification, and somewhat clearer demarcation from surrounding brain. Their involvement with cortex and tendency to grow slowly explains their frequent association with partial seizure disorders in otherwise asymptomatic patients. Low grade oligodendrogliomas are more likely than low grade astrocytomas to show some enhancement on CT or MR imaging. Mixed oligoastrocytomas are histological variants containing a mixture of regions with oligodendroglial and those with astroglial features. Survival for patients with well-differentiated oligodendroglioma is longer than that for well-differentiated astrocytoma. Whether the presence of astroglial features reduces patient prognosis relative to pure oligodendroglioma remains controversial. Malignant or anaplastic oligodendrogliomas can present *de novo* or progress from previously well-differentiated

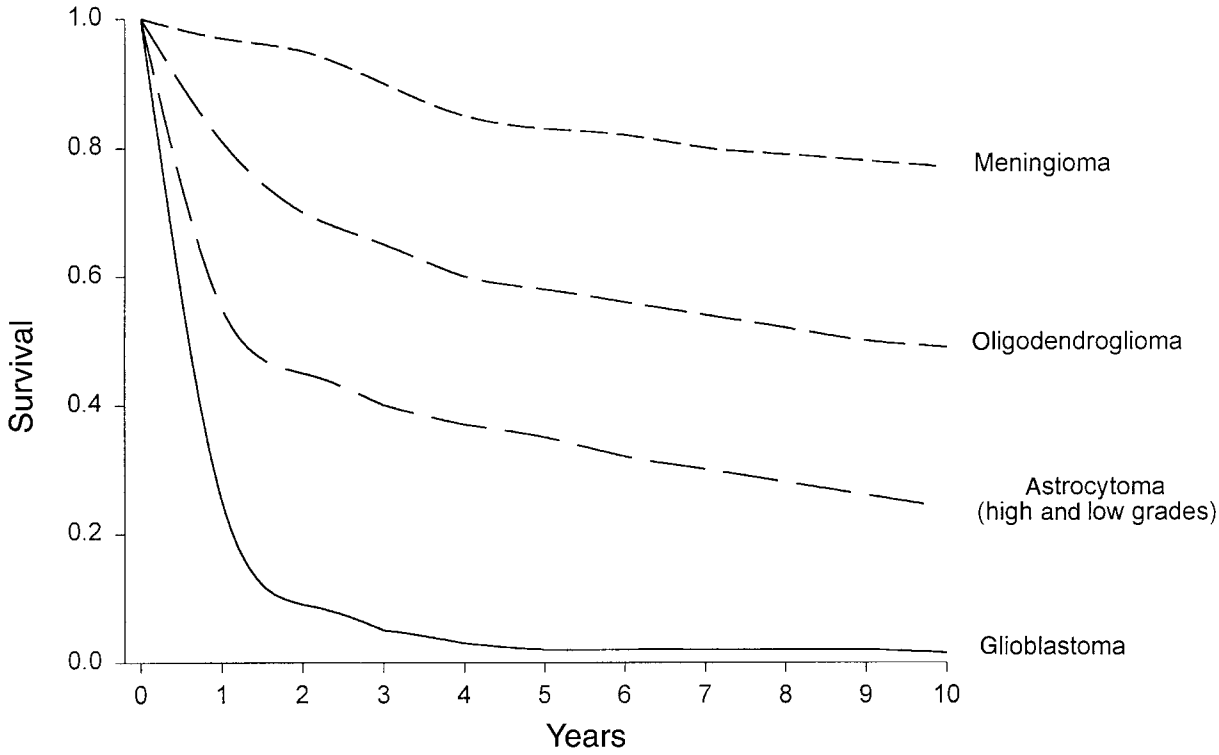

Fig. 87.1. Relative survival for adults according to histologically confirmed brain tumour type. (Modified from Davis et al., 1998.)

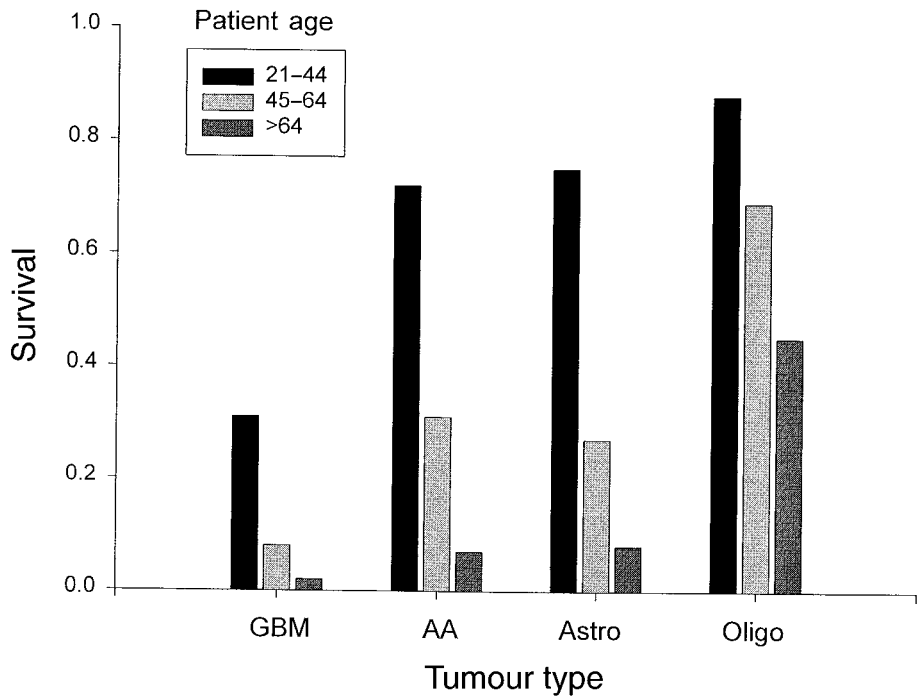

Fig. 87.2. Two-year relative survival for patients with specific brain tumours according to patient age at time of diagnosis (from SEER program of the National Cancer Institute, 1973–1994). (Modified from Wrensch *et al.*, 2000.)

oligodendrogliomas. Anaplastic oligodendrogliomas have many of the malignant features associated with the high grade astrocytomas, although an objective grading system remains to be established. These features include hypercellularity, cellular atypia, mitoses, vascular proliferation and necrosis. The combined loss of chromosomal segments 1p and 19q has recently been associated with prolonged survival and enhanced chemoresponsiveness in oligodendroglioma and anaplastic oligodendroglioma.

Ependymoma

Ependymomas are gliomas derived from the lineage of ependymal cells that line the ventricular system and central spinal canal. These tumours can develop throughout the neuraxis most commonly as intraventricular masses or within brain parenchyma next to the ependymal lining. Intracranial ependymomas arising within the posterior fossa are most commonly found in children. Ependymomas in adults most commonly present at supratentorial and spinal locations. Intracranial and true spinal cord ependymomas present with a spectrum of grades from well differentiated to anaplastic or progress over time from well differentiated to malignant. Anaplastic ependymomas display hypercellularity, mitoses, vascular proliferation, perivascular pseudorosettes and necrosis. Ependymomas of the filum terminale and sacrum are typically of the myxopapillary variant that is a benign, very well-differentiated lesion that rarely progresses to higher grade.

Meningioma

Meningiomas warrant inclusion in this overview, since they represent the second most common primary brain tumour. In contrast to the majority of gliomas diagnosed in adults, most meningiomas are well-circumscribed benign tumours that are frequently cured with surgical resection. Nevertheless, significant morbidity and mortality can result from histologically benign meningiomas that recur and progressively enlarge at sites from which they cannot be removed completely (e.g. cavernous sinus region, skull base) or from relatively rare invasive or malignant histological types. Meningiomas are derived from meningothelial cells of the arachnoid villi at their association with dural membranes. The most common locations are the parasagittal falx cerebri, lateral convexity, and sphenoid ridge, and less frequently tentorium, tuberculum (suprasellar), olfactory groove, and optic nerve sheath are affected. Intraventricular meningiomas occasionally arise from meningothelial cells of the choroid plexus of the lateral ventricles.

A large number of benign histologic variants of uncertain prognostic significance exist. The meningothelial (syncytial), fibrous and transitional meningiomas are the most common of these histological forms. Although described as discrete types, these histological forms are often seen together within single tumours. Meningothelial meningiomas consist of lobules of meningioma cells containing oval nuclei, solitary nucleoli, and nuclear–cytoplasmic inclusions. Indistinct cellular borders give the appearance of a syncytium. Fibrous meningiomas consist of elongated spindle-shaped cells with abundant extracellular collagenous matrix. Transitional meningiomas display both meningothelial and fibrous features and also contain prominent whorls and psammoma bodies consisting of laminated acellular mineral deposits.

Certain gross and histologic criteria are associated with an increased risk of progressive meningioma growth or recurrence (Perry et al., 1997). The majority of meningiomas are amenable to gross total surgical resection, and totally resected classic benign meningiomas have a low 10-year recurrence rate of about 20%. Obviously incomplete resection due to tumour location or involvement of vascular structures, or of cranial nerves, substantially raises the risk for subsequent growth. Histologic features associated with early recurrence include mitotic rates of $\geqslant 4$ per 10 high-powered fields, sheet-like growth, hypercellularity and cellular atypia. Meningiomas with these features are considered 'atypical'. Features of malignancy include invasion into adjacent brain, cellular anaplasia, necrosis, and the acquisition of sarcomatous features. Subtypes likely to pursue a more aggressive course are clear cell, choroid, rhomboid and papillary.

Cellular and molecular pathogenesis

It is now well recognized that cancer develops most commonly as a series of discrete molecular/genetic events that result in the stepwise accumulation of abnormalities in fundamental cell regulatory pathways (Vogelstein & Kinzler, 1993). Many of these defects act on growth factor signalling pathways that tightly regulate cell division, cell survival, differentiation, cell–cell and cell–matrix interactions, and angiogenesis that under normal circumstances control tissue growth, differentiation and response to injury. Dysregulation of these same growth factor pathways through the direct or indirect involvement of proto-oncogene or tumour suppressor gene products results in oncogenic transformation, uncontrolled cell growth and cancer.

The discovery that certain retroviruses cause oncogenic transformation in mammalian cells led to the detection of

specific viral oncogenes and ultimately to the identification of closely related normal cellular genes (proto-oncogenes) from which the viral oncogenes were derived. Mutational activation or overexpression of these proto-oncogenes is now recognized to play a fundamental role in cancer formation and malignant progression in humans. Proto-oncogenes code for a diverse array of gene products that include cell surface receptors such as the epidermal growth factor receptor erb2 and the scatter factor/hepatocyte growth factor receptor c-met, second messenger signaling molecules such as src and ras, and transcription factors that directly regulate gene expression such as fos, jun, and myc (Bos, 1989; Bottaro et al., 1991; Cantley et al., 1991; Wasylyk et al., 1998; Wong et al., 1987). Conversely, tumour suppressor genes coding for proteins that down-regulate oncogenic pathways under normal circumstances have been identified. Loss of expression or inactivation of tumour suppressor genes is equally important to proto-oncogene activation in the multistep process of initiation and progression of brain tumours (Fig. 87.3). The interplay between the increasing number of recognized tumour suppressors and proto-oncogenes is complex and the subject of numerous comprehensive reviews (Bronchud et al., 2000). Those pathways presently considered to be of particular importance are briefly summarized below.

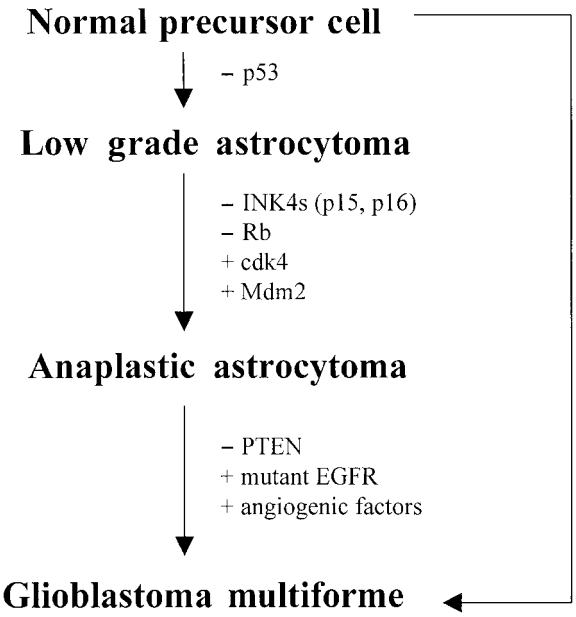

Fig. 87.3. Sequential loss of tumour suppressor and gain of tumour promoter functions commonly involved in the development and malignant progression of astrocytic tumours.

Tyrosine kinase receptor pathways

Numerous growth factors associated with tumour formation and malignant progression are now known to signal target cells via transmembranous cell surface tyrosine kinase receptors. Examples include epidermal growth factor, fibroblast growth factors, insulin-like growth factors, platelet-derived growth factor, scatter factor/hepatocyte growth factor, and vascular endothelial growth factor (Doolittle et al., 1983; Fleming et al., 1992; Friesel & Maciag, 1995). Depending upon receptor and receptor ligand expression patterns, such growth factors can function in an autocrine and/or paracrine fashion to enhance tumour growth and malignancy. For example, the malignant progression of solid tumours including gliomas from relatively low to high grades is linked to the emergence of an angiogenic phenotype that results from expression by tumour cells of angiogenic growth factors, some of which act exclusively upon vascular endothelial cells, i.e. vascular endothelial growth factor, VEGF (Bicknell et al., 1997; Senger et al., 1993). In contrast to VEGF, other glioma cell-derived growth factors, e.g. scatter factor/hepatocyte growth factor, act both in an autocrine fashion directly upon receptor-expressing tumour cells and in a paracrine fashion upon receptor-expressing endothelial cells (Abounader et al., 1999; Laterra et al., 1998). In certain circumstances, such as in the case of the epidermal growth factor receptor, somatic mutations result in expression of a truncated receptor that is constitutively activated in the absence of growth factor binding (Steck et al., 1988; Wong et al., 1992).

Growth factor binding to the extracellular domains of dimerized tyrosine kinase receptors results in the initiation of cytoplasmic signaling cascades mediated by a series of highly specific protein phosphorylation events (Weiss & Schlessinger, 1998). These cascades are initiated by receptor autophosphorylation at tyrosine residues within discrete cytoplasmic amino acid sequences. Phosphorylation creates binding sites for the recruitment and activation of proteins containing SH2 (src-homology 2) domains (Songyang et al., 1993). Binding and activation of these intermediate signalling proteins, in turn, selectively activate specific downstream enzymatic cascades that elicit specific cell responses. Examples of SH2 proteins are phospholipase C, the p85 subunit of phosphatidylinositol 3-kinase, Grb2, and the p120 Ras GTPase-activating protein. There is substantial interdigitation of the downstream signalling pathways activated by distinct receptor tyrosine kinases, which results in the ability of individual receptors typically to influence multiple pathways (Fig. 87.4) (Kazlauskas, 1994). Discrimination of downstream signaling events and their effects upon cellular physiology and

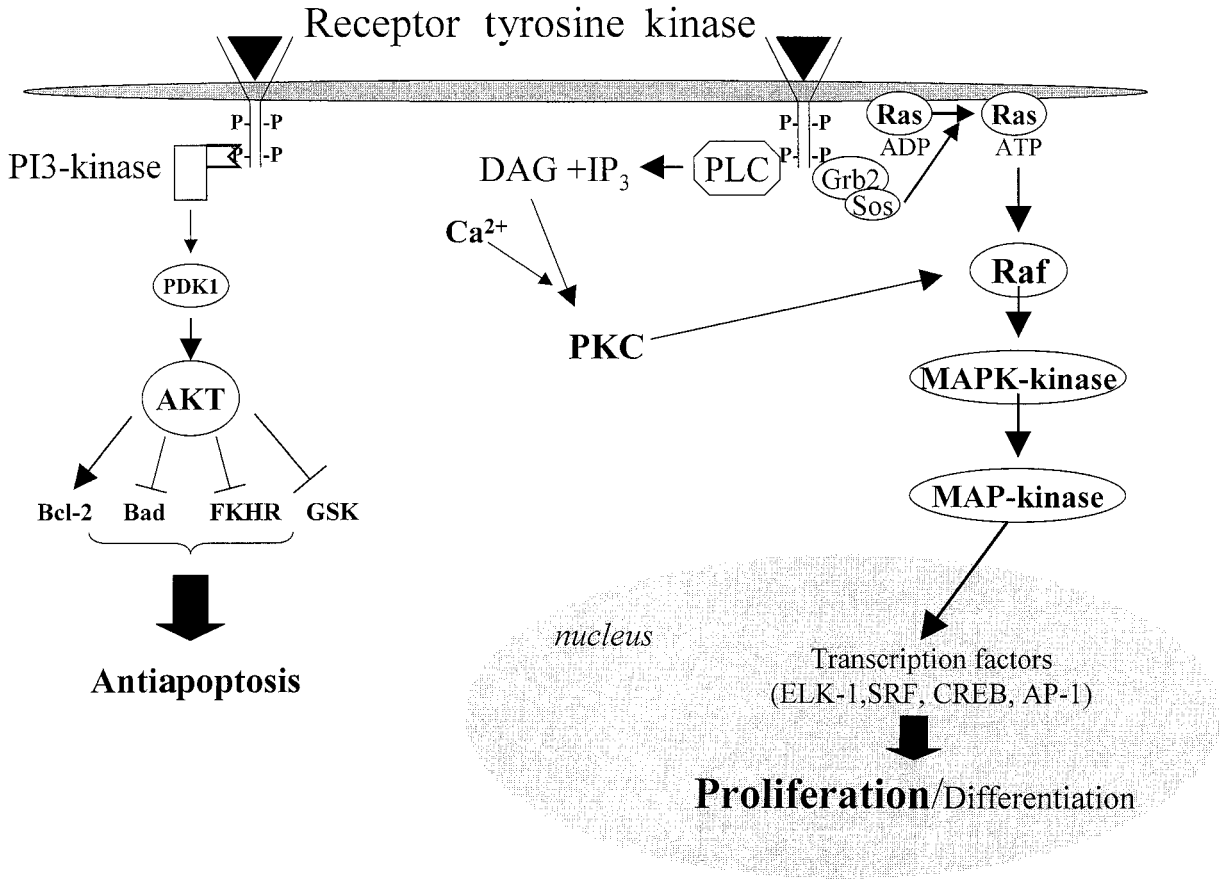

Fig. 87.4. Signalling pathways activated by extracellular ligand-binding to receptor tyrosine kinases in gliomas. PI3-kinase (phosphatidylinositol 3-kinase), PLC (phospholipase C), IP_3 (inositol-triphosphate), DAG (diacylglycerol), PKC (protein kinase C), MAPK (mitogen-activated protein kinase), FKHR (forkhead transcription factor), GSK (glycogen synthase kinase), SRF (serum-response factor), CREB (cyclic-AMP response element binding protein), AP-1 (activator-complex protein-1).

gene expression are influenced by receptor type, receptor number and degree of activation, cell type and the cell's overall environmental context.

The mitogen-activated protein kinase (MAP-kinase) pathway is one of the most prominent and well-characterized pathways activated by receptor tyrosine kinases (Lewis et al., 1998). Activated receptors bind the Grb2: SOS complex that activates Ras, a membrane-bound GTP/GDP exchanger that plays a pivotal role in regulating cell survival, proliferation, and differentiation responses to extracellular signals (Egan et al., 1993; Feldkamp et al., 1997; Rozakis-Adcock et al., 1993). Although mutations resulting in permanently activated Ras are associated with numerous cancers, they appear to play a minimal role in glioma oncogenesis and progression (Bos, 1989). There is great interest in developing pharmacological inhibitors of Ras, however, because of its central role in multiple signalling pathways involved in brain tumour malignancy (Guha et al., 1997). Activated Ras recruits the serine/threonine kinase Raf, which via intermediate kinases leads to the activation of MAP-kinase (Lewis et al., 1998). MAP-kinases are final effector cytoplasmic proteins that upon phosphorylation and activation translocate to the nucleus (Lenormand et al., 1993) where they activate gene expression through the activation of specific transcription factors such as Elk-1, serum response factor (SRF) and cyclic-AMP response element binding protein (CREB), and activator-protein-1 (AP-1) (Gille et al., 1995; Ginty et al., 1994).

Phosphatidylinositol 3-kinase (PI3-kinase) can be activated by binding directly to phosphorylated tyrosine kinase receptors via its p85 regulatory subunit or indirectly through activated RAS (Carpenter & Cantley, 1996). PI3-kinase-dependent RAS and MAP-kinase activation also occurs. PI3-kinase activation ultimately results in the acti-

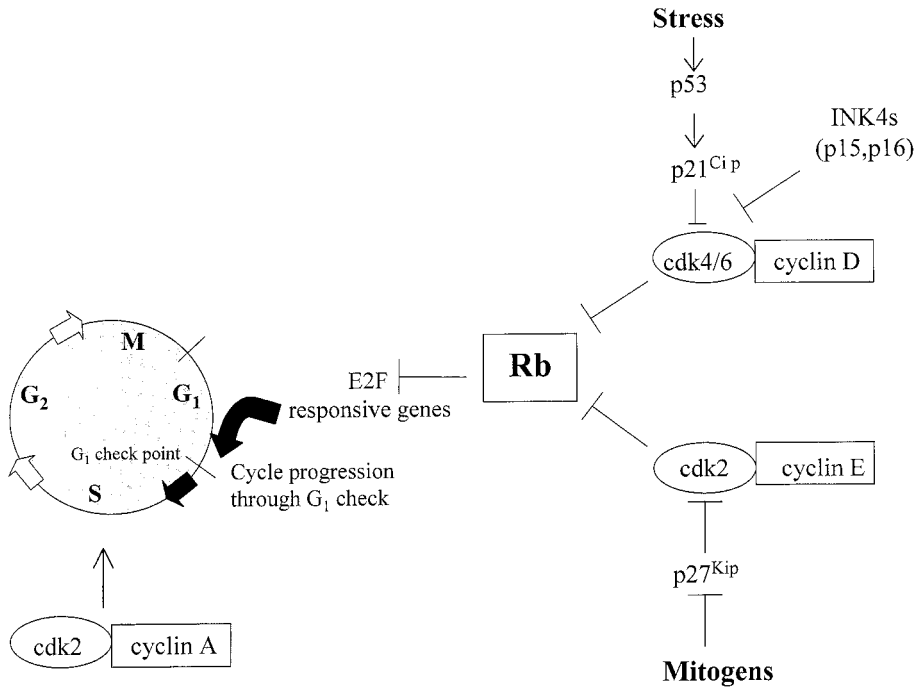

Fig. 87.5. Cell cycle regulatory pathways commonly altered in gliomas. Rb (retinoblastoma protein), cdk (cyclin-dependent kinase), INK (inhibitor of cyclin-dependent kinase).

vation of proteins containing pleckstrin homology domains (Lemmon et al., 1996). One of the most important is AKT (protein kinase B), an intermediate antiapoptotic signal that enhances tumour cell survival and resistance to cytotoxic therapies (Bowers et al., 2000; Downward, 1998). Just how AKT activation enhances brain tumour cell survival is not totally understood, but it appears to involve multiple effector pathways such as induction of Bcl-2, the inhibition of the proapoptotic factor Bad, activation of β-catenin, and phosphorylation of the forkhead family of transcription factors (Datta et al., 1997; Tang et al., 1999). Phospholipase-C (PLC) is activated by binding directly to phosphorylated receptors. Activated PLC catalyses the formation of inositol triphosphates and diacylglycerol from membrane phospholipids, resulting in elevation of free calcium and activation of protein kinase C (PKC) (Nishizuka, 1992). PKC feeds into the MAP-kinase pathway to activate immediate early response genes and subsequent AP-1-dependent gene expression.

The cell cycle

Normal somatic cell replication occurs as a cycle consisting of a sequence of tightly regulated events that control DNA replication (S phase) and the correct segregation of replicated chromosomes to duplicate daughter cells during cell division (mitosis, M phase). Gap phases G_1 and G_2 reside immediately before S phase and between S phase and mitosis, respectively. Quiescent cells reside in G_0 outside the cell cycle. Uncontrolled error-prone cell replication is a fundamental and prominent feature of cancer cells. Recent discoveries in the molecular biology of cell cycle regulation point to multiple control mechanisms altered in cancer. These range from genetic mutations to aberrant activation of growth factor signalling pathways that alter the expression and function of specific cell cycle regulatory proteins (Fig. 87.5) (Sherr, 2000).

Cells residing in G_1 are stimulated to complete a cell cycle and replicate by multiple environmental cues including growth factors, cell–cell interactions, and cell–matrix interactions. If proliferative signals are strong enough to drive cells beyond a certain point in late G_1, i.e. the restriction or check point, the cells commit to complete a full cycle and divide. Progression through the cell cycle is regulated by specific cyclin-dependent kinases (CDKs), their regulatory subunits known as cyclins, and cyclin-dependent kinase inhibitors (Morgan et al., 1985; Sherr, 1993; Sherr & Roberts, 1995). One of the key regulators of cell cycle progression beyond the restriction point is the growth suppressor Rb, the retinoblastoma protein. Under

conditions of relative mitogen deprivation, Rb forms complexes with and inhibits E2F transcription factors, thereby repressing the expression of E2F-responsive genes required for DNA synthesis and cell cycle progression (Nevins, 1998). Growth factor stimulation results in activation of cyclin D-associated CDKs (cdk4/cdk6) that phosphorylate Rb, releasing E2F transcription factors; these then translocate from cytoplasm to nucleus and transactivate S-phase-dependent genes, including cyclins E and A. Cyclin E-cdk2 complexes further amplify Rb phosphorylation and mediate passage through the G_1 check point independent of continued cell stimulation by mitogens and mitogen-dependent cyclin D-cdk4/6 activity (Hatakeyama et al., 1994). Cyclin A-cdk complexes mediate cell cycle progression in late G1 and S phases. Two families of cdk inhibitors, Cip/Kip and INK4 oppose cdk action and slow cell cycle progression (Cheng et al., 1999; Ruas & Peters, 1998). In unstimulated quiescent cells, levels of the cyclin E inhibitor $p27^{Kip1}$ are relatively high. Sequestration of p27 by cyclin D-cdk4/6 complexes facilitates activation of cyclin E-cdk2 and cyclin E-dependent cell cycle progression. Cyclin D-cdk4 inhibition by $p21^{Cip}$ plays an important role in p53-mediated G1 arrest that occurs in response to DNA damage (el-Deiry et al., 1993). The INK4 (inhibitors of cdk4) proteins slow cell cycle progression by binding and inhibiting cyclin D-cdk4/6 complexes, thereby releasing Cip/Kip proteins that in turn bind to and inhibit cyclin-dependent kinases. Overexpression of cdks and loss of cyclin-dependent kinase inhibitor expression play important roles in the malignant progression of numerous cancers, including the gliomas (Biernat et al., 1997) (Fig. 87.3).

p53 pathways

Loss of p53 function often occurs early in the course of glioma development (Chen et al., 1995; von Deimling et al., 1992). Possibly the most frequently mutated tumour suppressor gene in human cancer, p53 normally plays a fundamental role in preventing DNA injury and subsequent oncogenesis through two major actions: inhibition of the cell cycle and induction of apoptosis (Vogelstein et al., 2000). Under normal conditions, cellular levels of p53 remain very low because of its very rapid degradation via specific targeting to proteolytic degradation pathways (Kubbutat & Vousden, 1997; Maki & Howley, 1997). Activation of p53 through protein stabilization occurs in response to cellular stress signals associated with DNA damage and dysregulated cell proliferation. The mechanism by which p53 activation directs cells to either arrest growth or die is not completely clear, but it appears to depend upon the type and degree of cell injury (Vogelstein et al., 2000). Certain findings suggest that the preferential pathway is one of cell cycle arrest to allow subsequent DNA repair. Excessive DNA damage or uncorrectable mutations causing uncontrolled cell proliferation may tilt the response in favour of apoptosis (Chen et al., 1996). p53 exerts most of its effects through its ability to bind to gene regulatory sequences and act as a transcription factor. Activated p53 mediates G1 and G2 cell cycle arrest through the induction of the cyclin-dependent kinase inhibitor $p21^{Cip1}$ (el-Deiry et al., 1993). p53-inducible genes involved in the apoptosis response include the proapoptotic protein Bax, the cell surface death receptor Fas, and antagonists to certain cell survival factors (Fig. 87.6).

The accumulation and activation of p53 protein occurs through its stabilization in response to cell stress signals described above. Mdm2 and $p14^{ARF}$ are two proteins that play important and opposing roles in activation and stabilization of p53 (Kubbutat et al., 1997). Mdm2 binds to p53, blocks p53 transcriptional activity, and directs p53 to cytoplasmic degradative pathways. Mdm2 induction by p53 serves as a negative feedback loop to ensure against uncontrolled p53 activation. Expression of $p14^{ARF}$ is regulated by the E2F1 transcription factor that is activated under conditions of uncontrolled cell proliferation. $p14^{ARF}$ reverses Mdm2-mediated p53 inactivation and inhibits Mdm2-mediated p53 degradation (Bates et al., 1998; Ichimura et al., 2000; Newcomb et al., 2000). Thus $p14^{ARF}$ limits uncontrolled cell cycle progression even in the presence of Mdm2 expression. Genetic mutations leading to excessive Mdm2 activity and loss of $p14^{ARF}$ function are common in human gliomas (Reifenberger et al., 1993).

Angiogenesis and blood–brain barrier

Angiogenesis, the formation of new blood vessels from existing vessels, is necessary for the growth of solid tumours, including malignant brain tumours (Carmeliet & Jain, 2000; Guerin & Laterra, 1996). The extent to which angiogenesis contributes to the growth of highly infiltrative tumours such as gliomas that may obtain their blood supply from pre-existing brain vessels relative to that of non-invasive brain tumours such as meningioma has not been resolved (Wesseling et al., 1997). Blood vessel density increases concurrent with the malignant progression of brain tumours and glioblastoma multiforme is one of the most vascular of solid tumours (Brem et al., 1980; Brem, 1976). A number of angiogenic growth factors play a role in brain tumour angiogenesis, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF),

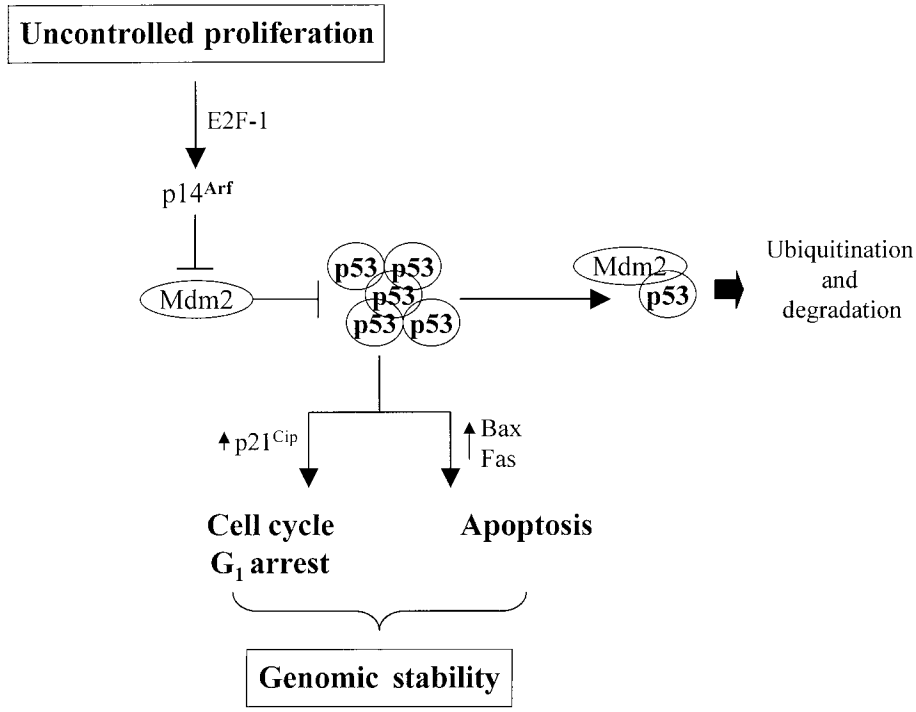

Fig. 87.6. Regulation of cell proliferation and survival by Mdm2-dependent p53 protein degradation.

and scatter factor/hepatocyte growth factor (SF/HGF) (Abounader et al., 1999; Plate et al., 1992; Schmidt et al., 1999). Endothelial cells express specific angiogenic growth factor receptors which, when activated, induce the expression of genes that stimulate otherwise quiescent endothelial cells to invade the perivascular extracellular matrix and proliferate. These genes include proteolytic enzymes such as plasminogen activators and matrix metalloproteinases and specific cell surface adhesion molecules such as integrin$_{\text{alpha v beta 3}}$ (Hsu et al., 1995; Landow et al., 1994; Liotta et al., 1991; Varner, 1997). Tissue invasion is accompanied by endothelial cell proliferation and ultimate reorganization into functional vascular loops that enhance nutrient delivery to the growing tumour. The mechanism by which VEGF expression is induced as low grade gliomas progress to malignant glioma is particularly well understood (Plate & Risau, 1995). As tumour growth rates increase, the tumour cells become relatively hypoxic due to an increasingly insufficient blood supply. Hypoxia results in the induction of hypoxia-inducible factor (HIF), a transcription factor that regulates many physiological and pathophysiological responses to hypoxia (Semenza et al., 2000). The VEGF promoter contains specific HIF-binding sites that, when complexed with HIF, enhance VEGF gene expression. The tumour cells surrounding zones of necrosis within malignant gliomas are the most hypoxic and likewise express the highest levels of VEGF (Plate et al., 1993). Recently, specific angiogenic inhibitors such as angiostatin and endostatin have been identified within tumours, but at concentrations inadequate to control the local pathological angiogenic response (O'Reilly et al., 1994, 1997). These naturally occurring angiogenesis inhibitors and pharmacologic inhibitors of the angiogenic growth factors or their receptors are currently under intense investigation for anti-angiogenic antitumour therapy.

The vasculature of gliomas differs substantially from vessels of the surrounding normal brain in its organization and degree of endothelial cell differentiation. Normal brain microvasculature is composed of highly differentiated endothelial cells, smooth muscle-like pericytes, and well-developed perivascular basement membrane, all ensheathed by perivascular astrocytic foot processes. The endothelial cells of normal brain express a number of characteristics specific to brain that collectively comprise the blood–brain barrier (Laterra et al., 1998). These consist of highly complex interendothelial tight junctions, reduced transendothelial vesicular transport, enzyme systems that limit the non-selective movement of substances from blood to brain and conversely, the up-regulation of specific biochemical transporters and enzymes that enhance the

entry of specific nutrients such as glucose and amino acids from blood to brain. These endothelial specializations are believed to result at least in part from the trophic influence of the perivascular astrocytes (Rubin et al., 1991). As gliomas progress from low to high grade, the vascular–astrocytic complex becomes increasingly disorganized as the normal perivascular astrocytes are displaced by increasingly malignant glioma cells. Glomeruloid bodies consisting of hypertrophied unperfused collections of endothelial cells are characteristic of glioblastoma. Underperfused and retrograde perfused tumour vessels lead to zones of hypoxia and inefficient systemic drug delivery (Carmeliet & Jain, 2000; Jain & Baxter, 1988). The endothelial cells of malignant glioma vessels lose their brain-specific structural and biochemical specializations required for blood–brain barrier function (Guerin et al., 1992a,b). The enhanced permeability to blood-borne substances, including proteins such as albumin, results in tumour-associated vasogenic brain edema and mass effect. Contrast-enhanced brain imaging is based on the ability of intravenously administered contrast agents to leak passively across the highly permeable tumour vessels.

Clinical features

The clinical manifestations of primary brain tumours can be attributed to their local and/or generalized effects on brain function. Early signs or symptoms can result from relatively small tumours if localized within eloquent areas such as within motor cortex, causing contralateral weakness or within speech areas, causing aphasia. Small tumours in such locations can produce more profound deficits than much larger tumours located in relatively silent brain regions, such as the anterior frontal lobes. Localized symptoms most typically result from compressive mass effect, but can also result from the more diffuse invasion of vital structures by glioma cells. Brain tumours, particularly those involving cerebral cortex, can be epileptogenic and cause focal symptoms manifested by either simple or complex partial seizures with or without secondary generalization. In the setting of an intraparenchymal brain tumour, seizures may occur at any time and do not necessarily indicate tumour growth. Spontaneous hemorrhage within a glioma occurs infrequently and can result in the acute or subacute onset of localized symptoms, including seizures or generalized symptoms of increased intracranial pressure if the hemorrhage is large or if it extends into the ventricular system.

Diverse mechanisms can produce increased intracranial pressure and generalized symptoms such as headache, diminished level of consciousness, incontinence, ataxia and vomiting. Masses adjacent to the Sylvian aqueduct or fourth ventricle frequently obstruct flow of cerebrospinal fluid, resulting in ventricular enlargement and obstructive hydrocephalus. Rare tumours residing within a lateral ventricle can obstruct CSF outflow through the foramen of Monro, causing either chronic or intermittent enlargement of a lateral ventricle. Communicating hydrocephalus can result from leptomeningeal spread of primary brain tumours, or from the malabsorption of CSF due, for instance, to elevated CSF protein derived from focal tumours residing within the subarachnoid space. Tumours growing in silent brain regions such as the anterior frontal lobes frequently remain asymptomatic until they compress and compromise adjacent brain, increase intracranial pressure or cause a seizure.

Stereotypic herniation syndromes can develop as a result of the expansion of a mass from one intracranial fossa to an adjacent one (Plum & Posner, 1982). For example, a growing mass within the anterior fossa may force the cingulate gyrus medially beneath the falx cerebri (i.e. cingulate or subfalcine herniation). Concurrent compression and displacement of the internal cerebral vein and ipsilateral anterior cerebral artery lead to ischemia and vascular congestion ipsilateral to the mass. These secondary events enhance the tumour-associated edema and may even cause cerebral infarction. Unilateral temporal lobe masses within a middle cranial fossa can expand medially and inferiorly through the tentorial notch to produce uncal herniation. An early sign of uncal herniation is an asymmetric enlarged ipsilateral pupil resulting from ipsilateral compression of the third cranial nerve. As uncal herniation worsens, false localizing ipsilateral pyramidal signs develop from compression of the opposite cerebral peduncle (‘Kernohan’s notch’). Central transtentorial herniation results from expanding bilateral supratentorial masses causing displacement of the diencephalon, midbrain and upper brainstem. Classical early signs of central herniation are diminished consciousness, miosis and Cheyne–Stokes respirations followed by progressive descending brainstem signs. Both uncal and central herniation can compress posterior cerebral arteries, causing occipital lobe ischemia, and compromise the medial perforating branches of the basilar artery, causing brainstem ischemia and infarction with potential reperfusion hemorrhage.

Imaging

The evaluation of primary brain tumours relies heavily on non-invasive imaging characteristics and most impor-

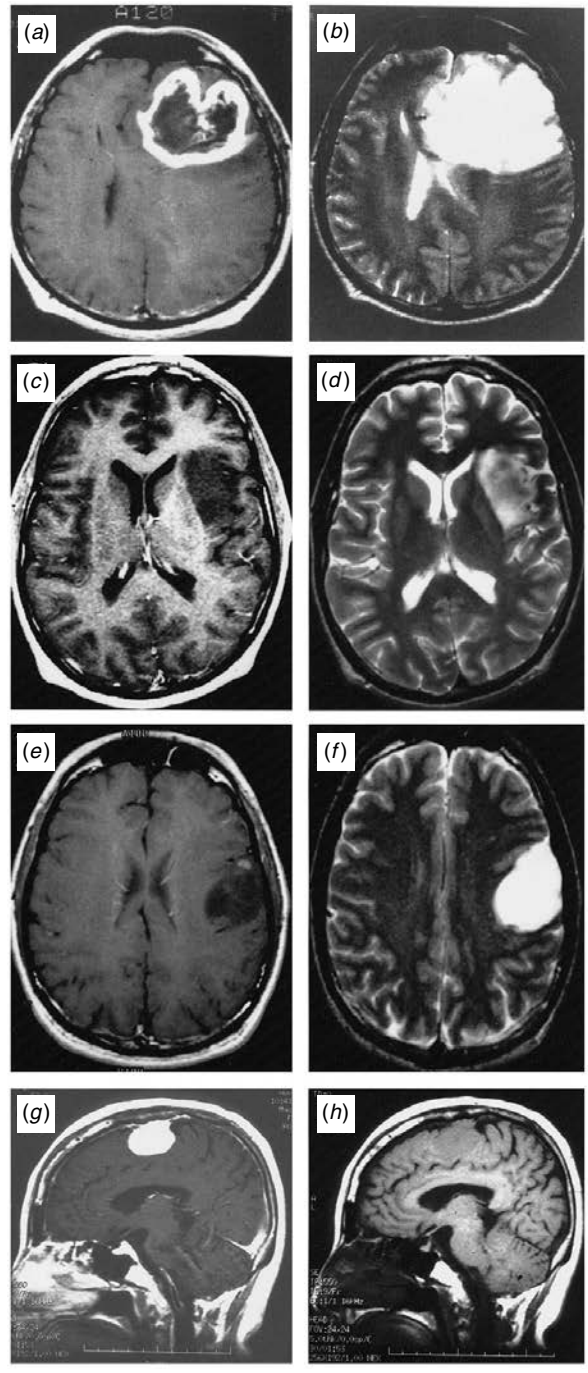

Fig. 87.7. Magnetic resonance imaging of glioblastoma multiforme (*a*), (*b*), low grade astrocytoma (*c*), (*d*), oligodendroglioma (*e*), (*f*), and meningioma (*g*), (*h*). Panels (*a*), (*c*), (*e*), (*g*) are contrast enhanced images following intravenous gadolinium. GBM displays typical rim enhancement with central necrosis (*a*). Astrocytoma is subcortical with more pronounced tumour infiltration as seen in T_2-weighted image in contrast to a typical oligodendroglioma that is cortical-based and relatively well-demarcarted ((*d*), (*f*), respectively). The parasagittal meningioma is isointense with surrounding normal brain in unenhanced T_1-weighted imaging (*h*), and enhances uniformly following administration of gadolinium (*g*). Note the prominant enhancing dural tails indicative of extraaxial meningial origin of meningioma (*g*).

tantly on subsequent histopathological assessment of tissue specimens obtained from either diagnostic biopsy or larger resections. Major advances have been made in structural, functional and biochemical brain imaging since the 1980s. Computerized tomography (CT) and magnetic resonance imaging (MRI) are complementary approaches for imaging the brain in patients suspected on clinical grounds to have a brain neoplasm. Tumour calcification, which is more common in certain tumours, such as meningioma and oligodendroglioma, is more reliably assessed by CT. In general, however, MRI is the preferred technique because it can distinguish between more diverse tissue properties, and its greater sensitivity increases the quality of surgical and subsequent therapeutic planning (Fig. 87.7).

Contrast enhancement after intravenous administration of contrast agent is a key component of brain tumour imaging. Iodinated contrast agents for CT and gadolinium-based agents typically used in MRI do not cross the normal intact blood–brain barrier. Contrast enhancement resulting from the intraparenchymal accumulation of contrast agent identifies regions containing overly permeable blood vessels that are characteristic but not diagnostic of neoplastic lesions. Contrast enhancement is uniformly present in the most malignant tumours such as glioblastoma multiforme and is typically absent in lower grade tumours such as grade II astrocytoma and well-differentiated oligodendroglioma. Certain benign tumours such as pilocytic astrocytoma and meningioma typically enhance after administration of contrast dye. T_2-weighted MRI sequences are most sensitive for detecting peritumoural edema. Meticulous comparison between MR imaging and histopathology of postmortem brains from patients with gliomas has demonstrated that regions of peritumoural edema match the regions of brain infiltrated by glioma cells (Burger et al., 1988). This is the scientific

basis for including the entire volume of peritumoural T2 abnormality during standard fractionated radiotherapy for glioma.

Positron-emission tomography (PET) and magnetic resonance spectroscopy (MRS) are relatively non-invasive methods for assessing the metabolic state of brain lesions. These imaging techniques can distinguish between neoplastic and non-neoplastic lesions and aid in assessing the malignancy of primary brain tumours. PET indirectly localizes sites of positron emission by directly detecting high energy photons that result from positron–electron annihilation (Phelps et al., 1982). Various positron-emitting radioligands designed to detect specific metabolic pathways or receptor–ligand interactions can be used in PET. The most common neuro-oncological application of PET is the imaging of glucose metabolic rates after systemic administration of ^{18}F-2-deoxyglucose (FDG), a substrate for hexokinase that upon phosphorylation is trapped within cells (Coleman et al., 1991). Malignant tumour cells are hypermetabolic and accumulate FDG-6-phosphate at excessive rates. FDG PET imaging can distinguish grade II from malignant grade III–IV gliomas and malignant gliomas from post-therapy radionecrosis (Di Chiro, 1987; Doyle et al., 1987). Practical limitations of PET include the technical difficulty in synthesizing radiolabelled ligands, poor spatial resolution and frequent false negatives, particularly because of the difficulty in distinguishing malignant tumours from metabolically active cerebral cortex. The specificity and sensitivity of FDG PET is enhanced by concurrent ^{82}rubidium PET for colocalizing regions of excessive blood–brain barrier permeability.

The hypermetabolic anerobic state of malignant gliomas produces elevated levels of lactate within the tumour. In addition, gliomas are rich in choline, a result of rapid membrane turnover, and relatively depleted of *N*-acetylaspartate in comparison to neuron-rich brain regions. Proton MRS can be used to quantify tissue lactate, choline and NAA relative to creatine and thereby distinguish neoplasms from non-neoplastic lesions (Vigneron et al., 1997) (Fig. 87.8). Advantages of MRS are that it is relatively accessible, has high spatial resolution, and does not require radioisotopes. False-positives are not uncommon, however, because of elevated choline levels in certain non-neoplastic lesions such as demyelinating plaques. Functional MRI (fMRI), a technique that detects regions of increased neuronal activity based upon changes in blood-flow and deoxyhemoglobin concentration, can be useful in determining the relationship between tumour and eloquent regions of brain subserving language and motor functions. This information can be important in surgical planning.

Diagnosis and therapy

All brain lesions suspected to be neoplastic on the basis of imaging characteristics and clinical symptomatology require pathological diagnosis preferably by craniotomy and resection. In addition to the probable benefits to survival, aggressive resection provides optimal amounts of tissue for the accurate histopathological analysis of what are frequently histologically heterogeneous tumours. Diagnostic biopsy through either a stereotaxic approach or after craniotomy is reserved for tumours that are either too deep or located in eloquent regions not amenable to aggressive resection.

The principles underlying the treatment of growing brain tumours revolve around the initial goal of reducing and, if possible, eliminating tumour burden. Aggressive resection with attention to minimizing surgical morbidity is the quickest way to eliminate symptoms and the toxicity associated with prolonged exposure to glucocorticoids used to treat tumour-associated edema. Aggressive resection is the treatment of choice for certain primary brain tumours (e.g. meningioma, pilocytic astrocytoma, and subependymoma) that can be cured through surgery alone. Unfortunately, most gliomas diagnosed in adults have poorly defined tumour margins due to their tendency to infiltrate surrounding brain and are therefore not amenable to complete resection. Although somewhat controversial, numerous studies have found a survival advantage from gross-total as opposed to partial resection even for infiltrative gliomas (Berger et al., 1994). This understanding has led to the use of increasingly sophisticated MRI-guided neurosurgical approaches to maximize tumour resection.

External beam gamma radiation is standard postsurgical therapy for all high grade gliomas including anaplastic astrocytoma (grade III), glioblastoma (grade IV) and anaplastic oligodendroglioma. This is supported by a randomized prospective trial showing that surgery plus radiation increases survival at 1 year from 3% to 24% when compared to surgery alone in patients with high grade astrocytoma (Walker et al., 1978). Radiation therapy for high grade glioma consists of 60 Gy delivered over 6 weeks in 30 fractions directed to tumour and peritumoural edema as defined by elevated T_2-weighted MRI signal plus an additional 2 cm margin. The relative benefit of early vs. delayed radiation therapy for patients with newly diagnosed low grade glioma is more uncertain. Two randomized prospective studies are currently under way comparing immediate postoperative with delayed radiation therapy. Preliminary data suggest that, in the absence of other progressive neurological symptoms, it is safe to postpone radiation

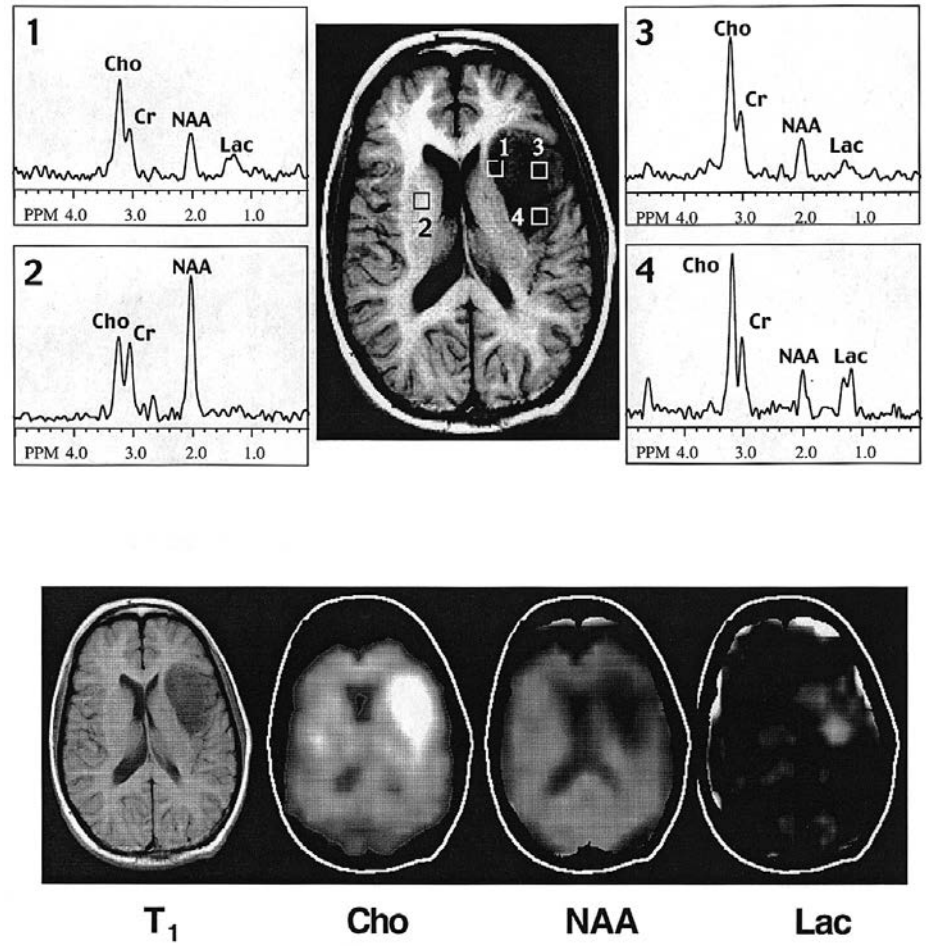

Fig. 87.8. Magnetic resonance spectroscopy of glioblastoma multiforme. (*Upper panel:* Single pixal spectrographs (1 to 4) corresponding to regions sampled within tumour (regions 1, 3 and 4) and contralateral normal brain (region 2) as shown in T_1-weighted magnetic resonance image. Normal brain (region 2) contains high *N*-acetylaspartate (NAA) relative to choline (Cho) and creatine (Cr), and no detectable lactate (Lac). All regions within tumour show elevated choline, elevated lactate, and diminished *N*-acetyl aspartate relative to creatine. *Lower panel:* Magnetic resonance spectroscopic imaging of same tumour depicting diffusely elevated choline, diffusely diminished *N*-acetylaspartate, and multifocally elevated lactate within tumour. (Courtesy of Peter Barker, PhD, Johns Hopkins School of Medicine.)

therapy until there is evidence for tumour growth in patients with low grade gliomas identified incidentally or following a seizure (Karim et al., 1998). The radiotherapy dose for progressive low grade gliomas is generally 54 Gy in 30 daily fractions. Significantly higher doses increase risk of radiation toxicity without any clearly defined benefit in survival.

The majority of gliomas recur within 2 cm of the original resection site and they frequently progress to a higher grade of malignancy at the time of tumour recurrence. Repeat resection of symptomatic recurrences is warranted if it is expected to improve performance status. Chemotherapy is useful for recurrent malignant glioma (Fine et al., 1993; Lesser & Grossman, 1994). Nitrosoureas, such as intravenous BCNU, oral procarbazine, or oral temozolamide, permeate the blood–brain barrier and are proven to have a modest therapeutic benefit in randomized studies (Lesser & Grossman, 1994). It has been proposed that combination therapy with procarbazine, CCNU, and vincristine (PCV) is of particular benefit to patients with anaplastic astrocytoma and anaplastic oligodendroglioma, although data from controlled trials directly comparing PCV to other regimens are not yet available (Smith *et al.*, 2000). Anaplastic oligodendrogliomas characterized by loss of chromosomal segments

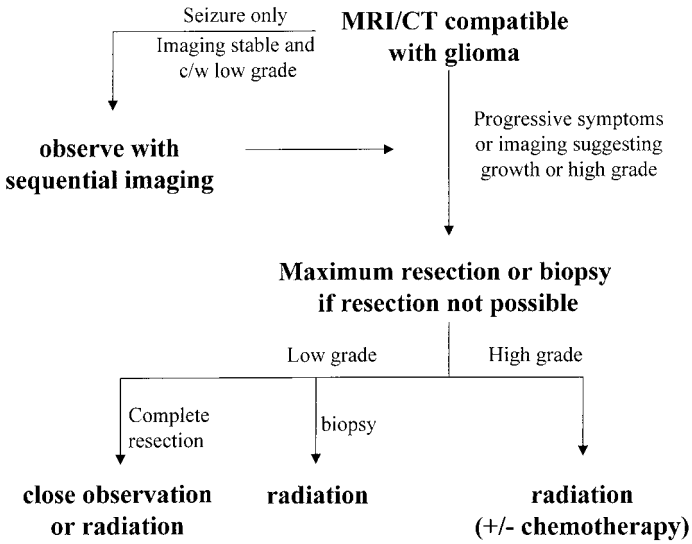

Fig. 87.9. General guidelines for treating adults with symptoms/signs and brain imaging consistent with glioma.

1p and 19q have recently been shown to be particularly sensitive to chemotherapy. The high frequency of local tumour recurrence supports the use of local interstitial chemotherapy administered at the time of tumour resection. A double blind placebo-controlled trial in which biodegradable polymers containing BCNU (Gliadel®) were implanted within the resection cavity of recurrent glioblastoma demonstrated a survival benefit (Brem et al., 1995; Valtonen et al., 1997). Delivery of chemotherapy locally directly within brain eliminates the systemic toxicity (e.g. bone marrow suppression) associated with intravenous chemotherapy. There is no proven role for cytotoxic chemotherapy in the initial treatment of low grade gliomas. A general approach to patients with newly diagnosed gliomas is summarized in Fig. 87.9.

Multiple factors contribute to the resistance of primary brain tumours to cytotoxic chemotherapy and radiation therapy. Neoplastic cells are inherently resistant to death signals due to activation of antiapoptotic pathways. Blood flow to solid tumours and hence drug delivery is inherently inefficient because of elevated interstitial pressures within tumours and their abnormal microvascular anatomy that causes stasis and retrograde perfusion. This also results in tumour hypoxia, reducing the effectiveness of cytotoxic therapies that require oxygen to generate DNA damage (i.e. gamma radiation, nitrosoureas) (Kayama et al., 1991). The blood–brain barrier restricts many chemotherapeutic compounds from reaching the tumour target cells, and tumour cells can express the cell surface transporter *p*-glycoprotein that actively pumps chemotherapeutic compounds out of cells (Henson et al., 1992). Glioma cells express enzymes such as glutathione-s-transferase and O^6-methylguanine-DNA methyltransferase (MGMT) that increase drug metabolism and repair nitrosourea-induced DNA methylation (Schold et al., 1989). Methylation and inactivation of the MGMT promoter in human gliomas predicts chemosensitivity to nitrosoureas such as BCNU (Esteller et al., 2000). Therapeutic trials are under way to overcome these resistance mechanisms (Rhines et al., 2000).

Because of the extremely poor prognosis associated with malignant gliomas numerous alternate therapeutic modalities continue to be developed and tested. Examples that have not fulfilled initial expectations include intra-arterial chemotherapy, chemotherapy concurrent with blood–brain barrier disruption, interstitial brachytherapy, and boron–neutron capture therapy. There is currently great emphasis in applying recent discoveries in molecular/cellular oncology to the development of genetic medicines and small synthetic compounds engineered to target specific molecules that regulate processes such as angiogenesis, apoptosis and the cell cycle that are linked to neoplasia. Present directions point to the therapeutic benefits of using these molecular/biological therapies to enhance the cytotoxic response to conventional chemotherapy and radiation therapy.

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Brain tumours in children

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Classification

Brain tumours are the most common solid tumours in children and the primary cause of cancer-related morbidity and mortality during childhood (Gurney et al., 1995; Hamilton et al., 1995). The intracranial location and histological type of childhood brain tumours differ markedly from patterns seen in adults. The majority of adult brain tumours arise in the cerebral hemispheres; more than half of all brain tumours in children older than 1 year are found infratentorially. Even for supratentorial locations, tumours of the optic pathway, hypothalamus, and pineal region are relatively uncommon in adults but not in children. Histological differences are also prominent. Whereas the majority of primary brain tumours in adults are malignant gliomas and meningiomas, the majority of childhood tumours are low-grade astrocytomas, primitive neuroectodermal tumours (PNET) and craniopharyngiomas (Table 88.1). The World Health Organization (WHO) Classification of Tumours of the Nervous System (International Agency for Research on Cancer, 2000) proposed brain tumour classifications based on standard light microscopy and tumour location but not on immunohistochemical or other molecular characteristics. The diagnostic categories of childhood brain tumours for which there is a relatively high level of interobserver diagnostic consistency include PNET and medulloblastoma, ependymoma, germinoma, teratoma, craniopharyngioma and pilocytic astrocytoma. By contrast, the diagnosis of astrocytoma, oligodendroglioma and mixed glioma may be more problematic and less consistent (CBTC, 1998).

Table 88.1. Distribution of common brain tumours in children, by location and histology

Location and tumour histological type	Percentage of tumours
Infratentorial	48
PNET/medulloblastoma	20
Low-grade cerebellar astrocytoma	15
Ependymoma	5
Malignant astrocytoma	3
Low-grade brainstem astrocytoma	3
Other	2
Supratentorial hemispheric	38
Low-grade astrocytoma	15
Malignant astrocytoma	8
Mixed glioma	4
Oligodendroglioma	2
Ependymoma	3
Choroid plexus tumours	2
PNET	1
Other	3
Supratentorial midline	14
Low-grade astrocytoma	5
Craniopharyngioma	5
Germ cell tumour	2
PNET	1
Others	1

Note:
Adapted from Pollack (1999).

Epidemiology and pathogenesis

Brain tumours represent 24% of all malignancies in children (Gurney et al., 1995). The incidence of childhood

primary brain tumours in the United States increased by 35% from 1973 to 1994 (Ries et al., 1998). Improvements in brain tumour detection and reporting coincident with the availability of high-resolution neuroimaging may contribute to this reported increase (Smith et al., 1998); however, serious concerns remain that environmental factors may play a significant contributory role.

Factors responsible for the initiation and progression of childhood brain tumours remain poorly understood. A model of tumour progression, proposed for malignant gliomas in adults (International Agency for Research on Cancer, 2000), is unlikely to apply to infants and children. In that model, EGFR amplification, CDKN2A deletion, and MDM2 amplification are common in adult malignant gliomas but not in similar childhood tumours (Sung et al., 2000). Furthermore, malignant transformation for low-grade astrocytoma to malignant glioma is uncommon in children but not in adults. The high incidence of tumours in the first year of life suggests that tumour suppressor genes, which are involved in normal development, play a major role in CNS tumourigenesis (Biegel, 1997). In primitive neuroectodermal tumours (PNET) including medulloblastoma (MB), the most common childhood malignant tumour, putative tumour suppressor locations have been identified on chromosome 17p and 9q. Nearly 40% of all PNETs exhibit a deletion of the short arm of chromosome 17 (Rorke et al., 1997). Another possible tumour suppressor gene is located on the long arm of chromosome 9 where allelic losses have been described in 10–18% of PNET (Schofield et al., 1995). This region also contains the locus of nevoid basal cell carcinoma syndrome (NBCCS), which has been mapped. The gene responsible for this syndrome has been identified as the human homologue of the *Drosophila patched* gene (*PTCH*). The incidence of posterior fossa PNET among NBCCS patients is nearly 5% and mutations in *PTCH* have been demonstrated in approximately 12% of sporadic PNET/MB (Raffel et al., 1997).

Several inherited genetic diseases are associated with an increased risk of brain tumours during childhood. The most frequent association is with the phakomatoses. In children with neurofibromatosis type 1 (NF1), astrocytomas are the most common CNS tumours. They may arise in any brain region; however, the most common sites include the optic nerves and, to a lesser extent, the brainstem and the posterior fossa (Riccardi, 1992). Neurofibromatosis type 2 predisposes to bilateral vestibular schwannomas (acoustic neuromas) and to a lesser extent to trigeminal schwannomas, ependymomas and meningiomas (Riccardi, 1992). Brain tumours in tuberous sclerosis are relatively common and are typically histologically characterized as subependymal giant cell astrocytomas. In patients with Von Hippel–Lindau disease, central nervous system hemangioblastomas (cerebellar, brainstem, spinal) occur at an increased frequency (Friedrich, 1999).Turcot's syndrome, a germline mutation in the adenomatous polyposis coli gene (chromosome 5q21–22), is characterized clinically by the concurrence of primary brain tumours and multiple colorectal adenomas. The predominant brain tumour in Turcot's syndrome is the posterior fossa PNET (Hamilton et al., 1995). Germline mutations in the TP53 gene (chromosome 17p13.1) are responsible for the majority of cases of Li-Fraumeni syndrome (Frebourg & Friend, 1992). This familial cancer syndrome is characterized by a high risk of breast cancer, soft tissue sarcomas, osteosarcomas, leukemia and brain tumours. The most common brain tumours that have been reported in children from such cancer-prone families include astrocytoma, PNETs and ependymoma (Avigad et al., 1997). Inherited genetic disorders of the immune system such as Wiskott–Aldrich syndrome and ataxia telangiectasia are associated with an increased risk of primary CNS lymphoma and other brain tumours.

The most important exogenous risk factor for childhood brain tumours is ionizing radiation. Prenatal diagnostic X-ray exposure has been related to CNS tumours in childhood (Shu et al., 1994). Various other reports identify an increased incidence of gliomas, meningiomas and other brain tumours in children who received radiation therapy to the head for tinea capitis or for prior malignancies (Shore et al., 1976; Relling et al., 1999). The estimated cumulative risk of a second malignant brain tumour after childhood ALL is 0.3% by 5 years from 3-year survival and 0.5% by 10 years (Jenkinson & Hawkins, 1999). Cranial radiation, when combined with some chemotherapeutic agents (e.g. methotrexate) may have a synergistic interaction to increase the incidence of glial tumours.

Diagnosis and treatment

The following sections address diagnostic and treatment issues for childhood brain tumours that pose unique or characteristic problems different from those in adults and discussed in Chapter 87. These will include PNET, brainstem glioma, low grade astrocytomas, germ cell tumours, ependymomas and brain tumours in infants. Accordingly, childhood supratentorial malignant gliomas, oligodendrogliomas, meningiomas and other tumours more commonly found in adults will not be addressed here specifically. A comprehensive assessment of these tumours in childhood can be found in recent reviews and monographs (Cohen & Duffner, 1994; Allen & Siffert, 1997: Pollack, 1999; Packer, 1999).

PNET/medulloblastoma

Primitive neuroectodermal tumours represent a group of malignant small-cell brain tumours, which include medulloblastoma (i.e. cerebellar location), pineoblastoma (i.e. pineal location), ependymoblastoma (ependymal rosette formation), and supratentorial PNETs. The classification of medulloblastoma is the subject of long-standing controversy. Because these tumours are essentially indistinguishable histologically, Rorke suggested that they be grouped together as primitive neuroectodermal CNS tumours (PNET) based on the assumption that they each arise from neoplastic transformation of pluripotent, uncommitted neuroectodermal precursors (Rorke et al., 1997; Rorke, 1983). Immunohistochemical analysis of these tumours supports this approach. By contrast, the WHO classification favoured subdividing the tumours by location based on the premise that, despite the histological similarity, these lesions arise from cells already committed to a location-specific pathway of differentiation.

Primitive neuroectodermal tumours, as a group, constitute nearly 25% of all pediatric brain tumours and are the most common malignant brain tumour in childhood (Gurney et al., 2000). Approximately 85% originate in the cerebellar vermis and are termed medulloblastoma (PNET/MB). Pineal and supratentorial PNETs constitute 10 and 5%, respectively, of all childhood PNETs (Rorke, 1999; Jakacki, 1999).

The midline cerebellar location of PNET/MB typically causes obstructive hydrocephalus. Accordingly, the clinical presentation of PNET/MB is dominated by signs and symptoms of increased intracranial pressure: headache, nausea and vomiting; drowsiness and other behaviour changes; and ataxia. These features are usually indistinguishable from other posterior fossa tumours, including ependymoma and cerebellar astrocytoma. Neuroimaging diagnostics emphasize the use of MRI. The MRI characteristics of PNET/MB include a high T1 signal precontrast, large-area, predominantly uniform contrast enhancement, and a high *N*-acetyl aspartate to choline ratio on proton magnetic resonance spectroscopy. Computer-based neural networks that combine data from neuroimaging studies with patient clinical data have a higher degree of accuracy in distinguishing PNET/MB from other posterior fossa tumour types (e.g. ependymoma, astrocytoma) than experienced neuroradiologists (Arle et al., 1997). However, the diagnosis of non-brainstem posterior fossa tumours requires direct histological confirmation in all cases.

Assessment and treatment of increased intracranial pressure is the most important aspect of preoperative management. Patients with papilledema and significant visual impairment require immediate placement of an external ventricular drain or emergency tumour resection. Prolonged delay between ventricular decompression and tumour resection increases the risk of transtentorial upward herniation. For patients with less severe signs and symptoms of increased intracranial pressure, corticosteroids and acetazolamide may be used to relieve symptoms, reduce tumour swelling, and permit further surgical planning.

The therapeutic management of PNET/MB can be considered in three distinct phases: surgical treatment; postoperative tumour staging; radiation and chemotherapy. The surgical objectives in PNET/MB treatment require that sufficient tissue be obtained to permit accurate histopathological diagnosis. Tumour removal should be as complete as possible since complete tumour removal favourably influences prognosis (Zeltzer et al., 1999). Finally, every effort should be made to re-establish normal CSF flow. The majority of children with PNET/MB will not need a permanent ventriculoperitoneal shunt. The incidence of tumour dissemination to the abdomen by ventriculoperitoneal shunt is uncommon and the clinical significance of this unusual complication has probably been exaggerated (Berger et al., 1991). Postoperative neurological complications of posterior fossa surgery include aseptic meningitis, pseudomeningocele formation and cerebellar mutism. The syndrome of aseptic meningitis occurs in up to 5% of patients undergoing posterior fossa surgery and is not limited to those with PNET/MB. Symptoms of fever and meningismus, ranging from mild to severe in intensity, typically develop 5–10 days after surgery. Although this complication may occur more frequently in patients with large postoperative pseudomeningoceles under tension, there are no reliable clinical features that distinguish this syndrome of presumed chemical meningitis from that of bacterial meningitis. Therefore, analysis and culture of cerebrospinal fluid is essential. If no infectious cause is identified, this complication is effectively treated with corticosteroids.

The syndrome of cerebellar mutism after resection of posterior fossa tumours was noted in the early 1980s (Hirsch et al., 1979; Wisoff & Epstein, 1984). It is characterized clinically by complete or near-complete loss of speech typically beginning 24–48 hours after surgery and is accompanied by severe lower cranial nerve, cerebellar, visual (Lui et al., 1998) and motor dysfunction (Liu et al., 1998; Kedar, 1997). Subsequent reports indicate that this syndrome is not rare, and occurs in up to 15% of children with large midline cerebellar tumours (Pollack, 1997). Cerebellar mutism is often found in cases of aggressive surgi-

cal pursuit of PNET/MB adherent to, or invading, the brainstem. Most patients with this syndrome recover functional speech within several weeks to months after surgery. Permanent residual speech, lower cranial nerve, and motor coordination dysfunction are common.

Clinical prognostic factors determine the postsurgical therapeutic strategy for all PNETs; therefore, postoperative tumour staging is an essential part of PNET/MB clinical management. Staging studies include: neuraxis staging evaluation by spinal MRI (preoperatively or 10–14 days after surgery) to identify metastatic tumour aggregates; CSF cytological examination (intraoperatively or 10–14 days after surgery) to identify leptomeningeal tumour spread; and postoperative neuroimaging to assess residual tumour. The most important clinical prognostic factor for PNET is the metastatic stage, followed by residual tumour bulk, tumour location (i.e. supratentorial vs. infratentorial) and patient's age at diagnosis (Albright et al., 1996; Cohen et al., 1995). Based on results of current staging studies, PNET/MB patients are separated into two groups. Standard-risk patients are limited to those without any evidence of metastatic disease, less than 1.5 cm^2 residual tumour, supratentorial location, and patient age younger than 3 years at diagnosis. Current clinical prognostic factors distinguish high risk patients from all others, but are not sufficiently powerful to identify low risk PNET/MB patients who may benefit from significantly different therapy regimens than standard- and high-risk PNET/MB. It is unlikely that additional clinical prognostic factors will be identified in the future. Therefore, the identification and use of biologically based prognostic factors may improve the accuracy of patient stratification and lead to better risk-adapted therapies. Recent retrospective studies indicate that high TrkC mRNA expression predicts a favourable outcome better than current clinical factors (Grotzer et al., 2000). Other potential biological prognostic factors include HER2/HER4 coexpression (Gilbertson et al., 1997), GFAP expression (Janss et al., 1996) and *MYC* amplification (Scheurlen et al., 1998). Large, prospective studies are planned to determine if these new biological factors will supplement or supplant current clinical prognostic factors in the determination of PNET/MB treatment.

The current treatment strategies for PNET/MB reveal several distinct trends. High-risk patients are treated with involved-field radiation to the posterior fossa, craniospinal radiation, and chemotherapy. To reduce major treatment-associated toxicities, standard-risk patients receive chemotherapy and an identical radiation dose to the tumour but less intensive craniospinal radiation. Infants and children less than 3 or 4 years of age are often treated with intensive chemotherapy alone to postpone or avoid the neurotoxic effects of radiation on the developing brain. Newer protocols combine systemic and intrathecal chemotherapy with highly focused conformal radiation therapy to the tumour bed. For patients with recurrent PNET/MB, the use of high-dose chemotherapy followed by peripheral blood stem cell (PBSC) rescue results in apparently increased survival rates, especially for patients with minimal residual disease before high-dose chemotherapy. The prognosis for recurrent PNET/MB remains very poor.

Radiation therapy is the foundation of PNET/MB treatment. A cumulative radiation dose to the tumour of 56 Gy is typically used. Doses less than 50 Gy are less effective (Silverman et al., 1982). In patients older than 3 or 4 years at diagnosis, the entire craniospinal axis should be treated, regardless of metastatic stage (Jenkin, 1996). Treatment with craniospinal and local radiotherapy (total tumour dose of 54 Gy) without adjuvant chemotherapy results in long-term disease control in approximately 60% of children with standard risk PNET/MB (Evans et al., 1990). However, after whole-brain radiotherapy, many children will have significant long-term neuro-cognitive sequelae, including a demonstrable decline in cognitive function.

Recognition of the severe late effects of radiotherapy on the developing nervous system prompted efforts to reduce craniospinal radiation therapy doses in standard-risk PNET/MB. A prospective single-arm study was recently completed in children with standard-risk PNET/MB. Treatment included lower-dose craniospinal radiation (23.4 Gy), standard local radiotherapy (55.8 Gy) and adjuvant vincristine, CCNU, and cisplatin chemotherapy administered during and after radiotherapy (Packer et al., 1999). The progression-free survival for 68 children aged 3 to 10 years with non-disseminated PNET/MB was 86 $\pm$ 4% at 3 years. The lowest craniospinal radiotherapy dose reported in clinical trials is 18 Gy in 10 fractions with 50.4–55.8 Gy to the posterior fossa in combination with chemotherapy during and after radiation. With a median follow-up time for living patients of 6.3 years, survival for these standard risk PNET/MB patients at 6 years was 70 % (Goldwein et al., 1996). These results suggest that a subset of PNET/MB patients can be cured with chemotherapy and reduced doses of craniospinal irradiation. However, the optimal craniospinal radiation dose remains to be determined.

PNET/MB are responsive to a variety of chemotherapeutic agents, including cisplatin, cyclophosphamide, vincristine, CCNU, and busulfan (Friedman et al., 1991). Chemotherapy plays a major role in the treatment of high-risk PNET/MB, a conclusion that has been supported by large prospective studies (Evans et al., 1990; Packer et al.,

1994b; Bailey et al., 1995). Use of cisplatin, CCNU and vincristine in a postradiation chemotherapy regimen for high-risk patients resulted in 5-year survival rates higher than 80% (Packer, 1990). However, the role of chemotherapy in standard-risk PNET/MB has not been demonstrated directly in clinical trials. Indirect evidence which demonstrated significantly higher survival rates for standard-risk patients treated with radiation therapy and chemotherapy (cisplatin, CCNU and vincristine) than for similar patients treated with radiation alone provided strong support for the use of effective adjuvant chemotherapy for all PNET/MB patients (Packer, 1990).

For patients with relapsed PNET/MB, use of high-dose chemotherapy with peripheral stem cell rescue has shown encouraging results (Kalifa et al., 1999). Several groups reported significant reduction in the size of recurrent tumours of children with recurrent PNET/MB using this strategy (Kalifa et al., 1992). More recently, prolonged survivals after recurrence have been reported. Finlay and colleagues treated more than twenty children with recurrent PNET/MB with high-dose chemotherapy (HDCT) consisting of carboplatin, thiotepa and etoposide followed by peripheral stem cell rescue. With a median follow-up interval of 54 months, nearly one-third of treated patients remain free of tumour recurrence (Dunkel et al., 1998). These results are superior to previously reported outcome statistics for recurrent PNET/MB patients. However, prospective collaborative clinical trials are needed to evaluate different HDCT regimens with respect to survival outcomes as well as to toxicity and quality of life.

Ependymoma

Ependymomas constitute approximately 7% of all childhood brain tumours and arise in the posterior fossa as well as in supratentorial periventricular regions. These tumours generally behave as localized, slow-growing, and relatively non-invasive neoplasms. The primary challenge in the treatment of childhood ependymoma is local control, since metastatic relapses occur rarely (Vanuytsel & Brada, 1991). In the posterior fossa, ependymomas typically arise from the floor of the fourth ventricle. Despite the infrequency of deep infiltration of the brainstem, efforts at complete resection of these tumours often result in major morbidity. Accordingly, complete removal is achieved in less than 50% of the patients. The frequency of gross total resections can be increased by sophisticated technologies including ultrasonic tissue dissociation, argon lasers and robotic localizing devices, by experience of the operator with children and by the intent and preoperative plan to perform a radical surgical resection (Allen et al., 1998). In future, the availability of the intraoperative neuroimaging may provide immediate confirmation of the degree of resection and allow the surgeon to reoperate, immediately, if necessary (Wirtz et al., 2000).

Several studies confirm the importance of complete surgical resection as a predictor of survival outcomes in patients with newly diagnosed ependymomas (Sutton et al., 1991; Robertson et al., 1997; Evans et al., 1996). For children with neuroimaging confirmation of gross total resections the 5-year progression-free survival rate ranges from 60% to 80%. For patients with incomplete resections, survival ranges from 0 to 30% (Pollack et al., 1995; Vanuytsel & Brada, 1991). Surgical management of residual tumour after the first operation remains controversial and includes the option to attempt re-resection immediately after the postoperative MRI reveals residual tumour. Alternatively, a second operation may be deferred until after the child recovers and completes radiation therapy or chemotherapy. The merits of these alternatives have not been formally studied.

Routine postoperative tumour staging for children with intracranial ependymomas is identical to that for PNET/MB; that is, postoperative neuroimaging of the tumour resection site to determine the presence or extent of residual tumour, complete spinal cord imaging by contrast-enhanced MRI to identify possible leptomeningeal metastasis, and lumbar cerebrospinal fluid cytological analysis to detect malignant cells. Unlike PNET/MB in which more than one-third of cases have leptomeningeal tumour spread at the time of diagnosis, metastatic spread of ependymomas is relatively uncommon.

Standard treatment for children older than 3 years at initial diagnosis involved field radiotherapy. Early studies of childhood ependymoma treatment reported a high rate of leptomeningal tumour dissemination. Based on these observations, 'prophylactic' craniospinal radiation was recommended for all children with ependymoma.Using this approach, a 50% 5-year overall survival rate was reported in children with ependymoma (Robertson et al., 1997). Large cooperative studies failed to confirm these findings and also noted that the incidence of isolated neuraxis relapse in ependymoma was also less than 5% (Goldwein et al., 1991). Accordingly, current therapy reserves craniospinal radiation for those patients with proven leptomeningeal metastases at diagnosis. The use of stereotaxic radiosurgery, either as a primary therapy or as a radiosurgical boost after conventional fractionated radiation therapy may improve local tumour control or improve survival outcomes in children with postoperative residual tumour (Grabb et al., 1996).

The role of chemotherapy for childhood ependymoma has been the subject of considerable study and generally

disappointing results. Ependymomas are generally regarded as chemotherapy-resistant tumours, and collaborative studies using postoperative chemotherapy (CCNU and vincristine) failed to show a survival advantage for combined modality treatment (Evans et al., 1996). More recently, a study of 19 children with newly diagnosed ependymoma reported a 74% 5-year progression-free survival for children with residual ependymoma who were treated with standard radiotherapy and *cis*-platinum-based chemotherapy (Needle et al., 1997). These results are higher than most published results for patient with postoperative residual ependymoma treated with radiotherapy alone and comparable to published results for children with completely resected tumours. Based on this provocative finding, current clinical trials use chemotherapy for patients whose postoperative imaging studies are positive for residual tumour.

The therapeutic options for patients with recurrent ependymoma are generally poor and cure after recurrence is exceedingly rare. When possible, re-resection represents a reasonable palliative strategy for patients in whom maximal radiation has been administered. Standard and experimental chemotherapy have been of modest or no proven benefit for these patients and the use of high dose chemotherapy with autologous stem cell rescue has not improved progression-free survival for children with recurrent ependymoma (Mason et al., 1998).

Brainstem glioma

Brainstem gliomas represent 8–12% of all childhood brain tumours and are considered to have among the lowest survival rates. Prior to the widespread availability and use of magnetic resonance imaging, brainstem tumours were considered to be a single group that was uniformly fatal despite the most intensive therapies. The majority of children with brainstem tumours die from progressive tumour within 18 months of diagnosis; however, it was also recognized that some patients had extremely indolent tumours and continuous progression-free survival in excess of 5 years (Greenberger et al., 1977). To assist in the prospective identification of good- vs. poor-risk groups, the MRI and clinical characteristics of a large group of brainstem tumours were analysed retrospectively (Barkovich et al., 1990). Results from these studies demonstrate that there are two major classes of brainstem gliomas. First and most common are the diffuse intrinsic brainstem gliomas, typically located within the pons and upper medulla. These carry a uniformly poor prognosis. Second are the focal brainstem gliomas, typically located in the upper midbrain or lower medulla. By contrast, these less common variants often have an excellent prognosis.

Intrinsic pontomedullary brainstem gliomas constitute approximately 70% of all brainstem tumours. The clinical presentation of diffuse pontomedullary brainstem gliomas typically includes one or more of the following abnormalities: cranial nerve palsies, typically VI and VII; ataxia; long tract signs, including hyperreflexia and extensor plantar responses. The prediagnostic symptomatic interval is usually less than 3 months. On MRI, these tumours show a diffuse infiltrative enlargement of the pons and rostral medulla (Albright et al., 1986). T_1-weighted MRI images usually demonstrate mass effect and low signal intensity when compared with the normal brainstem. T_2 MRI sequences reveal high-signal regions of tumour infiltration with rostral extension into the midbrain and brachium pontis and lateral extension into the cerebellar peduncles. Brainstem enlargement may be unilateral and is often asymmetrical at initial diagnosis. The fourth ventricle is usually distorted; however, obstructive hydrocephalus is distinctly uncommon at initial presentation.

Efforts to correlate the histological features of intrinsic brainstem tumours with their clinical outcome provided the impetus for biopsy and autopsy evaluations. These studies showed that a limited surgical procedure, either stereotaxic or open biopsy, can be accomplished safely with little added morbidity (Epstein & McCleary, 1986). However, biopsy results were not an accurate predictor of clinical outcome, possibly due to the difficulty of obtaining a sufficiently large, representative sample (Jennings et al., 1996). Standard diagnostic management of intrinsic brainstem tumours eliminated routine diagnostic biopsies when the clinical and neuroimaging features typical of diffuse pontomedullary brainstem gliomas are identified. Diagnostic biopsy may be indicated for brainstem lesions with an unusual MRI appearance or an atypical clinical course potentially indicative of a low-grade tumour, brainstem encephalitis, brainstem abscess or demyelinating disease.

But for rare circumstances, there is no defined role for resection of diffuse intrinsic brainstem gliomas. Early in the clinical course, tumour cells infiltrate widely throughout brainstem structures but still permit neurological function to remain at normal or near-normal levels. Consequently, removal of tumour is likely to result in severe neurological deficits. Some diffuse intrinsic brainstem gliomas may have cystic projections dorsally or laterally. Although these surface projections may provide a limited opportunity for tumour resection, it is uncommon that more than 50% of the tumour can be removed and there is no evidence that partial debulking affects progression-free or total survival. The incidence of leptomeningeal spread from diffuse intrinsic pontomedullary gliomas

is distinctly uncommon and routine tumour staging studies are not warranted

Diffuse brainstem gliomas are one of the childhood brain tumours most resistant to radiation therapy. Standard radiation treatment consists of 55 to 59 Gy external beam radiation administered to the local tumour region in single daily fractions of approximately 1.8–2 Gy. This approach results in median survival of 9–13 months from diagnosis (Jennings et al., 1996). Single institution reports suggested prolonged progression-free survival for children treated with multiple daily (i.e. hyperfractionated) radiation treatments in which total radiation doses reached 78 Gy. Subsequent large cooperative trials failed to demonstrate a significant advantage for hyperfractionated radiation and substantial toxicity was observed (Packer et al., 1994a,b; Kaplan et al., 1996; Mandell et al., 1999). Radiation implants (brachytherapy) are not appropriate for these tumours and the role of stereotaxic radiosurgery is uncertain, at best.

Chemotherapy trials have yielded similarly disappointing results. Single-agent or combination chemotherapy, when administered prior to radiation therapy, infrequently produces objective response rates that approach 25% (Jennings et al., 1996) It is unlikely that even these limited response rates will translate into significantly longer survival. A large multi-institution phase III trial using CCNU, vincristine and prednisone after radiation therapy failed to show a survival advantage for adjuvant chemotherapy when compared with radiation therapy alone (Jenkin et al., 1987). Even when the most aggressive chemotherapy strategies are used, such as high-dose chemotherapy followed by peripheral stem cell reinfusion, results are usually limited to relatively brief duration responses and few instances of significant tumour reduction lasting 12 months or longer (Bouffet et al., 2000). Based on these findings, it is difficult to justify the routine use of chemotherapy in brainstem gliomas outside the setting of formal cooperative group studies. However, the extremely poor prognosis for these patients justifies an aggressive search for more effective antitumour strategies.

Dorsally exophytic tumours represent one of the three more clinically benign brainstem tumour variants. These tumours arise from the floor of the fourth ventricle, often completely fill the ventricle, and may produce neurological signs for many years before causing obstructive hydrocephalus. Magnetic resonance images typically demonstrate a well-demarcated lesion that has low paramagnetic signal on T_1-weighted images, high signal on T_2-weighted images. In contrast to diffuse intrinsic pontomedullary gliomas, these tumours often enhance after gadolinium administration. Dorsally exophytic gliomas are characteristically low-grade astrocytomas. Upon evidence of clinically significant tumour growth or symptomatic ventricular obstruction, a complete or near-complete surgical tumour removal is often sufficient therapy. Use of local radiation therapy or chemotherapy should be limited to those uncommon cases of malignant histology or evidence of significant tumour growth after surgery (Pollack et al., 1993).

Cervicomedullary tumours are found in the inferior two-thirds of the medulla and the upper part of the spinal cord. These typically low-grade astrocytomas extend from the epicentre in conformance with the anatomical barriers (Robertson et al., 1994). Intratumoural cysts are infrequent. The clinical features of these tumours include lower cranial nerve and motor dysfunction and symptoms are often present for several years. In contrast to their dorsally exophytic relatives, obstructive hydrocephalus is rare. Surgical resection of cervicomedullary tumours may be considered upon clinical or neuroimaging evidence of significant symptomatic tumour growth. Although near-total resection is possible in some cases, the poorly defined interface between tumour and normal brainstem usually precludes complete surgical removal of these tumours. Long-term follow-up indicates that many patients will not have evidence of any growth for 5 years or so. When present, the rate of cervicomedullary tumour growth is often extremely slow, and malignant transformation has not been observed. Therefore, a conservative management approach is justified.

Cystic nodular brainstem tumours may be found in any region of the brainstem but are most often found in the midbrain. These tumours have a radiographic appearance that is identical to their cerebellar counterparts, and their histology typically proves to be pilocytic astrocytoma. Again, conservative management is warranted and therapeutic intervention should be limited to those cases of clinically and radiographically significant persistent tumour growth. When intervention is required, surgical resection of the mural nodule is often curative.

Optic nerve and hypothalamic astrocytomas

Low-grade astrocytomas occur anywhere within the brain (CBTC, 1988). For cerebellar astrocytomas, the predominant histology is pilocytic. For optic nerve and hypothalamic gliomas, the predominant histology is fibrillary. Optic nerve and hypothalamic gliomas are classified by location as: those anterior to but not involving the chiasm; chiasmal tumours with extension posteriorly along the optic radiations; and chiasmal/hypothalamic tumours for which the initial site of tumour growth cannot be determined.

Prechiasmatic optic nerve gliomas present clinically with progressive visual loss and/or proptosis. Their appearance on CT and MR imaging studies is usually sufficiently characteristic that, like brainstem gliomas, routine biopsy is not necessary. Prechiasmatic optic nerve tumours are often indolent tumours that should be treated conservatively. Progressive tumour growth yielding painful or disfiguring proptosis together with severe visual loss may warrant surgical resection and sacrifice of the affected optic nerve. Surgical resection is curative and no further therapy is required.

Chiasmal and chiasmal/hypothalamic gliomas account for 60–85% of optic pathway/hypothalamic tumours. These tumours, especially the very large chiasmal/hypothalamic glioma, often become clinically apparent at 5 years of age with symptoms of visual loss, and hydrocephalus. The symptom complex of older children is more likely to include visual disturbances and endocrine dysfunction. Children younger than 2 years of age may present with a diencephalic syndrome characterized by frequent vomiting, anorexia and failure to thrive (Gropman et al., 1998). In children with chiasmal tumours involving the optic nerve, the diagnosis of these tumours is frequently made by radiographic criteria alone. Especially in children with NF-1, diffuse enlargement of the optic chiasm, with extension posteriorly along the optic radiations to the geniculate bodies and beyond, is often sufficiently characteristic to permit reliable diagnosis without histological confirmation. However, for large tumours with hypothalamic extension, surgical biopsy is recommended. Though diagnostic confusion is not common, these tumours may have a clinical and neuroimaging appearance similar to other suprasellar tumours including solid craniopharyngiomas and germ cell tumours.

Most chiasmal and chiasmal/hypothalamic gliomas are not 'cured' by surgery, radiation therapy or chemotherapy, either alone or in combination. The slow and often erratic growth of these tumours may blur recognition of the fact that these 'benign' tumours may eventually be fatal. Decisions to initiate treatment should be based on clinical or radiographic evidence of tumour growth from serial observations rather than routinely initiating treatment at the time of tumour diagnosis. Whereas some patients show significant changes in visual acuity or neuroimaging scans within weeks or months of initial diagnosis, many others remain stable for months or years without interval treatment.

Chiasmal and chiasmal/hypothalamic gliomas cannot be resected without sacrifice of visual function and the risk of panhypopituitarism. There is, however, growing recognition that surgical debulking of large chiasmal/hypothalamic gliomas may provide rapid relief of symptoms caused by mass effect and hydrocephalus, delay the need for radiation therapy in young children, result in years of clinical stability without tumour growth, and improve the effectiveness of subsequent radiation therapy (Wisoff, 1992).

Radiation therapy has been shown to be effective in arresting tumour growth and reducing tumour volume in chiasmal and hypothalamic gliomas (Pierce et al., 1990; Erkal et al., 1997), but complete tumour regression after radiation therapy is rare. Because more than 90% of patients with optic pathway/hypothalamic gliomas survive longer than 10 years (Horwich & Bloom 1985), the late effects of radiation therapy, including damage to neuropsychologic function, endocrinopathy, optic nerve injury, and radiation-induced second neoplasms are important considerations. These concerns provided the impetus for clinical trials of alternative treatment approaches, including chemotherapy (Janss et al., 1995).

The role of chemotherapy in the treatment of optic pathway and hypothalamic gliomas is now well established. In a multi-institutional trial of carboplatinum and vincristine, 60% of progressive low-grade glioma patients had a significant reduction in tumour volume, and an additional 30% had prolonged stabilization of progressive tumours (Packer et al., 1997). Other chemotherapy regimens have been evaluated, including the use of procarbazine, 6-thioguanine, dibromodulcitol, CCNU and vincristine. Similar to results noted above for carboplatinum and vincristine, this strategy yielded long periods of disease stabilization with a median time to tumour progression of 132 weeks in children with low-grade gliomas (Prados et al., 1997). At the present time, it is not known whether the duration of clinical responses produced by chemotherapy is equal to that of radiation therapy. However, the ability of chemotherapy to produce durable responses in young children with optic pathway and hypothalamic tumours allows any consideration of subsequent radiation therapy to be postponed until a later age when the neurocognitive and other late effects may be less prominent. Currently used chemotherapy regimens for optic pathway tumours are generally well tolerated, can be administered in the outpatient setting, and do not have a high incidence of serious late effects. The successful use of chemotherapy in younger children has prompted efforts to extend use of these strategies to older children. However, it remains to be proven that the duration of progression-free survival for patients treated with chemotherapy is comparable to that for radiotherapy.

The incidence of optic pathway tumours in NF-1 patients is significantly greater than in the general population.

Nearly 15% of children in whom the diagnosis of NF-1 is confirmed have optic pathway tumours when they undergo screening neuroimaging (Listernick et al., 1989). The majority of these are anterior to the optic chiasm. However, only 52% of the children who have radiographically identifiable optic pathway tumours eventually develop clinically significant signs or symptoms of their tumours. When studied systematically, these tumours behave in a more benign fashion than in children who do not have NF-1. However, low-grade gliomas in children with NF-1 can be erratic in their natural history, at times showing signs of rapid growth followed by periods of spontaneous growth arrest. Treatment of anterior optic nerve glioma is necessary when there is persistent and significant evidence of tumour progression. Screening neuroimaging of asymptomatic NF1 patients is no longer recommended (Listernick et al., 1997). Because optic pathway tumours nearly always arise in children younger than 7 years of age (Listernick et al., 1994), current recommendations indicate that children with NF1 should have yearly ophthalmologic evaluations and assessment of growth to identify early signs of precocious puberty.

The management of children with NF-1 and optic pathway or hypothalamic gliomas is determined primarily by tumour location. Anterior optic nerve gliomas do not extend posteriorly into the optic chiasm. As noted earlier for non-NF1 patients, management for these patients depends entirely on the clinical symptoms. In most cases, chiasmatic gliomas can be observed conservatively by means of neuroimaging studies and ophthalmologic evaluations for a period of time (Listernick et al., 1997). Progressive tumours may be treated by surgery, radiotherapy or chemotherapy in individualized approaches (Pierce et al., 1990; Sutton et al., 1991; Packer et al., 1999).

Germ cell tumours

Germ cell tumours (GCT) as classified in two broad groups: germinomas (atypical teratomas); non-germinomatous germ cell tumours including typical and teratoid teratomas, teratocarcinomas, embryonal carcinomas, endodermal sinus tumours and choriocarcinoma. Intracranial germinomas are most common, representing approximately two-thirds of all intracranial germ cell tumours. Germ cell tumours characteristically occur during early adolescence. In addition to their unusual age distribution, they also show an unusual geographic distribution; that is, germ cell tumours constitute nearly 16% of all childhood brain tumours in Japan but only 3–5% in United States and Western European countries (Kretschmar, 1997).

Table 88.2. CSF and serum tumour markers for germ cell tumours (GCT)

	AFP	β-HCG
Germinoma	−	±
Non-germinomatous GCT		
Embryonal carcinoma	±	±
Yolk sac tumour	++	−
Choriocarcinoma	−	++
Teratoma, mature	−	−
Teratoma, immature-malignant	±	±
Mixed germ cell tumour	±	±

The majority of GCT is found in the pineal region, about one-third in the suprasellar region. Pineal tumours frequently obstruct the posterior aspect of the third ventricle and aqueduct of Sylvius, causing acute hydrocephalus with headaches, papilledema, nausea, vomiting and lethargy. As tumours grow anteriorly, the midbrain tegmentum and quadrigeminal plate are compressed, resulting in Parinaud's syndrome: paralysis of upward gaze, diminished pupillary response to light and retractory or convergence nystagmus. The clinical presentation of suprasellar GCT includes panhypopituitarism, diabetes insipidus, and visual disturbances with prediagnostic symptomatic intervals often exceeding 1 year.

Biochemical markers of germ cell tumours play an important role in the diagnosis and management of pineal and suprasellar region germ cell tumours (Table 88.2). When a germ cell tumour is suspected, CSF and serum should be evaluated for elevation of alpha-fetoprotein (AFP) and human chorionic gonadotropin (β-HCG). AFP is highly expressed during normal fetal development. It is produced initially by the fetal yolk sac and later by hepatocytes. Normal infants have high expression levels of AFP, which do not drop to adult values until 8 months of age or later. Detection of elevated levels of AFP in a brain tumour patient indicates the activity of primitive yolk sac elements and points to a diagnosis of malignant teratoma (Kretschmar, 1997). β-HCG is a specific marker for germ cell tumours with syncytiotrophoblast activity. Pure germinomas may express very low levels of β-HCG; however, the highest levels of this hormone are found in patients with choriocarcinomas. Placental alkaline phosphatase (PLAP) is a tumour marker that is characteristically expressed in patients with germinomas (Shinoda et al., 1988). Routine evaluation of PLAP levels in the CSF are not generally available; however, use of PLAP in immunohistochemistry eval-

uation of biopsy specimens has proven clinically valuable in germinoma diagnosis (Kretschmar, 1997).

The neuroimaging characteristics of germ cell tumours are not diagnostic in themselves and biopsy of these tumours is necessary (Kang et al., 1998). The diversity of tumour histologies in the suprasellar and pineal regions underscores the importance of adequate biopsy samples for accurate diagnosis. Small samples obtained from stereotaxic biopsy may not identify mixed tumour types. When possible, an open surgical biopsy approach is preferred. Intraoperative assessment of tumour histology by frozen section influences surgical management. For example, complete resection is curative for well-differentiated teratomas, whereas chemotherapy and radiation therapies are generally ineffective. Conversely, the extent of surgical resection is often of little importance for germinomas, which are quite sensitive to chemotherapy and radiation therapy.

Radiation treatment approaches differ according to germ cell tumour histological type. Germinomas are exquisitely sensitive to radiation. In the past, 'diagnostic' low doses of radiation therapy (e.g. 10–30 Gy) were administered to unbiopsied suprasellar or pineal region tumours. If significant tumour reduction was observed, the tumour histology was assumed to be a germinoma and radiation therapy was continued to doses ranging from 40 to 56 Gy. This strategy is unacceptable in modern clinical practice since patients with highly radiation-resistant tumours will be treated unnecessarily. Non-germinomatous or mixed GCT may show an early partial response radiotherapy; however, as the true diagnosis will not be known, the radiation dose administered is likely to be inadequate or may not include craniospinal radiotherapy which is standard for choriocarcinoma, endodermal sinus tumours, and other non-germinomatous germ cell tumours. Finally, there is growing evidence that non-germinomatous or mixed GCT benefit from chemotherapy and radiotherapy.

Craniospinal radiation is standard treatment for patients with germinoma and leptomeningeal metastases. However, the incidence of leptomeningeal metastasis in germinoma is up to 11% (Jennings et al., 1985) and its use for patients without MRI or CSF evidence of leptomeningeal spread is controversial. For patients with pure germinomas treated with radiation therapy alone, the 5-year recurrence-free survival rates are excellent and exceed 90% (Matsutani et al., 1997). Non-germinoma germ cell tumours (choriocarcinoma, embryonal carcinoma, yolk sac tumours and malignant teratomas) have a high incidence of leptomeningeal metastasis (Jennings et al., 1985) and craniospinal radiation therapy and radiation are important components of their treatment plan. Well-differentiated teratomas are generally unresponsive to radiation and use of radiation therapy is limited to unresectable recurrent or progressive teratomas in many centres. For these cases, stereotactic radiosurgery may prove to be of greater therapeutic benefit.

Chemotherapy has an established role in the treatment of many germ cell tumours. Germinomas are highly chemotherapy-responsive tumours, especially to regimens incorporating platinum chemotherapy compounds. Chemotherapy for pure germinomas is currently being studied with the specific objective of reducing the overall dose of radiation and therefore the late effects of radiation. However, chemotherapy alone for pure germinomas is less effective than radiation therapy alone for pure germinomas. The prognosis for non-germinomatous germ cell tumours ranges widely; however, all are considerably worse than pure germinomas (Matsutani et al., 1997). Accordingly, current studies attempt to improve survival in non-germinomatous GCT by use of intensive chemotherapy (Balmaceda et al., 1996), together with craniospinal radiation. Results from these efforts are very encouraging and a 4-year progression-free survival rate of 74% has recently been reported for patients with non-germinoma GCT treated with chemotherapy and radiation therapy (Robertson et al., 1997).

Brain tumours in infants

Approximately 20% of all childhood brain tumours occur in children younger than 3 years of age. Significant tumour differences are seen in this age group when compared with older children. During the first 6–12 months of life supratentorial tumour location predominates. By the second year, infratentorial tumours are more common. Tumour histologies are also different in infant brain tumours. Ependymomas, malignant gliomas, atypical teratoid/rhabdoid tumours and choroid plexus tumours are more commonly seen in infants than later in childhood. Unfortunately, the survival outcomes in this age group are significantly less favourable compared with older children, both overall and for specific tumour types (Kun, 1997).

Infants are at high risk for severe radiation-induced late effects, including mental retardation, growth failure, and leukoencephalopathy (Suc et al., 1990; Duffner et al., 1993). To address this problem, current therapy for children 3 years or older uses multiagent chemotherapy alone to postpone radiation therapy for 1 or more years or even to eliminate the need for radiation therapy. It is now apparent that some infants with PNET/MB can be effectively treated with chemotherapy alone. Nearly two decades ago, a group of infants with PNET/MB or ependymoma were treated

with a multiagent chemotherapy including mechlorethamine, vincristine, procarbazine and prednisone (MOPP). Eight of 12 children with PNET/MB and two of five children with ependymoma survived. Children treated with chemotherapy alone had normal growth and normal cognitive function (Ater et al., 1997). These encouraging results prompted a large collaborative study of chemotherapy in infant brain tumour patients sponsored by the Pediatric Oncology Group. Results of this study confirmed that the objective of delaying radiation therapy for one or more years was possible in nearly 40% of cases. Unfortunately, infants with PNET/MB had lower progression-free survival rate than expected; only 42% at 1 year and 34% at 2 years (Duffner et al., 1993).

Subsequent clinical trials increased the intensity of multiagent chemotherapy for infants with brain tumours. However, survival results have not improved substantially and it is apparent that the effectiveness of currently available chemotherapy is lower than that for combined chemotherapy and radiation therapy. Current cooperative group studies continue to evaluate chemotherapy dose intensification and the addition of intrathecal chemotherapy (Geyer et al., 1994). Advances in radiation therapy techniques allow the administration of a more restricted treatment volume to the tumour, significantly limit the radiation exposure of normal brain tissue, and may reduce the late toxic effects of radiation.

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Brain metastases

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Brain metastases are tumours that originate in tissues outside the brain and spread secondarily to involve the brain. Metastases to the brain are the most common intracranial tumours and outnumber primary brain tumours by at least ten to one. The treatment of these tumours is one of the few areas of Neuro-oncology where true progress has been made during the last 15 years. Although the development of brain metastases still usually indicates a poor prognosis for the patient, it is now possible to reverse most of the symptoms of brain metastases and give patients a meaningful extension of useful life.

Frequency

The frequency of brain metastases is difficulty to determine with precision. Older estimates, based on historical neurosurgical series, suggested that metastases made up only about 10–15% of the total number of intracranial tumours (Dunlap, 1932). However, due to the reluctance of surgeons in the past to operate on patients with known systemic cancer, older neurosurgical series grossly underestimated the actual occurrence of brain metastases. With modern neuroimaging techniques and more careful autopsy studies on cancer patients, it is now known that metastases to the brain as a group are actually the most common intracranial tumours and outnumber primary brain tumours in the general population (Cairncross & Posner, 1983; Walker et al., 1985; Posner, 1992). At present, the frequency of brain metastases in cancer patients is estimated to be 20–40% (Cairncross & Posner, 1983; Posner, 1992). These numbers may increase in the future as the ability to detect small tumours with magnetic resonance imaging (MRI) improves. The frequency of brain metastases may also be rising, due to the longer survival of cancer patients in general.

Table 89.1. Frequency of brain metastases by primary tumour type[a]

Primary tumour	Number of patients	Percentage
Lung	270	48
Breast	82	15
Melanoma	50	9
Colon	26	5
Other known primary	72	13
Unknown primary	61	11
Total	561	100

Note:

[a] Pooled data from references (Markesbery et al., 1978; Cairncross et al., 1980; Zimm et al., 1981).

The histological type of primary tumour is strongly associated with the frequency and pattern of intracranial spread (Table 89.1). In adults, the most common sources of brain metastases are the lung, breast, gastrointestinal tract, genitourinary tract, and skin (malignant melanoma) in that order. In patients less than 21 years old, brain metastases arise most often from sarcomas (osteogenic sarcoma, rhabdomyosarcoma and Ewing's sarcoma), and germ cell tumours (Vannucci & Baten, 1974; Graus et al., 1983; Bouffet et al., 1997; Tasdemiroglu & Patchell, 1997).

Cerebral metastatic disease in children is less frequent than the 20–40% reported in adults. Four retrospective studies have estimated the occurrence to be 6–10% (Vannucci & Baten, 1974; Graus et al., 1983; Bouffet et al., 1997; Tasdemiroglu & Patchell, 1997). The most common childhood solid tumours (other than primary brain tumours) are neuroblastomas and a variety of sarcomas including embryonal rhabdomyosarcoma, Wilm's tumour, Ewing's sarcoma and osteogenic sarcoma. In children

older than 15 years, germ cell tumours have the highest incidence (Graus et al., 1983). The clinical presentation and neurological manifestations of cerebral metastases in children are similar to those seen in adults, and the approach to diagnosis and treatment is the same.

Method of spread and distribution

Most tumour cells reach the brain by hematogenous spread, almost always through the arterial circulation. Most commonly, the metastasis originates in the lung from either a primary lung cancer or from a metastasis to the lung. A small proportion of tumour cells may reach the brain via the vertebral venous system (Batson's plexus). Batson (1942) suggested that this plexus provides a pathway for pelvic and retroperitoneal cancers to spread to the spine and proximally to the intracranial space; he noted an increased proportion of posterior fossa metastases with such tumours, often without other evidence of systemic spread. However, studies have not supported this theory. A retrospective study (Delattre et al., 1988) did not find an increased frequency of skull and spinal lesions in patients with abdominal or pelvic primary tumours, nor was there a corresponding decrease in the percentage of pulmonary metastases in such patients. The 'fertile soil' hypothesis suggests that certain tissues (in this case, brain) have characteristics that support the growth of metastases that are lacking in other organs (Cairncross & Posner, 1983; Delattre et al., 1988). This theory has been proposed to explain the observed distribution.

Within the brain, metastases most commonly are found in the area of the grey/white junction (Delattre et al., 1988; Hwang et al., 1996). This is due to a change in the size of blood vessels at that point; the narrowed vessels act as a trap for emboli. Brain metastases tend to be more common at the terminal 'watershed areas' of arterial circulation (the zones on the border of or between the territories of the major cerebral vessels) (Hwang et al., 1996). The distribution of metastases among the large subdivisions of the central nervous system follows roughly the relative weight and blood flow to each area. Accordingly, about 80% of brain metastases are located in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brainstem (Cairncross & Posner, 1983; Delattre et al., 1988).

Older studies, using computerized tomography (CT) scan data, indicated that metastases to the brain are multiple in slightly more than 50% of cases (Cairncross & Posner 1983; Delattre et al., 1988). More recent experience with MRI indicates that the proportion of multiple metastases is higher and is in the range of two-thirds to three-fourths of patients with brain metastases (Sze et al., 1990). It is probable that, with the widespread use of MRI and new improvements in MRI contrast agents and resolution, the proportion of multiple metastases will be found to be even higher in the future. A note on terminology is in order here. The phrase 'single brain metastasis' refers to those patients with an apparent single cerebral lesion; no implication is made regarding the extent of cancer elsewhere in the body. On the other hand, the phrase 'solitary brain metastasis' is properly used to describe the relatively rare subgroup of patients who have a single brain metastasis that is the only known site of metastatic cancer in the body. Metastases from colon, breast and renal cell carcinoma are often single, while malignant melanoma and lung cancer have a greater tendency to produce multiple cerebral lesions (Delattre et al., 1988).

Clinical presentation

Metastases to the brain are usually symptomatic, and more than two-thirds of patients with brain metastases have some neurological symptoms during the course of their illness (Posner, 1974, 1980; Cairncross & Posner, 1983). Brain metastases may be detected at the same time the primary is diagnosed (synchronous presentation) or more commonly the diagnosis of the primary antedates the development of the brain metastasis (metachronous presentation). Over 80% of brain metastases present some time after the diagnosis of systemic cancer has been made.

The clinical presentation of brain metastases is similar to that of other mass lesions in the brain (Tables 89.2 and 89.3). Headache is a common presenting symptom, and this may be followed after an interval of days or weeks by other focal symptoms or signs. However, the headache may be mild and is rarely of localizing value. Early morning headache (usually thought to be associated with raised intracranial pressure) is a presenting symptom in only 40% of patients with brain metastases (Posner, 1980). Headaches are more common with multiple metastases or with posterior fossa lesions. Raised intracranial pressure (and the accompanying headache) is associated with the clinical sign of papilledema. Since the advent of modern cranial imaging techniques, the frequency of papilledema in patients presenting with brain metastases is less than 25% (Posner, 1974, 1980, 1992).

Seizures, either focal or generalized, occur in approximately 10% of patients at presentation. They are more common in patients with multiple metastases (Posner,

Table 89.2. Symptoms of brain metastases[a]

Symptom	Number of patients	Percentage
Headache	163	42
Focal weakness	107	27
Mental change	121	31
Seizure	80	20
Gait ataxia	65	17
Sensory disturbance	24	6
Speech problems	40	10

Note:

[a] Pooled data from references (Cairncross et al., 1980; Zimm et al., 1981).

Table 89.3. Signs of brain metastases[a]

Sign	Number of patients	Percentage
Altered mental status	139	35
Hemiparesis	174	44
Hemisensory loss	36	9
Papilledema	36	9
Gait ataxia	49	13

Note:

[a] Pooled data from references (Cairncross et al., 1980; Zimm et al., 1981).

1980). Occasionally the seizure will be focal in origin, and this has localizing value. Abnormalities of higher mental functions may take the form of a non-focal encephalopathy (1 to 2% of patients with metastases) or may relate to localized dysfunction (e.g. aphasia). Focal weakness is second only to headache in frequency as a presenting symptom.

Five to 10% of patients may present with acute neurological symptoms caused by hemorrhage into the tumour or cerebral infarction from embolic or compressive occlusion of a blood vessel (Cairncross & Posner, 1983). Hemorrhage into a metastasis is particularly common with choriocarcinoma and melanoma (Mandybur, 1977; Nutt & Patchell, 1992). An unusual presentation of brain metastasis is episodic loss of function suggestive of a transient ischemic attack. Such symptoms may be manifestations of focal seizures that go unrecognized by the patient. However, the signs and symptoms related to cerebral lesions are varied, and the suspicion of brain metastases should be raised in all patients with known systemic cancer in whom new neurological findings develop.

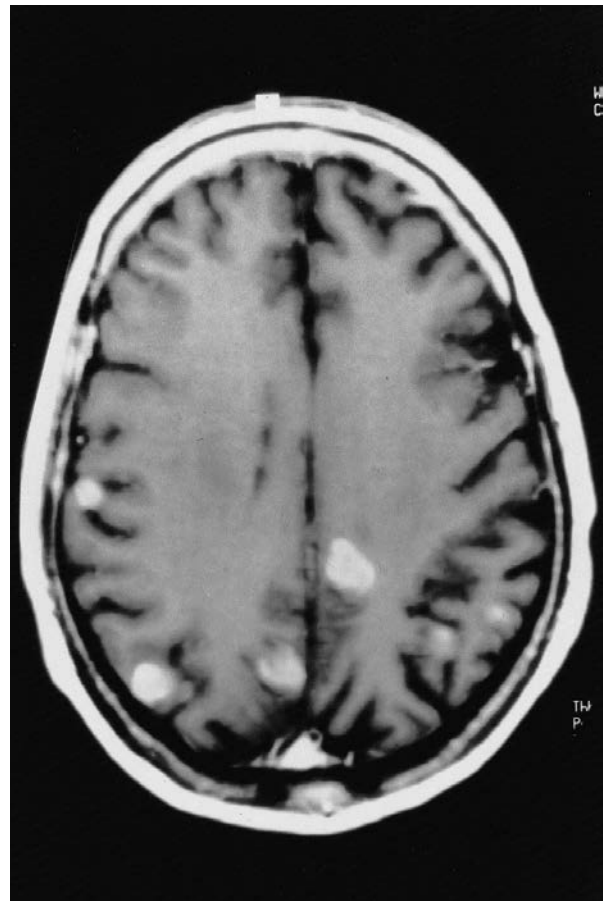

Fig. 89.1. T1 gadolinium-enhanced MRI of a patient with multiple enhancing brain metastases.

Diagnosis

The best diagnostic tests for brain metastases are contrast enhanced MRI (Fig. 89.1) and (to a lesser extent) CT (Sze et al., 1990; Davis et al., 1991). If the clinical history is typical and lesions are multiple, usually there is little doubt surrounding the diagnosis. However, it is important that metastases be distinguished carefully from primary brain tumours (benign or malignant), abscesses, and cerebral infarction and hemorrhages. It is equally important to identify those patients with single metastases whose subsequent management may be different.

Contrast enhanced MRI is more sensitive than enhanced CT scanning (including double dose delayed contrast) or unenhanced MRI in detecting lesions in patients suspected of having intracranial metastases (Sze et al., 1990; Davis et al., 1991). For both CT and MRI, multiplicity of lesions is a useful finding that usually distinguishes metas-

tases from gliomas or other primary tumours. Other imaging findings that favour metastases include a grey/white junction location, relatively smooth lesion margins, and a small tumour nidus with a large amount of associated vasogenic edema (Williams, 1985).

Although T_2-weighted sequences in MRI are sensitive in demonstrating the vasogenic edema as areas of increased signal intensity, not all metastatic lesions have sufficient edema to be identified (Price et al., 1990). In these cases, the lesions are typically less than 5 mm in diameter, may lie adjacent to a larger metastatic lesion, and may be located in the temporal lobes or in the cortical and subcortical areas. However, a study has shown that the false-positive rate, even when using contrast MRI for the diagnosis of single brain metastases, is approximately 11% (Patchell et al., 1990). Other diagnostic tests, such as arteriography or biopsy, may be needed to establish the diagnosis firmly.

The question often arises as to how far to pursue investigation in the patient with a brain mass demonstrated on a CT or MRI and with no previous history of systemic cancer. Because most metastases reach the brain by hematogenous spread through the arterial circulation, the lung is an important source of brain metastases. If the primary tumour is not pulmonary, it has probably spread to the lung before seeding into the arterial circulation and reaching the brain. More than 60% of patients with brain metastases will have a mass demonstrated on chest radiograph that is caused by either a primary lung cancer or a lung metastasis from the primary located elsewhere (Bentson et al., 1988; Delattre et al., 1988; Saphner et al., 1989). Therefore, careful radiographic examination of the chest is one of the most important diagnostic tests in patients with suspected brain metastases (Latief et al., 1997). When the chest radiograph fails to demonstrate a lesion, CT or MRI of the lung may show lesions and suggest the cause of the neurologic disorder. A CT or MRI of the abdomen occasionally will show an unsuspected renal or colon cancer. Further search for a primary tumour is almost never fruitful, especially if there are no positive findings on physical examination and no features of the history are suggestive of a specific primary tumour. In the few patients with brain metastases but no identifiable lesions in the lung, the pathogenesis of the brain metastases may be spread through Batson's vertebral venous plexus, tumour emboli through a patent foramen ovale (paradoxical embolus), or tumour filtered through the lungs with only local or microscopic growth.

Treatment

Newly diagnosed brain metastases

The optimum therapy of brain metastases (whether single or multiple) is still evolving. Several methods of treatment are available for patients with intracranial metastases. Corticosteroids, radiotherapy and surgical therapy all have an established place in management, and as a result of recent randomized trials, the role of radiosurgery is also becoming clearer. In addition, chemotherapy is useful in some patients with chemosensitive tumours. There are several things to be considered when determining the best treatment for each patient, including the extent of systemic disease, neurological status at diagnosis and the number and site of metastases

Brain metastases are associated with a poor prognosis regardless of treatment. Untreated patients have a median survival time of only about 4 weeks (Ruderman & Hall, 1965; Horton et al., 1971; Markesbery et al., 1978). Nearly all untreated patients die as a direct result of the brain tumour, with increasing intracranial pressure leading to obtundation and terminal cerebral herniation. The survival figure quoted here must be interpreted with caution because the information comes from retrospective studies done before the modern age of CT and MRI neuroimaging. Also, in the past as now, the patients who receive no treatment for their brain metastases are usually those with poor performance status, extensive systemic disease, and generally very poor prognoses. It is likely that the average patient diagnosed today would live longer than 1 month, even if untreated.

Anticonvulsants

Seizures occur in about 25% of patients with brain metastases and are the presenting complaint in 10–15% of patients (Posner, 1980, 1992; Cairncross & Posner, 1983; Glantz et al., 2000). Two randomized trials (Glantz et al., 2000) have shown that prophylactic anticonvulsants do not reduce the frequency of first seizures in patients with newly diagnosed brain metastases. Therefore, anticonvulsants should only be given to patients who have actually had seizures and should not be given routinely at the time of diagnosis of brain metastasis to all patients whether they have had seizures or not (Glantz et al., 2000).

Corticosteroids

Almost all patients with brain metastases should be started on corticosteroid (steroid) therapy at the time of diagnosis.

(Patients with small, completely asymptomatic lesions may not need steroids; however, steroids may reduce the side effects of cranial radiation and are rarely harmful in most patients for short periods of time.) The mechanism of action of corticosteroids is not completely understood, although a reduction in the edema surrounding the metastatic tumours is a frequent finding (Fishman, 1975). Dexamethasone is the preferred form of corticosteroid because it has minimal mineralocorticoid affect and a relatively low tendency to induce psychosis (Fishman, 1975; Ehrenkranz & Posner, 1980). More than 70% of patients improve symptomatically after starting steroids (Ehrenkranz & Posner, 1980). Symptoms reflecting generalized neurological dysfunction or brain edema respond more consistently than do focal symptoms such as hemiparesis.

The beneficial effects of steroids are noticeable within 6 to 24 hours after the first dose and reach maximum effect in 3 to 7 days (Gutin, 1975). The median survival time of patients treated with steroids alone is approximately 2 months (Horton et al., 1971; Chang et al., 1992), although much longer lengths of survival have been reported (Gottlieb et al., 1972; Gutin, 1975; Chang et al., 1992).

The usual starting dose of dexamethasone is 4 mg four times daily given either orally or intravenously. Occasionally, patients require higher doses. With stabilization of symptoms and the completion of more definitive treatment, the dose of dexamethasone should be tapered gradually over several weeks and then stopped to minimize long term toxicity. About 10% of patients do not tolerate the reduction in steroids and redevelop the signs of brain edema. In these patients, the lowest effective dose should be continued indefinitely.

Radiotherapy

Radiotherapy is the treatment of choice for most patients with brain metastases. Since the initial report of the use of ionizing radiation for palliative benefit in 1954 (Chao et al., 1954), there have been several studies that have attempted to determine the optimal treatment regimen. Unfortunately, there is still no consensus on the optimum radiation dose and schedule for the treatment of brain metastases.

Most patients are treated with whole brain radiotherapy (WBRT). This is because over two-thirds have multiple metastases at the time of diagnosis, which usually makes surgical treatment impossible. The best available data on the effect of dose and schedule for the treatment of brain metastases comes from several large scale multi-institutional trials conducted by the Radiation Therapy Oncology Group (RTOG) (Borgelt et al., 1980; Gelber et al., 1981; Kurtz et al., 1981). These studies have shown that there appears to be no significant difference in the frequency and duration of response for total radiation doses ranging from 2000 cGy over 1 week to 5000 cGy over 4 weeks. Regimens of 1000 cGy in a single dose, or 1200 cGy in two doses were less effective and are no longer in use.

Currently, typical radiation treatment schedules for brain metastases consist of short courses (7 to 15 days) of whole brain irradiation with relatively high doses per fraction (150 to 400 cGy per day) with total doses in the range of 3000 to 5000 cGy. These schedules minimize the duration of treatment, while still delivering adequate amounts of radiation to the tumour. Increased focal irradiation to the tumour site in the brain has not been demonstrated to be beneficial. A retrospective study has shown that giving a boost dose to the tumour site is no better than whole brain radiotherapy alone in preventing neurological recurrences or increasing length of survival (Hoskins et al., 1990).

Radiation cell sensitizing agents have been used in an attempt to increase tumour cell death. The rationale was based on the observation that hypoxic cells (often found centrally in a tumour) are more resistant to the effects of ionizing radiation. Agents such as misonidazole have the potential to increase cell sensitivity to irradiation. However, none of the radiation cell sensitizers tested to date has been shown to provide any additional benefit over conventional radiotherapy (Eyre et al., 1984; Komarnicky et al., 1991; Berk, 1995).

Whole brain radiotherapy increases the median survival to 3 to 6 months (Deeley & Edwards, 1968; Order et al., 1968; Horton et al., 1971; Berry et al., 1974; Markesbery et al., 1978; Cairncross et al., 1980; Zimm et al., 1981; Cairncross & Posner, 1983; Berk, 1995). Data from large retrospective studies has shown that more than half of patients treated with whole brain radiotherapy die ultimately of progressive systemic cancer and not as a direct result of brain metastases (Cairncross et al., 1980; Cairncross & Posner, 1983; Berk, 1995).

Retrospective studies on large numbers of patients treated in RTOG brain metastasis protocols have identified patient subgroups that were more likely to respond to whole brain radiotherapy (Deiner-West et al., 1989). More favourable outcome is associated with (i) Karnofsky performance scores (Karnofsky & Burchenal, 1949) in the range of 70% or above, (ii) absent or 'controlled' primary tumour, (iii) patient age less than 60 years, and (iv) metastatic spread limited to the brain. Building on these results, a recursive partitioning analysis (RPA) was applied to a combined group consisting of patients from several past RTOG radiotherapy studies (Gaspar et al., 1997). Three distinct prognostic groups were identified. The most favour-

able prognostic group was designated RPA class 1 and consisted of patients whose Karnofsky scores were 70% or higher, age was 65 years or less, primary tumours were 'controlled', and no extracranial metastases were present. RPA Class 3 patients had the worst prognoses; these patients had Karnofsky scores less than 70% (with or without other unfavourable factors). RPA Class 2 patients included patients who did not fit into Class 1 or 3 (i.e. patients who had Karnofsky scores 70% or higher but also had one or more of the other unfavourable factors). Performance status at the time of treatment for brain metastases is the most important prognostic factor.

Radiotherapy has complications. Almost all patients experience a temporary loss of hair; hair usually returns 6–12 months after completing therapy. Also, in the short term, patients may have a transient worsening of neurological symptoms while receiving therapy (Sheline et al., 1980; Cairncross & Posner, 1983). Many physicians believe that maintaining patients on steroids during radiotherapy will minimize radiotherapy complications, although conclusive proof of this has not been forthcoming. During initial days of treatment, mild symptoms such as nausea, vomiting, headache and fever are common. This acute reaction may relate to distorted cerebrovascular autoregulation or increased capillary permeability (Olsson et al., 1975). Rarely, radiation-induced parotitis and loss of taste may also occur with cranial irradiation (Cairncross & Posner, 1983).

The long-term side effects of radiotherapy are usually not a significant issue in the treatment of patients with brain metastases because of the relatively short survival time of these patients. However, reports (DeAngelis et al., 1989a,b; Paleologos et al., 1991; Crossen et al., 1994) have suggested that over 10% of long-term survivors (>12 months) will develop symptoms such as dementia, ataxia, and urinary incontinence. In these patients, imaging studies show cortical atrophy and hyperdense white matter changes. Although the pathogenesis of such alterations is unknown, it is speculated that high dose/large fractionation schedules may be a factor (DeAngelis et al., 1989a,b). Therefore, in patients with anticipated long length of survival, a more prolonged course of radiotherapy with smaller doses per fraction should be used. A reasonable schedule for patients with a good prognosis would be a total dose of 4500 to 5000 cGy given in daily fractions of no more than 200 cGy.

Surgery

Surgical therapy is usually not an option for most patients with brain metastases because of the presence of multiple lesions or extensive systemic cancer. However, in the subgroup of patients whose only metastatic disease is in the brain, it has been shown that death is more likely to be due to the brain metastases than to progressive systemic disease (Zimm et al., 1981). Therefore, in patients with controlled systemic cancer in whom brain metastases develop, the treatment of the brain disease is the factor that will most likely determine the length of survival. It is in this group that the question of more aggressive therapy, particularly surgery, for the brain metastases is usually raised. There have been several advances over the past 20 years that have decreased the risks associated with the surgical approach. Safer anesthesia, the widespread use of corticosteroids, the development of modern non-invasive cranial imaging technology and the introduction of stereotactic approaches have been foremost among these changes.

There are theoretical reasons for believing that the combination of surgical treatment followed by postoperative radiotherapy may be more effective than whole brain radiotherapy alone. Radiotherapy is most successful when used against small tumour volumes. In larger tumours, radiation is usually effective at the periphery of the tumour where cells are relatively small in number and well oxygenated. However, in the centre of the tumour, where tumour cells are more numerous and more hypoxic conditions exist, radiation may fail to destroy the tumour completely. Although there are documented reports of sterilization of brain metastases by radiotherapy alone (Cairncross et al., 1979), in most instances, residual tumour remains. Surgical treatment is most successful in removing large volumes of tumour, but small numbers of malignant cells may be left behind. Rational treatment plans combining surgical debulking and radiotherapy have been developed to overcome the deficiencies of both types of treatment (Bergonie & Tribondeau, 1959; Suit & Todoroki, 1985), and combined therapy has shown promise in patients with a variety of tumour types (Hellman, 1980).

There have been three prospective randomized trials assessing the value of surgical removal of single brain metastases (Table 89.4) (Patchell et al., 1990; Vecht et al., 1993; Mintz et al., 1996) These studies have had a similar design and have compared surgery plus postoperative WBRT with WBRT alone. In a trial (Patchell et al., 1990) performed at the University of Kentucky, there was a statistically significant increase in survival in the surgical group. In addition, the time to recurrence of brain metastases, freedom from death due to neurologic causes, and duration of functional independence were significantly longer in the surgical resection group. A second study (Vecht et al., 1993) conducted as a multi-institutional trial in the

Table 89.4. Surgery for single brain metastases: randomized trials

	N	Median survival (wks)	Length of functional independence (wks)	CNS death
S + WBRT				
Patchell[a]	25	40	38	29
Vecht[b]	32	43	33	35
Mintz[c]	41	24	8	46
WBRT ONLY				
Patchell[a]	23	15	8	50
Vecht[b]	31	26	15	33
Mintz[c]	43	27	9	63

Notes:
WBRT = Whole brain radiotherapy.
[a] = Patchell et al. (1990).
[b] = Vecht et al. (1993).
[c] = Mintz et al. (1996).

Netherlands, found that survival was significantly longer in the surgical group. There was also a non-significant trend toward longer duration of functional independence in the surgically treated patients. No data concerning recurrence of brain metastases were given. A third randomized trial, conducted in Canada by Mintz et al. (1996) failed to find a benefit from surgical treatment. No difference was found in overall survival. There was also no difference in causes of death or quality of life.

It is unclear why the Canadian study was not in agreement with the other two trials. In all three studies, the control arms (the radiation alone arms) had median lengths of survival in the 3–6 months range, well within the expected range for patients treated with radiotherapy alone. The major difference in the studies was the poor results obtained in the surgical arm of the Canadian trial. That study contained a higher proportion of patients with extensive systemic disease and lower performance scores. Also, the Canadian health care system sometimes discourages aggressive and expensive systemic treatment for patients with disseminated cancer. It is possible that these factors resulted in more patients dying of their systemic cancer before a long-term benefit of surgery was seen.

Although the data supporting surgery for single brain metastases were derived from relatively small randomized trials that were not uniformly positive, the results have generally been interpreted to show that the surgical resection is of benefit in selected patients. Surgical therapy plus postoperative WBRT is now the treatment of choice for patients with surgically accessible single brain metastases (Posner, 1990, 1992; Barr et al., 1992).

The value of surgery in the management of multiple metastases remains to be demonstrated. Two retrospective studies (Bindal et al., 1993; Hazurka et al., 1993) have come to opposite conclusions regarding the safety and efficacy of surgical removal of more than one brain metastasis. These two studies suggest that the postoperative morbidity and mortality rates for patients with multiple metastases treated with surgery are relatively low and are comparable with those reported in patients with single surgically resected metastases. However, it is difficult to draw firm conclusions regarding the efficacy of surgery for multiple metastases from the studies published to date. Current practice is to treat multiple metastases with WBRT alone. Currently, surgery is sometimes performed on patients with multiple metastases who have one life-threatening brain lesion. The intent of surgery in these cases is to remove the single life-threatening lesion without taking out the other lesions. Although this approach is speculative, long survival times have been achieved occasionally.

Despite the advantage of surgery in selected patients, WBRT alone remains the treatment for most patients with brain metastases. Single metastases occur in less than one-quarter of patients, and unfortunately, nearly half of patients in this group are not surgical candidates due to inaccessibility of the tumour, extensive systemic disease, and other factors (Patchell et al., 1986). Therefore, at most, only about 10–15% of all patients with brain metastases will benefit from surgical resection. The rest should be treated with radiotherapy.

The best results from surgery are seen in those patients with a single surgically accessible lesion and either no remaining systemic disease (true solitary metastasis) or with controlled systemic cancer limited to the primary site only. A study (Burt et al., 1992) from Memorial Sloan-Kettering Cancer Center has suggested that, in patients undergoing resection of brain metastases from non-small cell lung carcinoma, survival is significantly increased in those patients with complete resection of the primary lung disease. There was no correlation of survival with initial cancer stage *per se*. Also, surgical treatment may be indicated in those patients without known systemic cancer (to obtain a tissue diagnosis) and in patients with impending herniation due to pressure effects.

A point of controversy has been whether postoperative radiotherapy needs to be given as WBRT (as opposed to focal radiation) or whether radiotherapy is even necessary at all after a 'complete resection' of a single metastasis. There is no doubt that radiation therapy, when given as the

only treatment for brain metastases, results in longer survival. Postoperative WBRT is felt to be of benefit because there may be residual disease in the tumour bed or at distant microscopic sites in the brain. However, brain metastases tend to be discrete masses that are theoretically capable of being removed totally, and so postoperative WBRT may not be necessary.

Retrospective studies (Dosoretz et al., 1980; Smalley et al., 1987; DeAngelis et al., 1989a,b; Hagen et al., 1990; Armstrong et al., 1994; Skibber et al., 1996) that examined the role of postoperative radiotherapy in the management of single brain metastases failed to answer the question because of conflicting results. Only one randomized trial (Patchell et al., 1998) has addressed the question of postoperative radiotherapy. In that study, 95 patients who had single brain metastases that were completely resected (as determined by postoperative MRI scans) were randomized to treatment with postoperative WBRT (50.4 Gy) or to observation with no further treatment of the brain metastasis (until recurrence). Recurrence of tumour anywhere in the brain was less frequent in the radiotherapy group than in the observation group (18% vs. 70%, $P<0.001$). Postoperative radiotherapy prevented brain recurrence at the site of the original metastasis (10% vs. 46%, $P<0.001$) and at other sites in the brain (14% vs. 37%, $P<0.01$). As a result, patients in the radiotherapy group were less likely to die of neurologic causes than patients in the observation group (6 of 43 who died [14%] vs. 17 of 39 [44%]; $P=0.003$). There was no significant difference between the two groups in overall length of survival or in the length of time that patients remained functionally independent. The lack of difference in overall survival and quality of life may be explained by the fact that of the 32 patients in the observation group who had recurrence of tumour, 29 (91%) of them received WBRT at recurrence. This diluted the effect of WBRT given immediately postoperatively by most likely improving survival and quality of life in the observation group.

Several conclusions can be drawn from the randomized study. Radiotherapy prevents recurrence of tumour and reduces death from neurological causes. In addition, postoperative MRI scanning is relatively unreliable at detecting residual disease in the operative bed and at other sites in the brain. These factors justify the routine use of WBRT, even after apparently complete resections.

Radiosurgery

Stereotactic radiosurgery, a method of delivering intense focal irradiation using a linear accelerator (LINAC) or multiple Cobalt-60 sources (Gamma Knife), has been used with increasing frequency to treat single and multiple brain metastases. Radiosurgery does not replace conventional radiotherapy to the brain but may offer a substitute for surgical therapy in patients with lesions less than 3 cm in diameter.

To date, much of our information on radiosurgery comes from non-randomized studies. For single metastases, the combined results of many retrospective reports (Loeffler et al., 1990; Mehta et al., 1992; Auchter et al., 1996; Flickinger et al., 1996) suggest that radiosurgery prevents (or controls) local recurrence of 80–90% of treated metastases with about a 5–10% risk of radiation necrosis or new neurologic deficits. Despite these apparently promising results, it is important to note that, at present, radiosurgery has not been unequivocally established as an effective treatment in the management of single metastases. Prospective randomized clinical trials are still needed and are currently under way to determine the role of radiosurgery both in the initial treatment of patients with single metastases and in the management of recurrent brain metastases.

The role of radiosurgery in the treatment of multiple metastases has recently been the subject of three randomized trials. The first randomized trial on the subject was reported by Kondziolka et al. (1999). This study had only 27 patients in it and used non-standard endpoints. As a result, this study was uninterpretable. A second study reported by Chougule et al. (2000) contained methodological errors that made it impossible to draw firm conclusions from the data.

The RTOG has reported the results of a larger randomized study (Sperduto et al., 2000) involving patients with multiple brain metastases. This study (RTOG 9508) contained 144 patients with two or three brain metastases who were randomized to treatment with either WBRT (37.5 Gy) plus radiosurgery or WBRT (37.5 Gy) alone. There was no significant difference in local failure rates in the brain with 21% in the radiosurgery arm and 37% in the WBRT alone arm ($P=0.107$). There was also no significant difference in the length of survival of the two groups (median, 5.3 months for radiosurgery and 6.7 months for WBRT alone). Most noteworthy was the lack of significant difference between the fraction of patients in each group who died of neurological causes (33% radiosurgery vs. 35% WBRT alone). Lower post-treatment Karnofsky scores and steroid dependence were more common in the WBRT alone patients. Nevertheless, this was a completely negative trial with regard to the major endpoints of tumour control in the brain, overall survival, and prevention of death due to neurological causes.

The results of RTOG 9508 have forced a major re-evaluation of the use of radiosurgery in the treatment of

brain metastases. This was the largest and best trial done to date, and it failed to show a benefit of radiosurgery in the treatment of multiple brain metastases when radiosurgery was given in the initial management of newly diagnosed tumours. Treatment with WBRT alone would now appear to be the treatment of choice in these circumstances. However, radiosurgery may still have a place as salvage treatment in patients who have recurrent brain tumours after treatment with WBRT, but this remains to be demonstrated. There have been no definitive randomized trials of radiosurgery in the upfront management of single brain metastases, but RTOG 9508 has a second part evaluating radiosurgery in the management of single metastases that is still ongoing and will hopefully further define the use of radiosurgery in the future.

Interstitial brachytherapy

The use of interstitial brachytherapy, a technique involving the placement of radioactive implants within the area of tumour has been advocated in selected patients. The implants allow delivery of high dose focal radiation to the tumour while minimizing the risk of significant radiation exposure of the surrounding normal brain tissue because of the rapid fall-off of radiation intensity at the margins of the precalculated target area. Both permanent and removable implants have been in use. The placement may be accomplished stereotactically or during open surgery. The procedure is limited to relatively small metastases that are located in surgically accessible regions of the brain.

The role of brachytherapy in the primary management of brain metastases has yet to be determined. Preliminary studies (Heros et al., 1988; Prados et al., 1989; Alesch et al., 1995; Ostertag & Kreth, 1995; McDermott et al., 1996) have been inconclusive and the procedure has potentially serious complications. The major complication is radiation necrosis that may present with the clinical and imaging picture of an expanding mass months after treatment. Sometimes, a biopsy is required to differentiate tumour necrosis from recurrence, while steroids and, occasionally, a surgical resection help to reverse the neurological symptoms secondary to the radiation necrosis. The frequency of this complication varies with the amount of radiation given (Heros et al., 1988).

At present, brachytherapy cannot be recommended as initial therapy for brain metastases. However, this technique may offer an additional treatment option for patients with unresectable metastases or those who have received a prior maximum dose of whole brain radiotherapy.

Chemotherapy

The efficacy of chemotherapy in the management of brain metastases has not been demonstrated, although evidence has been accumulating that suggests that chemotherapy may have a role in the treatment of selected patients. Since more than half of the patients with brain metastases who are treated with surgery or radiotherapy will subsequently die of progression of the systemic disease, a chemotherapeutic agent that is effective against both systemic and brain disease is highly desirable. However, most systemically administered chemotherapeutic agents that have proven effective against the primary sites of cancer have been ineffective against cerebral metastases from the same cell population (Greig et al., 1983; Greig, 1984; Lesser, 1996; Korfel & Thiel, 1999). Drug delivery to the brain is a problem. The transport of material between the blood stream and cerebral tissue differs from other organs in the body. Tight intercellular junctions allow only the more lipid soluble materials to diffuse across capillaries within the brain. The blood–brain barrier is thought to be one of the major reasons that systemically administered anticancer agents do not reach cerebral metastases in adequate concentrations, or for adequate periods of time, to ensure effective tumour cell death. However, drug delivery cannot be the sole cause of the disappointing results in brain tumours. It is known that the blood–brain barrier is usually broken down at sites of brain tumours, and other factors must, therefore, contribute to the relative chemotherapeutic resistance seen with brain metastases (Greig et al., 1983). Tsukada et al. (1983) have suggested that the blood–brain barrier may increase the incidence of brain metastases following systemic chemotherapy by inducing a relative ‘pharmacological sanctuary’ within the central nervous system.

Chemotherapy has been used in the treatment of brain metastases from a variety of primary tumours; however, the results have generally been unimpressive (Greig, 1984; Hildebrand, 1988; Seigers, 1990; Lesser, 1996; Korfel & Thiel, 1999). Although some small uncontrolled series of patients with certain highly chemosensitive tumours (e.g. breast, small cell lung cancer, germ cell tumours) have been reported (Rosner et al., 1986; Hildebrand, 1988; Kleisbauer et al., 1988; Kristjansen & Pedersen, 1989; Seigers, 1990; Lesser, 1996; Korfel & Thiel, 1999; Boogerd et al., 1992). Chemotherapy is not usually the primary therapy for most patients and is seldom the only therapy.

At present, a reasonable use for chemotherapy for brain metastases would be in those patients with small, asymptomatic tumours from primaries that are known to be chemosensitive. If progression occurs with the patient

receiving chemotherapy alone, more definitive treatment with surgery, radiosurgery, or radiotherapy may be given.

Follow-up

There is no set standard for the follow up of brain metastases after treatment. MRI or CT scans are indicated at any time after therapy that patients develop new neurological symptoms. How frequently asymptomatic patients need follow up scans is controversial. For patients treated with surgery, a contrast MRI scan should be performed within 5 days after surgery to detect residual disease. This is especially important if consideration is being made to forgo postoperative radiation therapy. If residual disease is present, patients should be given WBRT. For all patients treated with WBRT, follow-up scans should be obtained at regular intervals after treatment. In general, it takes about 6 weeks after WBRT for a definite change to take place in the scan, and so, patients usually do not need scans immediately following the completion of radiotherapy. A reasonable schedule of follow-up scanning would be to get a scan 3 months after completion of last therapy (either WBRT or surgery) and then about every 4 months for the first year following treatment. The length of time between scans can then be gradually stretched out so that asymptomatic patients are scanned only once per year.

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Paraneoplastic syndromes

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The term 'paraneoplastic syndrome' refers to a group of disorders that are caused by a cancer but do not result from invasion of the affected organ by the tumour. Although indirect effects of cancer or its treatment, such as vascular disorders, infections, nutritional or metabolic dysfunction, can be considered paraneoplastic (Posner, 1995), most neurologists restrict the term paraneoplastic syndromes involving the nervous system to disorders of unknown cause that are also termed 'remote effects of cancer on the nervous system' (Brain & Norris, 1965). It is these remote effects of cancer on the nervous system that are addressed in this chapter (Table 90.1). Syndromes that are clinically and pathologically identical to paraneoplastic syndromes also occur in patients without cancer, but at a lesser incidence.

Table 90.1. Some paraneoplastic syndromes of the nervous system

Most affected structure	Example(s)
Cerebral hemisphere(s)	Limbic encephalitis
Cerebellum	Purkinje cell degeneration
Brainstem	Opsoclonus/myoclonus
Retina	Carcinoma associated retinopathy
Spinal cord	Necrotizing myelopathy ?Stiff person syndrome
Dorsal root ganglia	Sensory neuronopathy
Peripheral nerve	Sensory neuropathy Autonomic neuropathy
Neuromuscular junction	Lambert–Eaton myasthenic syndrome
Muscle	Dermatomyositis

General considerations

Incidence

Paraneoplastic syndromes can be considered either relatively common or quite rare, depending on how they are defined. If one examines patients with known cancer looking for a mild abnormality of nervous system function, either by clinical or electrophysiological examination, one finds abnormalities frequently. For example, Croft and Wilkinson (1965) reported neurologic paraneoplastic syndromes in 6.6% of 1465 patients with cancer. The majority had proximal muscle weakness and/or a mild peripheral neuropathy. Even higher figures are achieved when one uses quantitative sensory examinations or electrophysiologic assessment of peripheral nerves. Many (but not all) of these mild and subclinical abnormalities may be a result of metabolic or nutritional disturbances associated with far advanced cancer. If one considers only patients with clearly defined and significantly disabling neurological disorders, the incidence is much lower. In the same 1465 patients examined by Croft and Wilkinson there were only three with cerebellar degeneration, three with a myelopathy and none with sensory neuronopathy. It is likely that with the exception of the Lambert–Eaton myasthenic syndrome (LEMS), which affects about 3% of patients with small-cell lung cancer (Sculier et al., 1987), paraneoplastic syndromes affect fewer than 1% of patients with cancer.

Pathogenesis

Increasing evidence suggests that most, if not all, paraneoplastic syndromes affecting the nervous system are caused by an autoimmune reaction engendered by the cancer:

Table 90.2. Antineuronal antibody-associated paraneoplastic disorders[a]

Antibody antigen	Associated cancer	Syndrome	Antigen
Anti-Yo	Gyn, breast	Cerebellar degeneration	Cytoplasm, Purkinje cells 34, 62, kDa
Anti-Hu	SCLC neuroblastoma	Encephalomyelitis, sensory neuronopathy	All neuronal nuclei 35–40 kDa
Anti-Ri	Breast, Gyn, SCLC	Cerebellar ataxia, Opsoclonus	Neuronal nuclei CNS, 55, 80 kDa
Anti-CAR	SCLC, others	Photoreceptor degeneration	Retinal photoreceptor 23 kDa
Anti-amphiphysin	Breast cancer	Stiff-person encephalomyelitis	Synaptic vesicles 128 kDa
Anti-VGCC	SCLC	Lambert–Eaton myasthenic	Presynaptic VCGG
Anti-MysB	SCLC	Lambert–Eaton myasthenic	Presynaptic VCGG
Anti-Ma	Multiple	Cerebellar, brainstem dysfunction	Neuronal nuclei and cytoplasm, 37, 40 kDa
Anti-Ta	Testicular cancer	Limbic encephalitis, brainstem dysfunction	Neuronal nuclei and cytoplasm 40 kDa
Anti-Tr	Hodgkin lymphoma	Cerebellar degeneration	Cytoplasm neurons and Purkinje cells, spiny dendrites
Anti-CV2	SCLC, others	Encephalomyelitis cerebellar degeneration	Glia (subset) 66 kDa

Note:
[a] Modified from Dalmau & Posner (1998).

Antigens normally restricted to the nervous system (Voltz et al., 1999a) (or nervous system and testis (Dalmau et al., 1999), are expressed in a cancer. The immune system, recognizing the antigen in the tumour as foreign, directs an immune response at the tumour; the immune response is misdirected against the shared antigens or epitopes in the nervous system, causing neurological dysfunction. This immune response may be sufficient to retard tumour growth (Carpentier et al., 1998), explaining why so many tumours associated with paraneoplastic syndromes are small and often hard to detect. The evidence for the autoimmune hypothesis is best for the Lambert–Eaton myasthenic syndrome (LEMS) (Newsom-Davis, 1998a) but, as indicated in the next paragraph, current evidence suggests that other paraneoplastic syndromes are also immune-mediated.

Antibody positive paraneoplastic syndromes

In recent years the autoimmune hypothesis has been supported by identification of antibodies in the serum and CSF of some but not all patients with paraneoplastic syndromes (Dalmau & Posner, 1998). These antibodies react with both the target neurological tissue and the underlying tumour. The antibodies often identify patients with a specific clinical syndrome and a specific underlying tumour (Table 90.2). However, there are exceptions: patients with the same paraneoplastic antibody may have different clinical findings and different tumours. Conversely, patients with the same clinical findings may express different antibodies. For example, the anti-Yo antibody is almost always found in patients with paraneoplastic cerebellar degeneration (PCD) and gynecological tumours (Cao et al., 1999) and not in patients with gynecologic tumours who do not have PCD or PCD associated with non-gynecological tumours. However, the antibody is occasionally found in a male with a different tumour (Krakauer et al., 1996), and PCD similar to that in anti-Yo patients may be associated with other antibodies (Mason et al., 1997). Paraneoplastic antibodies typically occur at high titres in the serum; the relative activity is higher in the CSF, at least for those paraneoplastic disorders that clinically affect the CNS. In some instances low titres of the antibody are found in patients with the appropriate cancer but without a paraneoplastic syndrome (Graus et al., 1997).

The antibodies serve as markers indicating that a patient with an unknown neurological diagnosis has cancer as the cause. Particular antibodies also strongly suggest the histologic type of cancer. Thus, the finding of an autoantibody in a patient with a neurological disorder may help identify an occult and potentially curable underlying cancer.

Only a subset of patients with paraneoplastic syndromes have antibodies in their serum. What about the antibody negative patients? There are at least two possibilities. The first is that the antibody negative patients are truly antibody negative and that the disorder may not be immune mediated. The second and more likely possibility is that the disorders are immune mediated and that antibodies are present but have not been identified by current techniques. A good example is the LEMS. Standard histochemical and immunoblotting techniques do not identify an antibody; only by the special techniques of electron microscopic histochemistry or immune precipitation can the

P/Q type calcium channel be identified (Motomura et al., 1995). These findings give one some hope that, using better techniques, antibodies may likewise be found in some currently antibody-negative paraneoplastic syndromes.

Diagnosis

Clinical clues that suggest a diagnosis of a paraneoplastic syndrome include the following.

(i) Most paraneoplastic syndromes evolve subacutely. Many evolve over days or weeks and stabilize by the time the neurologist first sees the patient.

(ii) Paraneoplastic syndromes are usually severe. Most patients have substantial disability at the time they are first seen by the neurologist. Mild or waxing and waning neurological disorders are more likely to have another cause.

(iii) The syndromes are often characteristic. PCD (see below) is so characteristic that it is difficult to consider any other cause for the disorder. However, none of these syndromes, even the most characteristic, is invariably associated with cancer. Thus, only about two-thirds of patients with a LEMS have cancer (almost always a small-cell lung cancer). Probably more than half of patients with subacute cerebellar degeneration have cancer whereas cancer is less common in dermatomyositis and Guillain–Barré syndrome. (Although not all patients with even characteristic paraneoplastic syndromes are found to have cancer, one must evaluate negative reports with care since the neoplasms are often very small and may be overlooked even at autopsy.)

(iv) Paraneoplastic syndromes are often accompanied by CSF pleocytosis, elevated protein and increased IgG levels.

(v) Paraneoplastic syndromes often affect one particular portion of the nervous system with additional subtle or minor findings suggesting dysfunction outside that area. For example, many patients with PCD, in addition to severe ataxia, dysarthria and nystagmus, will be found to be mildly demented and have extensor plantar responses. It is these widespread changes that have led to the use of the term 'encephalomyelitis' when the central nervous system is involved and to the use of the term 'neuromyopathy' when the peripheral nervous system and muscle are involved.

Treatment

Some paraneoplastic syndromes, e.g. LEMS, respond to immunosuppression or the treatment of the underlying cancer (Table 90.3). Some syndromes resolve spontaneously (Mason et al., 1997) but, in general, treatment has been unrewarding (Uchuya et al., 1996) and most patients with paraneoplastic syndromes are left with severe neurological disability. Most of the therapies tried have been forms of immunosuppression, particularly for those syndromes that are associated with autoantibodies. It is possible that the rapid onset of these syndromes does not allow sufficient time for accurate early diagnosis and for treatment to begin before irreversible neuronal damage has occurred. With earlier diagnosis, e.g. specific laboratory tests for antibodies, therapy may be more successful.

Specific treatment (when available) of the individual paraneoplastic syndromes is considered in the sections that follow (Table 90.4).

Specific syndromes

Brain and cranial nerves

Paraneoplastic cerebellar degeneration

The disorder may complicate any malignant tumour but is most common with lung cancer (especially small-cell), gynecological neoplasms and Hodgkin's disease (Cao et al., 1999; Mason et al., 1997; Peltola et al., 1998). Males and females are both affected and the age of incidence reflects the age distribution of the cancer. Neurological manifestations precede detection of the associated tumour in over one-half of patients, rarely by up to 4 years. Alternatively, PCD may develop after diagnosis of the neoplasm. In some instances, the tumour is not found until autopsy. Typically, the disorder begins as gait ataxia that over a few days to months progresses to severe truncal and appendicular ataxia with dysarthria and often nystagmus. The nystagmus is frequently downbeating. Vertigo with, or without, nausea and vomiting is common and many patients complain of diplopia. The cerebellar signs are bilateral but may be asymmetrical. A more rapid onset within a few hours or days or a slower progression sometimes occurs. The cerebellar deficit usually stabilizes but, by then, the patient is often incapacitated. Spontaneous improvement sometimes occurs, particularly when associated with Hodgkin's disease.

The signs and symptoms are frequently limited to cerebellar or cerebellar pathway dysfunction but, in as many as 50% of the patients, other neurological abnormalities, usually mild, may be found on careful examination (Hammack et al., 1990; Peterson et al., 1992), including sensorineural hearing loss, dysphagia, hyperreflexia with or without extensor plantar responses, extrapyramidal

Table 90.3. Treatment of paraneoplastic neurological syndromes[a]

Syndrome	Treatment
Paraneoplastic syndromes that usually respond to treatment	
LEMS	Tumour therapy, plasma exchange, IVIg, 3, 4 diaminopyridine
Myasthenia gravis	Tumour therapy, plasma exchange, IVIg, immunosuppressants
Dermatomyositis	Steroids, immunosuppressants, IVIg
OM (pediatrics)	Steroids, ACTH, tumour
Carcinoid myopathy	Tumour therapy, cyproheptadine
Neuropathy (osteosclerotic myeloma)	Tumour therapy, radiation
Paraneoplastic syndromes that may respond to treatment	
Vasculitis (nerve/muscle)	Steroids
OM (adults)	Steroids, tumour, protein A column, clonazepam, diazepam, baclofen
PCD (Hodgkin's disease)	Tumour therapy
Opsoclonus/ataxia (anti-Ri)	Steroids, cyclophosphamide
Guillain–Barré (Hodgkin's disease)	Tumour therapy, plasma exchange, IVIg
Stiff-man	Tumour therapy, steroids, diazepam, baclofen, IVIg
Neuromyotonia	Plasma exchange
Paraneoplastic syndromes that usually do not respond to treatment	
Paraneoplastic cerebellar degeneration (PCD)	
SCLC (irrespective of anti-Hu)	
Anti-Yo antibodies (cancer of ovary, breast)	
Paraneoplastic encephalomyelitis/sensory neuronopathy	
Limbic encephalopathy (steroids)	
Cerebellar degeneration	
Brainstem encephalopathy	
Myelopathy	
Sensory neuronopathy	
Autonomic dysfunction (central or peripheral)	
Cancer-associated retinopathy	
Paraneoplastic syndromes that may improve spontaneously	
Acute motor neuronopathy and lymphoma	
PCD associated with Hodgkin's disease	
Acute polyradiculopathy associated with Hodgkin's disease	
Limbic encephalopathy	
OM (pediatric and adult population)	

Notes:
Abbreviations: LEMS: Lambert–Eaton myasthenic syndrome; OM: opsoclonus/myoclonus; PCD: paraneoplastic cerebellar degeneration; SCLC: small-cell lung cancer
[a] Modified from Dalmau & Posner (1998).

signs, peripheral neuropathy, dementia, and other cognitive abnormalities. One study, however, using formal cognitive testing found that dementia was not typical when testing was controlled for impaired motor and speech production, suggesting that perceived clinical changes in intellectual function may be more apparent than real (Anderson et al., 1988). Despite this finding, positron emission tomography (PET), performed in a few patients, has revealed hypometabolism in all areas of the neuraxis including the cerebral cortex, cerebellum, and brainstem (Anderson et al., 1988).

The CSF may be normal, but early in the illness usually shows a mild pleocytosis. The protein concentration remains. Elevated protein IgG concentration is increased and oligoclonal bands are present. Cytological examination of the CSF and contrast-enhanced MRI of the neuraxis rules out leptomeningeal metastases. MR scans typically are normal early but later show signs of progressive cerebellar

Table 90.4. Paraneoplastic syndromes affecting brain and cranial nerves

Subacute cerebellar degeneration
Opsoclonus–myoclonus
Limbic encephalitis and other dementias
Brainstem encephalitis
Optic neuritis
Retinal degeneration

atrophy with prominent cerebellar folia and a dilated fourth ventricle.

The pathologic hallmark of PCD is loss, often total, of Purkinje cells (Verschuuren et al., 1996), affecting all parts of the cerebellum. Less striking changes in the cerebellar cortex may include thinning of the molecular layer with microglial proliferation and astrocytic gliosis, proliferation of Bergmann astrocytes and slight thinning of the granular layer with decreased numbers of granule cells. Basket cells and tangential fibres are usually intact. Changes in the cerebellar white matter reflect loss of Purkinje axons, resulting in loss of myelinated fibres and reactive gliosis in the cores of the cerebellar folia and in the white matter surrounding the dentate nucleus. The deep nuclei of the cerebellum and the brainstem nuclei with cerebellar connections are well preserved except in cases with an associated encephalomyelitis.

Some patients with PCD have more widespread pathological abnormalities, including degeneration of spinocerebellar tracts, dorsal columns and corticospinal tracts, patchy demyelination, neuronal degeneration, microglial proliferation and perivascular lymphocytic infiltration in the brainstem, spinal cord and, sometimes, in the dorsal root ganglia. Lymphocytic infiltration may be confined to the dentate nuclei and the surrounding cerebellar white matter. Mild degrees of lymphocytic meningeal infiltration are observed. By contrast, inflammatory cell infiltration in the cerebellar cortex is rare.

When typical, the clinical picture of PCD is almost pathognomonic. When atypical, the disorder must be distinguished from a cerebellar tumour (primary or metastatic) and from leptomeningeal metastases (by MRI and CSF examination, respectively), from late-onset, non-paraneoplastic cerebellar degenerative disorders (Ropper, 1993), cerebellar hemorrhage and infarction, abscess, prion diseases, cerebellar ataxia related to 5-fluorouracil or high-dose cytarabine, and metabolic disorders, especially alcoholic cerebellar degeneration. In alcoholic cerebellar degeneration, the ataxia predominantly involves the lower extremities; dysarthria and nystagmus are unusual.

There have been occasional reports of a partial or near-complete remission of PCD following treatment of the primary tumour. The presence of ocular flutter or opsoclonus indicates a better chance of improvement but this may be a different paraneoplastic syndrome (see below). Only rarely is immunosuppression beneficial (Batocchi et al., 1999) and most patients do not respond. It is possible that, if begun early in the illness, before Purkinje cells are irreversibly damaged, plasmapheresis and immunosuppressive drugs might have a beneficial effect. Symptomatic improvement in the ataxia occurs in a few patients with clonazepam in doses varying from 0.5 to 1.5 mg daily. Buspirone may also give modest relief (Trouillas et al., 1997).

Antibody positive (anti-Yo) paraneoplastic cerebellar degeneration

Several different antibodies reacting with Purkinje cells have been reported in the serum of patients with PCD. The most common is an antibody designated anti-Yo (Table 90.2) (Cao et al., 1999). This antibody is found in the serum of patients with gynecologic or breast cancer and, rarely, other cancers, including those in men (Greenlee et al., 1999; Krakauer et al., 1996). The antibody reacts with the cytoplasm of Purkinje cells and with the tumour causing the disorder (Greenlee et al., 1999). It can be identified both histochemically and on Western blot. The genes coding for the antigen have been cloned and sequenced. One of the proteins (CDR2) appears to down-regulate the function of the *C-myc* gene. This down-regulation may promote apoptosis in Purkinje cells (Okano et al., 1999). In patients with anti-Yo positive PCD, activated, cytotoxic T-lymphocytes that recognize the antigen are found in both blood and CSF (Albert et al., 1998, 2000). One study, however, failed to detect cytotoxic T-cell activity against Yo protein (Tanaka et al., 1998). One report indicates that anti-Yo positive Japanese patients are HLA-A24 positive (Tanaka & Tanaka, 1996). We have not found a consistent HLA genotype in patients in the US.

A second antibody found in patients with pure paraneoplastic cerebellar degeneration is the anti-Tr antibody, named after John Trotter, who reported the first such patient in 1976 (Trotter et al., 1976). This antibody associated with Hodgkin's disease reacts with the cytoplasm of Purkinje cells and produces a characteristic punctate pattern in the molecular layer of the cerebellum (Graus et al., 1998). The antigens cannot be identified on Western blot and the gene has not been cloned. Unlike anti-Yo paraneoplastic cerebellar degeneration, the cerebellar degeneration in this disorder is sometimes reversible.

The anti-Hu antibody (discussed in detail in the next section) may also be associated with PCD but usually is part of a more diffuse encephalomyelitis (Mason et al., 1997).

The anti-Ri antibody (discussed in the section on opsoclonus) is associated with paraneoplastic cerebellar degeneration, usually as part of the opsoclonus/myoclonus syndrome.

Other less well-characterized antibodies have been reported in individuals or a few patients with relatively pure cerebellar degeneration. These include antibodies against glutamate receptors (Smitt et al., 2000). We have been unable to identify glutamate receptor antibodies in our patients with paraneoplastic cerebellar degeneration (Degenhardt et al., 1998). Other antibodies often associated with different paraneoplastic syndromes are occasionally associated with PCD (Honnorat et al., 1999; Mason et al., 1997).

Opsoclonus–myoclonus (OM)

Opsoclonus, a disorder of eye movements consisting of almost continuous arrhythmic, multidirectional, involuntary, high-amplitude conjugate saccades that are often accompanied by synchronous blinking of the lids is a paraneoplastic syndrome complicating neuroblastoma in children and a variety of tumours in adults (Digre, 1986). The movements usually persist when the eyes are closed and during sleep. Opsoclonus is exacerbated by attempts at visual pursuit or voluntary refixation. Opsoclonus may be an isolated neurologic sign but is often accompanied by myoclonus of the trunk, limbs, head, diaphragm, larynx, pharynx and palate, and ataxia. When opsoclonus is a paraneoplastic syndrome of adults it may be accompanied by PCD. OM is also associated with viral infections, postinfectious encephalitis, trauma, intracranial tumours, hydrocephalus, thalamic hemorrhage and toxic encephalopathies from thallium or lithium, amitriptyline overdose and diabetic hyperosmolar coma. Opsoclonus occurs in about 2% of children with neuroblastomas. Neurological symptoms precede identification of the neuroblastoma at least 50% of the time and the tumour often is not obvious on examination; thus, recognition of the neurological syndrome is an important clue to the presence of a neuroblastoma. When a neuroblastoma is associated with OM, there is a higher than expected incidence of intrathoracic tumours and of tumours with a benign histology. The prognosis of the neuroblastoma is better if OM is associated than when there is no neurological complication, an observation not explained by earlier diagnosis when neurological symptoms are present. The neurological disorder responds to ACTH and to intravenous immunoglobulin (Borgna-Pignatti et al., 1996) but not prednisone (Hammer et al., 1995). One report describes a combination of dexamethasone and intravenous immunoglobulin as effective when either alone was not (Veneselli et al., 1998). However, most patients suffer residual neurological damage, usually cognitive (Hammer et al., 1995).

OM is less common in adults. Nevertheless, about 20% of adult patients reported with OM probably have an underlying cancer (Digre, 1986). The most common tumour is lung cancer, but other cancers also cause the syndrome (Berger & Mehari, 1999; Corcia et al., 1997; Ducrocq et al., 1999). The neurological symptoms usually precede diagnosis of the tumour and commonly progress over several weeks although more rapid or slower progression may be observed. Opsoclonus often is associated with truncal ataxia, dysarthria, myoclonus, vertigo and encephalopathy. The CSF may show a mild pleocytosis and a mildly elevated protein. The MRI is usually normal but brainstem abnormalities have been reported.

Neuropathological findings have been variable. In some patients there are no identifiable abnormalities. In others, the changes resembled those of PCD with a loss of Purkinje cells, inflammatory infiltrates in the brainstem (Scaravilli et al., 1999), Bergmann gliosis and loss of cells from the granular layer of the cerebellum. Those patients with pathological changes in the cerebellum may have suffered from PCD as well as opsoclonus. The absence of neuropathological changes in some patients with clearly established opsoclonus and myoclonus suggests that the site of the pathology has not yet been identified.

The prognosis for recovery or partial remission of the neurologic disorder is better for paraneoplastic OM than it is for PCD. Improvement may follow treatment of the underlying tumour, and spontaneous partial remissions occur. Remissions have been reported to follow treatment of the tumour or immunosuppressive treatment including immunoadsorptive therapy using a protein A column (Batchelor et al., 1998a,b).

Antibody positive (anti-Ri) OM

Connolly and colleagues (Connolly et al., 1997) found that children with OM, whether or not caused by cancer, had antibodies that bound to the cytoplasm of Purkinje cells and some axons in the white matter. Western blot analysis revealed several bands including one at 210 kD, the site of the high molecular weight subunit of neurofilament. Our own (unpublished) observations have not identified neurofilament antibodies in any children with paraneoplastic OM, but have found autoantibodies that react with

the nervous system in children with neuroblastoma. These antibodies are more frequent in those with OM than in those without the disorder but none are specific.

Several autoantibodies have also been described in the small number of adults with the syndrome. The best characterized is the anti-Ri antibody (Luque et al., 1991). Histochemically, the antibody reacts with the nuclei of central nervous system neurons, giving an appearance virtually identical to that of the anti-Hu antibody. However, it does not react with neurons of the dorsal root ganglia or other peripheral neurons (Graus et al., 1993). On Western blot, using extracts of cortical neurons, the antibody gives two bands, one at 55 and one at 80 kd. The gene that codes for the antigen recognized by anti-Ri sera has been cloned, sequenced and named *Nova* by Darnell and his colleagues (Buckanovich et al., 1993). *Nova* is a family of genes that are neuron-specific RNA binding proteins. Different members of the family are expressed in different areas of the nervous system. Nova-1, expressed primarily in the brainstem, reacts with an inhibitory glycine receptor. Knockout of Nova-1 in mice yields a fatal clinical syndrome reminiscent of OM. The hypothesis is that the anti-Ri serum binds to the Nova-1 protein, interfering with normal function or synthesis of an inhibitory glycine receptor thus leading to uninhibited activity of the eyes and other muscles. The crystal structure of Nova-1 and 2 has been determined (Lewis et al., 1999) and how the Nova protein specifically binds to RNA has also been determined (Lewis et al., 2000).

Other antibodies have also been reported to be present in some patients with paraneoplastic OM. These include the antiamphiphysin antibody (Saiz et al., 1999). The role of these other antibodies in production of the disease seems less clear than the anti-Ri antibody.

Limbic encephalitis

Limbic encephalitis may occur as an isolated finding or as a more extensive encephalomyelitis (Dalmau et al., 1992; Gultekin et al., 2000). The neurologic symptoms often precede diagnosis of the tumour by up to two years; sometimes the cancer is not detected until autopsy. Symptoms usually progress over several weeks but the course may be more insidious. Anxiety and depression are common early symptoms but the most striking feature is a severe impairment of recent memory (Gultekin et al., 2000). Other manifestations include agitation, confusion, hallucinations, partial or generalized seizures, and hypersomnia. Progressive dementia usually occurs but there occasionally may be a spontaneous remission. The CSF commonly shows a pleocytosis and an elevated protein concentration. MR scans are usually normal but medial temporal abnormalities have been reported (Dalmau et al., 1992; Fakhoury et al., 1999).

Pathological changes affect the grey matter of the hippocampus, cingulate gyrus, pyriform cortex, orbital surfaces of the frontal lobes, insula and the amygdaloid nuclei (Scaravilli et al., 1999). In some patients the caudate nucleus, putamen, globus pallidus, thalamus, hypothalamus and subthalamic nucleus are affected. The pathologic changes consist of: (i) extensive loss of neurons, (ii) reactive gliosis and microglial proliferation and, (iii) perivascular lymphocytic cuffing which may be less prominent in long-standing cases. In a few patients who have been reported with the clinical picture no pathological changes have been found.

No treatment has proved uniformly beneficial although occasional spontaneous remissions have been reported and some patients have improved after treatment of the underlying tumour (Brennan & Craddock, 1983; Nokura et al., 1997).

The anti-Hu antibody (also called ANNA-1 (Lennon, 1994)) can be found in patients with isolated limbic encephalitis but more commonly is associated with a more widespread encephalomyelitis. The full blown anti-Hu syndrome consists of a sensory neuronopathy resulting from inflammatory damage to the dorsal root ganglia, and a widespread encephalomyelitis causing limbic encephalitis, brainstem encephalitis (see below), PCD, myelopathy, an autonomic neuropathy and sometimes other findings (Davis et al., 1991). The antibody reacts with a protein that binds messenger RNA and probably stabilizes it. How that finding relates to the disease is unknown. Other antibodies found in patients with limbic encephalitis include the anti-Ta antibody (Voltz et al., 1999), anti-Ma (Dalmau et al., 1999) and anti-CV2 (Honnorat et al., 1999).

Brainstem encephalitis

Paraneoplastic brainstem encephalitis often is associated with clinical and pathological evidence of encephalomyelitis elsewhere within the central and peripheral nervous systems but may occur as the dominant or an isolated clinical finding (Batchelor et al., 1998a,b; Heckmann et al., 1999; Voltz et al., 1999a,b). It is commonly associated with small-cell lung cancer but an identical clinicopathological syndrome may be seen in the absence of malignancy.

The clinical features vary according to the brainstem structures involved in the pathological process. Common manifestations include vertigo, ataxia, nystagmus, vomiting, bulbar palsy, oculomotor disorders and corticospinal tract dysfunction. Less common clinical features include deafness, myoclonus of the branchial musculature, hypo-

ventilation, and movement disorders including chorea or Parkinson's syndrome.

Neurological symptoms may develop before or after discovery of the malignancy. The pathological changes are identical to those observed in other forms of paraneoplastic encephalomyelitis including lymphocytic perivascular cuffing, gliosis, microglial proliferation and loss of neurons. No form of treatment, including treatment of the underlying tumour, has altered the course.

Table 90.5. Paraneoplastic syndromes affecting spinal cord and dorsal root ganglia

Necrotizing myelopathy
Subacute motor neuronopathy
Motor neuron disease
Myelitis
Sensory neuronopathy

Visual loss

Paraneoplastic syndromes can affect retinal photoreceptors, either rods or cones (Jacobson & Thirkill, 1995) or both. It can cause a retinal vasculitis (Remulla et al., 1995) or optic neuropathy (Antoine et al., 1993; Blumenthal et al., 1998; Lieberman et al., 1999; Malik et al., 1992). Paraneoplastic retinal degeneration, also called cancer-associated retinopathy, usually occurs in association with small-cell cancer of the lung (Goldstein et al., 1999), melanoma (Boeck et al., 1997; Gittinger & Smith, 1999) and gynecological tumours. Typically, the visual symptoms include episodic visual obscurations, night blindness, light-induced glare, photosensitivity, and impaired colour vision. Visual symptoms usually precede the diagnosis of cancer. The symptoms progress to painless visual loss. They may begin unilaterally but usually become bilateral. Visual testing demonstrates peripheral and ring scotomas and loss of acuity. Funduscopic examination may reveal arteriolar narrowing and abnormal mottling of the retinal pigment epithelium. The electroretinogram is abnormal. CSF is typically normal, although elevated immunoglobulin levels have been reported. Inflammatory cells are sometimes seen in the vitreous by slit-lamp examination.

Pathologically, a loss of photoreceptors and ganglion cells with inflammatory infiltrates and macrophages is usually noted. The other parts of the optic pathway are preserved, although a loss of myelin and lymphocytic infiltration of the optic nerve may occur.

Serum autoantibodies that recognize several proteins have been described in visual paraneoplastic syndromes. These include antibodies that recognize the photoreceptor protein recoverin (Adamus et al., 1997), a retinal-specific protein that is a member of the *Tubby* gene family and enolase-α (Adamus et al., 1998a,b) as well as several others not entirely characterized. Antirecoverin antibodies have been reported to induce apoptosis of photoreceptor and bipolar cells in vivo (Adamus et al., 1998a,b).

Treatment of cancer-associated retinopathy is usually unsuccessful, although a recent report describes improvement in some patients with the use of intravenous immunoglobulin (Guy & Aptsiauri, 1999).

Spinal cord and dorsal root ganglia (Table 90.5)

Necrotizing myelopathy

This is an extremely rare remote effect of cancer (Handforth et al., 1983; Hughes et al., 1992). An identical syndrome may occur with a variety of other diseases and in previously healthy individuals (Katz & Ropper, 2000). Some authors suggest that an association with cancer may be coincidental. The initial symptoms may be asymmetric, but eventually signs become bilateral and symmetric. Back or radicular pain may precede other neurological signs. Cerebrospinal fluid abnormalities may include an elevated protein and a mild pleocytosis. Swelling of the spinal cord may be apparent on MRI. Typically, the neurological deficit progresses rapidly over days or a few weeks, ultimately leading to respiratory failure and death. There is no effective treatment.

Pathologically, there is widespread necrosis of the spinal cord, often most marked in the thoracic segments. The necrosis involves all components of the spinal cord with white matter usually more affected than grey matter.

Motor neuron disease (amyotrophic lateral sclerosis)

All of the subcomponents of amyotrophic lateral sclerosis, progressive muscular atrophy and primary lateral sclerosis may be paraneoplastic (Rosenfeld & Posner, 1991). Gordon and colleagues (Gordon et al., 1997), report the association of motor neuron disease and a variety of lymphoproliferative disorders, including Hodgkin's disease, multiple myeloma, chronic lymphocytic leukemia and other lymphomas. Paraneoplastic syndromes include: (i) amyotrophic lateral sclerosis with both upper and lower motor neuron dysfunction (Rowland, 1997), (ii) progressive muscular atrophy, a pure lower motor neuron syndrome that is sometimes reversible (Schold et al., 1979) and also

associated with lymphoproliferative disorders, and (iii) primary lateral sclerosis, a pure upper motor neuron syndrome associated with solid tumours as well as lymphoproliferative disorders (Forsyth et al., 1997; Rowland, 1997). The clinical and pathological characteristics differ little from non-paraneoplastic motor neuron disease save for the fact that the paraneoplastic disorders are often more rapid in onset and evolution, sometimes reverse spontaneously and, at autopsy, may be more inflammatory than a non-paraneoplastic disorder.

The occurrence of these paraneoplastic syndromes, primarily in patients with lymphoproliferative disorders, suggests the possibility that opportunistic infection may play a role in pathogenesis. The pure lower motor neuron disorder is similar to an anterior horn cell degeneration in a strain of mice infected with the murine leukemia virus (Andrews & Gardner, 1974), although recent evidence suggests that neuronal damage can occur without direct viral invasion (Stoica et al., 2000).

Myelitis

Paraneoplastic myelitis is usually a part of the encephalomyelitis syndrome with inflammatory lesions elsewhere in the brain and dorsal root ganglia as well as spinal cord. The clinical picture is characterized by patchy wasting and weakness of muscles, sometimes combined with fasciculations. The upper extremities are often more severely affected than the legs, reflecting predominant involvement of the cervical spinal cord. There may be striking weakness of neck and intercostal muscles, resulting in respiratory failure. Sensory symptoms, if present, usually are a manifestation of an associated sensory neuronopathy, but patients with severe changes in the posterior horns may present with a clinical picture resembling syringomyelia. Corticospinal tract signs may reflect lesions in the spinal cord or in the brainstem. Autonomic dysfunction results from involvement of autonomic neurons.

Sensory neuronopathy

In contrast to the common axonal or demyelinating sensory neuropathies, paraneoplastic sensory neuronopathy (PSN) where the dorsal root ganglion is the site of pathology is a rare syndrome. The clinical picture of pure sensory loss often does not allow clinical distinction from the more peripheral disorder. Sensory neuronopathy can occur in previously healthy individuals and those with a variety of underlying autoimmune conditions including Sjogren's syndrome. It can also be caused by heavy metal intoxication, including the chemotherapeutic agent cisplatin. At least two-thirds of patients with paraneoplastic sensory neuronopathy have small-cell lung cancer. Symptoms typically begin before the cancer is identified, with dysesthetic pain and numbness in the distal extremities or occasionally in the arm(s), face or trunk. The symptoms may be asymmetrical at onset but progress over days to several weeks to involve the limbs, trunk, and sometimes the face, causing a severe sensory ataxia. All sensory modalities are affected, distinguishing this disorder from cisplatin neuropathy, in which pin and temperature sensation are spared. Deep tendon reflexes are lost, but motor function is preserved. The CSF is typically inflammatory. Sensory nerve action potentials are low in amplitude or absent, whereas motor nerve action potentials are normal and electromyographic (EMG) evidence of denervation is absent.

Early pathological changes are limited mostly to the dorsal root ganglia, in which both a loss of neurons and the presence of lymphocytic inflammatory infiltrates are noted. As the disease progresses, the inflammatory process may advance to the dorsal root, posterior columns, and peripheral nerve. PSN can occur as a pure syndrome or as part of a more diffuse encephalomyelitis. About 50% of patients with PSN have pathological changes that may be clinically inapparent in other regions of the nervous system. In most patients, treating the underlying tumour or removal of the autoantibody by plasmapheresis or immunosuppressive therapy does not alter the course of the neurological disease (Uchuya et. al., 1996), although there are isolated reports of responses to immunotherapy (Oh et al., 1997). Occasional patients have a mild and indolent neuropathy (Graus et al., 1994).

Peripheral nerves (Table 90.6)

Sensory and sensorimotor neuropathy

Peripheral neuropathies (PN), particularly mild distal sensorimotor neuropathies, are quite common in patients with cancer. In one study of lung cancer the incidence was 16%. The incidence is even higher if one defines the disorder by electrical evidence in clinically asymptomatic patients. However, many patients may have suffered from the metabolic or nutritional ravages of late cancer and would not be considered by the definitions here to have true paraneoplastic syndromes.

Some patients not known to have cancer, and who are not evidently systemically ill, present to the neurologist with a PN which may be quite severe and disabling. It is estimated that in those patients whose initial evaluations do not reveal an obvious cause (e.g. vitamin deficiency,

Table 90.6. Paraneoplastic syndromes affecting peripheral nerves

Subacute or chronic sensorimotor peripheral neuropathy
Acute polyradiculoneuropathy (Guillain–Barré syndrome)
Mononeuritis multiplex and microvasculitis of peripheral nerve
Brachial neuritis
Autonomic neuropathy
Peripheral neuropathy associated with myeloma

amyloidosis, diabetes), about 10% will eventually prove to have cancer as the underlying reason for the peripheral neuropathy. Therefore, one should seriously consider a cancer diagnosis in such patients.

Subacute sensorimotor neuropathy is predominantly a distal symmetrical polyneuropathy, more marked in the lower extremities, with weakness, glove-and-stocking sensory impairment to all modalities, and a loss of tendon reflexes. Bulbar involvement is exceptional. A few patients with paraneoplastic sensorimotor neuropathy follow the remitting and relapsing course typical of chronic inflammatory demyelinating polyneuropathy. These patients may respond to corticosteroid therapy. The CSF is typically acellular, with normal or slightly elevated protein concentration. Nerve conduction studies are consistent with an axonal neuropathy, with low-amplitude or absent sensory nerve action potentials and normal or decreased motor nerve conduction velocities. A few patients have marked slowing of motor conduction velocities consistent with a demyelinating process. Pathologically, there is usually axonal degeneration; in a few patients demyelination is prominent. Spinal cord demyelination and lymphocytic infiltrates of peripheral nerves have also been reported.

A particular sensorimotor neuropathy has been associated with breast cancer. Peterson and colleagues have described 9 patients with a slowly progressive sensorimotor, predominantly sensory, neuropathy, some of whom had additional features suggesting a myopathy (e.g. proximal weakness) or CNS dysfunction (e.g. hyperreflexia and extensor plantar responses) (Peterson et al., 1994). The disorder progressed very slowly over many years, was not disabling, and was frequently heralded by itching or muscle cramps. In one patient, itching, initially over the left breast and later diffusely, preceded identification of the cancer by 18 months. Most patients remained fully functional as neither the neuropathy nor the breast cancer was disabling (Peterson et al., 1994).

A relatively pure paraneoplastic sensory neuropathy (not neuronopathy) occurs with a variety of malignancies but cannot be distinguished from other causes of sensory neuropathy. In one series, when no cause of the sensory neuropathy was identified, cancer was subsequently identified as the cause in approximately one-third of patients. Mean time to cancer diagnosis was more than 2 years (Camerlingo et al., 1998).

Peripheral neuropathy due to microvasculitis is rare as a paraneoplastic syndrome. The disorder has been reported as part of the anti-Hu syndrome (Blumenthal et al., 1998). It also appears without obvious antibody involvement in patients with a variety of cancers (Oh et al., 1991). Vasculitic neuropathy can either present as a diffuse polyneuropathy or as a mononeuritis multiplex. The disorder can involve both peripheral and cranial nerves. The importance of making a diagnosis, which may require nerve biopsy, is that the condition may respond to corticosteroid treatment. PN may be associated with multiple myeloma and Waldenstrom's macroglobulinemia (Simmons, 1999). With the rare osteosclerotic form of myeloma, PN is present in about 50% of patients. Successful treatment of the myeloma often leads to amelioration of the neurological symptomatology. Amyloidosis associated with myeloma can also cause a PN that responds poorly to treatment.

Acute polyradiculoneuropathy is an uncommon remote effect with a striking association with Hodgkin's disease (Lisak et al., 1977). The clinical and pathological features and elevated CSF protein are typical of the Guillain–Barré syndrome (GBS). Symptoms may begin when the tumour is in remission, during active disease, or the PN may presage a relapse of Hodgkin's disease. The course of the neuropathy is independent of the Hodgkin's disease and may, like idiopathic GBS, respond to plasmapheresis or IVIg. This patient improved with steroids.

Brachial neuritis

Acute brachial neuritis (clinically undistinguishable from the idiopathic variety) occurs with increased frequency in patients with Hodgkin's disease (Lachance et al., 1991). Brachial neuritis should be differentiated from other causes of a brachial plexopathy in cancer, namely tumour infiltration, radiation fibrosis and radiation-induced tumours.

Autonomic neuropathy

This rare paraneoplastic syndrome usually is associated with lung tumours (Ahmed & Carpenter, 1975), especially small-cell cancers, but may occur with other neoplasms. It may precede or follow diagnosis of a malignancy. Typically,

Table 90.7. Paraneoplastic syndromes affecting neuromuscular junction and muscle

Lambert–Eaton myasthenic syndrome (Chapter 69)
Myasthenia gravis (Chapter 69)
Dermatomyositis, polymyositis, acute necrotizing myopathy (Chapter 70)
Neuromyotonic and stiff-person syndrome (Chapter 48)

there is subacute onset of intestinal hypomotility, postural hypotension, neurogenic bladder dysfunction, pupillary abnormalities, impotence and anhidrosis in varying combinations. Some cases are associated with PSN. The CSF shows an elevated protein without pleocytosis. The initial course is rapidly progressive but later may stabilize, although the patient often is severely disabled by the time this stage is reached. The autonomic neuropathy may improve following treatment of the underlying tumour. Nicotinic acetylcholine receptor antibodies may be found. Autonomic neuropathy also occurs as part of the anti-Hu syndrome.

Neuromuscular junction and muscle (Table 90.7)

Paraneoplastic disorders of the neuromuscular junction include the Lambert–Eaton myasthenic syndrome and myasthenia gravis. These disorders have a common pathogenetic mechanism, i.e. they are caused by antibodies against ion channels, and, whether paraneoplastic or not, they respond to immunological treatment. Another ion channel disorder included in this section is neuromyotonia, which is not confined to the neuromuscular junction. Finally, because of its similarity to neuromyotonia, the stiff-person syndrome is also included in this section. The stiff-person syndrome is discussed in detail in Chapter 48. Recent reviews of these disorders have appeared (Brown & Marsden, 1999; Newsom-Davis, 1998a; Vincent, 1999).

Lambert–Eaton myasthenic syndrome (LEMS)

LEMS results from a reduced release of acetylcholine at presynaptic nerve terminals. The same P/Q-type voltage-gated calcium channels are found in small-cell lung cancers. Interestingly, the richest source of P/Q-type voltage-gated calcium channels is the cerebellum, perhaps explaining the occasional relationship of paraneoplastic cerebellar degeneration and LEMS (Voltz et al., 1999a,b).

LEMS is a classic autoimmune disease (see Chapter 69) in that the binding of circulating IgG antibodies to the voltage-gated calcium channels reproduces the electrophysiologic abnormalities in experimental animals; removal of IgG antibodies from humans with the disorder improves neurological function (Vincent, 1999). LEMS is paraneoplastic in about 60% of patients. It is almost always associated with small-cell lung cancer. Antibodies that react with P/Q-type voltage-gated calcium channels are found in patients with or without paraneoplastic syndromes (Vincent, 1999). LEMS can be treated either by immunosuppression or by treatment of the underlying cancer when present (Newsom-Davis, 1998b). Patients with small-cell lung cancer associated with LEMS have a better prognosis than patients with small-cell lung cancer who do not develop a paraneoplastic disorder (Maddison et al., 1999).

Myasthenia gravis

Myasthenia gravis (MG) occurs in 30% of patients with thymomas, and approximately 10% of patients with MG are found to have a thymoma. Myasthenia is discussed in Chapter 69.

Polymyositis and dermatomyositis

These common inflammatory, probably autoimmune, muscle diseases are discussed in detail in Chapter 70 (Callen, 2000). Only a minority of patients suffering from these disorders have an underlying malignancy as their cause (Naschitz et al., 1999), particularly older patients. Dermatomyositis with typical cutaneous changes is more likely than polymyositis to be paraneoplastic. Females and males are affected in approximately equal numbers. Symptoms of the muscle weakness generally precede identification of the cancer. The tumour may be at any site, but breast, lung, ovarian, and gastric malignancies are the most common. Hodgkin's disease and prostate and colon cancer are also reported offenders.

The clinical and laboratory findings in dermatomyositis/polymyositis associated with malignancy resemble those in the idiopathic disease, although cancer patients often have more striking abnormalities on muscle biopsy. Patients characteristically present with proximal muscle weakness, elevated levels of serum creatine kinase (CK), and EMG evidence suggesting a myopathic process rather than nerve disease. A muscle biopsy specimen showing inflammatory myopathy confirms the diagnosis. Although laboratory findings do not distinguish paraneoplastic from non-paraneoplastic varieties, the presence of autoanti-

bodies, particularly common in the disorder associated with lung disease, is less common in patients with the paraneoplastic disorder. No laboratory test is absolutely diagnostic. Normal CK levels are occasionally found even in patients with profound muscle weakness, with or without malignancy; abnormal CK levels indicate a poor prognosis for the muscle disease. Weakness of respiratory and pharyngeal muscles may contribute to death. The prognosis is worse for the paraneoplastic disorder than for the non-paraneoplastic disorder.

Corticosteroids, cyclosporine and other immunosuppressants have been used successfully. Other reports suggest that high-dose intravenous immunoglobulin is useful in patients unresponsive to other forms of immunosuppression (Dalakas, 1999).

Neuromyotonia and stiff-person syndrome

Muscle cramps are a common complication of cancer, sometimes related to electrolyte imbalance or induced by chemotherapy. A much rarer but clinically significant paraneoplastic disorder is acquired neuromyotonia (Vincent, 1999). The disorder is characterized by muscle stiffness, cramps and obviously rippling and twitching muscles, sometimes leading to sustained abnormal postures. Relaxation after voluntary contraction is delayed. Symptoms persist during sleep, but are abolished by curare. Sudden prolonged bursts of high frequency involuntary repetitive muscle action potentials are seen on electromyography.

The muscle spasms and rigidity are sometimes precipitated by activity, forcing patients to become sedentary. The disorder arises from peripheral nerves and is sometimes a part of the encephalomyelitis syndrome. The disorder is usually non-paraneoplastic, but may be associated with cancer including thymomas and small-cell lung cancer. Antibodies against voltage-gated potassium channels are often positive. Plasma exchange improves the patient's condition. Some patients respond to anticonvulsants. Injection of IgG from affected patients into experimental animals can reproduce the syndrome.

The stiff-person syndrome may superficially resemble neuromyotonia, but has a central origin. It is clinically characterized by stiffness and rigidity with episodic spasms of axial muscles (see Chapter 48). A variant of the syndrome affects the limbs. Painful reflex spasms can occur in response to tactile stimuli or startle. Normal appearing muscle action potentials are found on electromyography, but the activity is continuous and excessive and increased by voluntary activity. The disorder is usually not associated with cancer, but in some patients the underlying syndrome is paraneoplastic. In those cases, the disorder is not associated with the typical antibodies against glutamic acid decarboxylase found in patients with the non-paraneoplastic syndrome. Instead, amphiphysin or antibodies that react with cerebellum may be found (Antoine et al., 1999; Saiz et al., 1999). Both the paraneoplastic and the non-paraneoplastic disorder may respond to immunosuppression. Some patients respond to drugs that enhance GABA neurotransmission, such as diazepam, gabapentin and baclofen. In the non-paraneoplastic disorder, antibodies against glutamic acid dehydrogenase, the rate-limiting enzyme for the synthesis of gamma aminobutyric acid, suggest that the disease is the result of interference with GABA metabolism.

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Harmful effects of radiation on the nervous system

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Radiotherapy (RT) is the mainstay of treatment of primary brain tumours which are not resectable and is the only treatment modality which has been demonstrated to prolong survival in patients with malignant gliomas. It is a potentially toxic treatment and therefore adequate controls must be in place to monitor the dose administered. This chapter describes the basic physical principles underlying the cellular and molecular mechanisms of RT-induced cell death and then discusses the harmful effects of radiation on the nervous system.

Physical principles of radiation

Radiotherapy is the use of electromagnetic radiation usually in the form of photons to produce cell damage and thereby destroy tumours. Electromagnetic radiation acts principally by ionizing molecules in irradiated tissues. Radiation energy is either absorbed directly into the DNA or indirectly via the generation of free radicals in the aqueous cytosol which produce further molecular damage. The end result of irradiation is DNA damage in the form of inter- and intrastrand cross-links, strand breaks and damage to nucleotide bases. The cellular repair capacity may not be sufficient to repair all DNA lesions, particularly double strand breaks and these may ultimately lead to cell death. The majority of human cells that sustain DNA damage die a mitotic rather than an apoptotic cell death.

The principal biological effect of radiation at tissue level is to inhibit cell proliferation thereby affecting dividing tumour cells rather than non-proliferating normal tissue cells. This results in tumour control, which equates with cure in some tumours, but only minimal damage of normal brain at conventional doses. The balance between tumour control and normal tissue damage is described as the therapeutic ratio. Maximum therapeutic ratio is achieved through exploiting biological differences between tumours and normal tissue (largely by fractionation) and by physically focusing high radiation doses to tumour while sparing surrounding normal brain.

In conventional external beam radiotherapy, radiation is usually given in the form of high energy X-rays (photons) generated by a linear accelerator or as gamma rays (also photons) from an external cobalt source. Radiation can also be delivered by insertion of small radioactive sources directly into a tumour and this is described as brachytherapy or interstitial radiotherapy. Electrons, generated by linear accelerators, are particularly useful for the treatment of superficial lesions and are rarely used for the treatment of CNS tumours. Cyclotron generated protons have been employed in the treatment of some deep-seated tumours but this technique is only available in a handful of centres worldwide.

Radiation sensitivity of tumours and tissues is defined by the ability of constituent cells to survive a given dose of radiation. This is measured in vitro with a clonogenic cell survival assay. The proportion of tumour cells surviving a dose of 2Gy is described as SF2 (surviving fractions of cells after radiation dose of 2Gy). Gliomas have relatively high SF2 while embryonal tumours, germ cell tumours and lymphomas have low SF2. While it is possible to increase tumour cell kill with higher doses per fraction, increased damage to tumour is usually associated with increased damage to normal tissue. The biological differences between radiation sensitivity of tumour cells and normal tissue are seen at lower doses and can be exploited by fractionation giving a number of repeated small doses over a period of time. The result is damage to tumour cells and recoverable damage to normal tissue therefore sparing the normal brain.

Conventional fractionation schedules for the treatment of intracranial tumours deliver radiation on a daily basis 5 days per week in 1.8–2Gy fractions over 6 weeks. Alternative

fractionation schedules which increase treatment intensity include accelerated and hyperfractionated schedules. Conversely, hypofractionated schedules (larger doses per fraction to lower total doses over a shorter time) generally deliver less intensive treatment usually for the purpose of palliation.

Within the central nervous system, the most sensitive normal tissues are oligodendroglia and vascular endothelial cells. The time to expression of damage is determined by the lifespan of the mature cells and ranges from months to years after irradiation. The severity of damage is related to the proportion of surviving cells and the consequent tissue viability and function. Small doses per fraction, adequate time interval between fractions allowing for cellular repair and total doses below tolerance of critical tissues minimize the damage to normal brain.

Pathological effects of radiation

There are three hypotheses to explain the mechanism of RT-induced damage to the CNS, which are not mutually exclusive. RT is most likely to be directly toxic to nervous system tissue, particularly the white matter and myelin-producing cells (oligodendrocytes and Schwann cells). It also damages vascular endothelium and leads to islands of endothelial proliferation, luminal occlusion and subsequent tissue ischemia and necrosis. Damage may also occur via a hypersensitivity reaction to intracellular contents released as a consequence of glial toxicity. This immune response in turn causes tissue necrosis and vascular damage. Experimental data in vivo suggests that both oligodendroglia and endothelial cells are targets of damage and the differential effect may be dose-dependent. Cellular damage with cytokine release may be responsible for further damage.

The tissue consequences of radiation injury range from histologically recognized and expressed necrosis to less well-defined encephalomalacia as well as minor functional deficit without obvious structural defect following lower radiation doses.

High doses of radiation beyond tolerance lead to necrosis largely confined to the white matter with damage to oligodendrocytes and endothelial cells. In the acute phase, radiation damage is expressed as hemorrhagic coagulation necrosis. Delayed radiation necrosis is characterized by fibrin exudation which may lead to either calcification or classical fibrinoid necrosis.

Necrotic lesions may commence as multiple foci, which later coalesce. The lesions are either resorbed by macrophages and evolve into cysts or remain as discreet white matter necrotic foci. Necrosis is commonly found within malignant gliomas and this is likely to represent the desired effect of radiation contributed to by inadequate blood supply to the tumour. It should not be considered a damaging consequence of radiation as seen in normal tissue.

Very high doses of radiation delivered by interstitial radiotherapy or radiosurgery (often in association with conventional high dose external beam radiotherapy) frequently cause localized necrosis as the doses used go well beyond the known radiation tolerance of the CNS.

The pathological features associated with late radiation effects, characterized by cognitive impairment and occasionally leading to dementia, are less well defined. White matter lesions predominate and include demyelination, white matter spongiosis and occasional small foci of necrosis. Children may develop mineralizing microangiopathy following low dose irradiation combined with chemotherapy. Radiation-induced vasculopathy may also be a contributing factor to late radiation effects.

Changes seen in the spinal cord following irradiation have been well described in experimental animals and mirror those seen in the brain. Excessive doses of radiation cause depletion of oligodendrocytes and damage to vascular endothelium leading to radiation necrosis. Radiation myelopathy expressed as progressive paraparesis is usually characterized by white matter atrophy and demyelination.

As can be seen, no part of the nervous system is immune from RT-induced damage. The nature, timing and severity of this damage is dependent on radiation-related factors including dose fractionation, total dose and target volume as well as host factors such as age, pre-existing systemic disease, particularly vasculopathy, and the use of concurrent chemotherapy.

Diagnosis of radiation damage to the nervous system

The development of neurological symptoms and signs in a patient should only be ascribed to the damaging effects of RT if the following conditions are met.

(i) The anatomy of the clinical signs corresponds to the radiation portals.
(ii) The dosage and fractionation are sufficient to damage that particular area of the nervous system.
(iii) The time elapsed between RT and the development of the neurological syndrome is compatible with the known effects of RT on the nervous system.
(iv) Tumour recurrence has been excluded, particularly in the brain where the clinical and radiological features of RT necrosis can be indistinguishable.

(v) Other differential diagnoses, e.g. intramedullary metastasis, paraneoplastic myelitis have been excluded.

Time course of RT-induced damage to the CNS

RT-induced damage to the brain and spinal cord is categorized according to the time at which the clinical syndrome is manifest into: (i) acute toxicity which occurs during RT; (ii) early-delayed toxicity which occurs within weeks of the completion of RT; (iii) late toxicity which occurs months to years following treatment.

As a general rule, acute and early-delayed toxicity are reversible and improve spontaneously or following the administration of corticosteroids, while late toxicity is largely irreversible. RT to the spinal cord is rarely associated with acute toxicity (Millburn et al., 1968; Tefft et al., 1969).

Specific syndromes

Acute brain toxicity

Acute toxicity is due to increasing brain edema caused by probable disruption of the blood–brain barrier and is rare with current dose fractionation protocols (1.8 to 2.0 Gy/day). It occurs most commonly in the presence of preexisting mass effect from a tumour that has not been debulked. The clinical manifestations are worsening focal deficit, fever and pressure symptoms of headache, drowsiness and vomiting. The syndrome responds to corticosteroids and, in rare instances where there is life-threatening raised intracranial pressure, mannitol may be helpful. It occurs more frequently following higher dose fractions. Acute toxicity has been reported in 50% of patients with brain metastases receiving 15 Gy in 2 fractions over 3 days (Young et al., 1974) and a large proportion of patients receiving a single fraction of 10 Gy (Hindo et al., 1970). Acute encephalopathy, responding to corticosteroids, has also been reported in children given low-dose cranial RT with concomitant intrathecal methotrexate as part of prophylaxis of meningeal leukemia (ALL) (Oliff et al., 1978).

Early-delayed brain toxicity

This usually occurs within 3 weeks to 3 months after the completion of RT and is postulated to be due to acute demyelination resulting from damage to oligodendrocytes. This may be due to either direct RT toxicity on myelin turnover or to the release of toxic radicals due to tumour cell lysis. In one patient who died 12 weeks after irradiation and 1 week after the onset of bulbar symptoms, postmortem examination of the brainstem revealed punched out areas of demyelination and perivenular inflammation that resembled the changes observed in acute multiple sclerosis (Lampert & Davis, 1964).

The most frequent manifestations are excessive fatigue and anorexia with occasional transient worsening or reappearance of a pre-existing deficit. In the immediate post-RT period it has been described as the somnolence syndrome (Faithfull & Brada, 1998). The symptoms peak 2 weeks and 6–8 weeks after RT and cause great concern because they may simulate tumour progression. The clinical deterioration occurs over several days to weeks and gradually resolves. In addition, transient tumour swelling following RT may exacerbate particularly focal symptoms. An awareness of this syndrome is important to avoid making therapeutic decisions regarding adjuvant chemotherapy within the first 2–3 months of RT (Hoffman et al., 1979). Imaging shows increased contrast enhancement and more pronounced surrounding edema, which resolve spontaneously, unlike the situation with tumour progression. The failure of the patient or scan to improve within 2 to 3 months of RT therefore does not necessarily imply treatment failure.

The somnolence syndrome was originally described following low dose (18–24 Gy) prophylactic whole brain irradiation (PCI) in childhood acute lymphoblastic leukemia (ALL) (Freeman et al., 1973; Littman et al., 1984). The incidence is 40–60% (Berg et al., 1983). The clinical features consist of headache, nausea, vomiting, anorexia and occasionally fever and papilledema. Investigations reveal diffuse slowing of brain activity on EEG, increased protein concentration and pleocytosis in CSF and white matter lesions characteristic of demyelination on MRI scanning. It usually resolves within 3 to 6 weeks and may be helped by a course of corticosteroids.

On rare occasions, patients develop a syndrome of bradykinesia, tremor and progressive cognitive decline within a few months of RT. This Parkinsonian state is characteristically dopa-resistant (Vigliani et al., 1999).

Imaging reveals cerebral atrophy, ventriculomegaly and white matter attenuation, which on postmortem examination is due to myelin loss and reactive astrocytosis (Asai et al., 1989). The development of a focal brainstem encephalopathy, characterized by ataxia, dysarthria, diplopia, has also been reported 8–11 weeks after high dose RT to extracranial structures. Most patients recover within 6 to 8 weeks, although it can be fatal.

Late brain toxicity

Late effects occur months to years after cranial RT and range from asymptomatic white matter signal change on MRI scanning to dementia, cerebrovascular disease, the development of second malignancies and radiation necrosis.

Radiation dementia

In a study of bone marrow transplant patients, subtle changes in brain volume were detectable one week after total body irradiation with a relatively small dose of 14.4Gy (Jager et al., 1996). This is an asymptomatic process but radiation encephalopathy, manifested by gradual intellectual decline and personality change, may progress to a full-blown dementia. In many patients treated with lower doses, memory loss is mild and non-progressive. Patients who progress to dementia may have initially mild impairment of recent memory, starting months to years after treatment. This is followed by gradual disorientation, progressive gait ataxia and urinary incontinence. The physical signs are variable but the patient is usually dysarthric, apraxic and has brisk reflexes with extensor plantar responses. CT/MRI scanning reveals generalized atrophy with ventricular enlargement and confluent subcortical white matter changes.

Cranial irradiation in children is associated with late cognitive impairment and the incidence and severity are related to age at the time of irradiation, RT volume and dose. Very young children are at greater risk (less than 4 years) as the CNS is still in an anatomically and functionally immature state.

A necrotizing leukoencephalopathy is seen in up to 15% of children receiving combined RT and methotrexate for ALL (Fig. 91.1) and in adults with primary CNS lymphoma treated with combined regimens where there is a short interval between chemotherapy and RT. Very delayed encephalopathy occurring decades after treatment has also been described (Duffey et al., 1996).

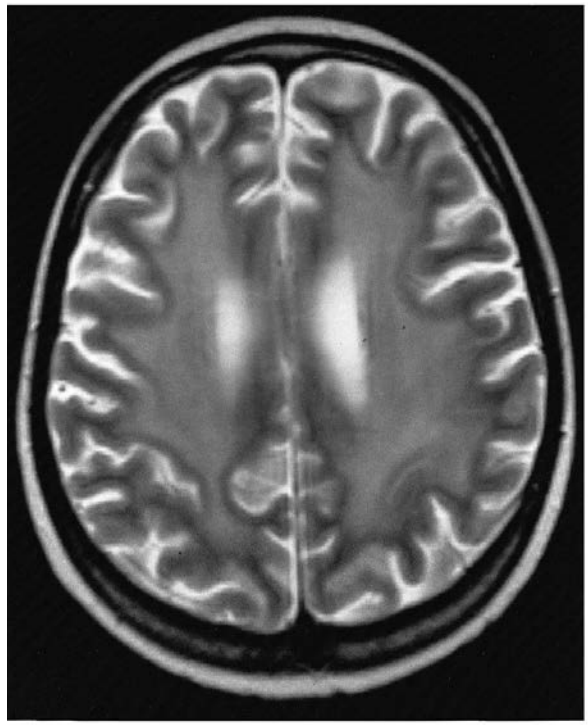

Fig. 91.1. Axial T2W MRI brain showing radiation leukoencephalopathy and generalized cortical atrophy. 19-year-old girl with Philadelphia positive ALL post bone marrow transplant (matched unrelated donor) who had received whole brain RT as part of the conditioning protocol and subsequently methotrexate. She presented with a 3-month history of personality change, withdrawal, perserveration, incontinence and abulia, and the MRI scan showed confluent high signal change throughout subcortical white matter. She died 2 weeks later.

Radiation necrosis

Delayed radiation necrosis is a recognized complication of treatment for primary brain tumours as well as extracranial tumours, particularly nasopharyngeal carcinoma where high dose radiation may lead to temporal lobe necrosis (Lee et al., 1998). It presents insidiously with headache, confusion, focal deficits and seizures several months to years following treatment. It is an uncommon complication of conventional localized external beam radiotherapy, occurring in 3–5% of patients receiving 50 Gy and 5–15% of patients receiving 60 Gy at ≤2 Gy per fraction. Small increments above 60 Gy are associated with an increased likelihood of necrosis. Clinical studies of the incidence of necrosis at different dosages have established the basis for standard RT for intracranial tumours. Benign or low-grade tumours receive ≤ 55 Gy in 30 fractions which carries virtually no risk of radionecrosis while malignant gliomas receive 55–60 Gy in 30 fractions, which is associated with a 3% risk of necrosis.

Radiation necrosis is currently seen more commonly in patients with malignant brain tumours treated with high dose focal treatments such as stereotactic radiosurgery and interstitial RT. High localized doses are given either as a radiation boost with the aim of improving local tumour control or at the time of recurrence. While high precision localized treatment techniques are postulated to avoid

damage to healthy tissue, there is almost invariably some normal brain within the high dose region. Radiation necrosis is also recognized following single fraction radiosurgery for AVMs (Brada & Kitchen, 2000) and for benign tumours and the frequency is volume and dose dependent.

In brain tumour patients, the appearances of radiation necrosis on CT/MRI scanning may be indistinguishable from recurrent tumour demonstrating an irregularly enhancing mass lesion with surrounding edema. Although FDG-PET scanning (DiChiro et al., 1988) and Magnetic Resonance Spectroscopy (Chong et al., 1999; Chan et al., 1999); may help to distinguish necrosis from tumour recurrence, the only sure way of making a diagnosis is by surgical biopsy. Treatment is by excision of necrotic material which shows hyalinization and fibrinoid necrosis together with demyelination and axonal loss. Steroids are only of temporary benefit. Hyperbaric oxygen therapy (Chuba et al., 1997) and anticoagulation (Glantz et al., 1994) are currently under investigation as a potential therapy.

Mineralizing microangiopathy

This usually occurs in children following PCI for ALL and is diagnosed by the presence of basal ganglia calcification and presents with headache, seizures, behavioural changes and ataxia. Histopathologically the small vessels are occluded by calcium deposits with the surrounding brain being mineralized and necrotic (Price & Birdwell, 1978).

Vascular disease

Radiation may affect vessels of any size. Small vessel occlusion is a component of radiation necrosis. Larger vessels may be occluded by an arteriosclerotic type occlusion. Vessel wall damage may lead to aneurysms. The pathology of large vessel stenosis and occlusion includes accelerated atherosclerosis, thought to be mediated by endothelial damage and necrotizing vasculitis of the vasa vasorum leading to ischemic lesions within the vessel wall (Zidar et al., 1997). Clinically, patients are usually younger than those with spontaneous atherosclerosis, do not have coexisting vascular disease in other circulations, and may have multiple lesions within the intracranial and extracranial vessels. The angiographic features of a RT-induced large vessel stenosis are variable. There may be a smooth, tapering occlusion, accelerated atherosclerosis with extensive plaque formation or a focal severe stenosis (Fig. 91.2). In cases of slowly progressive vascular occlusive disease, there is time for the development of a collateral circulation in a stenosed artery, giving rise to moyamoya disease. This has been reported particularly in children who had radiotherapy for optic nerve or hypothalamic gliomas (Beyer et al., 1986). In adults, the clinical picture is usually a thrombotic occlusion causing a stroke, which may be heralded by TIAs. This occurs after neck irradiation for lymphoma or head and neck tumours, particularly in the presence of hyperlipidemia, hypertension and pre-existing vascular disease. Increased incidence of CVA has also been reported in patients with pituitary adenoma (Rosen & Bengtsson, 1990). Although the etiology is multifactorial, radiation is likely to be one of the causative factors (Brada et al., 1999). Treatment is empirical and consists of the same medical and surgical options as in spontaneous atherosclerotic cerebrovascular disease. The role of antiplatelet agents and anticoagulants is uncertain both in treatment and prophylaxis.

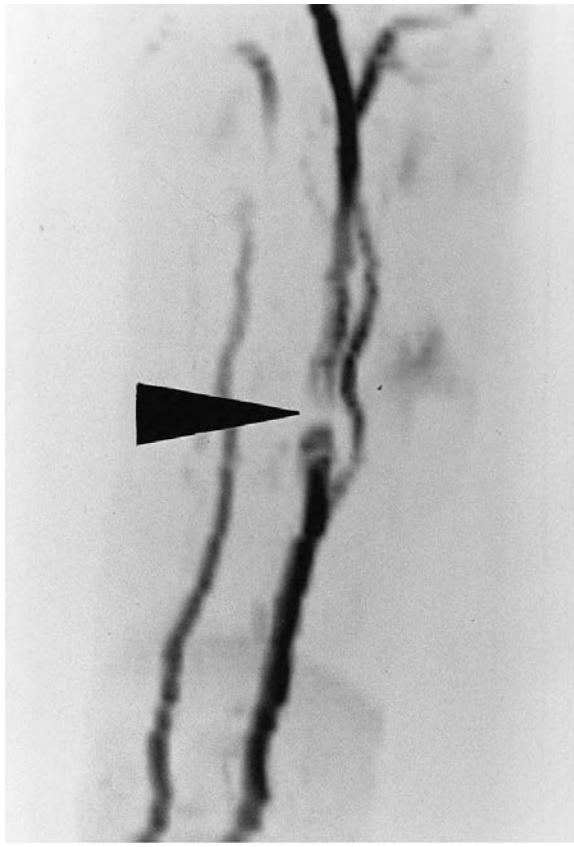

Fig. 91.2. MR angiogram of extracranial carotids showing focal severe stenosis of the left internal carotid artery. 59-year-old woman with left amaurosis fugax and loud left carotid bruit. She had received radiotherapy to her neck 25 years previously for metastatic tongue cancer. She also had a left brachial neuropathy.

Radiation-induced malignancies of the central and peripheral nervous systems

Radiation is recognized to be associated with increased risk of second malignancy and this has been described following systemic as well as cranial irradiation. Radiation for non-neoplastic conditions and benign tumours should therefore be used with considerable caution. The commonest RT-induced tumours include meningiomas, gliomas, cranial osteosarcomas, soft tissue sarcomas, schwannomas and peripheral nerve sheath tumours (PNSTs). They have been described following RT for tinea capitis (Ron et al., 1988), PCI for ALL (Neglia et al., 1991) and RT for pituitary adenoma (Brada et al., 1992).

Second tumours tend to lie within the radiation field, usually within lower dose regions and develop from a few years to many decades after irradiation. The reported median time to the development of gliomas is 7 years. Sarcomas develop with a longer lag time and meningiomas may be seen 30 or 40 years later. The histology is identical to spontaneous tumours although meningiomas are more likely to contain atypical features and have a worse prognosis. The treatment is the same as spontaneously occurring tumours and depends on a good histological examination. RT-induced meningiomas should be completely excised where possible, and adjuvant radiotherapy given only if it can be safely administered taking into consideration previous radiotherapy.

Cranial neuropathies

The cranial nerves are considered more resistant to RT than brain parenchyma and are rarely damaged by conventional irradiation. Transient anosmia and dysgeusia are well recognized and usually recover. The commonest cranial neuropathy, albeit rare, is optic neuropathy seen in patients treated for pituitary adenomas, craniopharyngiomas and nasopharyngeal tumours. It is characterized by painless monocular or bilateral visual loss, associated with an altitudinal field defect. The optic disc is usually normal, but may be swollen with telangectasiae and peripapillary and macular hemorrhages, cotton-wool spots and attenuation of the retinal arterioles. The condition is usually irreversible although steroids should be tried. Following pituitary irradiation to 45 Gy at $\leq$1.8 Gy per fraction the incidence is 1–2% (Brada et al., 1993). The likelihood of visual loss is increased by concomitant diabetes, previous tumour compression or chemotherapy and is particularly high following single fraction radiosurgery (Leber et al., 1998). Stereotactic radiosurgery may cause abrupt visual loss with swelling and enhancement of the optic nerves on MRI scanning (Girkin et al., 1997).

There is no specific treatment for radiation optic neuropathy, although it is important to exclude other causes such as arteritic ischemic optic neuropathy which may present in a similar way and respond to corticosteroids.

Other cranial nerves are less frequently affected. Facial and trigeminal neuropathy occur in patients with acoustic neuromas treated with single fraction stereotactic radiosurgery. (Miller et al., 1999; Flickinger et al., 1996). Permanent sixth nerve palsies have been noted after re-irradiation for nasopharyngeal carcinoma and lower cranial nerves may be damaged by high dose RT for head and neck tumours.

RT-induced spinal cord damage

Spinal cord damage following therapeutic radiation which includes the spinal cord follows the same pattern as radiation-induced brain damage with acute, early delayed and late syndromes. The most devastating is late radiation myelopathy, which is an uncommon complication of RT usually seen after treatment of paraspinal tumours. Unlike radiation encephalopathy it is not usually complicated by the presence of a spinal cord tumour. Patients with epidural spinal cord compression who deteriorate during RT either have progressive disease or suffer vascular occlusion from persistent or progressive tumour. However there have been reports of a fatal acute myelopathy following accidental local radiation overdose associated with a normal MRI scan in the acute phase despite neurological deficits (Alfonso et al., 1997).

Early-delayed myelopathy

As with early-delayed brain toxicity, a transient benign myelopathy occurs three to five months after radiotherapy to the spinal cord. The common clinical situations in which this occurs are mantle radiotherapy for Hodgkin's disease when the cervical or thoracic cord is included within the radiation portals and following head and neck and lung cancer irradiation. It has been reported in up to 15% of Hodgkin's disease patients (Word et al., 1980) and the incidence increases with radiation dose. The patient describes electric shock like sensations in the trunk and limbs, mainly provoked by neck flexion (Lhermitte's sign).

On the basis of circumstantial evidence (no postmortem data exist), it is thought that spontaneous discharges are generated by demyelinated sensory axons in the posterior

columns. The symptoms tend to resolve within a year, although some patients may continue to complain for years. There is no evidence that early-delayed myelopathy predisposes to a late-delayed myelopathy.

Late-delayed myelopathy

Delayed radiation myelopathy is slowly progressive and usually starts 1–4 years after RT. The main risk factors are older age and dose/fractionation parameters. The initial symptoms are sensory and usually start as a hemicord Brown–Séquard syndrome with paresthesiae and weakness in one leg and spinothalamic sensory loss in the other. Pain is uncommon. There is a distal to proximal progression up to the level of the irradiated segment and this eventually progresses to paraplegia or tetraplegia due to a complete 'transverse lesion' of the cord. Abrupt aggravation of symptoms and periods of temporary stabilization are common (Dynes & Smedal, 1960). Spontaneous remissions or recovery have not been described. The diagnosis is usually made after MRI scanning has excluded intramedullary or epidural tumour. Very rarely, patients can present with a subacute necrotic myelopathy as a paraneoplastic neurological syndrome, but this is an unlikely diagnosis as it usually presents before the cancer is diagnosed (Ojeda, 1984). CSF examination is usually normal or shows a high protein concentration. The MRI scan may show cord swelling acutely and occasionally complete spinal block with contrast enhancement but in the later stages the cord is atrophic and non-enhancing. Once the diagnosis is made, it is worthwhile treating with corticosteroids as remissions have been described (Godwin-Austen et al., 1975).

The pathological changes are centred on the white matter tracts with confluent areas of necrosis followed by fibrinoid necrosis and luminal occlusion in blood vessels. Areas of demyelination may be seen below the irradiated part of the cord, not associated with vascular changes, suggesting that vascular and glial damage occur independently (Schultheiss et al., 1988). Abnormal blood vessels are found only within the beam of radiation.

Lower motor neuron syndrome

A pure motor syndrome has been described following pelvic RT for testicular tumours (Fossa et al., 1969) and Hodgkin's disease (DeGreve et al., 1984). It is without sensory or sphincter disturbance and, as its name implies, is characterized by atrophy, fasciculations and areflexia confined to the lower limbs. It may remain restricted to one leg. The course is usually subacute and progressive followed by periods of stabilization with sufficient strength to maintain ambulation. The EMG shows denervation but normal motor conduction suggesting an anterior horn cell disease. The CSF protein concentration is elevated but is otherwise unremarkable as are imaging studies. The main differential diagnoses include subacute motor neuronopathy, a paraneoplastic neurological syndrome associated with non-Hodgkin's lymphoma (Schold et al., 1980), an isolated monomelic motor neuropathy or motor neuron disease.

Radiation-induced plexopathy

The major sites of peripheral nerve damage are the brachial plexus, after treatment for breast or lung cancer and the lumbosacral plexus after treatment for pelvic and lower abdominal malignancies. Most cases are late-delayed but early-delayed reversible reactions have been described (Salner et al., 1981; Enevoldson et al., 1992).

Brachial plexopathy following RT for breast cancer is a common clinical problem and the differential diagnosis lies between radiation-induced injury and neoplastic infiltration. There are no absolute criteria which can distinguish one from the other although tumour infiltration is more frequently characterized by severe and persistent pain. Other useful pointers towards a RT plexopathy are the rarity of an associated Horner's syndrome, the presence of paresthesiae as a predominant symptom and fasciculations or myokymia on the EMG (Lederman & Wilbourn, 1984). Similarly, in patients with lumbosacral plexopathy, slowly progressive weakness was usually the initial symptom of RT-induced plexopathy while pain marked the onset of tumour infiltration (Thomas et al., 1985). Radiation cases almost all went on to develop bilateral weakness while tumour patients typically had painful unilateral weakness. CT or MRI scanning is essential to exclude recurrent tumour and in cases with equivocal imaging surgical exploration may be necessary.

In conclusion, radiation is an important and effective treatment modality in the management of systemic and intracranial malignancies. Its use is associated with a recognized set of radiation-induced side effects. Modern radiation therapy offers treatment to the levels of radiation tolerance of the brain and spinal cord associated with a small risk of complications. In some circumstances higher doses of irradiation and shorter fractionations are used. This is possible either with localized irradiation techniques which minimize the dose to normal brain or with increasing doses

aimed at improving tumour control with an accepted increased risk of toxicity. While radiation is relatively safe, it is not devoid of side effects and these require recognition and appropriate management. Attempts are also being made to define the genetic predisposing factors, which may predict higher risk of damage to allow for individual tailoring of radiation doses.

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Part XII

Autoimmune disorders

92

Immune mechanisms in neurological disease

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The following chapter reviews principles of immunology to provide an understanding of how components of the nervous system are recognized by the immune system, how an autoimmune response is mounted, how immune cells and mediators enter the nervous tissue, and how tolerance against neural antigens is induced, maintained, and broken. Most of the general principles have been discovered since the 1980s but only with the new technology of targeted deletions and mutations (permanent and conditional knockout, knockin) can these principles be systematically explored at the molecular level. A brief discussion of multiple sclerosis, the Guillain–Barré syndrome, and myasthenia gravis will follow, while clinical aspects and disease-specific pathomechanisms of immune-mediated neurological disorders are presented in greater detail in individual chapters. Therapeutic consequences based on immunological principles are discussed in Chapter 93.

Categories of the immune response

The immune system is a multifaceted system of cells and molecules with specialized tasks in defending the organism from external agents, infectious or toxic. Moreover, the immune system plays a pivotal role in maintaining antigenic homeostasis in the body. Two types of responses to invading organisms can take place: an acute response launched within hours, and a delayed response occurring within days. The immediately responding system is termed innate immune system, and it evolves stereotypically and at the same magnitude regardless how often the infectious agent is encountered. In contrast, a more delayed response is delivered by the adaptive or acquired immune system and provides a more specific immunologic reaction which improves in efficiency on repeated exposure to a given infective agent, capitalizing on the formation of immunological memory. The immune system has traditionally been divided into innate and adaptive systems, each containing different cellular and molecular components. The main distinction between these two systems lies in the mechanisms and receptors used for immune recognition. These two systems are not separated, but are functionally connected allowing for intensive interactions (Carroll & Prodeus, 1998; Ochsenbein & Zinkernagel, 2000).

The innate immune system

During evolution, the innate immune system appeared before the adaptive immune system, and some form of innate immunity probably exists in all multicellular organisms. Characteristically, innate immune responses consist of all the immune defence mechanisms that do not require immunologic memory. Genetically, the molecular mediators and their receptors are highly conserved between species as far apart as *Caenorhabditis elegans*, *Drosophila*, and mammals.

The strategy of the innate immune response may not be to recognize every possible antigen, but rather to focus on a few highly conserved structures present in large groups of microorganisms. These structures are referred to as pathogen-associated molecular patterns, and the corresponding receptors of the innate immune system are called pattern-recognition receptors (Janeway, 1992). Examples of pathogen-associated molecular patterns are bacterial lipopolysaccharide, peptidoglycan, and bacterial DNA. Although chemically quite distinct, these molecules share common features: they are only produced by microbial pathogens, and not by their host, they represent in general invariant structures shared by large classes of pathogens, and they are usually relevant for the survival or pathogenicity of microorganisms (Medzhitov & Janeway, 2000).

Pattern-recognition receptors are encoded in the germ line, thus their specificity is genetically predetermined, evolved by natural selection. Structurally, these receptors belong to several families, and functionally they can be differentiated into three classes: secreted, endocytic, and signalling (Fearon & Locksley, 1996). They are expressed on many effector cells of the innate immune system, most importantly on macrophages, dendritic cells, and B-lymphocytes: all professional antigen-presenting cells. The total number of receptors involved in the innate immune response is thought to be in the hundreds, in contrast to the approximately 10^{15} somatically generated immunoglobulin and T-cell receptors of the adaptive immune response.

Once the pathogen-associated molecular pattern has been identified by a receptor, immediately signal transduction pathways are activated within the effector cell to induce the expression of various immune-response genes, such as costimulatory signals, inflammatory cytokines and chemokines. The effector cell is triggered to generate an immediate immune response rather than to proliferate, which accounts for the rapid kinetics of the innate immune system. The response of the innate immune system results in the recruitment and activation of antigen-specific lymphocytes and the subsequent initiation of adaptive immune responses, in concert with circulating antibodies and complement.

The adaptive immune system

The adaptive immune response is based on two classes of highly specialized cells, T- and B-lymphocytes. Each of these cells expresses a single kind of structurally unique receptor, resulting in a broad and extremely diverse repertoire of antigen recognition.

Both B- and T-lymphocytes are derived from primordial stem cells in primary lymphoid tissues such as bone marrow and fetal liver. Their development is guided by interactions with stromal cells, such as fibroblasts, and cytokines, including various colony-stimulating factors. However, the early phase of lymphocyte development is not dependent on the presence of any antigen, but once these cells express a mature antigen receptor, their further differentiation and survival becomes antigen dependent.

B-lymphocytes

The development of B-lymphocytes is characterized by successive steps in the somatic rearrangement and expression of immunoglobulin genes, and by changes in the expression of cell surface and intracellular molecules. In the bone marrow B-cell development proceeds in the absence of an antigen until a complete IgM molecule is expressed on the surface of the cell, which is defined as an immature B-cell. This cell population is subject to selection for self-tolerance and ability to survive in the periphery, a complex regulatory mechanism still not fully elucidated. After this selection, immature B-cells enter the periphery and access lymphoid follicles. The surviving cells form part of the long-lived pool of mature peripheral B-cells. These lymphocytes, coexpressing IgM and IgD, recirculate through the lymphoid organs, until they encounter their specific antigen. Once the immunoglobulin receptor on the B-cell surface interacts with a specific antigen, the B-cell will be activated. This process requires a series of additional stimulatory signals besides the direct contact between antigen and B-cell receptor. Some antigens, such as bacterial lipopolysaccharides can stimulate B-cells directly, and therefore are termed Type 1 T-cell-independent antigens. Type 2 T-cell-independent antigens containing repeating epitopes that cross-link B-cell antigen receptors similarly do not require cognate T-cell help but other soluble factors or cellular interactions to trigger B-cell mitogenesis. In contrast, most proteins and peptides depend on additional signals provided by T-helper cells, and are called T-cell-dependent antigens. After antigen recognition the B-cell is activated to divide. Selected B-cells will differentiate into plasma cells, which secrete large amounts of immunoglobulins, or into long-lived memory cells, which contribute to lasting protective immunity.

Besides synthesizing specific antibodies, B-lymphocytes are capable of binding, internalizing, and digesting antigen, and can re-express the digested protein fragments on their cell surface in the context of major histocompatibility complex (MHC) proteins. As such, B-cells can act as specific antigen-presenting cells as well.

B-cell receptor and soluble antibodies

The unique feature of B-lymphocytes is their ability to express and secrete antibodies. Antibodies or immunoglobulins consist of two identical heavy chains and two identical light chains that are held together by disulfide bonds. The N-terminal of each chain possesses a variable domain that binds antigen through three hypervariable complementarity-determining regions. The C-terminal domains of the heavy and the light chains form the constant regions, which define the class and subclass of the antibody and govern whether the light chain is of the κ or

Table 92.1. Human immunoglobulin isotypes

	IgG1	IgG2	IgG3	IgG4	IgM	IgA1	IgA2	IgD	IgE
Structure									
Heavy chain	γ1	γ2	γ3	γ4	μ	α1	α2	δ	ε
Molecular weight (kDa)	146	146	165	146	970	160	160	184	188
Half-life in serum (days)	21	20	7	21	10	6	6	3	2
Function									
Activation of classical complement pathway	++	+	+++	–	+++	–	–	–	–
Activation of alternative complement pathway	–	–	–	–	–	+	–	–	–
Binding to macrophages/phagocytes	+	–	+	–	–	+	+	–	+
Binding to mast cells/basophils	–	–	–	–	–	–	–	–	+++

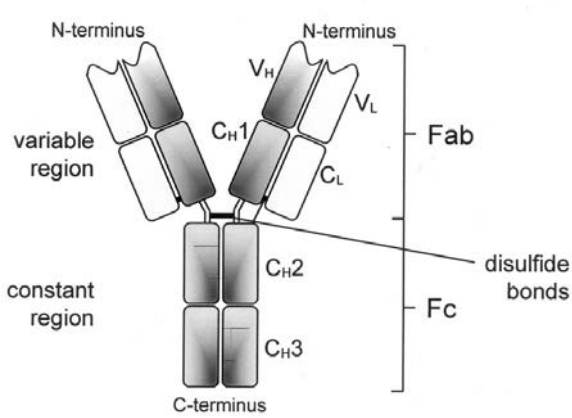

Fig. 92.1. Basic structure of an immunoglobulin molecule. Each immunoglobulin molecule consists of two heavy and two light chains, linked by disulfide bonds. The amino-terminal domain of each chain is variable in sequence (Fab fragment), whereas the remaining domains are constant (Fc fragment). Antibodies recognize conformational epitopes via the Fab fragment whereas the Fc fragment mediates binding to Fc receptors on immunoinflammatory cells and activates the classical complement pathway.

λ type (see Fig. 92.1). Five different classes of antibodies (IgD, IgM, IgG, IgA and IgE), four subclasses of IgG, and two subclasses of IgA are known, each of which exhibiting different functional properties (see Table 92.1). Each type of antibody can be produced as a soluble circulating immunoglobulin molecule or as a cell surface molecule anchored through a transmembrane domain in the B-cell membrane, where it acts as the B-cell receptor.

Most resting B-lymphocytes express IgD and IgM molecules on their surface. The antigen response starts with binding of the antigen to IgM-expressing B-cells resulting in the production of antibodies of the same specificity. After antigen contact, class switching will occur and most B-cells will produce IgG immunoglobulins. During a secondary response to the same antigen, a relative increase in IgG is observed. Depending on their environment, some B-cells will synthesize IgA (preferentially in the gut) or IgE (especially in the lung and the skin). The determinants of class switching are not completely understood.

Antibody genes continually change as B-cells encounter antigen and proliferate. Certain portions of the hypervariable regions are active sites of mutations, resulting in a continuous change of the antibody repertoire. Besides the increase in number of antibodies secreted, the affinity of individual antibodies against the stimulating antigen will increase over time, as B-cells expressing higher-affinity receptors on their surface are selectively activated. Moreover, the total binding force for antigens during this maturational process is termed antibody avidity. This process increases both the efficiency and the specificity of the immune response. A distinctive minor subset of B-cells termed B-1 cells, many of which carry the CD5 antigen, express a more limited V gene repertoire. They spontaneously secrete IgM antibodies that frequently bind microbial polysaccharides and some self antigens (Ochsenbein & Zinkernagel, 2000). These so-called natural autoantibodies may gain pathogenic significance if polyclonal activation raises their concentrations above the normal low levels. $CD5^+$ B-cell-derived IgM antibodies have been implicated in the pathogenesis of autoimmune neuropathies (Gold et al., 1999).

In various immune-mediated neurological diseases the entire functional spectrum of antibody responses can be observed. For example, in multiple sclerosis antibody

binding to the myelin sheath results in complement activation and, consequently, tissue destruction (Storch et al., 1998). In other diseases, such as myasthenia gravis or the Guillain–Barré syndrome and its Miller–Fisher variant, a direct blocking effect of antibodies on nerve conduction or neuromuscular transmission has been demonstrated (Buchwald et al., 1998, 2001; Drachman et al., 1982). Other mechanisms of humoral immunity are also involved in the pathogenesis of neuroimmunological diseases. The recognition of antibody-coated peptides by accessory effector cells triggers the activation of macrophages resulting in the release of inflammatory mediators in the surrounding tissue, thus perpetuating local inflammation. Moreover, antibodies binding to target antigens can activate, via Fc receptors, a toxic programme called antibody-dependent cell-mediated cytotoxicity (ADCC), directing an antigen-specific attack by an effector cell through the cellular release of cytoplasmic granules containing granzymes or perforins. Such mechanisms are critically involved, e.g. in the Guillain–Barré syndrome (Archelos & Hartung, 2000).

Antibodies may form immune complexes when binding circulating or tissue antigens. These can ignite complement and Fc receptor-dependent pathways of tissue damage. Immune complex-induced injury has been implicated in the pathogenesis of the vasculitides.

Major histocompatibility complex

The task of displaying the antigens of cell-associated microbes for recognition by T-lymphocytes is performed by specific molecules that are encoded by genes comprising the major histocompatibility complex (MHC). The physiological function of MHC molecules is the presentation of peptides to T-cells. Two types of MHC gene products can be distinguished, class I MHC molecules and class II MHC molecules, which differ functionally. Each MHC molecule consists of an extracellular peptide-binding cleft, or groove, and a pair of immunoglobulin-like domains, containing binding sites for the T-cell surface markers CD4 and CD8. By transmembrane domains MHC molecules are anchored to the cell surface. MHC molecules exhibit a broad specificity for peptide binding, whereas the fine specificity of antigen recognition resides in large parts in the T-cell receptor. Peptides from the cytosol are expressed by MHC class I molecules and presented to $CD8^+$ T-cells, whereas peptides generated in vesicles are bound to MHC class II molecules and recognized by $CD4^+$ T-lymphocytes. The two classes of MHC molecules are expressed differentially on cells. All nucleated cells exhibit MHC class I molecules, although hematopoietic cells express them at highest densities. MHC class II molecules, in contrast, are normally only expressed on professional antigen-presenting cells, such as macrophages, dendritic cells, and B-lymphocytes. The levels of both class I and II molecules can be markedly upregulated by cytokines, in particular IFNγ and TNFα.

A separate lineage of antigen-presenting molecules, structurally akin to MHC class I gene products, are the *CD1* molecules. They represent a class of related receptors, expressed by thymocytes, dendritic cells, and some B-lymphocytes, and are involved in the presentation of non-peptide (lipid and glycolipid) bacterial antigens to some T-cells (Schaible & Kaufmann, 2000).

T-lymphocytes

Cells destined to become T-cells, so-called *prothymocytes*, continuously migrate from the bone marrow to the thymus, where they develop into T-lymphocytes within the given microenvironment (Kruisbeek, 1999) and are subjected to a series of selection procedures (Anderson et al., 1996). Whereas antibodies detect an antigen in its native confirmational state, the T-cell receptor (of the α/β type) recognizes only short linear peptide fragments in the context of MHC molecules on the cell surface. Thus, part of the T-cell receptor recognizes the foreign peptide, and part of it recognizes the self MHC molecule. Only a minority of T-cells are able to perform this task, and a rigorous process of selection is necessary to determine those T-cells which can form the pool of lymphocytes to be exported from the thymus. This process is called thymic education and involves both positive and negative selection (Rathmell & Thompson, 1999; Sakaguchi, 2001; Sebzda et al., 1999). T-cells that do not recognize self-MHC molecules need to be eliminated, whereas those cells that have various affinities for binding self-MHC molecules are positively selected. However, many of these cells exhibit a high affinity to self-antigens, which makes them potentially harmful. Therefore they are eliminated as well (clonal deletion). As a result of the selective processes, more than 90% of T-cells in the thymus die, usually through apoptosis.

During thymic education the expression of various T-cell surface molecules is induced. Of specific interest is the expression of the surface molecules CD4 and CD8.

$CD4^+$ T-cells usually act as helper T-(T_H) cells and recognize preferentially extracellular peptide antigens presented by MHC class II molecules, whereas $CD8^+$ T-cells are usually cytotoxic and recognize cytosolic antigens presented by MHC class I molecules (see Fig. 92.2). The latter are expressed on all nucleated cells. Thus any infected cell can signal to $CD8^+$ T-cell and be destroyed, removing sites of pathogen replication. MHC class II molecules are expressed on the surface of professional antigen present-

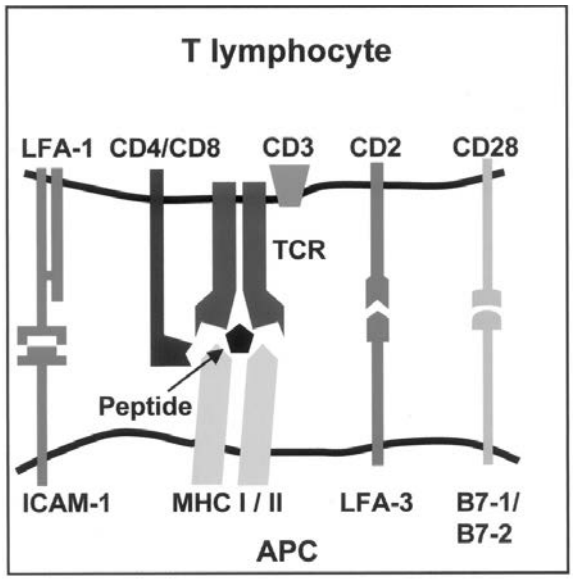

Fig. 92.2. Trimolecular complex. T-cell activation requires cognate dual recognition of peptide-MHC complex and costimulatory molecules displayed on antigen-presenting cells (APCs). T-cell–APC interaction is further strengthened by reciprocal recognition of accessory molecules.

ing cells only. Once a naive $CD4^+$ T-lymphocyte encounters a specific antigen on the surface of a professional antigen-presenting cell in the context of costimulatory molecules, such as CD80 or CD86, it gets activated, proliferates and differentiates into an armed effector T_H-lymphocyte (Abbas & Sharpe, 1999). Recently, a new serial encounter model of antigen recognition invokes a dynamic physical contact with T-cells literally crawling over and scanning the surface of multiple APCs (Friedel & Gunzer, 2001).

Three types of such effector T_H-cells can be distinguished: T_H1-cells manufacturing effector molecules that activate macrophages and T_H2-cells generating B-cell activating effector molecules. The third group, so-called T_H0-cells, from which both these functional classes derive also secrete molecules of both spectrums and may therefore have a distinct effector function (see Fig. 92.3). IFN-γ is the signature cytokine of T_H1-cells, which primarily act in phagocyte-mediated defence against infections, activated by macrophages or dendritic cells. In contrast, T_H2 populations produce IL-4 and IL-5 in response to helminthes and their principal effector functions can be seen in IgE and eosinophil/mast cell-mediated immune reactions. Thus, effector T-cells are critically involved in executing effector

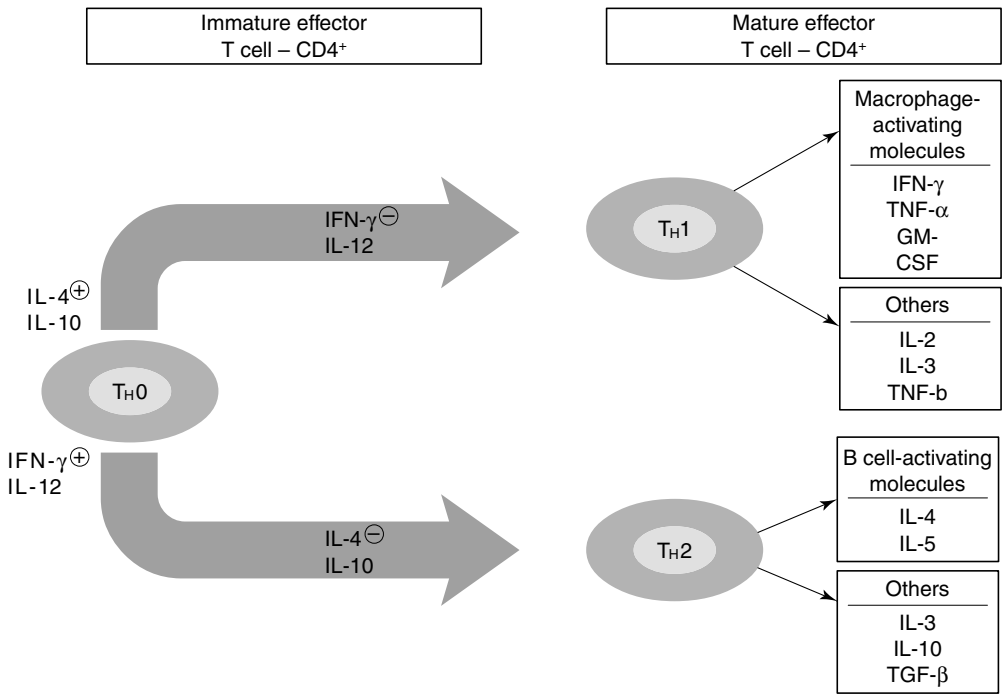

Fig. 92.3. T-cell activation. Once a naive CD4+ T-cells encounters its specific antigenic epitope displayed in the context of MHC class II gene products and sufficient levels of costimulatory molecules on an appropriate antigen-presenting cell, it starts to proliferate and differentiates into an immature effector cell, termed T_H0. This cell type carries the potential to become either a T_H1- or a T_H2-cell, which differ in their spectrum of cytokine production.

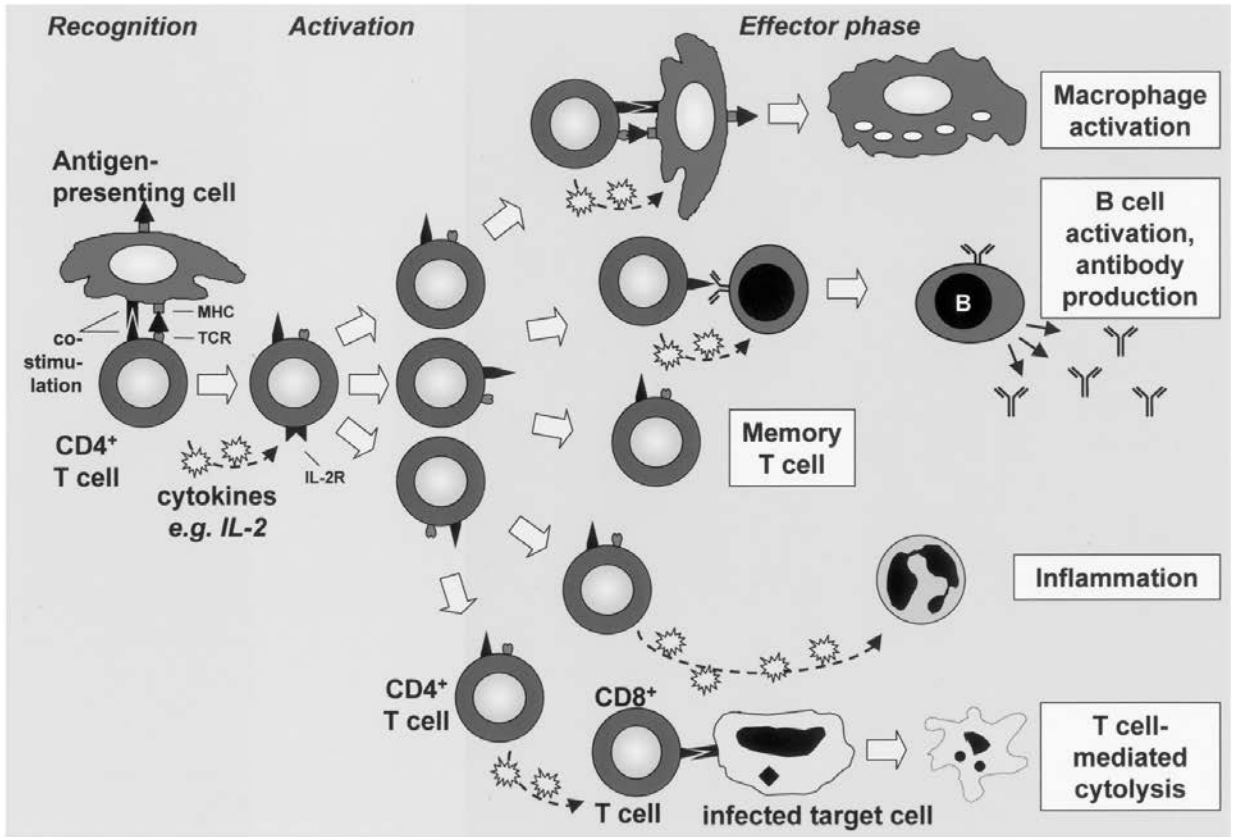

Fig. 92.4. The different stages of T-cell responses. T-cell activation first requires contact with processed antigenic epitopes associated with MHC class II molecules displayed on antigen-presenting cells and perception of additional costimulatory molecules. Up-regulation of IL-2 receptors (IL-2R) occurs and IL-2 drives T-cells into clonal proliferation during the activation stage. The effector stage is diverse. Multiple pathways lead to activation of macrophages and B cells. CD8 cells cause MHC class I restricted target cell lysis. CD4-driven responses can culminate in inflammatory tissue injury.

functions of the adaptive immune response (see Fig. 92.4). The cytokines produced by the individual subclass of T_H-cells not only determine their effector function but also regulate the development and expansion of the respective subset. For example, IFN-γ, produced by T_H1-cells, promotes further T_H1 differentiation and inhibits the proliferation of T_H2-cells. On the other hand IL-4, secreted by T_H2-lymphocytes, promotes T_H2 differentiation, whereas IL-10, also produced by T_H2-cells, inhibits activation of T_H1-lymphocytes. Thus, each T_H subset amplifies itself and down-regulates the reciprocal subset. Other factors, besides cytokines, affecting the development of T_H-cells are the avidity of MHC–peptide–TCR interaction, which is dependent on the type of antigen-presenting cell involved, the dose of the antigen, the affinity of peptide–MHC interaction, and on costimulatory molecules. Moreover, genetic factors appear to also modulate this process.

CD8 T-lymphocytes are instrumental in launching cytotoxic attacks on targets. They destroy them primarily by the release of cytotoxic granules, perforin and granzymes. A second mechanism of delivering a lethal hit, though in all likelihood more commonly utilized by a small proportion of CD4 cytolytic T-cells, involves up-regulated expression of Fas ligand and its interaction with Fas (CD95) exhibited on the recognized target (Suda et al., 1993).

T-cell receptor

Unlike antibodies, T-cell receptors are produced as transmembrane molecules only. They are composed as heterodimers and consist of an α- and a β- or a γ- and a δ-chain. Each chain contains a variable and constant domain. Similar to the immunoglobulins, the variable domains contain three complementarity-determining regions (CDR) (see Fig. 92.5). In the case of the α/β T-cell receptor these regions recognize a complex formed by a peptide seated within the groove of an MHC molecule. In contrast, most γ/δ T-cells do not recognize antigen in the form of

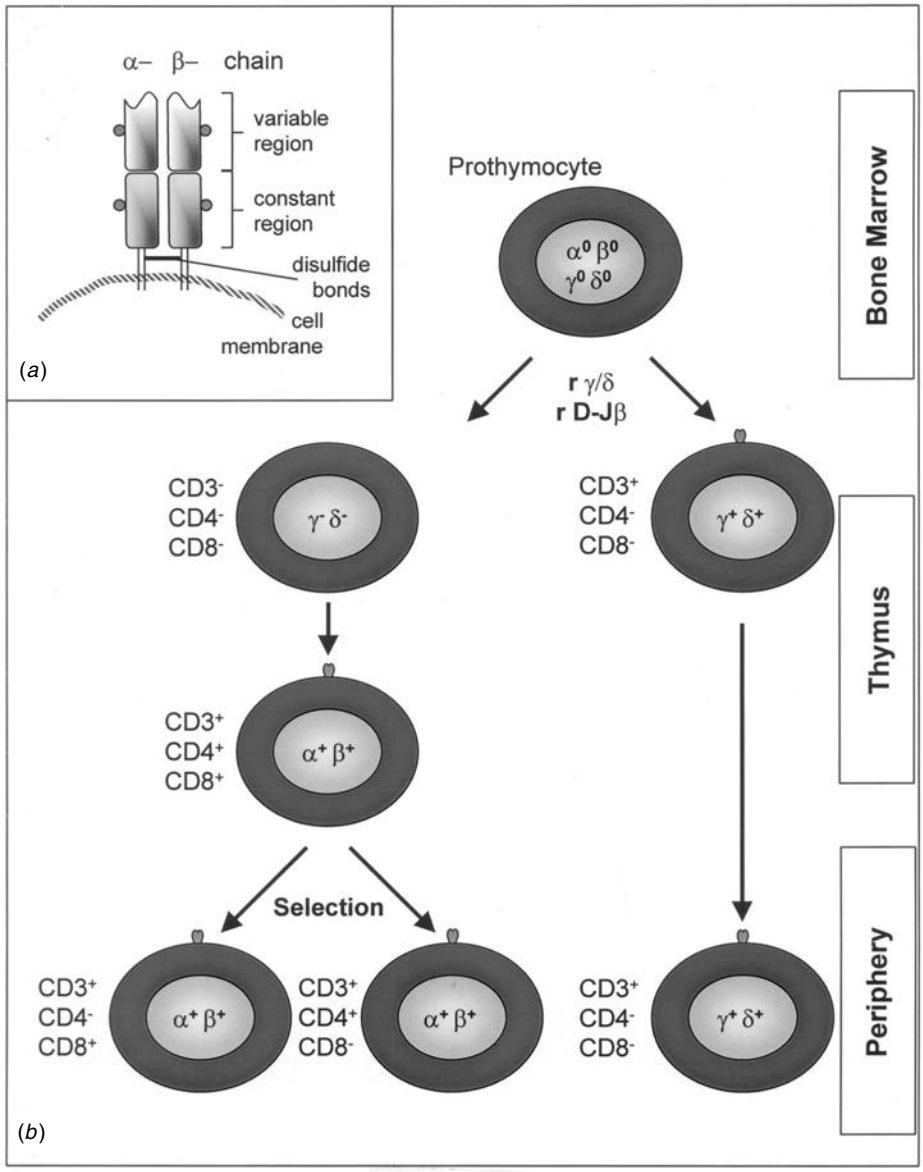

Fig. 92.5. Structure of the T-cell receptor and its distribution during T-cell development. The T cell receptor, expressed on the cellular surface only, is a heterodimer composed of two transmembrane glycoprotein chains, the α- and the β-chain. Both consist of a variable and a constant domain, and carry carbohydrate side chains. An alternative type of T-cell receptor is made up of different polypeptides designated γ and δ. During T-cell development various types of T-cells are selected.

peptide–MHC complexes. The antigen specificity of the T-cell receptor is determined by certain amphipathic amino acids in the antigen-binding cleft of the receptor. However, various different peptides can bind to the same T-cell receptor, and various T-cell receptors, produced by different genes, can exhibit similar peptide-binding capabilities ('degenerate' or 'promiscuous' antigen recognition) (Eisen, 2001; Hemmer et al., 1998). Thus, antigen specificity is not predictable on the basis of gene family expression. In contrast to the B-cell receptor, no further recombination or diversification of the T-cell receptor repertoire occurs once T-cells have matured. Paradoxically, the actual diversity of expressed γ/δ T-cell receptor is very limited, for unknown reasons. Functions of the γ/δ T-cells and molecular targets of γ/δ T-cell receptor recognition remain largely unresolved. One hypothesis holds that γ/δ T-cells are specialized to recognize antigens frequently encountered at epithelial boundaries (Hayday, 2000).

How does the immune system achieve the diversity of the antigen receptor repertoire? It has been estimated that

lymphocytes are capable of producing around 10^{15} different T-cell receptor variable regions and a similar number of antibody variable regions. Notably, this diversity is based on less than 400 different genes. Thus, multiple recombination processes that cut, splice, and modify the variable-region genes provide the large diversity of the B- and T-cell receptor repertoires (Tonegawa, 1983). The random generation of such a highly diverse repertoire of antigen receptors allows the adaptive immune system to recognize virtually any antigen. The price of this diversity, however, is the potential inability to distinguish foreign antigens from self antigens.

Binding of the antigen-specific T-cell receptor and either the CD4 or CD8 coreceptors to peptide–MHC complexes triggers an internal programme activating the effector T-cell (Bromley et al., 2001). The signalling events and functional consequences of T-cell antigen recognition may be altered by changing some of the T-cell receptor contact residues of a peptide antigen. Peptides eliciting responses different from those to native peptide ligands are termed altered peptide ligands (APL). They may be important in the regulation of T-cell activation in physiological or pathological situations. The T-cell response elicited by these peptides can induce only partial activation, while some APLs even deliver negative signals to the cell that inhibit their responses. Thus, APLs represent a mechanism by which T-cell activation can be regulated. This concept opens new avenues for therapeutic interventions (for details cf. Chapter 93).

Macrophages

Macrophages are bone-marrow derived cells that exhibit pleotropic functions in the immune system. They are the mature form of monocytes, which circulate in the blood and differentiate continuously into macrophages upon migration into the tissues.

Macrophages represent a cellular component of the innate immune system and as such do not exhibit specific antigen receptors, such as B- or T-lymphocytes, but possess receptors for carbohydrates and therefore can, to some degree, discriminate between 'self' and 'foreign' molecules. Moreover, they carry receptors for antibodies and complement. Opsonization ('coating') of pathogens with antibodies and/or complement will enhance macrophage activity. In some circumstances, macrophages are able to destroy pathogens by phagocytosis without the need for T-cell delivery of activating signals. However, in many clinically important settings $CD4^+$ T-cells are required to stimulate macrophages. The latter are rendered activated by membrane-bound signals issued by activated T_H1-cells as well as by the potent macrophage-activating cytokine interferon (IFN)-γ secreted by them. Once activated, macrophages can kill intracellular and ingested bacteria. Moreover, macrophages can also cause local tissue damage by the release of toxic oxygen free radicals, nitric oxide, metabolites, proteases, glutamate and a host of other proinflammatory mediators (Hartung et al., 1995; Pouly et al., 2000; Smith et al., 1999).

Antigen-presenting cells

Antigen presentation is crucial in triggering an effector T-cell response. The most important professional antigen-presenting cells are macrophages, B-lymphocytes and dendritic cells. Macrophages, as outlined before, are antigen-presenting cells that phagocytose antigens and present processed peptide fragments on their cellular surface. They exhibit MHC class II molecules at low levels, but their expression is inducible by IFN-γ. Thus, besides T-cell activation, IFN-γ enhances antigen presentation.

B-lymphocytes bind protein antigens with their receptors, internalize them and present fragments of the antigen to T_H-cells. The antigen-presenting function of B-cells is essential for T_H-cell-dependent antibody production.

Among professional antigen-presenting cells, dendritic cells are the most effective in initiating T-cell-dependent immune responses, a process also termed priming. Dendritic cells are derived from bone marrow precursors and most are related to the mononuclear phagocytic lineage. They are competent in presenting antigens to both $CD4^+$ as well as $CD8^+$ T-cells. By virtue of their anatomic location, they are often the first cells of the immune system to encounter foreign antigens. After antigen exposure, dendritic cells migrate to lymphoid organs, such as lymph nodes, the thymus, and the Peyer's patches, where they present the antigen to B- and T-cells. Moreover, dendritic cells are supposed to exhibit immunoregulatory functions by participating in the T_H1/T_H2 subtype-polarization, and by inducing T-cell anergy as well as T-cell apoptosis.

Other than these immune cells, the nervous system contains intrinsic cellular populations which have the potential to act as antigen presenters.

In the CNS, cells participating in the formation of the blood–brain barrier, specifically perivascular microglia or pericytes but also endothelial cells, can serve as competent antigen-presenting cells by up-regulation of class II MHC molecules. Microglia are the dominant parenchymal antigen presenters whereas the relevance of astrocytes in unclear (Antel & Becher, 1998; Aloisi et al., 2000). MHC class II inducibility in microglia cells appears to be regulated by neurotrophins released by electrically active neurons (Neuman et al., 1998), assigning an immunoregulatory function to neuronal cells within the CNS.

In the PNS, Schwann cells, besides forming the myelin sheath, can express MHC class II antigens and have been shown in vitro to present antigen to autoreactive T-cells. They also exhibit MHC class I antigens which mark them as targets for T-cell-mediated cellular cytotoxicity. Schwann cells can generate toxic and immunosuppressive mediators, such as leukotrienes, prostanoids and nitric oxide. This raises the possibility that these cells act as antigen presenters as well as immunoregulators within the PNS.

Complement

Complement is part of the innate immune system and represents one of the main effector mechanisms of antibody-mediated immunity. The complement systems encompasses more than 30 different proteins, all named by number in historical order, which, once activated, initiate a cascade generating bioactive components with various functions. The complement systems exhibit three main physiological activities: host defence against infections, acting as an interface between innate and adaptive immunity, disposal of immune complexes and neutralization of the products of inflammatory injury (Barrington et al., 2001; Walport, 2001). These effector functions can be activated through three different pathways: the classical pathway, triggered by an antibody, the mannan-binding lectin pathway, initiated by binding of a serum lectin, and the alternative pathway, triggered directly on pathogen surfaces. Once activated, all pathways converge at the point of cleavage of C3, eventually resulting in the formation of the membrane–attack complex (C5b–9) and subsequent lysis of the pathogen (see Fig. 92.6). Moreover, components of complement can opsonize pathogens for uptake by phagocytes or can act as chemoattractants recruiting immunocompetent cells to sites of infection.

It has become apparent that the activation of complement in disease may be harmful as well as helpful. In several immune-mediated disorders of the nervous system activation of the complement system plays a key role in the pathogenesis of the disease. In demyelinating diseases of the central as well as the peripheral nervous system, such as multiple sclerosis and the Guillain–Barré syndrome, respectively, complement activation results in myelin breakdown and axonal damage (cf. e.g. Jung et al., 1995; O'Hanlon et al., 2001; Storch et al., 1998). In myasthenia gravis, antibodies targeting the acetylcholine receptors on the postsynaptic membrane induce complement-mediated lysis (Engel, 1999). Similarly, in dermatomyositis and vasculitic disorders activation of the complement cascade results in severe tissue damage (Dalakas, 1998).

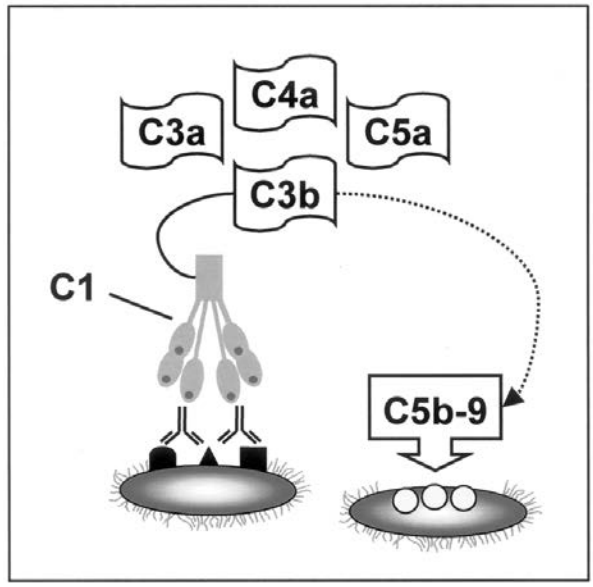

Fig. 92.6. Complement activation. The complement system can be activated by various pathways. In the classical pathway, C1 is activated by antibodies binding (e.g. to a microbial surface) or a surface molecule of a target structure (e.g. myelin sheath). This initiates a cascade of enzymatic cleavage processes generating larger and smaller fragments of various complement factors ('a' and 'b'). The larger C5b complex triggers the assembly of a membrane-attack complex (C5b-9), which can result in the lysis of a pathogen or as in the demyelinating disorders, of the myelin sheath.

Inflammatory mediators

Activation of the immune system results in the generation of an array of immunologically active mediators which primarily act locally and regulate the immune response. Some of these mediators, critically involved in immune-mediated disorders of the nervous system, will be discussed in the following section.

Cytokines

Cytokines represent a group of soluble low molecular mass proteins secreted by one cell to modulate the properties of the cell itself or of another cell in an autocrine or paracrine manner. They act as messengers both within the immune system but also in its dialogue with the nervous system, forming an integrated network that is intimately involved in the regulation of immune responses (Oppenheim & Feldman, 2001). Cytokines are synthesized *de novo* by all three types of effector T-cells and their effect depends on the target cell. T_H1- and T_H2-cells release different but overlapping sets of cytokines, which define their distinct

Table 92.2. Major cytokines and their function

Cytokine	Size (number of amino acids) and form	Producer cell	Actions
IFN-γ	143, heterodimer	T-cells, NK cells	Macrophage activation, increased expression of MHC molecules and antigen processing components, Ig class switching
TNF-α	157, trimers	Macrophages, NK cells, T cells	Local inflammation, endothelial activation
TNF-β	171, trimers	T-cells, B-cells	Killing, endothelial activation
TGF-β	112, homo- and heterotrimers	Chondrocytes, monocytes, T-cells	Inhibits cell growth, anti-inflammatory
IL-1	153 and 159, monomer	Macrophages, epithelial cells	Fever, T-cell activation, macrophage activation
IL-2	133, monomer	T-cells	T-cell proliferation
IL-4	129, monomer	T-cells, mast cells	B-cell activation, IgE switch suppresses T_H-cells
IL-5	115, homodimer	T-cells, mast cells	Eosinophil growth, differentiation
IL-10	160, homodimer	T-cells, macrophages	Macrophage suppression
IL-12	197 and 307, heterodimer	B-cells, macrophages	Activates NK cells, induces $CD4^+$ T-cell differentiation to T_H1-cells
IL-13	132, monomer	T-cells	B-cell growth and differentiation, inhibits macrophage inflammatory cytokine production and T_H1-cells
IL-18	157, monomer	Activated macrophages	Induces IFN-γ production by T- cells and NK cells, favours T_H1 induction

Notes:
IFN = interferon, TNF = tumour necrosis factor, TGF = transforming growth factor, IL = interleukin, NK cell = natural killer cell.

actions in immunity (O'Garra, 1998). T_H2-cells secrete, among others, interleukin (IL)-4 and IL-5, which activate B-lymphocytes, and IL-10, which inhibits macrophage activation. T_H1-cells secrete interferon IFN-γ, tumour necrosis factor (TNF)- α, and lymphotoxin (LT-α or TNF-β), potent proinflammatory molecules, which activate macrophages, inhibit B-cells and are directly cytotoxic for some cells.

Cytokines exhibit their action via receptors, which can be classified into equivalent families based on their distinctive structure. These families of cytokines and their receptors are also characterized by functional similarities. The specific functional effect of the individual cytokines is dependent on intracellular signalling events that are triggered by the binding of cytokines to their specific receptor. Their pleiotropism and redundancy make a simple statement about the function of individual cytokines difficult, although studies in knockout mice helped to clarify the physiologic role of certain cytokines (see Table 92.2).

One telling example of how a cytokine orchestrates the immune response and links innate and adaptive immunity is IL-12. This heterodimer is critical for initiating a sequence of responses involving macrophages, NK cells, and T-lymphocytes resulting in the eradication of the microbe. Macrophages and dendritic cells in response to the antigen produce IL-12. Secreted IL-12 stimulates NK cells as well as T-lymphocytes to produce IFN-γ, which then activates macrophages to kill the phagocytosed microbes. Moreover, IL-12 induces the differentiation of T-lymphocytes into IFN-γ-producing T_H1-cells, which express high affinity IL-12 binding, in contrast to T_H2-lymphocytes with low affinity IL-12 binding properties. Finally, IL-12 enhances the function of $CD8^+$ cytolytic T-cells and NK cells. This example demonstrates how immune mediators, especially cytokines, can regulate the immune response. Importantly, microglia, astroglia and Schwann cells are also sources of cytokines.

Chemokines

The burgeoning family of chemoattractant cytokines, so-called chemokines, comprises a large and diverse group of 8 to 10 kDa proteins that display between two and four NH_2-terminal cysteine amino acid residues. Based on the relative position of these cysteine residues in the mature protein, chemokines are divided into the CXC (or α), CC (or β), C (or γ), and CX_3C (or δ) subfamilies. So far, over 50 different chemokines have been recognized (Luster, 1998; Zhang et al., 2000; Zlotnik & Yoshie, 2000).

Secreted by a wide variety of leukocytes and other cell types, chemokines are functionally characterized by their capacity to induce the directional migration and activation of leukocytes. Furthermore, they promote humoral and cell-mediated immune reactions, regulate cell adhesion, leukocyte trafficking, and homing.

Chemokines induce their activity by binding to homologous transmembrane G protein-coupled receptors on target cells. To date, four human CXC chemokine receptors, eight human CC chemokine receptors, and one human CX_3C chemokine receptor have been identified. All receptors are expressed on various types of leukocytes: some appear to be restricted to certain cell types, whereas others are more widely displayed. Furthermore, in some cell types chemokine receptors are found to be constitutively expressed, whereas they are inducible on others. This diversity is also reflected in the expression pattern noted on T-helper cells: T_H1-cells preferentially express CXCR3 and CCR5, whereas T_H2-cells preferentially express CCR4 and CCR3. The migratory responsiveness is mirrored by the chemokine receptor expression pattern identifiable on these cell subtypes (Baggiolini, 1998; Cyster, 2000; Mackey et al., 1999; Ransohoff et al., 1997).

Matrix metalloproteinases

The matrix metalloproteinases (MMPs) comprise a large group of endoproteinases that share some structural features in the N-terminal catalytic domains. At least 25 members are known which can be categorized into the subfamilies of the collagenases, gelatinases, stromelysins, matrilysin, and membrane-type metalloproteinases (Nagase & Woessner, 1999; Yong et al., 1998).

With the exception of the membrane type MMPs, which are bound to the cellular surface, all other MMPs are secreted into the extracellular space by a wide range of cell types as latent proenzymes requiring activation by proteolytic cleavage of an amino-terminal domain to expose the active catalytic site. Since MMPs can catalyse the degradation of all protein components of the extracellular matrix, their finely tuned regulation is of critical importance to prevent tissue destruction (Birkedal-Hansen, 1995).

In recent in vitro studies the spectrum of MMP substrates was extended to proforms of MMPs, enzyme inhibitors, cell-membrane bound adhesion molecules, cytokine precursors, and cytokine receptors (Chandler et al., 1997). Shedding of the pro-form of the proinflammatory cytokine TNF-α is achieved by TNF-α converting enzyme (TACE), a unique disintegrin metalloproteinase with notable sequence identity to the adamalysin family of metalloproteinases (Black et al., 1997; Moss et al., 1997).

Termination of the immune response

To control the massive expansion of cellular and soluble immune mediators certain mechanisms must operate with high fidelity to regulate the immune response. Once the target antigen has been eliminated, or in the absence of infection, the activated effector cells are no longer needed. The cessation of the antigenic stimulus prompts the cells to undergo programmed cell death or apoptosis (Gold et al., 1997; Zipp et al., 1999).

The survival of lymphocytes depends on a delicate balance between death-promoting and death-inhibiting factors. Apoptosis is inhibited by some members of the intracellular Bcl-2 family, which block mitochondrial swelling, a process that leads to cell death (Chao & Korsmeyer, 1998; Hengartner, 2000). On the other hand, various mechanisms can induce apoptosis, e.g. through the interaction of the cell surface receptor Fas on T-cells with its ligand Fas ligand, a member of the TNF family (Krammer, 2000). Glucocorticoids promote T-cell apoptosis as well, an observation with therapeutic implications (Gold et al., 2001).

Tolerance and autoimmunity

The random generation of a highly diverse repertoire of B- and T-cell receptors allows the adaptive immune system to recognize virtually any antigen, including autoantigens, often referred to as self-reactive T-cells or autoantibodies. Tolerance is the process that eliminates or down-regulates such autoreactive cells (see Table 92.3). Consequently, a breakdown in this system can cause an autoimmune response or even autoimmune disease (see Table 92.4).

B-cell tolerance

Autoantibodies are characteristic for several autoimmune diseases of the nervous system, the prototype being myasthenia gravis. Autoantibodies bind to surface molecules or receptors leading to functional impairment of the affected cell. They can also bind to intracellular antigens and may thereby cause disease (Matsumoto et al., 1999).

The immune system has several mechanisms at hand to filter autoreactive B-lymphocytes out of the B-cell pool: (i) by clonal deletion of immature B-cells in the bone marrow (Nemazee & Burki, 1989), (ii) by deletion of autoreactive B-lymphocytes in the T-cell zones of secondary lymphoid organs, such as lymph nodes or the spleen (Rathmell et al., 1996), (iii) by induction of cellular anergy ('functional inactivation') (Goodnow et al., 1988), and (iv) by a process called 'receptor editing' which changes the

Table 92.3. Mechanisms of peripheral tolerance

Deletion (activation-induced cell death, apoptosis)
Anergy
Down-regulation of TCR, CD4/CD8
Partial activation (APL)
Suppression
Ignorance

Note:
TCR = T cell receptor, APL = altered peptide ligand.

Table 92.4. Mechanisms of autoimmunity

Loss of tolerance to self by:
Increased/aberrant expression of class II or costimulatory molecules
Molecular mimicry
Decreased activity of regulatory/suppressor cells
Defect in apoptosis
Superantigen-induced activation of autoreactive T-cells
Bystander activation of T/B-cells
Release of sequestered antigens

receptor specificity once an autoantigen has been encountered (Nemazee, 2000). At present, it remains unclear to what extent these mechanisms are of relevance in preventing autoimmune disorders in the nervous system.

T-cell tolerance

The basic principle of T-cell tolerance is the deletion of self-reactive T-lymphocytes in the thymus (van Parijs & Abbas, 1998). During the process of thymic education self-reactive T-lymphocytes are eliminated by complex mechanisms consisting of positive and negative selection. To delete all self-reactive cells, the presence of all autoantigens is required in the thymus. However, this is not always the case (Huseby & Goverman, 2000; Kamradt & Mitchison, 2001, Klein & Kyewski, 2000). Further, some autoreactive T-cells escape thymic education and enter the systemic immune compartment. Several mechanisms are required to keep T-cells in check and maintain peripheral tolerance (see Fig. 92.7).

Immunologic ignorance

Several mechanisms can cause immunologic ignorance: antigens may be physically isolated from self-reactive T-cells due to the separation in different biological compartments, e.g. by the blood–brain barrier marking the central nervous system as a potential immunologically privileged site (Barker & Billingham, 1977). Also, the level of antigen expressed might be below a certain threshold required for T-cell activation (Akkaraju et al., 1997; Ferber et al., 1994) or the physical encounters with APCs are not sufficiently frequent (Friedl & Gunzer, 2001). If tissues lack professional antigen presenters, resident antigens fail to activate T-cells and are therefore ignored. Importantly, autoreactive T-cells in such a setting remain functionally intact.

Peripheral clonal deletion

If abundant self-antigens in the periphery continually stimulate autoreactive T-cells, these may succumb to activation-induced cell death through apoptosis. The lack of growth factors may also lead to elimination of autoreactive T-cells.

Inhibition

T-cells require the presence of co-stimulatory molecules when detecting antigens presented by an MHC molecule. CD152 (or CTL-4) on T-cells binds the costimulatory molecules CD80 (or B7–1) and CD86 (or B7–2) with a higher affinity than the costimulatory receptor CD28. Thus, CD152 inhibits T-cell activation (Chambers & Allison, 1999) and results in anergy, i.e. functional unresponsiveness.

Anergy

If T-cells recognize antigens presented without adequate levels of costimulatory molecules, they are rendered unresponsive and cannot even launch a response when restimulated by antigen presenters expressing sufficient amounts of costimulators. This state is termed anergy. T-cell anergy can also be induced by altered peptide ligand which contains modified T-cell receptor contact residues.

Suppression

Regulatory T-cells, by the production of inhibitory cytokines such as IL-10 or transforming growth factor (TGF)-β inhibit or suppress the activation of T-lymphocytes. These inhibitory cells are called suppressor T-cells (T_S). However, attempts to isolate these $CD8^+$ lymphocytes or to purify and characterize the suppressor factors secreted have been extremely difficult. It is conceivable that suppression is exerted by different cell types and mediated by a variety of molecules (Chen et al., 1994; Powrie et al., 1996; Shevach, 2000).

Breakdown of tolerance

If one of the regulatory mechanisms outlined earlier fails, the specific immune response is mounted against self-

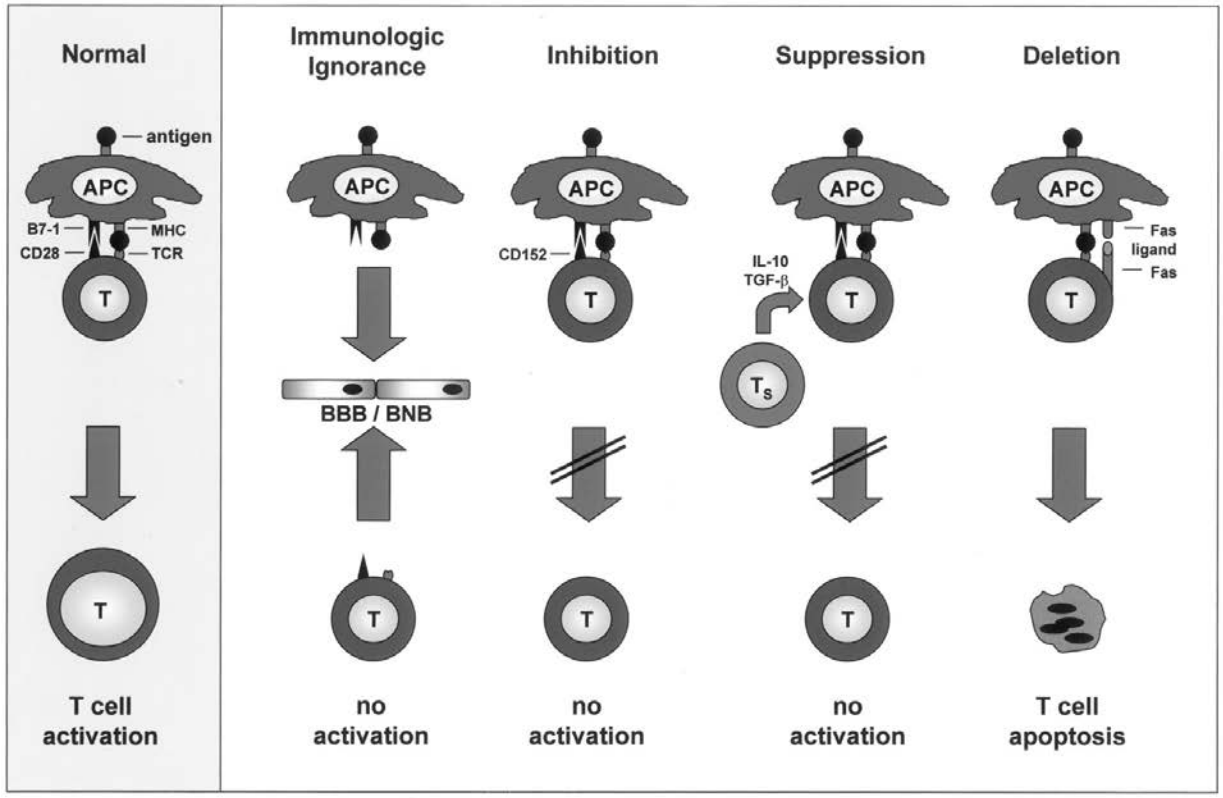

Fig. 92.7. Peripheral T-cell tolerance. Since self-reactive T-lymphocytes can escape thymic education, various mechanisms control the activity of these potentially autoreactive cells in the periphery. See text for details. BBB = blood–brain barrier, BNB = blood–nerve barrier.

antigens which leads to expansion of autoreactive effector T-cells, generation of autoantibodies through T-cell help, or both, and may give rise to severe tissue damage; a scenario which Ehrlich termed horror autotoxicus. Autoaggressive responses eventuate autoimmune disease. The autoimmune response persists because the immune system is not able to remove the offending autoantigen from the body, even worse, new hitherto hidden autoantigens could be released to amplify the response and broaden its epitope specificity, a process termed epitope spreading. The mechanisms of tissue damage in autoimmune diseases are essentially the same as those operative in other inflammatory disorders.

Various mechanisms are operative to promote or prevent tissue damage once an autoimmune reaction has started. Recruitment of large numbers of host monocytes/macrophages and T-cells and the release of cytotoxic cytokines and chemokines would serve to augment the injurious tissue reaction. Autoantibodies, either directly with the mediation of complement or via ADDC, are also active partners. Conversely, a suppressive/inhibitory local environment with only few or not fully competent APCs, anatomical distance of autoreactive cells to target structures, antiinflammatory cytokines or inappropriate antibody concentrations may help to defend against autoimmune tissue destruction. Finally, induction of apoptosis in activated T-cells may eliminate the autoreactive T-cells before the full inflammatory cascade is set in motion.

In most neurological autoimmune disorders the ultimate cause has not been established. One hypothesis holds that the extent of intrathymic deletion varies (Klein et al., 2000) and as such may not provide sufficient central tolerance. Another mechanism is the peripheral activation of potentially self-reactive T-lymphocytes in the normal repertoire by infectious agents. In autoimmune diseases such as multiple sclerosis or the Guillain–Barré syndrome (GBS) several lines of evidence implicate infection as a potential cause of the disease (Hafler, 1999; Karlsen & Dyrberg, 1998; Rose, 1998; Sheik et al., 1998). Alternatively, the release of sequestered autoantigens through tissue damage could provoke or perpetuate ongoing immune

reactions and, parenthetically, broaden their specifity (Miller et al., 1997, 2001). Another possible role in the genesis of autoimmunity has been attributed to a group of peptides derived from viral and bacterial pathogens, so called superantigens. They have a distinct mode of binding to MHC molecules that enables them to activate large numbers of T- or B-cells (Perron et al., 1997; Silverman, 1998). Bystander activation implicating the 'accidental' activation of effector immune cells may also play an important role (Infante-Duarte et al., 2000; Tough et al., 1997).

Alternatively, structural similarities between microbial and self-antigens could activate autoreactive T-cells, a mechanism termed molecular mimicry (Albert & Inman, 1999; Wucherpfennig & Strominger, 1995). T-lymphocytes can recognize microbial as well as self-peptides with similar amino acid sequence (Fujinami & Oldstone, 1985; Jahnke et al., 1985; Karlsen & Dyrberg, 1998). On the other hand, a single T-cell receptor can recognize several peptides with various degrees in sequence homology (Grogan et al., 1999; Hemmer et al., 1998; Maier et al., 2000). The first human autoimmune disorder proposed to result from such misguided T-cell cross-reactivity was rheumatic fever and its associated CNS disorder, Sydenham chorea, after infection with hemolytic streptococci. The principle of molecular mimicry has also been invoked in the pathogenesis of GBS following infection with *Campylobacter jejuni* or certain viruses (Hartung et al., 1998c; Hughes et al., 1999).

Several neurological disorders provide evidence that autoimmunity caused by autoreactive T-cells can be self-limited. Examples are monophasic diseases such as acute disseminated encephalomyelitis (ADEM) and GBS (Hartung & Grossman, 2001; Hartung et al., 1998b). Other forms of autoimmune diseases are episodic but persistent, such as relapsing–remitting forms of multiple sclerosis (MS), or chronic and progressive, such as primary or late stages of MS or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Which mechanisms determine the duration and extent of the autoimmune response remain unclear but apoptosis of autoaggressive T-cells or restoration of a disturbed Th1/Th2 balance have been proposed as underlying mechanisms.

Genetic control

It has long been established that autoimmunity is under genetic control. Clinical evidence points to hereditary susceptibility factors linked to MHC haplotype, immunoglobulin genes and others (cf. e.g. Compston, 1999). Genetic susceptibility was traditionally studied in animal models such as EAE or EAN where resistant and highly susceptible strains exist. In the resistant strains, experimental tools were developed to break tolerance and set off a fulminant autoimmune reaction.

Table 92.5. Witebsky's postulates: criteria for autoimmune diseases

A human disease can be assumed to be autoimmune in origin based on:
Demonstration of autoantibodies or autoreactive T-cells
Demonstration of immunoglobulin deposited on target structures
Reproduction of disease in experimental animals by immunization with putative autoantigens or passive transfer of autoantibodies/autoreactive T-cells
Disease should respond to immunosuppression or immunomodulation

Autoimmunity in the nervous system

To establish that a human disease is autoimmune in origin several criteria need to be met to satisfy Witebsky's postulates, the equivalent of Koch's postulates for an autoimmune pathogenetic sequence: (i) The existence of autoantibodies or autoreactive T-cells should be demonstrable, (ii) binding of autoantibodies should be detectable at target structures, (iii) experimentally, characteristic features of the disease should be reproducible by active immunization with putative autoantigen, passive transfer of autoantibody or autoreactive T-cells, (iv) the disease should respond to immunosuppression/modulation (Rose & Bona, 1993) (see Table 92.5).

The nervous system has long been considered an immunologically privileged site. This concept was based on the premise that (i) there is a more or less strict anatomic separation between the systemic immune compartment (blood) and the neural tissue, (ii) MHC molecules required for antigen presentation are absent under normal circumstances, (iii) there is no lymphatic drainage, and (iv) immune surveillance by T-cells is lacking. It is now obvious that most of these assumptions are not tenable. The blood–brain and the blood–nerve barrier do restrict access of immune cells and soluble mediators to a certain degree, however, this restriction is not complete, neither anatomically (e.g. the blood–nerve barrier is absent or relatively deficient at the roots, in the ganglia, and the motor terminals) nor functionally (Antel & Owens, 1999; Gold et al., 1999). Activated T-lymphocytes can penetrate intact barriers irrespective of their antigen specificity, and, under certain circumstances, release cytokines that up-regulate

Table 92.6. Immune-mediated disorders of the nervous system

Disorder	Target autoantigens (candidates)	Histopathology/pathomechanisms
CNS		
Multiple sclerosis	Myelin/oligodendrocyte proteins (e.g. MBP, MOG, MAG, PLP, αB cristallin)	Heterogeneous: multifocal inflammation, demyelination, axonal loss, loss of oligodendrocytes, colocalization of IgG and complement in the lesion
Stiff-person syndrome	GAD (glutamic acid decarboxylase) containing GABAergic neurons	No significant observations
Rassmussen's encephalitis	Glu-receptor-3 on neurons	Inflammation and neuronal loss
Neuromuscular junction		
Myasthenia gravis	Postsynaptic acetylcholine receptors (AChR); MuSK in some cases	Reduced folding and AChR density; deposition of IgG and complement
Lambert–Eaton myasthenic syndrome	Presynaptic voltage-gated calcium channels	Loss of calcium channels at the motor nerve terminal
Neuromyotonia (acquired)	Voltage-gated potassium channels	Heterogeneous
PNS		
Guillain–Barré syndrome	Gangliosides, such as GM1 (esp. axonal form), GQ1b (Miller–Fisher variant) and related glycolipids	Macrophage-mediated multifocal demyelination, axonal loss, IgG and complement deposition
CIDP	P0, glycolipids	Like Guillain–Barré syndrome
Multifocal motor neuropathy	Ganglioside GM1	Focal demyelination, deposition of IgM at the nodes of Ranvier
Monoclonal gammopathy associated neuropathies	MAG (myelin associated glycoprotein), also unknown targets	Segmental demyelination without inflammatory infiltration, IgM and complement deposition on the myelin sheath
CNS/PNS		
Paraneoplastic syndromes	Various, e.g. Hu, Ri, Yo	Neuronal loss, gliosis, perivascular inflammatory infiltration
Muscle		
Dermatomyositis	Unknown	Complement mediated vasculopathy, perimysial and perivascular infiltration with $CD4^+$ T-cells and B-cells
Polymyositis	Unknown	Endomysial infiltrates consisting of $CD8^+$ cells

Notes:
CIDP = chronic inflammatory demylinating polyradiculoneuropathy; CNS = central nervous system; GAD = glutamic acid decarboxylase; Glu = glutamat; MAG = myelin-associated glycoprotein; MBP = myelin basic protein; MOG = myelin oligodendrocyte glycoprotein; MuSK = muscle specific kinase; PLP = proteolipid protein; PNS = peripheral nervous system.

the expression of MHC class II molecules. Moreover, professional and non-professional antigen-presenting cells are abundantly distributed within the nervous tissue (Antel & Owens, 1999; Hartung et al., 1998a).

In the following section principal mechanisms underlying autoimmune disorders of the nervous system will be outlined. Table 92.6 enlists a range of neurological diseases considered to be autoimmune in nature or immune mediated and summarizes candidate antigens and potential pathogenic mechanisms. Detailed aspects of clinical presentation and treatment can be found in the individual chapters assigned to these diseases.

Immune cell trafficking

To mediate a local immune response within the CNS or PNS activated immunocompetent cells need to cross anatomically tight interfaces that separate the systemic

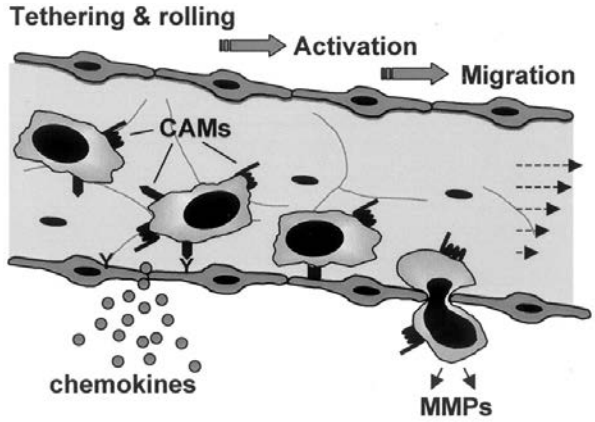

Fig. 92.8. Immune cell migration. The mechanism of immune cell trafficking is a multistep process occurring in an ordered sequential fashion. Leukocytes in the bloodstream become tethered to endothelial cells and start to crawl slowly downstream, facilitated by the interaction with various cellular adhesion molecules (CAMs). Probably by scanning the endothelial cell surface, rolling leukocytes respond to chemokines, which activate these cells and provide directional signals. The process of migration through the anatomical barrier separating the nervous system from the systemic compartment (blood–brain or blood–nerve barrier) is mediated by the release of matrix metalloproteinases (MMPs).

immune compartment from the nervous tissue, the blood–brain barrier (BBB) in the CNS and blood–nerve barrier (BNB) in the PNS.

This mechanism of transendothelial migration is a multistep process occurring in an ordered sequential fashion (see Fig. 92.8). In the first step, cellular adhesion molecules (CAMs) are expressed on the leukocytes and the vascular endothelium, resulting in a slowing and attachment of the circulating leukocytes along the vessel wall ('tethering' and 'rolling'). The flowing blood quickly dislodges cells that touch the vessel wall, thus adhesion molecules act as mechanical anchors, but also function as tissue-specific recognition molecules. Based on structural differences, CAMs can be categorized into four groups: the immunoglobulin superfamily, selectins, integrins and cadherins, all of which are involved in lymphocyte recruitment and extravasation. The specific function of individual CAMs has been elucidated by blocking their action with specific monoclonal antibodies in various animal models or by generating knock-out animals for the corresponding gene of a particular CAM.

The extravasation of leukocytes into the CNS parenchyma is facilitated by the expression of CAMs on both leukocytes and cerebral vascular endothelial cells (Archelos et al., 1999). The latter display various CAMs, of which two, vascular adhesion molecule-1 (VCAM-1) and E-selectin, are expressed only on activated endothelial cells. VCAM-1 can also be found on macrophages, dendritic cells, and epithelial cells and displays a prolonged expression on the endothelium after activation. Its counter-receptor on leukocytes is the very late antigen-4 (VLA-4). Another CAM important in mediating the attachment of lymphocytes to myelinated regions of the CNS is L-selectin (Archelos et al., 1998). It is expressed on various cell types, especially lymphocytes and neutrophils. Crucial in T-cell activation and enabling lymphocyte migration through vessel walls is the intercellular adhesion molecule-1 (ICAM-1). It binds to a T-cell integrin called lymphocyte function-associated antigen-1 (LFA-1) and is expressed on endothelial as well as antigen-presenting cells.

The coordinated up-regulation and expression of various CAMs along the endothelium within the blood vessel wall and on activated leukocytes increases their adhesive interaction. Initially, tethers are formed by CAMs, thus, circulating leukocytes within the bloodstream slow down, start rolling along the vessel wall and finally attach to it. This initially unstable interaction gets strengthened through the interaction of other CAMs, such as ICAM-1 with LFA-1, and VCAM-1 with VLA-4, respectively.

After interaction with the corresponding ligand various CAMs are shed or cleaved from the cell surface (Gearing & Newman, 1993). Thus they circulate within body fluids and are thought to regulate cellular interactions and to promote de-adhesion.

In the second step, chemokines come into play, providing signals to direct leukocyte migration into and within the extravascular space. Since lymphocytes must be positioned correctly to interact with other cells, the pattern and distribution of chemokines within the target tissue as well as the types of chemokine receptors expressed on the cell surface become critically important in orchestrating the ongoing immune responses (Campbell et al., 1998; Gerard & Rollins, 2001; Lindhout et al., 1999; Moser & Loetscher, 2001; Taub & Oppenheim, 1994).

Finally, in the third step, MMPs are secreted by the leukocytes in order to disrupt the BBB or BNB, thus facilitating the migration into the parenchyma of the nervous system (Bianchi et al., 1997; Kieseier et al., 1999).

Immune-mediated demyelination of the CNS

Multiple sclerosis (MS) is an immune-mediated neurological disease characterized by multifocal inflammatory demyelination and axonal damage in brain and spinal cord. Whereas the primary trigger of the abnormal

Table 92.7. Animal models for antigen-induced demyelination

Model	Antigens	Time course/ histopathology/ pathomechanisms
Lewis rat		
Active EAE	CNS myelin, MBP, MOG, PLP	Acute; T-cell inflammation, axonal damage, secondary demyelination
Adoptive-transfer EAE	MBP, S-100	Acute; T-cell inflammation, axonal damage (MBP)
Active EAN	PNS myelin, P2, PMP22	Acute; T-cell inflammation, strong demyelination
Adoptive-transfer EAN	P2, P0	Acute; T-cell inflammation, moderate demyelination
Congenic Lewis rat		
Active EAE	MOG	Relapsing–remitting disorder, mimicking the histopathology of MS
Murine EAE		
Active EAE	MBP, MOG, PLP	Relapsing–remitting and chronic courses; demyelination, axonal damage
Adoptive-transfer EAE	MBP, PLP	
Marmoset/ Rhesus monkey		
Active EAE	MOG, MBP	Acute; demyelination, T-cell inflammation

Notes:
CNS = central nervous system; EAE = experimental autoimmune encephalomyelitis; EAN = experimental autoimmune neuritis; MBP = myelin basic protein; MS = multiple sclerosis; MOG = myelin–oligodendrocyte glycoprotein; PLP = proteolipid protein; PNS = peripheral nervous system.
Sources: For details, cf. Gold et al. (2000).
Transgenic EAE models are reviewed in Owens et al. (2000).

immune reaction in MS remains unknown, collective evidence points to myelin-directed T-lymphocytes as key drivers of this complex process. Much progress in the understanding of immunological mechanisms involved in inflammatory demyelination of the CNS has been made through the investigation of experimental autoimmune encephalomyelitis (EAE), an animal model of MS. In principle, autoimmune model diseases can be induced by immunization with putative autoantigens in combination with non-specific immunostimulants (e.g. Freund's adjuvant); passive transfer of autoreactive T-cell lines or clones retrieved from diseased animals and propagated in vitro in the presence of autoantigen; by impairment of normal immunological function (e.g. irradiation or thymectomy, T-cell transfer to syngeneic T-cell-deficient mice); by infection (e.g. Theiler's virus-induced encephalomyelitis); or by genetic manipulation (transgenic models). Most commonly, EAE is induced in susceptible animals either by immunization with myelin components, such as myelin basic protein (MBP), proteolipid protein (PLP) or myelin oligodendrocyte glycoprotein (MOG), or adoptive transfer of $CD4^+$ T-cells specific for myelin antigens (see Table 92.7) (Gold et al., 2000; Martin et al., 1992; Steinman, 1999). The adoptive transfer experiments clearly established that EAE is a primarily T-cell-mediated autoimmune disease. More recently, transgenic overexpression or disruption of genes coding for T-cell receptors, cytokines and chemokines in the CNS of mice and rats allowed to reproduce different MS-related pathology and to dissect relevant immunopathogenic pathways (Owens et al., 2001).

Encephalitogenic T-cells are part of the normal T-cell repertoire and are not selected during thymic education (Schlüsener & Wekerle, 1985). Also healthy human individuals carry such autoreactive T-lymphocytes in their repertoire but these appear to be silenced (Hellings et al., 2001). The initial activation of these cells occurs in the systemic immune compartment outside the CNS, where T-lymphocytes encounter a specific autoantigen presented by MHC class II molecules and simultaneously perceive additional costimulatory signals, such as CD80 and CD86, on the cell surface of antigen-presenting cells (Kuchroo et al., 1995). Such autoreactive T-cells may reside quiescently in the systemic immune compartment where they cannot develop their autoaggressive potential. An external trigger, possibly an infective illness, most likely a viral infection, renders these cells active (Noseworthy et al., 2000; Soldan & Jacobson, 2001; Stohlman & Hinton, 2001; Talbot et al., 2001). Potential mechanisms include molecular mimicry, superantigen-driven broad T-cell proliferation, or cytokine-mediated bystander activation (Brocke et al.,

1998; Liblau & Gautam, 2000; Wingerchuk et al., 2001). To initiate a local immune response within the CNS, circulating T-cells, activated in the periphery, need to cross the BBB. Once within the CNS the T-cells encounter the specific autoantigenic epitopes displayed in the context of MHC and costimulatory molecules, e.g. on microglia, again, and, in consequence, become reactivated and expand clonally in situ and amplify the immune response by recruiting further immunocompetent cells through additional secretion of chemokines and cytokines. $CD4^+$ T-cells can be found in large numbers within the MS lesion (Raine, 1997), which can functionally be differentiated into two subsets of T-helper cells: T_H1 and T_H2. These trigger, based on the different profile of cytokines released, a polarized immunological response (Romagnani, 1997). Excess production of T_H1 cytokines and relatively deficient synthesis of T_H2 cytokines have been linked to acute exacerbations (Liblau et al., 1995).

It has been suggested that defective T-cell Fas function with subsequent lack of T-cell apoptosis is key in the failure to contain the autoaggressive T-cell response (Comi et al., 2000).

Once the BBB is damaged, passage into the CNS of soluble factors, such as circulating antibodies, which are supposed to contribute to the inflammatory demyelinative process, is greatly facilitated.

A pivotal role in this effector phase of the disease is played by macrophages/microglia (Benveniste, 1997). These cells act as local antigen presenters and as effector cells that effectively participate in and perpetuate immune-mediated demyelination by phagocytosis and the release of cytokines, proteases, and toxic mediators including glutamate (Bö et al., 1994; Brosnan et al., 1994; Hartung et al., 1995).

A vigorous inflammatory reaction within the CNS targeting the myelin sheath will also lead to axonal transection, which is supposed to be the pathologic correlate of the irreversible neurologic impairment in MS (Trapp et al., 1998) (see Fig. 92.9).

MS lesions contain $\alpha\beta$TCR- and in much smaller numbers $\gamma\delta$TCR-carrying T-lymphocytes (Battistini et al., 1995). These have been suggested to attack oligodendrocytes expressing heat shock proteins. The identification of MS-specific T-cell autoantigens has been one of the central issues in MS research over the last years. Based primarily on studies in EAE, MBP, a major protein component of myelin, was considered a prime candidate autoantigen for MS. Studying the human T-cell response against MBP revealed a rather complex recognition pattern (Martin et al., 2000). Certain MBP sequences were recognized more frequently than others ('immunodominant epitopes'); however, the antigen-specific receptors expressed by these reactive T-cell clones were also heterogeneous in their epitope specificity (Meinl et al., 1993; Pette et al., 1990).

It is now commonly accepted that many other myelin proteins, such as PLP, MOG, and myelin-associated glycoprotein (MAG) (Wallström et al., 1998) and even a non-myelin autoantigen, S100β, a calcium-binding protein of astroglia could be additional major autoantigens in MS (Gilden et al., 2001; Hartung & Rieckmann, 1997; Kojima et al., 1994; Martin et al., 2000; Pender et al., 2000; Schmidt et al., 1997).

B-cells are certainly also involved in the pathogenesis of MS. In patients with oligoclonal bands in the cerebrospinal fluid, plasma cells could be detected within white matter plaques (Farrell et al., 1985). In EAE the administration of MOG-specific antibodies resulted in widespread demyelination (Linington et al., 1988). In MS patients antibody responses against MBP, MAG, MOG, PLP, and αB crystallin have been identified in blood and CSF, and autoantibody binding in situ has been demonstrated (Archelos et al., 2000; Cross et al., 2001; Reindl et al., 1999; Steinman, 1996). Currently, MOG located on the surface of the myelin sheath is considered the most attractive candidate for an aberrant B-cell response culminating in demyelination (Wekerle, 1999). Given the heterogeneity of the pathology of MS lesions (Lucchinetti et al., 2000), it presently appears likely that the underlying pathogenetic pathways of tissue damage are multiple and diverse.

Immune-mediated demyelination of the PNS

Immune-mediated inflammatory disorders of the PNS are characterized by cellular infiltration, demyelination and axonal loss in the affected part of the nerve.

Most of these changes can be reproduced in the model disorder, experimental autoimmune neuritis (EAN). EAN can be elicited in susceptible animals by active immunization with whole peripheral nerve homogenate, myelin, myelin proteins P0 and P2 or peptides thereof, and galactocerebroside. It can also be produced by adoptive transfer of P2, P2 peptide-specific, P0, and P0 peptide-specific T-cell lines (see Table 92.7) (Gold et al., 2000; Linington & Brostoff, 1993).

The pathological hallmark of EAN is the infiltration of the PNS by lymphocytes and macrophages, which results in multifocal demyelination of axons predominantly around venules. Macrophages actively strip off myelin lamellae from axons, induce vesicular disruption of the myelin sheath, and phagocytose both intact and damaged myelin, as shown by electron microscopy (Griffin et al.,

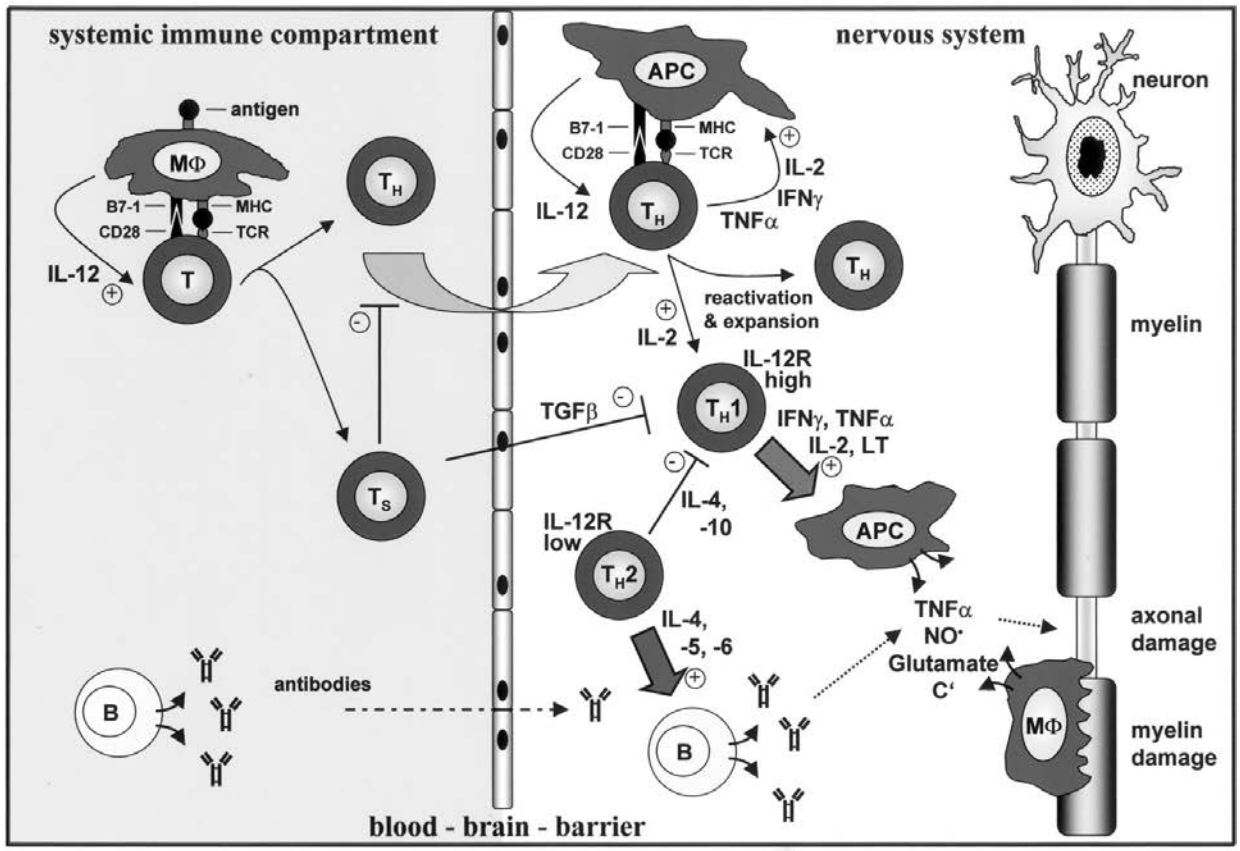

Fig. 92.9. Pathogenesis of immune-mediated inflammatory demyelination. Autoreactive T cells in the systemic circulation upon activation and guided by adhesion molecules on the blood–brain barrier can, attracted by chemokines, migrate into the CNS. Matrix metalloproteinases (MMPs) are utilized to penetrate the basal membrane. In the CNS, autoreactive T-cells when recognizing their antigen on an antigen-presenting cell displaying additional recognition and costimulatory molecules in a permissive cytokine microenvironment are reactivated, proliferate and secrete various cytokines. These can, in turn, activate microglia, macrophages or astrocytes to elaborate noxious inflammatory molecules. Cytokines can also impede impulse propagation. Autoreactive B-cells and autoantibodies can also be detected in blood and CSF. They can pass through a damaged blood–brain barrier and, upon activating the complement system with ensuing formation of the membrane attack complex, damage myelin. Antibodies can also bind to macrophages and stimulate them to antibody-dependent cytotoxicity. APC = antigen-presenting cell; Mϕ = macrophage; C = complement. See text for further explanation.

1993). Macrophages represent the predominant cell population in the inflamed PNS, and they reside in spinal roots as well as in more distal segments of the affected nerves (Hartung et al., 1998b; Kiefer et al., 2001). The fundamental need for this cell group in the pathogenesis of the disease, both in the induction and effector stage, was demonstrated by depletion experiments: macrophage elimination by intraperitoneal injection of silicon dust prevented all clinical, electrophysiologic, and histologic signs of EAN.

Crucial to the pathogenesis of inflammatory demyelination is the early invasion of the PNS by leukocytes. Circulating autoreactive T-cells need to be activated in the periphery in order to cross the BNB and to incite a local immuno-inflammatory response similar to the situation in the CNS. Breakdown of the BNB is one of the earliest morphologically demonstrable events in lesion development in EAN (Gold et al. 1999).

One pathogenic mechanism of special relevance to autoimmune neuropathies is molecular mimicry. In a proportion of patients with GBS epitopes shared between the enteropathogen *Campylobacter jejuni*, or *Cytomegalovirus (CMV)* or *Haemophilus influenzae* and nerve fibres have been identified as targets for aberrant cross-reactive B-cell responses (O'Leary & Willison, 2000). In a recent study,

antibody responses to the ganglioside GM1 were linked to axonal and motor injury, as seen in one clinical variant of GBS, in an experimental model induced in rabbits by active immunization with this glycoconjugate (Yuki et al., 2001). However, these observations cannot explain the entire clinical spectrum and laboratory findings of this disorder. Therefore GBS should be defined as an organ-specific immune-mediated disorder emerging from a synergistic interaction of cell-mediated and humoral immune responses to still incompletely characterized peripheral nerve antigens (Hahn, 1998; Sheikh et al., 1998).

Immune disorders of synaptic transmission

The neuromuscular junction (NMJ) is a prominent target for an autoimmune attack. Myasthenia gravis (MG) and the Lambert–Eaton myasthenic syndrome (LEMS) represent the two most common disorders of the NMJ, both mediated by an autoantibody-induced dysfunction of neuromuscular transmission. The pathomechanisms involved in these disorders are well elaborated (Patrick & Lindstrom, 1973; Toyka et al., 1975). In MG autoantibodies target muscle nicotinic acetylcholine receptors (AChR) on the postsynaptic membrane. Plasma exchange, removing circulating antibodies, results in a substantial albeit transient improvement in muscle strength lasting for several weeks. AChR antibodies in patients with the disease are IgG but heterogenous in light chain, subclass, and in their reactivity with the antigen, although the majority is directed against the so-called major immunogenic region located on the alpha subunit (Lindstrom, 2000). There is no evidence of T-cell infiltration in the NMJ, however, anti-AChR antibodies induce severe damage through complement-dependent lysis of the postsynaptic membrane and occasional macrophage infiltration. Moreover, the antibodies are able to cross-link the AChRs on the membrane surface, resulting in their accelerated internalization and degradation ('antigenic modulation') (Drachman, 1994; Engel, 1999). Thirdly, antibodies can inhibit AChR function directly.

The origins of the autoimmune response in MG remain uncertain. MG is an autoantibody-mediated disorder; as outlined before, B-cell responses are mostly T-cell controlled, thus the critical mechanism of loss of tolerance to the self-AChR could involve aberrant T-cell function. Autoreactive $CD4^+$ T-cells have been isolated from MG patients (Hohlfeld et al., 1984). In many patients, MG is associated with thymic hyperplasia or more rarely thymoma. Moreover, thymectomy is partially and transiently effective in treating the disease. Since the thymus is the major site of thymic education of T-lymphocytes, any alteration in thymic function would appear, at least in theory, to be potentially involved in the pathogenesis of MG. Thymic myoid cells express AchR epitopes and could sensitize CD4 T-cells whose epitope specificity would broaden once they exit the thymus. These lymphocytes probably interact with anti-AchR B-cells and precipitate the secretion of pathogenic autoantibodies.

Alternatively, cross-reactivity of antibodies against other antigens, particularly those shared with thymoma tissue, should be considered.

In about 15% of patients with MG, AChR antibodies are not detectable, and many of these patients have antibodies to another neuromuscular junction protein, muscle specific kinase (MuSK) (Vincent et al., 2001). MuSK is a receptor tyrosine kinase representing an essential component of the developing neuromuscular junction. At present its function in the fully developed NMJ remains elusive; however, a role in maintaining the high density of AChRs at the NMJ has been suggested (Hoch et al., 2001).

In LEMS, patients develop autoantibodies against presynaptic voltage-gated calcium channel proteins (VGCC). These antibodies reduce the number of active zone particles. In more than 60% LEMS is associated with a small-cell lung cancer (Dalmau et al., 1999). In this setting, VGCC detected on cancer cells apparently evoke an antibody response that cross-reacts with calcium channels at the NMJ (see Fig. 92.10) (Vincent, 1998). Some patients harbour antibodies to synaptotagmin which can reduce the quantal content of endplate potential (Takamori et al., 2000).

Yet another autoimmune disorder resulting from antibodies to some subtypes of voltage-gated potassium channels (VGPC) is neuromyotonia. These antibodies play an important role in the pathogenesis of the nerve hyperexcitability that characterizes the disease.

Inflammation and neuroprotection

Immune reactions in the nervous system may not be entirely destructive. Recent evidence suggests that immune responses can also be protective or aid in the repair of damaged neural tissue (Hohlfeld et al., 2000; Schwartz et al., 1999). For example, autoreactive T-cells may synthesize neurotrophic factors such as nerve growth factor (NGF) or brain-derived neurotrophic factor (BDNF) and deliver them at the lesion site (Kerschensteiner et al., 1999). However, spontaneous cellular immune responses do not exert sufficient protection

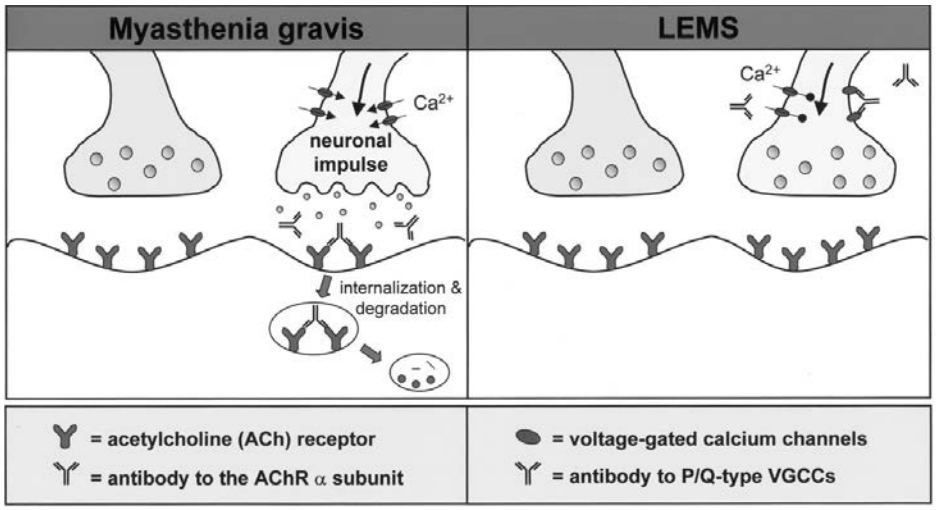

Fig. 92.10. Immune-mediated disorders at the neuromuscular junction. In myasthenia gravis autoantibodies bind to postsynaptic acetylcholine receptors (AChR) causing receptor internalization and degradation. In the Lambert–Eaton myasthenic syndrome (LEMS) autoantibodies target presynaptic calcium channels, thus inhibiting calcium influx required for the release of ACh into the synaptic cleft.

to cause significant improvement after neural injury (Schwartz & Moalem, 2001). The precise mechanisms underlying such neuroprotective effects are under current investigation.

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93

The basis of immunotherapy in neurological disease

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The first part of this chapter covers some general aspects of immunotherapy. In the second part, the mechanisms and side effects of the most widely used immunosuppressive and immunomodulatory agents are reviewed. The final part provides a brief overview of the most promising future strategies and therapeutic developments.

Principles of immunotherapy

Practical issues and general rules

Commencing with the trials of corticosteroids for treatment of rheumatoid arthritis in the late 1940s, numerous agents have been employed in many diseases with suspected or established autoimmune pathogenesis to abrogate excessive immunoreactivity. Unfortunately, the lack of specificity of these agents and their concurrent toxicities have limited their effectiveness. However, many formerly fatal or intractable diseases characterized by aberrant immunity can now be considered responsive to manipulation of the underlying defects in immune regulation. When making the decision to employ one of these agents, one should know as much as possible about the nature of the immune abnormality to be corrected and of the ability of a given drug to influence this process. Furthermore, the adverse effects of the agent should be weighed against the possible benefits (Machkhas et al., 1997).

The goals of treatment seem simple enough: to improve clinical deficits and to stop or slow progression of the disease process while keeping side effects to a minimum. Before initiation of any form of immunotherapy, and during therapy, a number of important points need to be considered and checked (Table 93.1). The diagnosis should be unequivocally established. Baseline variables (such as muscle strength, vital capacity, walking distance, etc.) should be documented so they may be measured on follow-up examinations to help in quantifying improvement. Certain medical conditions (e.g. chronic or undiagnosed infections, diabetes) must also be considered. Another major consideration before initiation of therapy is patient compliance. Usually, the risks associated with non-compliance outweigh the benefits of treatment, and non-compliance is a contraindication of immunosuppression. Regarding the duration of therapy, it is important that adequate dosages are given over a sufficient period of time. Otherwise, the agent is terminated prematurely and labelled a 'treatment failure', and will probably never be used again, even though in retrospect it is felt that incorrect dosages or insufficient duration of treatment were used. On the other hand, it is equally important that the effectiveness and tolerance of any immunomodulatory treatment is regularly assessed, and that the treatment is stopped if it turns out to be ineffective or accompanied by unacceptable side effects.

Implications of disease heterogeneity

In neuroimmunological as well as in other diseases, rational treatment depends on a thorough understanding of the disease's etiology and pathogenesis. MS provides a good example: Research into the pathogenesis of MS and especially the rapidly growing number of different animal models are beginning to reveal a remarkable heterogeneity and complexity of the pathogenetic mechanisms of inflammatory demyelinating CNS disease. In view of these developments, it seems likely that more refined classifications can be developed in the future for the disease we today call MS (Lucchinetti et al., 2000). This will increase the possibility of a more differentiated therapeutic approach. The evidence for an immunopathogenesis of

Table 93.1. General rules for immunotherapy

Checklist before treatment
Consider immunomodulatory treatment only if the diagnosis has been firmly established.
Attempt to tailor treatment to the individual patient.
Carefully weigh the risks versus potential benefits: In patients with a pronounced clinical deficit, immunosuppressive and immunomodulatory treatments are associated with increased risk and reduced benefit.
If several agents are indicated, begin with the least toxic.
Consider that not all immunomodulatory treatments can be combined, since one agent may depend on immune mechanisms suppressed by the other.
Do not underestimate the risks of long-term steroids.
Assure compliance by informing the patient in detail about the side effects and possible complications.
In case of cytotoxic immunosuppressive treatments, specifically mention the risks of infection and cancer, and emphasize the need for contraception.
Obtain written informed consent if necessary.
Check for agent-specific contraindications and perform appropriate laboratory tests to exclude conditions that might interfere with treatment (e.g. exclude IgA deficiency before treatment with i.v. IgG).
Before starting immunomodulatory therapy, make a treatment plan and have a concept of how to proceed if the therapy fails.
Provide the patient with an emergency passport that should be always carried and should indicate the diagnosis and medication.
Checklist during treatment
Re-evaluate the need for the therapy and for the present dose at regular intervals in all patients.
Always optimize symptomatic treatment before and during immunomodulatory treatment.
Remember that the clinical response is the single most important criterion for success or failure.
Monitor lab values (e.g. blood count, liver function) at regular intervals for early detection of side effects.
Treat infections early and efficiently and consider preventive measures in immunosuppressed patients.
Reconsider the diagnosis in treatment-resistant cases.

MS is strong, but indirect, because much of it has been derived from autoimmune animal models (Wekerle et al., 1994; Lassmann & Wekerle, 1998). Experimental support has accumulated for a variety of distinct autoimmune mechanisms, and it is likely that different human autoimmune diseases (and different forms of MS) are triggered by different mechanisms. In addition, different mechanisms may operate at different stages of the same disease. The identification of the etiology in individual cases is not an academic problem, but of the utmost relevance for therapy. Further, it is still unclear whether virus(es) or other infectious agents play a role. Although numerous viruses have been incriminated over the years, most of these claims have not been substantiated. This is not surprising as it is extremely unlikely that a single virus would be involved in all forms of MS. It is possible, however, that subtypes or 'variants' of MS are related to viral infection. For appropriate treatment it is essential to identify these cases.

Phase-specific immunotherapy

Common sense and clinical judgement suggest that the sooner immunotherapy is initiated, the better the chances are to prevent permanent deficits. Arguments against very early treatment include the high cost of long-term therapy and adverse reactions, which could diminish or abolish therapeutic effectiveness at a later stage when therapy is urgently needed. At the other end of the clinical spectrum, patients with severe impairment have an increased risk for various adverse reactions to immunotherapy. Furthermore, immunotherapy cannot be expected to reverse a pre-existing, stable chronic deficit, at least not in autoimmune diseases of the CNS. Therefore, patients with advanced CNS disease are bad candidates for immunotherapy, and aggressive immunosuppressive treatments are usually contraindicated.

Ideally, the intensity of immunosuppressive or immunomodulatory treatment should be adjusted to disease

activity. How can disease activity be measured? Again, consider MS as an example. One of the first lessons learned from MRI studies was that clinical activity is a very poor indicator of disease activity. It is probably unrealistic to assume that the currently available MRI techniques alone can provide reliable and feasible indicators of disease activity for therapeutic monitoring. However, the various imaging techniques have an enormous potential, and it is conceivable that they can in the future be developed into practical and reliable tools for assessing disease activity (McDonald, 1998). As regards laboratory markers of MS disease activity, none of the proposed 'activity markers' has yet proven suitable for routine monitoring of disease activity. There are many reasons for this, mostly related to limitations of the feasibility, reliability, sensitivity and specificity of the various assays. In spite of the unsolved problems, it is likely that more dependable and feasible laboratory tests of disease activity will soon be developed.

There are presently no reliable criteria for predicting the individual course and severity of MS. Such criteria are crucial for deciding whether and when to initiate immunomodulatory treatment. There is no need to treat benign MS, but MS cases with poor prognosis should be treated early. There is some evidence that imaging studies may help assess the prognosis in individual cases, but a precise prediction is not possible (Kappos et al., 1999). It is also unclear whether the clinical course provides helpful criteria to define subtypes of MS for differentiated therapy. The published clinical trials have differentiated (more or less rigorously) between relapsing–remitting and progressive MS, excluding primary progressive MS. More results are needed to decide whether such a distinction is meaningful.

Combination therapy

It seems logical to consider combining different immunotherapies that work via different mechanisms. Striking examples for the effectiveness of such therapy are provided by the combination of antiviral therapies in HIV infection and the combination of the immunosuppressive regimes routinely used in transplantation. The difficulty is to select the right agents to combine, as well as the right type of disease or disease type. An important general problem is that the different immune mechanisms targeted by different agents may depend on each other, so that one agent depends on the intactness of mechanisms inhibited by another agent. Clinical trials need to carefully look for such adverse interactions, which are difficult to predict.

Neuroprotective side effect of inflammation: Relevance for immunosuppressive therapy?

It has been proposed that inflammatory cells are not necessarily always harmful but under certain conditions even protective. For example, the intraperitoneal injection of MBP-specific T-cells protected optic nerve axons and retinal ganglion cells after experimental crush injury of the optic nerve (Moalem et al., 1999). The transferred T-cells were shown to home to the crush lesion. The exact mechanism of T-cell-mediated neuroprotection is still unknown. Unexpectedly, activated human immune cells express the classical neurotrophic factor, brain-derived neurotrophic factor (BDNF), in vitro and in inflammatory brain lesions of multiple sclerosis (Kerschensteiner et al., 1999). Therefore, it has been proposed that the functional neuroprotective effect of T-cells seen in the optic nerve crush experiments (Moalem et al., 1999) is related to the focal production of neurotrophic factor(s) by autoimmune T-cells (Hohlfeld et al., 2000).

Until recently, neurons were considered the major cellular source of BDNF in the nervous system (Hofer et al., 1990; Lewin & Barde, 1996). BDNF has potent effects on neuronal survival and plasticity during development and after injury. Considering that inflammation is a universal tissue reaction crucial for defence and repair, it is interesting to learn whether the immune cells accumulating in traumatic, degenerative, ischemic, infectious, and autoimmune lesions of the nervous system might provide an external source of BDNF. Activated human CD4+ T-cells, CD8+ T-cells, B-cells, monocytes as well as myelin antigen-specific T-cell lines produce BDNF (Kerschensteiner et al., 1999). The immune cell-derived BDNF supports neuronal survival in vitro. Furthermore, BDNF is expressed in inflammatory infiltrates in the brain of patients with acute disseminated encephalitis and multiple sclerosis. In a broader perspective, the expression of BDNF by immune cells provides a striking example for the close functional integration between the immune and nervous systems (Steinman, 1993; Neumann & Wekerle 1998).

The novel concept of 'protective autoimmunity' has far-reaching implications. Inflammatory reactions are very common not only in infectious and autoimmune diseases but also in ischemic, degenerative, traumatic, and metabolic lesions of the nervous system and muscle (e.g. stroke, Duchenne muscular dystrophy, adrenoleukodystrophy). It now appears that these lesions represent an attempt (often futile) of the immune system to protect the nervous system. An important implication for immunotherapy is that non-selective immunosuppressive treatments are likely to eliminate the neuroprotective autoimmune cells

along with the autoaggressive offenders. This may be one of the reasons why treatment with nonselective immunosuppressive agents often fails to have a convincing clinical benefit.

Immunosuppressive and immunomodulatory agents

Glucocorticosteroids

Glucocorticosteroids (GCS) are the most widely and frequently used immunomodulatory agents. For some indications treatment with GCS is limited to a short period of time (as in, e.g. multiple sclerosis), for others it is extended over many years (as in, e.g. giant cell arteritis). In principle, both short-term and long-term treatment with GCS can be associated with severe adverse reactions. As a general rule, however, side effects depend on the daily dose, dosing frequency, and duration of treatment. When GCS treatment becomes mandatory, efforts must focus on minimizing GCS side effects while maintaining therapeutic efficacy. Generally, these goals can be at least partially attained by using short-acting GCS medications at the lowest possible dose and the greatest dosing interval for the shortest period of time (Katz, 2000).

The anti-inflammatory and immunosuppressive effects of glucocorticosteroids have several compounds. First, steroids profoundly influence the distribution and trafficking of leukocytes. For example, steroids induce peripheral blood neutrophilia, whereas T-cells, monocytes and eosinophils are depleted from blood. Secondly, steroids alter the functional properties of T-cells and monocytes. Thirdly, steroids act on the synthesis and secretion of cytokines and immune mediators. Fourthly, steroids have an effect on microvascular permeability, which may contribute to the effects on leukocyte migration.

GCS bind to cytoplasmic receptors. After binding, the GCS–receptor complex traverses nuclear pores, binds to DNA at specific sites, leads to change in the transcription rates of GCS-sensitive genes, and results in regulation of proteins participating in the inflammatory response. The profound (but transient) effects of GCS on leukocyte trafficking differ depending on cell type. Due to both redistribution and deletion there is a rapid decrease of lymphocytes and monocytes. T-lymphocytes, in particular CD4+ T-helper cells, are more severely affected than B-cells. Natural killer cells are similarly resistant. At the same time, neutrophil numbers increase due to release from bone marrow and decreased egress from the circulation to inflammatory sites. Antibody-mediated responses including allergic reactions are suppressed as well as graft rejections. However, although total lympoid tissue shrinks during prolonged treatment, both cellular and humoral immunity are still functional at a reduced level.

Besides influencing the number and distribution of immune cells, GCS down-regulate the secretion of several lymphokines, including various interleukins, interferon-γ, and tumour necrosis factor-α. The antiinflammatory effects of GCS include the suppression of the secretion of arachidonic acid metabolites such as prostaglandins and leukotriene, the decrease of capillary dilatation, edema, fibrin deposition and the blockade of lysosomal enzyme degranulation.

Prolonged therapy with oral GCS is usually started as a single morning dose of a relatively short-acting GCS such as prednisone, prednisolone and methyprednisolone. These agents have a biologic half-life of approximately 12–36 hours, and can thus be considered as relatively short-acting GCS (Katz, 2000). By comparison, betamethasone and dexamethasone are long-acting CGS with a biologic half-life of 36–54 hours. The once-daily oral regime is maintained until the disease is stable or improved. At this time, therapy is tapered to an alternate-day regime. This approach permits a return to normal hypothalamic–pituitary–adrenal axis function while reducing the risk of side effects. High dose i.v. GCS pulse therapies (e.g. 500 or 1000 mg methylprednislone per day for 3 to 5 consecutive days), as are frequently used for acute exacerbations of multiple sclerosis, are sometimes efficacious in other situations and diseases, even when superimposed on a daily GCS regime. It is possible that such high dose pulse therapy with GCS has additional immunosuppressive effects, for example, by inducing apoptosis of inflammatory cells (Gold et al., 1997).

GCS have a large array of potential side effects. Therefore, steroid therapy must be managed with care, by clinicians experienced in its use. For some indications, it is advisable to hospitalize patients for initiation of steroid therapy. For example, patients with generalized myasthenia gravis may experience a transient steroid-induced exacerbation of myasthenic weakness.

The continued administration of GCS carries the risk of side effects for which patients should be closely monitored (Table 93.2). Hypothalamic–pituitary–adrenal axis suppression may occur with less than 2 weeks of systemic therapy. The most important side effects with long-term treatment are osteoporosis, hypertension, exacerbation or precipitation of diabetes, obesity, gastrointestinal ulcers, cataracts and occasional opportunistic infections. Typical signs of infection may be masked by GCS treatment. Blood pressure, weight, serum electrolytes and glucose level should be closely followed and adequately treated. Regular

Table 93.2. Side effects of glucocorticosteroid therapy

Characteristic early in therapy: essentially unavoidable
Insomnia
Emotional lability
Enhanced appetite or weight gain or both
Common in patients with underlying risk factors or other drug toxicities
Hypertension
Diabetes mellitus
Peptic ulcer disease
Acne vulgaris
Anticipated with use of sustained and intense treatment: minimize risk by conservative dosing regimens and steroid-sparing agents when possible
Cushingoid habitus
Hypothalamic–pituitary–adrenal suppression
Infection diathesis
Osteonecrosis
Myopathy
Impaired wound healing
Insidious and delayed: likely dependent on cumulative dose
Osteoporosis
Skin atrophy
Cataracts
Atherosclerosis
Growth retardation
Fatty liver
Rare and unpredictable
Psychosis
Pseudotumour cerebri
Glaucoma
Epidural lipomatosis
Pancreatitis

Source: From Katz (2000).

slit lamp examinations (every 6 months) help to detect cataracts early. In patients with a history of ulcer, histamine H2 receptor antagonists such as ranitidine, or H^+, K^+-ATPase inhibitors such as omeprazole should be given to protect the upper gastrointestinal mucosa from ulceration and bleeding.

GCS-induced osteoporosis is especially problematic in older individuals, particularly those who are estrogen deficient. To minimize steroid-induced osteoporosis, the single most effective measure is reduction of dosage or, if possible, complete discontinuation of the GCS. Calcium supplementation and postmenopausal estrogen repletion are helpful. The 24-hour urine calcium output should be measured after 1–3 months of GCS therapy and oral calcium and vitamin D should be given, based on the level of urinary calcium excretion. Cyclical, oral bisphosphonates prevent GCS-induced loss of bone mineral density in the spine and hip. Potassium replacement is necessary only in patients who develop hypokalemia.

Immunosuppressive and cytotoxic agents

Azathioprine and mycophenolate mofetil

Azathioprine has been used for many years for immunosuppressive treatment of neuroimmunological disorders. Because of its efficacy and tolerability, AZA remains one of the mainstays of immunosuppressive treatment.

The action of AZA is predominantly due to conversion into its metabolite 6-mercaptopurine. This completes with its analogue, hypoxanthine, a central component of nucleic acid synthesis and therefore has widespread effects on DNA and RNA synthesis. AZA acts primarily on proliferating lymphocytes and induces both B- and T-cell lymphopenia (Anstey & Lear, 1998). In vitro studies have demonstrated effects on both T- and B-cell functions, in particular the inhibition of surface receptor expression (for example CD2), blocking of mitogen-driven responses and antibody responses. Antigen- and mitogen-induced in vitro proliferative responses of T-cells are less inhibited by AZA than by cytotoxic agents like cyclophosphamide. AZA also has mild antiinflammatory properties, probably due to the inhibition of promonocyte cell division.

AZA is frequently used as an adjunct, e.g. to reduce the dose of CGS, but may be used alone. It is relatively easy to use as a therapeutic agent. Two major disadvantages of AZA are the following. First, up to 10% of patients show an acute idiosyncratic reaction, with general malaise, fever, skin reactions, and GI symptoms of nausea and vomiting. In this situation, the drug should be discontinued immediately. Secondly, the immunosuppressive effects develop slowly over several months. For this reason, 6 to 12 months of treatment are usually required to judge the efficacy of AZA treatment.

The incidence of serious side effects of azathioprine is relatively low. The most frequent adverse reactions encountered during long-term treatment in 104 patients with severe generalized MG in decreasing order of frequency were reversible marrow depression with leukopenia, gastrointestinal complications, infections and transient elevation of liver enzymes (Hohlfeld et al., 1988). The most serious observation, which may possibly have been related to 6 years of treatment with azathioprine, was renal lymphoma in one patient.

Mild intestinal discomfort, reported relatively commonly, can usually be alleviated by splitting the dose into

three or more divided doses, taking the drug after meals, starting treatment with a bedtime dose, and reducing the dose temporarily. A serious gastrointestinal complication is AZA-related pancreatitis. Elevation of liver enzymes up to three times the baseline is also common and may be tolerated, since it is usually reversible after the dose has been reduced. The risk of developing malignancies, especially lymphoma, is not certain, but seems to be lower in patients with MG than in organ transplant recipients. By contrast to what might be expected from experience in transplantation medicine, serious infections are rarely a problem in AZA-treated patients with neuroimmunological disease (Hohlfeld et al., 1988). Azathioprine is potentially teratogenic and mutagenic. Patients should be advised to use contraceptive measures during treatment and for at least several months after its completion. Data available from mothers treated with azathioprine for kidney transplant have not shown an increased rate of birth defects in their children, but no data on the actual risk are available.

Patients should be monitored carefully for side effects during treatment. Complete blood counts should be obtained at least weekly during the first 2 months, and monthly thereafter. If the total white blood count (WBC) is reduced to less than 3000/μl, the medication should be discontinued for a few days and treatment continued at a lower dose after the WBC returns to more than 3500/μl. The long-term dose can be adjusted to maintain the WBC around 4000/μl, and lymphocyte counts ranging between 800 and 1000/μl. However, it is not certain whether the immunosuppressive efficacy of AZA therapy in autoimmune diseases is directly correlated to the WBC or lymphocyte count.

In patients receiving AZA and steroids, the total WBC is usually elevated because of steroid-induced neutrophilia (see section on glucocorticosteroids). Therefore, the above suggestions for monitoring treatment by total WBC do not apply in patients who are concomitantly treated with GCS. During combined treatment, a WBC of approximately 6000 to 8000/μl can be used as the lower tolerable limit. Alternatively, the lymphocyte count, which is less markedly altered by corticosteroids, can be used for monitoring.

Another measure of drug effect is the mean corpuscular volume (MCV) of red cells, which is usually but not invariably elevated (up to 15%) during long-term treatment. This may be useful in situations when there is doubt about the compliance of patients in taking their medication.

Up to 10% of the population has a genetically reduced activity of the enzyme thiopurine-5-methyltransferase. In these patients, AZA metabolism is reduced and AZA toxicity increased. Mutations of the enzyme can be detected (ruled out) by PCR before treatment.

An important drug interaction occurs with allopurinol. Inhibition of xanthine oxidase by allopurinol impairs the conversion of azathioprine to 6-thiouric acid which accumulates and eventually leads to myelosuppression. If allopurinol must be administered concurrently, the dose of azathioprine must be reduced to 25% of the regular dose (approximately 0.5 mg per kg body weight) and the WBC should be closely monitored.

Mycophenolate mofetil is another immunosuppressive agent acting on DNA metabolism. In transplantation medicine, mycophenolate mofetil has proved useful and seems more powerful than AZA (Lipsky, 1996). In patients with neuroimmunological disease, e.g. myasthenia gravis, mycophenolate mofetil has been tried if AZA is not tolerated or contraindicated (Chaudry et al., 2001). Mycophenolate mofetil inhibits inosine monophosphate dehydrogenase and thereby depletes guanine nucleotides, leading to inhibition of DNA synthesis. Its adverse effects include gastrointestinal symptoms, gastrointestinal hemorrhage, leukopenia and infection. Compared to AZA, its hepatotoxicity is low, but its risk of secondary lymphoma seems slightly higher (Lipsky, 1996). In contrast to AZA, the combination of mycophenolate mofetil and allopurinol is not problematic.

Immunophilin-binding agents (cyclosporin, sirolimus and tacrolimus)

Cyclosporin, sirolimus (rapamycin) and tacrolimus (FK506) form the trinity of immunophilin-binding drugs. The immunophilin-binding drugs form complexes with abundant intracellular proteins called immunophilins: cyclosporin with cyclophilin (CP), and tacrolimus and sirolimus with the tacrolimus-binding protein (FKBP). The cyclosporin–CP and tacrolimus–FKBP complexes inhibit the phosphatase calcineurin and its substrate, the transcription factor NFAT, thus preventing the transcription of messenger RNAs for key cytokines, such as interleukin-2. The rapamycin–FKBP complex binds to a kinase called the target of rapamycin (TOR). TOR controls the phosphorylation of proteins involved in regulation of the cell cycle (Abraham, 1998).

Since NFAT is a validated target for two clinically important immunosuppressive drugs, interference with NFAT regulation might be expected to yield additional avenues for immunosuppression in the future (Kiani et al., 2000).

The immunophilin-binding agents very efficiently suppress transplant rejection, but presently are only rarely used in neuroimmunological disease. Cyclosporin was demonstrated to be effective in myasthenia gravis (Tindall et al., 1993), but has remained a second-line agent, mainly owing to its nephrotoxicity and high cost. A trial in multi-

ple sclerosis showed only modest benefit, and was associated with significant nephrotoxicity (The Multiple Sclerosis Study Group, 1990). It is likely that in the future immunophilin-binding agents will gain more importance in the treatment of neuroimmunological diseases. In addition to their immunosuppressive action, some of these substances or their derivatives seem to have neurotrophic effects (Steiner et al., 1997).

Cyclosporin is a cyclical undecapeptide isolated from two species of soil fungi. It targets the immune system more specifically than azathioprine or cyclophosphamide. Since its immunosuppressive effects were first noted, it has revolutionized transplant surgery leading to a dramatic increase in graft survival after cardiac, kidney, liver or pancreas transplants. The effects of cyclosporin focus on T-lymphocytes; B-cells and macrophages are apparently spared. The only appreciable effect of cyclosporin on accessory cells seems to be the disruption of lymphokine-dependent T-lymphocyte/macrophage interactions. Clinical improvement usually begins in 2–4 weeks.

Major side effects of cyclosporin include nephrotoxicity and hepatic disorders. In addition, cyclosporin can affect other organs such as the pancreas, CNS, bone and skeletal muscle. Further adverse reactions include arterial hypertension, tremor and hirsutism. Most of the adverse effects correlate with the dose and duration of treatment. Optimal dosage is monitored by measuring 'trough' drug levels, 12 hours after the last dose (i.e. first thing in the morning). For example, if the creatinine level increases by 50% over baseline levels or to more than 1.5 mg per 100 ml during treatment, the dose should be reduced or the drug discontinued. A more sensitive indicator of nephrotoxicity is the measurement of creatinine clearance. The encephalotoxicity of cyclosporin is discussed in Chapter 129. Cyclosporin must be discontinued if idiosyncratic or allergic reactions develop. The risk of late malignancies is not established, but may be similar to that of azathioprine.

Methotrexate (MTX)

Methotrexate is a chemotherapeutic drug used in oncology. For patients with neuroimmunological disease, it is used as a second-line immunosuppressive treatment, for example for treating inflammatory myopathies and, with limited success, advanced multiple sclerosis. For these indications, MTX is given orally at a dose from 10 to 20 mg 1 day each week.

MTX is a structural analog of folic acid acting as a folic acid antagonist. MTX inhibits the enzyme dihydrofolate reductase leading to a partial depletion of tetrohydrofolate cofactors and, as a consequence, inhibits purine and thymidilate synthesis. Due to its mechanism of action, MTX acts on rapidly dividing cells. Given satisfactory renal function and adequate hydration, MTX is excreted unchanged mainly in the urine within 12 hours of administration. Chronic extended use can lead to liver fibrosis and cirrhosis. Further adverse effects include bone marrow suppression, gastrointestinal complications, cystitis, lung fibrosis, alopecia and cutaneous vasculitis. Concurrent application of folate may reduce the incidence of side effects without significant reduction of therapeutic efficacy. Non-steroidal anti-inflammatory agents and trimethoprinsulfamethoxazole can potentiate the toxicity of MTX.

Cyclophosphamide

Cyclophosphamide (CTX) has been used as an immunosuppressive agent in vasculitis and neuroimmunological diseases refractory to other forms of immunosuppressive therapy. CTX belongs to the group of alkylating agents due to its ability to intercalate into the DNA helix. It is therefore primarily acting upon rapidly dividing cells from the lymphoid, gastrointestinal, urothelial systems, the hair follicles, ovarian and testicular tissue and certain tumour cells. The desired actions (i.e. immunosuppression and decrease of tumour growth) as well as the adverse effects (i.e. leukopenia, hemorrhagic cystitis, amenorrhea, oligospermia and transient alopecia) are caused by its effect on DNA. CTX acts upon the immune system in a number of different ways including the decrease of T-cells of various subclasses and, even more, B-cell numbers and function. Its efficacy in lupus nephritis, Wegener's granulomatosis and various vasculitides has led to its use in MS (Weiner et al., 1995) and other neuroimmunological disorders.

Cyclophosphamide may have serious side effects. The major and often limiting side effect is bone marrow suppression affecting leukocytes more than erythrocytes and platelets. The active metabolites are concentrated in the urine. This may damage the epithelium of the bladder (hemorrhagic cystitis, malignant transformation). This kind of toxicity can be reduced by a high fluid intake and, during pulse administration of high doses intravenously, by the simultaneous use of a uroprotective agent (mesna). In this connection, even microhematuria is an alarming sign that requires intense investigation to exclude a bladder tumour.

Patients should be informed that during prolonged therapy serious side effects may develop, and should be instructed to report signs and symptoms without delay. Permanent infertility may occur in both male and female patients. Alopecia may develop with short- and long-term therapy but is mild and reversible after treatment is stopped. Additional, rarer side effects include myocardial

damage and pulmonary fibrosis. After prolonged treatment, the potential for the development of leukemia, lymphoma, and urological cancers is of particular concern. Tumours can occur many years after therapy with CTX was stopped. The risk of malignancy depends on the cumulative dose, which should not exceed 85 grams. Like other cytotoxic agents, cyclophosphamide is potentially teratogenic and should be avoided during pregnancy, especially in the first trimester.

Cyclophosphamide is given orally at a dose of 1 to 2 mg per kg body weight per day, or by intermittent i.v. pulse theraphy (0.5–1.0 g/m^2). The i.v. pulses are repeated monthly for 6 months, and later in 3-month intervals for 1 to 2 years. If possible, therapy with CTX should be limited to 2 or 3 years because of its cumulative toxic and carcinogenic effects.

Mitoxantrone (MIX)

Mitoxantrone (MIX) is a synthetic anthracycline derivative that has been tested with promising results in relapsing and in chronic progressive MS (Hartung et al., 1999). The drug acts on both DNA and RNA synthesis. However, its molecular action is not yet fully defined. The interference with nucleic acid synthesis explains its influence on rapidly dividing and metabolically active cells such as tumour cells and immune cells. Mitoxantrone is given as a single infusion (12 mg/m^2 in 250 ml of 0.9% sodium chloride or 5% dextrose) over 30 min. Antiemetics (ondansetron or tropisetron) should be coadministered to prevent nausea. To maintain immunosuppression over longer periods of time, MIX has to be administered every 3 months. Although the acute toxicity is lower than that seen in patients treated with high dose cyclophosphamide, MIX like other anthracycline derivatives (doxorubicin and daunorubicin) is cardiotoxic. Congestive heart failure and decreased left ventricular ejection fraction have been observed with cumulative doses of 140 mg and higher. Patients with preexisting cardiac problems should therefore not be treated with MIX. In addition, each patient should be evaluated with an electrocardiogram and echocardiography before initiation of therapy and after one year of therapy. Frequent analysis (every other day during the first 2 weeks after therapy and then weekly) of laboratory values including blood counts, liver enzymes, uric acid and renal laboratory values should be obtained, because myelosuppression occurs within a few days after therapy. Patients who were treated with MIX for a tumour, e.g. breast cancer, have an approximately tenfold risk for later development of a secondary hematopoetic malignancy.

Patients should be informed that a bluish discoloration of urine and of the sclera occurs within 24hrs after administration. Besides cardiac problems, adverse reactions include bleeding, nausea and vomiting, jaundice, infections, renal failure, alopecia, seizures and headaches, cough and dyspnea and allergic reactions. The risks of administration must therefore be carefully weighed against the desired effects. Mainly because of its cumulative cardiotoxicity, MIX can only be applied for a relatively short time span, thus limiting its use in a chronic disease like MS. Patients should be carefully informed about the potential risks and benefits of this treatment.

Immunomodulatory agents

In contrast to immunosuppressive drugs, immunomodulatory agents do not globally suppress, but rather modulate immune functions in a complex way. They may even enhance certain immune functions. It is the overall effect on the immune system that translates into a clinical benefit. Interferon-beta can be considered the prototype of an immunomodulatory agent.

Interferons

Three different preparations of recombinant interferon-β (IFN-β) have been approved in different countries for treatment of MS, interferon-β-1b (Betaferon, Betaseron), interferon-β-1a (Rebif), and interferon-β-1a (Avonex). Initially, interferons were tested in MS for their antiviral effect (for review see Jacobs & Johnson, 1994). A pilot trial of systemic recombinant IFN-γ resulted in a sharp increase of clinical exacerbations (Panitch et al., 1987). In contrast, IFN-β turned out to have a beneficial effect, which has meanwhile been corroborated in several large controlled trials (Sibley et al., 1995; Jacobs et al., 1996; Ebers, 1998; Kappos, 1998).

Different trials of IFN-β showed a 30% reduction of the exacerbation rate, and/or a delay in time until sustained clinical progression. The precise mechanisms of the effects of IFN-β are unknown. Antiviral and antiproliferative actions might contribute, although immunomodulatory effects such as reduced transcription of MHC class II molecules are considered more important. Consistent with this notion, type I interferons are also effective in EAE.

Interferons have antiproliferative and various immunomodulatory effects (Arnason & Reder, 1994; Weinstock-Guttman et al., 1995; Yong et al., 1998; Hall et al., 1997). IFN-α is part of a multigene family, whereas IFN-β and IFN-γ are encoded by single genes. Because IFN-α and IFN-β share components of the same receptor, they are referred to as type I interferons. IFN-γ uses a separate receptor and is referred to as type II interferon. The receptor for type I IFNs is composed of at least two chains

Table 93.3. The many effects of interferon-beta

Process	Effect	Process	Effect
Activation		*Tissue damage*	
Major histocompatibility complex (MHC) class I expression	↑	Lymphotoxin production by TH1 cells	↓
MHC class II expression	↑↓	Tumour necrosis factor alpha production by macrophages	↓[b]
B7.1 expression on B cells	↓	Macrophage cytolytic activity	↑↓[b]
B7.2 expression on monocytes	↑	Release of mitogen and oxygen intermediates by macrophages	↑↓[b]
Suppressor cell function	↑[a]	CD14 expression on macrophages	↓[b]
Recruitment		*Recovery*	
Circulating lymphocyte numbers	↓	IL-10 production by macrophages	↑[b]
Lymphocyte entry to lymph nodes	↑	Transforming growth factor beta-1 production by peripheral blood mononuclear cells	↑[b]
Expansion		Prostaglandin E_2 release from macrophages	↓[b]
Interleukin (IL)-2 production by TH1 cells	↑[b]		
IL-2 receptor expression	↓[b]	*Other*	
T-cell proliferation	↓[b]	Antibody synthesis	↑
		Cytotoxic T-cell function	↑
Trafficking		Cytotoxic natural killer cell function	↑
Lymphocyte exit from lymph nodes	↓	Cytostasis	↑
Endothelial cell adhesion molecule expression	↓[b]		
Gamma interferon production	↑→↓		

Notes:
[a] restored to normal in people with MS; [b] in vitro; ↑ – increased; ↓ – decreased; ↑↓ – variable
Source: From: Mechanisms of Action and Clinical Effects of Beta-Interferon in Multiple Sclerosis. Proceedings of the MS Forum Modern Management Workshop, Venice, March 1999, with permission from Parexel MMS Europe, Ltd.

(IFNAR-1 and IFNAR-2). The receptor for IFN-γ is composed of at least two transmembrane chains, IFNGR-1 and IFNGR-2. Although the surface receptors are different, several components of the intracellular signalling pathways are shared between type I and type II IFNs. Thus, the signalling pathways of the different IFNs partially overlap (Darnell et al., 1994; Briscoe et al., 1996). Additional IFNs have been discovered, but they have not been as well characterized.

Type I interferons, the IFN-α family and IFN-β, are produced by almost all mammalian cells upon stimulation. One (but not the only) inducer of interferon synthesis is double-stranded RNA, which is part of the infectious cycle of most viruses, but is not found in mammalian cells. IFNs trigger the synthesis of many host-cell proteins that contribute to the inhibition of viral replication, and are believed to mediate most of the biological effects of the IFNs. Like IFN-γ, type I interferons increase expression of MHC class I and therefore enhance the ability of virus-infected cells to present viral peptides to CD8+ T cells. In contrast to IFN-γ, however, IFN-α and IFN-β do not induce but suppress the synthesis of MHC class II proteins. This effect may be important for the immunomodulatory activity of type I interferons (Weinstock-Guttman et al., 1995; Yong et al., 1998; Hall et al., 1997). The exact mechanism of IFN-β-mediated MHC class II inhibition is not completely understood. It appears that IFN-β reduces the activity of the class II transactivator CIITA, a factor necessary for IFN-γ-induced MHC class II transcription (Lu et al., 1995).

Apart from the inhibition of MHC class II expression, numerous other immunomodulatory effects of type I interferons have been described (Table 93.3). For example, IFN-β has been shown to up-regulate interleukin-10 expression and secretion by T-cells and monocytes (Rudick et al., 1996, 1998a; Rep et al., 1996; Weber et al., 1999), indicating that part of the clinical effects of IFN-β are in fact mediated by interleukin-10. Both IFN-β-1a and IFN-β-1b induce the production of IL-10 in MBP-specific CD4+ T-cell lines, but inhibit proliferation and production of lymphotoxin (Weber et al., 1999). Furthermore, IFN-β inhibits T-cell migration across basement membrane in vitro, presumably by decreasing the secretion of matrix-degrading enzymes

(Leppert et al., 1996; Stüve et al., 1996). This IFN-mediated inhibitory effect on the secretion of matrix metalloproteinases, as well as other consequences of IFN cellular responses, may be pertinent for the suppression of inflammation (i.e reduced numbers of enhancing MRI lesions and lessened CSF pleocytosis) observed in IFN-treated MS patients. Potential mechanisms include increase in soluble VCAM-1 (Calabresi et al., 1997b) and concomitant down-regulation of the corresponding partner adhesion molecule VLA-4 on peripheral blood lymphocytes (Calabresi et al., 1997a). Increased soluble VCAM-1 and decreased cellular VLA-4 would tend to block leukocyte–endothelial adhesion at the blood–brain barrier. Leukocytes also require stimulation by chemoattractants, called chemokines, during extravasation, and several chemokines are increased in the CSF of patients with relapses of MS. It is interesting that IFNs up-regulate the expression of chemokines by numerous cell types, including hematopoietic cells. Elevated levels of chemokines in the circulation would tend to reduce transvascular chemokine gradients, favouring the entry of cells into the CNS.

A myriad of other effects of IFN-β have been described (Table 93.3). The relative importance and mutual interdependence of this bewildering variety of actions are not well understood, so that at the present time the mechanisms of IFN-β treatment of MS remain unknown.

There is evidence that recombinant IFN-α also reduces exacerbation frequency (Durelli et al., 1994) and MRI activity (Myhr et al., 1999) in relapsing–remitting MS. Its efficacy as regards MRI activity was comparable to that observed in trials of IFN-β (Myhr et al., 1999). The profile of side effects was similar to that of IFN-β (see below). In addition, however, there was a high incidence of moderate to severe (reversible) hair loss (40% in the high dose group after 6 months) (Myhr et al., 1999). Whether IFN-α will ever be as important in MS treatment as IFN-β now seems doubtful. However, it should be noted that although IFN-β and IFN-α bind to the same receptor, they interact with the receptor in different ways. These differential binding modes of IFN-α and IFN-β result in differential cytoplasmic signalling and perhaps, different clinical effects.

The major short- and medium-term side effects of IFN-β observed in MS trials include 'flu-like symptoms and (usually mild) laboratory abnormalities (Walther & Hohlfeld, 1999). Skin necrosis at injection sites occurred in up to 5% of patients in trials of subcutaneous IFN.

Initially up to 75% of patients experience 'flu-like symptoms such as fever, myalgia, headache, fatigue, and chills. The reaction begins 3–6 hours after injection and usually improves within 24 hours. The individual pattern and intensity of these symptoms vary greatly from patient to patient and even from injection to injection. These transient 'flu-like symptoms are probably related to a temporary up-regulation of inflammatory cytokines such as interleukin-6 (IL-6), tumour necrosis factor alpha (TNF-α), and IFN-γ (Dayal et al., 1995; Brod et al., 1996). The flu-like reactions usually resolve during the first 3 months of treatment. Patients should be advised to take the injection before bedtime in order to 'sleep off' most of the side effects and to take non-steroidal antiphlogistics (NSAIDs) as comedication. Oral prednisone (10 mg per day) with or without NSAIDs is highly effective in reducing 'flu-like symptoms, if NSAIDs alone are not sufficient.

Many patients experience a transient worsening of pre-existing MS symptoms, especially increased spasticity. This usually appears within the complex of 'flu-like symptoms, especially in the first 12 weeks of treatment, and is probably similar in nature to the functional deterioration of the neurological status of MS patients as a consequence of stress, heat, fever, or inflammatory mediators. Symptoms typically appear 3–24 hours after IFN injection and can last between several hours to several days. Comedication with NSAIDs and, sometimes, antispasticity medication (e.g. baclofen) is helpful.

Neither IFN-β-1a nor IFN-β-1b has been associated with significant hepatic or renal dysfunction or bone marrow suppression. The most commonly observed laboratory abnormalities are lymphopenia, neutropenia, leukopenia, and raised liver aminotransferase values. These changes were seldom serious and always reversible during clinical trials and postmarketing surveillance. Complete blood counts should be obtained each month as well as serum chemistries with liver function tests in the first three months, and quarterly thereafter. If significant laboratory changes occur, the dosage should be temporarily reduced or discontinued. Once the parameters have normalized, it is usually possible to gradually increase the dosage of IFN without any complications. Although no evidence for any drug interactions has emerged so far, the concomitant administration of IFN-β and other potentially hepato- or myelotoxic medications such as anticonvulsants, antidepressants, or ticlopidine should be closely monitored.

Preclinical studies with both IFN-β-1b and IFN-β-1a in rhesus monkeys demonstrated that high doses of IFN-β were not teratogenic for the embryo, but they had a dose-dependent abortive effect. It is, however, not known if IFN-β is teratogenic in humans. It is generally recommended that interferon therapy should be discontinued before a planned pregnancy, and then during pregnancy. However, IFN-β therapy is not necessarily an indication for inducing

an abortion of an intact pregnancy once the drug has been discontinued until delivery. It is not known whether IFN-β is secreted into breast milk. Although the protein is most likely degraded in the acidic environment of the infant's stomach, therapy should nevertheless be discontinued during nursing for safety reasons. To lower the risk of a relapse postpartum, one can consider early weaning and begin treatment with IFN-β soon after delivery.

Symptoms of depression are frequent in MS patients. Up to 50% of patients who begin IFN-β therapy have unrealistically optimistic treatment expectations, and consequently their compliance is significantly less than that of patients with more realistic expectations. These facts should be taken into account when evaluating the significance of IFN-β in depression (Ebers et al., 1998). If depression and mood disorders appear during therapy with IFN-β, they should be treated like all other depressive syndromes, i.e. with antidepressant medication and psychotherapy. The individual pros and cons of IFN-β treatment in light of the actual course of the disease must be openly and critically discussed with the patient in order to decide whether IFN-β should be continued.

The incidence and character of injection site complications depends on the route of administration. Cutaneous reactions range from mild irritation to necrosis (IFNB Multiple Sclerosis Study Group, 1995; Jacobs et al., 1996; Ebers et al., 1998; Kappos et al., 1998). Generally, intramuscular injection causes less skin reactions, and so far no necroses have been reported. On the other hand, however, i.m. injection may be complicated by abscess formation.

The development of other autoimmune diseases is a rare but documented side effect of IFN-α therapy. Several cases of similar complications recently reported for IFN-β include myasthenia gravis, hyper- and hypothyroidism, Raynaud's phenomenon, autoimmune hepatitis, rheumatoid arthritis, and lupus erythematosus. Since autoimmune complications may be serious, other immunoactive drugs should be considered for MS patients with known autoimmune thyroid dysfunction or other autoimmune diseases.

A single case of a capillary-leak syndrome (CLS) associated with a pre-existing C1-esterase-inhibitor (C1-INH) deficiency and a monoclonal gammopathy in a patient treated with 8 MIU IFN-β-1b has been reported. The patient died within 80 hours postinjection due to shock and multiorgan failure (Schmidt et al., 1999). IFN-β should not be prescribed in MS if the patient's history or blood tests suggest a concomitant disease with abnormalities of the complement system or increased B-cell activation (e.g. monoclonal gammopathy of unknown significance).

Both IFN-β-1b and IFN-β-1a may be associated with a worsening of psoriasis vulgaris. Very rarely, anaphylaxis or shock may occur.

During therapy with IFN-β, patients may develop antibodies that neutralize its biological effects. Such neutralizing antibodies have been observed in MS patients treated with IFN-β-1b and in patients treated with IFN-β-1a (Jacobs et al., 1996; IFNB Multiple Sclerosis Study Group and UBC MS/MRI Analysis Group 1996; Ebers et al., 1998; Kappos et al., 1998; Khan & Dhib-Jalbut, 1998; Yong et al., 1998; Rudick et al., 1998b). The clinical significance of the neutralizing antibodies remains uncertain. It seems clear that they may attenuate or abolish the treatment effect. However, the following points should be considered. First, although the reported incidence of neutralizing antibodies varies between trials, the results of different trials are definitely not directly comparable because of different assays, cut-off levels and/or methods for confirmation of antibody positivity. Secondly, there are no reliable criteria to predict whether individual patients will develop neutralizing antibodies. Thirdly, antibody titres may fluctuate widely in individual patients. Notably, the antibodies may completely disappear despite continued treatment. Fourthly, some antibodies to IFN-β may serve as carriers, prolonging the half-life for biologic activity and enhancing the bioactivity.

Copolymer-1 (COP-1; glatiramer acetate)

Copolymer-1 (COP-1) is a rather unique immunomodulatory agent used for treatment of patients with relapsing MS. It is a synthetic basic random copolymer of L-glutamic acid, L-lysine, L-alanine, and L-tyrosine in a milar residue ratio of 0.14:0.34:0.43:0.1 and an average molecular mass of 4700–11 000 Da. COP-1 was originally studied along with other basic copolymers in an attempt to simulate the activity of MBP in inducing EAE, but was then found to suppress EAE in various species including the guinea pig, rabbit, mouse, rhesus monkey, and baboon (for review see Arnon et al., 1996).

It has been proposed that COP-1 competes with MBP and perhaps, other myelin autoantigens for binding to MHC class II molecules expressed on antigen-presenting cells (APC) (Arnon et al., 1996). COP-1 binds promiscuously to purified HLA-DR molecules (Fridkis-Hareli & Strominger, 1998). This would place COP-1 in the category of MHC inhibitors. Since D-COP-1, a stereoisomeric form of COP-1, binds as efficiently to MHC class II molecules as COP-1 but does not inhibit EAE, MHC binding seems to be a necessary but insufficient step that must be followed by a more specific step such as induction of regulatory cells or T-cell receptor antagonism.

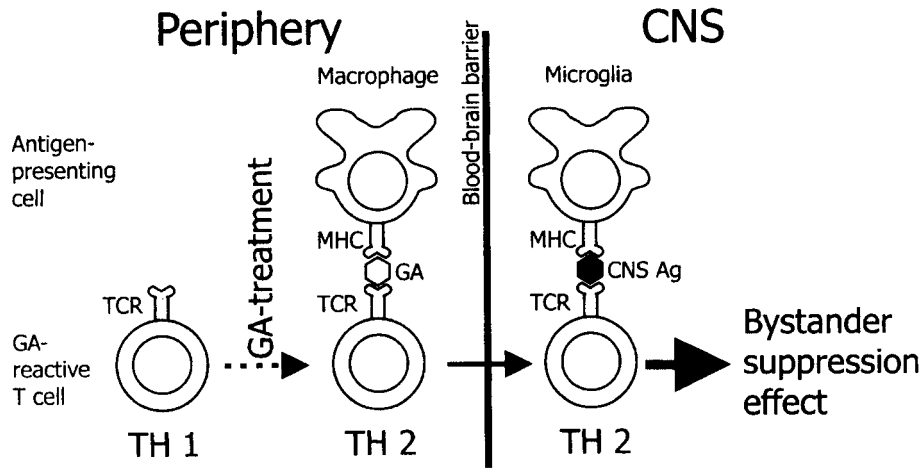

Fig. 93.1. Schematic view of the putative mechanism of action of glatiramer acetate (GA) (Neuhaus et al., 2001). In the periphery, outside the CNS, GA initially stimulates a population of TH1-like T-cells. During treatment, the properties of the GA-stimulated T-cells change, and they become more TH2-like (dotted arrow). The activated GA-specific T-cells enter the CNS, where they encounter CNS antigens like MBP bound to MHC class II and presented on the surface of microglia cells. The GA-reactive T-cells are stimulated to secrete down-modulatory cytokines like IL-4, which exert a bystander suppressive effect on other T-cells. TCR = T-cell receptor; MHC = major histocompatibility complex; Ag = antigen.

It is difficult to understand how COP-1 can compete with myelin antigens for MHC binding at the subcutaneous injection site. In this regard, the actions of COP-1 in MS may differ from those in EAE. In MS, COP-1 is abundantly available at subcutaneous injection sites. It is unlikely, however, that COP-1 peptides reach the brain. On the other hand, the repeated subcutaneous 'immunization' with COP-1 seems to induce a population of COP-1-reactive regulatory T-cells of the so-called TH2 type (Neuhaus et al., 2000). Since activated T-cells can traverse the blood–brain barrier (Wekerle et al., 1986), these COP-1-reactive regulatory cells should be able to reach the brain parenchyma and particularly, MS lesions. Here, they will be confronted with myelin degradation products, including MBP peptides bound to MHC molecules expressed on the surface of perivascular microglia and secondarily recruited macrophages. It can be further postulated that upon recognition of cross-reactive MBP, the COP-1 reactive 'suppressor' T-cells are activated (or modulated) to exert their down-regulatory functions. The suppressive effect might extend to T-cell responses against other myelin antigens, e.g., PLP ('bystander suppression; Fig. 93.1) (Neuhaus et al., 2001).

Conversely, systemically circulating MBP-reactive T-cells might be altered (e.g. down-regulated, 'tolerized', or shifted in cytokine profile) after recognition of cross-reactive components of COP-1 in the periphery. Indeed, there is some evidence that COP-1 peptides can act as 'altered peptide ligands' (APL) or 'T-cell receptor antagonists' on MBP-specific T-cells (Aharoni, et al., 1999). In vitro, human T-cells specific for MBP epitope 82-100 were inhibited when they were cocultured with APC pulsed with MBP and APC pulsed with COP-1, suggesting a TCR-antagonistic effect of COP-1 (Aharoni et al., 1999). Note that in contrast to MHC competition and TCR antagonism, APL-like effects do not require the simultaneous exposure of T-cells to both COP-1 and MBP. Therefore, APL effects could occur in the periphery at subcutaneous injection sites. After exposure to COP-1 in the periphery, MBP-specific T-cells might be altered in their properties and respond differently when they encounter their original antigen MBP in the brain (O. Neuhaus et al., unpublished data).

The therapeutic effects of COP-1 are reviewed in Chapter 99.

Intravenous immunoglobulins

Intravenous immunoglobulins have been widely used for therapy of neuroimmunological diseases, including neuromuscular disorders and multiple sclerosis (Said, 2000). Based on the first experience of i.v. Ig in idiopathic thrombocytopenic purpura, i.v. Ig is usually given as a cycle of 5 consecutive days of 0.4 g/kg body weight (summing up to a total of 2 g/kg body weight) in acute neuromuscular disorders (like Guillain–Barré syndrome). Whether a reduction of the dose or shortening of the cycle

Table 93.4a. Side effects of i.v. Ig therapy

Reported side effects of i.v. Ig therapy
Mild
Myalgia
Headache
Nausea
Fever
Malaise
Loss of appetite
Erythema
Superficial venous thrombosis
Transient liver function disturbance
Severe
Anaphylactic reaction
Transmission of hepatitis C
Acute renal failure
Alopecia
Retinal necrosis
Cerebral thromboembolic events
Myocardial thromboembolic events
Aseptic meningitis (mostly neutrophil pleocytosis)
Cerebral vasospasm
Hemolytic anemia
Neutropenia
Arthritis

Source: From Voltz and Hohlfeld (1996).

Table 93.4b: Recommended laboratory tests before treatment with i.v. Ig

Recommended laboratory tests before treatment with i.v. Ig
Renal function, e.g.
Serum: creatinine, Na, K
Urine: protein
Serology
Hepatitis
Other relevant, including CSF/serum index
e.g. *Campylobacter* in GBS
Other lab tests
ESR
Blood group
'Cross-match' of i.v. IG with patient's blood
IgA
Important points in history
IgA deficiency
Renal insufficiency
Previous side effects with i.v. Ig
Fructose intolerance
Diabetes mellitus

Source: From Voltz and Hohlfeld (1996).

would be similarly efficacious, has not been tested in controlled studies. In chronic treatment (like for CIDP), however, there is no reason why i.v. Ig should be given in 5-day cycles. Instead, impairment should be assessed in regular intervals, e.g. every 6 weeks (or less or more often, depending on the course) and at these intervals the dose should be adjusted according to the clinical course and individual response. In this manner, the dose of i.v. Ig is 'titrated' to the individual need of the patient.

The mode of action of i.v. Ig is still incompletely understood. Several early and long-term effects are considered, like blockade of Fc receptors, neutralization of circulating antibodies, or increased clearance of immune complexes. Which of these play a role in a given disease is still unknown.

Generally, i.v. Ig therapy is well tolerated and considered safe. However, there are reports of mild side effects in 1–15% of patients treated. In addition, occasional severe side effects including nephrotoxicity have been reported, which must be closely monitored in patients treated with i.v. Ig (list of reported side effects in Table 93.4a (Voltz & Hohlfeld, 1996)).

To minimize the risk of hepatitis C infections, anti-HCV-positive donors must be identified and excluded because chronic hepatitis C infection may be undiagnosed in potential donors. In the third generation of i.v. Ig preparations an additional virus inactivation step is included which does not alter the functional activity of the product. If fructose intolerance or diabetes is known in a patient, a choice may be made from different i.v. Ig preparations with different fructose or glucose contents.

Before treatment with i.v. Ig, the laboratory tests shown in Table 93.4b should be obtained: renal function, hepatitis serology, and other tests which will be distorted by i.v. Ig (Voltz & Hohlfeld, 1996). Because of the possibility of severe hemolytic anemia due to hemolytic antibodies, it has been advised to cross-match all patients' blood with the i.v. Ig preparation to be used. If IgA deficiency is suspected (i.e. when ataxia telangiectasia is present), IgA should be measured. If IgA deficiency is present (incidence about 1:1000), there is a 30% risk of having anti-IgA antibodies. The actual risk of developing anaphylactic reactions to i.v. Ig is not known. Whether to give i.v. Ig or switch to another treatment option, must be weighed individually.

Mild side effects may be abolished just by slowing the infusion rate. If severe side effects occur, i.v. Ig must be stopped and an alternative treatment considered. If necessary, immunomodulatory treatment with i.v. Ig can be continued through pregnancy.

Invasive immunomodulatory procedures

Plasmapheresis

During the 1980s, plasmapheresis (therapeutic plasma exchange) was tested and used in many neurological and neuroimmunological disorders. More recently, therapy with i.v. Ig has replaced plasmapheresis for many of the original indications, owing mainly to the better tolerability and more convenient application of i.v. Ig.

There are two major techniques of therapeutic plasmapheresis: plasma separation by a centrifugal plasma separator, and plasma separation by membrane filtration. A typical plasmapheresis protocol employs three to five exchanges of one or 1.5 plasma volumes per week until the patient shows satisfactory improvement. Usually, plasma exchange therapy is combined with immunosuppressive treatment, e.g. a combination of corticosteroids and azathioprine.

In the treatment of autoimmune diseases, plasmapheresis aims at the removal of circulating autoantibodies, inflammatory mediators, or both. One of best-established indications for therapeutic plasma exchange is the critical deterioration of generalized weakness in patients with myasthenia gravis (Hohlfeld et al., 1996). In MG, early clinical effects of plasmapheresis are occasionally observed in less than 24 hours. Such immediate improvement is probably due to the removal of those autoantibodies that have a direct functional effect on the ACh receptor. Often, the effects of plasmapheresis are more delayed and become obvious only after 2 or more days. This delayed improvement is usually due to the removal of antibodies that act indirectly, for example by increased receptor turnover or by complement-mediated lysis of the postsynaptic membrane.

Although there is practically no age limit for plasmapheresis if the patient is in good general health, it is the elderly patient with multiorgan disease who carries an increased risk for developing severe complications. The complications of plasmapheresis include cardiovascular systemic reactions, electrolyte disturbances, and infections. Thrombophlebitis, thromboses, pulmonary embolism, and subacute bacterial endocarditis have been observed, particularly in patients who have had arteriovenous shunts or grafts placed for vascular access. Bacterial respiratory tract infections are a common problem in myasthenic crisis. Immunoglobulin depletion after plasmapheresis may further decrease resistance to infection. In patients with infection, i.v. Ig is the preferred treatment for imminent or manifest myasthenic crisis.

Early administration of appropriate antibiotics is recommended in patients who develop infections during or after plasma exchange therapy. Intravenous immunoglobulins of both IgG and IgM isotype should be replaced in these patients. Serious infections may occur after plasma exchange in patients who were severely immunosuppressed, e.g., with cyclophosphamide. It is important to note that the removal of clotting factors during plasmapheresis results in impairment of hemostasis for about 24 hours.

As an alternative to standard plasmapheresis, selective immunoadsorption by tryptophan-linked polyvinylalcohol gels has been introduced. In MG, this procedure is as efficient as plasmapheresis (Yeh & Chiu, 2000). Since there is negligible adsorption of albumin, protein substitution is not required.

Thymectomy

Thymectomy is a form of invasive immunomodulatory treatment used in myasthenia gravis. Although there has never been a prospective controlled clinical trial of thymectomy in MG, this form of treatment has been found useful empirically and is widely applied. Because controlled studies are lacking, many questions regarding thymectomy cannot be answered conclusively. A recent survey reflects the limits of our knowledge and the present clinical practice in carrying out thymectomy (Gronseth & Barohn, 2000). Most reports did not show any correlation between the severity of myasthenic symptoms before surgery and the timing or degree of improvement after surgery. The time of the beginning of clinical improvement after thymectomy was relatively variable, and many patients improved only after several years. Most studies report better responses when thymectomy is performed early in the disease but the mechanism which produces benefit in MG is still uncertain (Gronseth & Barohn, 2000).

There is no consensus about the lower and upper age limits for thymectomy, the indication for thymectomy in pure ocular myasthenia, or the benefit of early or late thymectomy as compared with the natural course of MG (Lanska, 1990). However, a number of clinical recommendations seem reasonable in light of the available experience.

(i) The best results may be expected in patients between 10 and 40 years of age with relatively recent onset of MG (within 3–5 years).
(ii) Men have about the same chance to improve as women.

(iii) Improvement usually begins months to years after thymectomy, although it occasionally may become apparent within days or weeks. Rarely, late relapses occur in patients who experienced remission after thymectomy. It is possible that this is related to immunological activity or regrowth of thymic tissue that may not have been completely removed at surgery.
(iv) Children between 1 and 5 years are usually not submitted to thymectomy. There is no consensus about thymectomy in children between 6 and 10 years of age (Lanska, 1990).
(v) Patients with pure ocular myasthenia are usually excluded from thymectomy unless other therapies have proved unsuccessful or generalized symptoms appear. However, one study reported that thymectomy resulted in significant improvement in 80% of patients with MG confined to the ocular muscles (Schumm et al., 1985).
(vi) Patients older than 60–65 years are usually not thymectomized, except for thymoma.
(vii) Thymoma is generally considered an absolute indication for thymectomy.

The most widely performed surgical approach to the thymus is transsternal. A transcervical approach is not recommended because it does not ensure the removal of ectopic thymic tissue that may be widely distributed in the neck and mediastinum. When properly performed, thymectomy has a low mortality rate that is essentially that of anesthesia. However, it should be performed in a center with extensive experience and a neuromuscular consultant available. In patients with stable disease and after appropriate preparation (see above sections), the operation is very safe, and severe perioperative complications are virtually absent (less than 1%).

Bone marrow and stem cell transplantation

Recent advances in immunobiology and transplantation medicine have made it possible to mobilise, isolate and successfully transplant autologous hematopoetic stem cells. Prior to transplantation, the immune system of the recipient is ablated by aggressive chemotherapy. In the best and most experienced centres, the acute mortality of this procedure is now below 5%. For this and other reasons, autologous blood and marrow stem cell transplantation has been considered as a treatment option for autoimmune diseases. For example, international guidelines have been developed for autologous stem cell transplantation in MS (Comi et al., 2000). However, this approach faces not only clinical but also conceptual problems. For example, several reports have shown that after allogenic BMT, MS can exacerbate or even develop de novo in the transplant recipients (Jeffery & Alshami, 1998; Kelly et al., 1996). Needless to say, transplantation may be followed by serious early and late complications such as infections and tumours (Anderson et al., 1990). Further, one should consider the possibility that the transplanted autologous stem cells reconstitute not only the normal immune functions, but also the autoimmune component. For all these reasons, great scepticism and extreme caution are necessary when considering autologous stem cell transplantation as a treatment for MS.

Future developments

Advances in biotechnology have promoted the development of a new class of biotechnological products for immunotherapy and even immunological gene therapy. These biotechnological agents are used to manipulate the immune system by selectively mimicking, inhibiting, or otherwise interacting with naturally occurring polypeptides or oligonucleotides. A comprehensive review of these agents is beyond the scope of this chapter. Recent overviews on the subject may be found in (Hohlfeld, 1997; Compston et al., 1998; Weilbach & Gold, 1999; Hohlfeld, 1999) (Table 93.5). Some of the new biotechnological agents hold the promise of an unprecedented selectivity of action. However, these agents also present a number of specific problems, ranging from inconvenient application (by s.c., i.m., or i.v. injection) to immunogenicity (stimulation of neutralizing antibodies). Thus, it is obvious that biotechnological agents are not necessarily superior to chemical immunomodulators.

Ideally, immunotherapy would not have to be applied indefinitely, but only for a limited, short time to achieve a permanent result. Such tolerance-inducing therapy has indeed been achieved in experimental situations, especially in transplantation. These experiments demonstrate that it is possible to achieve a state of permanent and selective immune tolerance by combining different immunological manipulations. By analogy, it may be possible to 'silence' an ongoing immune reaction permanently by combining different immunotherapies. Possible approaches include combinations of antileukocyte differentiation antigens, combinations of anti-costimulatory agents, and various strategies for 'immune deviation' (Hohlfeld, 1997).

The introduction of interferon-β for the treatment of multiple sclerosis heralds a new era of immunomodulatory phamacotherapy. Interferon-β is the first approved cytokine therapy for any human autoimmune disease. However, the initial hope that the success of this agent would usher in a multitude of new cytokine therapies not been fulfilled so far.

Table 93.5. Biotechnological agents and experimental approaches for the immunomodulatory therapy of MS

Immunosuppressive agents
Anti-CD3 mAbs
Anti-CD4 mAbs
Anti-CD53 mAb (Campath-1H)
Anti-interleukin-2 receptor α-subunit mAbs (e.g. Daclizumab, Basiliximab)

Cytokines and cytokine inhibitors
Interferons
Interferon β-1a
Interferon β-1b
Interferon-α
Other interferons

TNF inhibitors
*TNF-receptor-IgG soluble dimeric p-55 (Lenercept^{R})
*Anti-TNF human/murine chimeric mAb cA2
Metalloprotease inhibitors (e.g. BB-3644)

Down-regulatory cytokines
Interleukin-1 inhibitors
Interleukin-4
Interleukin-10
Interleukin-13
*TGF-β2(BetaKine^{R})

Chemokine antagonists and -receptor blockers
Neurotactin antagonist
MCP-1 receptor antagonist
CXCR3 receptor antagonist
CCR1 receptor antagonist
CCR5 receptor antagonist

Therapies directed at cell interaction molecules
Adhesion molecules
Humanized anti-CD11/CD18 mAb (Hu23F2G)
Antagonistic peptide inhibitors of integrins
Anti-VLA-4 and anti-α4 integrin mAbs or peptide inhibitors
Anti-ICAM-1 (CD54) mAb

Costimulatory molecules
Anti-CD2 mAb
Anti-LFA-3 (CD58) mAb
Anti-CD154 mAb
CTLA4-Ig
Anti-CD45 mAb

Immunotherapies targeting the 'trimolecular complex'
Copolymer-1
MHC blockers
Altered peptide ligands (so far mostly MBP analogues)
*Oral tolerance (oral bovine myelin)
Other strategies of tolerance induction by modification of antigen presentation
Vaccination with T-cells or TCR peptides
Anti-TCR mAbs

Agents affecting both the immune and nervous systems (see Chapter by Scolding)
e.g. Neurotrophic factors

Notes:
Most treatments are experimental.
FDA-approved agents are printed in bold.
*Asterisk denotes treatments that were shown to be ineffective or unfavourable, or had unacceptable toxic effects.
Source: From Hohlfeld (1997); Weilbach and Gold (1999).

None of the other cytokines tested in pilot trials was truly promising, let alone superior to interferon-β. On the contrary, not only were trials with a soluble receptor for tumour necrosis factor-(TNF-)-α, and with an antibody against TNF-alpha, negative, but they showed clear evidence of treatment-induced exacerbation (Arnason et al., 1999). These results were completely unexpected in light of existing evidence that TNF-α is involved in MS pathogenesis, and that anti-TNF therapies previously worked in animal models (Arnason et al., 1999).

Selective, antigen-specific immunotherapies target the trimolecular complex (TMC) of T-cell stimulation, which is part of the 'immunological synapse' (Fig. 93.2). In principle, each component of the TMC can be targeted. The major histocompatibility (MHC) molecule could be blocked by anti-MHC antibodies or 'blocking peptides'; the antigen (or antigenic peptide) could be applied in such a way that the autoreactive T-cells are inhibited rather than stimulated; and the T-cell receptor (TCR) could be targeted with anti-TCR antibodies or by T-cell or TCR peptide vaccination. Although such antigen-selective immunotherapy may seem very promising, it poses a number of special problems. For example, it has been shown that the T-cell response to various candidate CNS autoantigens is much more complex in humans than it is in certain inbred rodent strains. This implies that selective immunotherapy needs to be 'individualized' (tailored for individual patients). Furthermore, there is growing evidence that the auto-

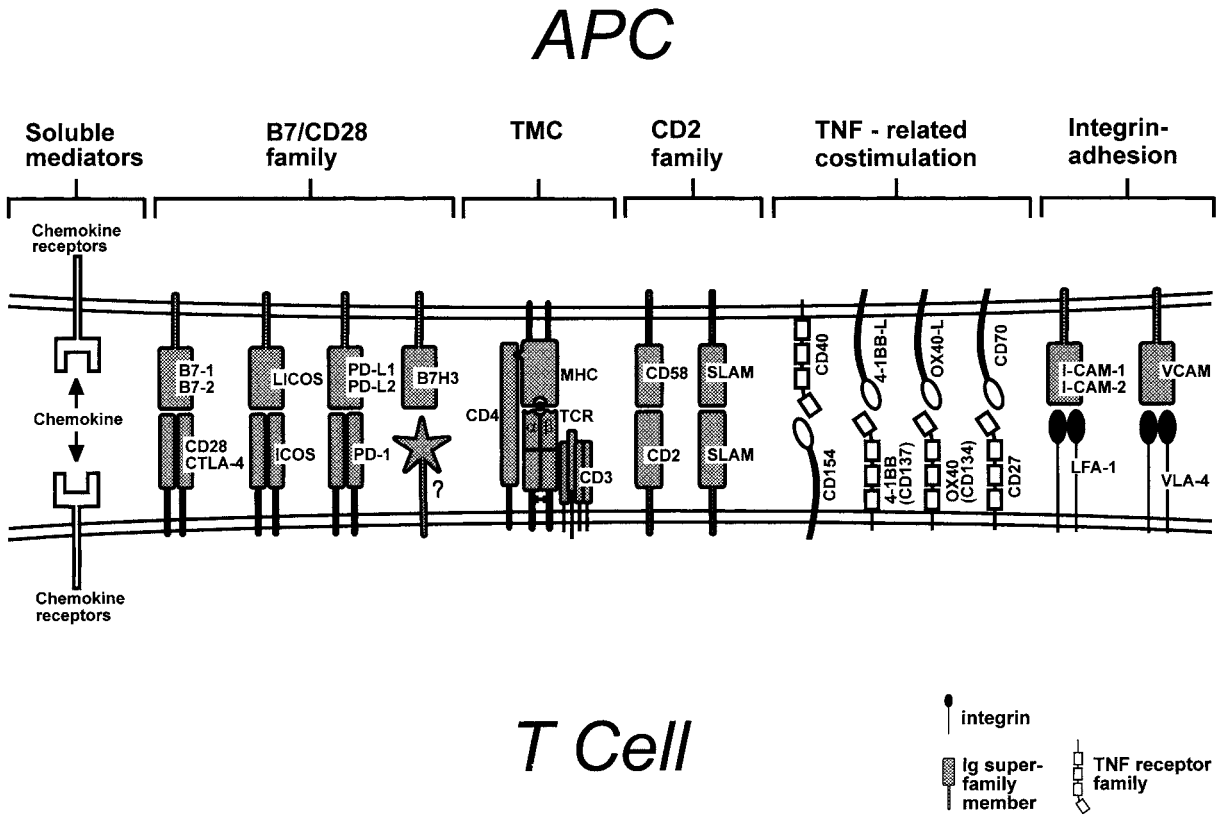

Fig. 93.2. Schematic view of the 'immunological synapse' (Molecular interactions at the interface between a CD4+ T-cell (bottom) and an antigen-presenting cell (APC; top); Hohlfeld, 1997). Antigen-specificity is conferred by the clonotypic T-cell receptor (TCR) that recognizes an antigen peptide (black dot) bound to an MHC class II molecule (trimolecular complex, TMC; centre). Signal transduction is mediated by the invariant proteins of the CD3 complex associated with the TCR. In addition to antigen-specific signalling via the TCR/CD3 complex, various costimulatory signals are transmitted by interactions between costimulatory molecules and their ligands (e.g. CD40 and CD40-L; CD28/CTLA-4 and B7-1/B7-2), or between cytokines and their receptors (left). Large arrows indicate direction of signalling. Interactions between various adhesion molecules strengthen the contact between the T-cell and the APC (right). Most adhesion and costimulatory molecules belong to either the integrin or immunoglobulin family.

immune response is not static but dynamic. For example, the autoimmune response may spread to include new autoantigens over time ('epitope spreading').

Thus far, copaxone is the only approved agent in the category of (semi)-selective, antigen-directed agents (Neuhaus et al., 2001). The synthesis of COP-1 was modelled after myelin basic protein (MBP), a prime candidate autoantigen of MS. Other agents in the same category of selective immunomodulators include an altered peptide ligand (APL) of MBP, soluble complex of MBP-peptide bound to the MS-associated HLA molecule DR2, and oral myelin preparations for induction of oral tolerance. Except for COP-1, none of these putatively selective therapies has so far proven a truly convincing clinical benefit to MS patients (Hohlfeld & Wiendl, 2001). On the contrary, two phase II trials of an APL called CGP77116 or NB 5788, derived from MBP peptide 83–99, had to be halted prematurely because of allergic reactions and clinical exacerbations of MS (Kappos et al., 2000; Bielekova et al., 2000).

For the future, it is to be hoped that new techniques will continue to advance our understanding of the immunopathogenesis of neurological autoimmune disorders, and that these advances in knowledge can be rapidly translated into therapeutic applications.

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94

Vasculitis of the central nervous system

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Vasculitis of the CNS presents one of the great diagnostic and therapeutic challenges in neurology. Diagnosing CNS vasculitis is difficult because the most common presenting symptoms, headache and mental status changes, are nonspecific. Moreover, almost any CNS abnormality including isolated dementia and intracerebral hemorrhage can occasionally be the result of CNS vasculitis. No imaging study is specific for CNS vasculitis, and even brain biopsies can be falsely negative in this condition. Designing treatment for CNS vasculitis is also difficult, as the rarity of the diagnosis has prevented the large treatment trials needed to define optimal therapy. Despite all of these challenges, the last two decades have yielded substantial information about the diagnosis and treatment of this disease. Guidelines are now possible to help physicians know when to suspect the disease, how to recognize the limits of imaging studies, how to identify the disorders that can mimic CNS vasculitis, and how to initiate therapy.

Classification and definition of terms

CNS vasculitis is not one disease but a collection of disorders (Calabrese et al., 1997; Lie, 1997; Moore, 1988). Traditionally, the classification of CNS vasculitis (Table 94.1) recognizes two main groups: primary disorders, which have no known cause, and secondary disorders, which are associated with identifiable diseases such as systemic lupus erythematosus or infection (Calabrese et al., 1997; Lie, 1997). Many designations have been applied to primary CNS vasculitis (Table 94.2), all of which have inevitable flaws. The term granulomatous angiitis of the central nervous system, for example, is inaccurate because less than half of the cases of primary CNS vasculitis demonstrate granulomas (Lie, 1997).This chapter bows to tradition and employs the term primary angiitis of the central nervous system (PACNS).

Table 94.1. Classification of vasculitis of the CNS

I.	Primary
	A. Histologically defined angiitis of the CNS
	B. Angiographically defined angiopathy of the CNS
II.	Secondary (e.g. SLE, Wegener's granulomatosis)

Table 94.2. Designations used in the medical literature for primary CNS vasculitis[a]

Name	Abbreviation
Primary angiitis of the CNS	PACNS
Isolated angiitis of the CNS	IACNS
Granulomatous angiitis of the CNS	GACNS
Benign angiopathy of the CNS	BACNS
Angiographically defined angiopathy of the CNS	ADACNS
Histologically defined angiitis of the CNS	HDACNS
Non-infections granulomatous angiitis of the CNS	
Granulomatous angiitis of the nervous system	GANS
Idiopathic granulomatous angiitis of the CNS	IGAMS

Note:
[a] From Woolfenden (1998); Lie (1997).

However, even this term has shortcomings: it has been applied both to cases that are biopsy proven and also to cases defined only by angiographic abnormalities. Since no angiographic abnormality is absolutely specific for vasculitis, and because cases of PACNS diagnosed by biopsy differ in important ways from those diagnosed angiographically (Calabrese et al., 1997), this chapter acknowledges these differences by also using the terms angiographically defined angiopathy of the CNS (ADACNS) and histologically defined

angiitis of the CNS (HDACNS), as proposed by Woolfenden (Woolfenden et al., 1998).

Historical perspective

The first cases of CNS vasculitis were described in 1922 (Harbitz, 1922). This report concerned two patients: a 26-year-old woman with headaches, encephalopathy, and ataxia whose condition worsened over 2 years to stupor, coma, and death; and a 46-year-old man with mental status changes and hallucinations progressing to coma and death over 9 months. Postmorten examination in both cases demonstrated granulomatous angiitis of the leptomeningeal arteries and veins (Harbitz, 1922). Nearly four decades later, Cravioto and Feigin first recognized that PACNS constituted a separate form of vasculitis and were the first to delineate its distinct features (Cravioto & Feigin, 1959). As recently as 1986 there had been only 46 cases of PACNS described in the medical literature, emphasizing how rarely the disorder was diagnosed (Calabrese, et al., 1997; Younger et al., 1997).

Increasing awareness of the disorder and advances in neuroimaging resulted in a total of approximately 200 cases reported in the medical literature by 1997 (Calabrese et al., 1997). Still, the relative rarity of CNS vasculitis is indicated by the fact that PACNS accounted for 1.2% of 2680 cases of all types of vasculitis at one centre (Lie, 1997).

Etiology and pathogenesis

The cause of PACNS is unknown (Calabrese et al., 1997; Lie, 1997; Moore, 1988; Younger et al., 1997). Efforts to define the pathogenesis have been hampered by the disorder's rarity and the infrequency with which histopathological specimens are obtained. Most theories about the etiology and pathogenesis of PACNS have focused on infections, altered immunity, and environmental toxins (Calabrese & Mallek, 1987; Calabrese et al., 1997; Lie, 1997). A variety of bacteria, fungi, and viruses are capable of causing vasculitis of the CNS (see below) (Arthur & Margolis, 1977; Calabrese et al., 1997; Reyes et al., 1976). However, in most PACNS cases no infection is identifiable by culture, immunochemical stains, or polymerase chain reaction (PCR) (Calabrese et al., 1997; Lie, 1997). The occurrence of CNS vasculitis in association with Hodgkin's disease suggested that immunodeficiency states might cause some cases of PACNS (Calabrese et al., 1997). It is recognized now, however, that immunodeficiency simply permits infections (especially with varicella-zoster virus), which are the usual case of CNS vasculitis associated with Hodgkin's disease (Calabrese et al., 1997). The association of CNS vasculitis with other rheumatic diseases, including systemic lupus erythematosus, Wegener's granulomatosis, and Cogan's syndrome, has suggested autoimmunity as a cause of PACNS. The presence of granulomatous inflammation implicates cellular immune processes. Immune complexes and autoantibodies have not been found in tissue samples (Moore, 1989b; Moore, 1995). Unspecified environmental toxins have been implicated by the number of cases associated with drug use, particularly cocaine, ephedrine, and amphetamines (see below) (Calabrese et al., 1997; Lie, 1997; Younger et al., 1997).

Pathology

PACNS affects medium- and small-sized arteries and arterioles of the brain and spinal cord. Veins are infrequently involved. Although the lesions can be distributed widely, the leptomeninges and cerebral cortex are involved most frequently (Calabrese et al., 1997; Lie, 1997; McCormick & Neuberger, 1958; Moore & Fauci, 1981). Vasculitic lesions contain predominantly lymphocytes, with variable numbers of eosinophils, neutrophils, histiocytes, and plasma cells (Lie, 1997). No immunohistological studies of the inflammatory infiltrates in PACNS have been reported, so the precise nature of the lymphocytic infiltrate remains undefined. Inflammatory cells infiltrate all layers of the arteries and cause fibrinoid necrosis in some specimens (approximately 25%) (Lie, 1997). Fewer than half of the lesions in PACNS demonstrate granulomatous inflammation with Langhans or foreign-body type multinucleated giant cells (Lie, 1997). The inflammation spreads along the vessel in a discontinuous fashion, characterized by skip lesions (Lie, 1997). Variable degrees of inflammation and healing (as manifested by intimal fibrosis) can often be demonstrated in different sites within the same biopsy specimen, indicating that the lesions develop or progress at different rates (Lie, 1997). Aneurysmal formation occurs much less often in PACNS than in polyarteritis nodosa. Thrombosis and vessel rupture can lead to infarction and hemorrhage of the CNS (Lie, 1997).

Clinical features

Symptoms and signs

Several authorities have argued persuasively that the clinical features of HDACNS differ from those of ADACNS

Table 94.3. Clinical and laboratory features of PACNS based on the method of diagnosis[a]

	HDACNS	ADACNS	*P*
Sex, no. (%)			
Males	78 (69.0)	17 (30.8)	<0.001
Females	38 (31.0)	38 (69.1)	
Age, mean ± SD	46 ± 17	33 ± 14	<0.001
Headache, no. (%)			
Yes	63 (55.8)	43 (78.2)	
No	50 (44.3)	12 (21.8)	
Stroke, no. (%)			
Yes	13 (13.5)	15 (32.6)	<0.008
No	83 (86.5)	31 (67.4)	
Seizure, no. (%)			
Yes	29 (30.2)	11 (23.9)	
No	67 (69.8)	35 (76.1)	
Cerebral hemorrhage, no. (%)			
Yes	13 (11.5)	5 (9.1)	
No	100 (88.5)	50 (90.9)	
Diffuse neurologic dysfunction, no. (%)			
Yes	77 (68.1)	26 (47.3)	<0.009
No	36 (31.9)	29 (52.7)	
Decreased cognition, no. (%)			
Yes	64 (83.1)	20 (76.9)	
No	13 (16.9)	6 (23.1)	
Days from symptom onset to diagnosis, mean ± SD	170 ± 261	46 ± 73	<0.001
Abnormal CSF (%)	80–90	50–53	<0.005

Notes:

[a] An abnormal cerebrospinal fluid (CSF) sample had >5 cells/mm^3 and/or protein >55 mg%. PACNS = primary angiitis of the central nervous system.

HDACNS: histologically defined angiitis of the CNS.

ADACNS: angiographically defined angiopathy of the CNS.

Source: (Modified from Calabrese, 1997; p. 1190 Table. 2).

(Calabrese et al., 1997; Lie, 1997; Vollmer et al., 1993; Younger et al., 1997). Therefore, these two entities are discussed separately (Table 94.3).

HDACNS preferentially affects middle-aged men. Men are affected about twice as often as women (Calabrese et al., 1997). Although HDACNS may strike at any age, the mean age at onset is 46. Headaches and diffuse neurologic dysfunction as manifested by encephalopathy constitute the most common presenting features (Calabrese et al., 1997; Ferro, 1998; Moore, 1989a; Vollmer et al., 1993). Focal neurological deficits eventually develop in about half of the patients; yet strokes are present in less than 20% at onset of the disease and are almost always accompanied by diffuse neurologic dysfunction (Vollmer et al., 1993). Strokes in the absence of diffuse cortical dysfunction are distinctly unusual for HDACNS (Vollmer et al., 1993). Brainstem or cranial nerve dysfunction develops in 40% of HDACNS patients, and seizures in 25% (Vollmer et al., 1993). Isolated dementia rarely develops in HDACNS (Vollmer et al., 1993). Spinal cord disease, manifested by myelopathy, develops in about 15% (Calabrese et al., 1997; Vollmer et al., 1993). The neurological manifestations of HDACNS typically unfold over 5–6 months before the diagnosis is made, but some cases develop more acutely (Calabrese et al., 1997). Only 20% of patients with HDACNS develop systemic symptoms or signs such as fever, weight loss, or sweats (Vollmer et al., 1993).

Common diagnostic tests are normal or yield non-specific abnormalities in HDACNS. Abnormalities of the serum hemoglobin level, the peripheral white blood cell count, and the erythrocyte sedimentation rate (ESR) occur in 17%, 42% and 65% of cases, respectively (Calabrese et al., 1997). The cerebrospinal fluid (CSF) is abnormal in approximately 88% of cases (Calabrese et al., 1997; Hellmann et al., 1992; Stone et al., 1994; Vollmer et al., 1993). The mean CSF protein level is 177 mg/dl, with a median of 100. A CSF lymphocytosis develops in about 65–75% of patients, with a mean cell count of 77/mm^3 (Calabrese et al., 1997). The CSF pleocytosis in HDACNS rarely exceeds 250 cells/mm^3 (Vollmer et al., 1993). Oligoclonal bands and increased CSF IgG synthesis have been reported in some patients with PACNS, but their diagnostic value has not been evaluated (Calabrese et al., 1997). Non-specific electroencephalogram (EEG) abnormalities occur in 93% of patients (Vollmer et al., 1993).

In comparison to HDACNS, ADACNS more frequently develops in young women (Table 94.3) (Calabrese et al., 1997). Some authors have speculated that the pathophysiology of ADACNS may relate more to a vasospasm-induced angiopathy than to true vasculitis (Calabrese et al., 1997). This has led to the occasional reference to 'benign' angiopathy of the CNS in the literature, an inappropriate term because the manifestations of ADACNS may include cerebrovascular accidents and other serious neurological events (Woolfenden et al., 1998). ADACNS is more likely to present with acute strokes (Table 94.3), but diffuse cortical dysfunction and CSF abnormalities occur less often than in HDACNS (Calabrese et al., 1997).

Imaging studies

Magnetic resonance imaging (MRI) almost always reveals abnormalities, albeit non-specific ones, in PACNS. Most

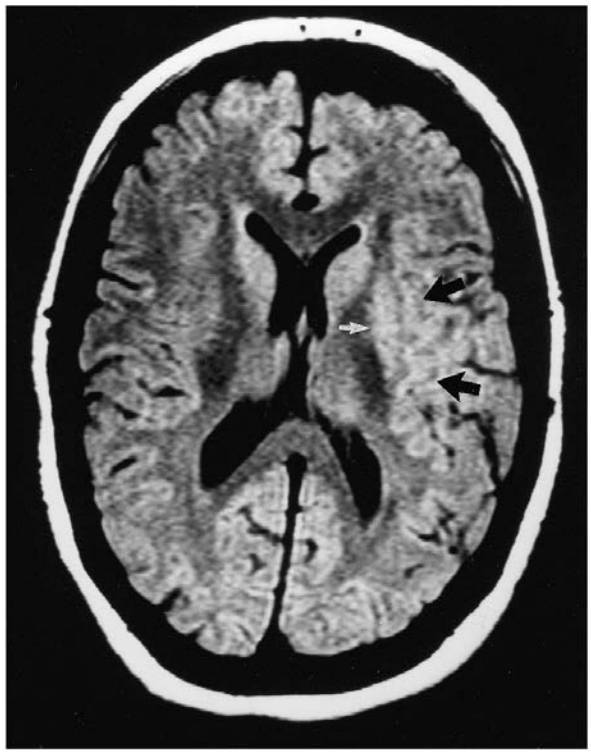

Fig. 94.1. MR in CNS vasculitis. Axial SE MR image (1500/30) shows high signal intensity in the left parietal cortex, subcortical white matter (*black arrows*), and in the left putamen (*white arrow*). (From Pomper, 1999 with permission.)

series report 100% sensitivity (Greenan et al., 1992; Harris et al., 1994; Vollmer et al., 1993; Woolfenden et al., 1998), but false-negative MR studies have been reported (Alhalabi & Moore, 1994; Pomper et al., 1999). Thus, a person with a completely normal MRI is unlikely to have PACNS. Having both a normal MR study and a normal CSF cell count and protein level virtually excludes the diagnosis (Hellmann et al., 1992; Stone et al., 1994). In general, CT is much less sensitive than MRI, detecting abnormalities in 50–68% of cases (Vollmer et al., 1993; Younger et al., 1997). However, CT is better than MRI at detecting hemorrhage (Harris et al., 1994).

On average, patients with PACNS have at least 3 MR lesions that are predominantly supratentorial and bilateral (Pomper et al., 1999) (Fig. 94.1). The most commonly involved regions are the subcortical white matter, followed by the deep grey matter, the deep white matter, and the cortex (Pomper et al., 1999). White matter lesions in PACNS are usually more irregular than those of multiple sclerosis which have an ovoid appearance and develop in the perivascular zones. Functional MRI has not been extensively studied but may be useful in separating vasculitic infarction from other processes. Yuh et al., suggest that perfusion imaging can assess microcirculating vasculopathy, and diffusion-weighted imagery may detect acute infarction, even when not visible on conventional T_2-weighted scans (Yuk et al., 1999; Miller et al., 1987). A minority of the MR lesions enhance after administration of contrast agents (Harris et al., 1994; Pomper et al., 1999). MR angiography is not usually helpful in evaluating patients with CNS vasculitis because the technique's resolution remains inadequate for the size of blood vessels typically affected by PACNS. The roles of SPECT and PET scanning have not been studied.

A variety of angiographic abnormalities occur in PACNS (Alhalabi & Moore, 1994; Calabrese et al., 1997; Ehsan et al., 1995; Hellmann et al., 1992; Hurst & Grossman, 1994; Pomper et al., 1999; Stein et al., 1987; Stone et al., 1994; Wynne et al., 1997). The most common abnormalities are alterations in the calibre of the arteries, including constriction, irregularity, and dilatation (Hurst & Grossman, 1994). 'Beading', produced by lesions of constriction or dilatation interspersed with normal areas, is the classic sign of PACNS (Fig. 94.2) (Hurst & Grossman, 1994). Stenoses range in length from a few millimetres to 3 centimetres (Alhalabi & Moore, 1994). Vasculitis of the CNS may also cause threadlike narrowing of vessels, cutoff signs, slowing of the circulation time, and delayed emptying of the arteries (Hurst & Grossman, 1994). Occlusions develop often, but microaneurysms are seen infrequently (Alhalabi & Moore, 1994). Over time, collateral vessels may develop. The most frequent sites of involvement are the middle and anterior cerebral arteries and their branches (Alhalabi & Moore, 1994). Posterior cerebral involvement occurs somewhat less often. Abnormalities proximal to the supraclinoid segment of the internal carotid artery occur rarely. Most cases demonstrate multiple, bilateral though not necessarily symmetrical lesions (Alhalabi & Moore, 1994). Lesions may be far more extensive than suggested by clinical findings (Alhalabi & Moore, 1994). Angiographic lesions are often more widespread than suggested by MR; only about half of the lesions seen on angiography have a corresponding lesion identified on MR (Pomper et al., 1999).

The sensitivity of angiography in PACNS has been reported to vary from 50–80% (Calabrese et al., 1997; Duna & Calabrese, 1995; Harris et al., 1994; Vollmer et al., 1993). Therefore, a normal CNS angiogram does not exclude the diagnosis of PACNS. Furthermore, unfortunately, even 'positive' angiograms are not specific for PACNS. Many conditions and disorders, including vasospasm, infection, emboli, radiation damage, hypercoagulable states, severe hypertension, pre-eclampsia, and drugs such as cocaine

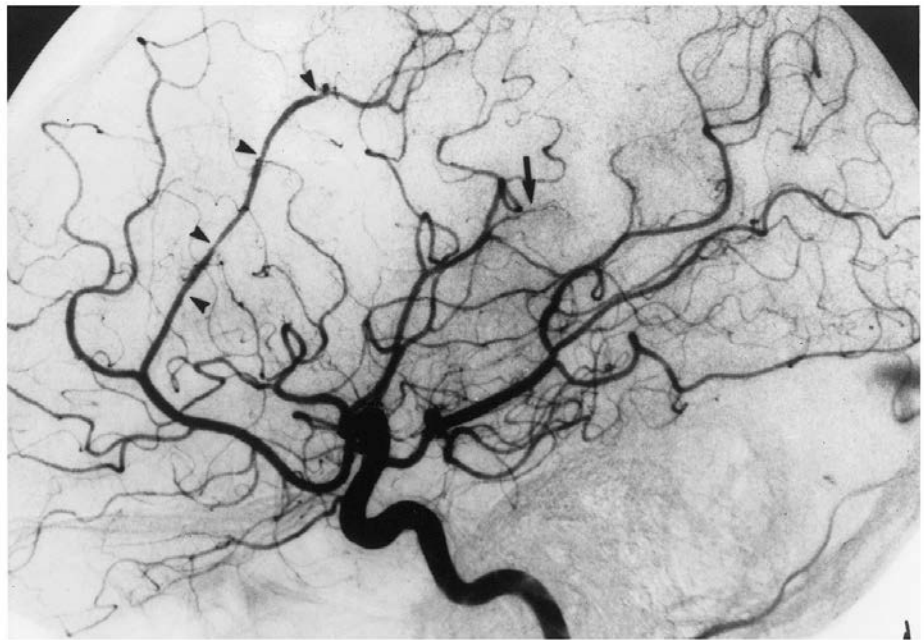

Fig. 94.2. Angiogram of the right internal carotid artery shows lesions in the ACA (pericallosal) (*arrowheads*) and severe narrowing of the distal MCA (*arrow*). (From Pomper, 1999, with permission.)

and amphetamines can produce similar angiographic findings (Alhalabi & Moore, 1994; Calabrese et al., 1997; Duna & Calabrese, 1995).

As an invasive test, angiography carries some risk. For patients suspected of having CNS vasculitis, angiography is associated with an 11.8% risk of a transient neurologic deficit and a 0.8% risk of permanent damage from a stroke (Hellman et al., 1992).

Brain biopsy

Because of the focal segmental distribution of lesions in PACNS, brain biopsies are falsely negative in approximately 25% of cases confirmed histologically by second biopsy or autopsy (Calabrese et al., 1997; Lie, 1997). For reasons of safety and optimal yield, the non-dominant temporal lobe tip is the most common biopsy site (Calabrese et al., 1997). Biopsies should sample the leptomeninges, as well as the brain parenchyma, because the leptomeninges are involved commonly in this disease (Calabrese et al., 1997). Stereotactic biopsies of deeper brain regions are of lower yield in some studies (Vollmer et al., 1993) but not in others (Alrawi et al., 1999). Brain biopsy carries a risk of serious morbidity ranging from 0–2% (Alrawi et al., 1999; Harris et al., 1994). In addition to histological examination, stains and cultures for bacteria, fungi, and viruses should be performed. Because of the relative inaccessibility of pathologic tissue in PACNS, a portion of the sample should be snap frozen for later investigations whenever possible. Although the yield of biopsy has been questioned, in one study of 61 patients with possible CNS vasculitis, brain biopsy established the diagnosis of PACNS in 22 (36%), an alternative diagnosis in 24 (39%), and no diagnosis in 12 (25%) (Alrawi et al., 1999). Alternative diagnoses were infectious encephalitis (7), primary CNS lymphoma (6), brain abscess (3), non-lymphomatous tumour (2), multiple sclerosis (2), and single cases of sarcoidosis, sterile infarct, and arteriovenous malformation (Alrawi et al., 1999).

Diagnostic criteria

The diagnosis of PACNS cannot be based entirely upon any individual part of the evaluation, but rather requires a comprehensive analysis of all clinical, laboratory, and radiological data. Criteria for the diagnosis of PACNS proposed by Woolfenden et al. (1998) include:

(i) History of clinical findings of an acquired neurologic deficit that is consistent with CNS vasculitis (e.g. headache, focal or multifocal neurologic deficit, encephalopathy, or seizure).

Table 94.4. Differential diagnosis of primary angiitis of the central nervous system[a]

Category	Examples
Rheumatic disorders	Systemtic lupus erythematosus, Wegener's granulomatosis, polyarteritis nodosa, Takayasu's arteritis, temporal arteritis, Behçet's disease, Sjögren syndrome, Cogan syndrome
Infections	Bacteria (e.g. endocarditis, bacterial meningitis, tuberculosis, syphilis, Lyme disease), fungi (e.g. histoplasmosis, aspergillus), viruses (e.g. *H. Zoster*, human immunodeficiency virus, hepatitis C)
Drugs	Cocaine, ephedrine, amphetamine, allopurinol, phenylpropanolamine, heroin
Vasculopathies	Atherosclerosis, antiphospholipid antibody syndrome, cerebral amyloid angiopathy, moyamoya, radiation-induced vasculopathy, vasospasm associated with severe hypertension or hemorrhage, arterial fibromuscular dysplasia, cardiac myxoma embolism, cholesterol embolism, pregnancy and postpartum-associated vasculopathy, sickle cell anemia, thrombotic thrombocytopenic purpura
Malignancy	Vascular lymphoma, Hodgkin's disease, small cell lung cancer
Heritable disorders	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
Other inflammatory disorders	Sarcoidosis, inflammatory bowel disease, celiac disease
Metabolic disorders	Pheochromocytoma

Note:
[a] From Lie (1997); Razavi (1999); Williamson, (1999); Younger (1997); Calabrese, (1997); Calabrese & Mallek (1987).

(ii) No evidence of systemic vasculitis or any other condition that could cause the clinical and pathologic features, despite a thorough evaluation.

The diagnosis of PACNS may be considered definite if these two criteria are met and there is histologic confirmation of vasculitis. The diagnosis may be regarded as probable if, in the absence of a positive biopsy, the CNS angiogram demonstrates abnormalities characteristic of vasculitis in multiple intracranial vessels, assuming the absence of atherosclerosis in proximal cervical arteries. With angiographic abnormalities that are less convincing, the diagnosis should be classified as possible (Woolfenden et al., 1998).

Differential diagnosis

The differential diagnosis of PACNS is challenging because of the myriad of secondary forms of CNS vasculitis, and the numerous non-vasculitic conditions that may mimic the clinical or radiographic features of PACNS (Table 94.4).

Several rheumatic disorders can cause CNS vasculitis or CNS vasculopathy, but rarely mimic PACNS convincingly. Although many rheumatic disorders are included in the differential diagnosis of PACNS, only a few cause CNS vasculitis with any frequency, namely, lupus and polyarteritis nodosa. In unusual cases, Wegener's granulomatosis also causes vasculitis of the brain parenchyma, but typically involves blood vessels below the resolution of conventional angiography. Cogan's syndrome and Churg-Strauss syndrome are very rare causes of CNS vasculitis, as are scleroderma, Sjögren's syndrome and rheumatoid arthritis. Takayasu's arteritis and temporal arteritis involve extracranial vessels, and intracranial involvement is exceptional. Finally, although Behcet's disease commonly involves the CNS (see Chapter 96), the CNS pathophysiology in Behcet's does not appear to be vasculitic in nature. In nearly all cases, rheumatic diseases that cause CNS vasculitis are accompanied by symptoms, signs, and serologic abnormalities that indicate systemic involvement and permit their distinction from PACNS

Chronic infections can cause vasculitis either by infecting vascular cells and inciting inflammatory responses or by contiguous spread from other CNS tissues (Table 94.4). CNS vasculitis secondary to infection should be suspected when the patient has: (i) systemic features (e.g. fever, weight loss) (Yanker et al., 1986); (ii) an immunodeficiency state (e.g. HIV, Hodgkin's disease, diabetes, alcoholism) (Greco et al., 1976; Rewcastle & Tom, 1962); (iii) extensive arteritis of the base of the brain with prominent cranial nerve involvement (often features of arteritis caused by fungi and tuberculosis (Stone et al., 1998); or (iv) a CSF monocytosis exceeding 250 cells/mm^3 (Vollmer et al., 1993).

One infection that mimics PACNS closely is varicella-zoster virus (VZV). Vasculitis of the CNS is a well-described

complication of VZV infections (Blue & Rosenblum, 1983; Bourdette et al., 1983; Doyle et al., 1983; Gilden et al., 2000; MacKenzie et al., 1981; Ojeda et al., 1984; Reshef et al., 1985; Reyes et al., 1976; Rosenblum et al., 1978; Vilchez-Padilla et al., 1982; Walker et al., 1973). Two forms occur: a large-vessel arteritis that chiefly affects immunocompetent individuals, and a small-vessel arteritis that affects patients with immunodeficiency states, such as Hodgkin's disease, leukemia, or the acquired immune deficiency syndrome (AIDS) (Gilden et al., 2000). Classically, the large artery variant presents in patients over 60 years old who develop an ipsilateral stroke (with contralateral hemiplegia) some weeks to months (mean 7 weeks) following an episode of zoster in the distribution of the trigeminal nerve (Gilden et al., 2000). Angiography reveals beading of the middle and anterior cerebral arteries (Gilden et al., 2000; MacKenzie et al., 1981). Microscopic examination demonstrates granulomatous inflammation, VZ antigen, Cowdry A inclusion bodies, and herpesvirus particles (Gilden et al., 2000). PCR studies confirm VZV DNA in affected arteries (Gilden et al., 2000). Although, the vasculitis can be confined to the same side as the trigeminal zoster, bilateral vasculitis does occur (Gilden et al., 2000). In addition, VZ-induced granulomatous vasculitis can occur without an antecedent rash (Gilden et al., 2000).

The smaller vessel variant of VZV-induced CNS vasculitis generally develops in immunodeficient patients. Clinical presentations include hemiplegia, aphasia, headache, vomiting, encephalopathy, and seizures (Gilden et al., 2000). MR demonstrates small infarctions, hemorrhages, or both, often involving the bilateral cortical and subcortical grey and white matter (Gilden et al., 2000; Lipton & Ma, 1996). The white matter lesions are smaller and less confluent than those in progressive multifocal leukoencephalopathy (Gilden et al., 2000). Thus, VZ-induced CNS vasculitis should be suspected in a patient with a recent episode of zoster or state of immunodeficiency. The diagnosis can be suggested by the characteristic radiological features, by positive VZV PCR in the CSF and confirmed by demonstrating VZV infection on brain biopsy (Gilden et al., 2000). Successful treatment has been reported with prednisone (60–80 mg/day for 3–5 days) accompanied by acyclovir administered for 2 weeks (or longer in severely immunosuppressed patients (Gilden et al., 2000).

A detailed drug history and toxicology screen helps identify patients with drug-induced CNS vasculopathy (Table 94.4). Cocaine, amphetamines, and ephedrine derivatives are the most common culprits (Bostwick, 1981; Glick et al., 1987; Kaye and Fainstat, 1987; Kessler et al., 1978; Rumbaugh et al., 1971a,b; Scully et al., 1993; Weiss et al., 1970; Wooten et al., 1983; Yu et al., 1983). In contrast to patients with PACNS, patients with drug-induced vasculitis are more frequently male, tend to be a decade younger (onset in the 20s or 30s), and more likely to demonstrate hemorrhage (either intracranial or subarchnoid) (Scully et al., 1993; Wooten et al., 1983). The angiographic abnormalities of drug-induced CNS vasculitis are similar to those of PACNS (Scully et al., 1993; Wooten et al., 1983). Normal angiograms with vasculitis documented on biopsy have been reported, especially with cocaine (Scully et al., 1993). Though the number of histopathologically proven cases is small, medications are capable of inducing frank vasculitis (Wooten et al., 1983). Whereas PACNS involves chiefly a lymphocytic infiltrate with giant cells and granulomas centred on the adventitia, drug-induced vasculitis is usually associated with a polymorphonuclear cell infiltrate focused on the intima, without giant cells or granulomas (Wooten et al., 1983).

A number of other conditions cause angiographic changes that resemble those of PACNS (Table 94.4) (Calabrese et al., 1997; Razavi et al., 1999). Atherosclerosis occasionally mimics PACNS, but usually is distinguishable by the presence of risk factors for atherosclerosis (e.g. advanced age, hypertension, hyperlipidemia, smoking) and by eccentric narrowing of the proximal and extracranial carotid arteries (Calabrese, 1997; Calabrese & Mallek, 1987).

Pregnancy history is also important because vasculopathy that clinically and angiographically mimics PACNS sometimes develops during pregnancy and the puerperium (Calabrese et al., 1997; Farine et al., 1984; Glick et al., 1987). In some of these patients, the disorder appears to be part of pre-eclampsia (Farine et al., 1984) and may be caused by vasospasm or severe hypertension. Other patients may have a true vasculitis since they have no history of pre-eclampsia, develop the symptoms weeks to months after delivery, and demonstrate vasculitis on biopsy (Glick et al., 1987). In these latter cases, the true relationship of vasculitis in the event of pregnancy is difficult to confirm.

Rarely, cerebral amyloid angiopathy (CAA) mimics PACNS. In CAA, amyloid is deposited in the walls of blood vessels in the leptomeninges and cerebral cortex (sparing the white matter), resulting in a wide range of vasculopathic changes such as cracking, 'double-barreling', fibrinoid necrosis, aneurysm formation, vascular ectasia, vessel occlusion, and perivascular inflammation (Fountain & Eberhard, 1996; Greenberg, 1998; Greenberg & Vonsattel, 1997; Mandybur, 1986; Scully et al., 1991; Vonsattel et al., 1991; Yamada et al., 1996). In addition to mimicking PACNS, CAA may also coexist with PACNS. Indeed, one study estimated that 10% of patients with PACNS also have

Table 94.5. Comparison of cerebral amyloid angiopathy (CAA) with PACNS[a]

	CAA (n=140)	PACNS (n=63)
Clinical feature		
Mean age (range)	76 (34–97)	44.8 (3–79)
Headache	36%	63%
Hemorrhage (CT, MRI)	nearly universal	rare
Angiography		
Concentric narrowing	rare	common
Biopsy	Amyloid deposition	Granulomatous inflammation

Note:
[a] Modified with permission pending from Fountain (1996) p. 192.

CAA (Fountain & Eberhard, 1996), raising the question of whether one condition contributes to the pathogenesis of the other.

The greatest risk factor for CAA is ageing: moderate to severe CAA rarely occurs before age 65, but is present at autopsy in 2.3% of those aged 65–74 and in 12.1% of those older than 84 (Greenberg, 1998). Only an Icelandic variant occurs before the age of 50. Most causes of CAA are asymptomatic (Fountain & Eberhard, 1996). Among those who become symptomatic, the most common presentation is acute intracranial hemorrhage (Greenberg, 1998). In contrast to hypertension, which predisposes to bleeding in the basal ganglia, thalamus, pons, and cerebellum, CAA-related hemorrhage (like vascular amyloid itself) favours the cerebral cortex (Greenberg, 1998). Pathologic studies reveal that vascular deposits in CAA can consist of β-protein amyloid, AL amyloid, AP amyloid or other proteins (Yamada et al., 1996). Rarely, CAA can present as dementia of acute onset accompanied by leukoencephalopathy in the absence of lobar hemorrhage.

Often, CAA and PACNS are readily distinguishable on clinical, radiological and pathological grounds (Table 94.5). In the absence of biopsy evidence of coexisting vasculitis, CAA is treated with measures to reduce the likelihood of hemorrhage, i.e. avoidance of anticoagulation. When PACNS and CAA coexist, immunosuppressive therapy has been reported to be beneficial (Greenberg, 1998).

Malignancies, particularly disseminated intravascular lymphoma, can mimic the clinical and angiographic features of PACNS (Calabrese, et al., 1997; Lie, 1997; Williams et al., 1998). In some series, mental status changes and fever are the most common presenting features (DiGiuseppe et al., 1994). A dramatic improvement following corticosteroids may further suggest PACNS. However, in the absence of a correct diagnosis and prompt initiation of intensive chemotherapy, most patients with intravascular lymphoma relapse rapidly and die (DiGiuseppe et al., 1994).

Finally, the disorder termed 'cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy' (CADASIL) may be mistaken for PACNS (Williamson et al., 1999). Detailed questions about family history of neurologic disease are therefore essential in the evaluation of patients with possible PACNS

Treatment and course

In the absence of treatment, almost all patients with HDACNS die of progressive neurological deficits (Younger et al., 1997). With corticosteroid therapy, cyclophosphamide treatment, or both, most patients stabilize or improve (Calabrese et al., 1997). Recent studies indicate mortality for either definite or probable PACNS has dropped to less than 5% (Calabrese et al., 1997). Although some studies suggested that cyclophosphamide plus prednisone gave superior results to prednisone alone (Calabrese & Mallek, 1987), these differences may be due to ascertainment biases caused by the fact that older cases in the literature were identified chiefly at autopsy (Calabrese et al., 1997). Some authors suggest that cyclophosphamide or other immunosuppressive drugs should be reserved for histologically proven cases that progress despite corticosteroid therapy (Calabrese et al., 1997). Typically, prednisone is administered at 40–60 mg/d for 3–6 months and then tapered to complete a 12 month course (Moore, 1989a). Pulse corticosteroid therapy (i.e. 1000 mg of methylprednisolone intravenously daily for 3 days) followed by daily oral prednisone (1 mg/kg) has been used as initial therapy for patients who have deteriorated rapidly. Monthly, intravenous pulse cyclophosphamide (750–1000 mg/m^2) is less likely than daily oral cyclophosphamide (2 mg/kg) to cause infections and hemorrhagic cystitis. However, oral daily cyclophosphamide may be more effective for certain forms of systemic vasculitis (Langford, 2001). Data comparing daily oral with monthly pulse cyclophosphamide in the treatment of CNS vasculitis are not available.

Treatment of ADACNS is also not well defined. Because some of these patients may have a vasculopathy related more to vasospasm than to arteritis, treatment with calcium channel blockers and prednisone (e.g. 30–60 mg/d) for 3–6 weeks may be sufficient therapy (Calabrese et al., 1997). Avoidance of drugs that promote thrombosis

or vasoconstriction (e.g. oral contraceptives, nicotine, and sympathomimetic drugs) is also recommended (Calabrese et al., 1997).

A substantial number of HDACNS patients may respond sufficiently to steroids alone, which may be tapered successfully over 6 months or more. Some ADACNS patients may do well with shorter courses of steroids and a longer course of treatment with a calcium channel blocker. Predicting which patients will fare well with less intense immunosuppression is difficult. Patients with severe deficits at presentation or radiologic evidence of vital brain regions at risk should probably be treated with the combination of cyclophosphamide and steroids from the onset.

Few studies have reported the neurological outcomes of patients with PACNS. In one study of 21 patients, 10 (48%) demonstrated some recovery (Alrawi et al., 1999). The recovery rate with ADACNS is probably higher (Calabrese et al., 1997).

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95

Sarcoidosis of the nervous system

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This chapter considers the often difficult diagnosis of neurosarcoidosis, its prevalence, pathology, differential diagnosis, treatment and prognosis. Although advances in imaging techniques have alerted clinicians to this potential diagnosis more frequently than in the past, there is still no definitive non-invasive investigation to provide certain confirmation of clinical suspicion. The diagnosis is one which should always be treated with a healthy degree of scepticism, as even typical granulomas may have alternative causes.

Epidemiology

Prevalence rates for intrathoracic sarcoidosis vary from greater than 50 per 100 000, for example in African–Americans and Irish, to under 10 per 100 000 (James & Hosoda, 1994). Much higher prevalence rates were obtained when consecutive postmortems were performed on approximately 60% of all deaths in an area of Sweden, when evidence of sarcoidosis was found in 43 individuals, only three of whom were known to have sarcoidosis during life, yielding a prevalence of 641 per 100 000 (Hagerstrand & Linel, 1964). The clinical significance of these findings is uncertain, but they suggest that the pathological process is far commoner than we recognize, although this may be limited to subclinical disease in most cases. Intermediate estimates for the prevalence of systemic sarcoidosis of 10–20 per 100 000 are likely for caucasians in London and New York.

Previous data from large series of patients with sarcoidosis have estimated that approximately 5% of such patients will have clinical involvement of the nervous system (Maycock et al., 1963; Stilzbach et al., 1974; Delaney, 1977; Stern et al., 1985), although postmortem studies suggest that antemortem diagnosis is only made in 50% with nervous system involvement (Iwai et al., 1993). Conservatively, we can therefore estimate that about 5 to 10 patients per million population will have clinical neurosarcoidosis, although this figure will vary according to local prevalence rates.

Clinical aspects of neurosarcoidosis

As with any rare disease, information concerning natural history, prognosis and treatment strategies is seldom based on large prospective cohort analysis, let alone on randomized trials.

Because nervous system sarcoidosis is relatively rare, few large series exist in the literature; the largest has been a British series of 68 patients (Zajicek et al., 1999). In assessing the available data it is important to be aware of how each series has been compiled. For example, there is no prospective analysis of consecutive cases and most series will either have been compiled from patients in a sarcoidosis/chest clinic or from neurology departments. These factors have inevitably led to referral bias so that data from thoracic departments are more likely to show pulmonary abnormalities, whilst patients presenting to neurologists may not have had any previous evidence of systemic disease. Variation also exists in the degree to which individual clinicians pursue a diagnosis, for example, although facial nerve paresis is a relatively common manifestation of neurosarcoidosis, 'Bell's palsy', on the other hand, is considered to have a generally benign clinical course, and such cases may not be fully investigated for neurosarcoidosis. A recent series of 265 cases of acute facial nerve palsy found 11% had abnormal cerebrospinal fluid, mostly due to Ramsey–Hunt syndrome, HIV or Lyme disease (Kohler et al., 1999), with only one case identified with sarcoidosis.

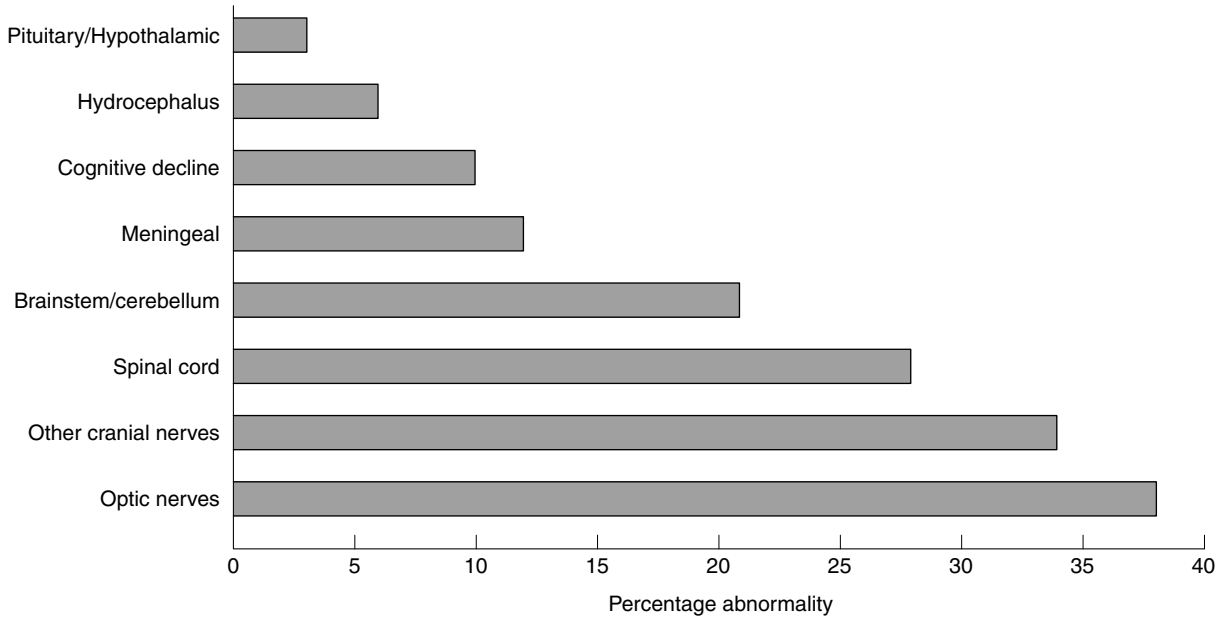

Fig. 95.1. Clinical presentations of neurosarcoidosis in 68 patients (Zajicek et al., 1999).

Allowing for these caveats, some useful information can be obtained by comparing some of the largest series in the literature (James & Sharma, 1967; Delaney, 1977; Stern et al., 1985; Oksanen, 1986; Chapelon et al., 1990; Zajicek et al., 1999). The total number of cases in these series is 247 and although the average percentage of cases with peripheral nerve and muscle involvement in all except the most recent series was in the order of 30%, Zajicek et al. found no cases with peripheral nervous system involvement. It certainly appears that such manifestations are rare in peripheral nerve clinics in the UK (P.K. Thomas, personal communication) and this may reduce one's tendency to obtain a tissue diagnosis using peripheral tissue.

There is no obvious sex difference in prevalence rates, and the mean age of presentation is around 40 years. In patients presenting with neurosarcoidosis to neurology clinics, there is an approximate 40% chance of their having had previous disease in other organs, most commonly chest or anterior uvea. Details of clinical features at presentation from one large series are summarized in Fig. 95.1.

Optic nerve disease is a very common presentation of neurosarcoidosis and up to 38% of patients may have evidence of a lesion at this site, approximately two-thirds of whom will have clinical evidence of unilateral and one-third bilateral disease. The characteristic picture is often an atypical optic neuritis, subacute in onset, which might recover following steroids or cause permanent visual impairment. Initial steroid sensitivity is occasionally followed by dependence, with symptoms deteriorating below a certain dosage level. In a prognostic analysis of patients with optic nerve disease who were followed up for lengthy periods, most of whom received corticosteroid treatment, there is an approximate 40% chance of appreciable recovery over 18 months or more.

When investigating patients for neurosarcoidosis, a full neuro-ophthalmological workup is therefore indicated, including a search for both anterior and posterior segment disease with slit lamp examination and fluorescein angiography, as well as seeking clinical and/or visual evoked potential evidence for optic nerve disease. Unfortunately, optic nerve disease has a tendency to be severe with profound impairment of visual acuity being all too common.

The propensity for sarcoidosis to produce a meningeal reaction probably explains the predominance of cranial nerve palsies in most series (see Fig. 95.2). If optic nerve disease is also taken into account, then around 60% of patients present with cranial nerve palsies in the combined series of 247 patients (see above). Approximately one-third of patients will have facial nerve paralysis, most commonly unilateral, although bilateral simultaneous or sequential paralysis carries a higher index of suspicion.

Facial nerve palsies are a classical manifestation of neurosarcoidosis and have been reported as carrying a good prognosis in previous publications (Delaney, 1977),

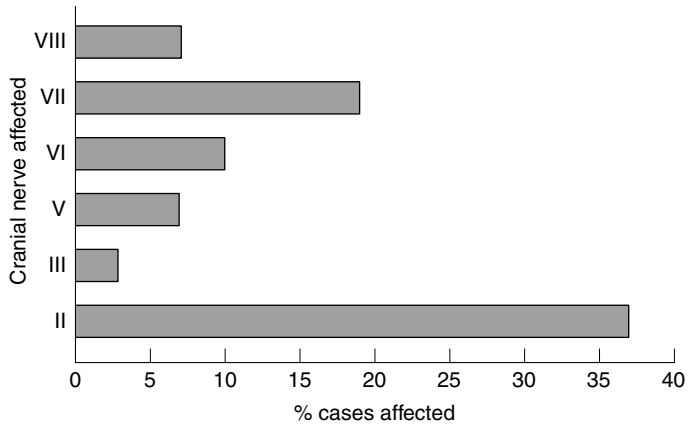

Fig. 95.2. Cranial nerve involvement in a series of 68 patients with neurosarcoidosis (Zajicek et al., 1999)

although this may not always be the case (Zajicek et al., 1999). There may well be a difference in prognosis depending on where the facial nerve is affected along its course. Certainly, examples of CSF abnormalities in cases of apparently pure facial palsy suggest that the lesion may result from a meningitic reaction, but the classical explanation for facial palsy in neurosarcoidosis is that it is secondary to inflammation in the parotid gland, although many early authors also noted the lack of temporal correlation between parotitis and facial palsy (Wilson, 1940). More detailed prospective studies are clearly needed to assess the site and significance of such palsies.

Spinal column disease has previously constituted up to 10% of large series of neurosarcoidosis cases (Oksanen, 1986; Stern et al., 1985; James & Sharma, 1967). Syndromes ranged from intramedullary tumour-like presentations to meningitic–radicular syndromes (for review see Zajicek, 1990). Zajicek et al. described 28% of patients with clinical signs of spinal cord disease. In ten patients this was clinically confined to the cord whilst nine patients also had clinical disease elsewhere in the neuraxis. Fifteen cases with spinal cord disease were followed up for more than 18 months, and 11 of these deteriorated (73%). These results suggest that such a presentation carries a poorer prognosis than certain other manifestations of neurosarcoidosis.

Brainstem and/or cerebellar presentation occurs in about 20% of patients, who principally exhibit limb or gait ataxia and eye movement abnormalities such as failure of vertical gaze. Internuclear ophthalmoplegia and central vomiting have also been reported with neurosarcoidosis. A small percentage (<10%) of cases may present with cognitive decline and a similar number may have a meningitic type illness at presentation.

Table 95.1. Causes of granulomatous reactions

1. Infections	*4. Inflammatory disorders*
Cryptococcus	Sarcoidosis
Histoplasma	Wegener's granulomatosis
Coccidiodes	Giant cell arteritis
Blastomyces	SLE
Aspergillus	Churg-Strauss syndrome
Toxocara	Melkersson-Rosenthal syndrome
Toxoplasma	Primary angiitis of the nervous system
Treponema	
Mycobacteria (TB)	*5. Others*
Whipple's disease	Radiotherapy
	Chemotherapy
2. Chemicals	Chronic granulomatous disease of children
Silica	
Beryllium	
Starch	
Zirconium	
Contrast agents	
3. Tumours	
Carcinoma	
Lymphoma	
Pinealoma	
Dysgerminoma	
Dermoid cyst	
Seminoma	
Reticulum cell sarcoma	
Malignant nasal granuloma	
Histiocytosis X	

Pathology and pathogenesis of sarcoid granulomas

The fundamental histological feature characterizing sarcoidosis is the presence of non-caseating epithelioid cell granulomata. Whilst the presence of such granulomata may seem pathognomonic of sarcoidosis, other disease processes are capable of provoking a granulomatous reaction, and it is only in the correct clinical context, when alternative explanations have been excluded, that the clinician may tentatively accept a diagnosis of sarcoidosis. This particularly applies in the nervous system where access to tissue is more difficult and clinical syndromes tend to be less clear cut (see Table 95.1).

Mononuclear phagocytes, including blood-borne monocytes, tissue macrophages, brain microglia and epithelioid cells (which may amalgamate to produce giant cells), constitute the predominant cell types in a granuloma. Well-formed granulomata usually contain macrophages with varying degrees of maturity, including

activated and non-activated cells. An example of meningeal sarcoidosis is demonstrated in Fig. 95.3, see colour plate section.

Macrophages in areas of early granuloma formation express the calcium-binding protein calgranulin Mac 387, which is an antigen shared by granulocytes and circulating monocytes but only a small proportion of tissue macrophages (Chilosi et al., 1990). This suggests that local recruitment from blood-borne monocytes is important in granuloma formation. Epithelioid cells retain macrophage markers within granulomas, confirming their lineage (Poulter, 1983). They also strongly express MHC class II molecules and act as antigen-presenting cells (van der Oord et al., 1984). Epithelioid cells possess numerous well developed cytoplasmic organelles containing material which is of intermediate electron density on electron microscopy. There is no evidence that these organelles contain fragments of microorganisms but it has been postulated that the epithelioid cells found in tuberculosis contain more prominent rough endoplasmic reticulum and fewer lysosymes, whereas the reverse may be true in sarcoidosis (Epstein, 1991).

As well as phagocytic cells, sarcoid granulomas also contain high numbers of lymphocytes, reflecting their importance in immunopathogenesis. Inorganic foreign body granulomas, for example those induced by silica, consist almost entirely of macrophages with very few lymphocytes. The inorganic material is resistant to degradation within macrophages and may induce cell death, leading to giant cell formation, but under these circumstances there is little evidence of T-cell activation, and these granulomata therefore do not resemble immunologically induced granulomata commonly found in sarcoidosis. Most lymphocytes found within sarcoid granulomata are CD4+ T-cells, found particularly at the centre of the lesion. CD8+ cells and B-cells tend to occur towards the periphery of a granuloma (Modlin et al., 1984), but $\gamma\delta$-T-cells may also play a role in the inflammatory process, and cell numbers may be raised both systemically and locally at the site of granuloma formation (Balbi et al., 1990).

Not surprisingly when investigators have looked at the cytokine and adhesion molecule profile within granulomata, a large array of molecules can be found. LFA-1 and ICAM-1 appear to be two of the major adhesion molecules expressed (Semenzato et al., 1994). IL-1 and γ-interferon are preferentially expressed at the granuloma centre and the overall pattern of cytokine involvement is skewed towards the proinflammatory T_H1 (TNF-α, Il-1, Il-2) rather than T_H2. It is beyond the scope of the present chapter to provide great detail on granuloma formation and this can be found elsewhere (Semenzato et al., 1994), but the end result of such granulomata is often fibrosis and scar formation which is not necessarily specific to sarcoidosis. Numerous proteins may be released which promote this process including PDGF, IGF-1, TGF-β as well as tissue breakdown products including collagenases and free oxygen radicals.

The fundamental question concerning the driving stimulus behind granuloma formation remains controversial and unanswered. Most observers would accept that there is undoubtedly an exaggerated immune response to an as yet unidentified antigen. The histological similarity between tuberculous and sarcoid lesions has led to a prolonged search for mycobacteria within granulomata. Whilst some investigators have detected mycobacterial DNA by polymerase chain reaction (PCR) in sarcoidosis tissue (Saboor et al., 1992; Mangiapan & Hance, 1995), others have been unable to do so (Vokurka et al., 1997).

The possibility that sarcoidosis may be caused by an abnormal reaction to other infectious agents has also been widely explored. Human herpes virus 8 (HHV-8) has been implicated in the development of Kaposi's sarcoma (KS) and other malignancies in HIV-related disease, and recently Alberti et al. (1997) reported HHV-8 DNA in biopsy specimens from eight patients with sarcoidosis, although others were unable to find serological evidence for HHV-8 infection in sarcoidosis patients, whilst such evidence was found in patients with HIV-related KS. Ishige et al. (1999) reported the presence of DNA from either *Propionibacterium acnes* or *Propionibacterium granulosum* in all lymph node samples from 15 patients with sarcoidosis, but only 2/15 patients with tuberculosis and 3/15 controls. The significance of these findings is uncertain as *Propionibacteria* can be present in tissue without pathological effects.

Genetic factors almost certainly govern disease susceptibility in sarcoidosis, and it has been argued that affected individuals possess a genetic predisposition to an exaggerated immune response which is able to eradicate the microorganisms early and thus make identification very difficult. Certainly familial cases of sarcoidosis have been described, and there appears to be a higher incidence in monozygotic rather than dizygotic twins (British Thoracic and Tuberculous Association, 1973). The recognition of varying prevalence rates in different ethnic groups has long been quoted as evidence for genetic predisposition in sarcoidosis and associations between human leukocyte antigens (HLA) of the major histocompatibility (MHC) group and sarcoidosis, has provided more concrete support for this hypothesis. Notable associations exist between HLA-B8 in British, Italian and Czech populations (Smith et al., 1981; Martinetti et al., 1995) and HLA-DR17 in Scandinavians

(Berlin et al., 1997). Because these associations have been inconsistent, they have recently been explored further by examining other genes around the MHC including the transporter associated with antigen processing (TAP) genes (Foley et al., 1999). Significant differences have been found between UK and Polish populations in susceptibility at these loci, and there appeared to be independent associations at the TAP and HLA-DPB1 loci. A recent study has also suggested that polymorphisms in the C-C chemokine receptor 2 gene (a major receptor for the monocyte chemoattractant protein (MCP) group of C-C chemokines) may confer susceptibility to sarcoidosis (Hizawa et al., 1999). These studies illustrate the importance of distinguishing populations when examining disease susceptibility. Although the causes of sarcoidosis remain unknown, as in other CNS inflammatory conditions (notably Multiple Sclerosis, MS), there is emerging consensus which supports the belief that sarcoidosis results from exposure of genetically susceptible individuals to specific environmental agents (American Thoracic Society 1999).

The diagnosis of neurosarcoidosis

An accurate diagnosis is the cornerstone of treatment, yet defining the diagnosis of neurosarcoidosis with certainty is often difficult. Most series in the literature rely on the presence of recognized neurological phenomena in the context of a granulomatous multisystem disease, so that tissue diagnosis is often made from organs such as the liver, lung or skin. However, this is really inadequate to be certain of CNS involvement in the same process. There are many reports of systemic sarcoidosis being identified, and the apparent CNS component of the illness being treated, yet the true CNS diagnosis may be entirely different and emerge only later. Histological diagnosis from the CNS is often an early feature in neurological series, particularly if biopsy is performed on the expectation that an alternative diagnosis is present. When early presentation occurs to the neurological clinic, systemic disease is less likely to be obvious, and once a tissue diagnosis from the CNS is obtained, clinicians are less liable to search for systemic disease. Certainly CNS histology is preferable to relying on systemic histology, but even here granulomatous reactions can exist around other pathologies, falling short of a 'gold standard' diagnostic test. There are those who argue that one cannot make a diagnosis of neurosarcoidosis in the absence of systemic disease, but in reality clinicians may be faced with sick patients, a histological diagnosis and pressure to treat, which often outweighs the desire to perform further investigations.

All this influences the confidence with which we can make a diagnosis of neurosarcoidosis, and we must accept that until the pathology is fully understood, errors in diagnosis will occur (some of which have already entered the literature and will continue to do so). Clinicians therefore make estimates of probability of disease and must manage patients according to these probabilities. Similarly, when cases are defined from the literature, there is an inevitable leap of faith that these cases do indeed suffer from neurosarcoidosis and are broadly representative of clinical practice.

The investigation of patients with possible neurosarcoidosis

It has been suggested that a definite diagnosis of neurosarcoidosis can only be made if nervous system histology is positive within a suitable clinical context (Zajicek et al., 1999). A greater precision in diagnostic definition not only allows for accurate prospective analysis of prognostic indicators, and better assessment and validation of indirect indicators of disease, but also enables therapeutic trials to be conducted in a meaningful fashion. However, biopsy of CNS tissue (Fig. 95.4) is required to make a definite diagnosis of neurosarcoidosis according to these criteria, and even in the largest series, this was only achieved in less than 20% of cases. When the patient is seriously ill with rapidly progressive disease in several parts of the neuraxis, it is important to achieve a diagnosis as quickly as possible in order that appropriate therapy can be commenced; under these circumstances guided stereotactic or open biopsy is often performed, either of meninges and/or of parenchymal lesions. With less severe disease and/or a more gradual course, it is often more appropriate to perform indirect investigations to look for systemic disease and treat accordingly (see below).

Retrospective analysis of the usefulness of biopsy to assess the specificity and sensitivity of any other single investigation inevitably introduces bias, as biopsy is undertaken selectively, e.g. on mass lesions, where the possibility of neoplasia has been raised, in patients with severe and rapidly progressive disease, or in cases where histology is relatively easy to obtain. The lesion site (which influences the decision to biopsy) will also influence the clinical presentation, for example, cortical lesions may be more likely to present with epilepsy and be biopsied, thus interpretation of the clinical presentation of this group of patients must be cautious. Another major difficulty with interpreting data from these patients is their lack of completeness, as investigations are often halted once tissue

diagnosis is achieved. Establishing the diagnosis of neurosarcoidosis is often difficult and the only way to acquire firm evidence for the value of any single investigation is to perform a prospective study using appropriate investigations in all patients, especially those in whom a definite histological diagnosis has been obtained. The understandable tendency not to perform further investigations once the diagnosis has been obtained has limited our knowledge on the usefulness of non-invasive methods for investigating neurosarcoidosis.

Most patients being investigated for neurosarcoidosis have a chest radiograph which at presentation to neurologists can be expected to be abnormal between one-third and two-thirds of the time, the most common abnormality being bilateral hilar lymphadenopathy, occasionally with additional pulmonary abnormality. Previous studies utilizing chest CT suggest it may assist in targeting transbronchial biopsy.

Historically, one of the most useful investigations in sarcoidosis is the Kveim antigen skin test, which is positive in around 85% of patients with neurosarcoidosis. This compares favourably with rates of positivity in other patients with systemic sarcoidosis (Scadding & Mitchell, 1985). The usefulness of this test compared to tissue diagnosis by other means has previously been assessed (Mitchell et al., 1980). That study reviewed the procedures by which histological confirmation was obtained in 79 patients with a final diagnosis of sarcoidosis. Transbronchial lung biopsy was performed in 42 cases and showed sarcoid-type granulomata in 37. Kveim tests were performed in 44 and were interpreted as being positive in 19 and equivocal in 11. Thus, whilst rates of granulomatous 'positive' Kveim test responses are usually lower than those obtained by appropriate tissue biopsy, a positive Kveim test can be regarded as comparable to that of finding granulomas in a biopsy of a site remote from that principally affected. Recent questions concerning safety of the test and particularly the idea that it may transfer sarcoidosis have been vigorously refuted (DuBois et al., 1993). However, since the appearance of variant CJD, it has become even more difficult to obtain Kveim antigen in the UK and the USA, and the lack of availability makes the routine use of this test problematical. A further major problem with the Kveim test lies in the 4–6 week time interval required to elapse before biopsy can be performed. This period may be crucial to the timing of intervention in the disease process, particularly when lesions occur in clinically critical sites. Concomitant use of corticosteroids may reduce systemic granuloma formation including the site of Kveim antigen insertion, and this is a likely explanation for negative Kveim results observed in cases of biopsy proven disease. In some series, all Kveim negative patients were being treated with systemic corticosteroids. Hence, although the Kveim test is an invaluable aid in the diagnosis of neurosarcoidosis, up to 3% may be false-positive, negative results may occur with concomitant corticosteroid therapy and lack of availability means alternative means of making a diagnosis are usually required.

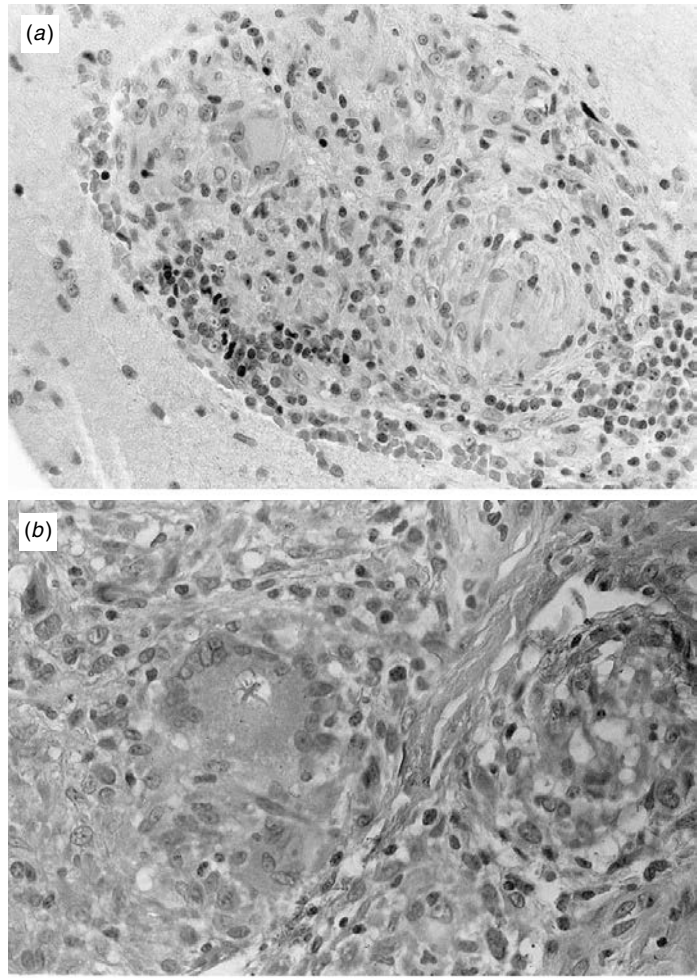

Fig. 95.4. (*a*) Photomicrograph of an intraparenchymal non-caseating sarcoid granuloma of the brain (×200). (*b*) Photomicrograph of a sarcoid granuloma in brain, demonstrating a multinucleated giant cell (×400) (From Aminoff, 2001, with permission.)

The usefulness of performing 'blind' biopsies from other organs, including liver and lung, in patients with suspected neurosarcoidosis, is uncertain. Whilst tissue diagnosis from sites outside the nervous system has previously been considered sufficient to establish the diagnosis of neurosarcoidosis in the context of an appropriate clinical syndrome, this should still only be considered as evidence for

systemic disease which by itself is insufficient to be certain of neurological involvement by granulomatous tissue.

CSF abnormalities are common in neurosarcoidosis and are present in over 80% of cases at presentation. The most common abnormality is an elevation in protein, sometimes to very high levels and around half of all cases will show a CSF lymphocytosis, with occasional rare neutrophils and monocytes. A similar proportion of patients may have CSF oligoclonal bands on immunoelectrophoresis: one-third of these cases providing evidence for systemic synthesis (the so-called 'mirror' pattern of similar oligoclonal bands in CSF and serum), the remainder fulfilling the criteria for local synthesis, with only a small proportion of this latter group of patients having normal CSF protein levels, which may be a way of helping to distinguish them from those patients with multiple sclerosis. If there is definite evidence for multisystem disease in the context of neurosarcoidosis, one is more likely to see a 'mirror' pattern and intrathecal local synthesis is less likely to be present (V. Chamoun, personal communication).

The significance of raised CSF ACE levels in the context of elevated protein concentrations or CSF cell counts remains uncertain, and this investigation is probably of little use. Any usefulness may be principally confined to that small number of patients where levels are raised out of proportion to the protein concentration, when the CSF does not contain large numbers of inflammatory cells and the serum ACE is not elevated. Other biochemical indices are generally unhelpful in establishing a diagnosis; serum calcium and erythrocyte sedimentation rate are rarely elevated.

Whole body Gallium scanning remains a useful indicator of systemic disease, which although again is a relatively non-specific measure, adds diagnostic probability to a case. Ga67 citrate is taken up at sites of active sarcoidosis and also by other inflammatory and malignant diseases, including tuberculosis and lymphomas, but the pattern of uptake among patients with active sarcoidosis is well recognized. Accordingly, as a component of the investigations relevant to the diagnosis of extrathoracic sarcoidosis it can be very helpful although constrained by the limitations imposed by subjective interpretation. In a consecutive unpublished series of 42 such patients a definite pattern of uptake was obtained in 18 (42%), whilst the pattern of uptake was considered equivocal in eight and negative in 16. In the British series, 45% of patients in whom this investigation was performed proved to have increased uptake which was usually in the salivary glands or chest.

MRI has greatly aided the investigation of patients with inflammatory brain disease and has consistently proved to

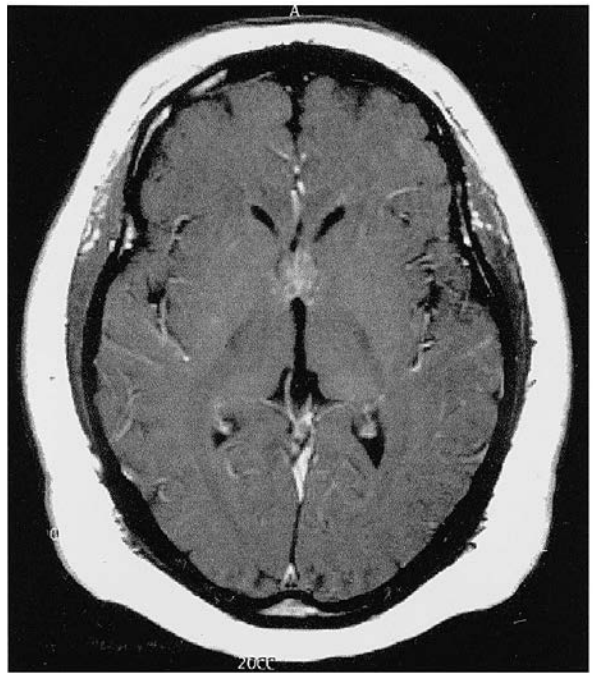

Fig. 95.5. Contrast-enhanced axial MRI scan demonstrates modularity around the optic chiasm, and anterior borders of the third ventricle in a patient with neurosarcoidosis.

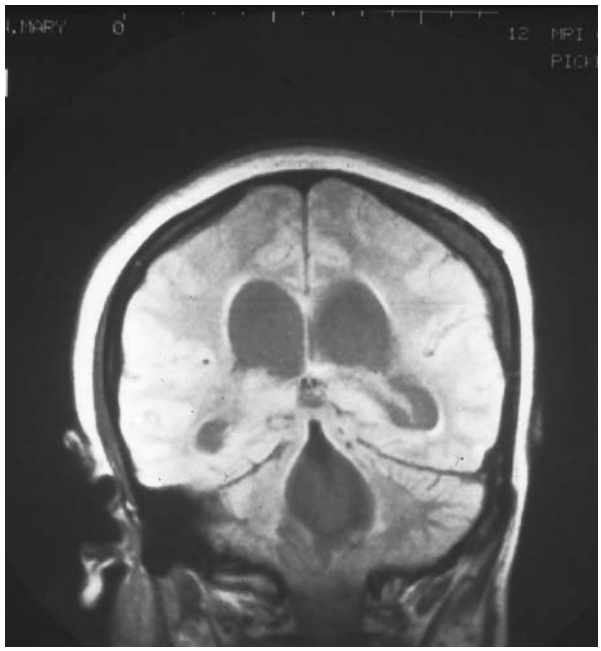

Fig. 95.6. Coronal MRI demonstrating hydrocephalus. (Courtesy of Dr J.C. McArthur.)

be more sensitive than CT. Although MRI does not provide a great deal of specificity, its sensitivity is around 82%. Multiple white matter lesions and leptomeningeal enhancement with gadolinium, are the most common MRI findings, occurring independently in about 40% of cases. MRI abnormalities have been well described in previous series (Miller et al., 1988; Seltzer et al., 1991; Zajicek et al., 1999; Christophoridis et al., 1999) and although there are no specific features distinguishing neurosarcoidosis from MS, meningeal enhancement or persistent enhancement (more than a few weeks) of parenchymal lesions are much more suggestive of a granulomatous process and are not expected in MS (see Figs. 95.5, 95.6).

An overall plan for the investigation of a patient in whom the diagnosis of neurosarcoidosis is being considered is shown in Table 95.2. The essential decision which the clinician needs to make is whether evidence of systemic disease is sufficient to justify treatment of an associated neurological syndrome, or whether neurosurgical biopsy should be sought. In the present era, when the morbidity of carefully conducted leptomeningeal or parenchymal biopsy is low, serious consideration must be given to such procedures, particularly if the clinician is considering the use of potentially toxic drugs.

Table 95.2. The investigation of patients with possible neurosarcoidosis

Investigations for systemic disease
Chest X-ray (possible chest CT if high index of suspicion)
Lung function tests
Gallium scan
Blood investigations (including ESR, serum calcium, liver function, urea, electrolytes, autoantibodies, anti-neutrophil cytoplasmic antibody, complement, complete blood count, serum ACE, and other tests depending on differential diagnosis.
Consider tissue biopsy via bronchoscopy, liver, skin or conjunctival biopsy depending on abnormality.
Investigations for eye/nervous system disease
Ophthalmological assessment, including slit lamp examination, fluorescein angiography, electroretinograms and evoked potentials.
MRI of brain and possibly spine, with gadolinium contrast administration, consider repeating after an interval to look for prolonged contrast enhancement.
Lumbar puncture, CSF analysis for glucose, protein, cells, cytology, immunoelectophoresis (with paired blood)
Consider leptomeningeal and/or parenchymal biopsy

Treatment of neurosarcoidosis

Prolonged follow-up, ideally under randomized controlled conditions is necessary to draw valid conclusions concerning treatment schedules in neurosarcoidosis. Forty-seven patients were followed up for at least 18 months in the series of Zajicek et al. (1999), 34 of whom received corticosteroids alone, usually as a combination of long term oral prednisolone with or without intravenous methylprednisolone boluses. Ten/34 (29%) improved or stabilized whereas 24/34 (71%) deteriorated. Other therapies were tried only as steroid treatment was becoming ineffective or side effects were too severe; such treatments included methotrexate, azathioprine and hydroxychloroquine. The number of patients treated with any other single regime was too small to draw firm conclusions. Cyclosporin was used in three instances and was associated with improvement in one. Cranial irradiation was used in two instances, in one case after cyclosporin had failed and in one case after corticosteroids proved ineffective. Intravenous cyclophosphamide was used at high dosage (400 mg/day until the peripheral white cell count fell to below 4×10^6/ml) in three cases, who all improved.

The absence of large prospective trials and the paucity of existing data renders it very difficult to identify those patients in whom early aggressive immunotherapy would be beneficial. Analysis of the available data would suggest that disease presenting in the spinal cord or optic nerve, together with epilepsy, carry a poorer prognosis than facial nerve palsies. Most patients are treated with systemic corticosteroids which often carry significant side effects as dosages tend to be high and prolonged. Although some patients improve on this treatment, many continue to have troublesome disease. It is often the case that symptoms tend to recur at doses of prednisolone less than 20–25 mg/day or the equivalent in other corticosteroid types, making cessation of corticosteroids difficult. The incidence of steroid-related side effects is extremely high with such prolonged treatment, and all patients should be considered for osteoporosis-prevention treatment if prolonged steroid administration is anticipated. Concomitant anticonvulsant therapy which induces hepatic microsomal enzymes may reduce prednisolone concentration and efficacy, necessitating even higher oral doses. Bolus pulsed intravenous methylprednisolone gives a high initial loading dose of corticosteroid, and may help to avoid side effects associated with long term oral treatment.

Even fewer data exist concerning the efficacy of other forms of immunomodulatory therapy. The use of chlorambucil (Kataria, 1980), methotrexate (Lower & Baughman, 1990; Soriano et al., 1990), chloroquine (Morse et al., 1961), cyclosporin (Kavanaugh et al., 1987; Cunnah et al., 1988; Stern et al., 1992), radiotherapy (Grizzanti et al., 1982; Bejar et al., 1985; Gelwan et al., 1988) and cyclophosphamide, have all been reported. Thalidomide has been used in the treatment of generalized, particularly cutaneous, sarcoidosis, but its use in neurosarcoidosis awaits assessment.

Several regimes of immunotherapy can be used and some of these are described in Zajicek et al. (1999). Methotrexate, usually used weekly in a dose of 10 mg, may be of value in maintaining optimal suppression together with i.v./oral prednisolone and this is often used as a first-line steroid-sparing agent. Hydroxychloroquine has also proved to be a very useful adjunct to steroids and at a dose of 200 mg/day. This can be used daily for up to about a year and is worth considering as a first-line agent together with methotrexate. Cyclosporin, cyclophosphamide and fractionated radiotherapy all need further assessment. One regime for the management of neurosarcoidosis consists of initiating treatment with 1g i.v. methylprednisolone for 3 days together with at least 25 mg of oral prednisolone or equivalent per day. i.v. methylprednisolone 1 g is then continued on a weekly basis for a number of weeks, allowing a reduction of oral prednisolone to 15–20 mg/day. During this period, oral methotrexate and hydroxychloroquine may be added, especially with severe disease or a poor initial response to steroids. In severe cases, the i.v. methylprednisolone may be continued for some months, with a gradually increasing interdose interval.

None of these recommendations can be considered to have withstood serious scientific scrutiny in clinical trials, to gain such information requires collaboration on a wide scale, which would not only allow for the refinement of diagnostic criteria, but also provide for better analysis of prognostic factors. At present we can only conclude that neurosarcoidosis is often difficult to diagnose, that if the illness doesn't respond to early corticosteroid therapy then it can also be problematical to treat, and furthermore the prognosis appears to be worse than other manifestations of the condition.

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96

Collagen–vascular disease and the nervous system

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The collagen–vascular diseases represent the systemic expression of the immune system gone awry. In many cases, combinations of immune system dysregulation and nervous system involvement lead to some of the most challenging clinical conundrums in the neurosciences. In this chapter, we review the collagen–vascular diseases and their impact on the brain and peripheral nervous system.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is the prototype of autoimmune diseases. The condition occurs throughout the world and is more prevalent in women (particularly during the reproductive years), with a female:male ratio of 9:1 (Gladman & Urowitz, 1998). To meet inclusion criteria for research studies as an SLE patient, a patient must demonstrate a minimum of 4 out of the 11 American College of Rheumatology (ACR) criteria (Table 96.1) (Tan et al., 1982). The criteria demonstrate the protean nature of SLE, which is capable of affecting any organ system. However, some patients clearly fit the spectrum of SLE yet do not fulfil minimum ACR criteria. Among the many neuropsychiatric manifestations of SLE, only seizures and psychosis were included in the 1982 criteria.

A 1999 nomenclature system for neuropsychiatric SLE (NPSLE) expanded the neuropsychiatric section of the ACR criteria, defining 19 neuropsychiatric syndromes associated with SLE. These are listed in Table 96.2 (ACR Ad hoc Committee, 1999). Usage of the terms 'CNS lupus', 'lupus cerebritis', 'CNS vasculitis', 'lupus headache', 'lupoid sclerosis', 'brief reactive psychosis', and 'organic brain syndrome' is discouraged. Neuropsychiatric manifestations may occur in up to two-thirds of patients with SLE (West, 1994) and range from anxiety, mood disorders, cognitive dysfunction and delirium to depression, frank psychosis, stupor and coma (Kovacs et al., 1993; Boumpas et al., 1995). Several conditions must be excluded before the attribution of neurological findings to NPSLE.

Pathogenesis

The pathogenesis of NPSLE remains elusive. It is probably more accurate to regard the 'disease' of SLE as a complex, heterogeneous group of disorders of unknown cause. Autopsy studies of patients with NPSLE have shown no pathognomonic lesions and frequently demonstrated poor correlation between clinical and pathological findings (West, 1994). In a classic 1968 paper, Johnson and Richardson reported that microscopic lesions were more common than macroscopic ones. Microinfarcts, microhemorrhages and increased pericapillary microglia were found in 20 of the 24 patients autopsied (83%) (Johnson & Richardson, 1968). Vasculitis was seen rarely, and inflammatory cells were present in only 3 out of the 24 patients (12.5%). Even some highly symptomatic patients, particularly those with diffuse CNS dysfunction, had few pathological abnormalities. In contrast, pathological abnormalities were found occasionally in patients who demonstrated no overt neurological manifestations of NPSLE during life. Other autopsy studies have provided similar results, the most common findings being a bland vasculopathy with endothelial proliferation, hyalinization, multiple microinfarcts, and microhemorrhages (Ellis & Veroty, 1979; Funata, 1979; Devinsky et al., 1988; Hanly et al., 1992).

Evidence suggests several possible etiological roles for a number of autoantibodies including antiribosomal P antibodies, anti-lymphocyte antibodies, antineuronal antibodies, and antiphospholipid antibodies (aPL). The precise mechanisms of how these antibodies conspire to cause NPSLE is unclear. In the 1980s and 1990s, research focused

Table 96.1. The 1982 revised ACR CRITERIA[a]

Criterion	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, sparing the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging: atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	Pleuritis: convincing evidence of pleuritic pain or rub heard by a physician or evidence of pleural effusion; o*r* Pericarditis: documented by electrocardiogram or rub or evidence of pericardial effusion
Renal disorder	Persistent proteinuria greater than 0.5 g/24 hours or greater than 3+ if quantitation not performed; *or* Cellular casts: may be red cell, hemoglobin, granular, tubular, or mixed
Neurological disorder	Seizures: in the absence of offending drugs or known metabolic derangement, e.g. uremia, ketoacidosis, or electrolyte imbalance; *or* Psychosis: in the absence of offending drugs or known metabolic derangement, e.g. uremia, ketoacidosis, or electrolyte imbalance
Hematological disorder	Hemolytic anemia with reticulocytosis; *or* Leukopenia: less than 4000/mm^3 on more than two occasions; *or* Lymphopenia: less than 1500/mm^3 on more than two occasions; *or* Thrombocytopenia: less than 100 000/mm^3 in the absence of offending drugs
Immunological disorder	Positive LE cell preparation; *or* Anti-DNA: antibody to native DNA in abnormal titre; *or* Anti-Sm: presence of antibody to SM nuclear antigen; *or* False-positive serological test for syphilis, known to be positive for at least 6 months, and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody test
Antinuclear antibody	An abnormal titre of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time in the absence of drug

Note:
[a] Tan et al. (1982).

on intraneuronal antigens, particularly in relation to the complications of psychosis and depression (Bluestein, 1997). Two studies showed moderately strong associations between serum antiribosomal P antibodies and psychiatric manifestations (Bonfa et al., 1987; Schneebaum et al., 1991; Teh & Isenberg, 1994). Schneebaum et al. found serum antiribosomal P antibodies in 51 of 269 patients with SLE (19%) (Schneebaum et al., 1991). Among the 82 patients with NPSLE symptoms, elevated levels of antiribosomal P antibodies were found in 29%, compared to only 14% of the 187 patients without NPSLE manifestations. In those patients with psychosis and depression, 45% and 88% were antiribosomal P antibody positive, respectively (Bluestein, 1997). Further investigations of antiribosomal P antibodies in SLE are indicated before widespread application in clinical practice (Teh & Isenberg, 1994; ACR Ad hoc Committee, 1999).

Serum and cerebrospinal (CSF) fluid IgG antineuronal antibodies have also been investigated (Bluestein et al., 1981; Temesvari et al., 1983; Robbins et al., 1988; Costalla et al., 1990; Matsunaga et al., 1991; Denburg et al., 1994; Wallace & Metzger, 1997). Serum antineuronal antibodies are present in 80% of patients with NPSLE (compared with only 5% of those without NPSLE features). However, CSF antineuronal antibodies have superior sensitivity and specificity for NPSLE (Bluestein et al., 1981; Bluestein & Zvaifler, 1983; Bluestein, 1997; Wallace & Metzger, 1997). Bluestein et al. found CSF antineuronal antibodies in 75% of patients with NPSLE, compared with only 10% in SLE patients without evidence of NPSLE, with the strongest

Table 96.2. Neuropsychiatric syndromes of SLE[a]

Central nervous system
Headache (including migraine and benign intracranial hypertension)
Acute confusional state
Psychosis
Mood disorder
Anxiety disorder
Cognitive dysfunction
Seizure disorders
Myelopathy
Demyelinating syndrome
Cerebrovascular disease
Aseptic meningitis
Movement disorder
Peripheral nervous system
Myasthenia gravis
Cranial neuropathy
Single/multiple mononeuropathy
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome)
Polyneuropathy
Plexopathy
Autonomic disorder

Note:
[a] American College of Rheumatology ad hoc Committee (1999).

correlation in those patients with diffuse CNS dysfunction (Bluestein et al., 1981).

Much investigation has also centred on the role of aPL in NPSLE. Intracranial thromboses causing cerebrovascular syndromes are strongly associated with aPL. These antibodies also occur in some patients with Libman–Sacks endocarditis. Embolization from cardiac foci and the formation of thrombi *in situ* cause strokes in some SLE patients. However, as with the other autoantibodies, not all patients with these antibodies have manifestations of NPSLE (Hirohata & Miyamoto, 1990; Susuki et al., 1995; Bluestein, 1997; Khoshbin et al., 1999).

With the exception of aPL, neither serum nor CSF levels of the autoantibodies discussed above have correlated consistently with specific neuropsychiatric syndromes in SLE. Use of these assays should be reserved for investigational use only.

Although no single pathogenetic mechanism currently explains the broad spectrum of NPSLE manifestations, in recent years, the process of apoptosis has attracted considerable attention as one that may explain many aspects of the initiation and propagation of SLE (Andrade et al., 2000). The central hypothesis in this theory is that failure to phagocytose and degrade apoptotic cells, followed by an autoamplification of the inflammatory process, leads to the clinical expression of SLE. In the genetically susceptible individual, a primary immune response directed against certain non-tolerized structures is initiated. In SLE, it is known that autoantigens are clustered and concentrated in the surface blebs of apoptotic cells, where they are modified by apoptosis-specific proteolysis and phosphorylation (Rosen & Casciola-Rosen, 1999). Many of these autoantigens are cleaved specifically by caspases during apoptosis, generating unique fragments. Other autoantigens are cleaved by granzyme B. In general terms, defective clearance of this apoptotic material and abnormal regulation of the immune response are likely susceptibility factors to this initiation phase. Access of the apoptotic material to the class II major histocompatibility complex pathway in the context of antigen-presenting cells may then initiate a primary immune response effectively. Once primary immunization has occurred, the repeated generation of apoptotic material (e.g. by sun exposure, viral infections, or drug triggers) may rechallenge the immune system effectively, leading to flares.

Laboratory testing/imaging studies

In patients suspected of possible NPSLE, a complete history and physical examination are the essential first steps. Laboratory analyses should include a complete blood count with differential; renal and hepatic function profiles; serum complement levels; an anti-dsDNA antibody assay; an erythrocyte sedimentation rate (ESR); and a urinalysis that includes microscopic examination. Assays for aPL (anticardiolipin antibodies and the lupus anticoagulant) are also indicated (see below). Other evaluations for hypercoagulable states may be indicated in patients with histories of vascular thromboses. Because of the frequent use of immunosuppression in SLE, a high index of suspicion for systemic or CNS infections is essential. Blood cultures, echocardiograms, and other studies may be indicated by certain clinical presentations.

Lumbar puncture provides important information in the setting of possible NPSLE. In addition to the cell count (with differential white blood cell count) and levels of protein and glucose, the CSF should also be assayed for cryptococcal antigen and cultured for bacterial, fungal and mycobacterial organisms. In the proper clinical settings, particularly when evaluating SLE patients with multiple sclerosis-like presentations, total IgG and albumin levels, myelin basic protein, and oligoclonal bands may be useful (West, 1994; Wallace & Metzger, 1997).

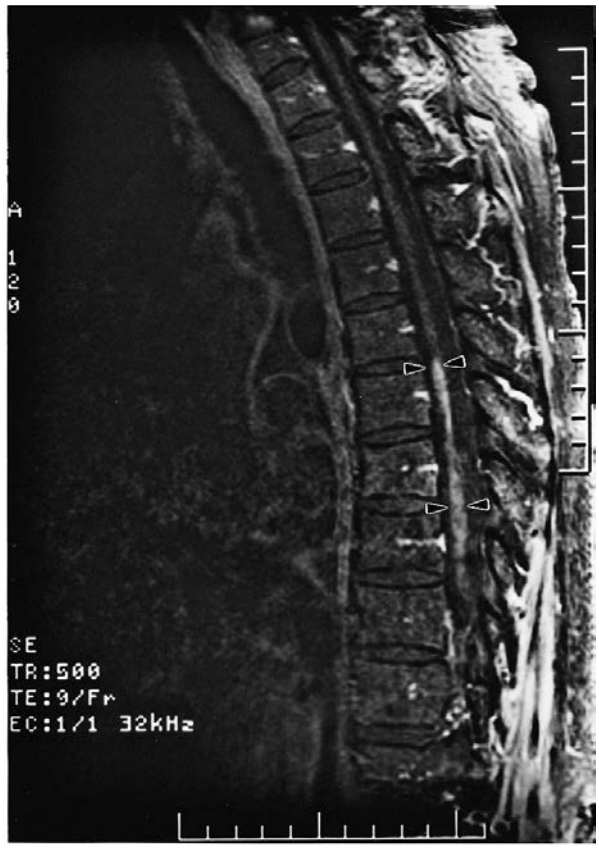

Fig. 96.1. Transverse myelopathy in systemic lupus erythematosus. Note increased signal intensity within the thoracic cord (arrowheads) corresponding to inflammation or ischemia extending over several segments. (Figure courtesy of Dr J.C. McArthur.)

Neuroimaging techniques play an important role in the evaluation of NPSLE patients but by themselves rarely yield diagnostic information. Radiology studies are often most helpful in excluding conditions that may mimic NPSLE, and must always be interpreted in light of the patient's clinical picture. Magnetic resonance (MR) imaging is superior to computerized tomography (CT) scanning for evaluating most NPSLE syndromes (Sibbitt et al., 1999). CT scans can be useful early in the diagnostic evaluation for the exclusion of large infarctions, intracerebral hemorrhages, massive cerebral edema, and mass lesions (e.g. brain abscesses or mycotic aneurysms) (Sibbitt et al., 1999). However, CT is comparatively insensitive to small lesions (infarcts or punctate lesions), diffuse brain injury and chronic white matter disease. Because MR imaging is much more sensitive for these lesions, it is by far the preferred imaging technique in NPSLE (Sibbitt et al., 1999). MR imaging (Fig. 96.1) should be performed promptly in the setting of neurological abnormalities, as some of the lesions associated with diffuse NPLSE disappear rapidly with the institution of glucocorticoid treatment (McCune et al., 1988; Sibbitt et al., 1989).

Headaches

Headache is a common symptom in SLE patients (Wallace & Metzger, 1997; Gladman & Urowitz, 1998). Migraine and tension headaches occur with increased frequency in SLE, and distinguishing these benign headaches from those of more serious etiology is sometimes challenging (Isenberg et al., 1982; Kovacs et al., 1993; Molad & Wysenbeek, 1997; ACR Ad hoc Committee, 1999). In the past, SLE patients with severe, disabling, and persistent headaches were labelled as having 'lupus headaches'. 'Non-specific intractable headaches' is now the preferred term (ACR Ad hoc Committee, 1999).

Benign intracranial hypertension (pseudotumour cerebri) may occur in SLE, with headache and papilledema as the presenting features (Li & Ho, 1989; Greeb et al., 1995). These patients have no focal neurologic deficits or abnormal CSF findings. aPL have been reported in patients with benign intracranial hypertension, but the true relationship between these antibodies and this clinical entity remains poorly defined (Wallace & Metzger, 1997). Benign intracranial hypertension occurs more commonly in adolescent women and is associated with dural sinus thromboses and steroid tapering (Parnass et al., 1987; Wallace & Metzger, 1997).

Acute confusional states

Diffuse CNS dysfunction in SLE may present with symptoms of an acute confusional state (ACS) (ACR Ad hoc Committee, 1999). Synonyms for ACS include 'organic brain syndrome', 'delirium', 'encephalopathy', 'lupus cerebritis', and 'CNS vasculitis'. With regard to the last term, autopsy studies demonstrate that true CNS vasculitis rarely occurs in SLE (Johnson & Richardson, 1968; Ellis & Veroty, 1979). Rather, diffuse CNS symptoms in SLE are much more likely to result from infections or complications of hypercoagulable states than from vasculitis (West, 1994).

The key feature of ACS is a disturbance in consciousness or level of arousal. ACS is characterized by deficits in attention accompanied by disturbances of cognition, mood, affect and/or behaviour, and may range from hyperactivity with delirium to coma. The syndrome typically develops over hours to days, and the patients' mental status may

fluctuate throughout the day. ACS can be complicated by psychosis and seizures. Varying degrees of cognitive deficits may occur, but if they occur without other manifestations of ACS, the term 'cognitive dysfuncton' is more appropriate (Carbotte et al., 1995). Before attributing a patient's symptomatology to ACS, other neurological disorders, drug-induced delirium (due to either prescription drugs or substance abuse), CNS infection and metabolic derangements must be excluded.

Glucocorticoids are the mainstay of therapy of ACS in SLE. Cyclophosphamide may be added in recalcitrant cases. Even following the institution of appropriate doses of immunosuppressive agents, ACS may require weeks or months to resolve.

Psychosis, anxiety and mood disorders

Psychosis, a severe disturbance in the perception of reality (including delusions and/or halluncinations), has been recognized as a manifestation of SLE for many years (Kovacs et al., 1993; Boumpas et al., 1995; ACR Ad hoc Committee, 1999;). Psychosis secondary to NPSLE may be difficult to distinguish from steroid psychosis in patients receiving glucocorticoids (Hall et al., 1979; Ling et al., 1981; Denburg et al., 1995). In this situation, steroids are rarely the cause of CNS dysfunction, and are responsible for less than 10% of psychotic events in SLE patients (Bluestein, 1992). The degree of SLE activity in other organs systems can be useful in separating steroid psychosis from NPSLE. Whereas auditory hallucinations are characteristic of steroid-induced psychoses, tactile hallucinations are more frequent in NPSLE (Bluestein, 1992).

Anxiety and depression commonly occur in SLE. Careful clinical evaluations, often with psychiatric consultation, will determine if anxiety and depression are reactive phenomena or true manifestations of NPSLE. In most SLE patients, anxiety is a reactive phenomenon rather than a direct manifestation of NPSLE. Depression may be severe in NPSLE and requires aggressive antidepressant therapy as well as treatment directed against SLE (Gladman & Urowitz, 1998).

Seizures

Both partial (focal) and generalized (primary/secondary) seizures occur in SLE (Scheuer & Pedley, 1990; ACR Ad hoc Committee, 1999). The frequency of seizures in large SLE series is between 6 and 26% (Wallace & Metzger, 1997). Seizures can occur as isolated events or in association with other neurologic symptoms such as strokes or intracranial hemorrhage (West, 1994). The etiology of seizures in SLE may be multifactorial, attributable to focal ischemia, any of the causes of cerebrovascular syndromes, cardiac emboli, and/or the presence of antineuronal/other autoantibodies. Other causes to consider include glucocorticoid withdrawal, high-dose intravenous glucocorticoid therapy, CNS infection, or chronic scar foci from previous neurologic events (Wallace & Metzger, 1997). Differentiation of seizures that are caused by active SLE, from those induced by treatment of the condition, can prove difficult (Mayes & Brey, 1996; Wallace & Metzger, 1997). Seizures caused by NPSLE respond well to glucocorticoid administration and may not require long-term anticonvulsant therapy (Russell et al., 1951; Presthus & Skulstad, 1957; Wallace & Metzger, 1997).

Myelopathy, optic neuropathy, and demyelinating syndromes

Transverse myelopathy (TM) occurs in only 1–2% of SLE patients, but can lead to the devastating sequelae of paraparesis or paraplegia (Andrianokos et al., 1975; Warren & Kredich, 1984; Kovacs et al., 2000) (Fig. 96.1). TM usually has a rapid onset with bilateral weakness of legs and/or arms, but may be asymmetric. Both sensory and motor deficits may occur, as may bowel and bladder dysfunction (Gladman & Urowitz, 1998; Kovacs et al., 1993, 2000). TM constitutes a medical emergency, and early diagnosis requires a high index of clinical suspicion. A recent retrospective review recorded a total 105 published cases of TM occurring in patients with SLE (Kovacs et al., 2000). This review found that TM often occurs early in the disease process, i.e. accompanying the initial presentation or within 5 years of disease onset.

The pathophysiology of TM in SLE remains elusive. Investigations are hindered by the paucity of pathologic material from these patients. The most commonly offered explanations are vasculitis of the spinal cord (Andrianokos et al., 1975) and thrombosis of the spinal vessels (perhaps mediated by aPL) (Lavelle et al., 1990). Either of these mechanisms (and other ones) may be operative in individual patients. One unusual steroid complication, epidural lipomatosis, may lead to compression of the anterior spinal artery, causing symptoms and signs that mimic TM (Bluestein, 1992).

The occurrence of TM in SLE may be difficult to distinguish from multiple sclerosis (MS). The term 'lupoid sclerosis' has been employed to describe SLE patients presenting with neurological features reminiscent of MS. MS may be associated with ANA (Dore-Duffy et al., 1982; Bluestein, 1992). In addition, an increased prevalence of aPL in SLE patients with TM and optic neuropathy (ON) has been

noted. In a recent review of TM, ON occurred in 48% of 105 cases of SLE patients with TM (Devic, 1894; April & Vansonnberg, 1976; Kinney et al., 1979; Kovacs et al., 2000). In SLE patients without TM, however, the incidence of ON is probably much lower. Occurrence of these symptoms in SLE may represent a combination of the two diseases, perhaps reflecting a shared autoimmune pathogenesis. 'Demyelinating syndrome' may be the best term for these neurologic features in SLE (ACR Ad hoc Committee, 1999).

Early, aggressive treatment of TM may improve patient outcomes (Harisdangkul et al., 1995). The combination of high-dose intravenous ('pulse') methylprednisone for 3 days and monthly intravenous cyclophosphamide is recommended (Kovacs et al., 2000). The benefit of plasmapheresis remains unproven. Unfortunately, residual neurological deficits can be devastating (April & Vansonnberg, 1976; Harisdangkul et al., 1995; Kovacs et al., 2000). In patients with compelling evidence of aPL in disease pathogenesis (e.g. strongly positive aPL titres, and other clinical features of APS), anticoagulation with coumadin is reasonable.

Cerebrovascular disease

Cerebrovascular disease (CVD) in SLE may result from arterial insufficiency/occlusion, venous occlusive disease, or hemorrhage, leading to transient or permanent neurologic deficits. CVD encompasses the following presentations: stroke syndrome, transient ischemic attacks (TIA), chronic multifocal white matter disease, subarachnoid/intracranial hemorrhage, and venous sinus thrombosis (Kelley et al., 1980; Fields et al., 1990; Wallace & Metzger, 1997; ACR Ad hoc Committee, 1999) (see Fig. 96.2). In recent years, there has also been greater awareness of the vasculopathy associated with long-term glucocorticoid use.

Aseptic meningitis

Aseptic meningitis (AS) presents with fever, headache, and meningismus. Lumbar puncture reveals a lymphocytic pleocytosis, most commonly with less than 200–300 WBC/mm^3 (Welsby & Smith, 1977; West, 1994). Nonsteroidal anti-inflammatory agents, commonly used in SLE, may also cause AS (Ballas & Konta, 1982; Hoppmann et al., 1991), as may azathioprine (rarely) (Lockshin & Kagen, 1972; Bluestein, 1992).

Movement disorders

Chorea (Lusius & Szilagyi, 1975; Bruyn & Padberg, 1984), hemiballismus, cerebellar ataxia (Singh et al., 1988; Al-Arfaj & Naddaf, 1995), and rarely Parkinsonism (Miyoshi et al., 1993) may complicate SLE. Of these, chorea is the most common, occurring in 1–4% of SLE patients (Wallace & Metzger, 1997). It can be the presenting feature of SLE, antedating other manifestations by up to 7 years (Donaldson et al., 1971). In a review of 29 cases, the majority of patients were girls (Groothius et al., 1977; Wallace & Metzger, 1997). In a subsequent review of 52 cases, chorea occurred early in the natural history of SLE, did not correlate with other neurological symptoms, lasted a maximum of 3 years, and was associated with pregnancy and the postpartum period (Bruyn & Padberg, 1984). Autopsy studies in SLE have revealed infarctions of the basal ganglia in patients with movement disorders (Wallace & Metzger, 1997). Since the advent of testing for aPL, many associations between chorea and these autoantibodies have been reported (Hadron et al., 1986; Asherson et al., 1987a; Petri, 1997).

Cranial neuropathies

Cranial neuropathies occur in 3 to 16% of SLE patients during the course of their disease (Wallace & Metzger, 1997). They tend to occur during flares of SLE in other organs (McCune & Golbus, 1988; West, 1994). Facial nerve palsies, third and fourth nerve palsies, trigeminal neuralgia, ON, internuclear ophthalmoplegia have all been reported. Other manifestations include tinnitus and vertigo. These usually are transient and respond to treatment with glucocorticoids (West, 1994).

Peripheral nervous system manifestations

The peripheral nerve manifestations of NPSLE include myasthenia gravis, autonomic neuropathy and peripheral neuropathy. Peripheral neuropathies are subdivided into acute inflammatory demyelinating polyneuropathies (Guillain–Barré syndrome), mononeuropathies, plexopathies, peripheral cranial neuropathies, and polyneuropathies (ACR Ad hoc Committee, 1999). Peripheral neuropathy may occur in 2 to 21% of SLE patients (Wallace & Metzger, 1997). Most patients are responsive to glucocorticoids but cytotoxic agents and plasma exchange have been used for refractory cases (Hughes et al., 1982; Wallace & Metzger, 1997).

The antiphospholipid syndrome

A major contribution to understanding the pathogenesis and treatment of many clinical manifestations of SLE has been elucidation of the antiphospholipid syndrome (APS).

Table 96.3. Revised criteria for the antiphospholipid syndrome[a]

Clinical criteria

(i) Vascular thrombosis:
One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ.

(ii) Pregnancy morbidity.

Laboratory criteria

(i) Anticardiolipin antibody of IgG and/or IgM isotype in blood in medium or high titre, on two or more occasions, at least 6 weeks apart.

(ii) Lupus anticoagulant present in the plasma, on two or more occasions, at least 6 weeks apart.

Definite antiphospholipid antibody syndrome is considered to be present if at least one of the clinical criteria and one of the laboratory criteria are met.

Note:

[a] Modified from Wilson et al. (1999).

Criteria for the diagnosis of APS are outlined in Table 96.3 (Wilson et al., 1999). Some clinicians classify patients with this syndrome as having either primary or secondary APS, depending on the absence or presence of an underlying condition, but the clinical features and antibody specificities of primary and secondary APS (as presently understood) are virtually identical (Alarcon-Segovia & Sanchez-Guerrero, 1989; Asherson et al., 1989a; Mackworth-Young et al., 1989; Vianna et al., 1994; Petri, 1997)).

APS is characterized by recurrent vascular thromboses, pregnancy losses and/or thrombocytopenia occuring in association with elevated levels of aPL (Harris, 1987; Petri, 1997; Wilson et al., 1999). The aPL include anticardiolipin antibodies and the lupus anticoagulant. Either or both may be present in individual patients. There is evidence that, in some APS patients, the target antigens are two phospholipid-binding plasma proteins, prothrombin and β_2-glycoprotein-1 (Roubey, 2000).

The spectrum of neurological manifestations in APS is broad (Levine & Welch, 1987; Petri, 1997) and includes strokes, TIAs, transient global amnesia, multi-infarct dementia, ischemic encephalopathy (Asherson et al., 1987b), ocular ischemia (Asherson et al., 1989b; Watts et al., 1990), severe migraines (Levine et al., 1990; Pope et al., 1991), pseudotumour cerebri, chorea (Hatron et al., 1986; Asherson et al., 1987a), apnea (Herkes et al., 1988), seizures, and TM (Harris et al., 1985; Lavelle et al., 1990). APS accounts for 36% of new strokes in those younger than 50 years of age (Kittner & Gorelick, 1992).

APS should be suspected in any SLE patient presenting with thrombosis. Other hypercoagulable states must also be excluded by appropriate testing. Thromboses can occur in any venous or arterial distribution throughout the body. Overall, the most common sites of thromboses are the deep veins, followed by the CNS. Although thrombocytopenia is not part of the APS criteria (see Table 96.3), it is a well-recognized clinical manifestation of the disorder, but other causes of thrombocytopenia in SLE must be excluded (Harris et al., 1986; Petri, 1997). APS has also been associated with leg ulcers, digital ischemia, superficial thrombophlebitis, hemolytic anemia, angina, cardiac valvular disease, pulmonary embolism, pulmonary hypertension, adrenal failure, myocardial infarction and livedo reticularis. Sneddon's syndrome, the occurrence of livedo reticularis and stroke/TIA, is a subset of APS in many cases (Sneddon, 1965; Petri, 1997). Some Sneddon's syndrome patients, however, do not have demonstrable aPL and do not meet criteria for APS (Jonas et al., 1986; Burton, 1988; Petri, 1997).

Occasionally APS patients present with the 'catastrophic antiphospholipid syndrome'. In this devastating complication, thromboses occur at multiple sites, either simultaneously or over a matter of hours, days or weeks (Greisman et al., 1991; Asherson, 1992). On presentation, the differential diagnosis of these critically ill patients includes disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, systemic vasculitis, and sepsis. APL assays are sometimes negative during this overwhelming cascade of clinical events (Drenkard et al., 1989; Greisman et al., 1991).

Following a thrombotic event, the treatment of APS necessitates long-term treatment with warfarin to avert further recurrences (Derksen et al., 1993; Khamashta et al., 1995; Petri, 2000). While some researchers have suggested a low-intensity warfarin schedule, most experts still advocate maintaining the International Normalized Ratio of greater than/equal to 3 (Khamashta et al., 1995).

Sjögren's syndrome

Sjögren's syndrome (SS) is a systemic inflammatory autoimmune disorder that primarily affects the exocrine glands. SS is characterized by lymphocytic infiltration of these glands leading to organ dysfunction and the principal manifestations of keratoconjunctivitis sicca and xerostomia (Tzioufas & Moutsopoulos, 1998). Typically, the syndrome begins with non-specific symptoms and develops slowly. Many patients are symptomatic for years before the diagnosis is made (Maini, 1987). SS can be either

primary (occurring alone), or secondary to other autoimmune conditions, such as systemic lupus erythematosus, rheumatoid arthritis, or systemic sclerosis (Fotini et al., 2000). It occurs at all ages but primarily affects females during the fourth and fifth decades of life. The disorder is nine times more common in women than men (Tzioufas & Moutsopoulos, 1998).

Laboratory testing may reveal a mild anemia of chronic disease, with leukopenia in 10% of cases (Tzioufas & Moutsopoulos, 1998). An elevated ESR and hypergammaglobulinemia is found in nearly 80% of cases and autoantibodies are common, particularly to Ro (SS-A), and La (SS-B), ANA, and rheumatoid factor (Tzioufas & Moutsopoulos, 1998). The cornerstone of diagnosis remains biopsy of a minor salivary gland and demonstration of focal lymphocytic infiltrates (Chisholm & Mason, 1968; Moutsopoulos, 1994). A European multicentre study led to widely accepted diagnostic criteria for primary SS (Vitali et al., 1993, 1996).

The most feared complication of primary SS is the development of B-cell lymphoma (5–10% of all patients, equating to a 44-fold increased risk compared with age-, gender-, and race-matched controls) (Kassan et al., 1978; Tzioufas & Moutsopoulos, 1998; Ioannidis & Moutsopoulos, 1999).

The neurologic manifestations of SS include peripheral neuropathies and, very rarely, CNS disease. Vasculitis, usually manifesting as purpura, urticaria, skin ulcerations and mononeuritis multiplex, occurs in 5% of SS patients (Tzioufas & Moutsopoulos, 1998). The peripheral neuropathy associated with SS is the result of a small vessel vasculitis, and is usually a symmetric, mild, sensory or sensorimotor neuropathy (Kaltreider & Talal, 1969; Mellfren et al., 1989; Andonopoulos et al., 1990). Nerve biopsy usually shows mononuclear cell infiltration (Mellfren et al., 1989). Although it is not clear if the peripheral neuropathy of SS always responds to immunosuppressive treatment, improvement has been reported (Mellfren et al., 1989). Cranial nerve involvement has been reported affecting the trigeminal and optic nerves (Kaltreider & Talal, 1969; Tzioufas & Moutsopoulos, 1998).

The frequency of CNS involvement in SS has probably been over-reported in the past. Reported CNS manifestations associated with primary SS are broad, and include seizures, hemiparesis, TM, AS, cognitive defects, encephalopathy and dementia, suggesting the possibility of both focal and diffuse involvement (Alexander, 1987; Tzioufas & Moutsopoulos, 1998; Niemela & Hakala, 1999). Although a 20–25% prevalence of CNS involvement in primary SS has been reported (Alexander, 1987; Alexander et al., 1994), this series probably suffered from substantial selection bias. Other investigators have sharply revised the estimate of CNS involvement in SS downward (Drosos et al., 1989; Moutsopoulos et al., 1993; Ioannidis & Moutsopoulos, 1999).

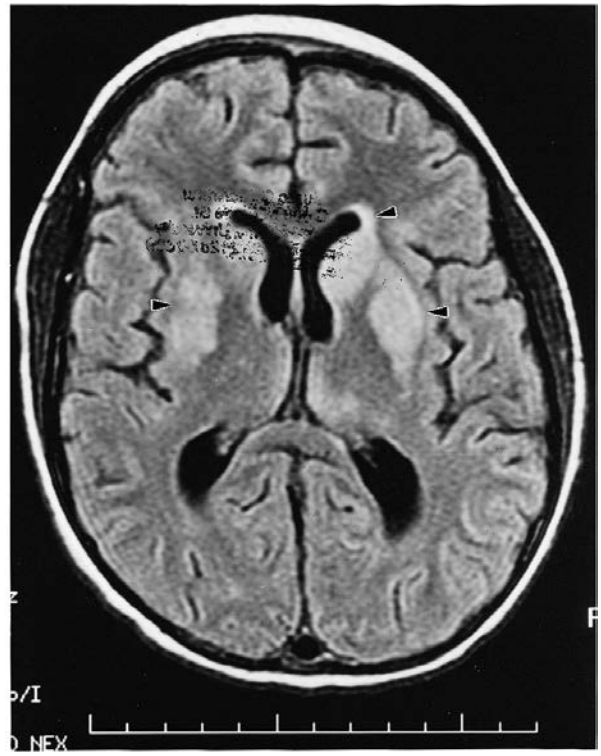

Fig. 96.2. MRI in cerebral lupus. Hyperintensities (arrowheads) in the left basal ganglion and right internal capsule.

Systemic vasculitides: polyarteritis nodosa

Polyarteritis nodosa (PAN), first described by Kussmaul and Maier in 1866 (Kussmaul & Maier, 1866), is defined as necrotizing vasculitis limited to medium-sized arteries (Jennette et al., 1994). Though protean in its manifestations, PAN demonstrates a striking predilection for certain organs, particularly the peripheral nerves (Fig. 96.3, see colour plate section), skin, gastrointestinal tract and kidneys. PAN usually begins with non-specific symptoms that may include malaise, fatigue, fever, myalgias, and arthralgias. Overt signs of vasculitis may not occur until weeks or months after onset of the first symptoms. Renal involvement, nearly universal at autopsy, produces few clinical symptoms during life aside from those related to renin-mediated hypertension caused by arteritic involvement of the medium-sized interlobar renal vessels (Heptinstall, 1992). Cardiac lesions, often striking at

autopsy, are usually subclinical (Cupps & Fauci, 1981). For reasons that are not understood, PAN usually spares the lungs.

The pathological changes in PAN are limited to arteries, sparing veins. In gross specimens, aneurysmal bulges of the arterial wall may be visible (Kussmaul & Maier, 1866). Histologic sections reveal infiltration and destruction of the blood vessel wall by inflammatory cells, accompanied by fibrinoid necrosis (Fauci et al., 1978). Whereas the acute inflammatory infiltrate is composed chiefly of neutrophils, mononuclear cells predominate in later stages. Varying degrees of intimal proliferation and thrombosis also occur. The lesions of PAN are segmental, and favour the branch points of arteries. A critical pathological feature of PAN is the absence of granulomas or granulomatous inflammation. A minority of PAN cases are associated with hepatitis B virus (HBV) infections (Goecke et al., 1970; Guillevin et al., 1995). Other microbial pathogens probably contribute to the remaining cases, but no definitive links with other infectious agents have been established.

A majority of patients with PAN (>80% in some series (Guillevin et al., 1995) have vasculitic neuropathy, typically in the pattern of a mononeuritis multiplex (MM). MM most often affects the peroneal, tibial, ulnar, median and radial nerves, leading to symptoms and signs in the distal extremities (e.g. foot or wrist drop) (Hellmann et al., 1987). Cranial neuropathies and radiculopathies are unusual, but reported. MM almost always causes sensory abnormalities, particularly painful dysesthesias; motor involvement occurs in one-third of patients. On clinical examination, advanced cases of MM may mimic confluent, symmetrical polyneuropathies. In such cases, electrodiagnostic testing may unmask an underlying asymmetry and confirm the presence of multiple axonal neuropathies. CNS disease in PAN usually results from hypertension rather than intracranial vasculitis, but vasculitic involvement of cerebral blood vessels sometimes occurs (Moore & Fauci, 1981; Guillevin et al., 1988).

The diagnosis of PAN requires either a tissue biopsy or an angiogram demonstrating the characteristic microaneurysms (Ewald et al., 1987). Biopsies of asymptomatic organs (e.g. the testicle) are rarely diagnostic (Albert et al., 1988; Dahlberg et al., 1989). In contrast, simultaneous nerve/muscle biopsies (e.g. sural nerve and gastrocnemius), are of high yield if there is clinical evidence of MM. Mesenteric angiography may demonstrate telltale microaneurysms, even in patients without gastrointestinal symptoms.

For patients with idiopathic PAN, prolonged immunosuppression remains the cornerstone of therapy. Approximately one-half of patients with PAN achieve remissions or cures with high doses of glucocorticoids alone (Guillevin & Lhote, 1998). Cyclophosphamide is indicated for patients whose disease is refractory to glucocorticoids or who have serious major organ involvement at diagnosis. Frequent monitoring of the white blood cell count (e.g. every 2 weeks) to avoid neutropenia is essential in order to prevent opportunistic infections. Prophylaxis against *Pneumocystis carinii* pneumonia with trimethoprim/sulfamethoxazole is also advisable.

In recent years, antiviral agents have improved the treatment of HBV-associated PAN substantially. One effective strategy involves the use of prednisone (1 mg/kg/d) to suppress the inflammation (Guillevin et al., 1995). Simultaneously with the start of glucocorticoid treatment, patients begin 6-week courses of plasma exchange (approximately 3 exchanges/week). After 1 week of glucocorticoids, prednisone is tapered off over 3–7 days, and antiviral therapy is started (e.g. lamivudine 100 mg/d).

The 'ANCA-associated' vasculitides

The 'antineutrophilic cytoplasmic antibody (ANCA)-associated' vasculitides (AAV) (Wegener's granulomatosis [WG], microscopic polyangiitis [MPA], and Churg–Strauss syndrome [CSS]) are characterized by pauci-immune, necrotizing vascular inflammation of small and medium-sized vessels (including veins as well as arteries). AAV have a particular tropism for the lungs, kidneys and upper respiratory tract. Among the neurological manifestations of these diseases, vasculitic neuropathy is extremely common (in CSS and MPA>WG) and potentially devastating. It should be noted that, despite rigorous serological evaluations, not all patients with 'ANCA-associated' vasculitis actually have detectable ANCA. Furthermore, the role of ANCA in disease pathogenesis of these conditions remains undefined. Rather than a primary etiological role, current evidence favours an ancillary role for ANCA in amplifying the ongoing inflammatory response (Hoffman & Specks, 1998).

Two types of ANCA tests, immunofluorescence (IF) and enzyme immunoassay (EIA), are now in common use. IF assays are more sensitive than EIAs, but their positive predictive values are low (Rao et al., 1995; Hagen et al., 1998). A host of non-vasculitic systemic illnesses may be associated with ANCA positivity, including infections, malignancies and other rheumatic conditions (Stone et al., 2000). Thus, positive IF assays for ANCA should be confirmed by EIAs for specific antibodies directed against proteinase-3 (PR-3) or myeloperoxidase (MPO), which are more specific for vasculitis (Hagen et al., 1998). ANCA titres are unreliable indicators of disease activity, and no treatment decisions should

be predicated solely upon elevations or declines in antibody titres.

Wegener's granulomatosis

Classic WG includes three pathologic hallmarks: (i) necrotizing granulomas of the upper and/or lower respiratory tract; (ii) vasculitis affecting arteries or veins; and (iii) segmental glomerulonephritis (GN), associated with necrosis and thrombosis of capillary loops, with or without granulomatous lesions (Godman & Churg, 1954). Approximately 90% of patients with WG have nasal involvement (Hoffman et al., 1992a). Cartilaginous inflammation may lead to nasal septal perforation and even to nasal bridge collapse (a 'saddle-nose' deformity). Erosive sinus disease is highly characteristic of WG. Subglottic stenosis, resulting from the predilection of WG to cause scarring inflammation below the vocal cords, may cause hoarseness or respiratory stridor, and sometimes requires a tracheostomy. Conductive hearing loss may result from granulomatous inflammation of the middle ear cavity and serous otitis media. Moreover, middle ear inflammation may compress the seventh cranial nerve as it courses through the middle ear cavity, leading to a peripheral facial nerve palsy. Sensorineural hearing loss occurs less often in WG, and its mechanism is poorly understood (Stone & Francis, 2000). WG has two signature ocular lesions: the retro-orbital mass and necrotizing scleritis.

The pulmonary manifestations of WG range from asymptomatic lung nodules to fulminant alveolar hemorrhage. Hilar and/or mediastinal adenopathy are rare. Renal involvement, the most ominous clinical manifestation of WG, is associated with segmental necrotizing GN and crescent formation, and presents clinically as rapidly progressive GN.

Parenchymal brain involvement has been reported in WG but is rare (Drachman, 1963; Fred et al., 1964), meningeal inflammation is a more common CNS manifestation of this disease. Meningeal WG typically presents with excruciating headaches, a CSF pleocytosis, cranial neuropathies caused by a basilar meningitis, and thickened meninges that enhance on MR imaging (Fig. 96.4). Because of the granulomatous inflammation, meningeal tuberculosis is a common misdiagnosis. MM may accompany WG but is more characteristic of MPA or CSS.

For WG patients with disease that threatens major organs, combined therapy with cyclophosphamide and glucocorticoids is indicated (Hoffman et al., 1992a). For those with 'limited' WG (Hoffman et al., 1992b), weekly methotrexate plus glucocorticoids is an appropriate first-line treatment strategy that avoids the potential toxicities of cyclophosphamide. However, durable remissions are unusual with this alternative regimen (Stone et al., 1999).

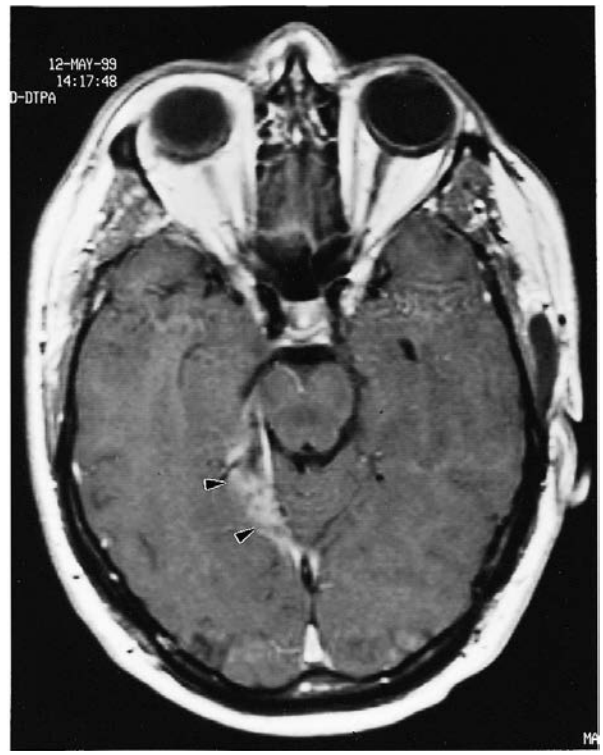

Fig. 96.4. MR in Wegener's granulomatosis: meningeal enhancement along right mesial temporal lobe (arrowheads). (Figure courtesy of Dr J.C. McArthur.)

Microscopic polyangiitis

Davson et al. (1948) proposed the division of PAN patients into two groups based on the presence or absence of GN. The 1994 Chapel Hill Consensus Conference (Jennette et al., 1994) validated the concept of microscopic polyangiitis (MPA) as a disease separate from classic PAN, defining MPA as a pauci-immune, non-granulomatous vasculitis affecting small (and perhaps) medium-sized blood vessels. The distinction between MPA and classic PAN is appropriate for several reasons. MPA, in contrast to PAN: (i) often involves the lung; (ii) may involve veins as well as arteries; (iii) rarely causes severe hypertension; (iv) is commonly associated with ANCA; (v) nearly always requires cyclophosphamide to induce remission; and, (vi) is more likely to flare following remissions.

GN (79%), weight loss (73%), MM (58%), and fever (55%) are the most common manifestations of MPA (Guillevin et

al., 1999a). The upper respiratory tract symptoms in MPA are milder than those of WG, but the cardinal distinction between MPA and WG is the absence of granulomatous inflammation. Approximately 12% of patients with MPA develop alveolar hemorrhage, which may constitute a rapidly evolving life-threatening complication (Guillevin & Lhote, 1998). Vasculitic neuropathy is common in MPA. Vasculitis involving the CNS occurs far less frequently, but is reported.

Churg–Strauss syndrome

Churg–Strauss syndrome (CSS) is a systemic vasculitis associated with eosinophilic infiltration of the blood vessel wall. The Chapel Hill Consensus Conference defined CSS as eosinophil-rich, granulomatous inflammation involving the respiratory tract, vasculitis of small to medium-sized blood vessels, asthma and eosinophilia (Jennette et al., 1994). CSS is often associated with substantial upper respiratory tract involvement in the form of nasal polyps and allergic rhinitis. In contrast to WG, however, the upper respiratory features of CSS are not destructive, and the typical pulmonary manifestation is asthma rather than nodules. Fleeting pulmonary infiltrates occur in up to one-third of patients.

CSS characteristically evolves through three distinct phases: (i) a prodrome accompanied by atopy, which may last from months to years; (ii) a peripheral eosinophilia/tissue infiltration phase, in which up to 60 000 eosinophils/mm^3 appear in the peripheral blood (eosinophils infiltrate the lung, gastrointestinal tract, and other tissues in this phase); and (iii) a vasculitic phase in which systemic vasculitis afflicts a wide range of organs. Greater than 90% of CSS patients have histories of asthma, typically of new onset. Cardiac involvement (usually congestive heart failure) occurs with comparatively greater frequency in CSS than in other AAV, and is a common mode of death (Guillevin et al., 1999b). Renal disease in CSS is less common and less malignant than in WG or MPA, but aggressive renal lesions sometimes occur (Clutterbuck et al., 1990). Finally, MM occurs with a remarkable frequency in CSS (77% in one series)(Guillevin et al., 1999b).

Because a substantial number of CSS patients achieve satisfactory responses with glucocorticoids alone, these agents are a reasonable first approach for many CSS patients. Concomitant cyclophosphamide use is indicated for patients with MM, rapidly progressive GN, or other indicators of severe disease. Interferon-alpha appears promising as a treatment for CSS (Tatsis et al., 1998), but larger studies are required.

Cryoglobulinemia

Cryoglobulins (CG) are antibodies that precipitate from serum under conditions of cold (e.g. refrigeration at 4 °C for several days) and resolubilize upon rewarming (Lamprecht et al., 1999). These proteins occur in association with a number of systemic conditions (e.g. autoimmune diseases and malignancies), and may lead to clinical complications that include vasculitis and hyperviscosity. CG are classified into three types (Types I, II, or III) based on the presence or absence of: (i) monoclonality; and (ii) rheumatoid factor activity (i.e. the ability to bind the Fc portion of IgG) (Table 96.4) (Meltzer & Franklin, 1966; Brouet et al., 1974; Lamprecht et al., 1999). Type I CG, which are monoclonal and lack rheumatoid factor activity, are associated with certain hematopoietic malignancies and often lead to the syndrome of hyperviscosity (addressed elsewhere in this text) rather than vasculitis. In contrast, collagen–vascular diseases are associated with Type II and Type III CG.

CG Types II and III are termed 'mixed' CG because they consist of both IgG and IgM antibodies. The IgM components in Type II and III CG both possess rheumatoid factor activity. Whereas the IgM component in Type II CG is monoclonal, the IgM in Type III is polyclonal. Either type of mixed CG may cause an immune complex-mediated small vessel vasculitis, through the deposition of cryoglobulin-containing immune complexes in blood vessel walls, leading to the activation of complement. Ninety per cent of patients with vasculitis secondary to mixed CG are hypocomplementemic, with C4 levels characteristically more depressed than C3 (Lamprecht et al., 1999). The most common manifestations of cryoglobulinemic vasculitis are recurrent crops of palpable purpura on the legs that sometimes coalesce to form large, painful ulcerations. Other common manifestations are vasculitic neuropathy, GN, arthralgias, malaise, and fatigue (Brouet et al., 1974; Lamprecht et al., 1999). Some patients develop mesenteric vasculitis, Raynaud's phenomenon, livedo reticularis or secondary SS. The typical features of Type II and III CG are virtually indistinguishable, except for the fact that only Type II is associated with glomerulonephritis (Lamprecht et al., 1999). CNS vasculitis occurs in a small minority of patients with CG.

Infection with the hepatitis C virus (HCV) accounts for at least 80% of the vasculitis cases associated with mixed CG (Agnello et al., 1992; Abel et al., 1993; Marcellin et al., 1993; Wener et al., 1996). Compared to serum levels, anti-HCV antibodies and HCV RNA in CG precipitates are concentrated 1000-fold. However, vasculitis occurs in only a minority of HCV patients, even though 50% of patients infected with HCV have demonstrable cryoglobulins. This

Table 96.4. Classification of cryoglobulins, their immunochemical features, and clinical associations

Type	Monoclonal	RF activity present[a]	Clinical syndrome	Disease association
I	Yes (usually IgG)	No	Hyperviscosity	Malignancy
II	Yes (IgM)	Yes	Vasculitis	Hepatitis C
				Rheumatic diseases
				Malignancy
				Idiopathic
III	No	Yes	Vasculitis	Hepatitis C
				Rheumatic diseases
				Idiopathic

Note:
[a] RF = Rheumatoid factor.

probably relates both to host genetic factors and to specific features of the infecting HCV quasi-species.

For CG patients with relatively mild disease (e.g. frequent purpuric lesions, shallow cutaneous ulcers), interferon-alpha (3×10^6 units 3 times per week) alone or combined with ribavirin (1000–1200 mg/d) may be effective; (Di Bisceglie et al., 1995; Poynard et al., 1995; Lamprecht et al., 1999). If antiviral therapy is initiated prior to control of the inflammatory process with immunosuppression, there is some risk of causing a temporary exacerbation of the vasculitic process (probably through alteration of the antigen: antibody ratio). For patients with MM or other manifestations of severe disease, glucocorticoids and cyclophosphamide are required, and plasmapheresis may be a useful adjunctive therapy. In such cases, antiviral therapy starts later.

Behçet's disease

Behçet's disease (BD) is among the forms of primary vasculitis most likely to involve the CNS (Shimizu et al., 1979; Kaklamani et al., 1998; Sakane et al., 1999). The hallmark triad of oral ulcers, genital ulcers and ocular inflammation was first described in 1937 (Behçet, 1937). BD may affect small, medium, and large arteries, and also has an unusual proclivity to involve veins as well as arteries. Most patients are in their third or fourth decade at disease onset. The cause is unknown. BD is most common in people with ancestry along the ancient Silk Route, i.e. the Eastern Mediterranean, Middle East, and Far East (Sakane et al., 1999). Genetic factors (e.g. the HLA-B51 allele) increase disease susceptibility (Mizuki et al., 1999).

The diagnostic criteria for BD and other prominent disease features are listed in Table 96.5 (Sakane et al., 1999). Virtually all patients have multiple, recurrent and often severe oral ulcers. Acute anterior uveitis frequently leads to a hypopyon, and chronically may cause irregular pupils because of synechiae between the iris and lens. Posterior uveitis, which usually results from vasculitis of the retinal veins, may be subclinical but eventually leads to devastating visual loss. Pathergy, the development of pustules at the sites of sterile needle pricks, occurs in only a minority of patients with BD, but is more likely among patients from areas of high disease prevalence (Sakane et al., 1999).

Although not included in the diagnostic criteria for BD, neurological involvement ('neuro-Behçet's') is common and often severe. The percentage of BD patients who develop clinical manifestations of neuro-Behçet's is at least 5% (Serdaroglu et al., 1989). In a large autopsy series, however, 20% of BD patients had pathological evidence of neurological involvement (Lakhanpal et al., 1985). The array of potential neurological complications may be divided into parenchymal and non-parenchymal lesions. The most common syndrome is brainstem inflammation, which often evolves over a period of days. Brainstem involvement may be associated with cranial neuropathies, oculomotor dysfunction, nystagmus, dysarthria, ataxia and bulbar weaknesss. Headache and meningismus usually accompany such brainstem lesions.

Meningoencephalitis is the second most common neurological syndrome in BD. Both spinal cord lesions (TM or the Brown–Sequárd syndrome) and hemispheric signs may complicate this presentation. Meningoencephalitis can also occur without focal signs, leading to a confusional

Table 96.5. Criteria for the diagnosis of Behçet's disease[a]

Finding	Definition
Recurrent oral ulceration	Minor aphthous, major aphthous, or herpeti-form ulcers observed by the physician or patient, which have recurred at least three times over a 12-month period
Recurrent genital ulceration	Aphthous ulceration or scarring observed by the physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, or cells in the vitreous on slit-lamp examination; or retinal vasculitis detected by an ophthalmologist
Skin lesions	Erythema nodosum observed by the physician or patient, pseudofolliculitis, or papulopustular lesions; or acneiform nodules observed by the physician in a postadolescent patient who is not receiving corticosteroids
Positive pathergy test	Test interpreted as positive by the physician at 24 to 48 hours

Notes:

[a] The criteria were drawn up by the International Study Group for Behçet's disease (Sakane *et al.*, 1999).

For the diagnosis to be made, a patient must have recurrent oral ulceration plus at least two of the other findings in the absence of other clinical explanations.

Additional features of BD sometimes include folliculitis; a peripheral arthritis (usually non-deforming, oligoarticular, involving large joints in an asymmetrical pattern); thrombophlebitis (often migratory); gastrointestinal disease (often difficult to distinguish from Crohn's disease); epididymitis; and large artery vasculitis (Sakane et al., 1999; Kaklamani et al., 1998; Zouboulis & Orfanos, 1998).

syndrome that is sometimes chronic and progressive, culminating in dementia, Parkinsonism, pseudobulbar palsy and quadriparesis. Parenchymal lesions in BD are usually associated with an active CSF characterized by a mixed pleocytosis and elevated CSF protein. In contrast to MS (with which neuro-Behçet's is often confused), most studies indicate no evidence of intrathecal immunoglobulin synthesis. MR imaging in BD correlates well with parenchymal lesions, and radiological lesions tend to improve or resolve completely following the resolution of clinical symptoms.

Venous sinus thrombosis is a common type of non-parenchymal complication in BD, and may occur with or without meningitis. Isolated intracranial hypertension (in the absence of dural sinus thrombosis) may also complicate BD and require shunting procedures. Unusual neurological manifestations of BD include peripheral nerve involvement, ON, sensorineural hearing loss and isolated vestibulopathy.

In terms of pathological findings, true vasculitis is rarely demonstrated in neuro-Behçet's. Far more common are acute inflammatory infiltrates within the parenchyma, comprised of neutrophils, lymphocytes, and occasional eosinophils. Patients with brainstem syndromes may have tissue swelling and multiple foci of cellular infiltration, with perivascular cuffing. Chronic cases show areas of necrosis and loss of all tissue elements, accompanied by brainstem atrophy.

Despite the severe nature of many neuro-Behçet's complications, patients may have complete recoveries from acute episodes if treated promptly. Long-term prognosis may be poor for patients who have relapsing neurological symptoms. The treatment of neuro-Behçet's is dictated by the type and severity of the neurological findings (Sakane et al., 1999). High doses of glucocorticoids are the cornerstone of therapy for major CNS involvement, but often these must be supplemented by additional agents either to control refractory disease or to avoid excessive glucocorticoid side effects. Early treatment with azathioprine favourably affects the long-term prognosis in Behcet's disease (Hamuryudan et al., 1997). Thalidomide is effective for the mucocutaneous features of Behcet's disease, but long-term use frequently leads to an irreversible peripheral neuropathy (Hamuryudan et al., 1998). For posterior uveitis and significant brainstem or other CNS lesions, cyclosporin, cyclophosphamide or chlorambucil may be indicated. Because of the potentially severe neurologic side effects of cyclosporin (which may be difficult to distinguish from neuro-Behcet's (Kotake et al., 1999), cyclosporin should be used with great caution in patients with neurological manifestations of the disease.

Giant cell arteritis

Giant cell arteritis (GCA), the most common form of primary systemic vasculitis, principally affects medium-

and large-sized extracranial branches of the carotid artery. For reasons that are not understood, documented intracranial disease in GCA is very rare. GCA occurs with increasing incidence in older patients and has a mean age of onset of 72. The disease virtually never occurs in individuals younger than 50. The disease is most common in Caucasians, particularly those of Northern European ancestry, but occurs in all races.

Headache is the most common feature of GCA (70–90%). The only distinguishing feature of GCA headaches is that they are unusual either in severity or location. Scalp tenderness, polymyalgia rheumatica, and jaw claudication are other classic symptoms of GCA. The most feared complication of GCA is blindness, the usual mechanism of which is anterior ischemic optic neuropathy (AION) caused by infarction of the posterior ciliary artery. Partial visual loss occurs in 10–15% of all patients with GCA, and bilateral blindness may occur. The onset of visual loss from AION is usually abrupt and irreversible. Other neuro-ophthalmological complications of GCA are amaurosis fugax and diplopia, the latter caused by cranial nerve vasculitis.

A substantial portion of patients with GCA present with atypical clinical features. Although intracranial vessels are generally spared by GCA, strokes may occur from thrombosis of, or embolization from, extracranial vessels (Caselli & Hunder, 1993). GCA may also involve the brachial plexus, leading to the sudden onset of pain and inability to abduct the shoulder, mimicking a C5 radiculopathy. Other misleading presentations of GCA include fever of unknown origin (Calamia & Hunder, 1981), persistent nonproductive cough, poorly localized pains in the region of the throat and lingual infarction. Complications of large artery involvement by GCA such as aortic dissection or aneurysm (thoracic>abdominal) may be catastrophic, and sometimes occur years after diagnosis (Evans et al., 1995). One population-based study, large artery involvement (thoracic or abdominal aortic aneurysms) occurred in 17% of the patients (Evans et al., 1995).

The diagnosis of GCA is usually confirmed by temporal artery biopsy. Because of the non-specific nature of many GCA symptoms, and the justification required for the use of a potentially toxic treatment (glucocorticoids), the importance of performing temporal artery biopsies in patients suspected of having GCA cannot be overemphasized. However, treatment should be instituted immediately once the diagnosis is suspected, not delayed until after performance of a biopsy. The diagnosis may be confirmed even after patients have been on glucocorticoid treatment for several weeks (Achkar et al., 1994). (Nevertheless, obtaining biopsies as quickly as possible is prudent.) Negative bilateral temporal artery biopsies have a negative predictive value of 91% (Hall et al., 1983). Arterial segments at least 2 centimetres in length should be removed during the procedure.

The pathological features of GCA are consistent with an antigen-driven T-cell response (Weyand, 2000). Cellular infiltrates are composed of CD4+ T-lymphocytes, macrophages and multinucleated giant cells, but B-cells are typically absent (Martinez-Taboada et al., 1996a). The T-cells are believed to enter the artery via the vasa vasorum in the adventitia, recruited by a specific (but still unknown) antigen or antigens (Martinez-Taboada et al., 1996b). The T-cells orchestrating the inflammatory response in GCA produce interferon (IFN)-γ. This cytokine may be essential in the conversion of polymyalgia rheumatica to GCA (Weyand et al., 1994). Under stimulation by T-cells, adventitial macrophages produce interleukin (IL)-1β and IL-6, but little tumour necrosis factor.

Despite the importance of the adventitia to orchestration of the disease, most of the tissue damage occurs in the media and intima. Macrophages in the media produce not IL-1 or IL-6, but rather matrix metalloproteinases (MMP). These enzymes are capable of digesting arterial wall components, and may contribute to the fragmentation of the internal elastic lamina. MMP are also essential for the mobilization and migration of smooth muscle cells from the media to the intima, where they undergo proliferation. The final step in the pathophysiology of GCA (culminating in luminal occlusion) is a hyperplastic reaction of the intima, driven by platelet-derived growth factor (PDGF) produced by multinucleated giant cells and macrophages situated at the border of the media and intima (Kaiser et al., 1998).

GCA is exquisitely sensitive to treatment with glucocorticoids. The usual starting dose is at least 60 mg/d of prednisone. The goal should be to decrease the patient's dose to 20 mg/d by the end of the second month of therapy, and to taper steroids off completely by 9–12 months. However, flares of disease frequently occur during steroid tapers in at least 50% of cases, and the mean length of prednisone therapy is approximately 2 years. A recent multicentre trial of methotrexate as a steroid sparing agent in GCA found no effectiveness of methotrexate for this purpose (Hoffman et al., 2000).

Takayasu's arteritis

Takayasu's arteritis (TA) is a form of large vessel vasculitis that tends to afflict young females. Because of its predilection for large elastic arteries arising from the aortic arch, TA frequently leads to diminished or absent pulses in the

upper extremities, hence the alternative name 'pulseless disease'. The disease is associated with granulomatous vasculitis focused on the media of the artery, histopathologically indistinguishable from GCA. Two frequently overlapping phases of the disease are described: (i) an inflammatory phase, in which findings of an acute inflammatory state exist (constitutional symptoms, elevated acute phase reactants); and (ii) a stenotic phase, in which damaged elastic arteries become either narrowed, leading to tissue ischemia, or dilated (potentially leading to rupture). The ascending aorta, aortic arch, and branch vessels are most commonly affected, including the carotid, brachiocephalic, subclavian, and vertebral arteries. The descending aorta may also be affected, and renal artery involvement sometimes results in hypertension. The pulmonary vasculature is involved in approximately one-half of all patients with TA, but is asymptomatic in many. Whereas most of the involved arteries become narrowed after some period of inflammation, the ascending aorta frequently dilates, sometimes leading to aortic dissection and aortic regurgitation.

Severe involvement of the extracranial large arteries supplying the brain (the carotids and vertebrals) may lead to cerebrovascular accidents, but intracranial involvement is surprisingly rare, as in GCA. Steal syndromes (e.g. the subclavian steal: Moncada et al., 1998) often result from such large artery involvement. Advanced carotid lesions may be associated with a host of ocular findings in TA. The first TA patient ever described had 'a peculiar, wreath-like sheathing' (Takayasu, 1908) of retinal blood vessels, representing an arteriovenous anastomosis. In addition to arteriovenous anastomosis, ophthalmological findings in TA include microaneurysms, retinal neovascularization and, as an eventual complication of retinal ischemia, vitreous hemorrhage, retinal detachment, and optic atrophy. Approximately 35% of patients in one series had eye findings directly related to TA, but many of these patients had few or no symptoms (Kiyosawa & Baba, 1998). Rare cases of AION (the classic lesion of GCA) have been described in TA (Schmidt et al., 1997). In some cases, retinal lesions such as microaneurysms have undergone dramatic resolution following bypass procedures to restore the patency of large vessel circulation to the head (Kiyosawa & Baba, 1998). Although most of the retinal findings in TA are associated with cerebral hypoperfusion, hypertensive retinopathy may also ensue from renal artery stenosis (Uyama & Asayama, 1976).

Determination of the degree of disease activity may be exceptionally difficult in TA. Forty-four per cent of patients undergoing surgery of stenotic lesions for presumed 'burned out' disease had active arteritis upon pathological examination of the specimens (Kerr et al., 1994). Acute phase reactants are unreliable parameters of disease activity in many patients. MR may have some role in assessing disease activity, but its role needs further investigation. The mainstay of treatment for TA is glucocorticoid therapy. Angioplasty, stenting, and bypass procedures may be indicated in certain patients.

Cogan's syndrome

Cogan's syndrome (CS) is defined by the occurrence of inflammatory eye disease and vestibulo/auditory dysfunction. The classic presentation of the disorder includes interstitial keratitis and sensorineural hearing loss. The interval between the onset of eye and ear symptoms is usually only several months (or less), but intervals of up to 2 years have been reported. This disorder affects young adults, with no gender predominance. In approximately 10% of cases, eye and ear inflammation is associated with arteritis of medium- and large-sized vessels (including aortitis) that mimics Takayasu's arteritis (Haynes et al., 1980; Vollertsen et al., 1986). Although the eye and ear findings in CS are sometimes attributed to vasculitis, their true pathophysiology remains obscure (Schuknecht & Nadol, 1994; St. Clair & McCallum, 1999).

Interstitial keratitis leads to the sensation of ocular irritation, excessive lacrimation and photophobia, and is accompanied by moderate reductions (generally reversible) in visual acuity. Slit-lamp examination of the cornea reveals stromal clouding in the anterior and middle cornea. Pathologically, the cornea shows infiltration of lymphocytes and plasma cells in the deep corneal layers, with varying degrees of neovascularization (Fisher & Hellstrom, 1961; Bernhardt et al., 1976). In addition to interstitial keratitis, many other forms of inflammatory eye disease may occur in CS, including conjunctivitis, uveitis, episcleritis, scleritis, exophthalmos, papilledema, retinal vasculitis, and ON (Haynes et al., 1980; Vollertsen et al., 1986).

The greatest cause of long-term morbidity in CS is the ear involvement. More than half of the patients with CS suffer some degree of irreversible sensorineural hearing loss (Haynes et al., 1980; Vollertsen et al., 1986; St. Clair & McCallum, 1999). A substantial percentage become profoundly deaf in at least one ear. The vestibular manifestations may also be severe, and usually present with the abrupt onset of vertigo, ataxia, tinnitus, nausea, vomiting, and sometimes oscillopsia.

Interstitial keratitis generally responds well to topical steroid therapy. Ear disease in CS must be treated promptly

and aggressively, with high doses of systemic glucocorticoids. Responses usually occur within 2 weeks, and total courses of immunosuppression lasting 2 to 3 months may be sufficient for the ear manifestations. In patients with suboptimal responses to glucocorticoids who still have salvageable hearing, cytotoxic agents (e.g. cyclophosphamide) are appropriate.

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Part XIII

Disorders of myelin

97

Myelination, demyelination and remyelination

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The relationship between injury and repair of the central nervous system is complex. Although long considered incapable of regeneration, the mammalian central nervous system can undergo neurogenesis and gliogenesis re-establishing axon–glial interactions needed for remyelination and safe conduction of the nerve impulse. In health, glia and neurons each exert survival effects on other constituents of the developing and mature central nervous system. Microglia mediate cell injury when activated but damaged tissue may be advantaged by the inflammatory process which delivers growth promoting and neuroprotective molecules to sites of tissue injury. Furthermore, bystander damage is limited whilst degenerate material is removed.

Myelination

Stem cells

Stem cells self-replicate through asymmetric division and differentiate down a variety of fate-committed lineages. They can be identified by surface markers or the behaviour of their progeny in defined environments. The principal source of neural stem cells during development is subventricular zone ependymal cells (Fig. 97.1, see colour plate section). Adult neural stem cells are present especially in the hippocampus and olfactory bulb but also in the neocortex (Maglivi et al., 2000). Embryonic stem cells are even less restricted retaining the ability to maintain the germline and differentiate to a cell-specific fate such as oligodendrocytes or dopaminergic neurons (Thompson et al., 1998). The need to select survivors from cells overproduced in the developing nervous system involves programmed cell death. Caspases cleave proteins supporting the nuclear membrane and cause apoptosis by activation of the endonuclease which digests DNA. Programmed cell death is influenced by the mammalian mitochondrial product *Bcl-2* and other antiapoptotic (*Bcl-X*) and proapoptotic molecules (*Bax*, *Bad* and *Bid*). Apoptosis makes it safe to retain a source of mitotic precursors in the mature nervous system, whilst avoiding uncontrolled growth.

Growth factors for neurones and glia

Acting together or in sequence, growth factors orchestrate development within the nervous system influencing proliferation, migration and differentiation. Many also support survival of fully differentiated cells.

Retinoic acid promotes embryonic cell differentiation down the neural lineage. Further in vitro manipulations yield mixed cultures enriched for oligodendrocytes (Brustle et al., 1999). Murine neural stem cells proliferate in response to epidermal growth factor (EGF). Their default differentiation pathway is gamma aminobutyric acid (GABA)-ergic neurones, but they can be directed towards dopaminergic and non-neuronal fates. EGF and fibroblast growth factor (FGF)-2 act sequentially in regulating neuronal development from stem cells. Glial cell line derived nerve growth factor (GDNF) induces a bias towards glial differentiation within cultured neural crest cells. Neurospheres derived from human embryonic tissue initially expand with fibroblast growth factor (FGF)-2.

There is a continued requirement for specific growth factors and cytokines once cell fate is committed. Many are also active on more primitive cell types. These growth-promoting molecules are produced by neurones, astrocytes and microglia. Platelet-derived growth factor (PDGF) is mitogenic for oligodendrocyte progenitors but they differentiate after a defined number of divisions (Raff et al., 1983); however, FGF-2 indefinitely suspends their maturation and promotes migration. EGF, neurotrophin (NT)-3, thyroxine and T3, retinoic acid and glucocorticoids each also stimulate oligodendrocyte differentiation and maturation from stem cells or committed precursors in vitro. Survival factors for cells of the oligodendrocyte lineage also

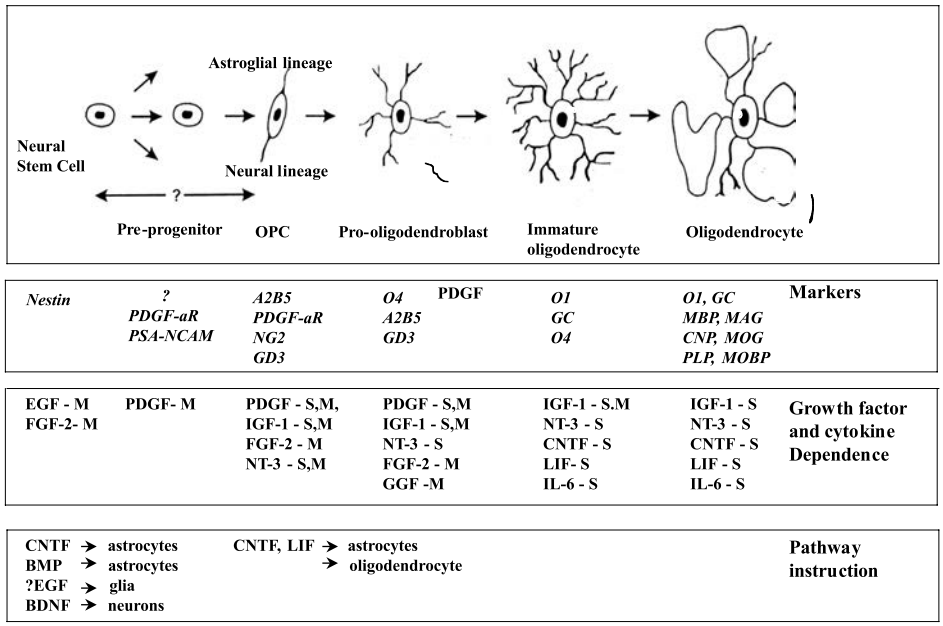

Fig. 97.2. Cells of the macroglial lineage develop under growth factor control acquiring cell surface markers with maturation and responding specifically to factors which orchestrate proliferation, migration, differentiation and survival. (Kindly prepared by Dr Siddarthan Chandran.)

include insulin like growth factor (IGF)-1 and -2, leukemia inhibitory factor (LIF), interleukin (IL)-6, NT-3 and ciliary neurotrophic factor (CNTF: Barres et al., 1992).

Macroglial lineages in the rodent and human nervous system

Astrocytes

Astrocytes contribute to formation of the glia limitans which defines the boundaries of the central nervous system and the blood–brain barrier. They contact cell bodies of neurones and the bare portions of axons and take up potassium following generation of the nerve impulse; astrocytes may also synthesize and insert axonal sodium channels at the node of Ranvier. Astrocyte reactivity in response to tissue injury, marked by increased expression of glial fibrillary acidic protein (GFAP), increases the availability of growth and neuroprotective factors (Komoly et al., 1992; Yao et al., 1995). Eventually, astrocyte reactivity leads to glial scar formation. FGF-2 and EGF stimulate the division of astrocytes. Proliferation is inhibited by transforming growth factor (TGF)-β.

Oligodendrocytes

Human oligodendrocyte precursors are born around the ventricles by 7–9 weeks gestation (Rivkin et al., 1995: Fig. 97.2). In the spinal cord, they increase progressively within the ventral and lateral portions of cervical and then lumbar regions, thereafter populating the lateral and dorsal cord by the time myelination starts at embryonic day 83 (Hajihosseini et al., 1996). The adult human central nervous system contains preoligodendrocytes which express the O4 marker but not galactocerebroside (GalC: Armstrong et al., 1992). Bipolar cells positive for A2B5 but negative for O4 and markers of mature oligodendrocytes or astrocytes, which proliferate and are bipotential in vitro, have also been recovered from the adult human central nervous system (Scolding et al., 1995). Although this adult human progenitor divides on a monolayer of human astrocytes, and neurons improve its survival, it does not proliferate in response to FGF-2, PDGF, IGF, BDNF, NT-3, NT-4/5 (alone or in combination), or rat astrocyte or neuroblastoma cell line (B-104) conditioned medium, stimuli known to promote division of the rat neonatal oligodendrocyte precursor.

Axon–glial interactions and myelination

The migration of oligodendrocyte progenitors is influenced by receptor–ligand adhesions with the extracellular matrix. Integrins are one of several families of molecules which determine cell–cell interactions in the developing and postmature nervous system. Myelination occurs when the membraneous processes of mature oligodendrocytes contact and ensheath axons of diameter 1 μm or more, and compact to form the myelin lamellae needed for saltatory axonal conduction. Stable myelination depends on additional cell surface and extracellular matrix molecules which promote and maintain interactions between myelin and axons. These include janusin, tenascin, laminin and fibronectin.

The axon–glial relationship is reciprocal. Oligodendrocyte progenitors are influenced by their axonal environment. Neurones are mitogenic for cells of the oligodendrocyte lineage. The molecular basis involves both diffusible and membrane-associated signals, which include PDGF. Electrical activity in axons also influences oligodendrocyte progenitor proliferation (Barres & Raff, 1993). Eventually, the number of mature oligodendrocytes is matched to local axon density, survival being orchestrated by the number of axons requiring myelination. Conversely, oligodendrocytes promote the survival, growth and calibre of retinal ganglion cells in the developing optic nerve; and oligodendrocytes secrete a factor needed for sodium channels to cluster at intervals appropriate for the diameter of developing axons in preparation for propagation of the nerve impulse. Neurons show a marked increase in survival when cocultured directly with oligodendrocyte precursors and differentiated oligodendrocytes and this effect is also reproduced using medium conditioned by differentiated oligodendrocytes (Wilkins et al., 2001). Neutralizing antibodies to IGF-1, but not other candidate trophic factors, block the soluble survival effect of oligodendrocytes; cells of the oligodendrocyte lineage produce IGF-1; and recombinant IGF-1 promotes neuronal survival under identical conditions. Neurons exposed to oligodendrocyte conditioned medium show enhanced neurite and axonal length; this effect is reduced by inhibitors of MAPkinase/Erk pathway whereas PI_3kinase inhibition reduces the effect of oligodendrocytes and conditioned medium on neuronal survival (Wilkins et al., 2002)

Once stable axon–glial contact is established, the elongated oligodendrocyte processes form a cup around the axon at the point of contact, extending lengthwise to form a trough whose two lips advance around the circumference of the axon until they meet. One then passes beneath the other to become the inner tongue of the future sheath, which rotates many times around the axon to form the multiple membrane layers or lamellae. During compaction, the cytoplasmic content of all except the inner- and outermost lamellae of the developing spiral sheath is gradually extruded, and the two inner leaflets of the surface membrane lipid bilayer fuse to form the major dense line visible in cross-section (Fig. 97.3). The developing myelin sheath extends lengthwise in both directions along the axon to form an internodal segment. Each layer of the spiral retains a bead of cytoplasm at the advancing edge, where the two inner leaflets of the surface membrane remain separate.

Electrical resistance is low at the node of Ranvier, due to the high concentration of sodium channels, and depolarization is thereby facilitated. In myelinated axons, the action potential generates electrical currents which, in turn, trigger depolarization not at the immediately adjacent myelinated (and insulated) internode, but preferentially at the next node of Ranvier. This saltatory conduction is considerably more rapid than continuous propagation of the nerve impulse.

Demyelination

The best hypothesis concerning events which underlie the pathogenesis of inflammatory brain disease requires extrapolation and integration from a combination of in vitro, experimental, pathological and clinical observations, which necessarily risks contaminating fact with fiction in the attempt to achieve overall coherence.

Cellular infiltration of the central nervous system

The blood–brain barrier prevents the passage of large molecules and cells, even though specific vesicular and other transport mechanisms provide the brain with essential nutrients and permit a degree of cellular traffic. It is composed of a layer of cerebral endothelial cells surrounded by a basement membrane and the Virchow Robin space, itself contained by astrocytes whose foot processes establish endothelial tight junctions.

Penetration of cerebral vessels occurs when endothelial cells extend microvillar processes and entangle inflammatory cells as they pass along the vessel wall. Vascular permeability also depends on alterations in expression of cell surface molecules on activated T-cells together with the secretion of enzymes that degrade the extracellular matrix of lining cells. The constitutive expression of specific molecules that determine immunological recognition and cellular adhesion alters under conditions of inflammatory cell activation, amplifying the steady state cellular surveillance that occurs in health and contributing to the perivenular concentration of inflammatory cells that characterizes most demyelinating diseases (Carrithers et al., 2000). Thus migration results from changes on endothelia and activated lymphocytes. Certain addressins highly concentrated on endothelial cells by the action of locally acting cytokines (IL-1 and tumour necrosis factor [TNF]α) interact with ligands on the surface of circulating lymphocytes or inflammatory cells. Specific receptor–ligand interactions include intercellular adhesion molecule [ICAM]-1 reacting with leukocyte function antigen [LFA]-1, LFA-3, which links exclusively with the T-cell ligand cluster defined [CD]-2, and CD9, which selectively adheres to B-lymphocytes. Other adhesion systems, such as complement activation products and CD44, are ubiquitously expressed and non-specifically enhance contact between

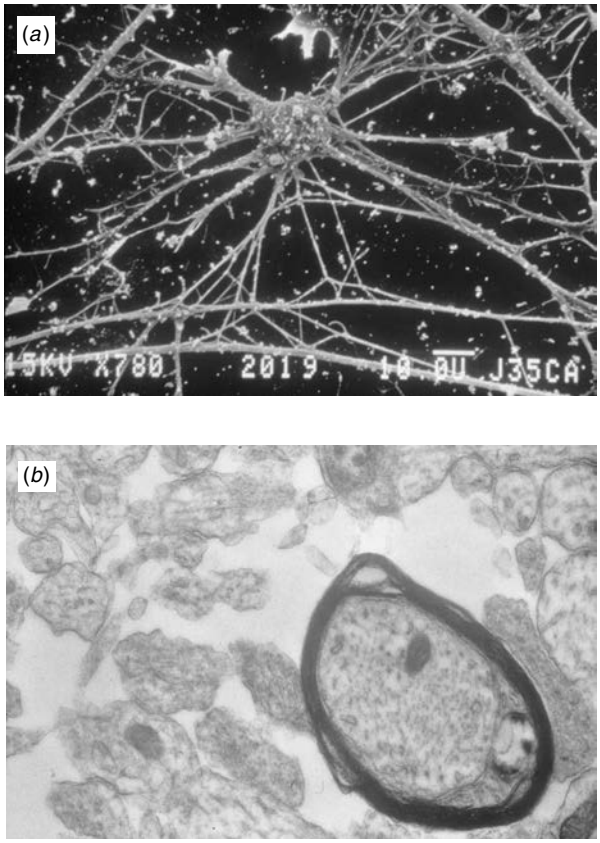

Fig. 97.3. (*a*) Rat O-2A progenitors associate in vitro with several bundles of dorsal rat ganglion axons shown by scanning electron microscopy; (*b*) formation of compact myelin sheaths around axons shown by transmission electron microscopy. (Kindly provided by Dr John Zajicek and reproduced with permission from Zajicek et al., 1992.)

circulating and endothelial cells. Soluble adhesion molecules, such as ICAM, inhibit mononuclear cell migration across endothelial barriers. Migration can be actively prevented by blocking antibodies directed, for example, at the α4 chain of integrins.

The critical factor in determining propagation of the immune response is that only those cells primed against central nervous system antigen persist in the brain, whereas those that do not encounter specific antigen die by apoptosis (Wekerle et al., 1986). Cellular traffic across the blood–brain barrier non-specifically permits a variety of other potentially pathogenic molecules to assemble on the abluminal surface of cerebral vessels, creating the conditions needed for cellular, antibody, complement and macrophage-mediated tissue injury.

Next in the cascade of events is outward migration of cells from the inflammatory nidus. This is largely promoted by local production of chemokines interacting with specific receptors on migrating cells, and by enzymes which degrade tissue barriers and extracellular matrices (Zang et al., 2000). Chemokines specific for T-cells are IP-10 and MIG; neutrophils respond to Gro-α and IL-8; and T-cells and monocytes to RANTES, MCP-1 and MIP-1α. The IP-10 receptor is CXCR3 and CCR5 binds the MIP-1α and RANTES ligands. IL-2-induces the secretion of metalloproteases by T-cells and this enhances their ability to adhere and migrate through endothelial barriers.

The role of microglia

Microglia are primary immunocompetent cells which have antigen-presenting and phagocytic properties (Fig. 97.4, see colour plate section). They can be distinguished phenotypically from brain macrophages by differential expression of CD45 and CD11. Microglia and bone-marrow derived macrophages play a complex and in some respects paradoxical role in development, injury and repair of axon–glial arrangements within the central nervous system.

Microglia and oligodendrocyte survival

Media conditioned by non-activated microglia increase the number of surviving GalC positive oligodendrocytes in vitro (Nicholas et al., 2000a). Survival results from inhibition of endogenous oligodendrocyte precursor apoptosis and promotion of oligodendrocyte differentiation by soluble factors released by non-activated microglia which over-rides the effects on maturation of PDGF and FGF-2 (Fig. 97.5, see colour plate section). These soluble factors act by up-regulation in oligodendrocyte precursors of nuclear factor of kappa-binding (NFk-B). Antiplatelet-derived growth factor antibody abolishes this effect even though PDGFα chain is expressed at similar levels within both non-activated and interferon (IFN)-γ activated microglia and both conditioned media have similar levels of PDGF-α chain bioactivity. However, the soluble factors produced by non-activated microglia recruit phosphatidyl-3-inositol kinase to the PDGFα receptor and synergize with endogenous PDGFα chain to increase NFk-B activation. These effects are not observed with supernatants from microglia treated with IFN-γ.

Therefore, depending on activation state, microglia produce soluble factors that promote oligodendrocyte development through an effect on PDGFα receptor signalling. These appear not to be any one of the many growth factors known to act on cells of the oligodendrocyte

lineage. Conversely, in their activated state, microglia mediate tissue injury. The most potent activators in vitro and perhaps in vivo are bacterium-derived lipopolysaccharide, the T-cell derived cytokine IFN-γ and the colony-stimulating factors (CSFs). Activated microglia change their morphology (becoming amoeboid and motile) and release proinflammatory cytokines, chemokines and mediators which orchestrate their immune functions.

Microglia as antigen-presenting cells

The terms professional and non-professional define antigen-presenting cells, which can initiate antigen-specific primary or secondary immune responses, respectively, reflecting differences in the quality of stimulation required for naive as opposed to memory T-cell activation. The issue of whether antigen presentation occurs exclusively within the central nervous system or uses cells (of peripheral or brain origin), which encounter antigen in draining lymph nodes and stimulate lymphocytes which then migrate into the central nervous system is not fully resolved. The best candidates for a brain-derived antigen-presenting cell are microglia or bone marrow-derived macrophages but astrocytes, cerebral vascular endothelial cells and pericytes are all capable of restimulating lymphocytes, and there is now experimental evidence that dendritic cells can migrate from the periphery and trigger the immune response (Perry, 1998).

The non-professional antigen-presenting role is assigned to the $CD45^{high}CD11b/c^{+}$ perivascular macrophage rather than to the $CD45^{low}CD11b/c^{+}$ parenchymal microglial cell. Unlike perivascular macrophages, microglia fail to produce IL-2, resulting in limited T-cell proliferation and the promotion of apoptosis. Microglia secrete IL-1 and constitutively express class II major histocompatibility complex (MHC) and the B7 accessory molecule following activation. Costimulation is most effectively delivered through CD28 and B7, and/or CD40 and its ligand. These costimulatory molecules are upregulated by IFN-γ and down-regulated by anti-inflammatory cytokines especially the Th-2 associated products IL-4, IL-10 and TGF-ß1. Antigen presentation by microglia to memory T-cells results in cytokine release, which reciprocally activates naive microglia, indicating that recall antigen presentation results in an environment which propagates the immune response (Hall et al., 1999). The effect is predominantly mediated by IFN-γ but amplified by TNFα.

Interactions between microglia and oligodendrocytes

Fully differentiated oligodendrocytes stimulated to divide by exposure to bFGF or nerve growth factor (NGF), transduce the mitotic signal and enter the cell cycle but cannot divide and either enter a resting non-myelinating state or die by apoptosis (Muir & Compston, 1996). Postnatal rat cortical oligodendrocytes, but not their progenitors (or astrocytes), are selectively killed by exposure to NGF, through binding to the p75 receptor when trkA is not co-expressed, whereas no such effect is seen with brain derived nerve growth factor (BDNF) or NT-3 (Casaccia-Bonnefil et al., 1996); p75 receptor may be up-regulated on oligodendrocytes within the lesions of multiple sclerosis. This apparent paradox is not so surprising since the trkA and p75 NGF receptors are part of the cell death pathway involving Fas and the TNFα receptor. Thus, there may be diametrically opposite effects of growth factors on cells of the same lineage depending on the expression of receptors, the signals transduced and their ability to enter the cell cycle.

Oligodendrocytes are especially sensitive to mediators of inflammation but also to anoxia and excitotoxic damage. Cells exposed to sublytic concentrations of complement or perforin show a transient increase in intracellular calcium during which pores forming in the membrane are gathered into vesicles and shed from the cell surface, thereby restoring membrane integrity and leaving the oligodendrocyte metabolically intact (Scolding et al., 1989). Oligodendrocyte recovery correlates with calcium oscillations suggesting that the calcium signal following insertion of the membrane–attack complex stimulates protective mechanisms and repair at the cellular level. This illustrates the principle of reversible oligodendrocyte injury, but the main relevance of complement activation in the context of inflammatory brain disease may be the breakdown of C3, releasing membrane-bound and fluid-phase products, which determine interactions between oligodendrocytes and macrophages or microglia. Differences in histological features of the lesions in multiple schlerosis suggest heterogeneity in the pathogenesis (Luchinetti et al., 1999): one variant (type 2) consists of perivenous demyelination with local deposition of immunoglobulin and terminal complement components within sharply defined lesions also having remyelination; these patients have the phenotype of clinically definite multiple schlerosis with an equal distribution of relapsing and progressive cases. Uptake of myelin by macrophages is enhanced by opsonization with complement, involves the CR3 receptor, induces a rise in intracellular calcium, and is associated with the production of TNFα and nitric oxide by these activated macrophages. The fact that oligodendrocytes possess receptors for TNFα and the related molecule *fas*, provides a basis for signalling events which activate both apoptotic and necrotic death pathways.

IFN-γ up-regulates the expression of an heterogeneous

group of molecules on microglia involved in the phagocytosis of opsonized particles. These include the FcR1 (CD64), FcRII (CD32) and FcRIII (CD16) receptors; complement components C1q, iCR3 and C5a; IL-8, TNF-R1 and the bacterial peptide f-Met–Leu–Phe. The pro-inflammatory responses of microglia are limited by the production of IL-4, IL-10, prostaglandin-E2 and TGF-ß which suppress several behaviours (proliferation, activation, adhesion, migration, phagocytosis, costimulation and mediator production), and by apoptosis of autoreactive T-cells using perforin and the Fas/Fas-ligand pathway. Microglia are themselves killed by apoptotic mechanisms in response to TGF-β and are not protected by Bcl-2. With some variations, the same checks and balances are provided by anti-inflammatory cytokines on the proinflammatory behaviour of astrocytes.

Significant cell death occurs when oligodendrocytes derived from mixed rat cortical glia are cultured without growth supporting factors. Soluble factors released from these cultures are chemotactic in vitro for microglia. This occurs before major cell loss has occurred; microglial chemotaxis is not due to the release of cellular debris since osmotic lysis of freshly plated oligodendrocytes does not reproduce the effect. IFN-γ activation increases the sensitivity of microglia to these chemoattractants (Nicholas et al., 2002a). The initial recruitment of microglia by stressed oligodendrocytes could represent part of a survival response engaged by injured cells.

Activated microglia mainly kill (opsonized) oligodendrocytes by cell–cell contact and local release of TNFα during cell contact (Zajicek et al., 1992). Receptor–ligand interactions allow microglia to recognize and then deliver the lethal signal to target cells. Antibody in low concentration, coating the surface of the oligodendrocyte or its myelin sheath, opsonizes the target cell for lytic damage by microglia using these Fc receptors. Demyelinated axons are coated with antimyelin oligodendrocyte glycoprotein (MOG) antibody in the lesions of acute multiple sclerosis (Genain et al., 1999). The potential role of MOG is further suggested by the high prevalence of intrathecal anti-MOG antibodies, which persist in multiple sclerosis from an early stage in the illness, unlike the evolving pattern of antibody responses to myelin basic protein (MBP).

Oligodendrocytes are resistant to physiological concentrations of soluble TNFα through protection by microglia-derived IGF-2 and CNTF; these growth factors act synergistically to block the oligodendrocyte toxicity otherwise caused by TNFα released by IFN-γ activated microglia (Nicholas et al., 2002b). The activity of c-Jun kinase (JNK) stimulated by TNFα receptor ligation confirms that these factors inhibit TNFα signalling. Irrespective of activation, conditioned media do not induce JNK activity in oligodendrocytes unless CNTF or IGF-2 activity are neutralized (Fig. 97.6, see colour plate section). The TNFα-containing medium of IFN-γ treated, but not non-activated, microglia is then toxic for oliogodendrocytes.

Thus, activation of microglia results in the release of molecules, which are potentially toxic for oligodendrocytes, but these effects are neutralized by simultaneous production of growth factors. In the context of inflammation, this safeguard would limit bystander damage to oligodendrocytes, whilst allowing cell contact-dependent mechanisms of injury to operate appropriately after microglial activation. Growth factor availability within an inflammatory lesion determines the extent of bystander damage. The stressed oligodendrocyte signals its distress and either summons assistance or suicidally attracts activated microglia, but this is a potentially dangerous liaison.

Microglia and neurones

Soluble factors released by activated microglia impair mitochondrial (cytochrome oxidase) activity of neurons in vitro. These functional effects are blocked by antibodies to TNFα. Cell death is prevented by intracellular release of NKk-B. Although this neuronal dysfunction is initially reversible (Nicholas et al., 2001b), a mechanistically different and generally more lethal sequence of events follows prolonged exposure to microglial soluble factors. Inducible nitric oxide synthetase but not its neuronal isoform is implicated in these less reversible events. However, by analogy with the simultaneous production of destructive and protective factors for oligodendrocytes, microglia in both their activated and non-activated states also produce factors which promote the metabolic activity of neurons remote from the immediate arena of nitric oxide-mediated injury (Golde et al., 2002).

Although axons do not generally regenerate in the central nervous system, due to active inhibition by macroglia, macrophages release IL-2 which transiently removes the inhibitory constituents from oligodendrocytes and astrocytes. Neuronal survival in the crushed optic nerve is enhanced if myelin-specific autoimmune T-cells are injected locally, perhaps by a mechanism which involves transient reduction in energy requirements due to reduced nerve activity. The functional advantage of allowing inflammation to enhance axon regeneration is shown by enhanced motor recovery in rats, made paraplegic by complete spinal cord transection, transplanted with macrophages first primed in vitro against peripheral nerve (Rapalino et al., 1998). Neuroprotection after spinal cord injury is also provided experimentally by systemic immunization with myelin basic protein specific autoreactive T-cells (Hauben et al., 2000). Functional recovery is associated with reconstitution of nerve fibres across the

lesion and restoration of motor conduction. No additional repair is achieved by manipulating growth factors within the lesions.

The pathogenesis of multiple sclerosis

The symptoms and signs of multiple sclerosis arise from patchy inflammation and demyelination within the brain and spinal cord. Disability occurs as a direct consequence of this inflammatory process and its relative failure to repair. The disease pattern, characterized by a course which is initially intermittent then episodic with incomplete recovery and eventually followed by slow progression, raises fundamental questions concerning the etiology of inflammatory brain disease and the basis for symptom onset and recovery (Fig. 97.7).

Genetic factors set the scene for events which underlie the clinical features of multiple sclerosis (Compston, 1999). Some, perhaps the majority, influence the immunological behaviour of susceptible individuals. Population studies demonstrate an association between the class II MHC alleles *DR15* and *DQ6* and their corresponding genotypes. Based on systematic searches of the genome, additional regions of interest are provisionally identified on several other chromosomes; some cluster in families which are, and others which are not, linked to the *DR15* haplotype. A major part of future studies in the genetics of multiple sclerosis will be to resolve the question of disease heterogeneity.

Although not yet fully defined, the initiating events culminate in brain inflammation. In addition to the migration of activated lymphocytes across cerebral and spinal endothelial barriers and microglial activation by IFN-γ, proinflammatory cytokines delivered by T-cells and released by microglia interfere directly with the function of myelinated fibres. The evidence partly derives from correlations between abnormalities of evoked potentials and inflammation detected by magnetic resonance imaging (Youl et al., 1991), and from the clinical observation that patients undergoing experimental treatments experience a significant but transient rehearsal of previously experienced symptoms coinciding with acute cytokine release during which conduction block can be demonstrated (Moreau et al., 1996; Coles et al., 1999). Experimental studies demonstrate that nitric oxide can reversibly impair conduction in normal or hypomyelinated spinal cord axons central (Redford et al., 1997), consistent with the in vitro studies. More prolonged exposure causes axon degeneration especially if the nerves are electrically active (Smith et al., 2001). Subsequently, a pentapeptide (Gln–Tyr–Asn–Ala–Asp), able to block sodium channels in human neuroblastoma-glioma NH15-CA2 cells, was shown to be present at ×3–14 concentration in cerebrospinal fluid from patients with multiple sclerosis compared to normal controls (Brinkmeier et al., 2000).

It therefore follows that recovery of function may sometimes merely reflect restoration of conduction following removal of proinflammatory cytokines through myelinated axons, which were never structurally damaged. Even where demyelination has occurred, function may be restored by rearrangement of sodium channels (England et al., 1990), providing a variety of alternative patterns of conduction. This principle is further illustrated by the demonstration that mouse strains susceptible to Theiler's virus which are class I but not class II MHC antigen deficient show few physiological or functional deficits due to increased density of sodium channels and preservation of axons (see below) despite extensive demyelination (Rivera-Quinones et al., 1998). There may also be a contribution to recovery of structure and function in multiple sclerosis from remyelination (Prineas et al., 1993: see below).

Progression and disability in multiple sclerosis are best explained by axon degeneration. Identified in the classical neuropathological literature, this has recently been re-emphasized histologically (see below) and by magnetic resonance imaging or spectroscopy showing atrophy and changes in *N*-acetyl aspartate in lesions (Davie et al., 1995), normal appearing white matter (Evangelou et al., 2000) and brain (De Stefano et al., 1998) and spinal cord lesions (Stevenson et al., 1998). The fate of axons is conditioned by the amount of early inflammation: they may be damaged directly during the initial inflammatory disease process; through exposure non-specifically to inflammatory mediators after demyelination; because nerve fibres have a limited ability to survive prolonged demyelination; or for all three reasons. Immunohistochemical staining for amyloid precursor protein suggests that axonal injury occurs as part of the acute demyelinating lesion (Ferguson et al., 1997; Trapp et al., 1998). Circumstantial evidence suggests that vulnerability of recently demyelinated axons to the inflammatory environment of acute lesions, or secondary degenerative effects of demyelination through loss of trophic support are more likely mechanisms than primary immunological injury to the intact axon by infiltrating mononuclear cells and their mediators. Recent histological assessments draw attention to the presence of axon degeneration not only in inflammatory lesions but also in inactive plaques and in areas of remyelination; the most extensive axonal injury is seen in secondary progressive multiple sclerosis but with surprisingly little typifying the lesions of primary progressive disease; amyloid precursor protein deposition is associated with macrophages and infiltrating CD8 lymphocytes but not TNFα or inducible

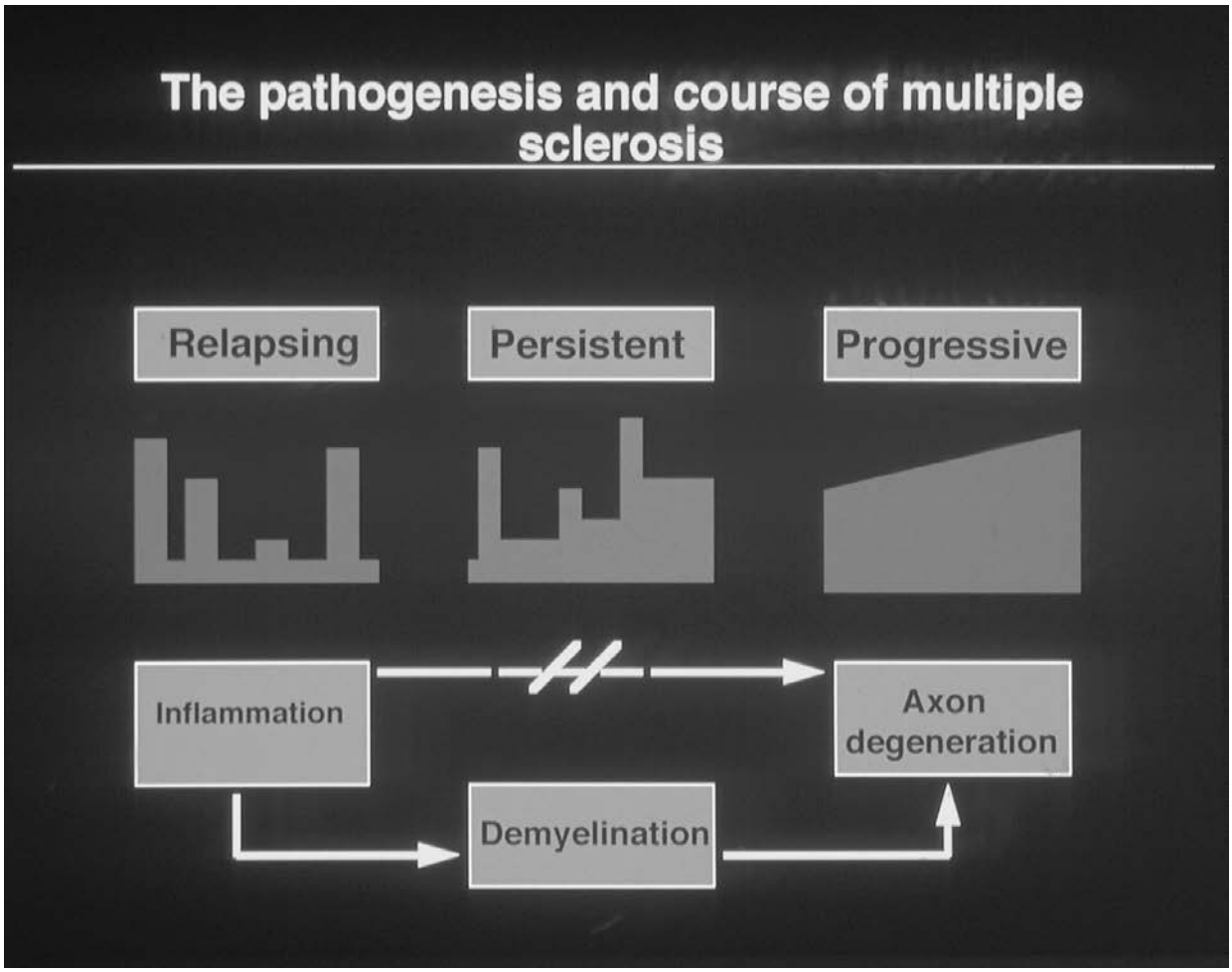

Fig. 97.7. Stages in the clinical course of multiple sclerosis. Inflammation causes transient alteration in conduction through the action of nitric oxide on myelinated fibres, providing one explanation for symptoms which recover. Inflammation drives demyelination, which may improve through remyelination, but otherwise accounts for persistent clinical deficits. There is a major contribution to secondary progression from axon degeneration which results both from inflammation and loss of trophic support from oligodendrocytes.

nitric oxide synthase (Bitsch et al., 2000). This analysis is consistent with experimental evidence that myelin or glia, and electrical activity provide survival factors for axons (Barres & Raff, 1993; Meyer-Franke et al., 1995; Sanches et al., 1996; Wilkins et al., 2001).

Remyelination

The extent to which remyelination is essential for the comprehensive treatment of multiple sclerosis hinges on the issue of when and why axons degenerate. For those axons which degenerate early as a direct result of the inflammatory process, efforts at remyelination may have little to offer; conversely, if the naked axon is resistant to the inflammatory milieu but has poor survival properties, remyelination is an essential part of the overall strategy for treating multiple sclerosis, and its timing is very important. A number of basic questions also arise with respect to the practicalities of repairing demyelinated but viable axons in multiple sclerosis. Can surviving oligodendrocytes remyelinate naked axons or must there be a source of precursor cells? Are stem cells for glia present in the adult human nervous system? If so, can they migrate from germinal centres to sites of injury? Can cells other than oligodendrocytes be used as surrogates for remyelination? Will growth factor therapy prove effective and well tolerated as a means of promoting repair? Will endogenous repair or assisted remyelination restore structure and function of the adult human nervous system? Some answers are already available.

The pioneering experimental studies, involving mechanical and gliotoxin induced demyelination, showed

that remyelination occurs endogenously and restores conduction both in young and adult nervous systems, but the capacity for repair by oligodendrocyte precursors is exhausted by repeated insult. With antigalactocerebroside antibody-mediated demyelination of the feline optic nerve, small glial cells derived from precursors located outside the lesion differentiate into oligodendrocytes and achieve extensive remyelination. They concentrate early at the margins of the lesion, suggesting local origin within the optic nerve (Carroll et al., 1998). This remyelinating cell is beyond reasonable doubt the in vivo counterpart of the oligodendrocyte progenitor, characterized in vitro.

The human preoligodendrocyte and its progenitor have each now been identified in the lesions of multiple sclerosis (Wolswijk, 1998; Scolding et al., 1998), but the fact that progenitors are present within persistently demyelinated lesions suggests that these have not successfully engaged naked axons. Demyelinated lesions of the central nervous system are preferentially repopulated by Schwann cells, but these are not precocious myelinators, mainly because each Schwann only captures a single axon and their territory is limited by host astrocytes. Reactive astrocytes bring to experimental demyelinating lesion cytokines or growth factors which promote repair (Komoly et al., 1992; Yao et al., 1995) as do reactive astrocytes in the lesions of multiple sclerosis (Stadelman et al., 2002).

Because it maximally recapitulates the range and variety of environmental conditions and local signals on which endogenous remyelination depends, transplantation is the preferred method for assessing the myelinating potential of macroglia. Although it was the prospect of clinical intervention which initiated and has since sustained research into remyelination, the main dividend (to date) from experimental studies of glial cell implantation has been an improved understanding of myelination and glial neurobiology (Fig. 97.8).

A source of precursor cells able to proliferate, migrate and differentiate in the vicinity of the demyelinated axon is essential. Postmitotic oligodendrocytes neither divide, differentiate nor remyelinate axons. The cell must proliferate and cell implantation does not achieve remyelination if division is inhibited by X-irradiation. Both findings suggest that the origin of the remyelinating cell is a precursor and not a dedifferentiated mature oligodendrocyte. Embryonic stem cell derived oligodendrocytes myelinate axons in vitro in the dysmyelinating *shiverer* mouse, even at some distance from the site of transplantation (Liu et al., 2000). Other transplanted glia have a limited capacity for migration. CG4 (oligodendrocyte lineage line) cells injected into the intact ventral horn of the rat spinal cord lesioned in the dorsal column, and with high dose X-irradiation in advance of cell implantation, migrate into the lesion as progenitors without undergoing differentiation and then remyelinate naked axons (Franklin et al., 1996). However, without X-irradiation, cell survival is restricted to the inoculation site with no surviving transplanted cells seen elsewhere in the spinal cord. Normal tissue apparently does not favour oligodendrocyte progenitor migration but the reactive change which occurs in and around lesions is sufficient to support both survival and movement of cells, presumably due to the local availability of cytokines and growth factors produced by reactive astrocytes and microglia. However, growth factor supplements appear not to make a substantial difference to histological outcome. Experimentally, remyelination restores conduction (Smith et al., 1981), and glial cell implantation alters structure and function in the central nervous system (Groves et al., 1993; Jeffery & Blakemore, 1997).

Transplantation of human glia using mixed cultures which include oligodendrocyte progenitors confirms that oligodendrocyte lineage cells fail to migrate but survive in clumps within the lesion (Targett et al., 1996). In this situation, oligodendrocytes extend processes, which contact rat axons, but without the formation of myelin sheaths. Instead, the membranes end in terminal loops where the processes abut onto demyelinated axons. Despite these imperfect results of initial attempts at reconstructing glial–neuronal interactions by cell implantation using human material, cells of the human oligodendrocyte lineage transplanted into myelin deficient rodents survive, even after prolonged cryopreservation, and myelinate central axons (Seilhean et al., 1996). Unlike animals injected with ethidium bromide, these *shiverer* mice have normal numbers of astrocytes. This may be important since human oligodendrocyte precursors proliferate and survive in response to astrocyte-derived factors. Given their ability to myelinate the central nervous system, human Schwann cells have been evaluated in experimental rodent models of demyelination (Brierley et al., 2001). Failure to purify the cell implant by immuno-affinity (using human NGF receptor) lead to extensive fibroblast overgrowth and axon degeneration, whereas remyelination was achieved using the enriched population.

Olfactory bulb glia have a permissive role on axon regeneration in adults and form myelin sheaths capable of restoring conduction of the nerve impulse in experimental rodent models of remyelination. Olfactory ensheathing cells have the advantage over Schwann cells of improved migration and the ability to integrate within areas of astrocytosis. Human olfactory ensheathing cells proliferate in astrocyte conditioned medium in vitro and can be identified by expression of the p75 low-affinity NGF receptor. After transplantation in the X-irradiated ethidium bromide gliotoxic lesion of the rat spinal cord, they adopt a remyelinating phenotype and capture a proportion of naked

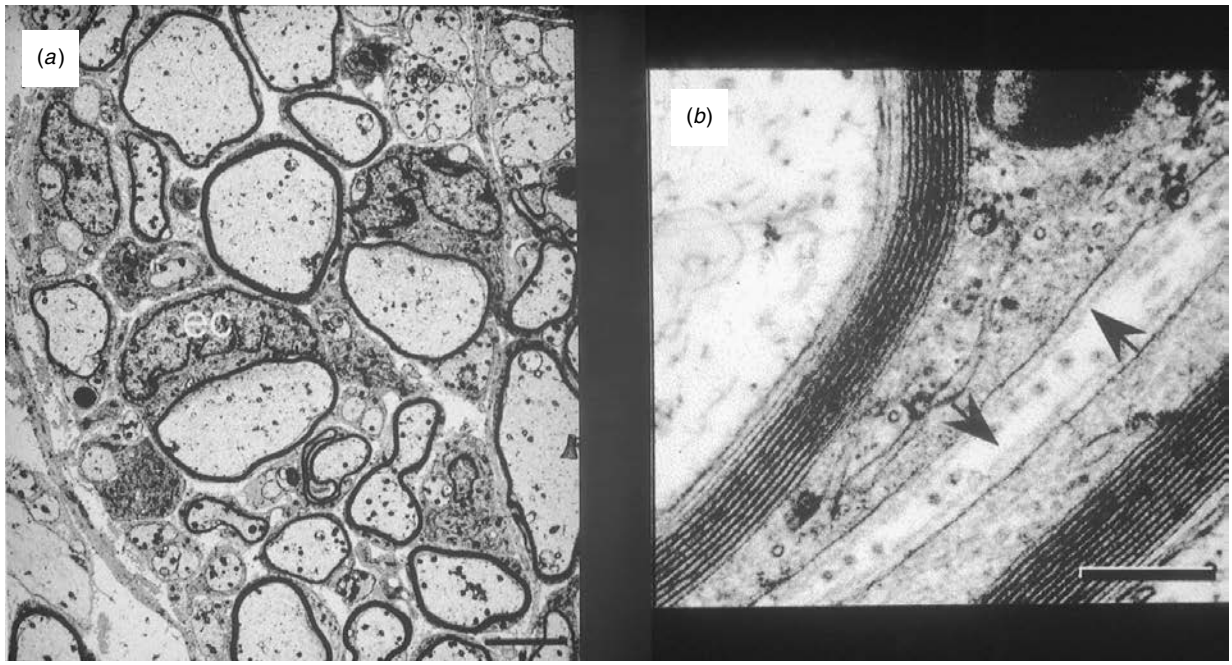

Fig. 97.8. Formation of compact myelin lamellae by human olfactory bulb ensheathing cells. (*a*) 6 weeks after injecting cells into gliotoxin-induced demyelinating lesions, many remyelinated axons are present in semi-thin sections stained with toluidine blue. (*b*) The myelin sheaths are similar to those formed by Schwann cells or olfactory bulb ensheathing cells having the periodicity of peripheral myelin and being surrounded by cytoplasm. (Kindly provided by Dr Robin Franklin and reproduced with permission from Barnett et al. (2000).)

axons with an histological pattern similar to Schwann cell repair (Barnett et al., 2000). Olfactory ensheathing and Schwann cells share the property of low morbidity access as the basis for clinical applications of cell implantation, since either could be obtained from the intended recipient and would therefore be suitable for autotransplantation, with all its immunological and ethical advantages.

Given the potential for endogenous remyelination of the central nervous system by oligodendrocyte progenitors and their progeny, it is reasonable to ask whether enhanced repair might be a dividend from containing tissue injury, the scales being tipped in favour of remyelination once the rate of injury has been restricted. Hints that immunoglobulin might both limit the disease process and promote remyelination come from the observation that spontaneous remyelination is much enhanced in Theiler's murine (demyelinating) encephalomyelitis virus when animals are treated with serum raised by immunization with spinal cord homogenate. The effect depends on IgM antibodies directed specifically against myelin basic protein (Rodriguez et al., 1996). This raises the question of whether increased remyelination is merely the consequence of successful disease suppression, promoting endogenous repair or depends directly on IgM which binds and stimulates cells of the oliogodendrocyte lineage, as suggested by the coassociation of inflammation and remyelination both in experimental lesions and multiple sclerosis. The available evidence suggests that pooled IgG and IgM fractions protect (rat) oligodendrocytes by inhibition of antibody-mediated phagocytosis and termination of the immune reaction by induction of apoptosis in infiltrating T-cells through nitric oxide and TNFα dependent mechanisms rather than by direct stimulation of oligodendrocytes. Hence, enhanced remyelination probably depends on manipulating the relationship between inflammation and repair rather than a direct growth-promoting effect (Stangel et al., 1999, 2000).

So what are the possibilities, based on contemporary experimental evidence, for repair of demyelinated pathways by cell implantation? One strategy is to wait until a therapy is available that can be given systemically and delivered simultaneously to all affected parts of the central nervous system. Another is first to prove that structure and function can usefully be restored in a single informative lesion before tackling the secondary task of making this intervention diffusely available in the central nervous system. If proof of principle involves cell implantation, the most promising present candidates are autologous periph-

eral nerve Schwann cells (Kohama et al., 2001) or olfactory bulb ensheathing cells (Barnett et al., 2000). The ideal lesion would be safely accessible, responsible for clinically significant and stable deficits resulting from persistent demyelination of intact axons, and at a site where the risks of failure would be acceptable through the presence of an intact paired structure or pathway. An unsuitable lesion would be at an inacessible site, where intervention would risk a strategic pathway, with an unstable or clinically irreversible deficit, and evidence for extensive axon degeneration. Attempts to enhance remyelination would need to be combined with adequate suppression of disease activity (Compston, 1996).

Most is known about the spinal cord and this might appear the obvious choice for a first clinical intervention. The symptoms are a major cause of disability, and can to some extent be measured using physiological and imaging techniques. But the risks of failure or increasing deficits within densely packed tracts would be high especially since it would be necessary to avoid patients with established chronic progressive disease and extensive axon degeneration. Magnetic resonance imaging usually shows many lesions in series within the corticospinal tracts so that remyelinating any one would be of limited value. Cord atrophy indicating severe axon degeneration is usually present in patients with stable or progressive deficits. The optic nerve is attractive because the symptoms are clinically eloquent, physiological assessment and imaging are well developed and there is a paired structure. Failure would not compromise vision in the intact eye. However, the natural history of optic neuritis is usually for recovery, which may occur over many months making it difficult to demonstrate that intervention had altered the natural history of visual recovery and the timing would need fine judgement, waiting for the establishment of persistent visual deficits but avoiding transplantation of a nerve with degenerate axons. Although the responsible lesion can usually be identified, this is often long, making for difficulty in placing implanted cells but there is evidence for early atrophy after unilateral optic neuritis despite the expected recovery of vision (Hickman et al., 2000) suggesting a need to protect axons from the loss of trophic support associated with persistent demyelination. The cerebellar peduncle is an alternative since this gives rise to symptoms which can be measured, and at a site where remyelination is known to occur and can be imaged. The typical severe proximal tremor is usually unilateral. It presents early and rarely recovers spontaneously. Failure would not be catastrophic and the pathway which involves the superior cerebellar peduncle and red nucleus has long been the target for stereotactic procedures. The responsible lesion can often be identified and has spectroscopic features, indicating demyelination with preserved axons near normal tissue integrity (C. Brierley, unpublished observations). In making the difficult transition between experimental and applied work, neurologists might feel more comfortable about early intervention here than in either the optic nerve or cerebellar peduncle than the spinal cord.

Many practical, clinical, ethical and biological problems remain to be overcome before remyelination of strategically placed lesions can become a reality for individual patients with multiple sclerosis.

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Multiple sclerosis and its pathophysiology

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Multiple sclerosis is an inflammatory demyelinating disorder and is one of the commonest causes of severe neurological disability in middle life in people of northern European origin. Classically, it begins with relapses and remissions of neurological impairment. In time, the remissions tend to be incomplete, and a phase of insidious progression with or without superimposed relapses, is entered (secondary progressive MS). In a small proportion of patients (approximately 10%) there is steady progression from onset, without clear cut relapses and remissions (primary progressive MS) (Thompson et al., 2000).

Prevalence

The prevalence of MS varies greatly throughout the world and appears to be influenced by a complex interaction between geographic position and genetic background (for reviews see Compston, 1998, 1999). In the temperate zones of northern Europe, North America and Australasia, rates in excess of 100 per 100 000 population have been recorded and have reached 300 per 100 000 in the Orkney and Shetland Islands (Kurtzke, 1993). By contrast, in Asia the prevalence is of the order of 5 per 100 000; fewer than 10 cases have been described in black Africans.

A closer inspection of the epidemiological data reveals a number of important details departing from the overall picture. There are a number of reports that migration from a high prevalence zone (e.g. Northern Europe) to a low prevalence zone (e.g. South Africa) before puberty lowers the risk of MS while migration after this time does not. Migration in the reverse direction has the opposite effect. Another interesting detail is the occurrence of significant local variations in prevalence (see below) and the occurrence of clusters of cases over limited periods of time in confined geographical areas. This has been reported from Iceland, and most strikingly, for the Faroe Islands. The numbers involved in these studies are small, and caution should be exercised in their interpretion. It is of interest that the recent data on MS in Australia does not support the notion of an effect of age at migration on the risk of MS, though it does confirm strikingly the latitudinal gradient which is greater there than in any other country for which data is available (Hammond et al., 2000).

Etiology

The latitude gradient, the influence of migration and the occurrence of clusters of cases have been interpreted as evidence for the involvement of an environmental factor in the etiology of multiple sclerosis. What this might be is uncertain. An infective agent has been postulated (see below), but confirmation of its presence has not been forthcoming.

The geographical prevalence of MS is probably also influenced by genetic factors. In the Northern hemisphere there are genetic clines, one of which is a north–south gradient of frequency of HLA DR15 (formerly DR2), an antigen long associated with multiple sclerosis (see below), the frequency in the Northern hemisphere being higher in the north than in the south (Compston, 1998, 1999). It has become increasingly clear that within the broad north–south gradient of prevalence there are significant local variations. For example in Enna, Sicily, the prevalence is 53 per 100 000 population, whereas in Malta at almost the same latitude it is 4 per 100 000 population. Similar discrepancies are found in Italy and Switzerland. These observations have led to the suggestion that local differences in genetic constitution may be influencing prevalence. A genome survey of European multiple sclerosis is currently addressing this question.

The most convincing evidence for a genetic effect comes from the studies of families. It has long been recognized that the risk of MS is increased in relatives of a proband. In Canada, the overall lifetime risk for MS is 0.2%, 3% for first-degree relatives and 1% for second-degree relatives (Sadovnick, 1994). The risk for adoptive children (Ebers et al., 1995) and marital partners (Robertson et al., 1997) is not increased, whereas the risk to children when both parents have multiple sclerosis is dramatically increased (Robertson et al., 1997). Large twin studies carried out in Canada and the UK have shown that the concordance rate in monozygotic twins is approximately 25% and in dizygotic twins and sibs 2%. These observations provide powerful support for the hypothesis that genetic factors are involved in determining susceptibility to multiple sclerosis, and (because approximately 75% of monozygotic twins are *not* concordant) for the implication of another factor (presumably environmental) as well.

What genes are involved? It is now nearly 30 years since the associations between MS and the HLA system were recognized (for review see Compston, 1999). It is tantalizing that the identity of the genes and their mode of action are still unclear. The field is confusing for the outsider, with different approaches (seeking association vs. linkage), different techniques (serological vs. cellular), conflicting reports, and periodic changes in terminology. Nevertheless, after a period in which little happened, progress is being made again.

The association between MS and *DR15* (formerly *DR2*) (encoded on the sixth chromosome) has been widely confirmed, including in three genome surveys conducted in the United States and France, Canada and the UK. Each of these investigations (and a smaller investigation in Finland) found indications for the involvement of genes on other chromosomes as well; there was however little consistency (for reviews see Compston, 1998, 1999). New surveys with more closely spaced markers are being conducted. A whole genome screen in the UK for association (the first of its kind) has shown four new associations, two of which coincide with previously identified regions of linkage (17q and 10p; S. Sawcer & A. Compston, personal communication). The probability of finding close association and linkage in the same region by chance alone must be low. This raises the possibility that these genes may indeed be involved in susceptibility to MS. Whether they are relevant in other populations remains to be seen. Looking at the evidence overall, it is clear that there is not a single gene which has a major effect on susceptibility to multiple sclerosis and it is probable that several genes with relatively small effects are involved.

A number of attempts have been made to see whether there are specific associations with particular forms of the disease. The only suggestive (albeit unconfirmed) association has come from Japan where MS is rare and more commonly takes the form of an optic–spinal illness than in Caucasians. The optic–spinal form there is associated with a haplotype different from that associated with the Caucasian form, the latter being the same as that commonly found in Northern Europe. There is no confirmed specific association with the primary progressive form of multiple sclerosis. A number of associations have been claimed to influence severity of course of disease (see Chapter 2), but a consistent picture has yet to emerge.

Symptomatology

The mean age of onset of MS is about 30 years and the illness is apporoximately twice as common in women as in men. The course is enormously variable. At one extreme rare cases are fatal in less than a year. At the other, occasional patients have little disability even after 50 years (benign MS; this term is often used to refer to patients with little disability after 10–15 years). Forty per cent of patients require assistance in walking after 15 years (Weinshenker et al., 1989). The median survival from onset is 28 years for men and 33 years for women (Bronnum-Hansen et al., 1994). The frequency of relapses varies widely, though on average it is approximately 0.8–1 per annum. Exceptionally, one, two or even three decades intervene between relapses. Relapses may be precipitated by intercurrent viral infection (Sibley et al., 1985) but the cause of the majority is not apparent.

MS commonly presents with weakness, tingling or numbness in the limbs, vertigo, double vision, unsteadiness or visual loss, reflecting the sites of predilection for lesions (plaques). Each of these features can first appear later in the course of the illness. Some manifestations are more common later. These include bladder and bowel disturbance (often progressing to incontinence), impotence and cognitive dysfunction; the latter is discussed in more detail below. The usual course of a relapse is for symptoms to develop over a matter of days, to persist for several weeks and to resolve gradually over a month or two.

Certain transient symptoms are characteristic of MS. The best known are Lhermitte's symptom (a surge of paresthesiae in the trunk and limbs on neck flexion) and thermolability. Many patients notice that their symptoms are reversibly increased by a hot bath, a hot meal or exercise and conversely that their symptoms are diminished by

a cool ambient temperature. Less commonly, patients may experience tonic spasms or episodes of ataxia. The latter often last a matter of seconds and may be repeated many times in an hour. Characteristically, these episodes are abolished by carbamazepine which is also effective in trigeminal neuralgia, a not uncommon manifestation of multiple sclerosis. Like other manifestations, it commonly occurs in episodes which tend to remit after several weeks. Overall, pain occurs in about one-half of patients and has a variety of causes including muscle spasm and lesions involving central pain pathways (Paty et al., 1997).

Disturbances of cortical function such as epilepsy and aphasia are rare, but well-documented, manifestations. Anosmia and deafness are other infrequent manifestations of the disease.

Clinically isolated syndromes

Three acute or subacute clinical syndromes: optic neuritis, brainstem disturbance and myelopathy, have attracted particular attention because they often herald the onset of MS. The most reliable predictor for the subsequent development of the established disease is the finding of clinically silent abnormalities on MRI scans of the brain at presentation, an observation which has been widely confirmed. In the longest follow-up to date, patients with these three syndromes were grouped together. After 10 years, 80–90% of those with additional abnormalities at presentation had developed multiple sclerosis, compared with 10–20% of those without such abnormalities (O'Riordan et al., 1998). The number and volume of the MRI abnormalities at presentation are predictive of the severity of disability later (Fillippi et al., 1994).

Cognitive and psychiatric abnormalities

There has been much progress in unravelling the cognitive and psychiatric manifestations of MS in the past decade. Accordingly, they are reviewed here at some length.

Cognitive impairment is subtle in patients with clinically isolated syndromes, and subjective symptoms are as a rule absent. Slowing of cognitive processing and impaired auditory attention were first reported in a group of patients with different clinical presentations (i.e. optic neuritis, brainstem or cord syndromes) who exhibited 'silent' MRI abnormalities in other brain regions (Callanan et al., 1989). These findings were later confirmed in a group of patients with optic neuritis who had white matter lesions elsewhere in the brain compared to those who did not (Feinstein et al., 1992b). In addition, impairment of working memory has been described in patients presenting with clinically isolated myelopathy (Pelosi et al., 1997). In this study event-related potential data suggested that both acquisition of memory traces and retrieval processes are impaired.

In patients with clinically definite multiple sclerosis (CDMS), cognitive abnormalities can be detected in 40 to 60% of patients and contribute significantly to the burden of disability (Rao et al., 1991b).

The pattern of cognitive abnormalities is characterized by a decline in intellectual ability, as measured by the difference between current and estimated premorbid IQ, and has been documented in 60% of CDMS patients attending hospital. In addition, memory and executive functions are often impaired to an extent that cannot be explained as a result of the general intellectual decline (Ron et al., 1991).

Impairment in memory tasks is characterized by poor recall, with better preserved recognition and normal forgetting (Rao et al., 1991a). This dissociation has also been reported in Huntington's disease and other conditions predominantly affecting subcortical structures. In some studies verbal memory appeared to be less impaired than visual memory (Ron et al., 1991). A dissociation between memory and attention deficits have been reported (Litvan et al., 1988), suggesting that the former are not a sufficient explanation for memory impairment, which is more likely to result from defective retrieval (Ryan et al., 1996).

Executive function deficits appear to be equally common. Impairment in working memory (Litvan et al., 1988; Grafman et al., 1990; Foong et al., 1997) has been described and may be partly due to decreased information processing speed (Demaree et al., 1999). Impairments in verbal fluency, use of strategy, planning and cognitive estimates have also been described (Foong et al., 1997), although not all executive functions are impaired to the same extent. Foong et al. (1997) have described relative preservation of planning ability with a pattern of deficits reminiscent of that found in HIV dementia, another white matter disease.

Language abilities have traditionally been considered to be spared by the disease, but Kujala et al. (1996) have described subtle abnormalities even in patients with mild cognitive impairment. These abnormalities, which involve semantic and circumlocutory naming errors, could not be explained as resulting from other cognitive abnormalities, which were often absent in this sample.

The natural history of these cognitive deficits is only partially understood. It is well established that cognitive deficits may remain static for many patients during the early stages of the disease (Hohol et al., 1997; Kujala et al., 1996,

1997). A 4-year follow-up study of patients with clinically isolated lesions (Feinstein et al., 1992b) found that cognitive deterioration had only occurred in those who had developed CDMS, and especially in those with secondary progressive disease. In such patients decline in auditory attention and visual memory were observed. Other follow-up studies (Amato et al., 1995) suggest that other deficits (i.e. linguistic disturbances and impaired abstract reasoning) emerge as the disease progresses, although the pattern of impairment varies from patient to patient.

The effects of relapses and remissions on cognitive ability are poorly understood. In a serial study testing patients every 2 weeks, performance on tests of attention and information processing speed declined only in those in whom there was an increase in MRI lesion load (Feinstein et al., 1993). In a group of patients tested during a relapse and again 6 weeks later Foong et al. (1998) described improvements in attention tasks only in those who were mildly impaired at the outset and in whom the volume of gadolinium-enhancing lesions diminished between tests. Memory impairment remained unchanged in all patients, suggesting that, for some patients, cognitive deficits, especially memory impairment, may be permanent.

Cognitive impairment tends to be more severe in those with secondary progressive disease (Ron et al., 1991; Patti et al., 1995; Amato et al., 1995), but cases of early severe cognitive impairment with only mild neurological disability are well documented (Fontaine et al., 1994). Cognitive decline cannot be fully explained as a result of fatigue or depression (Grossman et al., 1994). The pattern of cognitive abnormalities in patients with primary progressive disease does not differ significantly from that of patients with secondary progressive disease, and deficits in verbal memory, attention, verbal fluency and spatial reasoning have also been reported (Camp et al., 1999). Patients with primary progressive MS have been thought to have more severe cognitive deficits than those with secondary progressive disease (Comi et al., 1995), but this has recently been questioned (Foong et al., 2000).

Cognitive impairment has been found to correlate with MRI markers of disease, the most widely used of them being T2 lesion load (Ron et al., 1991), although even at best clinico-MRI correlations are only modest. The lack of neuropathological specificity of T2 abnormalities and the presence of pathology in the normal-appearing white matter (NAWM) probably account for the limited correlations. Other MRI parameters such as T1 lesion load and degree of brain atrophy may be better correlated with cognitive impairment, but reports are contradictory (Rovaris et al., 1998). Other techniques such as magnetization transfer and diffusion tensor imaging, sensitive indices of axonal and myelin integrity, may be more valuable in establishing the neuropathological substrate of cognitive deficits (van Buchem et al., 1998; Filippi et al., 2000; Rovaris et al., 2000).

Attempts to link regional MRI abnormalities (e.g. frontal lesion load) to specific cognitive deficits (e.g. executive functions) have met with variable success (Arnett et al., 1994; Foong et al., 1997) as could be expected in the presence of widespread, multiple lesions and generalized NAWM abnormalities. Strategically placed lesions may have severe cognitive consequences. This may be the case with lesions involving association fibres, especially in the prefrontal areas (Miki et al., 1998; Moriarty et al., 1999). Thus, the results of these studies point to the fact that the burden of the MS lesions, lesion location, severity of pathological damage in individual lesions, and the subtler changes in the NAWM contribute to cause cognitive impairment (Comi et al., 1999). Functional imaging studies hold greater promise to determine the common neural networks disrupted by lesions in different localizations. The PET study of Paulesu et al. (1996) goes some way towards achieving this aim. Decreased glucose metabolism in hippocampi and left thalamus was present in MS patients with memory impairment compared to those without. These changes in brain metabolism, which occurred in the absence of detectable temporal or thalamic lesions, may be caused by more distant or subtle pathology and are likely to represent the common substrate for these deficits. Another study by the same group (Blinkenberg et al., 2000) has found a significant correlation between reduction in cortical metabolism and total load of white matter lesions.

Psychiatric abnormalities in multiple sclerosis

Psychiatric morbidity is not increased in patients with clinically isolated syndromes (Logsdail et al., 1988), and there is little evidence that symptoms of depression or anxiety, without concomitant neurological symptoms or signs, are the presenting features of MS (Skegg et al., 1988). On the other hand, psychiatric morbidity is high in patients with CDMS. The prevalence of depression is close to 50% in hospital attenders (Ron & Logsdail, 1989); this is higher than in patients attending with non-neurological disability (due, e.g. to rheumatoid arthritis) and the lifetime risk of developing depression is of the same order (Sadovnick et al., 1996). A sevenfold increase in suicide has also been reported (Sadovnick et al., 1991).

The presence of depression is not closely related to the duration of illness, degree of disability or cognitive impairment, but may be commoner during relapses or when

neurological disability is progressive. It is uncertain whether there is a genetic predisposition to depression in these patients and while some studies have not found an increased risk for depression in first-degree relatives of depressed MS patients (Sadovnick et al., 1996) others have (Patten et al., 2000). Environmental factors, on the other hand, are clearly important in determining psychiatric morbidity. The degree of social stress and lack of support as perceived by the patients, correlates more closely with the presence of depression than other features of the illness or severity of MRI abnormalities (Ron & Logsdail, 1989).

The early report of increased incidence of depression in patients treated with interferon beta (IFNB Multiple Sclerosis Study Group, 1993) has not been confirmed (Borrás et al., 1999).

The increased rates of psychiatric morbidity in patients with MS and other brain diseases argues in favour of a causative role, although correlations with MRI lesion load have been disappointing (Ron & Logsdail, 1989; Pujol et al., 1997). Recent studies have focused on fronto-temporal circuits known to be relevant in depression and, as with cognitive impairment, a pattern is emerging (Pujol et al., 1997).

Bipolar affective disorder has been reported to occur more often in MS than in the general population (Schiffer et al., 1986), but this remains to be confirmed by appropriate epidemiological studies. A number of intriguing studies have suggested that unsuspected MS may be commoner than would be expected by chance in psychiatric inpatients (see review by McDonald & Ron, 1999).

Short-lived psychotic episodes with schizophrenic or affective symptomatology have also been described (Feinstein et al., 1992a), but they appear to be uncommon. These episodes occurred when neurological disability is well established and temporal lobe lesions appear to be particularly prominent in these patients. This is in marked contrast with the high incidence of schizophrenia-like psychosis in patients with metachromatic leukodystrophy (Hyde et al., 1992), suggesting that the age of onset of white matter disease (i.e. during childhood in the case of metachromatic leukodystrophy) may lead to very different psychiatric manifestations.

Euphoria is an uncommon symptom, best defined as a state of persistent cheerfulness without the motor overactivity of mania and is best considered as the type of personality change akin to that seen in patients with frontal lobe pathology. Its prevalence is around 10%, and is closely associated with the presence of brain pathology and cognitive impairment (Ron & Logsdail, 1989). Also recently, depression has been reported to be less frequent and quality of life less impaired in patients with loss of autobiographical memory (Kenealy et al., 2000). suggesting that even in patients without frank euphoria, specific cognitive deficits may have a mood elevating effect.

Pathological laughing and crying, an abnormal display of emotion not associated with the presence of depression occurs but is equally uncommon (Feinstein et al., 1997).

Pathology

The cardinal features of pathology in multiple sclerosis are (i) demyelination with relative preservation of axons; (ii) astrocytic gliosis; (iii) inflammation; and (iv) axonal loss. The latter, recognized by Charcot (1868) and repeatedly confirmed (Kornek & Lassmann, 1999) has achieved much prominence recently as it has become clear that it is an important factor determining disability. Remyelination occurs but is incomplete (for review see Prineas & McDonald, 2002).

The lesions of multiple sclerosis tend to be periventricular in distribution, though this orientation may be obscured in large, confluent lesions. Any part of the central nervous system can be affected, though there are certain sites of predilection, including the periventricular white matter, the optic nerves, brainstem and spinal cord.

In the past decade, the evolution of the new lesion has been subject to re-evaluation at two levels. First, the dynamics of the MRI visible lesions have been revealed by serial gadolinium-enhanced MRI (for review see Smith & McDonald, 1999). The earliest detectable damage in the majority of lesions in patients with relapsing–remitting and secondary progressive multiple sclerosis is an increase in permeability in the blood–brain barrier in association with inflammation. Demyelination detected by magnetic resonance spectroscopy (MRS) and by delay in evoked potentials occurs at about the same time. In some lesions, it may precede the appearance of gadolinium enhancement. Inflammation and edema resolve over 4–8 weeks. In primary progressive MS, however, only approximately 5% of new lesions enhance (Thompson et al., 1991), in keeping with the observation of a significantly lower level of inflammation at postmortem in primary progressive multiple sclerosis than in secondary progressive disease (Revesz et al., 1994).

It is important to realize that occasional cases classified as primary progressive multiple sclerosis for a number of years may experience a clear-cut relapse, a fact which serves to underline the difficulty of identifying homogeneous subgroups of cases in multiple sclerosis. This difficulty is further enhanced by the fact that patients may

Table 98.1. Histopathological features of different patterns of active multiple sclerosis lesions

	Type I	Type II	Type III	Type IV
Pathology				
Inflammation				
T-cells	++	++	++	++
B-cells / plasma cells	+	+	+	+
Macrophages	+++	+++	+++	+++
Complement activation	–	++	–	–
Demyelination				
Perivenous pattern	+	+	–	±
Lesion edge	Sharp	Sharp	Ill-defined	Sharp
Concentric pattern	–	–	~30% of cases	–
Oligodendrocytes				
Density in plaque	+++	+++	+ (↓)	+ (↓)
DNA fragmentation	±	±	++ (apoptosis)	++ (periplaque white matter)
Myelin protein loss	Even	Even	MAG ≫ others	Even
Remyelination				
Shadow plaques	++	++	–	–
Clinical phenotypes	Acute, RR, SP, PP	Acute, RR, SP, PP	Acute, RR, SP	PP
Proposed immunopathology	T-cell mediated autoimmunity	T-cell and antibody-mediated autoimmunity	Oligodendrogliopathy (? virus-induced)	Oligodendrogliopathy (? virus-induced)

Notes:
MAG = myelin associated glycoprotein; RR = relapsing remitting; SP = secondary progressive; PP = primary progressive.
Adapted from Lucchinetti et al. (2000).

forget minor episodes of neurological disturbance which may have preceded by many years the onset of progressive disease. Thus, caution must be exercised in associating particular kinds of lesion with particular patterns of clinical expression. This consideration is relevant to the oft-raised question as to whether multiple sclerosis is more than one disease, and in particular whether primary progressive multiple sclerosis is a specific entity. The failure to identify confirmed specific genetic associations further weakens the case. At present the question remains open.

The second approach to the evolution of the lesion, is histopathological. On the basis of the study of a large number of biopsied lesions and lesions observed at postmortem, Lassmann and his colleagues (Lucchinetti et al., 2000) have postulated that there are four types of lesion (see below and Table 98.1). This has led to the suggestion that there may be four distinct pathogenetic routes by which the classical multiple sclerosis plaque seen at postmortem may arise. How these mechanisms relate to the various clinical patterns of disease remains to be determined.

Pathogenesis and the immunology of multiple sclerosis

The most widely held view of the nature of multiple sclerosis is that it is an organ-specific autoimmune disease (Martin & McFarland, 1995), the hypothetical pathogenesis of which is summarized in Fig. 98.1. The central tenet of the autoimmune theory is that MS is mediated by antigen-specific autoreactive T-cells. Putative autoantigens implicated in MS include the myelin proteins: myelin basic protein (MBP), proteolipid protein (PLP), myelin associated glycoprotein (MAG), and myelin oligodendrocyte glycoprotein (MOG); other potential non-myelin autoantigens include transaldolase, 2′3′-cyclic nucleotide 3′-phosphodiesterases, and αB-crystallin (Steinman, 1995). These antigens, peptides derived from these antigens or the adoptive transfer of specific T-cells reactive to these antigens are capable of inducing experimental allergic encephalomyelitis (EAE), a model of MS, in several animal species (Petry et al., 2000). MS patients have myelin-reactive T-cells in their peripheral circulations that are clonally enriched in MS plaques (Oksenberg et al., 1993). Although

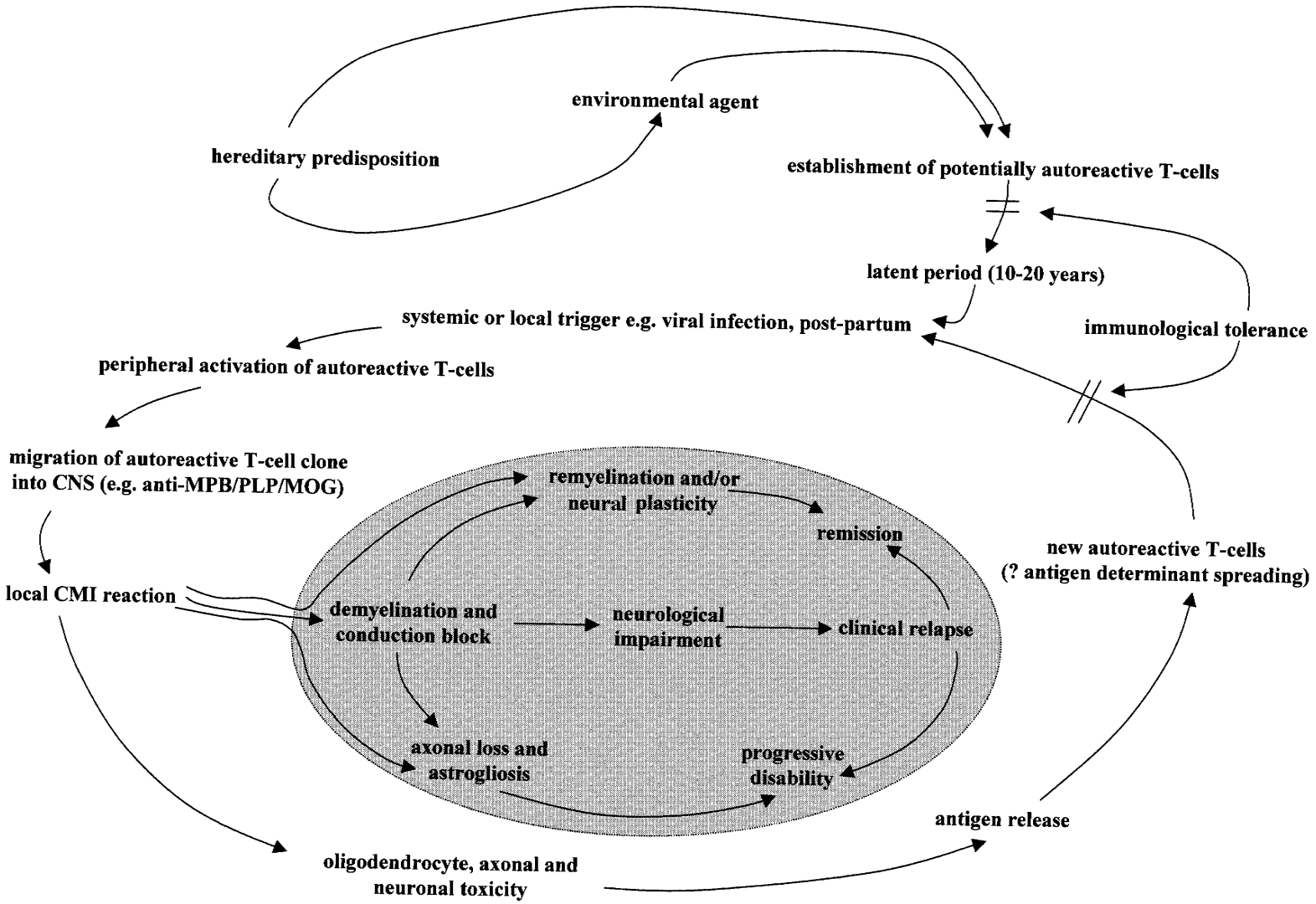

Fig. 98.1. Hypothetical scheme for the pathogenesis of multiple sclerosis. In subjects with a genetic susceptibility, childhood exposure to a putative environmental trigger or triggers induces autoreactive T-cells, which establishes a state of latent autoimmunity with the potential to develop disease. After a period of latency (Wolfson & Wolfson, 1993), estimated to be 10–20 years, a systemic trigger such as a viral infection activates these autoreactive T-cells, possibly as a consequence of molecular mimicry (Gran et al., 1999). Another possibility is exposure to a superantigen, which is capable of non-specifically activating a subset of T-cells. Once activated, these T-cells selectively cross the blood–brain barrier and on re-exposure to their autoantigen initiate a cell-mediated (Th1) inflammatory reaction. The resultant cell-mediated inflammatory cascade results in demyelination and axonal damage. Sequestered CNS antigens, which are then released are hypothesized to initiate further episodes of autoimmune-induced inflammation, by the process of intra- or intermolecular antigenic spreading. Events within the shaded oval represent the clinical correlates of the multifocal inflammatory reaction, which occurs in MS

auto-reactive T-cells are demonstrable in normal subjects, they probably occur at a lower frequency, their T-cell receptor (TCR) usage is generally not restricted and they are less likely to have undergone in vivo activation and proliferation compared to T-cells from MS patients (Hafler et al., 1996; Allegretta et al., 1990; Trotter et al., 1997). Despite these findings it remains a moot point whether or not these autoreactive T-cells are primarily involved in the pathogenesis of MS or occur as a secondary or non-specific phenomenon in response to tissue damage.

Evidence against the autoimmune theory has been the failure of multiple sclerosis to respond, except to a minor degree, to anti-T-cell therapies, including azathioprine (Yudkin et al., 1991), cyclosporin (The Multiple Sclerosis Study Group, 1990) and a depleting anti-CD4 monoclonal antibody (van Oosten et al., 1997). The failure of these therapies in multiple sclerosis should be contrasted with their striking efficacy in EAE and in allogenic solid organ transplant rejection, disorders in which antigen-specific T-cell involvement is well established. It has also not been possible passively to transfer multiple sclerosis to nude mice, i.e. mice lacking an immune system, using autoreactive T-cells derived from MS patients (Hao et al., 1994; Martino et al., 1994; Jones et al., 1995). The clinical observation that the disease course of MS is worsened by immunodeficiency due to HIV-1 Infection (Berger et al., 1989) also questions the role of T-cells in the pathogenesis of the disease. This evidence, however, is based on a very small number of cases and is therefore not conclusive and does not exclude specific T-cell involvement early in the course of the disease.

The immunological events, which are thought to occur within an individual MS lesion, are summarized in Fig. 98.2. Although current evidence supports MS as a disease mediated by Th1–CD4+ $\alpha\beta$T-cells (Martin & McFarland, 1995; Hohlfeld, 1997), additional cell types including CD8+ T-cells (Babbe et al., 2000), $\gamma\delta$T-cell (Borsellino et al., 2000), natural killer (NK) cells (Pouly & Antel, 1999), and B-cells (Archelos et al., 2000) are found in MS lesions have all been implicated in the disease process. CD8+ T-cells, $\gamma\delta$T-cells and natural killer (NK) cells are capable of producing potent cytotoxic mediators, granzyme and perforin, and may be actively involved in the disease process.

The intrathecal synthesis of oligocloncal IgM and IgG is an almost invariable feature of MS in Caucasians (McLean et al., 1990). The site of antigen specific B-cell ontogeny is presumed to be in the deep cervical lymphatics, although secondary lymphoid-like follicles have been seen within MS lesions (Prineas, 1979). Genomic analysis of immunoglobulin heavy chain sequences from MS lesions shows that the variable region IgG preferentially accumulates mutations in the complementary-determining regions relative to framework regions of the molecule (Smith-Jensen et al., 2000). This is a feature of a T-cell dependent antigen-driven response, which also occurs in central nervous system infections, e.g. subacute sclerosing panencephalitis (SSPE) (Smith-Jensen et al., 2000). Autoantibodies, such as anti-MOG are found in the CSF of MS patients and are capable of binding to the myelin and activating complement (Raine et al., 1999).

The focal inflammatory infiltrates produce a host of pro-inflammatory cytokines and non-specific mediators, which are responsible for tissue damage. However, these inflammatory cells are also capable of producing growth or trophic factors which may play a role in the process of tissue repair and remyelination (Hohlfeld et al., 2000). For example, brain-derived neurotrophic factor (BDNF), produced by T-cells, B-cells, macrophages and microglia, is expressed in MS lesions (Kerchensteiner et al., 1999). Similarly, insulin-like growth factor-1 (IGF-1), a survival factor for oligodendrocytes, IFG receptors and receptors for glial growth factor 2 (GGF2), which promote the proliferation and survival of the oligodendrocyte, are up-regulated in MS lesions. Antioxidants, particularly glutathione produced by astrocytes, have an important neuroprotective role in inflammatory CNS diseases (Heales et al., 1999).

As mentioned above, recent work suggests that there may be four distinct routes leading to the demyelinated plaque (see Table 98.1, Lucchinetti et al., 2000). The pathological subtypes appear to be associated with different immunological mechanisms involving antibodies, complement, T-cell cytotoxicity, and macrophage activation. Whether or not these pathological subtypes represent different stages of the disease or autoimmune or toxic/viral variants is speculative and is currently under investigations.

The immunological mechanisms underlying disease progression and the clinical or phenotypic spectrum of MS are unknown. Current proposals include failure of reparative and neuroprotective mechanisms, an imbalance between the Th1 and Th2 cell-mediated immune responses, dysregulated T-cell function, reduced T-cell apoptosis, antigen determinant spreading, pathological heterogeneity, and genetic differences responsible for tissue repair and/or protection against tissue damage. The specific role inflammation plays in disease progression is not well defined.

Immunosuppressive therapies, which are capable of reducing or stopping clinical relapses and suppressing MRI activity, generally do not stop disease progression.

The epidemiological evidence for an infective factor in the etiology of MS has already been mentioned (Kurtzke,

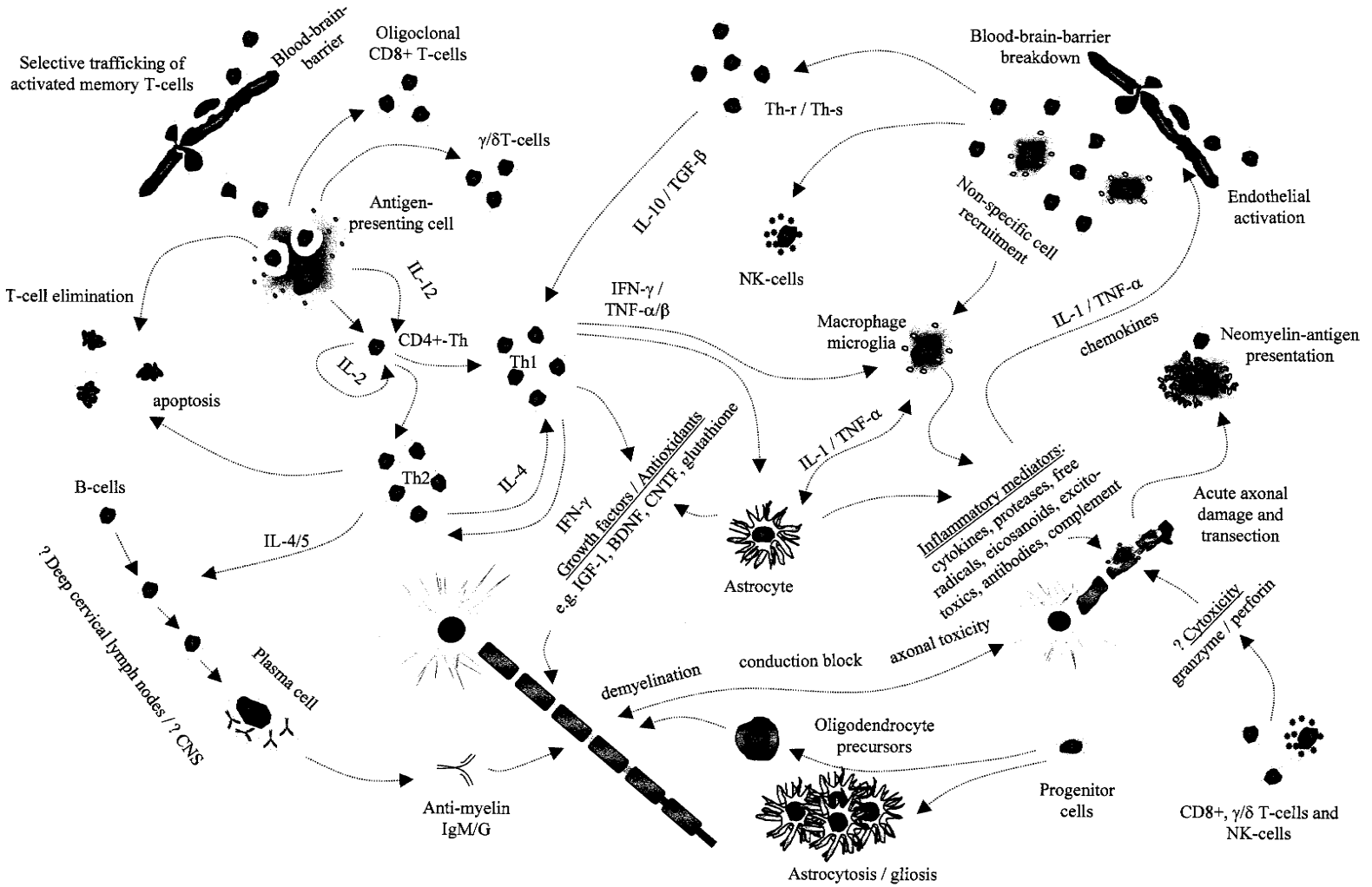

Fig. 98.2. Postulated local mechanisms of inflammation in MS. Activated $CD4^+$ and $CD8^+$ T-cells cross the blood–brain barrier selectively via the interaction of their cell surface adhesion molecules with those expressed on the central nervous system endothelium (Archelos et al., 1999). The T-cells then negotiate a path through the basement membrane and extracellular matrix, by secreting several metalloproteinases (Kieseier et al., 1999). Once within the perivascular space, these cells are activated by professional antigen presenting cells (probably macrophages or microglia). The T-cells then proliferate and produce cytokines. The profile of T-cell cytokines produced depends on the costimulatory signals received during activation (Racke et al., 2000). IL-12 favours Th-1 development and cytokine production (IL-2, IFNγ and TNFα/β). This initiates a classical cell-mediated inflammatory cascade, which activates macrophages, microglia, astrocytes and endothelial cells. Once activated, macrophages/microglia and astrocytes also produce proinflammatory cytokines, which recruit more inflammatory cells by the up-regulation of endothelial cell adhesion molecules and the production of chemokines. A host of toxic substances, including reactive oxygen (superoxide, hydrogen peroxide and the hydroxyl radical) and nitrogen (nitric oxide, peroxynitrite) species, proteases, eicosanoids, excitotoxic factors (kynurenic and quinolinic acid), which in combination with autoantibodies, complement activation and toxic effects of cytokines (particularly TNFα) cause oligodendrocyte cell damage or death by apoptosis with resultant demyelination. These local factors may also be responsible for axonal toxicity and damage and be capable of causing axonal transection (Trapp et al., 1999). Immunomodulatory cytokines (IL4, IL10 and TGFβ) produced by regulator/suppressor (Th-r/Th-s) and Th2 T-cells, growth factors and antioxidants may be important in down-regulating and controlling the inflammation, neuroprotection and stimulating repair.

1993). Numerous candidate organisms have been unsuccessfully implicated as the cause of MS (Johnson, 1994). Epstein–Barr virus (EBV) (Munch et al., 1997), human-herpes-virus-6 (HHV6) (Berti et al., 2000) and the MS-associated retroviruses (Perron et al., 2000) remain potential candidates. The autoimmune and infectious theories are not mutually exclusive and are potentially complementary. For example, following on the acute encephalitic phase of murine Theiler's virus infection, susceptible strains of mice develop an autoimmune demyelinating disease of the CNS, which is not too dissimilar pathologically from MS (Miller et al., 1997). Systemic infection also plays an important role in the induction of acute MS disease activity, presumably via a non-specific stimulation of the immune system. A third of clinical relapses follow an acute viral or bacterial infection (Sibley et al., 1985; Rapp et al., 1995).

In summary, MS is an inflammatory disease of the CNS with evidence of organ-specific cell-mediated autoimmunity directed at myelin components. Whether it is a true 'autoimmune disease' remains to be established. An infectious etiology cannot be excluded. Recent pathological evidence supports disease heterogeneity.

Pathophysiology

The mechanism of symptom production in MS has interested neurologists since the time of Charcot (1868). Experimental work since the 1960s together with the application of evoked potentials to the study of MS since the 1970s and the use of serial MRI since the 1990s, has revealed the probable mechanisms of many of the manifestations of MS; this despite the well-known (though explicable) discrepancies between clinical deficit and hyperintensities on T_2-weighted images. The whole subject has been comprehensively reviewed recently (Smith & McDonald, 1999).

The loss of function occurring in a relapse is a consequence of conduction block which develops partly because of the altered biophysical properties of the nerve fibre, and partly through the action of inflammatory mediators on the process of conduction. There is experimental evidence that nitric oxide, which is produced by macrophages which are abundant in the acute lesion, is implicated. The role of other inflammatory mediators remains to be determined.

Two major factors have so far been identified in the process of remission: resolution of inflammation and the acquisition of the ability of the demyelinated axons to conduct as a result of the insertion of new sodium channels into the denuded axon membrane. Although conduction in these circumstances is an order of magnitude slower than normal, clinical recovery is remarkably good. The usual persistence of conduction delays in adults, despite recovery of function, provides the basis for the use of the evoked potential to detect clinically silent lesions during diagnostic evaluation (Chapter 99). To the extent that remyelination occurs (Chapter 97) it will contribute to the recovery process.

The demyelinated axon has a number of other properties, which help to explain some of the characteristic features of MS. The exquisite vulnerability of conduction in the demyelinated axon to small changes in temperature (a rise of as little as 1 °C can convert intermittent conduction block into persistent conduction block) is likely to contribute to the effect of changes in body temperature on symptoms. The inability of demyelinated axon to conduct long trains of impulses faithfully at physiological frequencies probably contributes to functional impairment, and may contribute to fatigue, though the pathophysiology of this common and often disabling symptom remains to be elucidated fully.

The cerebral cortex in MS

There has recently been renewed interest both in the structure and the function of the cerebral cortex in MS. It has long been known that cortical plaques occur; they are in fact common (Kidd et al., 1999). It is also possible that there are secondary effects on cortical organization deriving from neuronal loss consequent upon axonal degeneration. This is perhaps particularly likely in the visual cortex, given the high frequency of involvement of the visual pathways in MS and the propensity for transynaptic degeneration in the visual symptom. By the same token, changes might also be expected in the retina. These possibilities have yet to be investigated. Clinically, little attention has been given to the contribution of high-level deficits (e.g. apraxia) to disability.

The importance of axonal degeneration in MS raises the question of whether adaptive changes might contribute to functional recovery. That they do so in stroke and are associated with changes in the pattern of cortical activation has been demonstrated by functional imaging (Weiller et al., 1993). Recent fMRI observations provide evidence for extensive changes in the pattern of cortical activation in patients who have recovered clinically from optic neuritis, but still have delayed VEPs. Numerous extrastriae visual areas are activated by a stimulus which normally produces activation confined to the occipital cortex (Werring et al.,

2000). These changes appear to be absent from those with normal latencies. These observations require confirmation. Similar changes have been observed in the motor system (Lee et al., 2000). Whether and to what extent the cortical changes contribute to remission from relapses, and whether they may help to retard the accumulation of neurological deficit in the continuously progressive phase of the disease, remains to be determined.

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99

The diagnosis and management of multiple sclerosis

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The 1990s have seen significant progress in both the diagnosis and management of multiple sclerosis (MS). The widespread use of magnetic resonance imaging (MRI) has enabled an earlier and more accurate diagnosis in many instances. An increasing range of effective strategies for symptom management have evolved as has the widespread introduction of partially effective disease modifying therapies. This chapter summarizes current approaches to diagnosis and management. As MS remains a disabling disease of unknown cause, the chapter concludes with a brief discussion of potential future therapeutic strategies.

Diagnosis

General requirements

The diagnosis of MS is based primarily on clinical features, but in the presence of a characteristic clinical picture, there is a number of laboratory investigations that are very helpful in supporting the diagnosis. The most widely used diagnostic criteria of recent decades have been those of Schumacher et al. (1965) and Poser et al. (1983). These have emphasized the requirement for there to be a history of multiple episodes separated in time, and signs on examination of multiple lesions affecting different parts of the central nervous system (CNS) white matter. Both sets of criteria have applied categories of definite, probable and possible MS, based largely on the completeness for the evidence for dissemination in time and space. An age range at diagnosis of 10–59 years is suggested, although rarely presentation will be seen at a younger or older age. There must be no better explanation for the clinical presentation. The Poser criteria added the results of laboratory investigations to increase diagnostic certainty. Thus, the presence of oligoclonal IgG bands in the cerebrospinal fluid (CSF) but not serum (indicating intrathecal production) could upgrade the diagnosis from clinically probable to laboratory supported definite MS. The presence of clinically silent lesions on MRI or evoked potential testing could be used, along with clinical signs of a single CNS lesion, to satisfy the criterion of dissemination in space.

The Poser criteria were formulated in 1982, when experience with MRI was limited. A new set of criteria incorporating the progress of the last two decades has been recommended by an International Panel in 2001 (McDonald et al., 2001; Tables 99.2–99.4). They represent a considerable simplification in the diagnostic classification. The outcome of a diagnostic evaluation is now 'MS', 'possible MS', or not MS.

Common clinical presentations: relapsing remitting MS

In 85% of patients, the presentation of MS is with episodes of acute and reversible neurological disturbance (relapses and remissions) affecting CNS white matter. Clinically definite MS (or MS on the new criteria) on the Poser criteria is diagnosed when there are at least two episodes, each lasting at least 24 hours and separated in time by at least 1 month, with signs on examination of involvement of two separate parts of the CNS. Relapses will normally last for longer, a typical duration being 2–6 weeks. Many clinicians will also feel more comfortable making a definite diagnosis only when the interval between the two episodes is longer than 1 month, e.g. 3 or 6 months, because the monophasic demyelinating disorder acute disseminated encephalomyelitis, although in practice a much rarer disorder in adults, can occasionally evolve over 1–2 months.

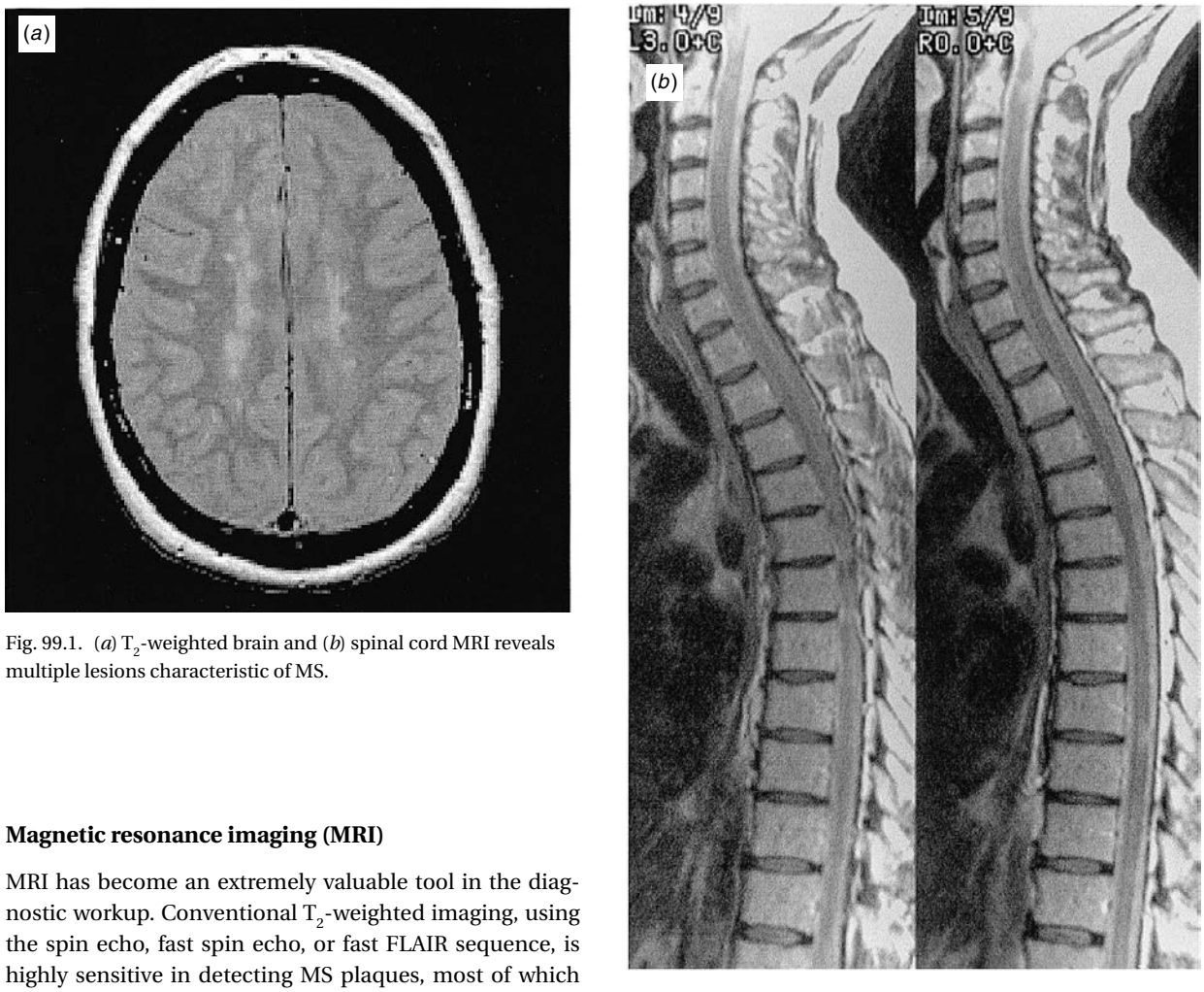

Fig. 99.1. (*a*) T_2-weighted brain and (*b*) spinal cord MRI reveals multiple lesions characteristic of MS.

Magnetic resonance imaging (MRI)

MRI has become an extremely valuable tool in the diagnostic workup. Conventional T_2-weighted imaging, using the spin echo, fast spin echo, or fast FLAIR sequence, is highly sensitive in detecting MS plaques, most of which are clinically silent. Brain MRI is abnormal in 95% of patients with clinically definite MS, and spinal cord MRI reveals lesions in about 75%; together, one or other region will reveal abnormalities in all but a very small number of patients (Fig. 99.1). MRI assists the diagnosis by demonstrating disseminated white matter lesions in space, but also by showing a profile of abnormalities that are characteristic of demyelination. Such characteristic features include the following: predominantly periventricular lesions with asymmetrical and irregular involvement; oval or round shaped lesions; corpus callosum involvement, lesions abutting the corticomedullary junction; brainstem lesions especially in the floor of the fourth ventricle or abutting the subarachnoid surface; gadolinium enhancement for the first few weeks of a lesion's appearance but not thereafter; nodular or ring shaped enhancement sometimes with an open (incomplete) ring; spinal cord lesions of less than 1–2 vertebral segments in length, with partial cross-sectional involvement, often wedge shaped and extending to the subarachnoid surface on axial images.

Despite these helpful features, specificity of MRI is limited and there are many other conditions, which produce white matter lesions (Table 99.1). Sometimes the clinical picture or pattern of MRI abnormalities are clearly such that MS is not part of the differential diagnosis. MRI diagnostic criteria have been developed to improve specificity (Barkhof et al., 1997; Fazekas et al., 1999; Tintoré et al., 2000). Nevertheless, no MRI finding is pathognomonic of MS, and diagnosis remains primarily clinical. A particular problem is that ageing *per se* produces cerebral white matter lesions due to small vessel disease; brain MRI is therefore least specific in older adults. Age-related lesions do not occur in the cord: MRI of this region is especially useful in older patients, or when brain imaging results are normal (Thorpe et al., 1996).

Table 99.1. Causes of white matter lesions on MRI

Common causes	Ageing (small vessel disease)
	Symptomatic cerebrovascular disease
	Multiple sclerosis
Less common	Acute disseminated encephalomyelitis
	Behçet's disease
	Decompression sickness
	Fat embolism
	HIV encephalitis
	HTLV-1 associated myelopathy
	Hydrocephalus
	Irradiation
	Isolated CNS vasculitis
	Leukodystrophies (many types)
	Migraine
	Mitochondrial encephalopathy
	Neurosarcoidosis
	Phenylketonuria
	Progressive multifocal leukoencephalopathy
	Subacute sclerosing panencephalitis
	Systemic lupus erythematosus
	Toxic leukoencephalopathy (several causes)
	Trauma
	Whipple's disease

Evoked potentials

These investigations include visual, brainstem auditory, somatosensory and motor evoked potentials. They are useful, like MRI, in demonstrating subclinical involvement of CNS fibre pathways, or in demonstrating objective CNS abnormality when the clinical features are equivocal. They are less sensitive than MRI and less often required in diagnostic workup. They are most useful when MRI findings are equivocal or negative or in older individuals when brain MRI is least specific. The visual evoked potential is the most useful in practice, and has been incorporated into the new diagnostic criteria (McDonald et al., 2001; Table 99.2). The characteristic abnormality in demyelination is a prolonged latency response with a well-preserved wave form.

CSF examination

The CSF exhibits a mild mononuclear pleocytosis (5–30 cells per mm^3) and mildly raised protein in 40% patients. Intrathecal oligoclonal IgG bands (i.e. not seen in matching serum), occur in 90% with clinically definite MS. CSF examination is most useful when the clinical and MRI findings are equivocal or in older individuals when brain MRI is less specific.

Other investigations

Other multifocal disorders, which produce relapsing CNS syndromes, need to be considered. Blood tests include a full blood count, ESR and autoantibody screen (thinking of SLE or vasculitis), borrelia and treponemal serology. In SLE, white matter lesions often have a subcortical predominance. Sometimes neurosarcoidosis is considered and may lead to chest X-ray, serum ACE, and neuro-ophthalmology assessment; gadolinium-enhanced MRI may reveal meningeal enhancement which is not a feature of MS. If the question of neuro-Behçet's disease arises, CRP and neuro-ophthalmology assessment may be performed; the most common parenchymal CNS syndromes in Behçet's disease involve the brainstem and diencephalon, and striking MRI abnormalities may occur in these regions. MS with prominent and permanent visual loss due to optic neuropathy may lead to a search for the mitochondrial DNA point mutations associated with Leber's disease; the coexistence of Leber's optic neuropathy and MS is rare but well recognized, especially in females (Harding et al., 1992).

Primary progressive MS

In 15% of patients, onset is with a slowly progressive CNS syndrome (primary progressive MS). Most often this is a progressive myelopathy with spastic paraplegia (80%); rarer presentations include progressive ataxia, dementia or visual loss. Because of the progressive and often unifocal onset, the diagnostic criteria used for relapsing remitting MS are less satisfactory. In cases of progressive myelopathy, spinal MRI is mandatory to exclude a surgically treatable compressive lesion or spinal arteriovenous malformation. The differential diagnosis also includes other intrinsic myelopathies including HTLV-1 associated myelopathy, hereditary spastic paraplegia, motor neuron disease, and adrenomyeloneuropathy. The most useful investigations for a diagnosis of primary progressive MS are brain and cord MRI, CSF examination for oligoclonal bands and, in the case of progressive myelopathy, visual evoked potentials. New diagnostic criteria have been published based on clinical and laboratory findings (Thompson et al., 2000; McDonald et al., 2001; Table 99.2). For a definite diagnosis, these require the presence of CSF oligoclonal bands plus the following MRI findings: *either* 9 brain lesions *or* 2 spinal cord lesions *or* 4–8 brain lesions plus one spinal cord lesion.

Clinically isolated syndromes (CIS)

A particularly important diagnostic issue arises in adult patients who present with a CIS, which is typical of MS, e.g.

Table 99.2. New criteria for diagnosis of MS

Clinical presentation	Additional data needed for MS diagnosis
Two or more attacks; objective clinical evidence of two or more lesions	• None[a]
Two or more attacks; objective clinical evidence of one lesion	• Dissemination in space, demonstrated by: → MRI[b] or → 2 or more MRI-detected lesions consistent with MS plus positive CSF[c] or → Await further clinical attack implicating a different site
One attack; objective clinical evidence of two or more lesions	• Dissemination in time, demonstrated by: → MRI[d] or → Second clinical attack
One attack; objective clinical evidence of one lesion (monosymptomatic presentation; clinically isolated syndrome)	• Dissemination in space, demonstrated by: → MRI[b] or → 2 or more MRI-detected lesions consistent with MS plus positive CSF[c] and • Dissemination in time, demonstrated by: → MRI[d] or → Second clinical attack
Insidious neurological progression suggestive of MS	• Positive CSF[c] and • Dissemination in space, demonstrated by: → (i) Nine or more T_2 lesions in brain; or (ii) two or more lesions in spinal cord or (iii) four to eight brain plus one spinal cord lesion or → abnormal VEP[e] associated with four to eight brain lesions, or with fewer than four brain lesions plus one spinal cord lesion demonstrated by MRI and • Dissemination in time, demonstrated by: → MRI[d] or → Continued progression for 1 year

Notes:
If criteria indicated are fulfilled, the diagnosis is MS; if the criteria are not completely met, the diagnosis is 'possible MS'; if the criteria are fully explored and not met, the diagnosis is 'not MS'.

[a] No additional tests are required; however, if tests (MRI, CSF) are undertaken and are NEGATIVE, extreme caution needs to be taken before making a diagnosis of MS. Alternative diagnoses must be considered. There must be no better explanation for the clinical picture.

[b] MRI demonstration of space dissemination must fulfil the criteria in Table 99.3.

[c] Positive CSF determined by oligoclonal bands detected by established methods (preferably isoelectric focusing) different from any such bands in serum or by a raised IgG index.

[d] MRI demonstration of time dissemination must fulfil the criteria in Table 99.4.

[e] Abnormal visual evoked potential of the type seen in MS (delay with a well-preserved wave form).

Source: From McDonald et al. (2001).

unilateral optic neuritis, or a partial myelitis. The traditional Schumacher/Poser criteria do not allow a diagnosis of MS until a second clinical episode has occurred. However, it is now clear that many of these patients will develop clinical MS and that MRI findings at presentation identify those most likely to do so. About two-thirds of patients with CIS already have disseminated brain lesions indistinguishable from MS. Follow-up for up to 10 years shows that most of this group (80–90%) will develop MS, whereas only 10–20% with normal brain imaging will do so (O'Riordan et al., 1998). Specific MRI features which increase the likelihood of early development of MS (within 3 years) are 4 or more periventricular lesions, gadolinium-enhancing lesions, corticomedullary junction lesions and infratentorial lesions (Barkhof et al., 1997). The presence of new lesions on a follow-up scan 3 months after presentation with a CIS and an abnormal initial scan have been associated with an increased likelihood of developing clinical MS within 1 year (Brex et al., 2001). Serial MRI in patients with CIS can satisfy the criteria for dissemination in space and time, and have been incorporated in the new diagnostic classification (Tables 99.2–99.4).

Table 99.3. MRI criteria for dissemination in space

Three out of four of the following:
(i) One gadolinium-enhancing lesion or nine T_2 hyperintense lesion if there is no gadolinium-enhancing lesion
(ii) At least one infratentorial lesion
(iii) At least one juxtacortical lesion
(iv) At least three periventricular lesions

Note:
One spinal cord lesion can substitute for one brain lesion
Source: From McDonald et al. (2001).

Table 99.4. MRI criteria for dissemination of lesions in time

(i) If a first scan is 3 or more months after the onset of the clinical event, the presence of a gadolinium-enhancing lesion is sufficient to demonstrate dissemination in time, provided that it is not at the site implicated in the original clinical event. If there is no enhancing lesion at this time, a follow-up scan is required. The timing of this follow-up scan is not crucial, but 3 months is recommended. A new T_2 or gadolinium-enhancing lesion at this time then fulfils the criterion for dissemination in time.
(ii) If the first scan is performed less than 3 months after the onset of the clinical event, a second scan done 3 months or more after the clinical event showing a new gadolinium-enhancing lesion provides sufficient evidence for dissemination in time. However, if no enhancing lesion is seen at this second scan, a further scan not less than 3 months after the first scan that shows a new T_2 lesion or an enhancing lesion will suffice.

Source: From McDonald et al. (2001).

Acute disseminated encephalomyelitis (ADEM)

This is monophasic but multifocal demyelinating CNS disorder, which arises in the differential diagnosis when patients present with a first clinical episode of CNS demyelination. It is common in children but rare in adults, the reverse of MS. It is often seen following infections and occasionally after vaccinations. Clinical features more typical of ADEM are obtundation, bilateral optic neuritis and complete transverse myelitis. CSF sometimes shows a marked pleocytosis (e.g. $>$100 white cells per mm^3). MRI findings may be indistinguishable from MS or sometimes show a more distinctive pattern with symmetrical lesions in the cerebellar peduncles and cerebral white matter; on follow-up the MRI lesions show partial or complete resolution and new lesions do not appear, unlike MS where new lesions are frequently found.

Devic's neuromyelitis optica

This is a syndrome in which a combination of optic neuritis and a severe myelitis are seen without clinical involvement of other CNS regions. It may be monophasic or multiphasic. Several clinical, laboratory and pathological features appear to distinguish it from classical relapsing remitting MS (Wingerchuk et al., 1999): a complete transverse myelitis, with sometimes poor recovery; relatively more common in non-Caucasian ethnic groups; brain MRI often normal; spinal cord MRI exhibits extensive lesions over many segments with swelling during the acute phase; CSF may exhibit a neutrophil pleocytosis and is often negative for oligoclonal bands; pathologically, the cord lesions may exhibit necrosis. It is a syndrome with several specific causes (e.g. SLE, ADEM) but in most cases a cause is not identified.

Management

Symptomatic treatment

The wide range of symptoms commonly seen in multiple sclerosis (MS) has already been discussed. It is relevant in this section to emphasize that in many patients some, if

not all, of these symptoms coexist and interact, resulting in complex disability which is often extremely difficult to manage (Thompson, 1998; Leary & Thompson, 2000). Furthermore, drug therapy for one symptom may aggravate another, e.g. the treatment of spasticity or pain with agents may worsen existing fatigue. This complexity argues for a comprehensive and carefully constructed management plan that is specific to the individual patient's needs. This is incorporated within the rehabilitation philosophy, which will be discussed later. In the approach to individual symptoms, it is almost invariably necessary to combine a number of key elements:

(i) education and information for the patient
(ii) therapy input (physiotherapy, occupational therapy, speech and language therapy, etc.)
(iii) drug treatment

Although this section will focus on the third of these essential components, it is important to appreciate that drugs in isolation are very limited in the treatment of common, disabling symptoms such as spasticity and ataxia (Kesselring & Thompson, 1997). It is also sobering to reflect on the paucity of evidence available to support the majority of agents in current clinical use and to underline the need for scientifically sound trials in the area of symptomatic management.

Of the variety of symptoms seen in MS, many, such as spasticity, ataxia, poor balance and sensory disturbance, affect mobility. However, from the patient's perspective, the most disabling symptoms are fatigue and bladder dysfunction, both of which may also limit mobility. Other symptoms, which have, until recently, been underreported, include pain and cognitive dysfunction. Temperature-related symptoms are also both common and disabling, as are bowel and sexual dysfunction. Finally, visual and bulbar symptoms such as speech, swallowing and respiratory difficulties may be extremely incapacitating.

Mobility-related symptoms

Spasticity

This common symptom, which only requires drug therapy if it is truly disabling, is an excellent example of the need to combine patient education, therapy and drug treatment. (Thompson, 2001). The latter may be given orally or by injection (intramuscular, intraneural or intrathecal). Of the oral agents, it is preferable to attempt to manage the symptom with a single agent; baclofen is the most effective, though not always well tolerated. It is a gamma aminobutyric acid (GABA) B agonist which acts on both pre- and postsynaptic terminals. Appropriately for MS, it is thought to be particularly effective for spasticity of spinal origin and in particular flexor spasms. It should be commenced at a low dose (5 mg tid) and increased gradually to between 60 to 80 mg per day. Patients should be monitored carefully by the physiotherapist to avoid problems with low tone, particularly in relation to the trunk muscles, and to identify side effects which, along with hypotonia and weakness, include drowsiness and fatigue. Abrupt discontinuation may result in severe withdrawal symptoms including hallucinations and seizures. Of the alternatives, it has been suggested that tizanidine may not cause so much weakness, though this is not so obvious in clinical practice. It acts by stimulating alpha-adrenergic receptors and has been evaluated in two relatively large randomized, placebo-controlled trials. It should also be started at a low dose (2 mg tid) and increased slowly up to a maximum of between 24 and 32 mg per day. It may also cause fatigue and a dry mouth, and liver function tests should be checked before starting and at monthly intervals for three months as transient hepatotoxicity may occur. Other agents include diazepam and clonazepam, which may be particularly useful for nocturnal spasms. Others, including gabapentin, memantine, and vigabatrin, have undergone small, uncontrolled studies. The use of cannabis has been advocated in a number of quarters, most vociferously by patients themselves, and a large randomized placebo-controlled trial is under way in the UK.

For more severe spasticity, the choice of intervention will depend on whether it is focal or generalized. For the former, intramuscular botulinum toxin or intraneural injection with either alcohol or phenol may be appropriate. A recent study has shown particular benefit from botulinum toxin in adductor spasticity though little functional effect was seen (Hymen et al., 2000). Focal spasticity is relatively uncommon in MS and for more severe genaralized spasticity giving baclofen by the intrathecal route utilizing an externally programmable pump may be useful in carefully selected patients. Because the drug is infused directly into the spinal fluid, only very small quantities are required to provide a powerful effect without systemic side effects. Marked reductions in tone and spasm frequency have been reported though the process is not without complications. If patients are very severely disabled and are not suitable for a pump, giving a single injection of intrathecal phenol could be considered provided the patient no longer has effective bladder and bowel control. Further injections are usually required as the effect tends to wear off.

Ataxia

This is one of the most frustrating and resistant symptoms in MS. It is usually seen in more disabled patients but can also occur early in the condition. The majority of patients

have an intention tremor, which is very disabling. Truncal ataxia can interfere with standing and sitting balance and be both distressing and incapacitating. Therapy has some effect, mainly focusing on improving posture and proximal stabilization and occasionally applying weights. Drug treatment is probably even more ineffective (Alusi et al., 2001a,b). A number of agents have been tried in small studies including isoniazid (with pyridoxine), clonazepam, primidone, propranalol and, more recently, gabapentin and the 5H3 antagonist ondansetron (Alusi et al., 1999). The latter appeared useful when given intravenously but this was not convincingly demonstrated in a subsequent study when it was given orally (Rice et al., 1999).

Surgical intervention, either by thalamotomy or thalamic stimulation, has also been used in MS with variable success, certainly not as effective as in Parkinson's disease (Schuurman et al., 2000; Alusi et al., 2001a,b). There have been no controlled studies of thalamotomy of the ventral intermediate nucleus (VIM) and functional benefit is variable. Serious side effects occur in up to 10% of patients and include hemiparesis, dysphasia and dysphagia. Thalamic stimulation may be more effective and appears to have a lower incidence of side effects, but again there are few controlled studies (Montgomery et al., 1999). Further work is under way to identify more effective targets for this procedure.

Fatigue

Fatigue is considered by most to be the most disabling symptom in MS. This overwhelming feeling of exhaustion must be distinguished from depression, which may often coexist. Common, practical issues such as a poor sleep pattern resulting from painful spasms or nocturia must also be considered. Fatigue management programmes are the cornerstone of treatment though drug treatment may be useful in a minority of patients. Amantadine has been shown to be effective while pemoline has not (Krupp et al., 1995). More recently, promising results have been presented for the 'wake-promoting' agent modafinil given at a dose of 200mg daily (Rammohan et al., 2002). The theoretical potential for the potassium channel blockers 4-aminopyridine and 3,4-diaminopyridine to improve fatigue has never been realized.

Bladder, bowel and sexual dysfunction

These symptoms, which often occur in tandem as a result of spinal cord disease, are extremely disabling (see Chapter 56). Active management is crucial. In relation to bladder disturbance, pelvic floor exercises may have a useful role, particularly in women (Vahtera et al., 1997) and biofeedback may also be considered. The combination of clean, intermittent catheterization and an anticholinergic agent such as oxybutinin (tolteridene tartrate is a useful alternative) is usually sufficient to address the incomplete emptying and hyperreflexia so commonly seen in this condition (Hussain & Fowler, 2000). The use of a bladder stimulator may also improve emptying, particularly in mobile patients. The synthetic antidiuretic hormone desmopressin, given by nasal spray, is useful in the management of nocturia. The anticipated side effect of hyponatremia is rare though needs to be considered more carefully in elderly patients. Finally, in very severe disease, the neurotoxic agent capsaicin, which acts on C fibres, may reduce detrusor hyperreflexia (Fowler et al., 1994). The potential benefits of an ultrapotent capsinoid substance resiniferotoxin and a sublingual cannabinoid preparation are currently being evaluated. Permanent catheterization may eventually be necessary and suprapubic placement is usually the preferred option.

The most common bowel symptoms are constipation and fecal incontinence, which may coexist. There is little evidence to support particular interventions. However, establishing a bowel programme is usually advocated and increasing dietary fibre together with bulk laxatives such as lactulose may be helpful in mild constipation; when more severe, stimulant laxatives such as senna and bisacodyl may have a role. The iso-osmotic laxative movicol has been found to be particularly useful and possibly more effective that lactulose (Attar et al., 1999).

Sexual dysfunction is now acknowledged to be a frequent symptom in MS and the underlying mechanisms are better understood (Zorzon et al., 1999). The recent licensing of sildenafil (Viagra) represents a major breakthrough in the management of erectile dysfunction in men, and a potential role in women is currently being investigated. In a recent randomized, placebo-controlled trial involving 217 men with MS, the ability to achieve and maintain erections was significantly better in the treated group with 92% of that group reporting an improvement of sexual activity (Fowler et al., 1999). Adverse events were mild in nature with headache and flushing the most common (23% and 13.5%, respectively) and there were no cardiac events in the treated group. In relation to intracorporeal pharmacotherapy, papaverine has been replaced by prostaglandin E1 (alprostadil) and more recently this has been developed as a pellet into the urethra via a small applicator.

Pain and other paroxysmal symptoms

Pain is common in MS and can have a major impact on both activity and participation (disability and handicap) (Archibald et al., 1994). It is chronic in nature in about 85% of cases and acute/paroxysmal in the remainder. In the

latter group, trigeminal neuralgia is the most common symptom and carbamazepine is the drug of choice. If this is ineffective or poorly tolerated, other anticonvulsants including phenytoin, lamotrigine and gabapentin may be considered and recent small studies have suggested that the prostoglandin E1 analogue misoprotol may be helpful. In a small proportion of patients, a percutaneous procedure may be necessary and rarely microvascular surgery may be helpful. Other paroxysmal symptoms include paroxysmal dysarthria and ataxia, tonic spasms and sensory symptoms including Lhermitte's symptom. Again, carbamazepine is the most useful therapy but gabapentin may also have a role. Finally, epilepsy occurs in 5% of patients with MS and may, in some cases, relate to cortical/subcortical plaques. Treatment should be with anticonvulsants though drug therapy may not need to be continued indefinitely.

Chronic pain is common, often multifactorial and difficult to treat. Amitriptyline may be useful in chronic dysesthetic pain. Physiotherapy to improve posture in sitting and standing is the cornerstone of management of chronic lumbar pain. Non-steroidal anti-inflammatory drugs, transcutaneous electrical nerve stimulation (TENS) and heat may all play a role. However, referral to a specialized pain clinic may be necessary in more resistant cases.

Visual and brainstem symptoms

Severe reduction in visual acuity may follow serial episodes of optic neuritis or result from progressive visual loss, which may occur late in the condition and requires referral to a 'low vision' clinic. Involuntary eye movement disorders, such as pendular nystagmus, oscillopsia and opsoclonus, may also cause debilitating visual dysfunction. Treatment with prisms or occasionally medications such as baclofen, gabapentin, isoniazid and, most recently, memantine may be useful (Starck et al., 1997).

Vertigo is another disabling symptom. It may be helped by prochlorperazine or cinnarazine, while physiotherapy, including Cawthorne–Cooksey exercises, may be useful if the situation becomes chronic. Dysphagia may occur in up to 45% of patients and symptoms such as coughing when eating, choking and change in swallowing function should alert the clinician. Mild dysphagia can usually be managed by assessment and advice from the speech therapist. If severe, a videofluoroscopy may be indicated and percutaneous gastrostomy may be required if swallowing is obviously unsafe or intake is inadequate. Dysarthria is common and again requires assessment and active management from a speech therapist. Finally, respiratory insufficiency may occur in advanced MS but may also complicate acute episodes, usually resulting from respiratory muscle weakness.

Cognitive, psychiatric and psychological dysfunction

All of these areas may be affected in MS, as has been described in the previous chapter. In relation to the management of cognitive dysfunction, a detailed assessment is crucial to define the deficits (which may often be quite subtle) and plan appropriate management strategies. There is little evidence to support cognitive rehabilitation but a computer-based retraining programme for specific attentional deficits may be beneficial.

Diagnosis of psychiatric disturbances is important as symptoms such as depression may worsen fatigue and cognitive function. Depressive symptoms are usually quite mild and often do not require antidepressant medication. Finally, many patients have great difficulty coping with both the diagnosis and subsequent disability in MS. This may be, in part, abated by education and support but some patients may require counselling or psychotherapy.

Neurological rehabilitation

Patients with MS require comprehensive management that incorporates the expertise appropriate to their symptoms and is sufficiently flexible to respond rapidly to their changing pattern of need. They require information and support to facilitate their involvement in the management of their own condition, retain a sense of control and maximise their independence (Hatch, 1997). The philosophy of rehabilitation, which emphasizes patient education and self-management, is ideally suited to meet the needs of people with this fluctuating, unpredictable and incurable condition. This philosophy must be based on a thorough understanding of the mechanisms underlying disability and recovery in MS (Thompson, 2000a,b). It is translated into practice by carrying out goal-orientated rehabilitation programmes which are based on expert multidisciplinary assessment and evaluated through appropriate clinical outcome measures and monitoring of goal achievement (Rossiter et al., 1998).

Tentative evidence now exists to support the use of components of the rehabilitation process including physiotherapy (Wiles et al., 2001) and aerobic exercise (Petajan et al, 1996). Attempts to evaluate the potential benefit of the full rehabilitation package have focused primarily on the in-patient setting and have attempted to identify which areas are likely to improve and whether that improvement is maintained following discharge into the community. Although recent studies have methodological limitations, they are an improvement on earlier work and, perhaps most importantly, demonstrate that such studies are feasible (Thompson, 2000a,b). Despite small numbers, inpatient rehabilitation resulted in a significant benefit in

disability and handicap in a UK study of patients with progressive MS and benefit in disability and aspects of quality of life in a less disabled Italian cohort (Freeman et al., 1997; Solari et al., 1999). The duration of benefit has not been looked at in a randomized controlled trial, but a single group study suggested that benefits in disability and handicap persist for approximately 6 months, while the positive effect on quality of life and emotional well-being may continue for longer (Freeman et al., 1999). This study emphasized the important link between hospital and community in attempting to provide a continuum of care for patients with MS and their families throughout the course of their condition (Thompson & Freeman, 2000). More recently, this link has been provided by MS nurse specialists (Johnson, 1997). Few studies have attempted to evaluate the different models of care available, but a recent study from Rome has suggested that coordinated multidisciplinary care may be more beneficial when compared to medical care alone (Pozzilli et al., 1999). The development of standards of care for the management of MS is an important first step and should serve to emphasize both patient needs and the paucity of evidence available to guide the way in which they are met (Hatch et al., 1999).

Treatment of acute relapses

Corticosteroids

In placebo-controlled trials, a short course of high dose intravenous methylprednisolone (IVMP; 1 g/day for 3 days or 0.5 g/day for 5 days) has been shown to shorten the duration of functional impairment during relapses of MS (Milligan et al., 1987). Such a treatment is often used to hasten recovery from functionally disabling relapses. A similar beneficial effect has been seen with a 2-week course of ACTH, but this is rarely used nowadays. A 3-week course of oral methylprednisolone in standard dosage was associated with a similar outcome as the use of IVMP in one study, but has not been compared directly with placebo in MS relapses (Barnes et al., 1997). Some clinicians use a short course of oral corticosteriods (up to 3 weeks) as an alternative to IVMP in treating MS relapses. In optic neuritis, oral prednisone alone was not associated with accelerated visual recovery whereas IVMP followed by oral prednisone was (Beck et al., 1992). There is no evidence that the final outcome of relapses is affected by steroid therapy, either in MS or optic neuritis. Because of an increased likelihood of side effects, and lack of evidence for long-term benefits, steroids should not be used chronically in MS.

Plasma exchange

A single small study, with placebo controls, has investigated the use of plasma exchange in patients with severe, disabling relapses due to MS or to similar inflammatory CNS disorders such as Devic's' syndrome, in whom there had been no useful improvement following IVMP (Weinshenker et al., 1999). Significantly more patients treated with plasma than sham exchange experienced a functional improvement.

Disease modifying treatments

The last 10 years have witnessed the first introduction of licensed drugs for modifying the course of the disease. In the USA, the FDA has licensed β interferons, glatiramer acetate (formerly known as copolymer-1) and mitoxantrone. The effects and role of these and other agents is reviewed.

Beta interferons

In relapsing remitting MS, three β interferon preparations (β-interferon-1b 8 mU subcutaneously on alternate days; β-interferon-1a 30 μg intramuscularly once per week; β-interferon-1a 22 μg and 44 μg subcutaneously three time per week) have all been shown to reduce relapse rate in randomized, double-blind, placebo-controlled trials of 2 to 3 years duration (IFNB Study Group, 1993; Jacobs et al., 1996; PRISMS Study Group, 1998). The magnitude of the relapse reduction is around 30%. There is evidence that the severity of relapses is also reduced, along with the number of steroid courses and hospital admission required to treat relapses. A similar effect on relapses, reported as a delay until the development of clinically definite MS, has been found in patients with CIS and brain MRI abnormalities (Jacobs et al., 2000). In two of the three relapsing remitting trials, the proportion of patients developing a confirmed increase in disability (i.e. for at least 3–6 months) was reduced in the β-interferon arm compared to placebo. In all trials, β interferons have been shown to reduce the frequency of new or enhancing MRI lesions by 50–70%, the effect being immediate and sustained.

There have also been three large trials completed in patients with secondary progressive MS. In only one trial was there an effect on progression in disability measured using the Kurtzke expanded disability status scale. In this trial, a higher percentage of patients had a history of superimposed relapses in the two years preceding the trials (European Study Group, 1998). Whereas interferons appear to reduce disability accumulation as a result of incomplete recovery from relapses, they probably have little, if any effect on secondary progression *per se*.

As a result of these trials, β interferons have been widely used as the disease-modifying treatment of choice for ambulant patients with relapsing remitting MS, who are experiencing frequent relapses. They are usually well tolerated. The most common adverse effects are injection site reactions (rarely skin necrosis with subcutaneous preparations), 'flu-like symptoms (which usually subside within a few weeks and can be ameliorated by concurrent use of non-steroidal anti-inflammatory drugs such as ibuprofen or by paracetamol), leukopenia, and abnormal liver function tests. The effects on pregnancy are unknown and treatment should be discontinued in women wishing to become pregnant; they are also contraindicated during lactation. The interferons are expensive treatments, and in some countries their cost effectiveness has been questioned; health economic assessments of these agents are hampered by uncertainties in extrapolating from the duration of the existing randomized trials to the period over which major disabilities most often accrue (see below).

The therapeutic mechanisms of β interferons are not well understood. Potentially important mechanisms include interfering with γ-interferon-mediated up-regulation of class II HLA expression on antigen-presenting cells, and stabilization of the blood–brain barrier. All three available preparations are produced by recombinant DNA technology in tissue culture. β-interferon-1a and 1b have a number of structural differences: the former is glycosylated and has an amino acid sequence identical to that of natural β-interferon; the latter is non-glycosylated and serine is substituted for cysteine at position 17.

The long-term effects of β interferons are unclear. This is an important issue in a disease in which the major disabilities typically evolve over 10–20 years. Particularly crucial questions are: does treatment in early relapsing remitting MS delay the development of secondary progression and major locomotor disabilities? Do neutralizing antibodies, which develop in 20–40% patients, modify the long-term course of the disease? Are there hitherto unrecognized long term adverse effects, for example, could there be an increased risk of neoplasia as occurs with some other therapies which modify the immune system? Because of the variable and unpredictable course of MS, systematic long-term follow-up will be needed to address these issues.

Glatiramer acetate

This therapy is a polymer composed of 4 amino acids: L-alanine, L-glutamic acid, L-lysine and L-tyrosine. It is given in a dose of 20 mg by daily subcutaneous injection. In a single, randomized, double-blind, placebo-controlled trial of ambulant patients with relapsing remitting MS, it was shown to reduce relapse rate by 29% (Johnson et al., 1995). It did not affect the proportion of patients experiencing a confirmed increase in disability during the 2-year trial. A subsequent trial has shown that it reduces the rate of new MRI lesions by about 30%, the effect becoming apparent after several months (Comi et al., 2001). There is currently no data on the effect of glatiramer in progressive forms of MS or CIS. Its mechanism of action is uncertain, there is some evidence that it enhances regulatory T-cell functions. It is being used in some countries as an alternative therapy to interferons for reducing relapse rate. It is well tolerated; a small number of patients experience a systemic but self-limiting reaction with flushing, chest pain, dyspnea and palpitations. Its long term effects are uncertain.

Mitoxantrone

This is an anthrecenedione antineoplastic agent that intercalates with DNA and exerts a potent immunomodulating effect, suppressing both humoral immunity and T-helper cell function. In a group of patients with a relapsing remitting or secondary progressive course, a major increase in disability over the previous year, and with enhancing lesions on MRI, a randomized trial was performed in which patients were given either mitoxantrone 20 mg/month plus IVMP 1 g/month or IVMP 1 g/month alone, over 6 months (Edan et al., 1997). The mitoxantrone arm exhibited a major reduction in the frequency of enhancing lesions, reaching 90% at 6 months; this group also experienced fewer clinical relapses, especially during the second 3 months and an improvement in disability, although the clinical component of the assessments was unblinded. A more recent 2-year trial in secondary progressive MS, in which mitoxantrone was given every 3 months (at doses of 5 mg/m^2 or 12 mg/m^2) and compared with placebo, also reported beneficial effects on clinical and MRI outcomes (H-P. Hartung, personal communication).

The drug has recently been licensed by the FDA, for reducing neurological disability and/or the frequency of relapses in patients with secondary progressive, progressive relapsing or worsening relapsing–remitting MS. Its use should be tempered by potential risks. Cardiac toxicity may occur with cumulative doses. Although no cases of cardiac failure were observed with the doses used in the above two trials, confirmation of a normal left ventricular ejection fraction (LVEF) is required before treatment is started. LVEF should be checked again if the cumulative dose exceeds 100 mg/m^2, and it is recommended that the cumulative lifetime dose should not exceed 140 mg/m^2. It causes marked but temporary leukopenia, maximal about 2 weeks after infusion. It may cause alopecia, amenorrhea, nausea and vomiting, and an increased risk of intercurrent infections. The long-term efficacy and risks (beyond 2 years) are uncertain.

Intravenous immunoglobulins

A single trial of moderate size reported a reduction in relapse rate in relapsing remitting MS, but no clear evidence for an effect on sustained progression in disability (Fazekas et al., 1997). Further studies are needed to define the efficacy of this therapy.

Azathioprine

This therapy has been evaluated in several large randomized trials and in a subsequent meta-analysis (Yudkin et al., 1991). It appears to have a modest effect in reducing relapse rate, but little if any effect on progression. Its use in MS is tempered by moderately frequent short term side effects, and a slightly increased risk of neoplasia in the long term. Anecdotal experience in Devic's neuromyelitis optica suggest that it may reduce relapse frequency in this condition.

Other therapies

Other immunosuppressive therapies have shown an ability to suppress MRI lesion formation, often very substantially. Examples include Campath-1H, an antilymphocyte antibody, cladribine, and peripheral stem cell transplantation. However, the clinical effects are much less clear. In a trial in progressive forms of MS, cladribine had no effect on progression in disability (Rice et al., 2000). A small uncontrolled trial of Campath-1H suggested that relapses could be suppressed but not progression in disability (Coles et al., 1999). Clinical trials of cyclophosphamide have yielded conflicting results; a large randomized, placebo-controlled Canadian multicentre study in chronic progressive MS was negative (Canadian Cooperative Multiple Sclerosis Study Group, 1991).

Future prospects

A striking observation in the recent trials has been an ability of several immunomodulatory or immunosuppressive agents, most notably β interferon, to suppress new enhancing lesions on MRI. These lesions represent inflammatory and demyelinating foci, and their suppression is in accordance with the suppression of relapses, which has been shown by the same agents, albeit to a lesser extent. On the other hand, clear evidence that the phase of slow progression in disability can be modified, be it primary or secondary, is lacking. Both pathological and MR studies, the latter using techniques such as MR spectroscopy, magnetization transfer imaging and measures of atrophy, suggest that a neurodegenerative process with axonal loss is underlying the progressive forms of MS (Miller & Thompson, 1999). The relationship between axonal loss, inflammation and demyelination is unclear. An important area of work is to elucidate the mechanisms of axonal loss, through which new strategies to prevent it can be developed. There is increasing interest in strategies that aim at neuroprotection, repair and remyelination.

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100

Leukodystrophies

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The term leukodystrophy was first introduced by Bielschowsky and Henneberg (1928). In his review of the neuropathology of the leukodystrophies, James Powers et al. (2000) recommended that the term leukodystrophy should be applied only to 'those progressive diseases of myelin in which a molecular abnormality is responsible for metabolic defects in myelin sheaths or myelin forming cells resulting in confluent destruction, or failed development, of central white matter'. Since the 1990s, remarkable progress has been achieved in the definition of the biochemical defect and the molecular basis of the leukodystrophies (Table 100.1).

In line with this recommendation, this chapter focuses on those genetic disorders in which central nervous system myelin is affected out of proportion to other elements of the nervous system, a judgement which may be somewhat arbitrary and subject to change as knowledge advances. Van der Knaap and Valk (1995) provide an excellent guide to the differential diagnosis of white matter abnormalities demonstrable on MRI and the acquired and genetically determined disorders of myelin that mimic the leukodystrophies. Experience in tertiary referral centres indicates that more than 50% of patients referred for 'second opinion' have leukoencephalopathies in which the cause cannot be determined utilizing diagnostic techniques that are currently available. The utilization of new neuroimaging techniques, such as magnetic resonance spectroscopy, combined with gene linkage analysis, has led to important recent advances and makes it likely that additional leukodystrophies will be defined in the near future (Alexander, 1949; Brenner et al., 2001; Verloes et al., 1997; van der Knaap et al., 1995, 1999; Topcu et al., 2000; Leegwater et al., 1999).

X-linked adrenoleukodystrophy

Background and general features

X-linked adrenoleukodystrophy (X-ALD) (Moser, 1997; Moser et al., 2000a,b) was described first in 1923. It was at first thought to be a variant of Schilder's disease 'encephalitis periaxialis diffusa' (Schilder, 1924), a disease category which has been analysed retrospectively and shown to be heterogeneous (Poser & van Bogaert, 1956). One of the three patients described by Schilder is now thought to have had X-ALD while the others had subacute sclerosing leukoencephalopathy and multiple sclerosis, respectively. In 1976 it was shown that X-ALD is associated with the abnormal accumulation of very long chain fatty acids (VLCFA) (Igarashi et al., 1976). The defective gene was identified in 1993 (Mosser et al., 1993). X-ALD must be distinguished sharply from neonatal adrenoleukodystrophy (NALD), which is disorder of peroxisome biogenesis that resembles the Zellweger syndrome (Kelley et al., 1986) and has an autosomal recessive mode of inheritance.

Clinical features

X-ALD shows a wide range of clinical manifestations (Moser, 1997). The childhood cerebral form is the most severe. It affects about 35% of the patients with the X-ALD gene defect. It presents most commonly between 4 and 8 years of age. Initial manifestations resemble those of hyperactivity or an attention deficit disorder, but then progress with defects in cognitive function, vision, hearing and later motor disturbances which may lead to total neurological disability within two years and death at varying intervals thereafter. Adrenomyeloneuropathy (AMN) is the most common form of X-ALD and affects 40 to 45%. It presents most commonly in young adults as progressive paraparesis

Table 100.1. Leukodystrophies in which the gene defect has been defined or localized

Disorder	Biochemical abnormality	Enzyme-protein defect	Gene map	Mode of inheritance
Gene defect defined				
adrenoleukodystrophy, X-linked	VLCFA excess	ALDP deficiency	Xq28	X-linked
Alexander		GFAP excess		autosomal dominant
Canavan	NAA excess	aspartoacylase deficiency	17p13-ter	autosomal recessive
Cerebrotendinous xanthomatosis	cholestanol	sterol 27 hydroxylase	2q33-qter	autosomal recessive
Globoid leukodystrophy	psychosine excess	galactocerebrosidase	14q25-31	autosomal recessive
Lipomembranous osteodysoplasia with leukodystrophy		TYRO protein tyrosone kinase		autosomal recessive
Metachromatic leukodystrophy	sulfatide excess	arylsulfatase A	22q13	autosomal recessive
Pelizaeus Merzbacher disease		proteolipid protein deficiency	Xq22	X-linked
Sjogren Larrson		fatty aldehyde dehydrogenase	17p11.2	autosomal recessive
Gene defect localized but not defined				
Vacuolating megalencephalic leukodystrophy with subcortical cysts			22qter	autosomal recessive
Childhood ataxia with diffuse central nervous system hypomyelination/ vanishing white matter disease			3q27	autosomal recessive

and sphincter disturbances, which are often misdiagnosed as multiple sclerosis. It is slowly progressive over a period of decades, and some patients have survived to the eighth decade with only moderate disability. Approximately 40% of AMN patients develop varying degrees of cerebral involvement which in approximately half of these patients is rapidly progressive (Van Geel et al., 2001). Seventy per cent of X-ALD patients have primary adrenocortical insufficiency. Approximately 30% of X-ALD patients have primary adrenocortical insufficiency (Addison disease) without evidence of neurological involvement, but many of these patients develop evidence of AMN in adulthood. The various X-ALD phenotypes often occur in the same kindred or nuclear family. Approximately half of the women heterozygous for X-ALD develop a relatively mild AMN-like syndrome in middle age or later. Only 1% of X-ALD heterozygotes have adrenal insufficiency.

Gene defect

The X-ALD gene has been mapped to Xq 28. It codes for a peroxisomal membrane protein, ALDP, which is a member of the ATP binding cassette (ABC) transporter superfamily (Higgins, 1992). The minimum combined incidence of X-ALD males and females in the United States is 1:16800 (Bezman et al., 2001). More than 200 mutations have been identified (Smith et al., 1999) and are continually updated and listed in the website *www.x.ald.nl.* Many mutations are unique to kindreds. There is no correlation between the nature of the mutation and phenotypic expression.

The mechanism by which the X-ALD gene defect leads to the accumulation of VLCFA has not been determined. When X-ALD cells are transfected with ALDP, they acquire the capacity to degrade VLCFA through mechanisms that have not yet been defined (Steinberg et al., 1999). ABC transporter proteins function as dimers (Higgins, 1992). ALDP is a monomer. The human peroxisome membrane contains four different ABC transporter proteins (Smith et al., 1999). ALDRP, which has been mapped to chromosome 12, is of particular interest since its amino acid composition (Lombard-Platet et al., 1996) and gene structure (Broccardo et al., 1998) bear a close resemblance to ALDP, and it can substitute at least in part for the function of ALDP in respect to VLCFA metabolism (Kemp et al., 1998). The ABC transporters functions as dimers. ALDP can form a dimer either with another ALDP molecule (homodimer) or form a heterodimer with one of the other peroxisomal ABC transporters, such as ALDRP. The existence of such heterodimers has been demonstrated in vitro (Kemp et al., 1998). The extent to which such heterodimers are formed

in vivo is uncertain, since in the nervous system ALDP and ALDRP show different patterns of ontogeny and cellular distribution (Aubourg & Dubois-Dalcq, 2000).

Animal model

A mouse model of X-ALD has been developed by Kobayashi and associates (1997) and in two other laboratories. This mouse model lacks ALDP. VLCFA accumulate in the brain and adrenal gland, and the adrenal gland exhibits lamellar inclusions equivalent to the human disease. The animals do not show clinical evidence of neurological or adrenal dysfunction. At 24 months of age they show statistically significant reductions in peripheral nerve conduction velocity compared to age-matched controls and myelin abnormalities which resemble those in AMN. They do not show evidence of the inflammatory demyelinating process seen in patients with the cerebral forms of X-ALD.

Pathology and pathogenesis

There are two distinct pathological processes: an inflammatory demyelinating process that involves children most frequently and approximately one-third of the adults, and a distal axonopathy that affects adults.

Children and adults with the cerebral forms of the disease show an inflammatory process that affects the central nervous system white matter (Powers et al., 1992). There are confluent symmetric lesions that contain three zones. The lesions occur most frequently in the parieto-occipital regions, and advance caudo-rostrally. In the outermost zone there is an astroglial reaction and the astrocytes in this zone contain tumour necrosis factor alpha. The second zone exhibits a perivascular inflammatory response associated with demyelination and the accumulation of cholesterol esters that contain a high proportion of VLCFA. The perivascular cells include macrophages, T-cells and B-cells, and contrast neuroimaging studies have shown breakdown of the blood–brain barrier. This zone resembles what is seen in multiple sclerosis. In the innermost zone there is extensive gliosis with loss of myelin and reduction or absence of the inflammatory response. Axons are involved to varying degrees in zone 2 and frequently in the innermost zone. The inflammatory response in X-ALD is unique among the leukodystrophies. It is the cause of the rapid progression of the disease. It may be initiated through as yet undefined autoimmune mechanisms, possibly involving reactions to lipids that contain excess amounts of VLCFA, or at times by trauma, and then is maintained and amplified by a destructive cascade which may be cytokine mediated.

Powers et al. (2000) provide strong evidence that AMN is a distal axonopathy that involves mainly the long tracts of the spinal cord. It may be a consequence of the abnormalities in lipid membrane structure and function caused by accumulation of VLCFA (Ho et al., 1995; Whitcomb et al., 1988).

Diagnosis

The most frequently used diagnostic assay is the demonstration of increased levels of VLCFA in plasma or cultured skin fibroblasts (Moser et al., 1999). These assays are reliable for the identification of affected males, provided that they are performed in a qualified laboratory, but a 15% false-negative rate occurs in heterozygotes (Moser et al., 1999). Mutation analysis is the most reliable procedure for the identification of heterozygotes (Boehm et al., 1999). MRI findings in patients with the cerebral form of the disease are often characteristic (van der Knaap & Valk, 1995). They show symmetric, confluent T_2 signals in the white matter of the parieto-occipital region, with a garland of contrast enhancement at the advancing edge of the lesion (Fig. 100.1). MRI findings are atypical in approximately 15% of patients with abnormal MRI. The brain MRI is normal in more than half of the patients with AMN, and in many others who are free of neurological symptoms. MRI abnormalities usually precede symptoms in patients with cerebral involvement, and the brain MRI is of prognostic value (Moser et al., 2000a,b). Abnormalities in magnetic resonance spectroscopy studies often precede MRI changes and appear to be of value in setting prognosis and the selection of patients for bone marrow transplantation.

Therapy

It is essential to monitor adrenal function, which is impaired in approximately 70% of patients, and to provide adrenal steroid hormone replacement therapy when it is deficient. This is mandatory and can be life-saving. Adrenal hormone replacement therapy does not alter the neurological aspects of the disease.

Bone marrow transplantation (BMT) is the most effective therapy for the cerebral forms of the disease, but must be applied in the early stages of the disease. Under these circumstances it can provide long-term stabilization and at times improvement (Shapiro et al., 2000). Selection of patients for BMT requires clinical judgement, because it is a procedure that carries considerable risk. It is not recommended for patients with advanced neurologic involvement, since in these patients the risk of complications and continued disease progression is high. It is not

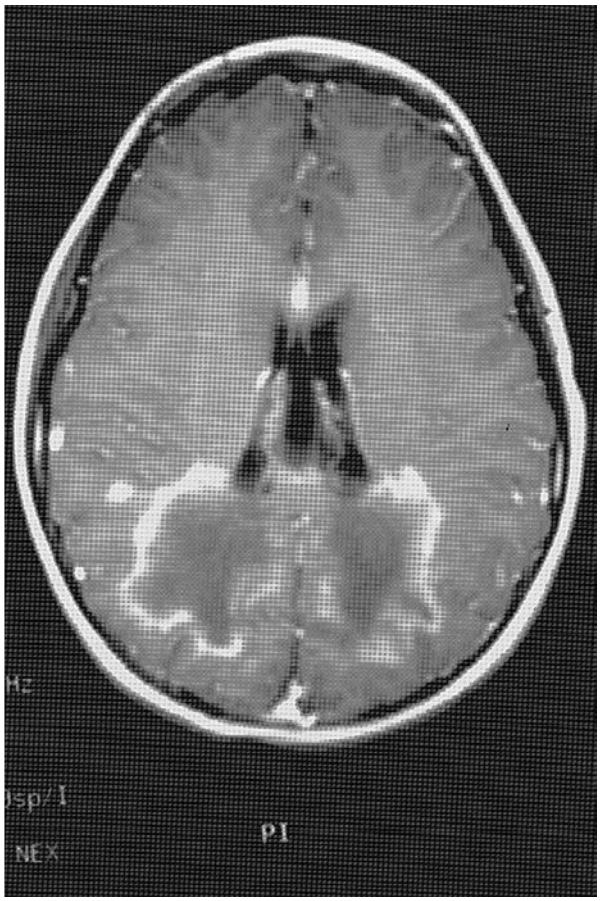

Fig. 100.1. T_1-weighted image with contrast in a 7-year-old boy with childhood cerebral X-ALD. Note symmetrical parieto-occipital lesions with contrast enhancement at margin.

recommended for AMN patients because there is no evidence that BMT benefits the myelopathy. BMT is not appropriate for persons who have the *X-ALD* gene defect, but do not have evidence of neurological involvement by MRI. Natural history data indicate that more than half of these patients will escape the cerebral forms of the disease even without therapy (Moser et al., 2000a,b).

Dietary therapy with a 4:1 mixture of glyceryltrioleate and glyceryltrierucate, referred to as Lorenzo's Oil (Rizzo et al., 1989) has been used extensively. Recent studies suggest that it is not of benefit in patients who are already neurologically symptomatic (van Geel et al., 1999). An international collaborative study, aimed to determine whether administration of the oil to asymptomatic patients can diminish the frequency and severity of subsequent neurologic involvement, will be completed in 2001.

Two new therapeutic approaches have been proposed recently; Lovastatin and 4-phenylbutyrate. Lovastatin has been reported to improve the capacity of X-ALD cells to metabolize VLCFA (Pahan et al., 1998; Pai et al., 2000) and to reduce the inflammatory response (Stanislaus et al., 1999; Pahan et al., 1997). 4-phenylbutyrate increases the capacity to metabolize VLCFA in cultured X-ALD cells and reduces VLCFA levels in the brain and adrenal gland of the X-ALD mouse model. It also increases the expression of ALDRP, which resembles ALDP (Lombard-Platet et al., 1996; Broccardo et al., 1998) and can substitute for its function at least in part. This approach has been proposed as an example of pharmacological gene therapy (Kemp et al., 1998). Therapeutic trials of both agents are planned.

Metachromatic leukodystrophy: sulfatide lipidosis

Background and general features

The key abnormality in metachromatic leukodystrophy is the accumulation of sulfatide (galactosylceramide-3-sulfate). This acidic glycolipid accumulates in the white matter of brain and peripheral nerves and also in the kidney, gall bladder and urine and causes metachromatic staining with aniline dyes. Accumulation of metachromatic lipids in brain tissue was first reported by Perusiniu and Alzheimer in 1910. In 1921 Witte also noted metachromatic lipids in the kidney, and predicted that in vivo diagnosis might be achieved by examination of the urine, and this was accomplished by Austin in 1957 (Kolodny & Fluharty, 1995). Sulfatide accumulation can be caused by three distinct genetic defects. (i) Deficient activity of the lysosomal enzyme arylsulfatase A (ASA) which catalyses the hydrolysis of sulfatide to galactosylceramide. This is by far the most common cause. Its estimated incidence is 1:40 000–1:100 000. (ii) Multiple sulfatase deficiency (MSD). Fifty cases of MSD had been reported by 1995 (Kolodny & Fluharty, 1995). In MSD the activities of at least seven sulfatases are deficient and mucopolysaccharide and steroid sulfate esters accumulate in addition to sulfatide. The gene defect abolishes the posttranslation modification of sulfatases. This modification involves the conversion of a cysteine residue to formylglycine. It causes a change in protein folding and appears to be required for the enzymatic action of all of the sulfatases that are defective in MDS. (iii) The third and least frequent cause of sulfatide accumulation is a genetically determined deficiency of Saposin D (Waring et al., 1998), one of the sphingolipid activator proteins which is required for the biological activity of arylsulfatase A but not the other sulfatases.

Clinical presentation

MLD may present in late infancy, adolescence or adulthood. The late infantile form is the most common. It presents between 1 and 3 years of age, with loss of previously acquired motor skills, such as ability to walk, followed by ataxia, dysarthria and dysphagia and later by impairment of cognitive function, vision and hearing. It is progressive and leads to death after several years. Neurological examination shows evidence of both central nervous and peripheral nerve function as evidenced by the association of hypotonia and diminished deep tendon reflexes with positive Babinski sign, ataxia, dystonic movements and nystagmus. The manifestations of the juvenile form resemble those of the late infantile form but progress more slowly. In the adult form behavioural and cognitive changes precede motor changes by years or even decades. The patients may present with a frontal lobe syndrome, which may include disinhibition, impulsivity, poor judgement, emotional lability, social inappropriateness and poor attention span (Shapiro et al., 1994). MSD patients can be differentiated from late infantile MLD because they show more severely impaired early development, mild coarsening of facial features, and sometimes corneal clouding, hepatosplenomegaly, stiff joints and ichthyosis.

Gene defect

MLD is transmitted as an autosomal recessive trait. The gene that encodes ASA maps to 22q13. More than 40 mutations have been identified. Three are relatively common. Homozygosity for mutations that abolish function completely causes the severe late infantile phenotype. Missense mutations in which up to 3–5% of normal activity is maintained tend to be associated with the adult form of the disease. Patients who are heterozygous for a null mutation and one of the milder missense mutation, often have the juvenile phenotypes (Gieselmann et al., 1998).

Animal model

ASA-deficient mice have been generated by homologous recombination. These animals accumulate sulfatide. Unlike what is seen in humans, the most severe demyelination occurs in the acoustic ganglion and the animals become deaf at 6–12 months (Gieselmann et al., 1998).

Pathology and pathogenesis

The central and peripheral nervous system show demyelination associated with the accumulation of metachromatic bodies with a characteristic lamellar pattern that when viewed under the electron microscope has been likened to tuffstone (Kolodny & Fluharty, 1995). Several factors may contribute to the pathogenesis of the demyelination. These include impaired function and loss of oligodendrocytes and Schwann cells, impaired stability of myelin due to increased sulfatide content, and the accumulation of sulfogalactosylsphingosine, the degradation of which is impaired in MLD. Accumulation of a related compound, galactosylsphingosine, which is also referred to as psychosine, has been shown to be a toxic agent in globoid leukodystrophy (Suzuki, 1998).

Diagnosis

Clinical recognition of the late infantile and juvenile forms is based upon evidence of progressive nervous system dysfunction associated with loss of myelin both in the central and peripheral nervous system. The adult form of the disease is often misdiagnosed as a psychosis in adults. An abnormal MRI often provides the first clue to the existence of a metabolic abnormality. The MRI demonstrates symmetric and confluent high signal in the periventricular anterior and posterior white matter on T_2-weighted images (van der Knaap & Valk, 1995).

Measurement of ASA activity in white blood cells is the most frequently used initial laboratory assay (Kolodny & Fluharty, 1995). If the results of this assay are normal, the diagnosis of MLD can be excluded, except for the rare disorder cited previously in which sulfatide excess is due to deficiency of the saposin D cofactor (Waring et al., 1998). The clinical presentation of saposin D deficiency resembles late infantile or juvenile MLD. Urinary sulfatide excretion (Natowicz et al., 1996) is increased but ASA activity is normal. MSD can be distinguished from MLD because of its earlier onset, and the presence of the additional biochemical abnormalities cited previously (Kolodny & Fluharty, 1995). ASA is the only sulfatase that is deficient in type 1 MLD. In MSD the activities of arylsulfatases B and C and of mucopolysaccharide sulfatases are also deficient (Kolodny & Fluharty, 1995).

Interpretation of diminished ASA activity requires caution. Demonstration of deficient ASA activity is not sufficient for the laboratory diagnosis of MLD. Confirmation of the diagnosis requires clinical or laboratory evidence of sulfatide storage in addition to the diminished enzyme activity. Reduced levels of ASA activity, sometimes equivalent to what is seen in MLD, may also be associated with a condition referred to as pseudosulfatase deficiency (PSD). PSD is a benign and common condition. It is associated with a loss of polyadenylylation signal and

an *N*-glycosylation site in the ASA gene that reduces but does not abolish enzyme activity (Gieselmann et al., 1989). The carrier frequency for the PSD is 7% or higher. Persons with PSD do not have symptoms. Urinary sulfatide excretion (Natowicz et al., 1996) is increased in MLD but not in PSD. Peripheral nerve conduction velocity, which is almost always reduced in MLD, is normal in PSD, and the brain MRI is normal. The molecular changes associated with PSD can be identified by DNA analysis (Gieselman et al., 1989). It is important to recognize that demonstration of this abnormality does not exclude MLD, since PSD is common and persons who are PSD carriers may also have MLD. Identification of MLD carriers requires mutation analysis. Prenatal diagnosis of MLD can be achieved with the ASA assay, but subject to the caution expressed previously. Normal activity excludes fetal involvement, but interpretation of reduced levels may require additional studies such as in vitro sulfatide loading studies and DNA analysis (Kolodny & Fluharty, 1995).

Therapy

Bone marrow transplantation (BMT) can stabilize or diminish the rate of progression of nervous system dysfunction, but does not appear to influence the peripheral nerve involvement (Krivit et al., 1995). Consideration for BMT is recommended only for patients with relatively mild nervous system involvement and particularly in asymptomatic patients identified by tests of at-risk relatives, with care taken to differentiate MLD from PSD. The procedure is not recommended for patients with advanced nervous system involvement, where it is associated with high risk of additional worsening of the disability. Gene therapy is under investigation in cultured cells (Sangalli et al., 1998) and in the animal model, but is not yet ready for human testing. Gall bladder surgery is required occasionally in patients who have sulfatide-containing gallstones.

Globoid-cell leukodystrophy (Krabbe disease: globoid leukodystrophy

Background and general features

Globoid-cell leukodystrophy (GLD) is caused by a genetic deficiency of galactosylceramidase (galactocerebroside-beta galactosidase (GALC) (Suzuki et al., 1995). This lysosomal enzyme normally degrades galactocerebroside to ceramide and galactose. Galactocerebroside is a sphingolipid consisting of sphingosine, fatty acid and galactose and normally is present almost exclusively in the myelin sheath. Accumulation of galactocerebroside leads to the formation of characteristic multinucleated cells which led to the designation of this disorder as globoid cell leukodystrophy.

GALC also catalyses the degradation of psychosine (galactosylsphingosine) to sphingosine and galactose. Psychosine accumulates in patients with GLD and this accumulation is a key factor in the pathogenesis of the disease (Suzuki, 1998). GLD was described first in 1916 by Krabbe in Denmark in two siblings who died of an 'acute infantile diffuse sclerosis of the brain'. The enzyme defect was defined in 1971 by Suzuki (Suzuki & Suzuki, 1970) and the gene abnormality in 1993 (Chen et al., 1993).

Clinical features

The infantile form is most common, with an estimated incidence between 1:100000 and 1:200000. The child, apparently normal during the first few months of life, becomes hyperirritable, hypersensitive to auditory, tactile or visual stimuli and shows some limb stiffness. This is followed by rapid and severe motor and mental deterioration, with marked hypertonicity, optic atrophy, and a decerebrate state. Patients rarely survive beyond 2 years. Juvenile (Krivit et al., 1998) and adult forms also occur. The adult patients may present with progressive spastic paraparesis progressing to tetraparesis followed by optic atrophy, dementia and neuropathy (Suzuki et al., 1995).

Gene defect

GLD is transmitted as an autosomal recessive trait. The gene has been mapped to 14q25–31. The human *GALC* gene is 58 kb in length and consists of 17 exons and 16 introns (Wenger et al., 1997). Sixty-five disease-causing mutations were described by 1999 (Jardim et al., 1999). A 502T/del mutation is the most common. Its origin has been traced to Sweden and it is present in 40% of GLD patients who are of European origin. The mutation consists of a 30 bp deletion in intron 10. It eliminates activity in expression studies. The second most frequent mutation is a C $\rightarrow$T change at nucleotide 1538 (T531M). It is found in approximately 10% of patients with the infantile phenotype. All mutations responsible for the adult forms of GLD are missense mutations located at the 5′ end of the gene. Genotype–phenotype correlations are complicated by the existence of polymorphisms. The most frequent polymorphism, which is present in 35 to 45% of the general population, involves a T$\rightarrow$C change at position 1637, which in COS-1 cell expression studies reduced expression of GALC to 30%.

Animal models

Animal models of GLD have been described in mice, sheep, dogs, and monkeys. The murine model, referred to as the twitcher mouse, and the canine model are being used extensively in studies of pathogenesis and therapy (Wu et al., 2000; Wenger et al., 1999, 2000).

Pathology and pathogenesis

The main histopathological changes are extensive demyelination, gliosis and the presence of characteristic multinucleated cells, referred to as globoid cells. Intracerebral injections of galactocerebroside into rat brain produced cells that are similar to the globoid cells in GLD. Globoid cells are cells of mononuclear phagocytic lineage that become multinucleated as a response to galactocerebroside. The number of oligodendrocytes is greatly decreased. Peripheral nerves show endoneurial fibrosis, proliferation of fibroblasts, segmental demyelination and perivascular accumulation of macrophages containing periodic acid Schiff (PAS) positive material.

While it is well documented that galactocerebroside causes the formation of globoid cells, intracerebral injection of this substance did not lead to severe pathological changes. Galactocerebroside levels are not increased in the small amount of myelin that can be isolated from the brain of patients with GLD. Suzuki and associates have presented strong evidence that the accumulation of psychosine (galactosphingosine) is the principal toxic mechanism (Suzuki, 1998).

Diagnosis

Diagnosis in infants is suspected on the basis of the characteristic clinical presentation and confirmed by assay of GALC activity in white blood cells or cultured fibroblasts (Suzuki et al., 1995). The peripheral nerve involvement leads to diminished conduction velocity and the level of protein in the cerebrospinal fluid is increased. Brain MRI shows high intensity signal in the deep white matter on T_2-weighted images (van der Knaap & Valk, 1995). Diagnosis in juveniles and adults is more difficult since the symptoms of progressive neurological deterioration are less specific. Progressive paraparesis is the most common presenting symptom in adults and MRI abnormalities may be confined to the corticospinal tracts (Fig. 100.2). Demonstration of reduced GALC activity in amniocytes or cultured chorion villus cells permits prenatal diagnosis. Identification of heterozygotes requires mutation analysis.

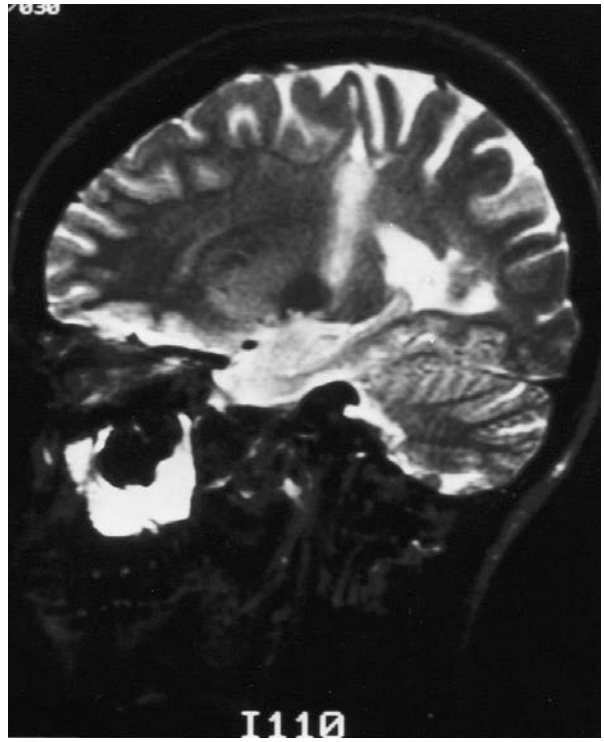

Fig. 100.2. Globoid leukodystrophy. 23-year-old female presents with intact intelligence and progressive hemiparesis since 18 years of age. Male sibling has similar presentation. T_2-weighted sagittal images demonstrate isolated high-signal intensity of corticospinal tract and involvement of occipital regions.

Treatment

Allogeneic hematopoetic stem cell transplant (BMT) has been found to be beneficial in four patients with the juvenile form of the disease (Krivit et al., 1998). All four of the patients showed stabilization or improvement in neurological cognitive function and MRI. Peripheral nerve conduction velocity improved in one patient and remained unchanged in two. BMT is also beneficial in the twitcher mouse model. It increases survival, weight and peripheral nerve function, but falls far short of a cure (Suzuki, et al., 1995). The beneficial effect appears to be due to infiltration of hematogenous lineage cells into the demyelinating central nervous system. In the twitcher mouse this infiltration into the demyelinating regions is greater than in controls, and appears to be related to the expression of chemoattractant proteins in these regions (Wu et al., 2000). BMT so far has not been shown to alter significantly the course of the infantile form, which is the most severe and the most common form of GLD. It is likely that additional approaches will be needed. Gene therapy is being examined

in the canine model of GLD (Wenger et al., 1999) and in cultured cells. The possibility of a different therapeutic approach is suggested by the demonstration that subcutaneous administration of L-cycloserine, an inhibitor of sphingosine synthesis which presumably would also reduce levels of psychosine and galactocerebroside, reduces levels of psychosine and galactocerebroside and slows clinical and pathological progression in the twitcher mouse (Levine et al., 2000).

Pelizaeus Merzbacher disease

Background and general features

Pelizaeus Merzbacher disease (PMD) was recognized initially by Pelizaeus in 1885, who described a family with a progressive neurologic deficit. Merzbacher in 1910 made a report on the same family and noted that deficiency of myelin was a central feature and that the disease affected males predominantly. Seitelberger on the basis of extensive clinical, morphological and epidemiological studies (Seitelberger, 1970) described 'classical' (Type I), 'connatal' (Type II) and 'transitional' (Type III) forms, which he joined together as a single entity on the basis of certain unique patterns of demyelination in postmortem tissue and a sex-linked recessive mode of inheritance. He also included three other types (Types IV to VI), which are now no longer considered part of the spectrum. Important advances in knowledge resulted from neurochemical and genetic studies in mouse mutants. It was shown in 1985 that the gene that codes for proteolipid protein (PLP), one of the major myelin proteins, is located on the X-chromosome, and in 1986 that the *jimpy* mouse, a mutant that had been identified in 1964, is deficient in this protein. PLP deficiency and mutations in this gene were demonstrated in PLP patients in 1987 and 1989, respectively. In 1994 it was shown that X-linked spastic paraplegia (SPG2 MIM 31290) type 2 and PMD are allelic (Saugier-Veber et al., 1994). This has added a new dimension to the understanding and classification of PMD. The designation PMD/SPG2 now encompasses all patients with disease-causing abnormalities that involve the PLP gene.

Clinical presentation

The principal clinical features of classic Type 1 PMD are (i) the presence of abnormal eye movements (horizontal or rotatory) with onset within the first few months of life; (ii) the occurrence of psychomotor deterioration before 2 years of age, and (iii) the appearance of bilateral pyramidal tract signs, dystonia and often ataxia during the first years of life (Boulloche & Aicardi, 1986). Laryngeal stridor also occurs frequently. In the connatal type II, intrauterine movements of the affected fetus are reduced, there is congenital laryngeal stridor, and psychomotor retardation is severe. SPG2 presents with mild spastic paraparesis in the late subteens or early teens. It is slowly progressive over decades. Involvement of upper limbs, ataxia and cognitive dysfunction may occur in the late stage of the illness. Patients with abnormalities of the PLP gene may have phenotypes intermediate in severity between PMD type 1 and SPG2 (MIM 308840).

Gene defect

PMD is transmitted as a sex-linked recessive trait, but with the caveat that some female heterozygotes (Nance et al., 1996) or female animal models (Cuddon et al., 1998) may develop neurological symptoms. The PLP gene is located on Xq22. It is an integral membrane protein with four transmembrane domains. The amino and carboxy terminals are oriented toward the cytoplasmic surface. It is 17 kb in length and comprises 7 exons. PLP contains 276 amino acids. An alternative splicing site leads to the formation of the related protein DM-20, which differs from PLP by the absence of an internal 35-amino acid peptide in the intracellular loop region (Seitelberger, 1970). The cellular mechanisms of classical and connatal forms of PMD have been examined in transfected COS-7 cells (Gow & Lazzarini, 1996). In classical PMD, PLP protein accumulated in the endoplasmic reticulum (ER), presumably due to protein misfolding which interferes with the secretory pathway, whereas the shorter isoform DM-20 was transported normally. In contrast, in cells transfected with mutant genes of patients with the connatal phenotype, there was ER accumulation of both DM-20 and PLP, indicating that the more profound secretory deficit causes the most severe phenotype. Forty different mutations in the PLP gene have been identified, which in the aggregate are present in 25 to 38% of PMD/SGP2 patients. The most frequent abnormality, however, is duplication of the PLP gene. This was demonstrated in 62% of 82 patients with sporacic PMD/SGP2 (Mimault et al., 1999). Duplications are associated with the milder phenotypes (Sistermans et al., 1998). Neurological manifestations in female heterozygotes occur more commonly in those kindreds in whom affected males have relatively mild phenotypes (Sivakumar, et al., 1999).

Animal models

The *jimpy* mouse is a model of the severe forms of PMD. The 'rumpshaker' mouse is a model of SGP2 (Seitelberger,

1970). The 'shaking pup' canine model has a phenotype that is intermediate in severity between the *jimpy* and the rumpshaker mouse and is a valuable model for the evaluation of therapeutic interventions (Cuddon et al., 1998).

Pathology and pathogenesis

Myelin stains reveal a marked myelin deficiency especially in the deeper cerebral parts, and a patchy tigroid appearance due to the presence of somewhat better preserved islands of myelin which often are located around blood vessels. Oligodendrocytes are reduced in number and astrocytes increased. PLP is absent. In the connatal form the myelin deficiency is more widespread (Seitelberger, 1970). The peripheral nerves are intact in all forms. Transgenic mice with two-fold overexpression of PLP protein show hypomyelination and severe neurological deficits. This demonstrates that precise control of the PMP gene is essential for normal oligodendrocyte differentiation (Readhead et al., 1994).

Diagnosis

Suspicion of the diagnosis is based upon the signs of progressive central nervous system impairment as described above in the presence of intact peripheral nerve function. The major confirmatory technique is the application of DNA-based analyses. Search for duplications is of particular importance, because they represent the most frequent gene abnormality (Mimault et al., 1999; Sistermans et al., 1998; Woodhead et al., 1998; Hodes et al., 2000).

Therapy

There is no specific therapy at this time.

Canavan disease

Background and general features

The first complete clinical and pathological description of Canavan Disease (CD) was provided by van Bogaert and Bertram in 1949. Several leukodystrophy patients who excreted large quantities of *N*-acetylaspartate in the urine were reported between 1986 and 1988 by Divry et al. (1988). In 1988 Matalon and colleagues established the association between NAA aciduria and CD and demonstrated that this was due to deficiency of aspartoacylase (ASPA). They cloned the gene in 1993 (Kaul et al., 1993) and in 2000 developed a knockout mouse model (Matalon et al., 2000). ASPA gene replacement therapy in two children with CD has been reported (Leone et al., 2000), the first time that this has been attempted in leukodystrophy patients.

Clinical presentation

Most children become symptomatic between 10 weeks and 4 months of age after an uneventful prenatal and perinatal course (Traeger & Rapin, 1998). Initial manifestations are lack of visual fixation and tracking, poor suck and irritability and delay in acquisition of head control. Macrocephaly (>90th percentile) was noted in 54 of 59 children and nystagmus in 51/58. Feeding difficulties, irritability and seizures are common. Psychomotor development is severely impaired. In a series of 60 patients only one was able to sit unsupported, and only two spoke a few words. Survival in this severely handicapped state ranged from 7 months to 30 years.

Gene defect

The mode of inheritance is autosomal recessive. The gene that codes for ASPA has been mapped to 17p13-ter (Matalon et al., 1995). It codes for a 340 amino acid protein and is expressed in most tissues. Mutations are most frequent in the Ashkenazi Jewish population, where the carrier frequency is 1:37.7, leading to an estimated disease frequency of 1:5000. Two mutations predominate in this population. The *E285A* mutation was found in 84% of alleles, and the *Y231X* in 14%. CD is much less frequent in the non-Jewish population and the mutations are different. An *A305* E mutation was present in 39.5 of alleles, and eight other less frequent mutations were identified in 31 of 38 alleles (Shaag et al., 1995). The nature of the mutation does not correlate with clinical severity.

Animal model

Matalon and associates have developed a knockout mouse in which ASPA is absent and NAA accumulates (Matalon et al., 2000). Homozygous animals develop macrocephaly, tremors, ataxia and impaired mobility and balance. Half of the mice died at age of weaning, but others survived to 9 months. Neuropathological studies showed extensive vacuolization in subcortical white matter, deep cortex, and striatum. Vacuolization was observed in retinal ganglion cells, hippocampus and cerebellum. Increased brain NAA levels were demonstrated by biochemical studies and by magnetic resonance spectroscopy.

Pathology and pathogenesis

The size and weight of the brain is increased. The characteristic microscopic change is widespread vacuolization in the lower layers of the cortex and subcortical white matter, the more central zones being relatively spared. The Purkinje cell layer of the cerebellum is affected early. There is widespread lack of myelin which involves the areas of spongy degeneration and far beyond. Axis cylinders are relatively preserved. Oligodendrocytes are preserved. There is a conspicuous increase in the size and number of protoplasmic astrocytes (Banker & Victor, 1979).

The main biochemical abnormality in CD is the accumulation of NAA. NAA is present in high concentration in normal brain, second only to glutamate in terms of free amino acid concentration (Clark, 1998). It is present in highest concentration in neurons. The enzyme responsible for NAA synthesis is present only in the nervous system, but ASPA, the enzyme which degrades it, and which is deficient in CD, is expressed in many tissues. In the nervous system ASPA is present mainly in white matter. Astroglia contain a specific transport mechanism for NAA (Sager et al., 1999). An understanding of the pathogenesis of CDS requires clarification of the physiological role of NAA. It may play a role in protecting neurons against osmotic stress (Clark, 1998). Baslow has hypothesized the existence of an intercompartmental cotransport of water uphill against a gradient of a hydrophilic osmolyte, and that the metabolic defect in CD leads to a buildup of NAA–water in the extracellular space between the axon-wrapped glial–myelin repeating lamellar membranes (Baslow, 1999). NAA is the precursor of the dipeptide *N*-acetylaspartylglutamate (NAAG). NAAG is present in high concentration in normal brain and appears to play a role in glutaminergic transmission. Levels of NAAG are increased in the urine of CD patients (Burlina et al., 1999). If such an increase also exists in brain this could also contribute to pathogenesis. Acetate and aspartate are the products of NAA degradation and play a role in myelin synthesis (Sager et al., 1999). The deficiency of this degradation in CD may contribute to the failure of myelin formation.

Diagnosis

NAA levels in the urine of CD patients are elevated 80-fold and can be measured accurately by a stable isotope dilution assay (Jakobs et al., 1991). Measurement of NAA levels in amniotic fluid is the most reliable procedure for prenatal diagnosis (Bennett et al., 1993). Mutation analysis (Shaag et al., 1995; Kaul et al., 1994) is reliable when the mutation has been identified in an affected family member. MRI studies show diffuse hypodensity of the white matter of the cerebral hemispheres and cerebellum. The subcortical white matter is involved most severely at all stages of the disease, with relative preservation of central structures. The globus pallidus is often involved with sparing of the caudate nucleus and putamen. MR spectroscopy shows increased levels of NAA (Leone et al., 2000).

Therapy and prevention

Leone et al. (2000) have reported on *ASP* gene transfer in two severely disabled CD patients who were 19 and 24 months old. The gene was condensed using poly-L-lysine and encapsulated with liposomes to form 60–100-nm particles and injected intraventricularly into the lateral ventricle through a burr-hole in combination with the intraveneous administration of mannitol. There were no adverse side effects. ASPA RNA could be detected by reverse transcriptase reaction in the cerebrospinal fluid of one of the children 1 year following the gene injection, but not in the other. Some evidence of mild clinical and radiological improvement was noted in the former child, but the data were insufficient to evaluate clinical efficacy. The recently developed animal model is expected to facilitate the evaluation of this and other therapies. The demonstration that two readily identifiable mutations account for 97% of gene abnormalities in CD patients of Ashkenazi Jewish descent makes it possible to identify CD carriers in this population. This will permit the identification of two-carrier couples and reduction of disease frequency through genetic counselling, analogous to the programs that are now being conducted for Tay Sachs disease.

Other leukodystrophies

Alexander disease

Alexander disease (AD) was first described in 1949 (Alexander, 1949). Infantile, juvenile and adult forms have been described (Johnson, 1996). The infantile form presents during the first or second year with developmental delay, megalencephaly, seizures followed by progressive psychomotor retardation, spasticity and quadriparesis. Death occurs 1 to 10 years after onset. Juvenile and adult forms, often with slower progression, have been described. The most striking and characteristic feature is the accumulation of Rosenthal fibres (RF). These are intracellular inclusions found exclusively in astrocytes, which under the light microscope appear as small round or ovoid bodies up

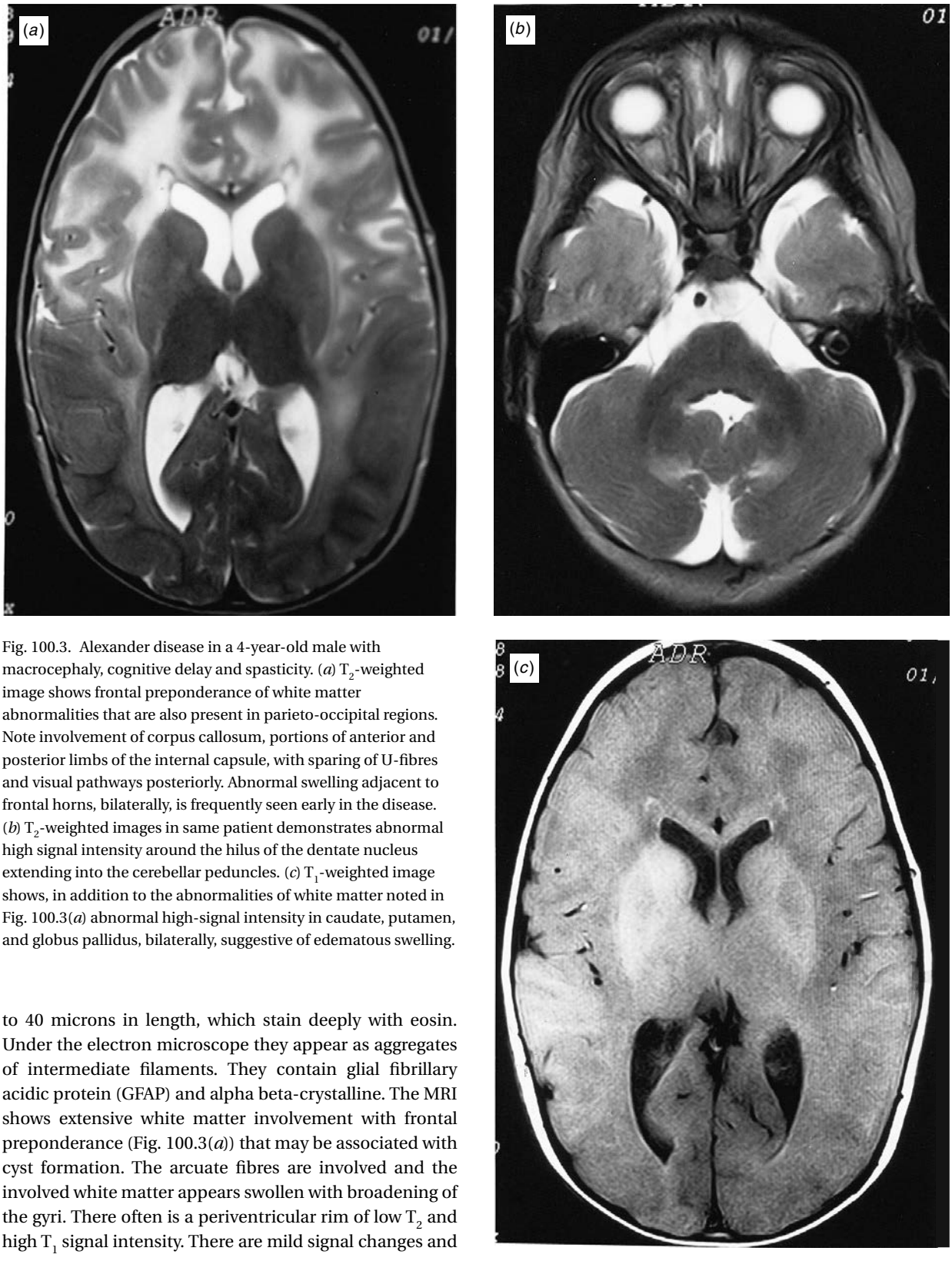

Fig. 100.3. Alexander disease in a 4-year-old male with macrocephaly, cognitive delay and spasticity. (*a*) T_2-weighted image shows frontal preponderance of white matter abnormalities that are also present in parieto-occipital regions. Note involvement of corpus callosum, portions of anterior and posterior limbs of the internal capsule, with sparing of U-fibres and visual pathways posteriorly. Abnormal swelling adjacent to frontal horns, bilaterally, is frequently seen early in the disease. (*b*) T_2-weighted images in same patient demonstrates abnormal high signal intensity around the hilus of the dentate nucleus extending into the cerebellar peduncles. (*c*) T_1-weighted image shows, in addition to the abnormalities of white matter noted in Fig. 100.3(*a*) abnormal high-signal intensity in caudate, putamen, and globus pallidus, bilaterally, suggestive of edematous swelling.

to 40 microns in length, which stain deeply with eosin. Under the electron microscope they appear as aggregates of intermediate filaments. They contain glial fibrillary acidic protein (GFAP) and alpha beta-crystalline. The MRI shows extensive white matter involvement with frontal preponderance (Fig. 100.3(*a*)) that may be associated with cyst formation. The arcuate fibres are involved and the involved white matter appears swollen with broadening of the gyri. There often is a periventricular rim of low T_2 and high T_1 signal intensity. There are mild signal changes and

swelling in the basal nuclei and thalamus (Fig. 100.3(*b*)). The brainstem and cerebellum are involved (Fig. 100.3(*c*)). The pathogenesis and genetics of AD have been clarified recently. Messing and associates developed a transgenic mouse that overexpresses GFAP. These mice showed pathological features that resemble AD (Johnson, 1996). This finding led to a search for mutations in the *GFAP* gene in patients (Brenner et al., 2001). Ten of 11 AD patients, with the infantile, juvenile and adult phenotypes represented, had mutations in the *GFAP* gene, none of which were present in 100 controls. Seven different mutations were identified. No abnormalities were observed in the parents. These results indicate that mutations in the *GFAP* gene are responsible for the majority of AD cases. The gene is autosomal dominant and appears to act as dominant negative. Most cases appear to be due to new mutations in the parental germline or the fetus, consistent with the historical clinical observation that most cases are sporadic.

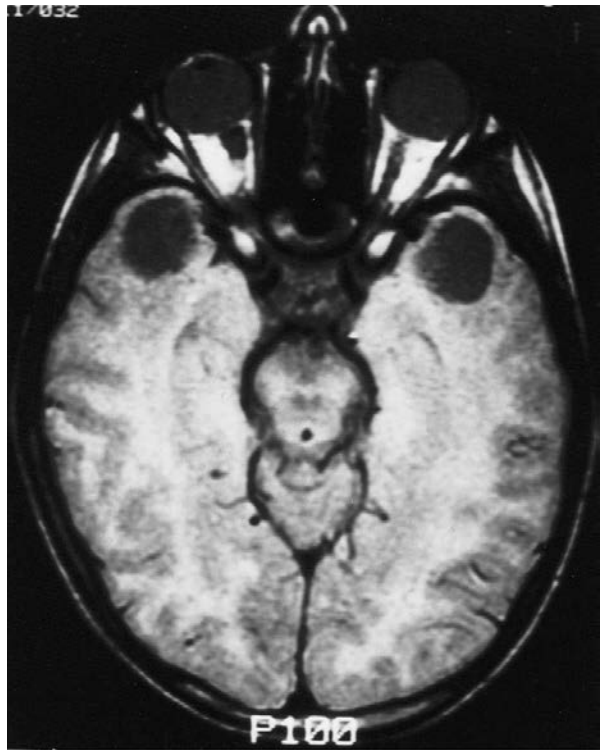

Fig. 100.4. Vacuolating leukoencephalopathy (van der Knaap et al. (1995)): 8-year-old female patient with mild learning disability, macrocephaly and spasticity. Flair images demonstrate diffuse high-signal intensity of white matter, including U-fibres. Note large vacuoles in temporal lobes bilaterally.

Cerebrotendinous xanthomatosis

Cerebrotendinous xanthomatosis (CTX) was described first by Bogaert, Scherer and Epstein in 1937. It presents during the first decade with bilateral juvenile cataracts and diarrhea, followed in the second or third decade by neurological signs and symptoms such as spasticity, ataxia, seizures, mental retardation, dementia, behavioural disturbances and peripheral neuropathy. Tendon xanthomata, often emphasized as a hallmark of the disease, rarely are seen in patients who are less than 20 years old (Verrips, et al., 2000b). Neuropathological abnormalities are widespread and include granulomatous and xanthomatous lesions in the cerebellar hemispheres, globus pallidus and cerebellar peduncles as well as demyelination gliosis in the cerebral hemispheres and the long tracts of the spinal cord and peripheral neuropathy (Federico & Dotti, 1996). The most characteristic abnormality on MRI is a high T_2 intensity lesion in the cerebellum surrounded by a rim with low T_2 intensity. Cerebellar foliae may be prominent, suggesting atrophy. The underlying defect is a deficiency of the mitochondrial sterol 27 hydroxylase, a cytochrome P-450 enzyme which together with two protein cofactors, adrenodoxin and adrenodoxin reductase, hydroxylates steroids at the C27 position. The gene for this enzyme, which maps to 2q33-qter, has been cloned (Cali et al., 1991). Twenty-eight mutations have been identified. Forty-one per cent involve the adrenodoxin and heme protein binding sites (Verrips et al., 2000a). The main biochemical abnormalities are the accumulation of cholestanol in tissues and body fluids demonstrated first by John Menkes in 1968 (Menkes et al., 1968), decreased formation of bile acids, resulting in markedly diminished formation of chenodeoxycholic acid and increased levels of bile alcohols and their conjugates in bile, urine and plasma (Federico & Dotti, 1996). Assay of serum cholestanol levels is the most frequently used diagnostic assay. Mutation analysis is required for carrier detection. Oral administration of chenodeoxycholic acid reduces cholestanol levels and improves neurologic function (Berginer et al., 1984). Simvastatin and plasma exchange have also been used, but require additional appraisal. In theory, liver transplantation might be a curative treatment, but has not been performed in patients with CTX (Federico & Dotti, 1996).

Sjogren Larsson syndrome

Sjogren Larsson syndrome, a disorder in which a leukoencephalopathy is associated with mental retardation, cerebral palsy and ichtyosis, has been shown to be due to a defect in fatty aldehyde dehydrogenase. The defective gene is located at 17p11.2. Thirty-five different mutations have been identified. This syndrome, as well as other inherited disorders of fatty alcohol metabolism, have been reviewed recently (Rizzo, 1998).

Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy

A loss of function mutation in a TYRO tyrosine kinase protein has been reported recently in Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (MIM 221770) (Paloneva et al., 2000). This is a rare leukodystrophy associated with destructive changes in the skeleton and presenile dementia observed in isolated populations in Finland and Japan (Verloes et al., 1997).

Recently identified leukodystrophies

Analysis and grouping of patients based initially upon MRI findings has led to the identification of three additional leukodystrophies. These are *vacuolating megalencephalic leukoencephalopathy with subcortical cysts* (van der Knaap et al., 1995) (Fig. 100.4) which has been mapped to 22q (Topcu et al., 2000) *leukoencephalopathic vanishing white matter*, also referred to as childhood ataxia with diffuse central nervous system hypomyelination, which has been mapped to chromosome 3q27 (Leegwater et al., 1999) and a *leukoencephalopathy associated with a disturbance in the metabolism* of polyols (van der Knaap et al., 1999).

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Part XIV

Infections

101

Host responses in central nervous system infection

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Infections of the central nervous system (CNS) can occur in two anatomically distinct tissue compartments: the subarachnoid and leptomeningeal spaces (meningitis) and the parenchyma of the brain and spinal cord (encephalomyelitis). While an intact blood–brain barrier (BBB) ordinarily deters microorganisms from invading either tissue compartment, it also excludes most circulating components of the immune system, making the CNS susceptible to infection once such invasion does occur. Cells of the immune system can extravasate into the CNS in response to infection, but they appear to do so in a tightly regulated manner. Within the brain, neural cells have restricted immunological function, and the local microenvironment of the CNS can also down-modulate various effector responses of recruited inflammatory cells. In general, a successful host immune response against a CNS infection must overcome these structural and functional barriers to eradicate infectious organisms without causing excessive damage to non-renewable neural cell populations. In some cases, however, the host response is not fully controlled and actually contributes to the neurologic deficits associated with CNS infection. This chapter will review these concepts by citing examples from both human disease states and laboratory-based experimental systems.

Anatomical considerations

There are several anatomical features of the nervous system that influence how local and systemic immune responses are mounted in response to CNS infection. These include: (i) the BBB which stands as a physical barrier against the passage of immune elements from the periphery into the CNS, (ii) the Virchow–Robin spaces immediately surrounding blood vessels that penetrate into the brain where important immunologic reactions can take place, and (iii) cerebrospinal fluid (CSF) recirculation pathways, which may disseminate microorganisms throughout the neuraxis and cause infectious antigens to be carried out of the CNS via particular routes, therefore influencing how they are detected by the immune system in the periphery.

Under normal circumstances, structures that comprise the BBB generally prevent the entry of infectious pathogens, inflammatory cells, and circulating proteins such as antibodies and cytokines into the CNS. Cerebrovascular endothelial cells maintain tight intercellular junctions and very low rates of vesicular transport that differentiate them from the more permeable endothelium found in other tissues. A dense basement membrane ensheathes the cerebrovascular endothelium which is itself surrounded by a network of pericytes and astrocytic foot processes that collectively maintain the integrity of the BBB. In only a few specific locations is the BBB 'fenestrated' and easier to traverse; infectious pathogens circulating in the bloodstream are quite effectively excluded from the brain. Yet once this barrier is breached, many infections take firm hold within the CNS as there is limited intrinsic immune capacity of neural tissues and effective host responses must also surmount the BBB from the periphery.

The Virchow–Robin spaces immediately surrounding many blood vessels that penetrate the surface of the brain are actually extensions of the subpial space (Fig. 101.1). These spaces contain macrophage-like cells with phagocytic and antigen-presenting capacities not found within the brain parenchyma itself. These so-called perivascular macrophages or perivascular microglial cells are of bone marrow origin and actively repopulate themselves within the CNS over the life of the host (Hickey & Kimura, 1988; Hickey et al., 1992). Foreign antigens and lymphocytes also pass through these spaces as they are carried into the lymphatic channels of the head and neck. As a result, the

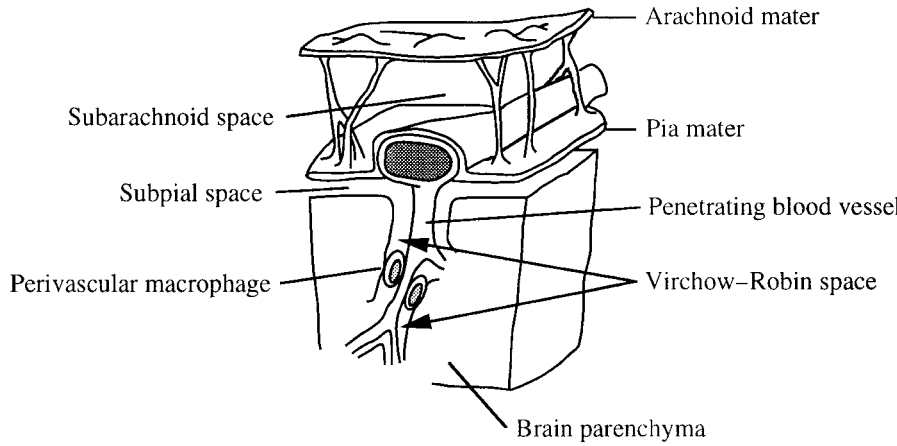

Fig. 101.1. The Virchow–Robin space. These extensions of the subpial space contain perivascular macrophages and can serve as a conduit through which foreign antigens and other leukocytes leave the CNS. Important neuroimmunological reactions occur in these spaces.

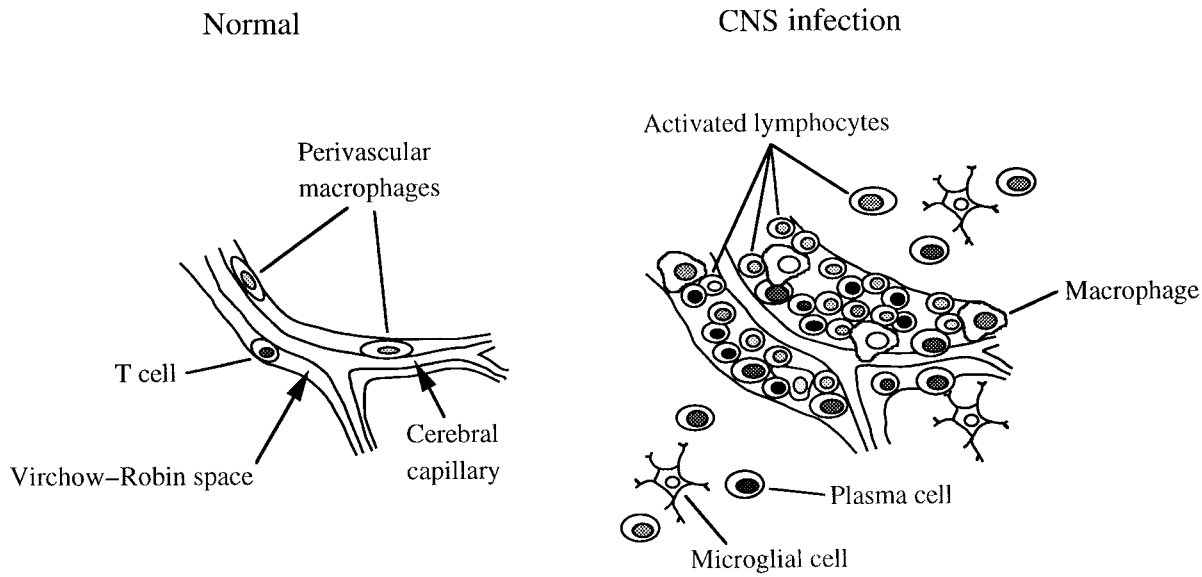

Fig. 101.2. Perivascular inflammation within the Virchow–Robin space. Infections of the CNS can recruit many types of circulating leukocytes across the blood–brain barrier into the Virchow–Robin spaces. These cells (or their products) can then pass into the brain parenchyma itself, allowing for direct interaction with infectious organisms and infected neural cells.

Virchow–Robin spaces form well-defined sites, physically outside of the brain parenchyma itself, where important neuroimmunologic reactions take place (Esiri & Gay, 1990). These spaces become engorged with inflammatory cells during a variety of acute and chronic infections of the CNS (Fig. 101.2).

CSF is produced by cells of the choroid plexus within the ventricles of the brain. Its protein content, including antibodies and complement which are the primary immune mediators present at baseline, is almost entirely derived from the blood. However, these proteins are present in CSF at less than 1% of circulating levels (Fishman, 1992). In contrast, CSF contains abundant nutrients (glucose, amino acids, etc.) that many infectious pathogens can utilize (Fishman, 1992). This fluid normally recirculates within the subarachnoid space which may disseminate

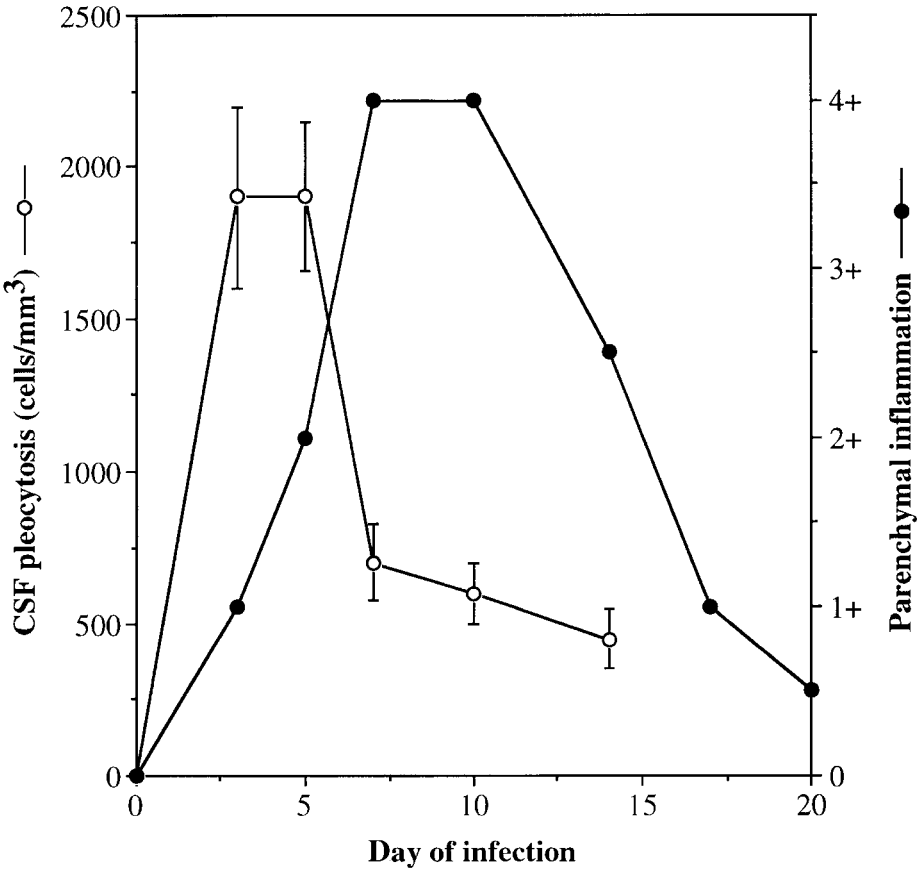

Fig. 101.3. Kinetics of mononuclear leukocyte appearance in the CSF and brain parenchyma of mice with acute Sindbis virus encephalitis. In this infection, cells rapidly infiltrate the CSF before any parenchymal inflammation is seen. CSF cell counts then fall precipitously as cellular infiltration of the brain itself becomes maximal. (Adapted from Moench & Griffin, 1984.)

invading micro-organisms throughout the neuraxis. In addition, protein antigens delivered directly into the CSF of experimental animals elicit enhanced humoral (antibody) and suppressed cell-mediated (T-cell) immune responses compared to when proteins are administered via a peripheral route (Cserr & Knopf, 1992; Gordon et al., 1992). In these models, cervical lymph nodes are an important site where antigen-specific immune responses develop (Harling-Berg et al., 1989; Cserr & Knopf, 1992). Likewise, these lymph nodes also serve as an important site where virus-specific cytotoxic T-lymphocytes (CTL) are generated, following the experimental inoculation of neurotropic viruses into the CNS (Lynch et al., 1989). In this case, however, the degree to which the virus-specific immune response gets skewed in favour of a humoral response, as occurs with more simple protein antigens, remains unknown. Yet, despite any qualitative effects on the elicited immune response, inflammatory cells, antibodies and immunoregulatory cytokines collect within the CSF during many CNS infections. In one experimental model of acute viral encephalitis, the accumulation of mononuclear cells in CSF actually precedes immune infiltration of the brain (Fig. 101.3); CSF inflammation is already subsiding when parenchymal inflammation becomes maximal (Moench & Griffin, 1984). Such differences in the kinetics of leukocyte infiltration suggest that recruited inflammatory cells may either traffic from one CNS compartment to another (i.e. from CSF to brain) or that their capacity to extravasate into each site is controlled by different mechanisms and/or occurs via different pathways. It also implies that, when CSF is sampled diagnostically in viral encephalitis, the findings may not fully reflect the degree of abnormality present in the underlying brain parenchyma itself.

Immune capabilities of neural cells

Most neural cells lack constitutive expression of major histocompatibility (MHC) class I and class II molecules that are necessary for antigen presentation to T-cells. While astrocytes and cerebrovascular endothelial cells can both be induced to express these molecules in vitro (Fierz et al., 1985; Risau et al., 1990), only perivascular macrophages and parenchymal microglial cells are reliably induced to express MHC antigens during CNS infection in vivo (Tyor et al., 1990, 1992a). Even then, MHC Class II expression necessary for antigen presentation to CD4+ T-cells may not be sufficient; ligation of various costimulatory molecules is required to fully activate naive T-cells and drive them to proliferate (Steinman, 1991). Microglial cells, however, can reactivate memory T-cells and induce some antigen-specific cytokine production without stimulating proliferation (Ford et al., 1996). This 'partial' activation is followed by the prompt induction of T-cell death via apoptosis (Ford et al., 1996). In this manner, microglial cells may actually protect the CNS from lymphocytes recruited during infection by allowing them to exert some local effector function but also by discouraging their full activation and limiting their survival.

The issue of whether any neural cell can present infectious antigens to a naive T-cell (i.e. a T-cell that has not yet encountered such an antigen outside the CNS) remains unclear. In early pathogenesis studies, viruses inoculated experimentally into the CSF or the brain parenchyma of animals were introduced in relatively large volumes; this typically produced a rapid viremia thereby allowing specific activation of the immune system in the periphery (Mims, 1959). In a more careful study of this issue, a large volume injection of influenza virus into the brain parenchyma or CSF of mice elicited systemic cellular and humoral antiviral immune responses comparable to those which developed following intranasal challenge (Stephenson et al., 1997). However, when the same amount of virus was delivered directly into the CNS parenchyma in a very small volume, there was no detectable immune response elicited over the first 10 days and less than half of the mice eventually mounted such a response more than 80 days later (Stephenson et al., 1997). Not only does this highlight the fact that infectious pathogens elicit variable local immune responses based on their accumulation in different CNS compartments, but it also demonstrates that the brain parenchyma itself has a surprisingly deficient capacity to initiate a primary immune response. While this may have evolved to minimize the risks of CNS autoimmunity, it may also allow infectious pathogens to remain sequestered behind the BBB and hidden from the immune system.

The CNS, however, is not totally devoid of intrinsic immune function. In a murine model of acute viral encephalitis, transcripts encoding multiple cytokine genes are induced in the brain well before overt inflammation can be detected (Wesselingh et al., 1994). This strongly suggests that endogenous neural cells rapidly produce these mediators in response to infection. Proinflammatory cytokines can be localized within microglial cells and astrocytes from autopsy cases of chronic human CNS infections as well as from experimental CNS infections induced in laboratory animals (Frei et al., 1989; Tyor et al., 1992a; Wesselingh et al., 1993, 1996). A role for these soluble immune mediators as an important component of the acute host response to infection has now been demonstrated; both pharmacological and genetic strategies to inhibit their production in experimental systems lead to enhanced pathogen replication within the CNS and/or more lethal disease (Geiger et al., 1995; Tucker et al., 1996; Byrnes et al., 2000). However, the long-term production of cytokines and other inflammatory mediators within the CNS has been associated with neurotoxicity and severe neurological symptoms such as myelopathy and dementia in chronic diseases such as human immunodeficiency virus (HIV) infection (Tyor et al., 1992a; Wesselingh et al., 1993; Adamson et al., 1996). Nevertheless, endogenous neural cells are now recognized to be immunologically active, at least with regard to their capacity to produce cytokines and other inflammatory mediators during CNS infections. As discussed, this response may work either to the benefit or the eventual detriment of the infected host.

Endogenous cells of the brain may also possess other immunological functions relevant to different CNS infections. Certainly phagocytosis, a function served primarily by macrophage-lineage cells including microglia and perivascular macrophages, can help to control extracellular pathogens such as bacteria. Following their stimulation with inflammatory cytokines, astrocytes can generate a complete, functional complement cascade (through both the classical and alternative pathways) that may participate in the opsonization and killing of infectious pathogens within the brain (Morgan & Gasque, 1996). More recently, certain astrocyte populations have also been recognized to express perforin, a cytotoxic protein previously only found in T-cells and natural killer cells (Gasque et al., 1998). While dysregulation of these endogenous immune pathways has been implicated in a variety of inflammatory and degenerative diseases involving the CNS, their identification also highlights the fact that brain is not entirely the 'immune privileged' site it was once considered to be.

Recruitment of inflammatory cells into the CNS

It is generally assumed that inflammatory cells which accumulate in the perivascular spaces of the brain during various CNS infections do so by extravasating directly from the circulation across the BBB. Such leukocyte extravasation is likely to be a multistep process triggered by chemoattractant signals arising from within the CNS. Once such a signal is detected, circulating leukocytes must then bind to the luminal surfaces of cerebral vessels. In other tissues, this binding occurs via the actions of specific adhesion–ligand pairs (Springer, 1990). Bound leukocytes then traverse the endothelial and basement membrane barriers before they can begin to exert effector functions in response to the eliciting infection. While it is assumed that specific signals are also required to retain inflammatory cells within the brain, the precise mechanisms and routes of cell efflux from the CNS remain poorly understood.

An enlarging number of chemoattractant cytokines ('chemokines') have been identified which signal leukocytes to migrate along a gradient via the actions of specific chemokine receptors. α-Chemokines are the primary attractants for neutrophils, while β-chemokines can modulate both macrophage and T-cell migratory responses (Baggiolini et al., 1994). In general, these molecules operate via redundant pathways to attract overlapping populations of inflammatory cells into various tissue sites. Chemokines can be produced within the CNS by different glial, and possibly even neuronal, cell populations (Glabinski et al., 1995). Their role during CNS infection has been most carefully investigated in chronic disorders such as HIV; the increased number of activated macrophages found within the brains of patients with HIV-associated dementia compared to non-demented control patients has been correlated with higher CSF (and presumably brain) levels of certain β-chemokines (Kelder et al., 1998). The HIV tat protein can directly induce cultured astrocytes to secrete high levels of monocyte chemoattractant protein-1 (MCP-1), the principal β-chemokine associated with HIV dementia (Conant et al., 1998; Kelder et al., 1998). It is likely that chemokines direct the recruitment of inflammatory cells into the CNS during other acute and chronic neurologic infections as well.

In the absence of disease, cerebrovascular endothelial cells express few adhesion molecules making non-activated lymphocytes and circulating monocytes unable to enter the CNS with any efficiency. Following viral infection, however, a variety of adhesion molecules are up-regulated on cerebrovascular endothelial cell surfaces (Irani & Griffin, 1996). This probably occurs via local cytokine production from within the CNS as cultured cerebrovascular endothelial cells can up-regulate various adhesion receptors following cytokine stimulation in vitro (Wekerle et al., 1991). Activated lymphocytes and monocytes, which themselves express higher levels of adhesion molecules compared to resting cells, then bind to cerebrovascular endothelium without regard to their antigenic specificity (Irani & Griffin, 1996). Such binding, although not necessarily sufficient to gain entry into the CNS, is certainly a prerequisite step for circulating inflammatory cells to cross the BBB.

Once bound to the luminal surface of a CNS blood vessel, leukocytes must pass through endothelial cell tight junctions and then traverse the surrounding basement membrane. Like those found in other tissues, the BBB basement membrane is composed of multiple extracellular matrix proteins including type IV collagen, heparin sulfate proteoglycan, laminin, and entactin. Activated lymphocytes produce a matrix-degrading heparan sulfate endoglycosidase and presumably other matrix degradative enzymes as well (Naparstek et al., 1984). Matrix metalloproteinases (MMPs) are a family of zinc-containing endopeptidases that degrade specific components of the extracellular matrix found within the CNS; these enzymes have received significant recent attention because they are made by activated lymphocytes and monocytes and specific MMP inhibitors can block the extravasation of these cells across the BBB (Yong et al., 1998). Endogenous neural cells may also be stimulated to generate MMPs which may contribute to BBB changes seen during chronic CNS infections such as HIV (Power et al., 1993; Maeda & Sobel, 1996). In disease situations where the CNS inflammatory response may actually be detrimental to the neurological function of the host, local CNS production of MMPs may contribute to disease progression. Not only does a damaged BBB make it easier for excessive numbers of circulating leukocytes to enter the CNS, but it may promote exposure of the brain to potentially toxic serum proteins including serine proteases such as thrombin (Turgeon & Houenou, 1997).

Unlike their entry into the CNS, which can occur without regard to antigenic specificity, the retention of lymphocytes within the CNS during infection appears to depend strongly on the antigen that each cell recognizes. Thus, at least during viral infection of the CNS, virus-specific T-cells are selectively retained within the CNS compared to cells of an irrelevant specificity (Irani & Griffin, 1996). In this case, it is assumed that the process of recognizing viral antigens on neural cells induces changes that cause these T-cells to remain in place. How the 'irrelevant' T-cells exit the CNS is now known, and some evidence suggests that they may not actually leave the CNS but instead undergo apoptosis

locally within the brain (Barac-Latas et al., 1995; Irani et al., 1997). Thus, the brain may possess endogenous mechanisms that keep relevant leukocytes within its confines, while causing unnecessary inflammatory elements to either depart or be eliminated. Any breakdown of this system, however, might predispose to immune-mediated neurological injury.

Local regulation of inflammatory cell function within the CNS

In addition to mechanisms that control the recruitment of inflammatory cells into the brain, there is evolving evidence to suggest that the CNS has some capacity to regulate the local effector function of recruited inflammatory cells. Such a capacity may have evolved to prevent overactive immune responses from damaging non-renewable cell populations such as neurons. For example, T-cells that have extravasated into the brain parenchyma may produce cytokines and exert some cytolytic activity, but there is little evidence that they proliferate locally in response to antigenic stimulation. Perivascular and parenchymal lymphocytes do not divide within the brains of animals with viral encephalitis when assayed using in vivo techniques to label DNA in proliferating cells (Irani et al., 1997; Hawke et al., 1998). Furthermore, lymphocytes isolated from the brains of these animals and placed into culture eventually recover the capacity to divide suggesting that the local CNS microenvironment exerts this antiproliferative effect (Irani et al., 1997). While this may in part derive from inhibitory signals generated during local antigen presentation (Ford et al., 1996), it is also clear that neuronal membrane lipids can affect various T-cell responses such as proliferation, cytokine production, and survival (Irani et al., 1996, 1997). Infiltrating T-cells probably encounter these membrane glycolipids once they infiltrate the brain, thereby coming under their local regulatory effect. This provides another potential mechanism to control local T-cell function to the advantage of the CNS.

The brain may also be able to exert local control over the effector functions of leukocytes other than T-cells. Sensory neurons can regulate immunoglobulin secretion by B-cells via the release of soluble factors (Hikawa & Takenaka, 1996), and various neuropeptides have been shown to modulate the production of inflammatory cytokines by human monocytes (Lotz et al., 1988). Astrocytes may also contribute to local immune regulation within the brain by producing immunomodulatory cytokines such as transforming growth factor-β (Wilbanks & Streilein, 1992). This particular mediator has received attention because it is constitutively expressed within the brain, CSF, and aqueous humor of the eye (Streilin, 1993). Based on these and other data, immune privilege within the CNS is now viewed as an active process whereby local tissue factors interact with and alter the functional programs of various cells of the immune system. It remains unclear, however, exactly to what degree such endogenous immunoregulatory pathways are altered during various infections of the CNS.

Host responses against specific types of infectious pathogens within the CNS

Viruses invade the CNS either through hemotogenous dissemination and direct spread across the BBB or through retrograde axonal transport up nerve processes that extend from the periphery into the CNS (Johnson, 1998). As intracellular pathogens, the tropism of viruses for different neural cell populations and their effect on host cell function and survival are major determinants of the severity of disease. The paucity of MHC antigen expression within the CNS, particularly on neurons, can limit direct CTL-mediated clearance of certain viruses and may predispose to chronic or relapsing neurologic infections (Joly et al., 1991). Their capacity to establish latency also allows viruses to avoid detection by the immune system. In other cases, however, T-cell-mediated clearance of viruses from the CNS can occur via the local production of soluble anti-viral mediators such as interferon-γ (Kündig et al., 1993). T-cells can also protect experimental animals from otherwise lethal CNS viral challenges without actually decreasing the amount of infectious virus in the brain (Stohlman et al., 1986). In still other cases, antiviral antibodies can shut off virus production by infected neurons in a non-cytolytic manner (Levine et al., 1991). This strategy is attractive because recovery from disease can occur without cytolytic destruction of non-renewable cells and because the immune system can generate an antigen-specific response that acts without requiring target cell expression of MHC molecules. Such non-cytolytic strategies have their drawbacks, however, as the viral clearance can be incomplete allowing viral nucleic acids to persist long-term within the CNS (Levine & Griffin, 1992). This can be enough to stimulate persistent CNS inflammation which has been hypothesized to predispose the CNS to eventual immune-mediated damage (Tyor et al., 1992b; Hawke et al., 1998). Endogenous neural cells can mount non-specific antiviral responses via the production of cytokines (Tucker et al.,

1996; Byrnes et al., 2000), but as discussed earlier, the long-term generation of mediators such as tumor necrosis factor-α (TNF-α) within the CNS during chronic infections such as HIV may actually promote the development of neurologic systems (Wesselingh, et al., 1993; Tyor et al., 1995).

Bacteria require specific virulence factors to invade the CNS and produce neurological disease. Organisms that cause acute meningitis are usually encapsulated; this inhibits activation of complement through the classical pathway and delays bacterial phagocytosis outside the CNS. As a result, encapsulated bacteria survive longer in the bloodstream, produce more robust bacteremias, and are more likely to invade the CNS (Tunkel & Scheld, 1991). Once within the subarachnoid space, favourable local conditions (i.e. limited intrinsic host defences, abundant nutrients) allow for rapid and unimpeded bacterial multiplication. Inflammatory cytokines, particularly interleukin-1 and TNF-α, are eventually secreted in response to bacterial cell wall products and help induce endothelial expression of adhesion molecules important for neutrophil egress (Springer, 1990). The local production of other chemotactic stimuli including interleukin-8 also recruits neutrophils, but low overall levels of opsonins, antibodies, and complement within the CSF limit bacterial phagocytosis by infiltrating cells. Slow growing bacteria such as mycobacteria have adapted to survive inside macrophages and typically induce mononuclear inflammatory responses in the CSF.

Fungi are generally avirulent pathogens; most individuals with disseminated fungal infections that spread to the CNS have some underlying immune deficiency. The particularly high frequency of these disorders in patients with impaired cell-mediated responses implies that these immune elements serve as the primary host defence against fungal pathogens that invade the CNS. In these hosts, fungi can survive longer in the bloodstream (their presumed route to the CNS), are more likely to cross the BBB, and then grow unchecked in the CSF without eliciting much of an inflammatory response. For *Cryptococcus neoformans*, the ability to produce melanin, which may act as an antioxidant to protect the organism from host immune damage, has been proposed as an important virulence factor (Kwon-Chung & Rhodes, 1986). Once CNS infection has been established, these organisms are difficult to completely eradicate and often require long-term antifungal therapy. Mortality in general is high.

Only a few parasites frequently invade the nervous system. Free-living amebae that cause acute meningoencephalitis likely enter the CNS by direct invasion across the olfactory mucosa. This can occur following aquatic exposure such as swimming in infected water (Cegielski & Durack, 1991). Macrophages, neutrophils, and the complement system all can respond to these organisms, but once CNS invasion occurs, the infection typically overwhelms host defences and is invariably fatal (Cegielski & Durack, 1991). Most other parasites are assumed to enter the CNS from the bloodstream. Intracellular pathogens such as *Toxoplasma gondii* may establish latent CNS infection in the form of inert cysts that evade host immune clearance. Otherwise, various T-cell-derived cytokines are particularly active against these organisms, in part, via their capacity to activate phagocytic macrophages (Dukes et al., 1991). Clinically apparent CNS toxoplasmosis almost always develops in hosts with acquired cellular immune deficiencies such as those caused by chronic HIV infection. In contrast, the cysticerci of *Taenia solium* can induce an intense parenchymal CNS inflammatory reaction. These organisms are eventually killed leaving behind calcified nodules, which themselves can produce neurological symptoms such as seizures. Malaria can induce an acute encephalopathy associated with the adhesion of parasitized erythrocytes to cerebral capillary endothelial cells. In fatal cases, diminished cerebral blood flow and petechial hemorrhages often ensue, although emerging data suggest that the host immune response also contributes to disease pathogenesis. Inflammatory cytokines can be induced within the CNS of patients with cerebral malaria that may serve to up-regulate endothelial adhesion molecules and promote further erythrocyte adhesion (Fujioka & Aikawa, 1996). Brain hypoxia, along with varying degrees of the hypoglycemia that is common in this setting, may be the substrate that underlies the neurological disease.

In conclusion, an effective host immune response to infection of the CNS requires a careful interplay between the nervous and immune systems. This response must overcome a series of structural and functional barriers imposed by the CNS in order to eradicate infectious organisms without causing excessive damage to non-renewable neural cell populations. These barriers have evolved to protect the brain, which certainly can sustain more injury from an activated immune system than from an infection itself. Such a protective system, however, often allows invading organisms to replicate behind the BBB in an unimpeded manner or limits their full eradication from the CNS. Either of these situations may be as detrimental to the host as an overexuberant local immune response. The neuroimmunologic lessons taught by studying host responses during CNS infections have broad relevance to understanding nervous system–immune system interactions in general.

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Viral diseases of the nervous system

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Viral routes and host defenses

Many viruses once they reach the central nervous system (CNS) are capable of infecting cells and producing varying types of clinical syndromes. If the virus infects primarily meningeal cells lining the brain, meningitis develops. If the virus widely infects many types of brain cells, such as neurons and glia, encephalitis ensues. Some viruses infect only selective cell types producing specific clinical syndromes. For example, poliovirus infects only neurons of the motor pathway producing a paralytic disease called poliomyelitis. To date, viruses have not been implicated as a cause of brain abscesses or subdural empyemas.

Viral infections of the CNS usually begin with a primary focus of infection associated with their route of entry. Enteroviruses establish an initial infection in the gastrointestinal tract. Mumps virus establishes a primary infection in the respiratory tract. Rabies virus is directly inoculated through the skin via saliva during the bite from an infected animal and establishes a primary infection in the subcutaneous tissue and underlying muscle. Arboviruses are inoculated through the skin by a vector (infected mosquito or tick) and infect subcutaneous tissue and traversing blood vessels. The primary systemic infection usually is asymptomatic but prodromal syndromes can occur (gastroenteritis or upper respiratory infection). As viral replication continues at the primary site of infection, progeny virions spread into adjacent blood vessels or lymphatic channels. A viremia of varying duration then develops seldom causing a CNS infection. For example, less than 2% of susceptible individuals infected with poliovirus develop viral infection of the spinal cord and paralysis (Melnick, 1996).

For a viremia to cause a CNS infection, several important host barriers must be overcome. The reticuloendothelial system (RES) is an efficient filter of viruses circulating in blood. Clearance of small viruses, such as arboviruses, from blood is over 90% within 1 hour. However, some viruses overcome the RES by constantly releasing viral particles into the bloodstream following infection of vascular endothelial cells or lymph nodes (Johnson & Mims, 1968). Other viruses circumvent the RES by infecting circulating blood cells. Mumps virus can replicate within leukocytes and human immunodeficiency virus (HIV) can replicate in T-helper lymphocytes and monocytes/macrophages. In this manner, viruses are protected by RES phagocytosis or circulating neutralizing antibody.

Humoral and cellular immune responses are other defences that effectively terminate viremias. However in a primary infection, several days are required for the host immune system to establish the immune response. The delay may allow the virus to cross the blood–brain barrier and establish the CNS infection.

The final hindrance for a virus to reach the CNS is to overcome the blood–brain barrier. This barrier is usually highly effective in preventing all micro-organisms from reaching the CNS. However, some arboviruses breech the barrer by infecting cerebral capillary endothelial cells, replicating, and exiting directly into the brain (Johnson, 1965). Other viruses, such as mumps, appear capable of penetrating the fenestrated walls of the choroid plexus blood vessels to infect and replicate within the choroid plexus cells and subsequently enter the ventricular cerebrospinal fluid (CSF) (Wolinsky et al., 1976).

A few viruses reach the CNS via peripheral or cranial nerves. Rabies virus appears to infect peripheral sensory nerves in the initially infected muscle and travel retrograde to reach the spinal or trigeminal ganglia and into the spinal cord or brainstem (Murphy et al., 1973). Herpes simplex virus has been hypothesized to reach the brain by spread within sensory fibres of the trigeminal ganglia (Davis & Johnson, 1979).

Table 102.1. Estimated frequency of neurological syndromes in systemic viral infections

Virus	Meningitis	Encephalitis	Myelitis
Enterovirus	+++	++	+
Poliovirus	+++	+	+++
Human immunodeficiency virus	+++	++	++
Arbovirus	+++	+++	++
Herpes simplex			
(congenital)	++	+++	+++
(adult)	++ (type 2)	+ (type 1)	+ (type 1,2)
Varicella-zoster	+	+	+
Epstein–Barr	+	+	+
Cytomegalovirus			
(congenital)	+	+++	+
(immunosuppresssed adult)	++	++	+
Influenza	+	+	+
Parainfluenza	+	+	+
Rubeola (measles)	++	++	+
Rubella			
(congenital)	+	+++	+
(child or adult)	+	++	+
Mumps	+++	++	+
Lymphocytic choriomeningitis	+++	++	0
Reovirus	+	+	+
Dengue	++	++	0
Adenovirus	++	++	0
Parvovirus B19	+	++	0
Rabies		+++	+++
Papovavirus (JC strain)		+++	0
Prions		+++	0
(Creutzfeld–Jakob disease)			

Notes:
+++ = common, greater than 1 per 1000 primary infections.
++ = Less common, less than 1 per 1000 primary infections.
+ = Uncommon, only scattered reports in literature.
0 = No or questionable reports in literature.

The brain is not a homogeneous organ, such as liver. Viral infections directed towards different brain locations or cell types result in differing signs and symptoms. Thus, the neurological signs and symptoms are due to the location of the viral infection in the CNS and not the specific virus. The specific virus determines the severity of the CNS infection and its duration.

This chapter discusses the major neurological illnesses that are caused by viruses. Table 102.1 lists the types of infections that different viruses can cause and their estimated frequency. However, one is referred to major textbooks of infectious diseases for information regarding details of specific viruses and the types of CNS infection they can cause (Mandell et al., 2000; Long et al., 1997; Davis & Kennedy, 2000).

Viral infections of the meninges

Viral meningitis is part of a broader syndrome with similar features called aseptic meningitis. Viral meningitis is characterized by (i) acute onset, (ii) signs and symptoms of meningeal inflammation, (iii) characteristic CSF findings, (iv) absence of organisms when CSF is cultured on routine bacteriologic media, and (v) relatively short and benign clinical course (Davis, 1997). Aseptic meningitis has

similar clinical characteristics to viral meningitis but the meningitis is not always brief or benign. Non-viral causes of aseptic meningitis include drugs, biologic products, unusual bacterial or parasitic agents, systemic or immunologically mediated diseases, neoplastic diseases, and parameningeal conditions (Table 102.2).

Etiologies and epidemiology

Worldwide, enteroviruses (coxsackieviruses and echoviruses) and mumps virus are the most common causes of viral meningitis. In countries administering mumps vaccine to children, enteroviruses account for over 80% of cases. In the United States, the Centers for Disease Control and Prevention report over 10 000 cases of aseptic meningitis each year (Centers for Disease Control and Prevention 1992). However, the true incidence likely is much higher as many cases are not reported to state agencies. Recent studies of enterovirus meningitis suggest that over 75 000 such cases occur annually (Rotbart, 1995). In epidemiology studies, the incidence of aseptic meningitis has been estimated to be about 18 cases per 100 000 population per year but can locally increase during seasonal epidemics (Modlin, 1999). The majority of cases occur in children, with a peak incidence occurring in summer and early fall when epidemics of enteroviruses prevail.

Clinical manifestations

Prodromal illnesses may preceded the viral meningitis. The characteristics of the prodromal illness are usually vague and mild and consist of gastrointestinal distress, rashes or 'flu-like symptoms (Table 102.3). However, meningitis from mumps virus may be preceded by parotitis or orchitis and from herpes simplex virus by genital vesicles.

Table 102.4 lists the signs and symptoms of viral meningitis. The onset of symptoms is usually quite abrupt and patients reach marked symptoms within hours of onset. Marked lethargy or seizures suggests viral invasion of the brain parenchyma and the development of meningoencephalitis. The presence of coma, papilledema or focal neurologic signs is rare in viral meningitis and raises the possibility of a CNS mass from a different cause.

Laboratory findings

The hemogram is usually normal or has a mild leukocytosis (usually lymphocytosis). Other blood tests vary depending on the etiology. Table 102.5 lists the common CSF abnormalities. In uncomplicated viral meningitis, the electroencephalogram and neuroimaging are usually normal.

Differential diagnosis

The major causes of aseptic meningitis are listed in Table 102.2. It is important to distinguish the patient with viral meningitis from patients with pyogenic bacterial, tuberculosis, or fungal meningitis. Distinguishing features between viral and bacterial meningitis are listed in Table 102.5. Of note, occasional patients with proven viral meningitis (especially mumps and herpes simplex viruses) may have CSF obtained in the first day of the illness that contains predominately neutrophils and mildly depressed glucose. However, patients with viral meningitis should not have markedly depressed CSF glucose levels (below 20 mg/dl) or bacteria seen by Gram stain of the CSF sediment. In patients with atypical viral meningitis, repeat lumbar puncture 12–24 hours later usually demonstrates a CSF with a normal or near normal glucose level and predominance of lymphocytes (Sells et al., 1975).

Diagnosis

The etiology of viral meningitis is established if there is: (i) a characteristic prodrome (such as parotitis or genital vesicles), (ii) isolation of virus from CSF, stool or throat secretions, (iii) positive polymerase chain reaction (PCR) assay for viral nucleic acid in CSF, or (iv) a four-fold rise in antibody titre to a specific virus between the acute and convalescent serum samples. Table 102.3 lists the most common methods to diagnose each virus. The ease of culturing viruses from CSF depends on the etiology. Viruses most often are isolated from CSF in the first 12–24 hours of symptoms. However, isolation of the virus from the gastrointestinal tract or throat often occurs for days. Use of PCR assays in CSF to establish the diagnosis of enterovirus or herpes simplex virus (HSV) meningitis is becoming widely used (Read & Kurtz, 1999; Riding et al., 1996). PCR assays for enteroviruses have primers and probes directed against a conserved 5′ non-coding region of the viral genome and thus detect most enterovirus strains. The newer PCR assays report over 90% sensitivity and 100% specificity for enteroviruses. A similar sensitivity and specificity is reported for HSV PCR assays. PCR assays for mumps and other viruses may soon be available (Poggio et al., 2000). Studies are under way to determine whether a battery of PCR assays can be used to detect several infectious agents in CSF (Read & Kurtz, 1999; Hosoya et al., 1998).

Management

The first step is to determine that the patient has aseptic meningitis, likely due to a virus, and not acute pyogenic

Table 102.2. Major causes of aseptic meningitis

Viruses
Enteroviruses (echovirus and coxsackievirus)
Mumps
Herpes simplex, types 2 and 1
Arboviruses (Eastern equine encephalitis, Western encephalitis, Venezuelan encephalitis, St. Louis encephalitis, Powassan, California, Colorado tick fever, West Nile, and many strains found outside of the United States
Human immunodeficiency virus
Lymphocytic choriomeningitis virus
Poliovirus
Varicella-zoster virus
Parvovirus B19
Epstein–Barr virus
Adenovirus
Rubeola virus (measles)
Rhinovirus
Cytomegalovirus
Vaccine viruses (mumps, measles, rubella, poliovirus)

Other infectious agents
Borrelia Burgdorferi
Treponema pallidum (syphilis)
Taenia solium (cysticercosis)
Leptospira sp.
Brucella sp.
Bartonella sp. (cat scratch fever)
Agents of bacterial endocarditis
Toxoplasma gondii
Mycoplasma pneumonia
Trichinella spiralis (trichinosis)
Rickettsia rickettsii (Rocky mountain spotted fever)
Rickettsia prowazekii (typhus)
Ehrlichia chaffeensis
Agents of human granulocytic ehrlichiosis
Babesia sp.
Chlamydia trachomatis
Angiostrongylus cantonensis and Baylisacaris procyonis (eosinophilic meningitis)

Parameningeal conditions
Sinusitis
Epidural or subdural empyema
Mastoiditis
Dermoid or epidermoid cyst
Cranial osteomyelitis
Brain abscess
Infection or inflammation related to ventricular shunts
Posterior fossa surgery

Drugs
Trimethoprim-sulfamethoxazole
Ibuprofen, Sulindac, Tolmentin, Naproxen
Azathioprine
Sulfasalazine
Ciprofloxacin
Amoxicillin
Isoniazid
Carbamazepine
Chemical meningitis from drugs or radiographic agents instilled in CSF

Biological products
Murine monoclonal antibody OKT3
Intravenous gammaglobulin (IVIg)
Influenza vaccine (killed virus)

Systemic or immunologically mediated diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Polyarteritis nodosa
Granulomatous arteritis
Mixed connective tissue disease
Sjogren syndrome
Lymphomatoid granulomatosis
Wegener granulomatosis
Sarcoidosis
Behçet disease
Kawasaki disease
Mollaret meningitis
Vogt–Koyanagi–Harada syndrome
Familial Mediterranean fever
Status epilepticus

Neoplastic diseases
Leukemia
Carcinoma
Lymphoma
Craniopharyngioma
Teratoma
Astrocytoma
Meduloblastoma

Source: Table was modified from Davis (1997).

Table 102.3. Prodromes and methods of diagnosis of CNS viruses

Virus	Prodromes	Virus isolation	Polymerase chain reaction and serology
Enterovirus	None or mild gastroenteritis, pharyngitis syndrome or hand–foot–mouth syndrome for 1–3 days	**CSF, throat, stool**	**PCR assay available** Acute, convalescent sera
Mumps	Parotitis or occasional orchitis for 2–10 days	**CSF, throat**	PCR assay is research **Acute, convalescent sera**
Herpes simplex	Genital vesicles for 1–7 days	**Genital lesions** CSF	**PCR assay available** Acute, convalescent sera for primary type 2 infection
Arboviruses	Fever, rash, malaise, myalgia for 1–5 days	–	**Acute serum IgM antibody capture enzyme immunoassay** **Acute, convalescent sera**
Human immunodeficiency	'Flu-like' syndrome with arthralgia, myalgia, maculopapular truncal rash, lymphadenopathy 2–6 weeks after HIV exposure	CSF, blood	**PCR assay available** **Serology positive 4–6 weeks after primary infection**
Lymphocytic choriomeningitis	Fevers, 'flu-like' syndrome for 5–21 days	CSF, blood	PCR assay is research **Acute, convalescent sera**
Poliovirus	Gastroenteritis, myalgia for 1–2 days	**Stool, throat**	**Acute, convalescent sera**
Varicella-zoster	Chickenpox or zoster rash for 1–5 days	**Skin vesicles** CSF	**PCR assay available,** **Acute, convalescent sera**
Parainfluenza	Cough, myalgia for 1–4 days	CSF, throat	Acute, convalescent sera
Rotavirus	Gastroenteritis for 1–5 days		**Stool, CSF for rotavirus antigen immunoassay**
Adenovirus	Cough, pharyngitis, pneumonia, conjunctivitis for 1–4 days	CSF, **throat**	PCR assay, experimental Acute, convalescent sera
Rubeola	Cough, coryza, conjunctivitis, rash for 1–7 days	**Throat,** blood lymphocytes	**Acute, convalescent sera**

Notes:
Boldface indicates the most common methods of making diagnosis.

bacterial, tuberculous, or fungal meningitis. Once the illness is determined to be an aseptic meningitis, efforts should be made to determine the etiology (see Tables 102.2 and 102.3).

The decision whether to hospitalize the patient or treat the patient as an outpatient varies. Experience in emergency rooms has shown that the diagnosis of aseptic meningitis can usually be correctly made and the older child or adult can be managed as an outpatient (Waisman et al., 1999). In general, hospitalization should be considered in neonates, infants, elderly, or immunosuppressed individuals in which the clinical features of more serious forms of meningitis may be masked. As noted above, patients with CSF containing predominantly neutrophils or depressed glucose levels are usually hospitalized and treated for possible bacterial meningitis for the first day until the repeat lumbar puncture shows the typical pattern of viral meningitis or the PCR assay for enterovirus or mumps virus returns positive. Detection of enterovirus RNA in CSF by PCR assay often allows for shortening of hospital stays.

The majority of cases of viral meningitis are brief, self-limited and do not benefit from antiviral treatment. Patients with severe meningitis from herpes simplex virus, type 2, respond to acyclovir at an oral dose of 200 mg/day five times a day for 5 days (DeBiasi & Tyler, 2000). For maximum benefit, the acyclovir must be started as early as possible in the clinical course. However, most patients with herpes simplex viral meningitis do well without acyclovir treatment. Pleconaril is a new antiviral drug designed to block enteroviruses from attaching and entering a host cell

Table 102.4. Signs and symptoms of viral meningitis

Common
Fever
Headache
Stiff neck
Anorexia, nausea, vomiting
Photophobia
Irritability
Relative preservation of mental status
Uncommon
Lethargy
Seizures
Rare
Focal neurological signs
Papilledema
Babinski sign
Stupor or coma

Table 102.5. Distinguishing CSF features between viral and bacterial meningitis

CSF feature	Viral meningitis[a]	Bacterial meningitis[a]
White blood cells	Predominantly mononuclear	Predominantly neutrophils
Protein	Normal to mildly elevated	Elevated
Glucose	Normal to minimally depressed	Depressed
Gram stain of sediment	Negative	Positive
Bacterial culture	Negative	Positive

Notes:

[a] These CSF features are usually present but all the features will not necessarily be present in every patient.

(Pevear et al., 1999). Pleconaril is currently in clinical trials to determine its efficacy for the treatment of severe cases of enteroviral meningoencephalitis, especially in hypogammaglobulinemic patients.

If the headache is severe, use of analgesics may lessen the discomfort. Narcotics should be given cautiously as they may induce nausea and vomiting. If nausea or vomiting is prolonged and severe, antiemetics orally or rectally may help. Fever may be reduced by acetaminophen.

Prognosis

Most patients fully recover within 1 to 3 weeks (Sells et al., 1975; Lepow et al., 1962). Complications are rare. Obstructive hydrocephalus, deafness and cortical blindness have been reported in mumps meningitis (Thompson, 1979). Neonates and infants under 3 months have been reported to develop intellectual impairment, transient speech delay, or hyperactivity (Sells et al., 1975; Lepow et al., 1962).

Specific viral meningitis syndromes

Enterovirus meningitis

Enteroviruses comprise about 67 different strains, with a limited number of strains predominating each year in the United States, and account for over 80% of cases of viral meningitis in the United States (Rotbart, 1995). Enteroviruses are stable at room temperature, stable at acidic pH as low as 3.0, and resistant to lipid solvents because they lack a lipid envelope. These viruses are therefore well suited to survival in water and sewage. Infection

occurs by a fecal–oral route with primary replication occurring in the gastrointestinal or upper respiratory track (Jubelt, 1984; Rotbart, 1995). Most infections are asymptomatic or cause mild upper respiratory tract symptoms, rashes, gastroenteritic or hand–foot-and-mouth disease. Although transient viremia is common, only in about 1–5% of individuals does the virus cross the blood–CSF barrier to infect meningeal cells. The infected meningeal cells elicit an immune-mediated lymphocytic inflammatory response. Humoral and cellular responses to the virus usually eliminate the virus in CSF within 1–3 days. The exceptions are individuals with agammaglobulinemia who have difficulty eradicating the virus and experience a meningoencephalitis with prolonged viral persistence in CSF and stool (McKinney et al., 1987). While most enteroviruses cause only viral meningitis, a few strains such as enterovirus 71, are becoming recognized to cause a severe meningoencephalitis that can be fatal (Huang et al., 1999; Komatsu et al., 1999). Most causes of severe meningo encephalitis occur in infants less than 2 weeks of age. Spinal cord infections producing a flaccid limb paralysis occasionally are produced by enteroviruses (Figueroa et al., 1989).

The diagnosis of enterovirus meningitis is best done by PCR assay of CSF. The PCR test detects most strains of enterovirus, is recognized to have a sensitivity and specificity about 90%, and is considerably more sensitive than viral culture of CSF (Rotbart, 1995). Acute and convalescent serological studies are difficult to perform because of the many different strains of enteroviruses.

Herpes simplex virus, type 2 meningitis

HSV type 2 is the most common cause of neonatal herpes simplex encephalitis (Whitley, 1988). However, in adults this virus is mainly associated with viral meningitis that may be recurrent (DeBiasi & Tyler, 2000). In patients with primary genital herpes viral infection (usually from type 2 virus), viral meningitis develops in 11 to 36%. The virus becomes latent in sacral sensory ganglia and about 20% of patients with one episode of herpes simplex meningitis experience subsequent meningitic episodes that are usually milder and shorter in duration. This diagnosis should be suspected in sexually active adults with genital vesicles or in which the meningitis occurs in the winter or spring (periods when enterovirus infections are less common).

Viral infections of the brain

The term encephalitis implies a diffuse inflammation of the brain parenchyma. Viral infections represent the most common cause of encephalitis. In the United States, herpes simplex virus and arboviruses account for most cases, but other viruses also cause encephalitis (Table 102.1).

Table 102.6. Signs and symptoms of viral encephalitis

Common
Fever
Headache (dull), nausea, vomiting, malaise
Mental changes, confusion, delirium, lethargy, stupor
Seizures: generalized or focal
Hyperreflexia, Babinski signs, spasticity
Mild stiff neck
Less common
Coma
Tremors of arm or face, Parkinsonism
Hemiparesis
Aphasia
Cranial nerve palsies
Ataxia
Papilledema
Visual loss
Rare
Peripheral neuropathy

Epidemiology

Viral encephalitis occurs in all seasons but peaks in summer and early fall. The summer peak represents cases of arbovirus encephalitis from the bite of infected mosquito or tick. These vectors disappear in the winter as do cases of arbovirus encephalitis. The Centers for Disease Control and Prevention report from 1000 to 5000 cases of encephalitis per year with the number of cases varying depending on whether epidemics of arbovirus encephalitis developed. Viral encephalitis can occur at any age but the elderly and infants tend to have more severe encephalitis.

Clinical manifestations

The onset is usually abrupt, with the clinical course rapidly progressing over 1 to 3 days (Table 102.6 lists the most common signs and symptoms. The clinical features are similar for all forms of viral encephalitis but some distinguishing features can be recognized (Table 102.7). The strain of encephalitic virus determines the severity of the signs and symptoms (Table 102.8).

Table 102.7. Characteristic features of viral encephalitis in North America

Virus	Characteristic features
Most common causes	
Herpes simplex virus type 1	Sporadic, any season, all ages
La Crosse strain of California virus	Geographic restriction to upper midwestern and eastern states, occurs mainly in children, occurs summer and early fall, follows bite of infected *Aedes triseriatus* mosquito
St Louis encephalitis virus	Geographic restriction to midwestern and eastern states, occurs summer and early fall, follows vite of infected *Culex tarsalis* mosquito.
Western equine encephalitis virus	Geographic restriction to western states, occurs summer and early fall, follows bite of infected *Culex tarsalis* mosquito
Enteroviruses, esp. enterovirus 71	Prodromal rash, gastroenteritis, herpangina
Less common causes	
Eastern equine encephalitis	Geographic restriction to East and Gulf Coast, occurs summer and early fall, follows bite of infected *Culiseta melanura* mosquito
Colorado tick fever	Geographic restriction to Rocky mountain area, occurs spring and summer, follows bite of *Dermacentor andersoni* tick
Venezuelan equine encephalitis virus	Geographic restriction to Central America and south western states, follows bite of *Aedes* and *Culex* mosquitoes
Mumps virus	Parotitis and/or orchitis, often occurs during mumps epidemics in winter or spring in children who have not received mumps vaccine
Varicella-zoster virus	Often follows shingles by weeks, occurs in immunosuppressed individuals
Adenovirus	Often pneumonia, more common in children and individuals with hypoglobulinemia, serotypes 1, 6, 7, 12, 32 most commonly affect CNS
Herpes simplex virus type 2	Mainly occurs in neonates in first few weeks after vaginal delivery
West Nile virus	Common in Africa and parts of Europe. In the United States recently has occurred in the east coast area. Follows bite of a mosquito and has clinical picture similar to St. Louis encephalitis but has more flaccid paralysis
Least common causes	
Human herpes virus 6	Occasionally follows roseola infantum in children
Epstein-Barr virus	Infectious mononucleosis, adenopathy, pharyngitis
Powassan virus	Geographically restricted to upper midwest states, occurs in spring and summer, follows bite of infected *Ixodes cookei* or *marxi* tick
Cytomegalovirus	Occurs mainly in congenital infected newborns (congenital inclusion body disease) and immunosuppressed individuals, esp. AIDS
Rubeola virus	Occasionally follows measles in immunosuppressed individuals, more commonly causes acute disseminated encephalomyelitis
Reovirus	Rare cause of encephalitis that may follow enteritis in children
Nipah virus	Newly recognized virus in Indonesia that is associated with pigs and causes a severe encephalitis
Lymphocytic choriomeningitis virus	Follows exposure to infected pet hamsters and wild mice
Rabies virus	Follows bite of rabid animal (dog, skunk, raccoon, fox, bat, mongoose), pain and paresthesias of bitten limb may be first clinical sign

Notes:
Estimates on the frequency of the above infectious agents are based on the following clinical series (7,51–55) and the author's personal experience.

The geographical restriction implies the part of the world where the infectious agent is located in nature. If the patient has recently visited that area, that infectious agent should be included in the differential diagnosis.

Table 102.8. Mortality rate and frequency of neurologic sequelae in viral encephalitis

Virus	Approximate mortality rate (%)	Approximate rate of neurological sequelae (%)
Herpes simplex virus	70 untreated, 20–30 treated	90 untreated 50 treated
Arboviruses		
Eastern equine	20–40	30–50
Japanese B		
Russian spring summer		
Murray Valley		
Western equine	<20	5–20
St. Louis		
West Nile		
La Crosse		
Colorado tick fever		
Powassan		
Venezuelan		
Enteroviruses	<3	<10
Mumps virus	<1	<5
Varicella-zoster virus	50–80	>75
Rabies virus	99+	100

Notes:
Many of these figures are the author's estimates based on reviews of case reports since large clinical series of the less common types of infectious encephalitis are not available.

Laboratory Findings

The blood leukocyte count is often elevated. Blood urea nitrogen, creatine kinase, and transaminase levels may be elevated, particularly in arbovirus infections. A lumbar puncture shows a normal or elevated opening pressure. The CSF contains 5 to 300 WBC/mm^3, 50 to 200 mg/dl of protein, and normal glucose. Gram stain of CSF sediment is negative and bacterial cultures are sterile. The EEG is always abnormal and typically shows diffuse background slowing with occasional epileptiform or electrographic seizure activity (Gibbs et al., 1964). Early in the illness, MRI studies often show areas of increased signal intensity on T_2-weighted images. The CT scan may appear normal early in the clinical course with subsequent demonstration of areas of cerebral edema, necrosis or hemorrhage.

Differential diagnosis

The diagnosis of encephalitis must be distinguished from the more common encephalopathy (a general term implying diffuse dysfunction of the brain without inflammation) and acute disseminated encephalomyelitis (ADEM). Encephalopathies that may mimic encephalitis include metabolic (anoxia, hypoglycemia, hypatic, uremic, hyponatremia, endocrine), systemic infections (cerebral malaria, typhoid fever, Sydenham's chorea, Reye's syndrome, bacterial endocarditis, and critical illness (sepsis) encephalopathy), toxic substances (Wernicke's encephalopathy, sedating drug and aspirin overdoses, and arsenic intoxication), closed head trauma, hypertensive encephalopathy, paraneoplastic encephalomyelitis, central nervous system lupus erythematosus, and neuroleptic malignant syndrome (Davis, 2000). Acute disseminated encephalomyelitis or postinfectious encephalomyelitis will be discussed later in the chapter.

Diagnosis

The clinical diagnosis of infectious encephalitis is made on the following characteristics: (i) acute onset of fever and progressive mental status deterioration that may also include focal neurological signs and seizures (generalized or focal), (ii) CSF containing lymphocytic pleocytosis, normal glucose and elevated protein, (ii) abnormal MRI,

and (iv) abnormal EEG. Table 102.7 lists some characteristic features of the common viruses.

The specific etiology of the viral encephalitis is often made by (i) PCR assay of CSF, (ii) CSF IgM antibodies to some but not all viruses, (iii) virus isolation from throat or stool for some but not all viruses, (iv) acute and convalescent serum antibody titre rise, or (v) brain biopsy with virus culture. Virus is seldom isolated from CSF. Table 102.3 lists the recommended method of diagnosis for each virus. Unfortunately, most clinical series report up to 50% of cases of encephalitis in which no etiology was established (Koskiniemi et al., 1991; Studahl et al., 1998; Sivertsen & Christensen, 1996).

Management

Patients with encephalitis may rapidly deteriorate and become comatose. Therefore, patients should be hospitalized and placed in an area where they can receive intense nursing care. Patients should have a cardiac monitor as cardiac arrhythmias can develop. A determination should be made as to whether the patient requires isolation and, if so, what type of isolation. Patients with herpes simplex or arbovirus encephalitis do not require isolation. In both, virus is not present in body secretions and in arboviral infections, the viremia is too low a magnitude to transmit virus to a biting mosquito. However, patients suspected of rabies should be in isolation with saliva precautions. If a rash is present, isolation should be considered until a definite diagnosis can guide recommendation.

Treatment of symptoms for all patients includes control of seizures and elevated intracranial pressure (ICP). Seizures occur in 30–60% of patients and may be generalized or focal, single or multiple. If seizures develop, they should be treated promptly as seizures transiently elevate ICP, which could adversely affect the patient's cerebral blood flow. Lorazepam or diazepam can be given if seizures are multiple. Fosphenytoin or phenytoin can be administered I.V. in a loading dose to prevent further seizures.

Increased ICP usually develops a few days into the clinical course and may be elevated enough to impede cerebral blood flow or cause brain herniation. Treatment is difficult. Intubation and mechanical hyperventilation to keep the arterial Pco_2 between 25 and 30 torr and mannitol administration are the most commonly used methods (Chapter 125). Corticosteroids are controversial as they may inhibit the host immune response necessary to eradicate the infection. Patients may have excessive hypothalamic release of antidiuretic hormone leading to the syndrome of inappropriate antidiuretic hormone secretion with retention of free water, hyponatremia, and increase in cerebral edema (Brinker & Monath, 1980).

The acute clinical course usually lasts 1–2 weeks. During convalescence, patients often require physical therapy and speech therapy to regain their motor and verbal skills.

Prognosis

The mortality and morbidity rates vary greatly depending on the encephalitic virus as shown in Table 102.8.

Specific viral encephalitis syndromes

Herpes simplex encephalitis

Herpes simplex encephalitis (HSE) is important to diagnose rapidly as early administration of acyclovir definitely improves outcome. Herpes simplex virus (HSV), type 1, accounts for over 90% of HSE in children and adults. Herpes simplex virus, type 2, is the cause of most neonatal HSE.

In the United States, HSE is the most common sporadic encephalitis (Whitley, 1995) with an incidence of about 2 cases per 1 million individuals per year (Skoldenberg et al., 1984). HSE occurs in both sexes, at all ages, and at any time of the year.

The pathogenesis of HSE remains incomplete. The primary infection occurs in children and usually is a stomatitis and pharyngitis that resembles a 'strep' throat. Virus ascends sensory fibres from the mouth to reach the trigeminal ganglia where it becomes latent (Baringer & Swoveland, 1973). Spontaneous exacerbations occur frequently producing the typical 'fever blister' around the mouth.

HSE appears to develop by at least two routes. In newborn and young children who lack antibody to herpes simplex virus, a primary HSV infection in the oral pharynx rarely may reach the brain, possibly by infection of olfactory nerves in the nose (Ojeda, 1980). However, older children and adults usually have existing HSV antibody on admission suggesting that the encephalitis resulted from exacerbation of a latent viral infection. Davis and Johnson (1979) have hypothesized that latently infected ganglia in the second division of the trigeminal ganglia occasionally activate sending viral particles to one temporal lobe base via sensory fibres to that region.

Within the brain, HSV infects both glial cells and neurons often producing Cowdry type A intranuclear inclusion bodies. The virus spreads directly from cell to cell meaning that specific cellular immunity, not humoral

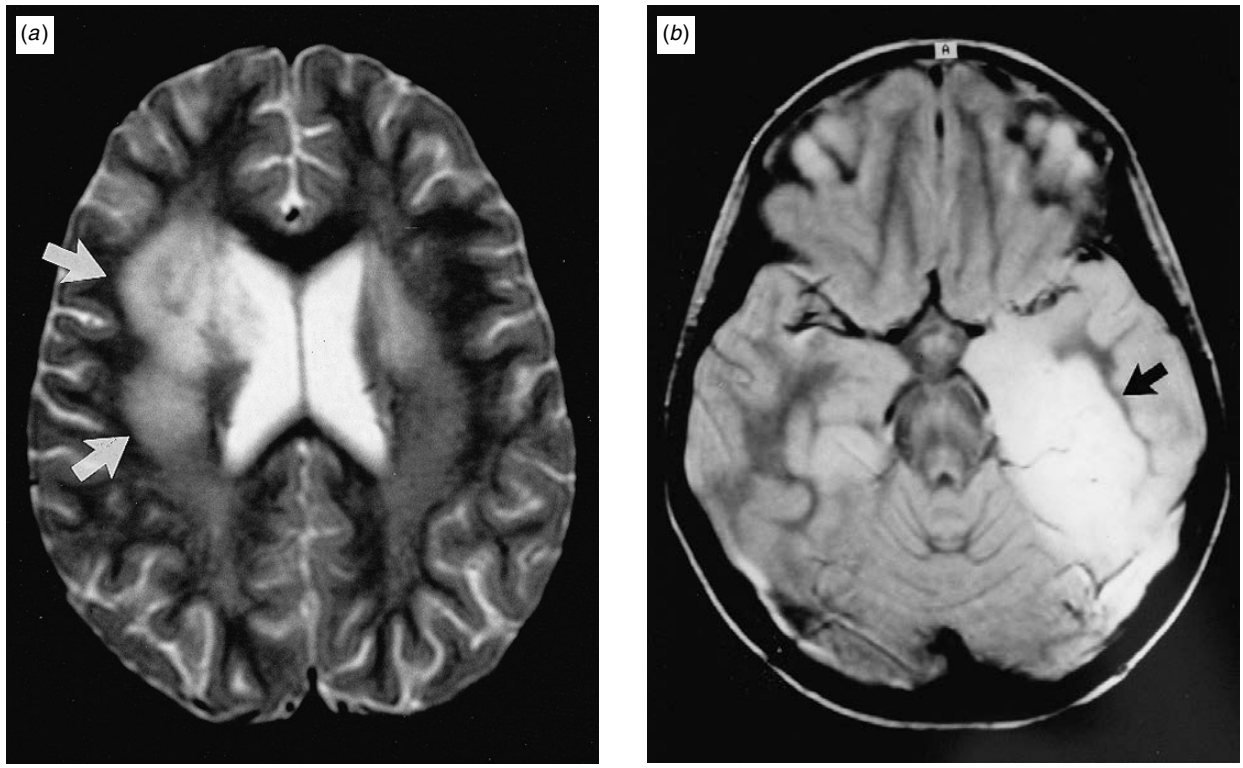

Fig. 102.1. (*a*) Acute disseminated encephalomyelitis in a 13-year-old child: T_2-weighted magnetic resonance image demonstrates multiple hyper intense lesions in cerebral white matter. (*b*) Herpes simplex encephalitis in a 40-year-old man: T_2-weighted magnetic resonance image demonstrates hyperintense lesion in the mesial temporal lobe. (From Davis, 2000.)

immunity, is essential to eradicate the infection. The infected brain regions show marked inflammation, necrosis and areas of focal hemorrhage.

There appears to be no set of symptoms or signs that clearly distinguishes HSE from other types of viral encephalitis. In two studies, cases of suspected HSE were confirmed by brain biopsy in only 50% (Whitley et al., 1986; Whitley & Lakeman, 1995). A history of 'fever blister' is of no diagnostic value because the majority of all adults occasionally experience 'cold sores'. Likewise, the presence of a 'fever blister' on admission or isolation of HSV from the mouth may occur in any type of encephalitis.

The onset is usually abrupt, with the clinical course rapidly progressing over 1 to 2 days. Table 102.6 lists the most common signs and symptoms. Although the encephalitis begins in the temporal lobe, acute memory loss occurs in only 20%.

With the advent of a PCR essay to establish the diagnosis of HSE, it is now recognized that a few patients with confirmed HSE have atypical clinical features. These patients have had a milder clinical course (with or without acyclovir), lack focal neurological signs, and progress at a slower rate than the classical disease (Fodor et al., 1998; Domingues et al., 1997).

Several laboratory values are abnormal but not specific for HSE. The peripheral white blood count may be elevated with a shift to the left but the total WBC is rarely above 20 000/mm^3. Liver and renal tests are usually normal. The CSF is similar to other infectious encephalitis but the CSF of occasional patients has red blood cells (10–500 cells/mm^3) or a mild hypoglycorrhachia (30–40 mg/dl). Only 5% of patients have a normal CSF (Whitley et al., 1989). HSV is rarely isolated from CSF (Nahmias et al., 1982).

Later in the clinical course, patients may develop a characteristic EEG pattern of high-voltage, periodic, lateralizing epileptiform discharges (PLEDS) at a rate of 2–3 Hz originating from the temporal lobe (Ch'ien et al., 1977). While PLEDS are suggestive of HSE, they are not diagnostic.

Magnetic resonance imaging (MRI) is often abnormal early in the clinical course and may suggest HSE. The MRI often demonstrates damage to the blood–brain barrier with accumulation of edema and necrosis in the medial aspect of a temporal lobe (Tien et al., 1993) (Fig. 102.1(*b*)).

In one clinical series, patients with HSE had 89% of their MRIs showing hyperintensity in the temporal lobe on T_2-weighted images compared to only 10% of other forms of encephalitis (Domingues et al., 1997). HSE lesions may also be seen in the orbital surfaces of frontal lobes, insular cortex, cerebral convexity, and cingulate gyrus. Lesions are seldom seen in the basal ganglia, brainstem or cerebellum. The CT scan is less sensitive and may be normal during the first few days of HSE. It then becomes abnormal with focal regions of hypointensity similar to the MRI and foci of hyperintensity due to small brain hemorrhages.

HSE should be clinically suspected if the (i) encephalitis occurs in winter or early spring, (ii) encephalitis occurs as an isolated case, (iii) MRI shows focal medial temporal lobe abnormality and (iv) EEG shows PLEDS. The diagnosis of HSE is confirmed by detection of fragments of herpes simplex viral DNA in CSF by PCR assay, or brain biopsy showing (i) diffuse inflammation with intranuclear inclusion bodies, (ii) identification of HSV particles by electron microscopy, (iii) viral antigen identification by immunohistochemistry, (iv) herpes simplex DNA fragments detected by PCR or (v) isolation of HSV from the tissue. The diagnosis of HSE is faster and easier with the development of widely available PCR assays for HSV. Current PCR tests detect HSV DNA in CSF in more than 95% of patients with HSE during the first week of the encephalitis (Lakeman et al., 1995). PCR assays are sensitive (more sensitive than viral isolation methods), rapid (assay usually completed within one day), and less expensive than other methods of diagnosis. While PCR assays are accurate, they require meticulous technique to avoid false positive or negative tests that can occur when hemoglobin or inhibitors, such as heparin, are present in the CSF.

Treatment with the antiviral drug acyclovir (acycloguanosine) has dramatically improved both the number of patients who survive and the quality of their survival. Acyclovir is relatively non-toxic to normal cells. The drug is effective because in the presence of thymidine kinase from HSV, acyclovir is monophosphorylated. Host cell thymidine kinases then phosphorylate the drug to its active triphosphate state, which inhibits DNA synthesis of the virus (Balfour, 1999). Development of resistance to acyclovir in the treatment of HSE has not been recognized.

The drug is most beneficial when given early in the clinical course and before the patient becomes comatose (Whitley et al., 1986). The standard dose of acyclovir is 30 mg/kg per day divided into 3 doses and given i.v. for 14 days. In immunosuppressed patients, the duration is often extended to 21 days to mimimize the risk of relapse. Drug complications are few and include thrombophlebitis at the needle site, elevation in serum transaminase levels, and transient renal failure from too rapid i.v. administration. When there is clinical suspicion of HSE, it is prudent to administer acyclovir immediately while awaiting PCR confirmation of the diagnosis.

When classical HSE is untreated, up to 70% of patients die and fewer than 3% resume a normal life (Whitley, 1995; Whitley et al., 1977). Early treatment with acyclovir can reduce the mortality rate to 20% to 30% (Skoldenberg et al., 1984; Whitley et al., 1986). Of survivors, 45% have a good to excellent outcome.

Arboviral encephalitis

There are more than 200 strains of arthropod-borne viruses (arboviruses) in the world. Arboviruses comprise alphaviruses, flaviviruses, and bunyaviruses and are responsible for miningitis, encephalitis, hemorrhagic fever, hepatitis and rashes. The majority of arbovirus strains occur in troptical regions. The normal life cycle of many arboviruses is between birds and mosquitoes. Man becomes an accidental host when bitten by an infected mosquito or tick. The same type of mosquito does not transmit all strains of arboviruses. Hence, there is a regional distribution of arboviral infections that depends on the location of the specific vector required for viral transmission. In other circumstances, such as West Nile virus, cases of encephalitis are developing in the USA east coast region because this arbovirus appears to have been recently introduced into the region (Asnis et al., 2000).

Killed virus vaccines are available to prevent Japanese B and Russian spring summer encephalitis viruses but human vaccines are not available for US strains.

Arbovirus encephalitis occurs only in the summer and autumn when the vector is present in the community. Over 95% of primary arbovirus infections result in an asymptomatic infection or a mild fever and myalgias (Monath, 1980). The encephalitis occurs in both sexes and at all ages. Some strains of arbovirus, such as St. Louis encephalitis virus, cause a more severe illness in the elderly (Southern et al., 1969) while Western equine encephalitis virus causes a more severe illness in infants and the elderly (Earnest et al., 1971). Geographical distribution and frequency of encephalitis of the North American arboviruses is listed in Table 102.7.

In the United States, an infected mosquito is the most common vector. During the bite, virus is inoculated into the subcutaneous tissue and blood vessels beneath the skin. Primary viral replication occurs in lymph nodes, spleen and endothelial cells resulting in a persistent viremia. In brain capillaries, some strains of arboviruses disrupt the blood–brain barrier by replicating within cerebral endothelial

cells. Hence, the resulting encephalitis begins in multiple areas throughout the brain. The incubation period for most arbovirus infections is from 4 to 21 days.

Within the brain, arboviruses cause a widespread infection of neurons and glia of the cerebral cortex, basal ganglia, brainstem, cerebellum and spinal cord. There is neuronal necrosis, perineuronal and perivascular edema inflammation (Adams & Weinstein, 1948). In severe cases, widespread necrosis and hemorrhage occur.

The viremia is terminated when the host produces antibodies (often around the first day of encephalitis). Eradication of virus from the brain usually requires both humoral and cellular immune reactions. Gliosis of damaged brain develops during recovery.

Some patients develop a prodromal illness of fever, nausea, malaise, and headache for several days before the encephalitis begins. Less than 10% of infected individuals develop encephalitis or meningitis. Table 102.8 lists the clinical signs of the acute encephalitis. Patients with West Nile viral encephalitis tend to be older (over 60 years) and usually develop the typical signs of encephalitis. However, about one-fourth of patients develop limb weakness from spinal cord infection (Nash et al., 2001). The encephalitis progresses rapidly over a few days and lasts 1 to 2 weeks (Brinker & Monath, 1980). The severity of the encephalitis depends on the strain of arbovirus (Table 102.7). Convalescence may take months, with patients often complaining of headache and fatigue.

Most patients have a moderate blood leukocytosis. The CSF shows typical changes for viral encephalitis. Virus is rarely isolated from CSF. The MRI usually shows multiple areas throughout the brain of hypointense signal demonstrating foci of edema and necrosis. The CT scan may be normal early in the illness and later can demonstrate areas of hypointensity (edema and necrosis) and hyperintensity (hemorrhages) in severe cases.

Clinical suspicion of arboviral encephalitis should be raised in an individual with encephalitis who develops the illness in summer or fall when the vector is present or is part of a cluster or epidemic of similar encephalitides. The diagnosis is established by: (i) detection of specific arbovirus IgM antibody in serum by IgM antibody capture immuno-assay (available for many US arboviruses), (ii) a fourfold or greater antibody titre rise to the arbovirus between the acute and convalescent serum samples, or (iii) isolation of virus from a brain biopsy. The diagnosis of arboviral encephalitis by PCR assay of CSF is currently experimental but may become more widely available.

There presently is no effective antiviral therapy available. Patients should be symptomatically managed as given above in the general encephalitis section.

The mortality and morbidity of arboviral encephalitis varies with the strain of virus (Table 102.8).

Rabies

Although rare in developed countries, rabies encephalitis kills up to 50 000 individuals per year mainly in Asia (Hemachudha & Mitrabhakdi, 2000). In the United States, infected bats are the major route of human transmission with some cases due to bites of infected raccoons, foxes, coyotes, skunks and dogs. In developing countries, infected dogs are the primary carriers along with mongooses and wolves. Following a bite of an infected animal, rabies virus replicates locally in muscle fibres to reach nerves in the muscle. The virus then infects the nerve endings and spreads retrograde in axons to reach the spinal cord and dorsal root ganglia. Once within the spinal cord or brainstem (via cranial nerves), the virus spreads widely throughout the brain by infecting neurons (Murphy et al., 1973). Virus then travels down nerves to reach salivary glands, where local replication also occurs producing infected saliva. The incubation period of rabies varies from a few weeks to over 1 year. It is unclear where the virus is located during the prolonged incubation period.

In contrast to most cases of virus encephalitis, the brain demonstrates little inflammation. As a consequence, the CT scan may appear normal. However, MRI often shows hyperintense signals in the brainstem, thalamus, hypothalamus, and spinal cord. The CSF usually has a minimal lymphocytic pleocytosis, mildly elevated protein level and normal glucose level.

The clinical features of rabies are of two types: furious and paralytic (dumb) rabies. In both, some patients may experience a prodrome of fever, burning, numbness, paresthesias or local myalgias around the wound that progresses to involve the entire limb. About 80% of patients develop furious rabies, which is characterized by periods of agitation, confusion, excessive motor movements, muscle spasms, vocal cord paralysis, seizures, focal limb paralysis, and coma. Hydrophobia (violent, jerky contracting of diaphragm and accessory muscles of inspiration triggered by attempts to swallow liquids) occurs in about half the patients. Abnormalities of the autonomic nervous system are common. Paralytic or dumb rabies presents with an ascending paralysis that resembles the Guillain–Barré syndrome.

The diagnosis should be suspected in an individual who has been bitten or scratched by a suspected rabid animal and develops signs consistent with furious or paralytic rabies. The risk of developing rabies in an individual who is bitten by a rabid animal but never receives rabies immu-

Table 102.9. Infections and vaccines associated with acute disseminated encephalomyelitis

	Vaccines
Viruses	
Rubeola (measles)	Rabies (especially non-cell culture vaccines)
Varicella-zoster (chickenpox)	Measles
Rubella	Yellow fever
Mumps	Japanese B
Epstein–Barr (infectious mononucleosis)	Rubella
Influenza A and B	Influenza
Enteroviruses	Diphtheria–pertussis–tetanus (DPT)
Hepatitis A and B	Smallpox
	Tetanus
Bacteria	Hepatitis B
Mycoplasma sp.	
Borrelia burgdorferi (Lyme disease)	
Salmonella typhi (typhoid fever)	
Legionella cincinnatiensis (Pontiac fever)	

nization is about 50%. The diagnosis is established by (i) identification of the virus (isolation from brain or saliva, PCR assay of salivia, (ii) detection of viral antigen by immunohistochemical staining of nuchal skin biopsy or corneal impression smear or (iii) identification of rabies virus antibody in serum of an unimmunized individual (Hemachudha & Mitrabhakdi, 2000). Unfortunately, rabies antibody may not be present early in the hospital course.

There are no antiviral drugs presently available and virtually all patients who develop neurological symptoms die. As such, prophylaxis is the only mechanism to prevent rabies. The criteria from the Advisory Committee on Immunization Practices for unvaccinated individuals with single or multiple bites from a suspected or confirmed domestic or wild animal or animal unavailable for observation, state that one should immediately administer rabies immunoglobulin (preferably of human origin) locally at the site of the wound and then vaccinate with rabies vaccine (preferably a live attenuated tissue culture vaccine) (see ACIP, 1999 for details and other postexposure treatment recommendations).

Postviral encephalomyelitis or acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM), a monophasic syndrome that predominately affects CNS white matter, usually follows a systemic, often viral, illness or a vaccination by 1–3 weeks (Tyler, 1951; Siriam & Steinman, 1984; Miller et al., 1956). Although some patients experience diverse clinical signs from multiple widespread white matter lesions, others develop signs referable only to one part of the nervous system, such as cerebellar ataxia, optic neuritis, or transverse myelitis. ADEM is thought to account for about 20% of all encephalitis cases. The majority of cases occur in children. Childhood infections such as measles, mumps, chickenpox, and rubella and vaccines are associated with most cases (Table 102.9). Worldwide, rubeola (measles) infections have the highest incidence and are thought to produce ADEM in 1 per 1000 measles cases (Johnson, 1998).

The pathogenesis of ADEM is currently thought to be immune mediated rather than conventional viral replication in brain cells. Details are covered in Chapter 98. The brain pathology is characterized by perivenular inflammation (perivascular cuffing) and adjacent demyelination that is all of the same age.

The clinical onset is abrupt and usually occurs towards the end of the predisposing illness or 1–4 weeks after vaccination. Patients develop a monophasic illness characterized by depression of mental status, seizures, headaches, and focal neurologic signs that include hemiparesis, visual loss, ataxia, etc. Less common signs include choreoathetosis, myoclonus, and cranial nerve palsies. Table 102.10 lists some differences between ADEM and infectious encephalitis that may be helpful.

The MRI in over 50% of patients demonstrates lesions in the subcortical white matter, corona radiata, and centrum semiovale (Murphy et al., 1999). Multiple areas of hyperin-

Table 102.10. Comparison of acute disseminated encephalomyelitis and infectious encephalitis

	Acute disseminated encephalomyelitis	Infectious encephalitis
Clinical features		
Most common age	Children	Any age
Recent vaccination	Common	Uncommon
Prodromal illness	Usually	Occasionally
Fever	May occur	Common
Visual loss (one or both eyes)	May occur	Uncommon
Spinal cord signs	May occur	Uncommon
Laboratory findings		
Blood	Leukocytosis occasionally occurs	Leukocytosis common
MRI (T_2-weighted)	Multiple focal areas of hyperintensity that are the same age and involve white matter of both hemispheres, basal ganglia, brainstem, cerebellum and spinal cord	Areas of hyperintensity involving grey matter of both cerebral cortices and its underlying white matter. To a lesser extent, basal ganglia, brainstem and cerebellum.
Culture of virus from brain	Rare	Common
Brain pathology	Perivenular inflammation, adjacent demyelination and edema	Perivascular inflammation, brain inflammation, neuronal and glial cell necrosis, edema, and inclusion bodies in some infections.

tensity on T_2-weighted and FLAIR images are seen that range from less than 1 to 4 cm in diameter, are the same age and involve white matter of both cerebral hemispheres (Fig. 102.1(*a*)). Up to 50% of patients also will have lesions in the thalamus, caudate, putamen (often bilateral), and in cerebellar white matter. Less than 10% develop lesions in the spinal cord. T_1-weighted lesions are hypointense and occasionally enhance with administration of gadolinium. Individuals with only cerebellar ataxia are the least likely to have abnormal neuroimaging (Connolly et al., 1994; Murphy et al., 1999). The CSF usually shows a lymphocytic pleocytosis, elevated protein and normal glucose but can be normal in up to one-third of patients.

General management of a patient with ADEM is similar to a patient with infectious encephalitis. Although there is no proven specific treatment for ADEM, many clinicians attempt to reduce or suppress the immune reaction through administration of corticosteroids (Straub et al., 1997), plasmapheresis (Kanter et al., 1995), or immunoglobulins (Nishikawa et al., 1999). Presently, many patients are treated with high dose intravenous mythylprednisolone in doses similar to those used to treat acute attacks of multiple sclerosis. Support of this treatment consists of case reports (Hauley, 1998). However, small series of ADEM patients treated with oral corticosteroids have reported no benefit (Swanson, 1956).

Recovery from ADEM often takes weeks to months depending upon the maximum severity of signs. Children often require rehabilitation for problems of weakness, hemiparesis, ataxia, mental confusion and behavioural changes. The neuroimaging abnormalities resolve slowly over months and may remain abnormal for prolonged periods after the patient has completely recovered. Mortality rates range from 5% to 25% and neurological sequelae are reported in 5% to 35% of survivors (Tyler, 1951; Siriam & Steinman, 1984; Miller et al., 1956).

Rare patients develop a more fulminant disease called acute hemorrhagic leukoencephalitis (AHLE) (Adams et al., 1949). This disease is clinically more severe than ADEM with coma, seizures and focal neurologic signs developing. Treatment of AHLE generally has been similar to that of ADEM (Byers, 1975). However, the mortality rate is about 50% and survivors are often left with seizures, mental retardation and focal neurological signs.

Optic neuritis

Optic neuritis has been associated with several viruses including measles, mumps, Epstein–Barr, and varicella-zoster (Bradley, 1967). Visual symptoms usually begin at the termination of the viral infection. Patients develop a rapidly progressive loss of central vision with falling visual

acuity. The visual loss is unilateral in three-fourths of patients. There is often drabness or desaturation of coloured objects (especially red). A light shown in the affected eye is perceived as less bright and triggers a weaker direct and consensual pupillary constriction than the same light in the good eye (Marcus Gunn phenomenon). The retina and disk are often edematous with blurred disk margins. Flame-shaped hemorrhages may be seen in the retina. The CT is usually normal but T_2-weighted MRI images may demonstrate a focus of hyperintensity (edema) in the optic nerve. The CSF is usually normal.

Acute treatment with IV methylprednisolone (250 mg every 6 hours) for 3 days followed by oral prednisone (1 mg/kg for 11 days) has proven superior to treatment with oral prednisone alone (Beck et al., 1992). Most patients make a good recovery of 20/40 or better visual acuity, but some are left with a relative central visual deficit and some with colour desaturation. Some adult patients may have repeated attacks of optic neuritis or develop multiple sclerosis (Optic Neuritis Study Group, 1997). If the MRI demonstrates discrete lesions in subcortical white matter, the risk of subsequent development of multiple sclerosis is increased to about 50%.

Subacute and chronic viral infections

Although most CNS viral infections either kill the patient or are eradicated by the host's immune system within 2 weeks, some viruses can produce a persistent or chronic infection of the brain. The resulting infection often produces severe, often fatal, progressive CNS damage (e.g. rubeola virus in subacute sclerosing panencephalitis or J C papovavirus in progressive multifocal leukoencephalopathy), but occasionally the virus can persist producing limited brain damage (e.g. HIV virus). Immunosuppression of the host predisposes to a chronic viral infection but rubeola virus (measles) can persist in the brain of immunocompetent individuals. Below are several forms of chronic viral infections.

Subacute sclerosing panencephalitis (SSPE)

This childhood disease follows a typical measles infection with rubeola virus with a latency of months to years. Early in the clinical course, children develop personality changes becoming more irritable and having difficulty in concentrating (Dyken, 1985). There is no fever or nuchal rigidity. The illness progresses over months with the child developing dysarthria, myoclonic jerks, hyperkinesia and ataxia. School performance deteriorates. By 6–12 months, the child becomes demented, blind and spastic. The EEG often demonstrates a characteristic pattern of slow and sharp waves occurring at 3 to 10 second intervals. The CSF has a mild lymphocytic pleocytosis, normal glucose, elevated total protein, elevated gammoglobulin, and the presence of oligoclonal bands.

The diagnosis is usually made by identification of very high rubeola virus antibody titres in CSF. Rubeola virus has been difficult to isolate from CSF or brain but cultivation of brain with permissive tissue culture cells can result in a rubeola virus isolate that is highly cell associated and has mutations resulting in failure to produce M, H and F viral proteins (Cattaneo et al., 1988). The pathogenesis of how wild rubeola virus mutates to cause SSPE is unclear. No antiviral drugs have yet to prove effective. SSPE is usually fatal within 12 months but occasional cases with arrest in the disease progression have been reported. In countries where the measles vaccine is administered to children, SSPE has practically disappeared.

Progressive multifocal leukoencephalopathy

The JC virus, a human polyomavirus of the family papovaviridae, is the cause of progressive multifocal leukoencephalopathy (PML). About 75% of normal adults have antibodies to this virus from a prior asymptomatic infection. The virus appears to become latent in the kidney and other unknown sites. In the presence of immunosuppression from AIDS, chronic leukemia, Hodgkin's disease, lymphomas, systemic lupus erythematosus, or immunosuppressive drugs, the virus appears to reactivate and infect oligodendroglia producing intranuclear inclusion bodies and resulting in poor or absent myelin production with multiple foci of demyelination and infects astrocytes giving them a bizarre appearance (Demeter, 2000).

Patients develop a progressive neurologic illness that is insidious and lacks signs of systemic illness, fever, headache or elevated white blood cell count. Neurological signs and symptoms usually indicate multifocal lesions involving both hemispheres, brainstem, and cerebellum (Berger et al., 1987; Brooks & Walker, 1984; Krupp et al., 1985). Common signs include a progressive hemiparesis, visual field deficits, ataxia, aphasia, cranial nerve palsies and cognitive impairment. The CSF is usually normal. MRI scan is usually abnormal with the presence of one or more hyperintense areas in the white matter on T_2-weighted images (Mark & Atlas, 1989).

The diagnosis is established by brain biopsy with characteristic histopathology. In the presence of an appropriate clinical setting with MRI or CT brain lesions, the presence of JC virus genome fragments detected in CSF by PCR assay

is highly suggestive (McGuire et al., 1995; Demeter, 2000). However, a negative PCR assay does not rule out PML and a positive PCR assay in CSF occasionally can occur in immunosuppressive patients without clinical disease. No antiviral drug has proven efficacy but cidofovir is currently being studied in an open label trial (Demeter, 2000). Most patients die within 6 months of diagnosis, but occasional patients have spontaneous disease fluctations for up to 3 years.

Varicella-zoster encephalitis

The most common CNS complication of varicella-zoster virus (chickenpox) is cerebellar ataxia that develops about 1 week after the chickenpox rash onset in immunocompetent children (Connolly et al., 1994). Neuroimaging is usually normal. The ataxia usually clears within weeks.

In immunosuppressed individuals, more serious encephalitis can develop days to months after an episode of shingles. The main pathology is a vasculitis involving medium and small blood vessels of the CNS resulting in multiple brain infarctions mainly in subcortical white matter (Amlie-Lefond et al., 1995). Varicella-zoster virus also infects adjacent oligodendroglia producing intranuclear inclusions.

Patients develop an insidious progressive illness characterized by headache, fever, cognitive impairment, seizures, and focal neurological deficits relative to the brain infarctions (Gilden et al., 2000a,b). Other patients may develop acute stroke symptoms from large artery granulomatous arteritis following shingles most often in the trigeminal distribution (Gilden et al., 2000a,b).

The diagnosis is usually made by detection of varicella-zoster DNA in CSF by PCR assay (Gilden et al., 2000a,b) or by intrathecal synthesis of varicella-zoster virus antibody, especially of the IgM class (Gilden et al., 1998). The diagnosis can also be made from brain biopsy with characteristic histopathologic changes, identification of varicella-zoster antigen within blood vessel walls or oligondendroglia, or detection of viral DNA in tissue by PCR assay.

Patients should be treated with acyclovir (1500 mg/m^2 per day divided into 3 doses i.v., which is usually 30 mg/kg per day in adults) for 14–21 days (Gilden et al., 2000a).

Viral infections of the spinal cord

Viral infections of the CNS not infrequently include the spinal cord. The resulting infection can result in a diffuse spinal cord infection (myelitis or poliomyelitis) or an infection or immune reaction localized to one part of the spinal cord (transverse myelitis).

Paralytic poliomyelitis

Paralytic poliomyelitis is the classic infection of the spinal cord. The majority of cases are from infection with polioviruses, serotypes 1, 2, and 3 although occasional cases are associated with other enteroviruses and arboviruses (Figueroa et al., 1989). In particular, the cases of West Nile encephalitis in the USA east coast region commonly have a flaccid paralysis (Asnis et al., 2000).

Until recently, polioviruses were found worldwide. With the success of poliovirus vaccination programs, cases of paralytic poliovirus are now confined mainly to Asia and Africa. Like other enteroviruses, poliovirus spreads through contaminated water. In temperate climates, epidemics have occurred mainly in the summer. Cases of paralysis mainly occur in children.

Following ingestion of poliovirus by a non-immune individual, the virus replicates initially in the oral pharynx and intestine. Secondary replication occurs in tonsils, Peyer's patches and lymph nodes producing a viremia. Over 95% of primary infections are asymptomatic or result in mild gastroenteritis. Only 1% of infected patients develop spinal cord infection with paralysis and 1–2% develop viral meningitis. The virus reaches the spinal cord most likely from the viremia but in experimental animals poliovirus can reach the spinal cord via retrograde axoplasmic flow in peripheral nerves. In the spinal cord, necrosis and loss of neurons occurs mainly in the anterior horn accompanied by inflammation and perivascular cuffing with lymphocytes. Occasionally, virus spreads to the brainstem tegmentum, precentral cortex, and hypothalamus.

After an incubation period of 9–12 days, the illness begins with fever, headache, malaise, nausea and back stiffness (Price & Plum, 1978; Melnick, 1996). Weakness with myalgia begins 1–2 days later. The pattern of weakness is asymmetrical with more involvement of legs than arms and proximal muscles more than distal muscles. Muscle tone is flaccid and reflexes are hypoactive. Muscle atrophy begins about a week after the onset of weakness and continues for several weeks. About 5–20% of patients develop involvement of cranial nerves X, IX, and VII resulting in pharyngeal, laryngeal and facial muscular weakness. In some patients with involvement of thoracic and bulbar muscles, breathing is impaired to the point of requiring mechanical ventilation.

The blood may be normal or show a mild leukocytosis. CSF typically contains 20–200 WBC/mm^3 with a mildly elevated protein level and normal glucose level. The MRI

demonstrates areas of hyperintensity within the spinal cord, particularly in the lumbar region.

The diagnosis should be suspected in an individual who develops acutes progressive asymmetrical limb paralysis with a CSF pleocytosis. Virus can easily be isolated from the throat or stool but only occasionally from CSF. The virus isolate should be sent to reference laboratories, such as the Centers for Disease Control and Prevention, to determine whether the isolate is wild type or vaccine-like. In the United States, use of the live oral poliovirus vaccine was associated with 1–5 cases of paralysis each year. Currently, most advisory committees are recommending use of the killed vaccine that could eliminate vaccine-associated cases. Poliomyelitis also causes a diagnostic four-fold or greater rise in neutralizing or complement fixing antibodies between acute and convalescent serum specimens (Melnick, 1996).

Acute treatment requires hospitalization with careful monitoring for respiratory failure and the necessity of mechanical ventilation. Good hydration is required to prevent kidney stones. Rehabilitation is clearly beneficial.

Death occurs in about 8% of patients from bulbar involvement. In most patients, recovery begins in several weeks. By 6 months, 80% of patients make a good to excellent recovery. Paralytic poliomyelitis can be prevented by vaccination before wild virus exposure with either killed or live attenuated poliovirus (Melnick, 1996).

A postpolio syndrome develops in about one-quarter of recovered paralysed patients 20 or more years later. These patients develop progressive weakness in their involved limbs and fatigue. New muscle weakness, fasciculations, cramps, and dysarthria may be seen. Patients may also develop arthritis, tendinitis, and ligament strain from chronic incorrect posture and misuse of joints. Some patients develop increasing scoliosis, and occasionally swallowing difficulties (Dalakas et al., 1986). To date, a persistent poliovirus infection has not been demonstrated but there is histologic evidence of new active denervation and resulting muscle atrophy (Dalakas et al., 1984). It appears that during recovery from poliomyelitis, surviving motor units enlarge by sprouting terminals to reach the denervated muscle fibres. These enlarged motor units then become unstable years later (Johnson, 1965). Rehabilitation programs using mild to moderate exercise to strengthen weakened muscles do not seem to accelerate disease progression.

Transverse myelitis

Transverse myelitis may be due to an infectious agent or postinfectious immune-mediated process. The criteria for diagnosis is (i) acutely developing paraparesis, affecting motor and sensory systems as well as sphincters, (ii) spinal segmental levels of sensory disturbances, (iii) stable, nonprogressive clinical course after the acute phase, (iv) no evidence of spinal cord compression, and (v) absence of other known neurological diseases that affect the spinal cord such as syphilis, severe back trauma, multiple sclerosis, encephalitis, or malignant disease with spinal metastases (Berman et al., 1981).

Varicella-zoster virus following an episode of shingles by 1–2 weeks can produce an infectious paraparesis with a sensory level and sphincter impairment (Gilden et al., 2000a). The spinal cord viral infection occurs more commonly in immunosuppressed individuals. The CSF may be normal or show a lymphocytic pleocytosis and elevated protein level. MRI shows gadolinium enhanced areas within the spinal cord. While the diagnosis is often made solely on clinical grounds, varicella-zoster viral DNA has been detected by PCR in CSF. Varicella-zoster virus is rarely isolated from CSF. Treatment with acyclovir 15–30 mg/kg per day for 10–14 days appears beneficial but patients are often left with a mild to moderate paraparesis or quadriparesis.

Immune-mediated transverse myelitis has been associated with several viruses that include rubeola, mumps, influenza, Epstein–Barr, dengue, rubella and hepatitis. The rabies and smallpox vaccines have also been implicated (Hemachudha & Mitrabhakdi, 2000). With the older killed rabies (Semple) vaccine prepared from infected mouse or rabbit spinal cords, cases of transverse myelitis could occur as often as 1 per 600 to 6000 vaccinations. In fatal cases the spinal cord demonstrated perivenous demyelination and perivascular cuffing.

Patients should be hospitalized and placed in the intense care unit. Catheterization of the bladder is often necessary. High dose i.v. corticosteroids or immunoglobulins (polyclonal IgG) are often given but the evidence for benefit is anecdotal. About one-third of patients made a good recovery; one-third make a fair recovery; and one third make a limited recovery and are left with varying degrees of paralysis.

Viral infections of peripheral nerves

While viruses, such as herpes simplex and rabies, can infect peripheral nerves and travel within the axon, they do not produce significant damage to the nerve. Shingles, from varicella-zoster virus does damage peripheral nerves. In immunosuppressed individuals, such as AIDS, cytomegalovirus can cause an acute lumbosacral polyradiculitis

(So & Olney, 1994). Many viruses have been associated with immune-mediated Guillain–Barré syndrome.

Shingles or Herpes Zoster

The hallmark of shingles is a vesicular skin eruption that follows a unilateral dermatomal pattern. About half the eruptions appear in thoracic dermatomes and 25% develop over the face (Hope-Simpson, 1965). The skin eruption begins as a localized reddening of skin, followed by a maculopapular lesion that develops into a blister or vesicle about 2–3 mm in diameter (Burgoon et al., 1957). The vesicle then ruptures and becomes a pustule that crusts over and heals in 1–3 weeks. The number of vesicles can vary from few to hundreds. Pain, the second characteristic, follows the dermatomal distribution. The pain may be burning, lancinating (electric-like and brief), and allodynic (dysesthetic sensations triggered by light mechanical stimulation of the involved dermatome) (Watson et al., 1988). The pain usually subsides within 2–6 weeks as the lesions heal. Rarely, one may experience dermatomal pain without the skin eruptions (zoster sine herpete) (Lewis, 1958).

During the chickenpox skin infection, virus ascends the sensory nerves and becomes latent within dorsal root or trigeminal ganglia neurons. Years later, shingles results when the dormant virus reactivates, replicates in the ganglion, and travels down sensory root nerves in a dermatomal pattern (Gilden et al., 2000a,b). The incidence increases in individuals over age 60 and with illnesses that depress cellular immunity, such as Hodgkin's disease, leukemia and AIDS.

The diagnosis of shingles is usually clinically made in a patient with typical unilateral, painful vesicular rash that follows a dermatome. The diagnosis is confirmed by isolation of virus cells at the base of vesicles, by detection of viral DNA by PCR of vesicle fluid, by immunohistochemical identification of viral antigen in vesicle cells, or by identification of multinucleated giant cells by Giemsa staining of vesicle cells (Tzanck smear).

Treatment of acute shingles depends on the severity and location of the dermatomal rash and immunocompetence of the individual. Individuals with a mild rash may require only symptomatic treatment with non-narcotic analgesics. When shingles is severe or develops in the presence of immunosuppression, antiviral treatment is recommended with famciclovir (500 mg orally three times daily for 7 days) or valaciclovir (1 gm orally three times daily for 7 days). Both drugs are well tolerated with few side effects. In severe cases or where the virus has disseminated, acyclovir (5–10 mg/kg i.v. every 8 hours for 5–7 days) can be given (Gilden et al., 2000a,b). When these antiviral drugs are started within the first few days of rash onset, the drugs shorten the period of viral shedding from the vesicles and shorten the time to rash healing. The drugs may lessen the severity and duration of dermatomal pain, but it is unclear whether the drugs prevent postherpetic neuralgia. Treatment of the dermatomal pain is a challenge and may require ibuprofen, acetaminophen, or opiates depending on the severity. Carbamazepine (200 mg p.o. three to four times a day) may reduce lancinating pain (Killian & Fromm, 1968) and amitriptyline (25–50 mg P.O. twice or three times a day) or gabapentin (900–1800 mg/day divided into three daily doses) may reduce burning and allodynia pain (Max, 1994). Isolation is seldom required but vesicle fluid should be considered infectious. Shingles patients cannot give shingles to others but can spread chickenpox to children who have not had chickenpox or received the attenuated varicella-zoster virus vaccine.

Acute complications of shingles occasionally occur. Herpes zoster ophthalmicus develops in some patients with shingles involving the upper face. Ocular involvement cases severe eye pain with loss of vision. These patients should be seen by an ophthalmologist and given i.v. acyclovir and acyclovir eye drops as the inflammation may lead to monocular blindness, cicatricial lid retraction, ptosis, conjunctivitis, scleritis, uveitis, and chorioretinitis. Herpes zoster oticus occurs when varicella-zoster virus in the geniculate ganglia reactivates. Vesicles develop on the ear pinna and external auditory canal walls (Adour, 1994; Aleksic et al., 1973). Patients develop peripheral facial palsy resembling Bell's palsy. The facial nerve inflammation may spread to involve auditory and vestibular nerves. About 20% of patients develop tinnitus or hearing loss and 10% experience vertigo. Antiviral treatment is usually given. Recovery of facial muscles is usually good but may not be excellent. Recovery of balance and hearing usually occurs. Peripheral motor neuropathy develops in 3% of shingles patients most likely from virus spreading from the involved ganglion to involve the neighbouring mixed nerve. Slow recovery of the myotome muscle weakness usually occurs but 25% are left with residual weakness (Thomas & Howard, 1972).

A dreaded complication is postherpetic neuralgia. In this syndrome, pain in the affected dermatomal distribution persists, often for years. The pain is often severe and has marked allodynia characteristics such that the patients try to prevent clothing from touching the involved skin area. The pathogenesis of postherpetic neuralgia is unknown. The incidence is unusual following shingles in individuals under age 60 years but increases with advancing age. Treatment is difficult and often requires a combination of

opiates, carbamazepine, amitriptyline and gabapentin in doses described above. Use of capsaicin or lidocaine creams over the involved skin is occasionally beneficial.

Guillain-Barré syndrome

Idiopathic polyneuritis or Guillain-Barré syndrome (GBS) commonly follows a viral infection (Ropper, 1992). About 50% of patients experience an upper respiratory tract or gastrointestinal infection 1 to 3 weeks before the onset of weakness. Numerous viruses have been associated with GBS that include Epstein–Barr, hepatitis A, enteroviruses, hepatitis B, cytomegalovirus, herpes simplex, mumps, measles, rubella, HIV, and vaccinations with influenza A/New Jersey, mumps/rubella, and smallpox vaccines. Patients usually develop an ascending symmetrical progressive flaccid weakness beginning in the legs that progresses up to 2 weeks (Ropper, 1992). Some patients develop marked autonomic dysfunction or respiratory weakness sufficient to require mechanical ventilation. CSF is acellular but may contain elevated protein levels. Please see Chapter 67 for details of the clinical course, pathology and treatment.

Sudden deafness and acute vertigo

Mumps, measles, varicella-zoster, rubella, influenza, and herpes simplex viral infections have been associated in children and adults with the sudden development of deafness, unilateral hearing loss or acute vertigo (Okamoto et al., 1994; Adour, 1994; Davis & Johnsson, 1983). Syphilis may also cause the vertigo and deafness. Patients may complain of tinnitus, nausea or vomiting. Otitic pain is uncommon. High frequency hearing loss and/or hypoactive caloric response on the involved side is seen on objective testing. Treatment with the antiviral drug, acyclovir, has not shown benefit (Stokross et al., 1998). The vertigo usually resolves in weeks but the hearing loss is often permanent. Congenital viral infections with cytomegalovirus or rubella may produce severe bilateral hearing loss in newborn infants (Davis et al., 1981; Menser & Forrest, 1974). In occasional children with congenital cytomegalic inclusion disease, the hearing loss may suddenly worsen 5 to 20 years later (Stagno et al., 1977).

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103

Neurological manifestations of HIV infection

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Since the initial descriptions in 1981 of cases of a rare disease, *Pneumocystis carinii* pneumonia, among homosexual men in Los Angeles, AIDS has expanded to become a global pandemic. In the past two decades, millions of people worldwide have died of AIDS, and one in every 200 Americans is infected with HIV-1 (UNAIDS, 2000). Our concept of the biology of HIV infection has changed radically to a model of continuous active HIV replication throughout HIV infection (Ho et al., 1995). The introduction of highly active antiretroviral therapy (HAART) regimens in the mid-1990s has resulted in a 50% decline in AIDS death rate, decreased maternal–infant transmission rates, reductions in incidence rates of opportunistic infections (Fig. 103.1), and a 40–50% decrease in the incidence of HIV-associated dementia (Brodt et al., 1997). Nonetheless, AIDS-associated neurological diseases continue to be major causes of morbidity and mortality, and because the blood–brain barrier may prevent the CNS penetration of antiretroviral agents, the brain may serve as a sanctuary for HIV, with persistent HIV replication within macrophages and microglia, the principal target cells in the CNS.

Epidemiology of HIV infection and AIDS

The World Health Organization (WHO) estimates that worldwide there have been 13.9 million deaths from AIDS and the number of infected people reached 54 million in 2000 (UNAIDS Joint United Nations Programme on HIV/AIDS, 1998) with 16000 new infections occurring each day. In the USA, through June 1999, surveillance has identified 711344 cases of AIDS and 420201 AIDS deaths (Centers for Disease Control and Prevention, 1999) and 431924 Americans are estimated to be living with HIV/AIDS. The proportion of AIDS cases among women has increased from 8 to 23% with proportional decreases among homosexual men. Though the disease was first recognized in the USA among homosexual men and injection drug users, heterosexual contact now constitutes the most frequent risk factor worldwide. In developed countries, in utero transmission from mother to infant has been significantly reduced through the use of antiretrovirals during pregnancy (Connor et al., 1994). Blood products are now an infrequent source of HIV infection in the USA, with the risk of HIV infection estimated at 1 in 493000 units of blood (Schreiber et al., 1996). In 1995, AIDS surpassed cancer as the predominant cause of death in young Americans (25–44 years) in the USA (Centers for Disease Control and Prevention, 1995) but a 60% fall in death rates was seen in the US from 1996 to 1998, attributable to the use of combination antiretrovials (Palella et al., 1998). The results of clinical trials of combination antiretroviral therapy, and the subsequent widespread introduction of highly active antiretroviral therapy (HAART) have produced a new era of optimism for HIV-infected people, and their providers (Shapiro et al., 1999). For the majority of HIV-infected persons worldwide these expensive treatments are simply out of reach. Only financial support from developed countries will enable millions to receive antiretroviral treatment. The most frequent disease manifestations of AIDS include *Pneumocystis carinii* pneumonia, *Candida esophagitis* and HIV wasting syndrome (Table 103.1).

Biology of HIV infection

The virus

The retrovirus family, *retroviridae*, is composed of three major subfamilies: lentivirus, to which HIV

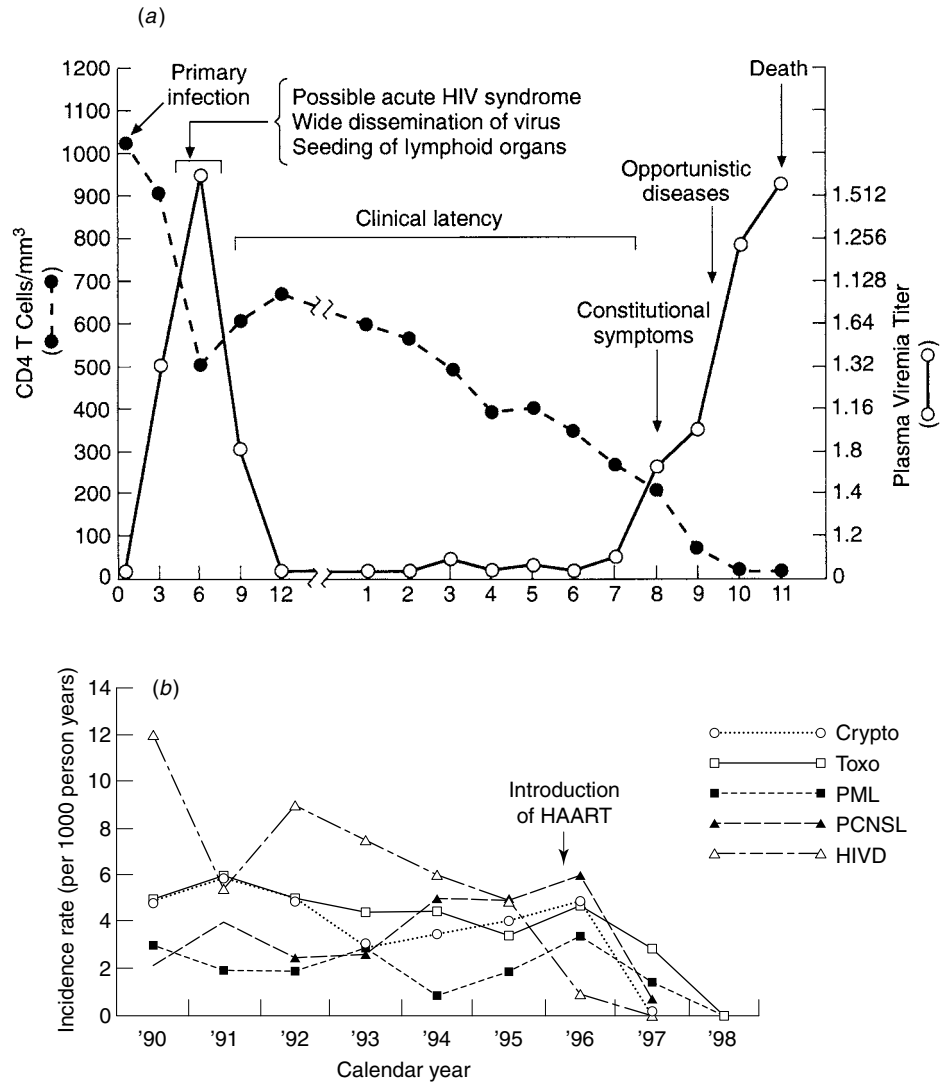

Fig. 103.1.(*a*) Relationship between neurologic disease and systemic disease stage. (*b*) Declining incidence of neurological diseases associated with HIV/AIDS (from Sacktor et al., 2000a).

belongs (lenti:slow); oncovirus, to which HTLV-1 belongs (onco:tumour); and spumavirus (spuma:foam). Of these three subfamilies, only members of the lentivirus and oncoviruses have been linked to neurological disease in humans. The retroviruses share genomic and morphological similarities and may have originally derived from an ancestral virus. The retroviruses include a number of RNA viruses which replicate in a unique manner; their other distinguishing characteristics are listed in Table 103.2. The lentiviruses or 'slow viruses,' of which HIV-1 is a member, share certain pathogenic similarities, and there are important parallels between human and animal lentivirus infections, because all lentiviruses cause an encephalitis (Johnson et al., 1988). All lentiviruses have evolved mechanisms by which they evade host defences and immune clearance and cause persistent infection. They share morphological and genomic characteristics, have long incubation periods, and are typically associated with chronic diseases. The lentiviruses comprise: visna virus, caprine arthritis encephalitis virus; equine infectious anemia virus; bovine immunodeficiency virus; and feline immunodeficiency virus. Human infection with HIV-2, murine immunodeficiency virus, and simian disease with SIV-1, which produces an AIDS-like syndrome after experimental inoculation in macaques, complete the currently recognized list. HIV-2 is a retrovirus distinct from HIV-1,

Table 103.1. Neurological complications of HIV-1 infection[a]

HIV-1-associated
HIV-1 encephalopathy
HIV-1 meningitis
Vacuolar myelopathy
Peripheral neuropathies
HIV-associated polymyositis
Opportunistic infections
Cerebral toxoplasmosis
Tuberculosis
Cryptococcal meningitis
Cytomegalovirus retinitis/encephalitis
Progressive multifocal leukoencephalopathy
Other fungal/bacterial CNS infections
Neoplasms
Primary CNS lymphoma
Metastatic systemic lymphoma

Note: [a] Not including toxicities of treatment.

Table 103.2(a). Common properties of lentiviruses

Contain RNA genome and reverse transcriptase
Host specific
Prolonged incubation period
Persistent infections in natural hosts
Restricted viral replication
Cytopathic effects in vitro
Infect cells of the immune system

Table 103.2(b). Differentiation of HIV dementia from opportunistic infections

Disorder	HIV dementia	CMV encephalitis	PML
Features	memory, mental slowing, gait	delirium, seizures, brainstem signs	focal neuro signs
Course	several months	days–weeks	weeks–months
Typical CD4 range	<500	<100	<100
MRI	diffuse atrophy/ diffuse hyperintensity in deep WM	normal or periventriculitis	subcortical WM lesions T_1 hypotense
CSF	non-specific: immune activation	PCR+90%	PCR+60%

which is prevalent in part of Western Africa, and is remarkably similar to SIV-1, which is endemic among sooty mangabeys (De-The et al., 1989). Evidence from phylogenetic analyses, prevalence data, and the geographic incidence of HIV-1 strains suggests that the AIDS pandemic most likely originated in Western Equatorial African during the early part of the twentieth century (Hahn et al., 2000). The most likely introduction of AIDS to humans occurred from the transmission of SIV viruses derived from chimpanzees and sooty mangabeys, probably from direct contact during the hunting and slaughtering of these primates. The theory that oral polio virus trials conducted in the Belgian Congo during the late 1950s may have used infected chimpanzee kidney cells has been discounted.

HIV is a non-transforming retrovirus that produces a cytopathic or lytic effect on T-cells, although the precise mechanisms for T-cell depletion are uncertain. The CD4 receptor is the principal target site for HIV; however, specific chemokine receptors appear to serve as important secondary cellular receptors for HIV (He et al., 1997; Premack & Schall, 1996). Additionally, specific lectins on dendritic cells may serve to stabilize HIV for later presentation to susceptible T-lymphocytes or monocytes (Steinman, 2000). HIV-1 strains have been divided into T-tropic (preferring to replicate in T-lymphocytes) and M-tropic (preferring macrophages) on the basis of in vitro experiments. In vivo, the M-tropic (or R5) strains predominate in early infection, while the T-tropic (R4) strains evolve later, usually with advanced disease. Chemokine receptor usage is different for each, with T-tropic viruses making use of CD4 and CXCR4 (or fusin, the receptor for SDF-1), and M-tropic viruses using CCR5 (the receptor for RANTES) (Fig. 103.2).

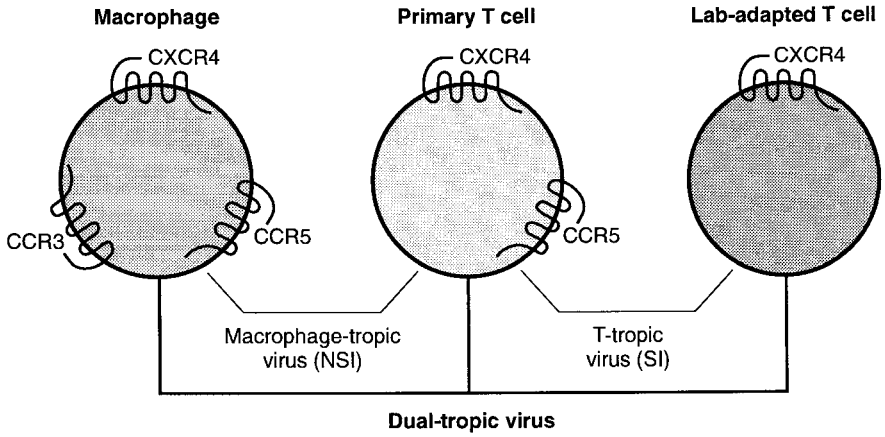

Fig. 103.2. Patterns of chemokine receptor usage for HIV-1 (from McArthur, 2000).

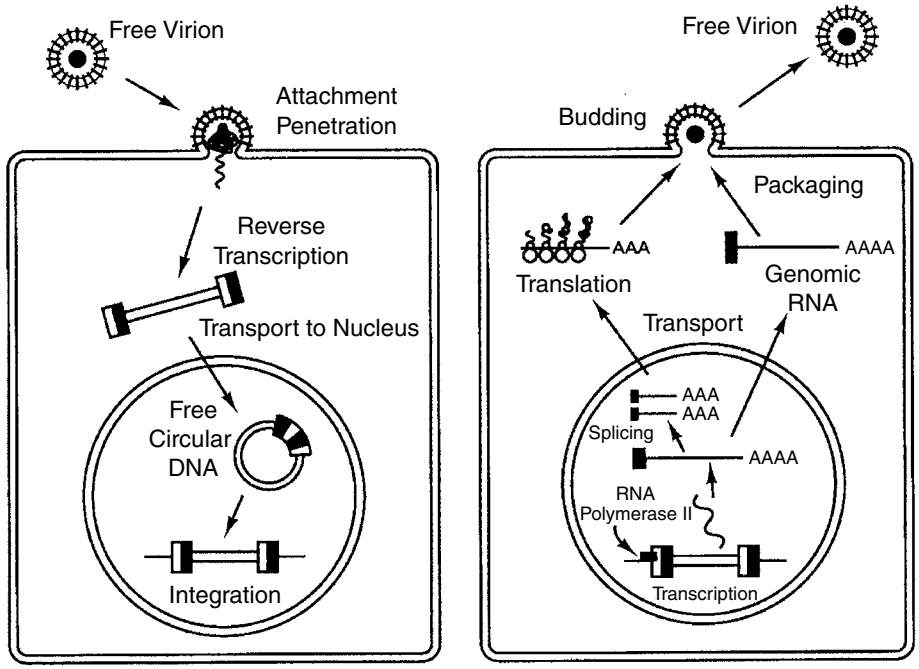

Fig. 103.3. HIV-1 life cycle: stages of HIV-1 replication (from Harrrison & McArthur, 1995).

A genetic variant of CCR5, Delta32, has been found to be protective against HIV infection in homozygotes and to delay disease progression in heterozygotes (Kostrikis et al., 1998; Barroga et al., 2000).

HIV structure and life cycle

HIV and other retroviruses can be distinguished from other viruses because they carry a unique pair of enzymes; first, an RNA-dependent DNA polymerase (reverse transcriptase), which uses RNA as a template to make a complementary DNA strand, and a second enzyme (a ribonuclease) which breaks down the original RNA strand, thus allowing a complementary DNA strand to be synthesized on the remaining DNA strand. After the double-stranded DNA has been synthesized, it is incorporated by the enzyme integrase into the host cell DNA and replicates with it (Fig. 103.3). Once integrated into the host cell genome, it is termed a provirus, and may remain latent for months or years, without affecting cellular function. With

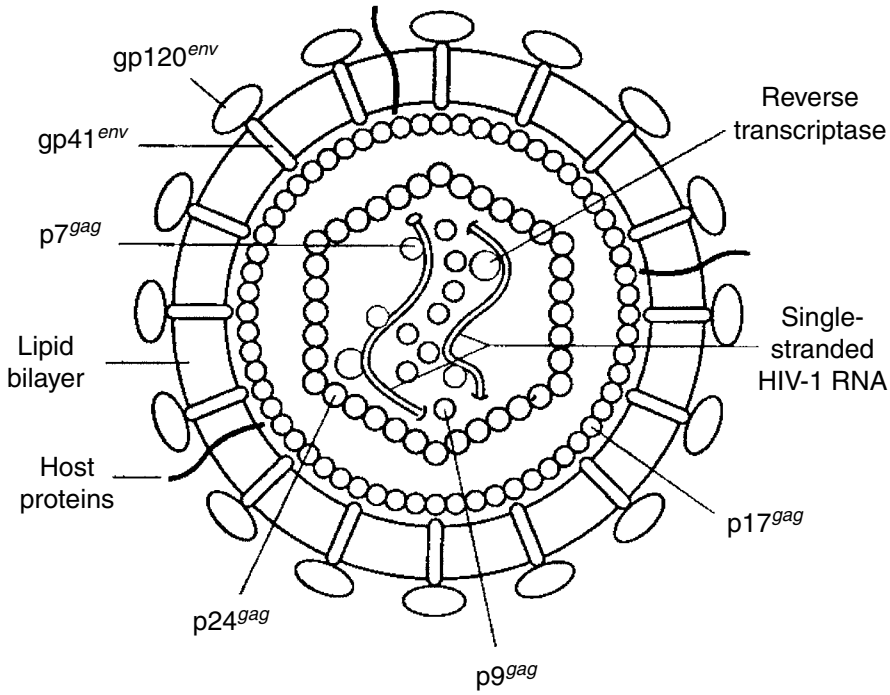

Fig. 103.4. HIV structure. Structure of the HIV virion (from Harrison and McArthur, 1995, after Greene, 1991).

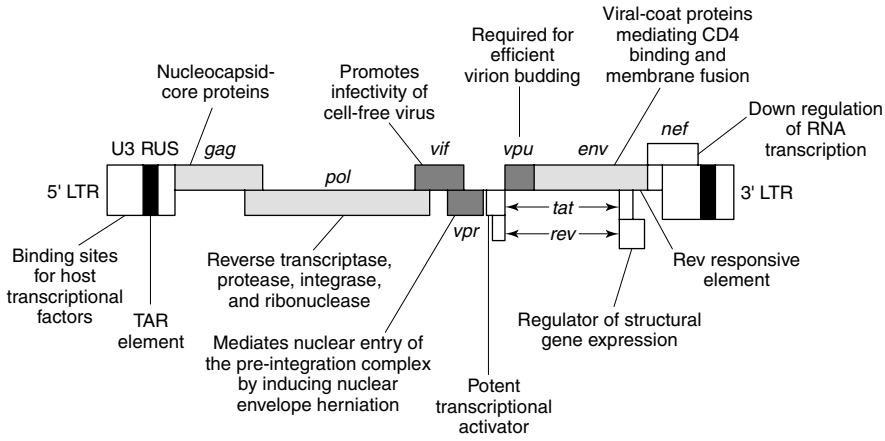

Fig. 103.5. Genome of HIV-1 (revised from Harrison & McArthur, 1995, after Greene, 1991). The proposed functions of the regulatory genes are indicated.

cell activation, the provirus may separate from the host cell DNA to produce retrovirus mRNA, which directs viral protein synthesis. Macrophages are apparently able to sustain a productive infection without cellular activation, and may therefore serve as an important reservoir of virus, both in the body and particularly in the brain.

The HIV virion is a relatively large, icosahedral structure with numerous external spikes (Fig. 103.4). The envelope spikes are composed of gp120 with a transmembrane component, gp41. The lipid bilayer is derived from host cell proteins during viral budding. The core is formed from four nucleic capside proteins: p24 (the major component), p17, p9 and p7. Genomic structure of HIV includes genes that code for structural proteins and several genes that code for regulatory proteins (Fig. 103.5). The three groups of structural proteins are coded for by the *gag*, *pol*, and *env*

regions of the HIV gene. The *env* gene encodes for the two major envelope proteins, gp120 and gp41; gp120 is a large glycoprotein that forms the surface spikes of the virion, while gp41 is a transmembrane glycoprotein. The two envelope proteins are critical for viral binding and cell fusion. The *pol* region codes for reverse transcriptase, a protease and an endonuclease. Endonuclease is critical for the integration of DNA into the host denome and the protease cleaves the polyproteins encoded for by gag and pol into their active forms. The gag region encodes for the core proteins, including p24, the nucleoid shell and several smaller proteins. Additional information is available in two reviews (Levy, 1989; Greene, 1991). At least five genes (*tat*, *rev*, *nef*, *vif*, and *vpr*) are involved in the regulation of HIV-1 replication (Fig. 103.5). After reverse transcription, the 'preintegration complex' appears to travel to the host cell nucleus along the host cell's microtubules, and crosses the nuclear envelope. The mechanisms for this critical step are unclear, but it has been hypothesized that the viral matrix protein serves as a 'nuclear address label', i.e. a nuclear localization signal recognized by cellular proteins that permits transport into the nucleus. It is likely that the viral matrix protein is not the only mediator of HIV nuclear importation. Vpr may also assist with binding to the nuclear pores, or may disrupt the nuclear membrane by inducing blebbing and rupturing, with the subsequent ingress of cytoplasmic soluble components (Henklein et al., 2000).

Initially it was thought that, after infection and integration of HIV DNA into the host cell genome, there followed a longer period of of virological and clinical latency. Recent work has shown that, even during this period of clinical latency, there is very active viral replication and release of active virions (Michael et al., 1992; Ho et al., 1995). There appears to be a very rapid turnover of CD4 lymphocytes (approximately 2 billion daily), with release of approximately 10 billion new virions daily (Coffin, 1996; Saag, 1997). With millions of replicative cycles daily, and a relatively high error rate in RNA transcription, resistant mutants can arise readily unless HIV replication is suppressed. This rapid replication leads to the establishment of a swarm of related HIV quasispecies within an individual. Quiescent memory CD4+ T-lymphocytes, and macrophages may serve as a long-lived reservoirs for latent HIV infection (Saag, 1997; Finzi et al., 1997). The resting memory T-lymphocyte has been shown to be a particularly important reservoir which prevents eradication because HIV remains either latent, or maintains a low level of replication for years (Finzi et al., 1997). In addition, the concern exists that the brain may serve as a sanctuary for unchecked HIV replication, both because the blood–brain barrier may prevent CNS penetration of antiretrovirals, and also because macrophages, the principal target cells within the CNS, may be long-lived sequestered sites for HIV (Finzi et al., 1997; Wong et al., 1997).

After acute infection with HIV, the immune system is stimulated to control the virus and a lower level of HIV viremia is established after the initial peak viremia. The level of this viral 'set-point' appears to be an important predictor of subsequent disease progression. HIV-specific immune responses, both antibodies and cellular (cytotoxic T-cells) develop to a variable degree. Some individuals appear to be able to control HIV replication even without antiretrovirals, and have no or a very slow progression of disease. These 'long-term non-progressors' constitute about 10–15% of chronically infected individuals. HIV enters the nervous system early after infection, but productive infection is rarely established before immunosuppression has developed. It is more likely that CNS reseeding, with the establishment of productive CNS infection only occurs later in HIV disease, after the development of immunosuppression. The major direct effect of HIV infection on the immune system is the profound and progressive loss of CD4 lymphocytes. This, of course, leads to the impaired cellular immunity, and the development of reactivated latent infections or infections with organisms which are normally not pathogenic ('opportunistic'). In addition, the loss of the regulatory CD4 subset appears to lead to a dysregulation of macrophages, with the overproduction of a variety of proinflammatory cytokines and chemokines. The activation of circulating monocytes is probably a critical step which permits their ingress into the brain (Gartner, 2000). This macrophage activation within the CNS and PNS may be particularly important for the development of HIV dementia and sensory neuropathy, as is discussed below (Tyor et al., 1995; Gartner, 2000).

Advances in antiretroviral therapy

In the past few years several important advances have led to concrete improvements in the care and prognosis of HIV-infected individuals. The first is an understanding of the direct relationship between viral replication and immunological and clinical progression, which reinforces the need to suppress viral replication to control the infection. The second is the wider availability of multiple, potent antiretroviral regimens that can provide effective suppression of HIV (Table 103.3a.) The third major change is the ability to monitor the response to therapy through regular measurement of plasma HIV RNA levels which, with CD4 counts, has become a routine part of clinical

Table 103.3(a). Anti-HIV drugs: CSF: plasma concentration ratios

	Date approved	CSF: plasma
Nucleoside RT inhibitors		
Retrovir (zidovudine, AZT)	3/87	0.3–1.35
Zerit (stavudine, d4T)	6/94	0.16–0.97
Ziagen (abacavir)	12/98	0.3–0.42
Videx (didanosine, ddl)	10/91	0.16–0.19
Epivir (lamivudine, 3TC)	11/95	0.11
Hivid (zalcitabine, ddC)	6/92	0.09–0.37
Non-nucleoside RT inhibitors		
Viramune (nevirapine)	6/96	0.28–0.45
Rescriptor (delavirdine)	7/97	0.02
Sustiva (efavirenz)	11/98	0.01
Protease inhibitors		
Crixivan (Indinavir)	3/96	0.02–0.06
Fortovase (saquinavir)	12/95	<0.05
Viracept (nelfinavir)	4/97	<0.05
Norvir (ritonavir)	3/96	<0.05
Kaletra (lopinavir + rit)	1/00	<0.05
Agenerase (amprenavir)	3/99	<0.05

Table 103.3(b). Initial HAART Regimen DHHS Guidelines (One drug from column A and one combination from column B in the preferred category)

	Column A	Column B
Preferred	Efavirenz	d4T/3TC
	Indinavir	AZT/ddl
	Ritonavir/Saquinavir	AZT/3TC
	Ritonavir/Lopinavir	d4T/dd
Alternative	Abacavir	ddl/3TC
	Amprenavir	AZT/ddC
	Delavirdine	
	Nevirapine	
	Ritonavir	
	Saquinavir (Fortovase)	
	Nelfinavir/Fortovase	
No recommendation (insufficient data)	Hydroxyurea	
	Ritonavir/Indinavir	
	Ritonavir/Nelfinavir	
Not recommended	Saquinavir (Invirase)	ddC/ddl
		ddC/d4T
		ddC/3TC
		AZT/d4T

Source: From: Bartlett & Gallant (2000–2001).

care. In addition, resistance to antiretrovirals can now be relatively easily measured with genotypic or phenotypic assays. Incomplete adherence, underdosing, and pharmacokinetic interactions with other medications can result in the development of drug resistant strains of HIV-1 (Condra & Emini, 1997). Of the 15 antiretroviral agents available in the USA, these act either to inhibit reverse transcriptase, or are protease inhibitors. Further details can be found in a recent review (Sepkowitz, 2001). New agents in development may block fusion steps or the integration of HIV-1. Guidelines for the use of antiretroviral (ART) therapy have been developed by expert panels, and include the broad recommendation that all symptomatic patients, and asymptomatic patients with immunodeficiency (CD4 $<350/\mu l$) or plasma HIV RNA levels >55 000 copies/ml be treated with combination ART regimens (Table 103.3) (http://www.hivatis.org). These regimens might include either three nucleoside RT inhibitors (NRTIs), or two NRTIs + one non-nucleoside RTI, or two NRTIs + a protease inhibitor (Table 103.3b). Potent antiretroviral treatments have resulted in significant improvements in survival, for example, the mortality among people with CD4 counts $<100/mm^3$ has dropped from 35:100 person–years (PY) in 1993 to 10:100 PY in 1997 (Palella et al., 1998). Structured treatment interruption has been proposed as a strategy to reduce the cumulative toxicities of HAART, and to allow for stimulation of HIV-specific immune responses. However, a recent study of HAART interruption showed prompt rise in plasma HIV RNA levels, with falls in CD4 counts, and increases in viral replicative capacity (Deeks et al., 2001). It is beyond the scope of this chapter to discuss the long-term effects of potent antiretroviral regimens; however, it is now clear that these combinations can produce significant metabolic effects, including hypertriglyceridemia, fat remodelling or lipodystrophy, pancreatitis, lactic acidosis, and mitochondrial toxicity. Peripheral neuropathy has become one of the common treatment-limiting effects.

As CD4 counts decline with advancing HIV infection the range of cellular responses, or 'repertoire', constricts. With HAART, dramatic reductions in plasma HIV levels can be seen within weeks, producing a sustained (or 'durable') virological suppression. Immunological response occurs over a few months, and can be dramatic, with normalization of CD4 counts. Initially, the rise in CD4 counts is from a redistribution or expansion of existing T-lymphocytes from the lymphoid tissue. These are mainly memory cells, and will only respond to specific antigens, so that the overall immune response remains constricted with a 'limited

Table 103.4. CNS AIDS indicator illnesses reported in 1997, United States

Opportunistic process	Number	Percentage
Cryptococcal meningitis	1168	5
Toxoplasmosis	1073	4
CMV retinitis	811	3
Progressive multifocal leukoencephalopathy	213	1
Primary CNS lymphoma	170	1

Source: CDC HIV/AIDS Surveillance Report (1997).

Table 103.5. Clinical features of HIV-associated sensory neuropathies

Pain in soles	62%
Paresthesias	38%
C/o weakness	0%
⇑ sensory thresholds	71–85%
Absent/reduced ankle reflexes	66–96%
Distal weakness	33%
Atrophy or wasting	30%
Fasciculations	0%

Source: From Cornblath & McArthur, 1988; Tagliati et al., 1999.

repertoire'. A reduction of T-cell activation and improved CD4+ reactivity to recall antigens is then seen (Autran et al., 1997). Even later, naive T-cells (CD45RA+/CD27+) are produced from the bone marrow and thymus and the repertoire of T-cell responses can potentially increase (Roederer, 1998; Powderly et al., 1998). Prolonged therapy may produce continuing immune improvement, with the restoration of specific immune responses to pathogens (Autran et al., 1997). Prophylactic therapies can be safely discontinued in individuals whose CD4 count has been restored by HAART to above 200/mm^3 (Furrer et al., 1999). With reconstitution of the immune system a variety of inflammatory responses have been reported to opportunistic infections leading to apparent 'flares' in the activity of opportunistic infections, and probably representing a heightened immune response (Race et al., 1998). Whether this will be important for neurological diseases remains uncertain.

Several attempts have been made to augment the immune system in patients with HIV infection, including structured treatment interruptions, interleukin-2 therapy to stimulate T-cells, and IL-12 therapy to stimulate y-IFN and promote TH1 immunity. Interleukin-2 therapy is probably the most widely tested at this point, although it it expensive and has associated side effects. IL-2 stimulates the production of CD4 cells, and theoretically might also activate latent HIV producing a transient increase in circulating HIV levels.

Neurological manifestations of HIV infection (Table 103.4)

Most neurologic illnesses are confined to the later stages of HIV disease, after cellular immunodeficiency has developed (Johnson et al., 1988) (Fig. 103.1a). HIV may affect the nervous system in two ways: directly, producing distinct neurological syndromes, or indirectly, by causing immunodeficiency with a resultant susceptibility to opportunistic infections and neoplasia. CNS infection with HIV-1 can produce a wide spectrum of clinical manifestations, ranging from asymptomatic infection to severe, life-threatening opportunistic infections. For example, within 6 weeks of infection, an acute seroconversion illness can occur with meningoencephalitis, or inflammatory demyelinating neuropathies. The common reactivated or opportunistic processes include cerebral toxoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy (PML), tuberculous meningitis, and primary CNS lymphoma. The incidence rates of most have fallen since the introduction of HAART, because of immune restoration in HAART-treated patients (Brodt et al., 1997; Sacktor et al., 2001). Effective treatments have been developed for several of these processes, and primary prophylaxis is particularly useful for toxoplasmosis (Johnson et al., 1988).

HIV-associated dementia, myelopathy and sensory neuropathy (Table 103.5)

The HIV-associated syndromes, dementia, myelopathy and sensory neuropathy, are novel, debilitating conditions which generally do not develop until advanced HIV infection. Typically, patients will have had other AIDS-defining illnesses before the onset of these neurological syndromes.

HIV-1 associated dementia (HIV-encephalopathy/ AIDS dementia complex

HIV-1 infected individuals are susceptible to developing a progressive and frequently fatal dementia. This syndrome was added as an AIDS indicator illnesses in 1987, and termed HIV-1 encephalopathy (or HIV-associated dementia (HIV-D)). Occasionally HIV-D develops before profound immunosuppression, but in general, it is rare among

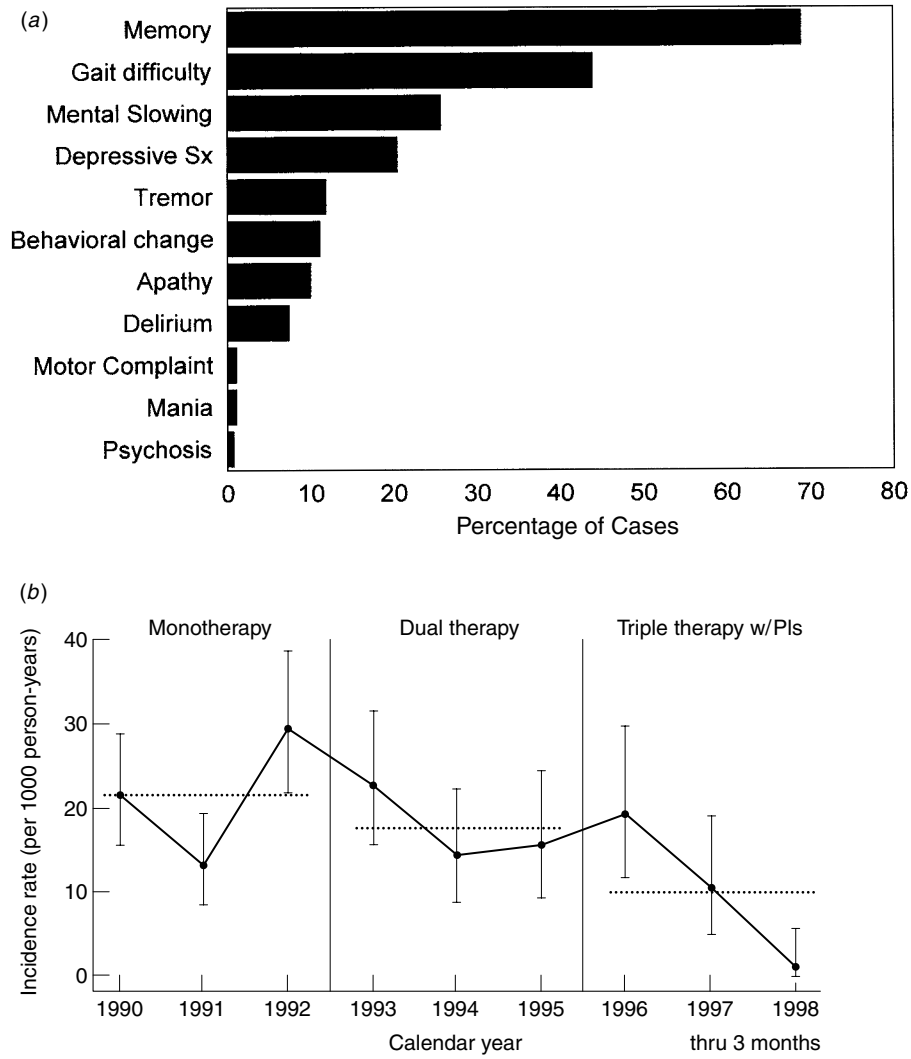

Fig. 103.6.(*a*) Frequency of neurological symptoms in HIV-D. (From McArthur, 2000.) (*b*) Declining incidence of HIV-associated dementia with successive improvements in antiretroviral therapy. (After Sacktor et al., 2000a).

healthy HIV-1 infected persons. The cumulative prevalence of HIV-D during the lifetime of an HIV+ person is estimated at 15%, and risk factors include high plasma HIV RNA levels, low CD4+ counts (Childs et al., 1999) anemia, low body mass index, older age, more constitutional symptoms before AIDS (McArthur et al., 1993), injection drug use (Janssen et al., 1992), and female sex (Chiesi et al., 1996). More subtle forms of cognitive impairment termed minor cognitive/motor disorder (MC/MD) exist in 20% of symptomatic HIV-seropositive adults (Janssen et al., 1989). Children can also be affected by a progressive encephalopathy, with an estimated prevalence of 30% (Belman et al., 1988) and a typical survival of 6 to 24 months (Epstein et al., 1985; Mintz et al., 1989). The incidence of HIV-D has declined by about 50% since the introduction of HAART (Fig. 103.6a).

HIV-D occurs in all groups at risk for HIV-1 infection, including children. Clinical features in pediatric cases include microcephaly, developmental delay, then loss of developmental milestones, leading to death unless treated with antiretrovirals. In adults, the clinical manifestations of HIV-D are often stereotypic, developing over a few months; however, occasionally the course is more fulminant. A typical presentation includes cognitive, behavioural, and motor dysfunction, and has been characterized as a subcortical dementia. The initial symptoms may be subtle,

Table 103.6. Radiological pattern of HIV-related CNS disease

Disorder	Number	Pattern	Enhancement	Location
HIV dementia	diffuse	ill-defined	0	deep white
Toxoplasmosis	1 – many	ring mass	++	basal ganglia
1° lymphoma	1 – several	solid mass	+++	periventricular
PML	1 – several	discrete lesions	0	subcortical white
Cryptococcus	1 – many	'lacunar'	0	basal ganglia
CMV encephalitis	1 – several	confluent	++	periventricular

Source: Modified from Price, R.W. American Academy of Neurology Course, 1991 (personal communication).

and therefore overlooked, and can be misdiagnosed as depression. In the early stages, memory loss, mental slowing, reading and comprehension difficulties, and apathy are frequent complaints. Table 103.2(b) illustrates some of the salient features which differentiate HIV-D from CMV encephalitis and PML. Other conditions which may mimic HIV-D include cryptococcal meningitis, primary CNS lymphoma and depression (Table 103.6). Gait disturbance, with non-specific complaints of stumbling and tripping, is frequent, and tremor may develop, with impairment of fine manual dexterity. Examination findings include impaired rapid movements of eyes and limbs, diffuse hyperreflexia, and release signs. New onset mania develops in 5% of patients. Neuropsychological abnormalities include a preferential impairment of psychomotor speed and memory. As the dementia advances, more widespread deficits develop, including a global dementia, often accompanied by myelopathy and neuropathy. The course of HIV-D is variable, and some individuals remain stable for prolonged periods of time, particularly with HAART. In addition, a less severe form, termed HIV-associated minor cognitive–motor disorder, has been defined, which frequently heralds the later development of HIV-D.

Cerebrospinal fluid abnormalities are common, with elevated CSF levels of HIV RNA and immune activation markers occurring in most demented individuals. CSF levels of HIV RNA correlate with the severity of neurological deficits (McArthur et al., 1997; Brew et al., 1997). Decline in CSF HIV RNA with HAART correlates with the successful reversal of neurological deficits (Marra et al., 1999; Ellis et al., 2000). Various CSF markers of immune activation such as neopterin (Brew et al., 1990), $\beta 2$ microglobulin (Brew et al., 1989), and quinolinic acid (Heyes et al., 1991) also correlate with the severity of HIV-D, and also decline with treatment. Magnetic resonance imaging demonstrates both cortical and central atrophy (Table 103.6), and characteristic confluent signal abnormalities within the deep white matter (see Fig. 103.7). These represent increased water content, and can be reversible with HAART. Magnetic resonance spectroscopy has shown increases in myoinositol and choline levels, reflecting chronic inflammation and astrocytosis, and reductions in *N*-acetyl aspartate, indicating neuronal injury (Fig. 103.8). Brain metabolite levels correlate strongly with various clinical and biochemical indices of neurological progression in HIV+ individuals such as severity of HIV-D, overall functional level, CD4 cell count, plasma viral load, and CSF viral load (Chang et al., 1999). Cerebral metabolite levels can normalize after 9 months of treatment with HAART, although the changes appear to lag behind improvements in CD4 count and CSF HIV RNA levels (Chang et al., 2001).

HIV probably gain access to the CNS from the blood stream by the ingress of infected or activated monocytes (Gartner, 2000). Productive HIV-1 infection occurs principally in perivascular macrophages and multi-nucleated giant cells (Fig. 103.9, Fig. 103.10, see colour plate section), and rarely in astrocytes, endothelial cells or neurons (Takahasi et al., 1996). The pathological features include multinucleated giant cells, which represent the fusion of HIV-infected macrophages, and a marked activation of macrophages and astrocytes. Immunocytochemical studies show a preponderance of productive HIV infection within the basal ganglia, brainstem, and deep white matter (Kure et al., 1991; Brew et al., 1995). In situ PCR studies have confirmed that most productive infection is contained with macrophages and microglia, with a non-productive infection of astrocytes (Takahashi et al., 1996). These observations suggest that initial infection occurs in the deep brain regions, probably from infection of perivascular macrophages by trafficking monocytes.

Diffuse rarefaction of white matter occurs commonly, with breakdown of the blood-brain-barrier (Thompson et al., 2001) with astrocyte apoptosis and eventually, dendritic simplification and neuronal loss. Morphometric studies have shown an approximate 40% reduction in

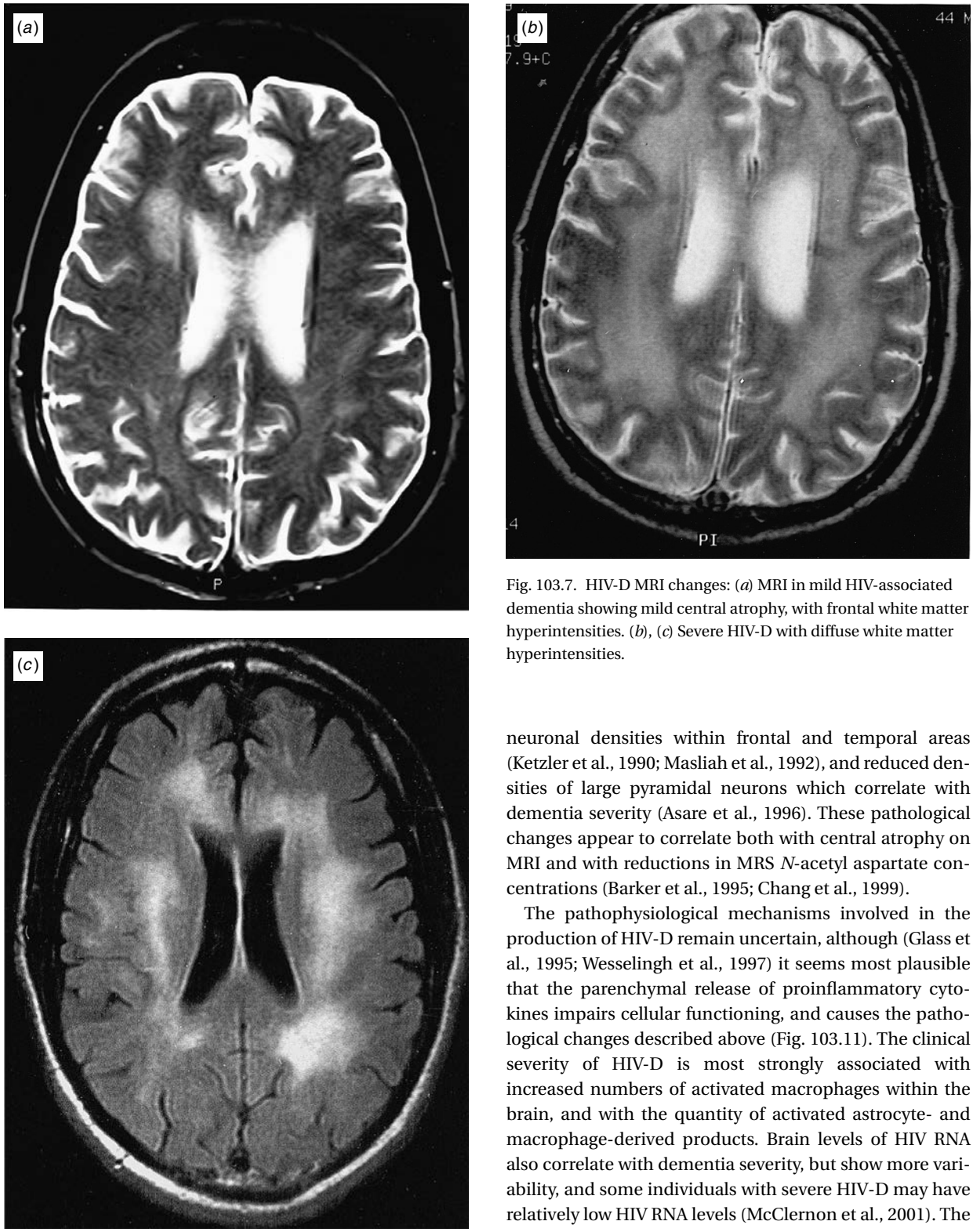

Fig. 103.7. HIV-D MRI changes: (*a*) MRI in mild HIV-associated dementia showing mild central atrophy, with frontal white matter hyperintensities. (*b*), (*c*) Severe HIV-D with diffuse white matter hyperintensities.

neuronal densities within frontal and temporal areas (Ketzler et al., 1990; Masliah et al., 1992), and reduced densities of large pyramidal neurons which correlate with dementia severity (Asare et al., 1996). These pathological changes appear to correlate both with central atrophy on MRI and with reductions in MRS *N*-acetyl aspartate concentrations (Barker et al., 1995; Chang et al., 1999).

The pathophysiological mechanisms involved in the production of HIV-D remain uncertain, although (Glass et al., 1995; Wesselingh et al., 1997) it seems most plausible that the parenchymal release of proinflammatory cytokines impairs cellular functioning, and causes the pathological changes described above (Fig. 103.11). The clinical severity of HIV-D is most strongly associated with increased numbers of activated macrophages within the brain, and with the quantity of activated astrocyte- and macrophage-derived products. Brain levels of HIV RNA also correlate with dementia severity, but show more variability, and some individuals with severe HIV-D may have relatively low HIV RNA levels (McClernon et al., 2001). The density of apoptotic astrocytes correlates with the rapidity of progress of HIV-D (Thompson et al., 2001). Using in situ

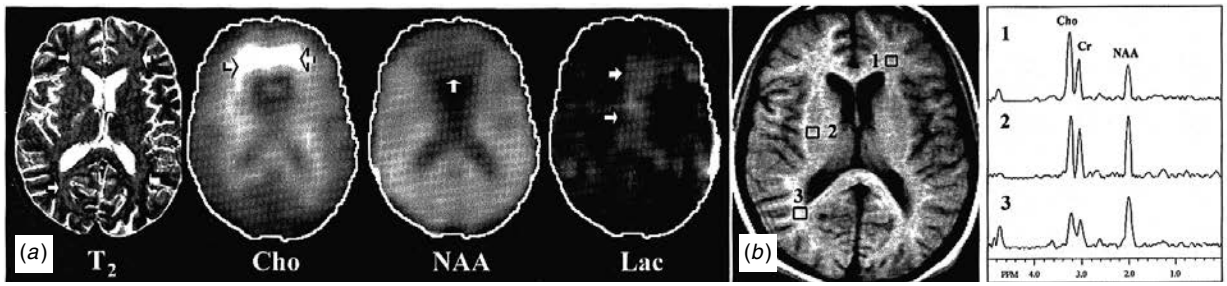

Fig. 103.8. (*a*) MRS: Magnetic resonance spectroscopic imaging in patient with mild to moderate HIV-associated dementia: Spectra are strikingly abnormal, particularly in the frontal lobe white matter. MRI shows minimal atrophy and some hyperintensity in the T_2 images in the periventricular white matter. Spectroscopically, a markedly decreased NAA is apparent throughout much of the brain, especially in the frontal lobe (white arrow). Choline is also elevated throughout the white matter (arrows), with the highest levels in the frontal lobe. A small lactate signal can also be observed in the ventricles (arrows). (*b*) Single voxel MRS indicating three separate voxels with spectra for Cho, Cr, and NAA. NAA peak is reduced in frontal area (1).

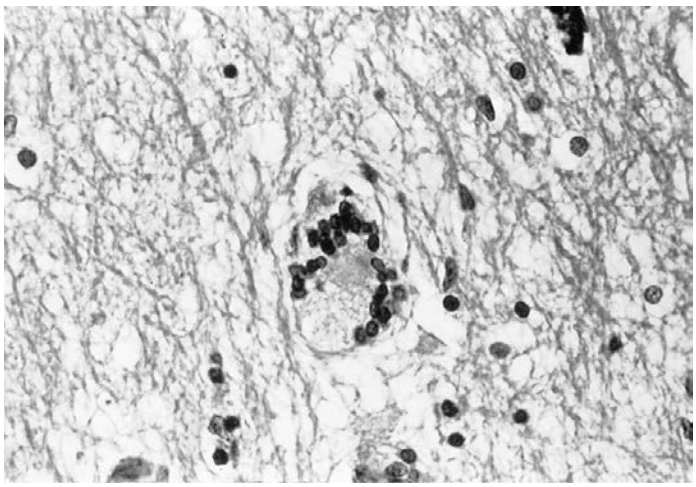

Fig. 103.9. HIV-D: multinucleated giant cell in focus of HIV encephalitis.

PCR, a greater number of astrocytes contained HIV DNA in the rapid progressor group. This suggests that there is both an increased rate of astrocyte apoptosis in rapidly progressive dementia and increased rates of astrocyte infection.

A very wide range of inflammatory mediators has been implicated in the pathogenesis of HIV-D, and it is unlikely that any one 'factor' is directly causative. These products include proinflammatory cytokines, eicosanoids, nitric oxide, and extracellular matrix-degrading proteases (Griffin, 1997; Adamson et al., 1999; Wesselingh et al., 1997). Platelet activating factor, nitric oxide, and matrix metalloproteases can be neurotoxic (Epstein & Gendelman, 1993) and may also have important effects on synaptic structure and function (Yong et al., 1998; Vos et al., 2000; Patton et al., 1998). Monocytes may contribute to the development of HIV dementia through multiple mechanisms. Activated and/or HIV-infected monocytes release a number of potent toxins, including viral gene products such as tat and gp120, as well as cellular gene products such as TNFα, nitric oxide, and platelet activating factor (Lipton & Gendelman, 1995). The precise role of viral proteins in pathogenesis is uncertain, and is reviewed in detail (Nath & Geiger, 1998). Tat is a non-structural viral protein, which acts as a trans-acting nuclear regulatory protein, and is essential for viral replication. It may be released into the extracellular space (Ensoli et al., 1993), and both in vitro and in vivo may be neurotoxic for selected neuronal populations (Hayman et al., 1993). Tat also stimulates the release of proinflammatory cytokines in the brain (Chen et al., 1997), and induces the migration of monocytes in a blood–brain barrier model (Nath, 1999; Nath et al., 2000; Magnuson et al., 1995). The envelope glocoprotein, gp120, is also a potent neurotoxin, in vitro, and it has been proposed that the neurotoxicity is mediated indirectly through actions on glial cells.

The products of activated monocytes can activate astrocytes, leading to the release of astrocyte-derived cytokines and chemokines, as well as to altered neurotransmitter uptake (Fig. 103.11). These products may also sensitize astrocytes and neurons to the effects of glutamate (Conant et al., 1998). Astrocytes participate in the inactivation of neurotoxins, particularly excess excitatory amino acids, such as glutamate and aspartate, and their loss may perturb the regulation of extracellular glutamate leading to neuronal injury. In situ studies have shown that monocyte–macrophages are the dominant source of toxins including TNF-α, and that apoptotic neurons are generally detected in close proximity to activated macrophages (Gelbard et al., 1995). Both monocytes/microglia and astrocytes are also capable of producing MMPs, which may

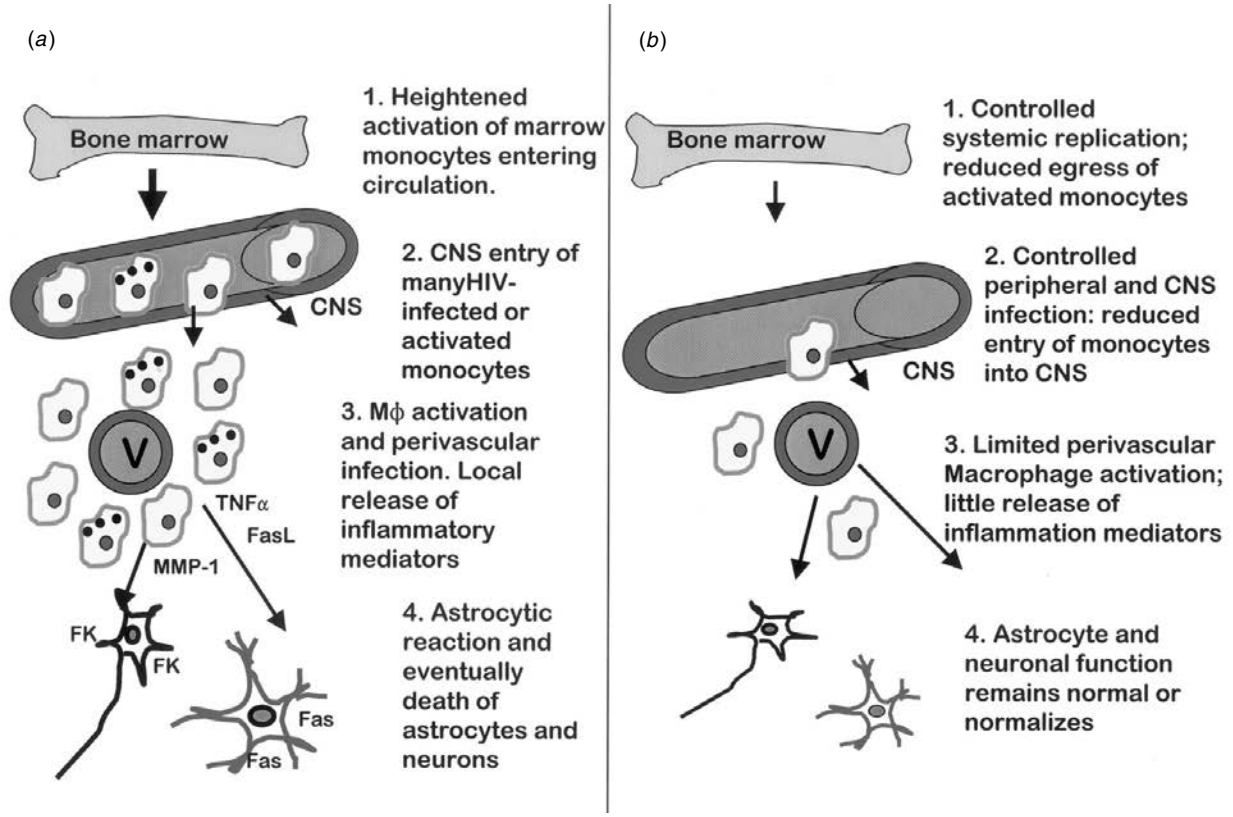

Fig. 103.11. Cartoon of pathogenesis of HIV-D: illustrates hypothetical reversible and irreversible phase of neuropathology. (*a*) No antiretroviral treatment: activation of monocytes in marrow and blood results in enhanced monocyte ingress to CNS. This produces perivascular inflammation and foci of productive infection. End result: neuronal/astrocytic death leading to progressive irreversible dementia. (*b*) Successful antiretroviral treatment: with virological suppression there is reduced ingress of activated/infected monocytes. CNS inflammation is reduced and productive HIV infection in CNS is limited with less injury of neurons and astrocytes and reversible dementia.

lead to breakdown of the BBB, and exposure of the brain to circulating substances. Locally produced chemokines may stimulate the ingress of additional activated monocytes. Importantly, this inflammatory cascade may become 'self-sustaining' so that even if HIV replication is suppressed, there may be continuing macrophage-mediated damage (Fig. 103.11).

Treatment of HIV-associated dementia

Neuropsychological testing has traditionally been used to measure progression in HIV-D, with particular emphasis on timed tasks. While specific neuropsychological instruments that measure psychomotor speed may indeed be sensitive to HIV-D, the relationship of changes in neuropsychological performance to improvements in function has not yet been demonstrated. Increasingly, surrogate markers of improvement are being introduced into clinical practice, including CSF HIV RNA levels, CSF markers of immune activation, and MRS. The primary principle of antiretroviral therapy in HIV-D is to produce complete virological suppression both in plasma, and the CNS. While it is still debated whether particular combinations might be more effective at penetrating the blood–brain barrier and therefore for use in HIV-D (Clifford, 2000), recent data have not demonstrated a difference in CNS efficacy between different HAART regimens (Sacktor, 2001).

Initial open-label studies with zidovudine (AZT) monotherapy in HIV-D showed promising improvements in clinical function, and neuropsychological performance (Fischl et al., 1987). The initial multicentre licensing trial (Fischl et al., 1987) suggested that AZT improved neuropsychological function in the short term, but no clear predictors of response were identified. There is very limited information about the therapeutic effect in HIV-D of the other nucleoside reverse transcriptase inhibitors, didanosine (ddl) or

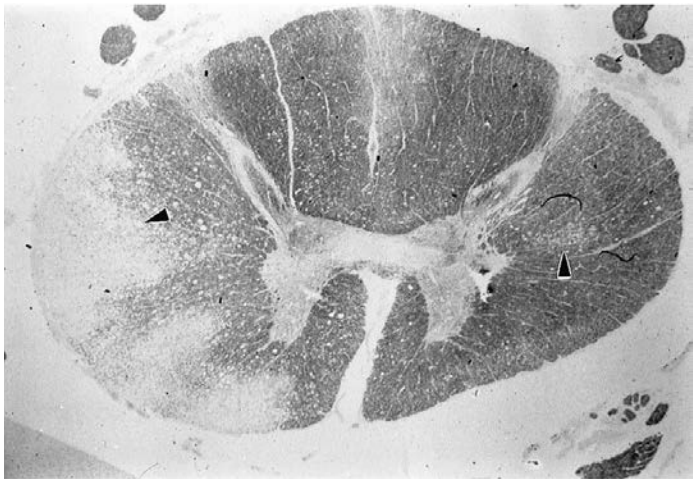

Fig. 103.12. Photomicrograph of spinal cord in vacuolar myelopathy. Innumerable vacuoles are identifiable, particularly in corticospinal tracts (arrowheads).

dideoxycytidine (ddC). The only placebo-controlled trial of AZT in HIV dementia suggested that improvement is seen with doses of AZT around 2000 mg daily (Sidtis, 1993), a dose that is rarely tolerated. Few of these studies have examined why some demented patients respond, and others fail to, and there has been little study of the kinetics and durability of treatment response. For example, Tartaglione et al. (1991) noted neurological improvement in most patients with mild HIV-D, but no relationship between treatment response and CSF AZT concentrations, cumulative AZT dose, or HIV isolation from CSF. There is no longer any role for monotherapy in the treatment of HIV-D. The effect of more potent antiretroviral regimens was examined in a multicentre trial of 1313 adult HIV+ subjects with CD4 counts $<$50 cells/mm^3. Four combinations consisting of AZT, alternating monthly with ddI; or AZT + ddC; AZT + ddI; or AZT + ddI + nevirapine were tested. A four-item quantitative neurological performance battery score was administered. Triple therapy and the AZT/ddI combination preserved or improved neurological performance compared with the alternating dual therapy ZDV/ddI and ZDV/ddC regimens ($P<0.001$, paralleling their impact on survival (Price et al., 1999). Other studies have also confirmed the effects of HAART in reversing the neurocognitive deficits of HIV-D (Sacktor et al., 2000a,b; Fernando et al., 1998).

Given that aberrant immune activation is likely to play a pivotal role in sustaining or magnifying the CNS damage induced by HIV-1, attention has focused on adjunctive therapies targeted at attenuating the CNS effects of inflammatory products. These have included the NMDA-antagonist memantine, the calcium channel blocker nifidepine, the platelet-activating factor antagonist lexipafant, the TNF-α antagonists pentoxifylline and CPI1189, and an experimental antioxidant, thioctic acid. The result of most trials have been disappointing, with either no or only modest effects on neuropsychological function. One agent, the MAOB inhibitor selegiline, has been shown to improve memory in two separate placebo-controlled studies (Sacktor et al., 2000a; Schiffito et al., 2001). Although its mechanism of action is speculative, a larger Phase II trial is under way in the USA.

Further information about the symptomatic management of HIV-D is beyond the scope of this chapter and the reader is referred to Gendelman et al. (1998).

HIV-1 associated vacuolar myelopathy

The most common myelopathy associated with HIV-1 is a slowly progressive myelopathy characterized by prominent vacuolar changes in the ascending and descending tracts. It affects 5–10% of patients with AIDS, but has been identified pathologically in almost 50% at autopsy (Dal Pan et al., 1994). It manifests as a progressive spastic paraparesis, with sensory ataxia, and is often associated with HIV-D. Typically, there is no back pain, or sensory level, and spine MRIs are usually normal. Occasionally, the myelopathy develops before, or without, dementia but usually the two progress in parallel. The differential diagnosis includes HTLV-1 associated myelopathy (see Chapter 104), CMV myeloradiculitis and HIV-myelitis, which is accompanied by HIV replication within the cord, and may be associated with contrast-enhancing foci.

The major pathological finding is vacuolation in the spinal white matter, particularly in the lateral and posterior columns of the thoracic spinal cord (Fig. 103.12). Productive infection, as indicated by multinucleated giant cells, is rare, however, there is marked macrophage activation and cytokine release within the spinal cord (Wesselingh et al., 1997). Because of some similarities to the myelopathy induced by vitamin B12 deficiency, this has been implicated in AIDS, however the role remains unclear. As with HIV-D, the role of local macrophage activation is probably critical (Tyor et al., 1995; Lipton & Gendelman, 1995). Antiretrovirals have not been convincingly proven effective for VM, however, a trial of methionine suggested some benefit (Dorfman et al., 1997).

Peripheral nerve disorders associated with HIV-1

Although the CNS complications of HIV-1 infection constitute the most significant neurologic disorders with respect

to morbidity and mortality, the peripheral nervous system may become involved in diverse ways. Not only do novel and distinct clinical syndromes exist, but the timing of onset varies, suggesting that diverse pathogenic mechanisms may produce the different peripheral neuropathies.

A number of possible immune-mediated phenomena have been described in association with HIV-1 infection, including polymyositis, inflammatory demyelinating polyneuropathies (IDPs) and thrombocytopenia. The IDPs typically occur in a relatively early stage of HIV-1 infection before profound immunodeficiency, and typically present with the acute onset of profound motor weakness and Guillain–Barré syndrome. In contrast to GBS occurring in HIV-seronegative individuals, CSF pleocytosis commonly occurs with GBS in the setting of HIV infection. The IDPs are often self-limited or respond to immunomodulatory therapy. Since IDPs resemble autoimmune diseases and occur early in infection, they probably result from an autoimmune phenomenon directed against peripheral nerve antigens, and triggered by HIV-1 (Sheikh et al., 1998). Further details of these disorders are discussed elsewhere (Cornblath et al., 1987).

Up to 30% of patients with AIDS will develop sensory neuropathies, characterized by painful sensory symptoms usually in the feet. In contrast to the IDP's discussed above, HIV-associated sensory neuropathies (HIV-SN) usually occur late in HIV-1 infection, in association with multiple opportunistic infections and profound immunodeficiency. Some of the dideoxynucleoside antiretrovirals produce neurotoxicity, and induce peripheral neurotoxicity (antiretroviral toxic neuropathy, ATN) which is indistinguishable from the neuropathy associated with HIV, distal sensory polyneuropathy (DSP) (Table 103.4). DSP is characterized by a length-dependent axonal degeneration of sensory fibres, with minimal evidence of nerve fibre regeneration. (Fig. 103.13, see colour plate section) Both large myelinated fibres and unmyelinated nerve fibres are lost, so DSP can therefore approximately be classified with conditions like diabetes and amyloidosis that have prominent small sensory fibre involvement. DSP conforms to the concept of a 'dying back' neuropathy (Cavanagh, 1964), with degeneration of the rostral gracile tract (Rance et al., 1998), the CNS counterpart of the peripheral degeneration. The degree of pain and 'positive' neuropathic symptoms are frequently out of proportion to the neuropathic signs, and to the degree of nerve fibre loss in the epidermis (Polydefkis et al., 2001) (Fig. 103.14, see colour plate section). This suggests that the neuropathic pain associated with HIV-SN and ATN derives from the spontaneous activity of uninjured C fibres after injury in neighbouring nerve fibres, an observation that has been made in rodent models of neuropathic pain (Wu et al., 2001). The overt neuropathological changes in DSP include inflammatory infiltrates of lymphocytes and activated macrophages, decreased numbers of DRG neurons and increased frequency of nodules of Nageotte (Nagano et al., 1996; Rizzuto et al., 1995; Shapshak et al., 1995; Pardo et al., 2001) (Fig. 103.15, see colour plate section). Although HIV infection of DRG neurons has been suggested using PCR in situ hybridization (Brannagan et al., 1997), it seems more likely that the virus is predominantly localized in perivascular inflammatory cells and the nodules of Nageotte (Yoshioka et al., 1994; Nagano et al., 1996). The most consistent pathology in the DRG, however, appears to be the activation of inflammatory mechanisms that indirectly leads to damage to DRG neurons (Kolson & Gonzalez-Scarano, 2001). The presence of proinflammatory cytokines including TNF-α, IFN-γ, IL-6, and other mediators including nitric oxide, have consistently been demonstrated in DRGs in AIDS. This aberrant inflammatory response probably plays a critical role in damaging or sensitizing DRG neurons, and axons, and subsequently affecting the inputs to central pain pathways. This aberrant inflammatory response might lead to the up-regulation of sodium channels within the dorsal root ganglia leading to neuronal hyperexcitability, as has been seen in animal models (Waxman, 1999). The loss of unmyelinated input into lamina II of the substantia gelatinosa might lead to ingrowth of Aβ fibres, and the aberrant processing of sensory inputs (Baba et al., 1999).

Very little is known about the pathology of ATN, although sural nerve biopsies obtained from patients with ATN have shown severe axonal destruction, prominent in unmyelinated fibres (Dalakas & Cupler, 1996; Lewis & Dalakas, 1995). Prominent mitochondrial abnormalities have been demonstrated in association with NRTIs (Chen et al., 1991). Other complications of NRTI therapy include ATN (with all dideoxynucleosides), pancreatitis (DDI, D4T), myositis (zidovudine) and macrocytosis, as well as metabolic abnormalities, and lipodystrophy. Some of these clinical manifestations resemble genetic mitochondrial diseases (Lewis & Dalakas, 1995) suggesting that the pathogenesis of many specific NRTI side effects may be related to drug-induced mitochondrial dysfunction. This theory is further supported by evidence of increased serum lactate level (Brew et al., 2001) and reduced serum levels of acetylcarnitine (Famularo et al., 1997) in patients with ATN. Further support for the potential role of mitochondrial dysfunction is derived from in vitro observations of a graded inhibition of gamma DNA polymerase by the different nucleoside reverse transcriptase inhibitors (Martin et al., 1994). Dideoxynucleosides are the most potent inhibitors of the enzyme in vitro; and zidovudine, lamivudine, and abacavir have only minimal effects. The effect of

NRTIs on mitochondria is manifest in vitro as a reduction in the copy numbers of mtDNA (Chen & Cheng, 1989; Chen et al., 1991) resulting in NRTI-associated metabolic abnormalities (Brinkman et al., 1998, 1999). The mechanism of dideoxynucleoside toxicity leading to sensory neuropathy has been hypothesized to involve a selective inhibition of mitochondrial gamma DNA polymerase. In vitro studies of neuron-like cultures have shown that the dideoxynucleosides inhibit neurite outgrowth in a dose-dependent manner (Cui et al., 1997).

Unfortunately, animal models of dideoxynucleoside toxicity have been disappointing, so that, for example, rats exposed to ddC at very high concentrations, even in doses up to 100 mg/kg intraperitoneally for several months, have not shown any evidence of epidermal nerve fibre degeneration (J.C. McArthur, unpublished data). This might be explained by differences in absorption, bioavailability, or species differences in the selectivity of gamma DNA polymerase to ddX agents. In human studies, assays are being refined to measure mitochondrial DNA levels in various tissues, including peripheral blood leukocytes, and subcutaneous fat (Gahan et al., 2001) to help understand the mechanisms of lipodystrophy and peripheral neuropathy.

In summary, the pathogenesis of the neuropathic pain in HIV-SN may be multifactorial. First, because of nutritional deficiencies, alcohol exposure, substance abuse or other nonspecific factors, a mild degree of distal axonal degeneration develops, resulting in the loss of axons in the distal sensory nerves. This damage may be magnified by cumulative exposure to NRTIs, and hepatitis C. As in other types of Wallerian-like degeneration, macrophages would then be recruited into the affected nerves. These macrophage responses to axonal degeneration are 'hyperactive' in HIV infection compared to other axonal neuropathies. Multifocal inflammation in the nerve and DRG leads to further loss of both large myelinated and unmyelinated fibres. The macrophage-dominated pathology of the PNS has obvious parallels to the microglia/macrophage activation characteristic of HIV-associated dementia (Wesselingh et al., 1993). The development of spontaneous activity in uninjured nociceptive fibres, changes in the patterns of expression of ion channels, and remodelling within the dorsal horn leads to persistent neuropathic pain.

Treatment of HIV-associated sensory neuropathies

At this stage, while the pathogenic mechanisms of HIV-SN are being explored, no specific therapy can be offered. For ATN, it is reasonable to discontinue the offending HAART regimen, provided that there is an alternative regimen to offer. Failing this, a patient may need to remain on the regimen with pain-modifying agents added. After discontinuation of a toxic dideoxynucleoside, symptomatic improvement can be expected in 3 months (Blum et al., 1996). A variety of pain-modifying agents have been used for HIV-SN, as for diabetic polyneuropathy, including tricyclic antidepressants, anticonvulsants, and narcotics. The results of placebo-controlled trials have demonstrated a modest benefit on neuropathic pain for amitriptyline (Kieburtz et al., 1998), and a larger effect for lamotrigine in two separate studies (Simpson et al., 2001). In severe neuropathies narcotic analgesics may be required. Transdermal fentanyl, long-acting morphine or oxycodone preparations, or methadone are particularly useful. Specific prescribing guidelines should be followed, particularly if there is a history of substance abuse. Further management details are provided in Pardo et al. (2001).

Regenerative strategies have been attempted by HIV-SN, utilizing recombinant human nerve growth factor, which has also been tested for diabetic polyneuropathy. The rationale is that nerve growth factor is trophic for small sensory neurons, and in both in vitro and in vivo models stimulates the regeneration of damaged nerve fibres (Apfel et al., 1998). In a study of 270 patients with HIV-SN, a modest effect on neuropathic pain and pin sensibility was demonstrated (McArthur et al., 2000). Unfortunately, the clinical development of nerve growth factor has been halted, and interest has now moved to the prosaposin and neurophilin classes of compounds.

HIV-associated polymyositis

Polymyositis is an uncommon complication of HIV-1 infection that is probably another autoimmune phenomenon. In the early years of the AIDS epidemic, when zidovudine was the only available antiretroviral agent, and it was used in higher doses than today, myotoxicity would develop frequently. Clinically, polymyositis presents with proximal weakness, elevated levels of serum CPK, and irritative changes on EMG. The pathology of HIV-associated polymyositis includes myofiber necrosis and inflammatory infiltrates, and is indistinguishable from polymyositis with HIV (Dalakas et al., 1990). Polymyositis sometimes responds to immunomodulatory agents such as corticosteroids or intravenous IgG.

CNS opportunistic infections in HIV/AIDS

Introduction

Infections in immunocompromised patients are generally with 'opportunistic' infections or 'reactivated' infections.

Opportunistic infections generally result from exposure to ubiquitous organisms which are normally of low pathogenicity, but cause an infection in immunocompromised hosts. Reactivated infections include organisms which may have caused a remote primary infection with few or no symptoms, which become reactivated in the setting of immune deficiency. Opportunistic infections and neoplasms of the CNS develop frequently in association with HIV infection, but usually do not develop until the CD4+ count is below 200, reflecting the underlying immunodeficiency. The immune restoration associated with HAART has produced significant reductions in the incidence rates of opportunistic infections (Brodt et al., 1997). Although highly active antiretroviral therapy often produces dramatic increases in CD4 counts, the circulating memory CD4 lymphocytes may still have only a limited repertoire of cellular responses.

There are some general differences between CNS OIs in AIDS and those occurring with other immunodeficiency states. First, HIV-infected patients may have multiple concurrent opportunistic processes, or opportunistic processes may coexist with HIV-related neurological disorders. Thus, the assessment of an immunosuppressed HIV+ may be more complex. Secondly, the immunodeficiency associated with HIV infection is usually progressive without antiretrovirals, with an annual loss of 50–100 CD4 cells/mm^3. Thus, after developing an OI an AIDS patient is usually at lifelong risk for developing other OIs or a recurrence. Lifelong maintenance therapy for secondary prophylaxis will generally be required, although with improvements in immune function with antiretrovival therapy this is now being debated. Thirdly, the OIs associated with HIV infection are somewhat predictable, and primary prophylactic regimens have been developed for many of the systemic and CNS OIs and are usually initiated when CD4 counts drop to 200/mm^3 or below. The success of these prophylactic regimens hinges on complete adherence with medications, and improving adherence has become a major focus of most HIV programs. Finally, the incidence of CNS OIs in AIDS has changed in recent years because of the introduction of potent antiretroviral regimens.

The most common CNS opportunistic processes are presented in Table 103.1. These and other common neurological opportunistic processes are discussed briefly below. The diagnosis of several of these processes has been facilitated in recent years with the introduction of sensitive PCR assays which can be performed on CSF. Brain biopsy may occasionally be necessary to differentiate lesions, but increasingly non-invasive techniques are used for diagnosis. Management strategies are beyond the scope of this article and readers are referred to other sources (Marra, 1999).

Cerebral toxoplasmosis

T. gondii is an obligate intracellular protozoan pathogen of humans and animals, which causes necrotic and inflammatory brain abscesses. Cerebral toxoplasmosis occurs in 5–10% of patients with AIDS, but the incidence has been declining because of the widespread use of timethoprim-sulfamethoxazole as prophylaxis against *P. carinii*. This agent is also an effective prophylactic for *T. gondii* (Brodt et al., 1997). Cerebral CNS toxoplasmosis is the result of reactivation of a latent infection, rather than a primary infection. In some areas, for example France, central or south America, or Florida, the prevalence of toxoplasmosis is significantly higher. This is because seroprevalence rates are much higher in these areas, around 70–80%, than in the UK (22%) or the north-eastern USA (25%). This wide variation in the prevalence of latent infection among different populations reflects differences in dietary and other sociocultural factors. Grant et al. (1990) estimated that the 3-year probability of developing CNS toxoplasmosis is 28% for HIV-infected patients also seropositive for antibodies to *Toxoplasma gondii*; thus primary prophylaxis is mandated for those with positive toxoplasma antibodies and CD4 $<$ 200. Contact with the oocyst or egg form generally occurs in childhood from exposure to the definitive host the cat in feces. Eating undercooked meat which contains the encysted forms can also transmit infection. After ingestion, sporozoites are released into the small intestine, penetrate the gut wall and are spread hematogenously. Tissue cysts, or bradyzoites form within the muscles, eyes and brain (see Fig. 103.16(*b*), see colour plate section), and can become activated if cellular immunity wanes, releasing the active form, the tachyzoite (Fig. 103.16(*c*), see colour plate section). The mechanisms by which the encysted forms of *T. gondii* are normally controlled are uncertain, but presumably depend principally on cellular rather than humoral immunity.

Reactivation within the brain produces multifocal abscesses, scattered throughout the cerebral hemispheres (Fig. 103.16(*a*), see colour plate section). Pathologically the encephalitis is a focal, necrotizing process with tissue cysts rupturing, releasing tachyzoites, and inducing inflammation. A typical clinical presentation is with development of fever, altered mentation, seizures, and focal neurological signs evolving over a few days. Imaging studies demonstrate multiple 'ring-enhancing' mass lesions (see Fig. 103.17); however, this radiological appearance is not specific for toxoplasmosis and can be mimicked by primary CNS lym-

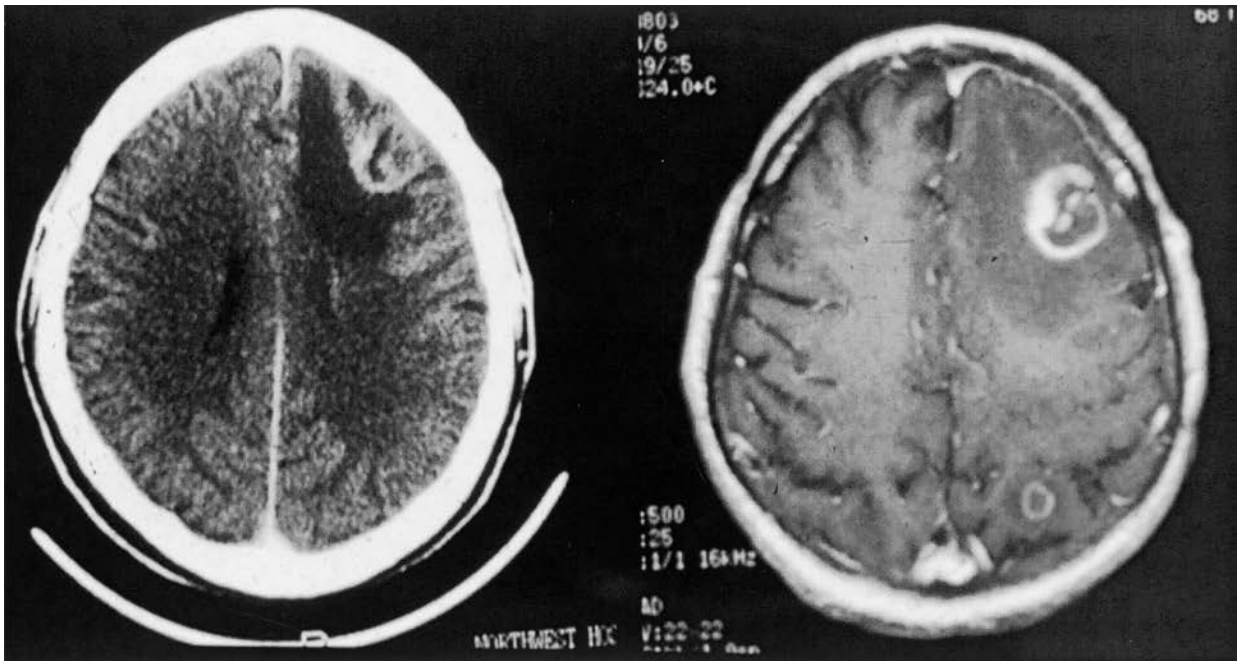

Fig. 103.17. CT scan (left panel) showing a single contrast-enhancing lesion in toxoplasmosis. Right panel: MRI from same patient showing multiple contrast-enhancing 'ring' abscesses, with surrounding edema.

phoma, or other causes of abscess, including tuberculomas or polymicrobial bacterial brain abscesses in injection drug users. Because this is a reactivated infection, most individuals will already be seropositive for *T. gondii* at the time of presentation; however, serological testing is not particularly helpful because of a high false-negative rate of 15% (Navia et al., 1986; Harrison & McArthur, 1995).

The prompt initiation of antimicrobial therapy with the combination of the dihydrofolate reductase inhibitor pyrimethamine, and sufadiazine, a dihydrofolate synthetase inhibitor leads to clinical and radiologic improvement in 90% of patients within 10 days (Porter & Sande, 1992; Katlama et al., 1996). Folinic acid is usually given to counteract the hematological toxicity of this combination. Treatment must be used for at least 6 weeks, and then doses reduced to provide secondary prophylaxis. In sulfa-allergic patients clindamycin can be substituted for sulfadiazine. Recrudescence occurs in 30%, usually because of incomplete adherence with secondary prophylaxis.

CNS tuberculosis

Mycobacterium tuberculosis is a non-motile bacillus, an obligate aerobic parasite, and humans serve as the only natural reservoir. *M. tuberculosis* is one of the most common opportunistic infections worldwide, with high rates of HIV and TB coinfection (De Cock et al., 1992). This frequent state of coinfection has led to a reversal in the previously declining rates of TB in the USA (Anon, 1988a). The degree of immunosuppression for CNS TB need not be as severe as for some of the other CNS OIs. For example, in one series (Dube et al., 1992), CD4 counts varied from 7 to 251/mm^3. The pathophysiology of CNS tuberculosis in HIV/AIDS is similar to that described before the AIDS epidemic. CNS infection begins with the inhalation of airborne infectious particles, usually from exposure to an active case of pulmonary TB. There is initially widespread hematogenous dissemination with trapping of organisms in the brain and meninges (Rich, 1946). It is usually a reactivation of latent disease (as discussed in Chapter 110), and tuberculosis of the meninges results from the rupture of small subependymal foci. A thick tuberculous exudate fills the subarachnoid space, and may impede CSF flow resulting in hydrocephalus or cranial nerve deficits. Parenchymal tuberculomas or, less commonly, tuberculous abscesses may develop. In the spine, a diffuse inflammatory arachnoiditis can develop with a similar pathology to the intracranial disease. Intramedullary tuberculomas can develop, but tuberculous osteomyelitis is more common, with epidural masses causing root and cord compression (see Chapter 110, Fig. 110.4). In contrast to bacterial spinal epidural abscess, tuberculous osteomyelitis usually results in

epidural masses anterior to the cord, producing localized or radicular pain, followed by weakness, bowel or bladder dysfunction, and eventually paralysis. With TB meningitis in HIV/AIDS, the clinical presentation of headache, altered mentation and fever does not differ from that seen in non-AIDS patients (Berenquer et al., 1992). In the late stages, seizures, coma and severe neurological deficits occur. Up to 66% of those with CNS TB will have pulmonary or extrapulmonary TB (Barnes et al., 1991). The diagnosis is usually made from positive skin tests, characteristic chest X-ray findings, and sputum smears. Cutaneous anergy is common in HIV/AIDS, so skin tests are less reliable. The typical CSF profile in TB meningitis is a high protein, and depressed glucose. A moderate pleocytosis is typical, with a mononuclear differential and up to 300 WBC/mm^3. Elevated adenosine deaminase or depressed chloride are not specific findings. CSF cultures may take several weeks to become positive, and the sensitivity of PCR is still unproven, with reported sensitivities of 83% (Kaneko et al., 1990). Treatment is with quadruple antituberculous therapy: isoniazid, pyrazinamide, ethambutol or rifampin for 2 months, followed by 4 months with two drugs (Anon, 1988b). Multidrug resistant TB has become a concern in many areas (Fischl et al., 1992), largely as a result of incomplete medication adherence.

Cryptococcosis

Cryptococcus neoformans, a ubiquitous encapsulated yeast, is the only encapsulated fungus. The thick polysaccharide capsule is composed of α-kinked D-mannopyranoside residues, and in the CNS may prevent an effective inflammatory reaction against the yeast. *C. neoformans* has been subdivided into various serotypes, and *C. neoformans* var. *neoformans* is most commonly the cause of cryptococcosis in HIV/AIDS. The organism is widely distributed in the environment and has been found in pigeon and other bird droppings and fruit. After inhalation, *C. neoformans* is ingested by alveolar macrophages, but the capsulate may render the fungus resistant to killing. With disturbance of cellular immunity, as in HIV/AIDS, the organism escapes from the lungs, spreads hematogenously, and can seed the prostate, skin and particularly the meninges. *C. neoformans* causes meningitis in about 5–10% of AIDS patients (Larsen et al., 1990), and in a significant proportion is the first recognized opportunistic infection. Incidence rates have dropped in the USA, both as a result of the widespread use of antifungals for treatment of oropharyngeal candidiasis and because of immune reconstitution following the introduction of HAART. Coincident antifungal use may decrease the hematogenous seeding of the meninges by *C. neoformans*. The most common presentation is with headache (82%), fever (75%), nausea and vomiting (46%), and altered mentation (24%) (Graybill, 1998). Papilledema, cranial nerve deficits and seizures are frequent. Meningismus occurs only in a minority of cases, presumably because the polysaccharide capsule does not elicit much inflammation. For the same reason, the cerebrospinal fluid (CSF) may have normal cellular and protein constituents in up to half (Dismukes, 1988). In severe cases, massive collections of cryptococcal yeast forms (termed cryptococcomas) accumulate within the basal ganglia, having spread centripetally along the Virchow–Robin spaces (see Fig. 103.18). Intracranial hypertension occurs frequently, and can lead to headache, visual blurring, sixth nerve palsies, other cranial nerve deficits and herniation (Denning et al., 1991). The development of intracranial hypertension suggests a very poor prognosis (Graybill et al., 2000), and other prognostic factors include very high titres of cryptococcal antigen, presence of altered mentation, CSF WBC <20/mm^3, and hyponatremia (Chuck & Sande, 1989). This constellation of symptoms can mimic bacterial meningitis, cerebral toxoplasmosis or occasionally, if protracted, HIV-D, however, fungal cultures are uniformly positive with detectable cryptococcal antigen in $>95\%$ (Kovacs et al., 1985). Antifungal therapy (with amphotericin B) is only of moderate efficacy in AIDS-associated cryptococcal meningitis, and is poorly tolerated because of side effects. While antifungals may suppress the infection initially and lead to clinical improvement, complete clearance rarely occurs. At best, current regimens achieve rates of CSF sterilization of about 60% after 2 weeks. Current recommendations are to treat with a combination of amphotericin B and 5-flucytosine for 2 weeks, followed by fluconazole 400 mg/day for 8 weeks, then 200 mg/day for life (Larsen et al., 1990; van der Horst et al., 1997). Lipsomal forms of amphotericin are now available, and although more expensive, can reduce nephrotoxicity (Leenders et al., 1997). Relapses are frequent even with lifelong suppressive treatment with fluconazole, and frequently follow poor adherence with secondary prophylaxis.

Cytomegalovirus encephalitis/retinitis

In the 1980s and early 1990s the DNA virus cytomegalovirus (CMV, a member of the Herpes family) was a common pathogen during the advanced stages of AIDS. CMV produces retinitis, encephalitis or infection of nerve roots (polyradiculitis) typically when the CD4+ count is <100 cells/mm^3. CMV-induced disease represents reactivation of latent cytomegalovirus infection, which is almost ubiquitous among homosexual men. The introduction of

potent antiretrovirals has reduced the incidence of CMV disease significantly in the USA. CMV frequently causes an opportunistic infection of the retina, producing painless visual loss in patients with profound immunodeficiency (Kupperman et al., 1993). Less commonly, CMV leads to an encephalitis, which usually presents more acutely than HIV-D, with acute encephalopathy, seizures, and detectable CMV DNA in CSF using PCR (Cinque et al., 1992; Holland et al., 1994). The third neurological complication is an infection of the lumbosacral nerve roots which presents as a subacute cauda equina syndrome (Miller et al., 1990; Eidelberg et al., 1986). In other immunodeficiency states, for example, after bone marrow transplantation, retinitis and polyradiculitis are very rare. Several antivirals are available to treat CMV neurological complications: ganciclovir, Foscarnet, cidofovir, and the recently introduced agent, valganciclovir, which is the only oral anti-CMV agent.

Progressive multifocal leukoencephalopathy (PML)

PML will develop as a complication in 2–4% of AIDS cases, and is a demyelinating CNS disorder caused by infection of oligodendrocytes and astrocytes following reactivation of JC virus, a member of the papovaviridae, which has at least four different genotypes (Agostini et al., 1997). Primary infection with this DNA virus, although usually clinically silent, is common in childhood and early adulthood, with 80–90% of the general population infected by middle adulthood (Elliot et al., 1997; Albrecht et al., 1997). Papoviridae remain latent within the bone marrow, kidney and circulating B lymphocytes, but not within the brain (Houff et al., 1988; Major et al., 1992; Berger et al., 1987). The reactivated papovavirus enters the brain, and infects glial cells, damaging the hemispheric white matter, and producing patchy foci of demyelination, which may become confluent (Fig. 103.19(*a*), see colour plate section). Giant atypical astrocytes and oligodendroglia with markedly enlarged nuclei are seen and inflammatory infiltrates may appear (Fig. 103.19(*b*), see colour plate section). Electron microscopy may reveal intranuclear papovavirions. PML appears to be more common with JCV type 2 (usually considered to be of African/Asian origin) (Elliot et al., 1997; Albrecht et al., 1997). Prior to the description of AIDS, PML was seen most frequently in patients with lymphoma, leukemia, or receiving immunosuppressive drugs for treatment of rheumatoid arthritis, sarcoidosis, or following organ transplantation. PML typically presents with the progressive, slow accumulation of focal or multifocal neurological deficits: aphasia, hemiparesis, or ataxia. Dementia, altered mentation and seizures are very unusual. Prior to the introduction of HAART, the median survival was 16 weeks. Diagnosis is usually made by recognition of a typical clinical course with characteristic imaging studies (see Fig. 103.19(*c*), see colour plate section), and a + PCR test in CSF for JCV PCR. The MRI appearance is characteristic, with discrete subcortical hyperintensities, usually non-enhancing. In contrast to HIV-D, PML lesions are usually hypodense on T_1-weighted images. Potent antiretroviral regimens may improve, or even reverse the course of PML, probably by improving immune function (Clifford et al., 1999). Other antivirals, including cytosine arabinoside, cidofovir, and alpha-interferon have been tried without any convincing effect on disease progression (Clifford, 2001; Geschwind et al., 2001).

Other opportunistic infections

It is beyond the scope of this chapter to cover the other opportunistic infections in depth. The reader is referred to sources such as Gendelman et al. (1998). Some of the other infections and neoplasms will be briefly discussed.

Syphilis

The spirochete *T. pallidum* can cause various neurological diseases during the lifetime of the untreated HIV-positive patient. In the USA, the rates of syphilis have begun to increase again since 1986, after five years of steady decline. Some US cities (including Baltimore) are in the midst of epidemics fuelled by the 'crack-for-sex' phenomenon. While not strictly an opportunistic infection, the course of syphilis may be accelerated by the disturbance in cellular immunity accompanying HIV-1 infection (Hook, 1989), and the time course from primary to tertiary syphilis shortened (Johns et al., 1987; Passo & Rosenblum, 1988). Common presentations in HIV-infected persons include syphilitic meningitis, ocular complications and meningovascular syphilis. In general, the interpretation of serological tests for syphilis is not affected by HIV infection, and treatment recommendations are similar to those for HIV-negative patients. However, the rate of recurrence or treatment failure in HIV-positive patients is around 30% even after intravenous regimens of ceftriaxone or penicillin (Marra et al., 1996, 2000).

Bacillary angiomatosis

This is an unusual vascular lesion, which may involve skin, bone, and even brain. The related angioproliferative lesion affecting the liver and spleen is termed bacillary peliosis. Both are associated with infection with a fastidious gram-negative bacilli caused by two species, *Bartonella henselae* or *B. Quintana*. Macrolide antibiotics are usually preventive and MAC prophylactic regimens which include a

macrolide may also provide simultaneous prophylaxis against Bartonella infection. Bacillary angiomatosis and Kaposi's sarcoma can be difficult to differentiate clinically and may require tissue biopsy. *B. henselae* infection usually causes peliosis hepatis and lymph node involvement, whereas *B. quintana* results in subcutaneous infection and lytic bone lesions. Cat scratch disease is associated only with *B. henselae* and over 40 000 cases are reported annually in the US.

Human herpes virus-8 (HHV-8)

Several investigators have shown that a herpesvirus-like agent (KSHV/HHV-8) has an etiologic role in the development of Kaposi's sarcoma and potentially in lymphomas, both in people with and without HIV infection (Chang & Moore, 1994, 1996; Moore & Chang, 1995). HHV-8 may produce malignancy by encoding for a gene with homology to the cytokine IL-6 which enhances B-cell survival and proliferation. After seeding of endothelial sites, HHV-8-infected monocytes may stimulate the local upregulation of cytokines. Interestingly, the anti-CMV agent ganciclovir may have a prophylactic effect against HHV-8. In a study comparing ganciclovir intraocular implants to systemic ganciclovir for patients with CMV retinitis, there was a 75% (for oral ganciclovir) – 93% (for intravenous) reduction in KS rates (Martin et al., 1999).

Primary CNS lymphoma (PCNSL)

Up to 3% of AIDS patients develop PCNSL, making AIDS the most common disease associated with this malignancy. It remains controversial whether the incidence of PCNSL is changing in the era of HAART. For example, the EUROSIDA study suggested a three-fold increase in the proportion of AIDS defining illnesses represented by non-Hodgkin's lymphoma (including both systemic and PCNSL) from 1994 to 1998, irrespective of CD4 count. This does not, however, necessarily mean that the absolute number of PCNSL cases has increased. By contrast, in the US Multicenter AIDS Cohort Study, the incidence rates of PCNSL were stable when adjusted for progressive immunosuppression within the cohort (Bacellar et al., 1994). In the last 3 years in observing 800 HIV-positive individuals, only four cases of PCNSL have been reported (L. Jacobson, personal observation).

In AIDS, PCNSL is almost always associated with EBV infection, however the mechanisms leading to the induction of the malignancy are unknown (MacMahon et al., 1991). The latent membrane protein 1 of EBV is now thought to play an important role in the malignant transformation of B-lymphocytes in immunosuppressed states including AIDS by mimicking members of the family of TNF-α receptors, and transmitting growth signals to the nucleus (Liebowitz, 1998). HHV-8 has been linked to some cases, however, this requires further study (Corboy et al., 1998). PCNSL is usually a high or intermediate grade malignancy, and either large cell immunoblastic or small cell non-cleaved B-cell type. Although clinically the tumour may present with a single large lesion, on pathological study it is almost always multicentric, with a perivascular location. About one-half of these B-cell-derived tumours are clinically silent and detected only at autopsy (Rosenblum et al., 1988). The tumours are of similar histological appearance to those observed in immunosuppressed renal allograft recipients. The majority of PCNSL cases occur when the CD4+ count is less than 50 cells/mm^3 (Levine et al., 1991), and a typical presentation is with slowly progressive neurological deterioration with headaches, focal neurological deficits, and mentation changes, leading to death within 1–2 months. Imaging studies in PCNSL show large contrast-enhancing mass lesions, however, these radiological features can overlap cerebral toxoplasmosis since the radiological appearance of both may be multicentric with edema surrounding contrast enhancing lesions. In general, toxoplasmosis lesions tend to be smaller and more numerous, with a simple 'ring-enhancing pattern' in contradistinction to a more complex heterogeneously enhancing PCNSL lesion (Dina, 1991). PNCSL can be differentiated from cerebral toxoplasmosis or bacterial brain abscesses by their uptake of the radioisotope thallium on SPECT scans (Fig. 103.20, see colour plate section). Both false-positive and false-negative scans can occur, depending on radiological expertise, size of the lesion, and particularly if the lesions are close to the base of the brain where the scalp and soft tissues can produce interference. Trypanosomiasis is a differential in S. America. CSF cytology is positive in $<$10% of cases, but assay of CSF EBV PCR has a sensitivity of about 60% (Cinque et al., 1993). The diagnosis may be made by stereotactic biopsy, or empirically on the basis of a failed toxoplasmosis therapy trial, and positive thallium scan and CSF EBV PCR. A patient with contrast-enhancing mass lesions, who has failed to respond to empiric antitoxoplasmosis therapy for 10 days, and who has positive CSF EBV DNA PCR and positive uptake on a thallium SPECT scan is highly likely to have PCNSL (Report of the Quality Standards Subcommittee of the American Academy of Neurology (1998)). In some centres, including our own, consideration of empirical radiation therapy without biopsy would be given, because of the high probability of PCNSL in this situation, and the relatively high morbidity of brain biopsy (7%) (Skolasky et al., 1999) in this population. The only proven treatment is cranial radiotherapy,

which can prolong survival and prevent further neurological progression. Whole brain radiation remains the standard therapy despite encouraging reports in small series of intrathecal chemotherapy (Chamberlain & Kormanik, 1999). Systemic chemotherapy prior to radiation therapy does not appear to improve survival based on a small pilot study of single cycle CHOP given prior to cranial radiation (Ambinder et al., 2001). In the era of HAART, patients with PCNSL can now survive for years after radiation, provided that they have an immunological response to antiretrovirals.

Metastatic systemic lymphoma

Most lymphomas are extranodal, diffuse high-grade malignant lymphomas of B-cell origin. Central nervous system involvement occurs in over 50% of patients with systemic lymphoma, and complications include cranial neuropathies, meningeal involvement, cerebral metastasis, and spinal cord compression.

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Neurological manifestations of HTLV-I infection

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Human T-cell lymphotropic virus type I (HTLV-I) is the causative agent for adult T-cell leukemia (ATL). ATL was first proposed as a clinical entity in Japan (Takatsuki et al., 1976; Uchiyama et al., 1977). The association of this disease to a new human retrovirus, HTLV-I, was discovered by independent research groups in USA (Poiesz et al., 1980) and Japan (Miyoshi et al., 1980; Hinuma et al., 1981; Yoshida et al., 1982). This same virus was found to be related to another human disease, a progressive spastic paraparesis, independently in two areas of the world, the Caribbean basin and Japan. In Martinique, 59% of patients with tropical spastic paraparesis (TSP) had antibodies to HTLV-I (Gessain et al., 1985). In Japan, a high prevalence of primary lateral sclerosis or spinal spastic paraparesis was found in South Kyushu (Osame et al., 1975). A follow-up study of this disorder established the existence of a new disease associated with HTLV-I which was named as HTLV-I associated myelopathy (HAM) (Osame et al., 1986, 1987; Osame & Igata, 1989). The disease is now known under the acronym, HAM/TSP (World Health Organization, 1989; Osame et al., 1990a).

HTLV-I virus

HTLV-I is a type C retrovirus, subfamily Oncoviridae. In contrast to the human immunodeficiency virus (HIV), HTLV-I causes disease in only about 5% of infected people. HTLV-I is estimated to infect approximately ten million people worldwide. There are large endemic areas in southern Japan, Central and West Africa, the Caribbean and South America, and smaller foci in the aboriginal populations of Australia, Papua New Guinea and northern Japan. In Europe and North America the virus is found chiefly in immigrants from these endemic areas and in some communities of IV drug users. Within the endemic areas, the seroprevalence varies between 1% and 20%. The number of the patients with ATL and HAM/TSP is estimated to be more than 3000 and 5000, respectively.

There are three important modes of transmission: parental and neonatal infection from a seropositive mother, in which breastfeeding is a significant factor; sexual transmission, particularly from males to females; and transmission by infected blood, either by transfusion or by sharing of needles among drug users. Transmission of the virus depends on transfer of cells from infected people. Blood for transfusion is now routinely screened for HTLV-I in several countries, including Japan (Osame et al., 1990b), the USA and Brazil.

HTLV-I is known as a complex retrovirus: in addition to the three genes present in other typical replication-competent exogenous retroviruses (*gag*, *pol* and *env*), it encodes at least two further proteins: Tax, which stimulates transcription of the proviral genome, and Rex, which controls the splicing of HTLV-I mRNA.

Although it can infect a wide variety of cell types in vitro, HTLV-I appears to replicate efficiently only in CD4+ (helper) T-cells; these are the cells that are transformed in ATL. Antibodies against the Gag protein are the first to appear after infection, and they predominate in the first 2 months. Thereafter, anti-Envelope antibodies predominate, and about half of infected individuals subsequently produce antibodies to the Tax protein. Diagnosis of HTLV-I infection depends on the detection of specific antibodies by particle agglutination or ELISA assays, and confirmation by PCR or western blot assay.

Adult T-cell leukemia lymphoma

A person infected with HTLV-I has about a 5% lifetime risk of developing ATL.

The main features of ATL consist of: (i) age of onset from about 20 to 70 years, the mean age at onset of ATL being about 60 years in Japan, and 40 years in the Caribbean and Brazil: the reason for this difference being not known; (ii) lymphadenopathy and hepatosplenomegaly; (iii) skin lesions similar to mycosis fungoides, or Sezary syndrome; (iv) presence of proliferated T-cell lymphocytes with flower-like nuclei; (v) hypercalcemia; and (vi) poor prognosis with a mean survival of 10 months (Uchiyama et al., 1977). ATL clinically presents in four different ways: (i) acute ATL whose clinical manifestations are those listed above; (ii) chronic ATL; (iii) smouldering ATL; and (iv) lymphoma type ATL (Takatsuki et al., 1985).

Southern blot analysis indicates the presence of oligoclonal or monoclonal proliferation of CD4+ cells that carry the HTLV-I provirus in the cellular DNA.

The mean survival times (untreated) for acute, lymphomatous and chronic (smouldering) ATL in Japan are 6.2, 10.2 and 24.3 months, respectively. The disease often responds initially to standard chemotherapeutic regimes, but early relapse is common, and the disease typically becomes refractory to further chemotherapy after 2–6 months. Recently, significant progress has been made with the discovery that a combination of extensive chemotherapeutic regimes and bone marrow transplantation can lead some patients to complete remission.

More than half of ATL cases will have neurological complications during the course. These manifestations mainly consist of the following: (i) altered consciousness derived mainly from hypercalcemia; (ii) dementia; (iii) seizures; (iv) hemiparesis and pyramidal tract signs; (v) cranial nerve deficits; (vi) meningeal irritation; and (vii) polyneuropathy. Except for altered consciousness, these complications have been associated with direct tumour cell invasion in most of the cases (Tara et al., 1989).

HTLV-I associated myelopathy (HAM/TSP) and other inflammatory diseases associated with HTLV-I

HTLV-I has shown to be associated not only with HTLV-I associated myelopathy (HAM/TSP) but also with uveitis (Sasaki et al., 1989; Nakao & Ohba, 1993; Nakagawa et al., 1995; Mochizuki et al., 1996), T-lymphocyte alveolitis (Sugimoto et al., 1987; Vernant et al., 1988; Nakagawa et al., 1995), polymyositis (Higuchi et la., 1995, 1996), arthritis (Kitajima et al., 1989; Nishioka et al., 1989), and sicca syndrome (Vernant et al., 1988). There are also less certain associations with chronic infective dermatitis (LeGrande et al., 1990), Behçet disease (Kanazawa et al., 1993; Igakura et al., 1993), pseudohypoparathyroidism (Yoshida et al., 1993) and systemic lupus erythematosus (Takayanagui et al., 1997).

The prevalence of HAM/TSP is between 0.1 and 2% of HTLV-I-infected individuals. The lifetime risk of developing this disease among carriers is estimated to be 0.23% in Japan (Kaplan et al., 1990). About two-thirds of patients are female (Nakagawa et al., 1995). Other known risk factors for HAM/TSP include a high proviral load of HTLV-I (Nagai et al., 1998) and a certain HTLV-I subgroup (Furukawa et al., 2000). Most people infected with HTLV-I mount a strong cytotoxic T-lymphocyte (CTL) response to the virus (Jacobson et al., 1990; Bangham, 2000). This strong CTL response protects against the development of HAM/TSP by reducing the proviral load (Jeffery et al., 1999). However when the proviral load exceeds a threshold level, HTLV-I-specific CTL could contribute to inflammation (Nagai et al., 1998; Jeffery et al., 1999). The immunological response to HTLV-I is now beginning to be clarified (Bangham, 2000).

Clinical features of HAM/TSP

HAM/TSP is characterized by a spastic paraparesis that is slowly progressive, or in some cases static after initial progression, and anti-HTLV-I antibody positivity in serum and cerebrospinal fluid (Osame et al., 1986, 1987). Almost all patients show spasticity and/or hyperreflexia of the lower extremities, initially presenting as gait and urinary disturbances. Many patients manifest with low back pain, weakness of the lower extremities and a poorly defined (mild) sensory involvement. Rarely, the disease presents as cerebellar ataxia. Patients with younger age of onset (<15 years old) tend to have short stature and slow progression of the disease, while patients with older age of onset (>61 years old) show faster progression regardless of the mode of transmission (Nakagawa et al., 1995).

The clinical and laboratory guidelines for the diagnosis of HAM/TSP are summarized in Table 104.1, based on the recommendation of the WHO meeting (World Health Organization, 1989; Osame, 1990).

Patients with HAM/TSP have high antibody titres to HTLV-I both in serum and CSF (Osame et al., 1990). The presence of antibodies can be detected by ELISA or particle agglutination method and confirmed by Western blot (Osame et al., 1987) or PCR. Aside from HTLV-I antibody positivity, other characteristic laboratory findings include lymphocytic pleocytosis in the CSF and increased CSF neopterin levels (Nomoto et al., 1991, Nakagawa et al., 1995). In MRI, hyperintensities T_2-weighted are observed

Table 104.1. Diagnostic Guidelines for HAM/TSP

I Criteria

The florid picture of chronic spastic paraparesis is not always seen when the patient first presents. A single symptom or physical sign may be the only evidence of early HAM/TSP.

A *Age and sex incidence*

Mostly sporadic and adult but sometimes familial, occasionally seen in childhood; females predominant.

B *Onset*

This is usually insidious, but may be sudden.

C *Main neurological manifestations*

1 Chronic spastic paraparesis which usually progresses slowly, sometimes remains static after initial progression.
2 Weakness of the lower limbs, more marked proximally.
3 Bladder disturbance usually an early feature, and constipation usually occurs later, and impotence or decreased libido is common.
4 Sensory symptoms such as tingling, pins and needles, burning, etc. are more prominent than objective physical signs.
5 Low lumbar pain with radiation to the legs is common.
6 Vibration sense is frequently impaired, proprioception less often affected.
7 Hypeneflexia of the lower limbs, often with clonus and Babinski's sign.
8 Hyper-reflexia of upper limbs, and positive Hoffmann's and Tromner signs frequent. Weakness may be absent.
9 Exaggerated jaw jerk in some patients.

D *Less frequent neurological findings*

Cerebellar signs; optic atrophy; deafness, nystagmus, other cranial nerve deficits; hand tremor; absent or depressed ankle jerk. Convulsions, cognitive impairment, dementia or impaired consciousness are rare.

E *Other neurological manifestations which may be associated with HAM/TSP*

Muscular atrophy; fasciculations (rare); polymyositis; peripheral neuropathy; polyradiculopathy; cranial neuropathy; meningitis; encephalopathy.

F *Systemic non-neurological manifestations which may be associated with HAM/TSP*

Pulmonary alveolitis; uveitis; Sjögren's syndrome; arthropathy; vasculitis; ichthyosis; cryoglobulinemia; monoclonal gammopathy; adult T-cell leukemia/lymphoma.

II Laboratory diagnosis

A Presence of HTLV-I antibodies or antigens in blood and cerebrospinal fluid (CSF).
B CSF may show mild lymphocyte pleocytosis.
C Lobulated lymphocyte may be present in blood and/or CSF.
D Mild to moderate increase of protein may be present in CSF.
E Viral isolation possible from blood and/or CSF.

in the white matter similar to those found in multiple sclerosis (Newton et al., 1987; Kira et al., 1998; Furukawa et al., 1989). Swelling or atrophy of the spinal cord has been reported in few cases of HAM/TSP (Tashiro et al., 1989).

Histopathologic features of HAM/TSP

Autopsied cases mostly reveal severe involvement of the thoracic spinal cord. Histopathologic features include mononuclear cell infiltration, marked myelin and axonal destruction and astrocytic gliosis. Lesion distribution suggests that a chronic inflammatory process starts in the mid to low thoracic cord levels and extends both rostrally and caudally. Meningeal thickening involving the arachnoid has been seen with some cell infiltration. A non-random distribution of affected regions was suggested by an autopsy study which showed that the mainly affected regions are the so-called 'watershed' zones of the thoracic spinal cord in patients with HAM/TSP (Izumo et al., 1992). Inflammatory changes are inversely correlated with the duration of the disease, and significant cellular inflammation with expression of inflammatory cytokines and major histocompatibility complexes (MHC) (class I and II) is observed in cases of short duration (Umehara et al., 1993, 1994a). In presumably early lesions, the axons are relatively preserved. A predominance of CD8+ cells has been observed in cases of longer disease duration (Umehara et al., 1993). Both HTLV-I proviral DNA and HTLV-I tax gene expression were observed only in the CD4+ infiltrating

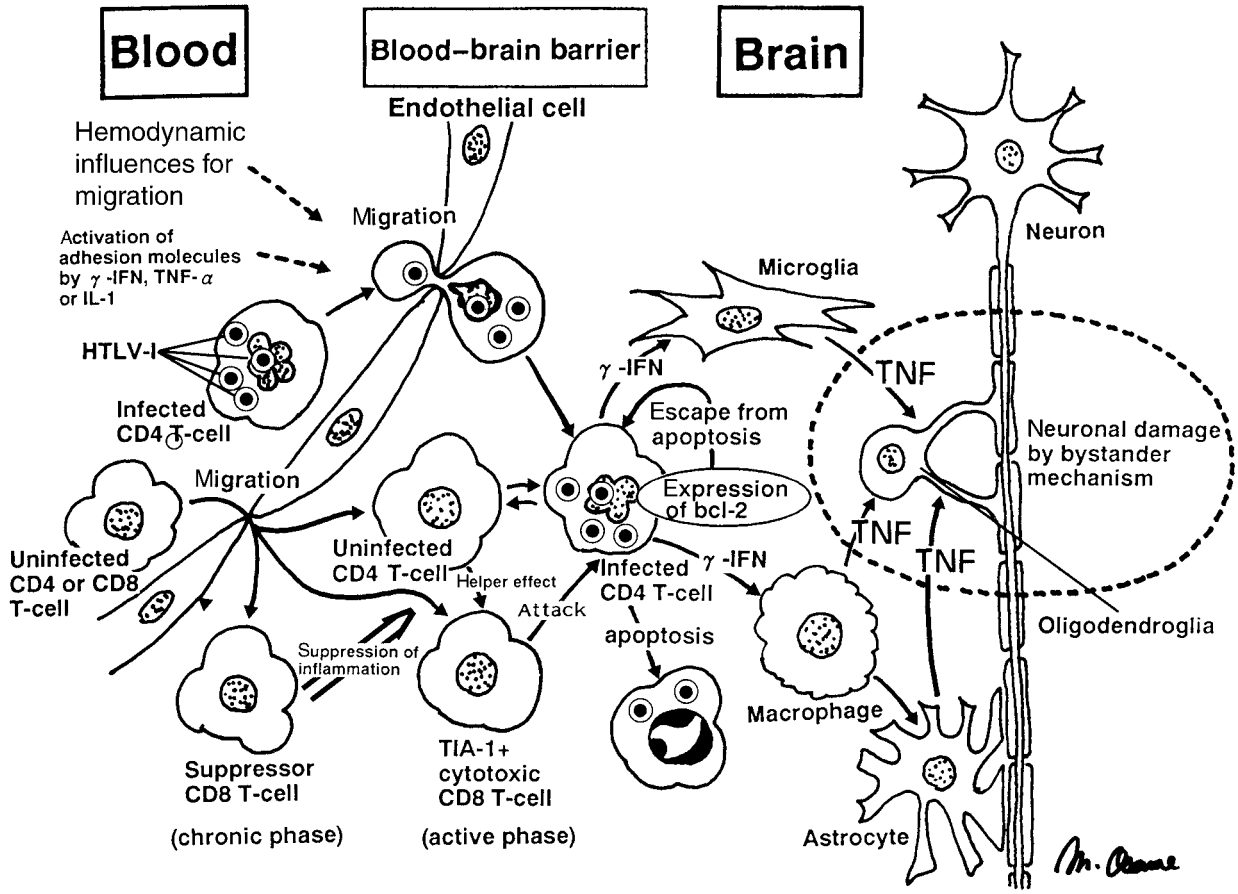

Fig. 104.1. Proposed pathogenesis of HAM/TSP based on currently available information.

mononuclear cells and not in other tissue cells in the spinal cord lesions (Moritoyo et al., 1996; Matsuoka et al., 1998). Activity of inflammation corresponded well with the amount of HTLV-I proviral DNA in situ, and responded with the presence of apoptosis of CD4+ T cells (Umehara et al., 1994b). The spinal cord lesions had greater expression of the adhesion marker, VCAM-1 on the endothelium compared with those of controls (Umehara et al., 1996). In the brain, perivascular mononuclear cell infiltration was also seen, but parenchymal infiltration was very sparse and was not associated with tissue destruction (Aye et al., 2000). The proposed pathomechanism of HAM/TSP is shown in Fig. 104.1.

Treatment of HAM/TSP

There is no definitive treatment yet established for HAM/TSP. Several clinical trials have shown transient beneficial effects of the following: corticosteroids, alpha-interferon, azathioprine, high-dose vitamin C, pentoxifylline, danazol, and plasmapheresis (Nakagawa et al., 1996). A double blind, multi-centre study on the therapeutic effect of treatment with natural interferon-α showed a significant treatment effect (Izumo et al., 1996). There is recent evidence that treatment with the nucleoside analogue lamivudine can reduce the provirus load of HTLV-I (Taylor et al., 1999), but the clinical impact of such treatment is not yet known.

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Clinical features of human prion diseases

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Introduction

Human prion diseases are rare disorders affecting the central nervous system, characterized by protracted incubation periods, progressive and eventually fatal neurological deficits and the deposition in the brain of prion protein (PrP) (Prusiner, 1994). Scientific interest in this group of diseases has been stimulated by the accumulating evidence in support of the prion hypothesis, which proposes that the transmissible causal agent is a post-translationally modified 'infectious' form of a normal host-encoded protein, PrP (Prusiner, 1982) (Chapter 6). There has also been an extraordinary level of public interest in prion diseases following the occurrence of bovine spongiform encephalopathy (BSE) and the proposition that this cattle disease has been transmitted to humans to cause a novel human prion disease, variant Creutzfeldt–Jakob disease (vCJD) (Will et al., 1996).

Although human prion diseases are rare, concern about the possibility of such a diagnosis is not uncommon, particularly after the extensive media coverage of the potential risks of BSE to public health. This chapter describes the clinical features and diagnosis of human prion diseases.

Classification of human prion diseases

Table 105.1 lists the different forms of human prion disease, which are classified according to etiology and distribution. Genetic forms of human prion diseases are associated with mutations of the prion protein gene (*PRNP*) which is located on chromosome 20 in humans (Gambetti et al., 1999). Codon 129 of *PRNP* is a polymorphic region, expressing either methionine or valine, and variations in genotype can influence susceptibility to disease and/or clinicopathological phenotype in all human prion diseases (Table 105.2).

Kuru

Kuru was transmitted from person to person through the consumption of infected tissues during cannibalistic rituals (Gajdusek, 1981). Women and children were most often affected, because they consumed the tissues such as brain, which contained the highest levels of infectivity (Alpers, 1979). The incidence of kuru has declined since the cessation of cannibalism in the late 1950s, but cases are still occurring with incubation periods exceeding 40 years (Klitzman et al., 1984).

In kuru homozygosity at codon 129 of *PRNP* is associated with an earlier age at onset and possibly a shorter incubation period than heterozygotes (Cervenakova et al., 1998). The codon 129 genotype does not have a major influence on the clinical features, but can influence the pathology with plaque deposition being more frequent with a methionine allele.

Sporadic CJD

This is the most common form of human prion diseases, accounting for about 90% of cases, and occurs worldwide with an incidence of approximately one case per million per annum (Will et al., 1998). Studies of the geographical distribution of cases within individual countries suggest a random distribution with no good evidence of clustering to suggest a point source of infection (Cousens et al., 1997). Case control studies have not identified any common environmental or medical risk factor for the development of disease (Wientjens et al., 1996) and the cause of sporadic CJD is unknown. It may be due to the spontaneous development of the disease-associated form of PrP within the brain with subsequent self-replication and eventual disease.

Over 70% of cases of sporadic CJD are methionine homozygous at codon 129 of *PRNP* in comparison to about 40% of the general population with this genotype

Table 105.1. Human prion diseases

Disease	Distribution	Etiology
Creutzfeldt–Jakob disease	Worldwide	Sporadic
Familial Creutzfeldt–Jakob disease	Many countries	Genetic
Gerstmann–Straussler–Scheinker syndrome	Many countries	
Fatal familial insomnia	Many countries	
Kuru	Papua New Guinea	Transmitted
Iatrogenic Creutzfeldt–Jakob disease	Many countries	
Variant Creutzfeldt–Jakob disease	UK (112 cases)	
	France (4 cases)	
	Republic of Ireland (1 case)	

Table 105.2. The codon 129 *PRNP* genotype distribution in the normal population and in human prion diseases (percentages)

	MM	MV	VW
Normal white population	39	50	11
Sporadic CJD	71	13	16
Kuru	30	45	25
Iatrogenic CJD			
central route	74	20	6
peripheral route	47	21	32
Variant CJD	100	0	0

(Alperovitch et al., 1999). Overall, in sporadic CJD the duration of illness is shorter and the age at death younger in methionine homozygotes, but the influence of *PRNP* codon 129 genotype on disease phenotype is complex (see below).

Familial prion disease

Familial forms of human prion disease account for about 10% of all cases and all are associated with mutations of PRNP (Gambetti et al., 1999). The majority are classified as familial CJD and are linked to point or insertional mutations in the open reading frame of *PRNP*. Gerstmann–Straussler–Scheinker syndrome (GSS) was originally associated with a point mutation at codon 102 of *PRNP* (Hsiao et al., 1989), but other mutations result in a similar phenotype. Fatal familial insomnia (FFI) is associated with a mutation at codon 178 of *PRNP* (Medori et al., 1992) and the importance of codon 129 in modulating expression of disease is underlined by the phenotypic variability with mutations at this locus. Cases expressing methionine in association with the 178 mutation develop FFI, while those expressing valine have a phenotype similar to sporadic CJD (Goldfarb et al., 1992).

Iatrogenic CJD

CJD has been transmitted accidentally from person to person in the course of a range of medical or surgical treatments (Brown et al., 2000) (Table 105.3). All these iatrogenic transmissions have involved potential transfer from patient to patient of the high levels of infectivity found in the central nervous system in prion diseases. Human growth hormone (HgH) and gonadotrophin were extracted from cadaveric human pituitary glands and the eye is known to contain significant levels of infectivity in prion diseases. Accidental transmission of CJD through blood or blood products has not been documented (Wilson et al., 2000) and guidelines have been introduced to minimize the risks of iatrogenic transmission, for example the recommendation that all neurosurgical or ophthalmological instruments should be destroyed after use in patients with CJD.

The incubation period in sporadic CJD is unknown, but in iatrogenic CJD the incubation periods can be estimated. With a central route of infection into or adjacent to the brain the incubation period is 1.5 to 6 years, while with the peripheral route, as in HgH injections, the incubation period mean is about 12 years with a range of 4.5 to over 30 years.

Homozygosity at codon 129 of *PRNP* predisposes to iatrogenic CJD, with an excess of methionine homozygotes in dura mater related cases and an excess of valine homozygotes in HgH recipients with CJD (Brown et al., 2000). There is little evidence that codon 129 genotype influences disease expression in iatrogenic CJD, but heterozygosity

Table 105.3. Summary of iatrogenic cases of CJD from all causes

Mode of infection	Number of patients	Agent of entry into brain	Medical incubation period (range)[a]	Clinical signs on presentation[b]
Corneal transplant[b]	3	Optic nerve	16, 18, 320 mos	Dementia/cerebellar
Stereotactic EEG	2	Intra-cerebral	16, 20 mos	Dementia/cerebellar
Neurosurgery	5	Intra-cerebral	17 mos (12–28)	Visual/dementia/cerebellar
Dura mater graft	114	Cerebral surface[c]	6 yrs (1.5–18)	Cerebellar (visual/dementia)
Growth hormone	139	Hematogenous (?)	12 yrs (5–30)	Cerebellar
Gonadotrophin	4	Hematogenous (?)	13 yrs (12–16)	Cerebellar

Notes:

[a] Calculated from the mid-point of treatment to the onset of disease.

[b] One definite, one probable, and one possible case.

[c] In two cases, dura was used to embolize vessels of non-CNS tissues, rather than as intracranial grafts.

may prolong the incubation period in HgH-related CJD (Deslys et al., 1996).

Variant CJD

This novel form of human prion disease was identified in the UK in 1996 (Will et al., 1996) and it was proposed that this human disease might be caused by BSE. Since 1996 there have been 112 cases of vCJD in the UK, 4 in France and 1 in Ireland, consistent with the relative sizes of the BSE epidemics in these countries. The clinical and pathological features of vCJD have not been identified in any historical case of CJD, and laboratory transmission studies have demonstrated that the characteristics of the transmissable agent in vCJD are very similar to the BSE agent (Bruce et al., 1997; Hill et al., 1997a; Scott et al., 1999). There is now compelling evidence that BSE is the cause of vCJD, and it is thought that the most likely mechanism of transmission was through human consumption of bovine CNS tissues containing high levels of infectivity (Will, 1999). The future number of vCJD cases cannot be predicted.

All tested cases of vCJD have been methionine homozygous at codon 129 of *PRNP*. However, cases of human BSE infection in association with other codon 129 genotypes could occur in the future, perhaps with a different clinical or pathological phenotype.

Clinical features of human prion diseases

Kuru

There is a prodrome of headache and limb pains followed by a progressive cerebellar syndrome involving midline trunkal ataxia, tremor and titubation (Alpers, 1987). Dysarthria and gait ataxia develop as the illness progresses and, although terminally there is severe neurological disability, myoclonus does not occur and dementia is conspicuous by its absence. Even in the terminal moribund, akinetic and mute state, most patients can attempt to carry out simple commands. In juveniles the overall clinical picture is similar to adults, although brain stem signs are common, including nystagmus, strabismus, facial weakness and ptosis.

The total duration of illness ranges from 12–18 months in adults and 3–12 months in children.

Sporadic CJD

The characteristic clinical features of sporadic CJD are rapidly progressive dementia, myoclonus and death within a few months (Will & Matthews, 1984). These features are associated with a range of focal cortical deficits, which accumulate rapidly and lead to severe neurological disability. The mean duration of illness in sporadic CJD is only about 4 months, although there is a wide range with about 10% of cases surviving for over a year and 5% over 2 years (Fig. 105.1). Sporadic CJD is mainly a disease of late middle age with a mean age at death of about 65 years (Fig. 105.2).

The presenting symptoms (Table 105.4) of sporadic CJD vary with dementia, ataxia and behavioural disturbance occurring most frequently. Rare presentations include a pure cerebellar syndrome (The Brownell–Oppenheimer variant), cortical blindness with visual hallucinations (the Heidenhain variant) and a stroke-like onset (McNaughton & Will, 1997). One striking feature of sporadic CJD is the relentless multifocal progression in

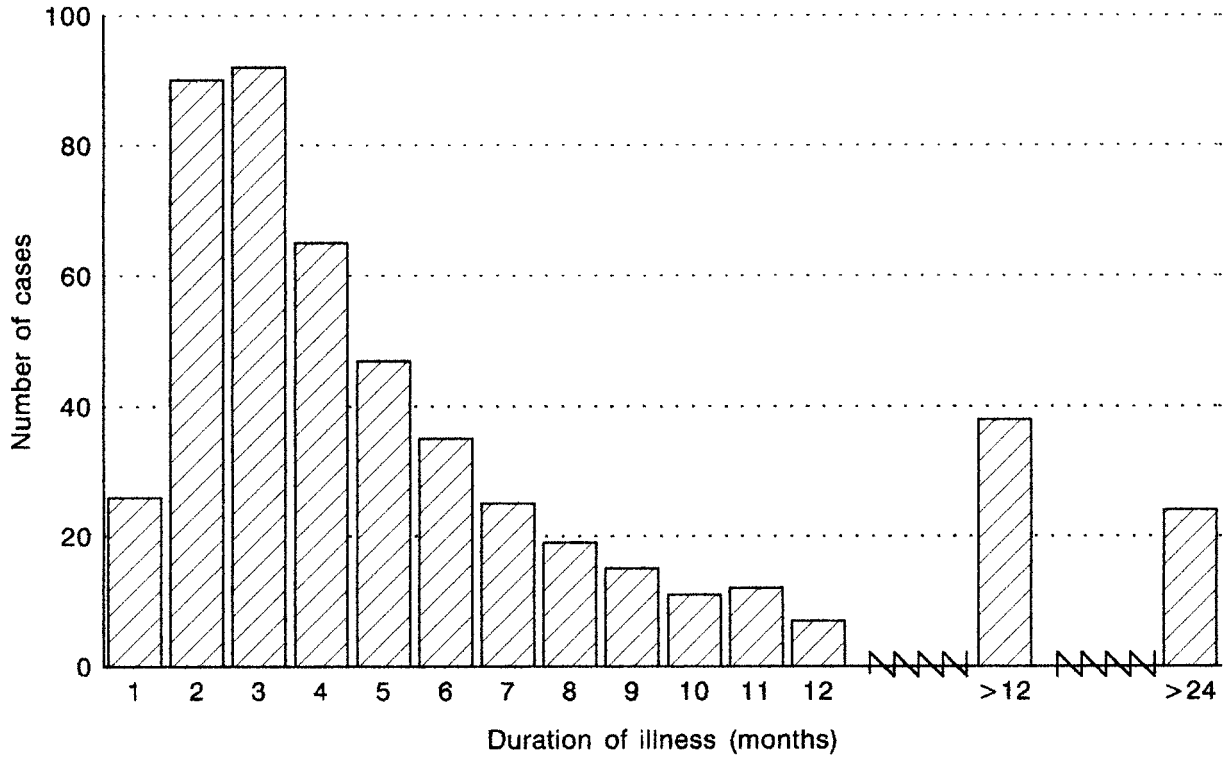

Fig. 105.1. Sporadic Creutzfeld–Jacob disease UK Study 1 May 1990–November 2001 ($n = 506$). Duration of illness (months).

neurological deficits. Patients with initial ataxia may develop dementia, myoclonus and rigidity, while patients with initial dementia may develop ataxia, cortical blindness and dysphasia. There may be great variation in the symptoms during the illness, but the rapid evolution of deficits involving multiple cortical areas is typical of sporadic CJD.

The signs in sporadic CJD (Table 105.4) parallel the variation in clinical symptomatology. The most frequent initial signs are cognitive impairment or ataxia, but as the illness evolves a range of neurological signs may develop, including myoclonic involuntary movements of the limbs and/or trunk in about 80% of cases (Brown et al., 1994). All patients develop dementia and the majority ataxia and paratonic rigidity of the limbs. Other signs include dysphasia, cortical blindness and primitive reflexes. Lower motor neuron signs are rare. Terminally most patients develop akinetic mutism and death is often due to intercurrent infection such as pneumonia.

The clinical presentation in sporadic CJD is relatively stereotyped, but there are atypical cases with a long duration of illness (Brown et al., 1984) or with a relatively young age at onset of symptoms. Western blot analysis has led to the identification of two types of PrP that can be deposited in the brain in sporadic CJD (Parchi et al., 1996) and this, combined with the codon 129 genotype, has led to the identification of 6 subgroups of sporadic CJD with largely different phenotypes (Parchi et al., 1999) (Table 105.5). The majority of cases are MM or MV type 1 and have a phenotype typical of sporadic CJD. The other subtypes represent the atypical forms of sporadic CJD, for example VV type 1 cases which have a prolonged clinical illness and a young age at death.

Familial prion disease

The clinical features in familial forms of human prion disease vary overall according to the underlying mutation of *PRNP* (Table 105.6), but there are inconsistencies in phenotype both between and within families (Gambetti et al., 1999). As a group the mean age at death is about 10 years less in hereditary cases compared to sporadic cases and the clinical illness is often more protracted and can extend to many years.

Worldwide, the codon 200 mutation is the most frequently identified and is associated with a clinical picture

Table 105.4. Symptoms at presentation and signs during clinical course in sporadic CJD (percentage of cases)

Symptom	Percentage	Sign	Percentage
Unsteadiness	30	Dementia	100
Forgetfulness	29	Myoclonus	82
Behavioural change	23	Cerebellar	64
Visual	14	Pyramidal	62
Dizziness	11	Dysphasia	60
Headache	8	Akinetic mutism	57
Speech disturbance	5	Primitive reflexes	44
Sensory	4	Cortical blindness	32
Involuntary movements	3	Lower motor neuron	11

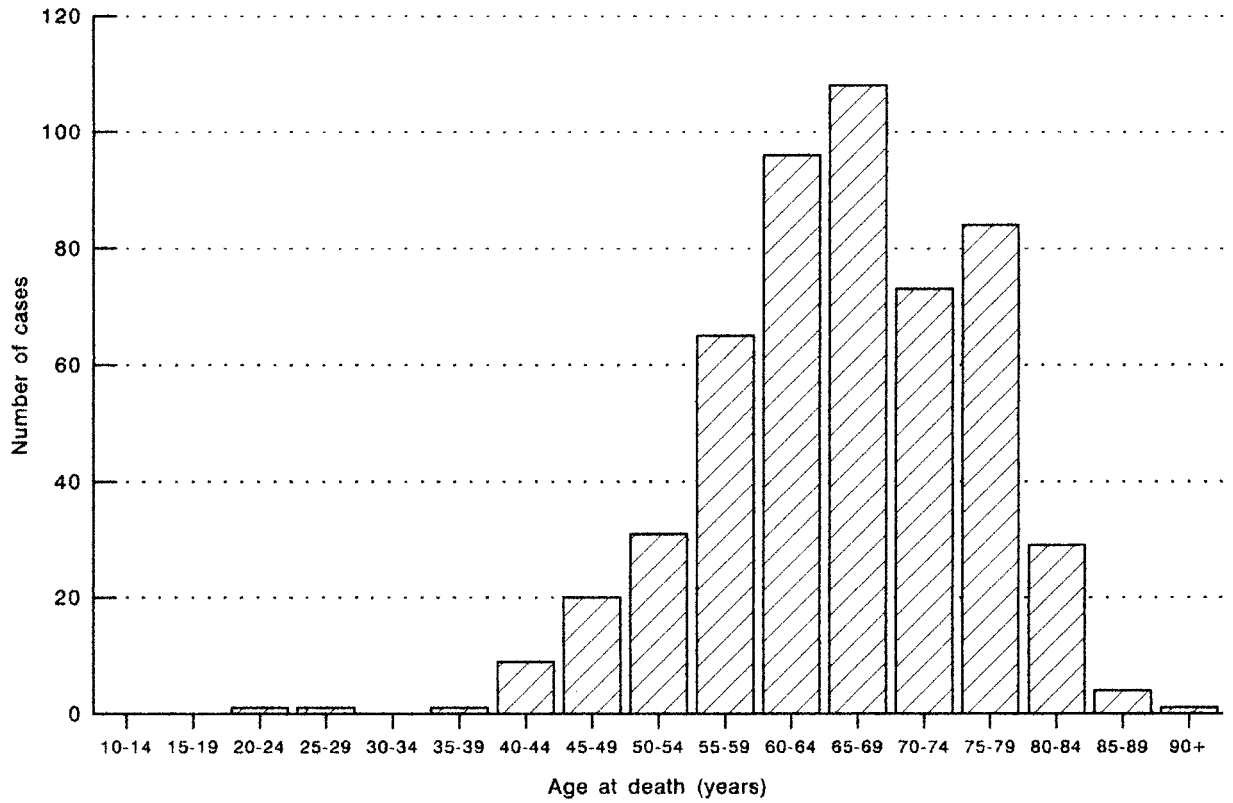

Fig. 105.2. Age at death in sporadic CJD UK Study 1 May 1990–November 2001 ($n = 523$).

that is very similar to sporadic CJD (Brown et al., 1991a). Other mutations with a similar phenotype to sporadic CJD are listed in Table 105.6 and include the codon 178 mutation in association with valine at codon 129 of *PRNP*. GSS is characterized clinically by slowly progressive ataxia with pyramidal signs and cognitive impairment later in the clinical course (Brown et al., 1991b). The clinical features in insert mutations are variable with some cases similar to sporadic CJD and others to GSS. The codon 178 mutation associated with methionine at codon 129 of *PRNP* causes the FFI phenotype with early insomnia and dysautonomia followed only later by cognitive impairment and sometimes other features reminiscent of sporadic CJD (Gambetti et al., 1993).

Table 105.5. Variants of sporadic CJD classified by codon 129 genotype and prion protein isotype[a]

Sporadic CJD Variant	Percentage of cases	Clinical features	Neuropathological features
MM1 or MV1	70	Rapidly progressive dementia Myoclonus Typical EEG	Classic sporadic CJD pathology
VV2	16	Ataxia at onset Late dementia EEG often not typical	Subcortical involvement including brain stem PrP staining shows plaque-like focal deposits
MV2	9	Ataxia and progressive dementia EEG not typical Long duration	Similar to VV2 but with amyloid-kuru plaques in the cerebellum
MM2 – thalamic	2	Insomnia, ataxia and cognitive impairment EEG not typical	Prominent atrophy of the thalamus and inferior olive Little spongiosis PrP detected in lower amount than in other subtypes
MM2 – cortical	2	Progressive dementia EEG not typical Long duration	Large confluent vacuoles with perivacuolar PrP staining Cerebellum relatively spared
VV1	1	Young age at onset (mean 40 yrs) Progressive dementia EEG not typical Long duration	Severe pathology in the cerebral cortex and striatum Sparing of brain stem and cerebellum

Notes:
[a] adapted from Parchi et al. (1999).

Table 105.6. Mutations of the prion protein gene

Mutation	Description	Typical clinical features
178M	Fatal familial insomnia	Insomnia, dysautonomia, late dementia
102	GSS	Slowly progressive cerebellar syndrome, late dementia
105	GSS	Spastic paraparesis, late dementia
117	GSS	Dementia, Parkinsonism
198	GSS	like GSS with 102 mutation
212	GSS	like GSS with 102 mutation
217	GSS	like GSS with 102 mutation
178V	Familial CJD	Like sporadic CJD
145	Familial CJD	Slowly progressive dementia
180	Familial CJD	Like sporadic CJD
200	Familial CJD	Like sporadic CJD
208	Familial CJD	Like sporadic CJD
210	Familial CJD	Like sporadic CJD
232	Familial CJD	Like sporadic CJD
Insert	Familial CJD	Mixed – usually like sporadic CJD but can be similar to GSS

Iatrogenic CJD

In iatrogenic CJD the clinical phenotype is determined by the route of infection (Brown et al., 1992). With introduction of infection in, or adjacent to, the central nervous system, the clinical picture is similar to sporadic CJD. With infection by a peripheral route, as in HgH recipients, there is a progressive cerebellar syndrome, without myoclonus, and cognitive impairment does not develop until late in the clinical course, if at all. The mean duration of illness also varies, with survival of approximately 2–12 months with central infection and 8–18 months following infection by a peripheral route.

Variant CJD

The clinical features of vCJD are remarkably consistent in comparison to the variation seen in other human prion diseases and are also relatively distinct (Zeidler et al., 1997). The mean duration of illness in vCJD of about 14 months is significantly more prolonged than sporadic CJD (Fig. 105.3), and vCJD affects a younger age group with a mean age at death of 29 years (Fig. 105.4).

In vCJD there is an initial phase, lasting for months, in which there are psychiatric symptoms including

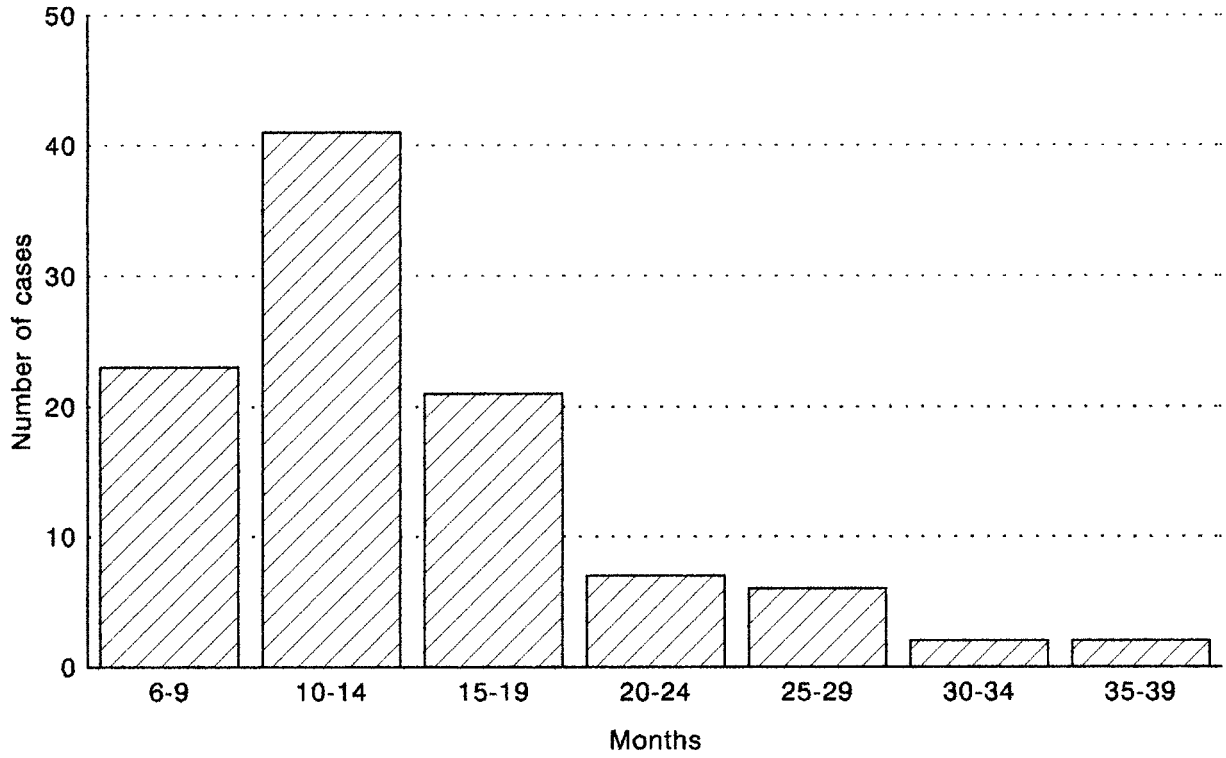

Fig. 105.3. Definite or probable vCJD UK Study 1995–November 2001 ($n = 102$). Duration of illness (months).

depression, anxiety and withdrawal, which may be impossible to differentiate from conventional psychiatric illness (Will et al., 1999). During this period some patients develop painful sensory disturbance in the limbs, trunk or face and some describe unsteadiness of gait or forgetfulness. After about 6 months, ataxia of gait develops, sometimes with associated dysarthria, and there is progressive cognitive impairment. Involuntary movements develop and may include chorea and dystonia as well as myoclonus (Will et al., 2000). Terminally the illness is similar to sporadic CJD, with a proportion of cases developing akinetic mutism. Death often follows intercurrent infection such as pneumonia.

Diagnosis of human prion diseases

In the absence of any serological test for infection, the diagnosis of all forms of human prion disease depends on recognition of the clinical features and applying a range of investigations to provide support for the diagnosis and to exclude other conditions. A definite diagnosis requires neuropathological validation, usually after postmortem. Diagnostic criteria for sporadic, iatrogenic, familial and variant CJD have been proposed and partially validated (Tables 105.7 and 105.8). Cases fulfilling criteria for 'probable' sporadic or vCJD are very likely to be suffering from the disease.

- The diagnosis of sporadic CJD is usually suspected because of the suggestive combination of rapidly progressive dementia, focal neurological deficits and myoclonus. The electroencephalogram (EEG) and the cerebrospinal fluid (CSF) 14-3-3 immunoassay are the most helpful investigations.
- Familial forms of human prion disease may be suspected because of a family history of a similar disorder. However, a positive family history of CJD is found in only about a third of mutation-related cases and about a further third have a family history of other neurodegenerative disease. *PRNP* gene analysis is necessary to confirm the presence of a mutation.
- The possibility of iatrogenic CJD may be raised by the development of a progressive neurological disorder in an individual with a recognized risk factor.
- The diagnosis of vCJD depends on the recognition of suggestive neurological features such as depression,

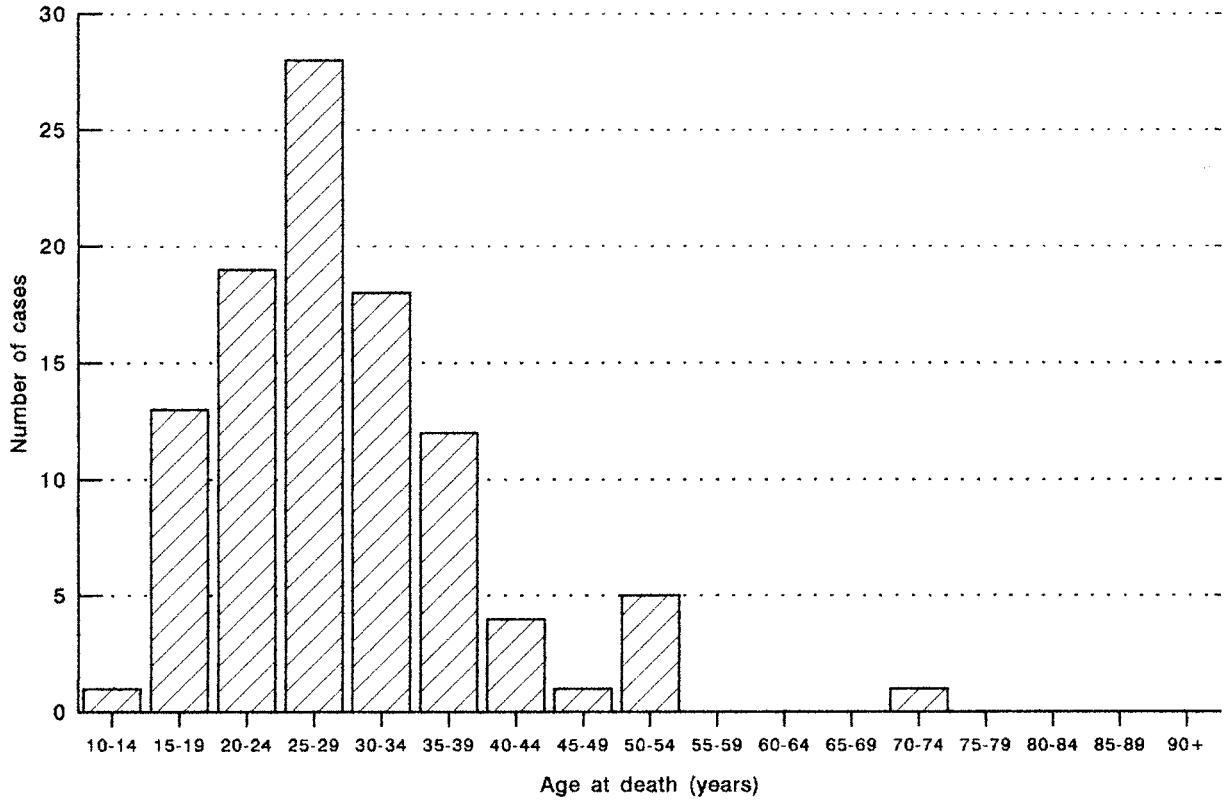

Fig. 105.4. Age at death in variant CJD UK Study 1995–November 2001 ($n = 102$).

ataxia and chorea in a patient of relatively young age. The MRI brain scan is the most helpful investigation.

Investigations in human disease

Routine hematological and biochemical tests are usually normal in human prion diseases, although a minority of cases of sporadic or vCJD may have minor abnormalities in liver function tests. The CSF is acellular, but may show an elevated protein content. The CSF 14-3-3 protein is a marker of neuronal damage and is elevated in over 90% of cases of sporadic CJD (Zerr et al., 2000), in a proportion of cases with familial or iatrogenic CJD and in about 50% of cases of vCJD (Green et al., 2001). In the appropriate clinical context a positive 14-3-3 CSF immunoassay has a high sensitivity and specificity for the diagnosis of sporadic CJD, but is less useful in the diagnosis of other forms of human prion disease.

The EEG is the most important investigation in sporadic CJD, showing generalized periodic complexes (Fig. 105.5) in about 70% of cases (Bortone et al., 1994). These changes are relatively specific for sporadic CJD, although they can be seen in some metabolic and toxic disorders. In vCJD the EEG is either normal or shows non-specific slow wave changes.

CT brain scan does not show any specific findings in CJD, but is important in the exclusion of other conditions, some of which may be treatable. Although cerebral atrophy may occur, particularly in cases with long survival, many patients have a normal scan as this investigation is often carried out relatively early in the clinical course as part of the diagnostic work-up. MRI brain scan is a more useful investigation, as high signal in the basal ganglia or thalamus supports the diagnosis of CJD. In sporadic CJD observational studies have suggested that a significant proportion of cases have symmetrical high signal changes on T_2-weighted images in the caudate and putamen regions (Finkenstaedt et al., 1996) (Fig. 105.6). However, the MRI findings have not yet been included in the diagnostic criteria for sporadic CJD as the sensitivity and specificity of the MRI abnormalities are uncertain. In vCJD the MRI scan shows symmetrical high signal changes in the pulvinar region of the posterior thalamus on T_2-weighted images in at least 75% of cases (Zeidler et al., 2000) (Fig. 105.7) and these abnormalities can be more apparent on FLAIR or diffusion-weighted images. These MRI scan

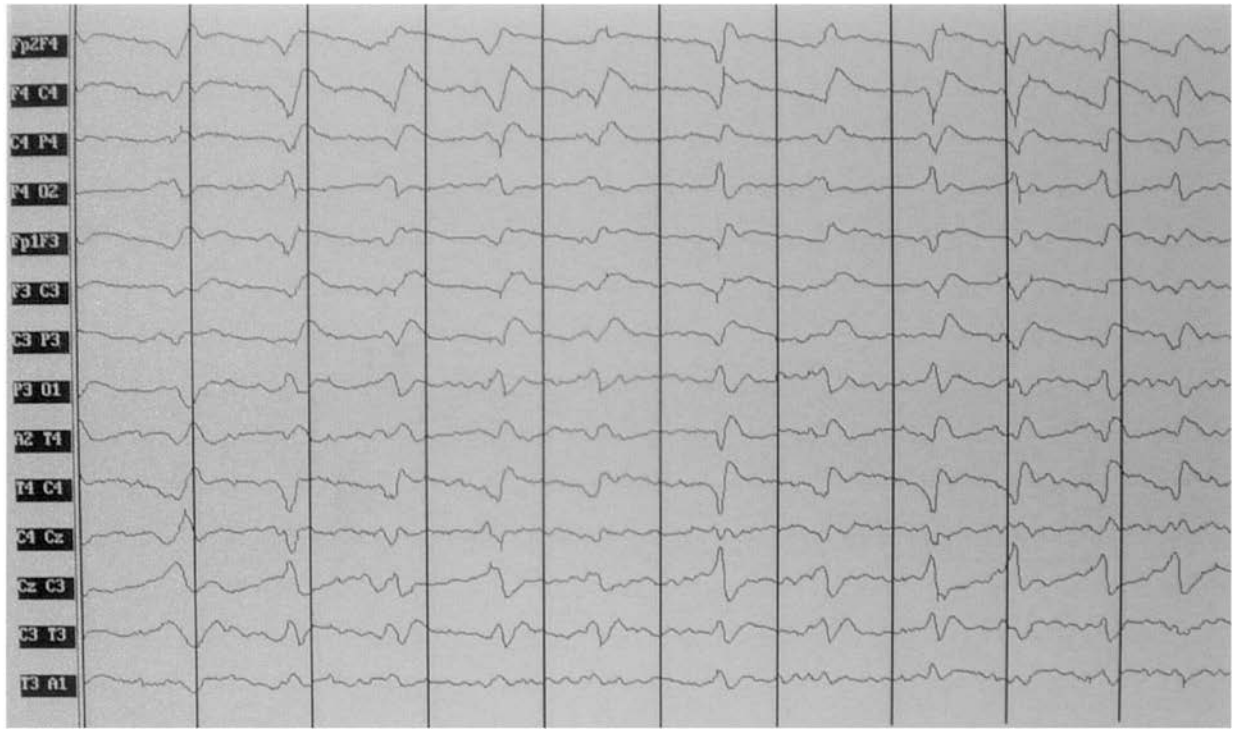

Fig. 105.5. EEG in sporadic CJD showing periodic complexes.

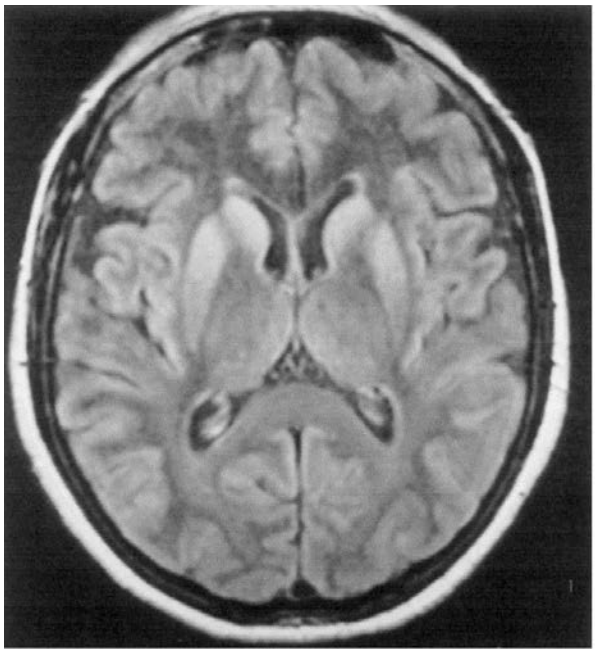

Fig. 105.6. Sporadic CJD: FLAIR axial image. High signal is seen in the putamen and caudate head laterally.

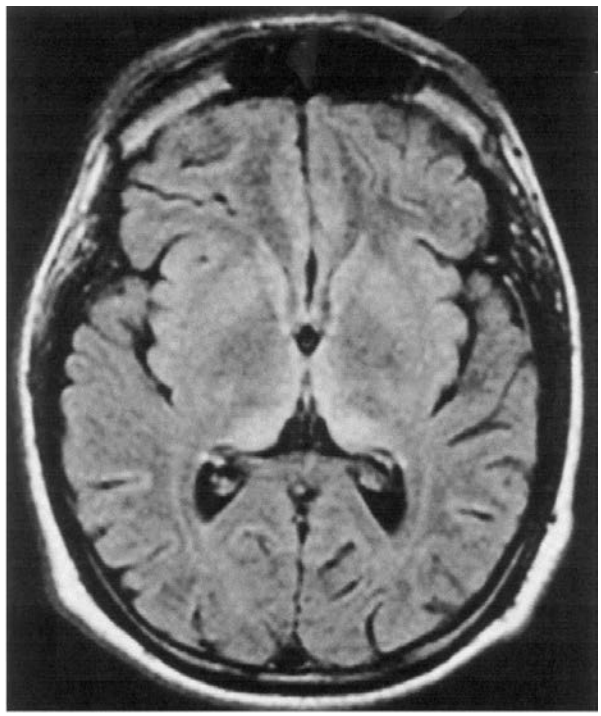

Fig. 105.7. Variant CJD: FLAIR axial image. Symmetrical high signal is seen in the pulvinar of the thalamus. This is known as the 'pulvinar sign of vCJD'.

Table 105.7. Diagnostic criteria for sporadic, iatrogenic and familial CJD

1	*Sporadic*		
	I		Rapidly progressive dementia
	II	A	Myoclonus
		B	Visual or cerebellar problems
		C	Pyramidal or extrapyramidal features
		D	Akinetic mutism
	III		Typical EEG
1.1	Definite:		Neuropathologically/ immunocytochemically confirmed
1.2	Probable:		I + 2 of II + III or Possible + positive 14-3-3
1.3	Possible:		I + 2 of II + duration <2 years
2	*Accidentally transmitted CJD*		
2.1	Definite		
	Definite CJD with a recognized risk.		
2.2	Probable		
2.2.1			Progressive cerebellar syndrome in human pituitary hormone recipients.
2.2.2			Probable CJD with recognized risk.
3	*Familial TSEs*[a]		
3.1	Definite		
	Definite TSE plus definite or probable TSE in a first-degree relative.		
3.2	Probable		
3.2.1			Probable TSE plus definite or probable TSE in a first degree relative.
3.2.2			Progressive neuropsychiatric disorder plus disease-specific mutation.

Notes:
[a] Including GSS and FFI.

Table 105.8. Diagnostic criteria for variant CJD

I	A	Progressive neuropsychiatric disorder
	B	Duration of illness >6 months
	C	Routine investigations do not suggest an alternative diagnosis
	D	No history of potential iatrogenic exposure
	E	No evidence of a familial form of TSE
II	A	Early psychiatric symptoms[a]
	B	Persistent painful sensory symptoms[b]
	C	Ataxia
	D	Myoclonus or chorea or dystonia
	E	Dementia
III	A	EEG does not show the typical appearance of sporadic CJD[c] (or no EEG performed)
	B	Bilateral pulvinar high signal on MRI scan
IV	A	Positive tonsil biopsy[d]

DEFINITE:	I A and neuropathological confirmation of vCJD[e]
PROBABLE:	I and 4/5 of II and III A and III B OR I and IV A[d]
POSSIBLE:	I and 4/5 of II and III A

Notes:
[a] depression, anxiety, apathy, withdrawal, delusions.
[b] this includes both frank pain and/or dysesthesia.
[c] generalized triphasic periodic complexes at approximately one per second.
[d] tonsil biopsy is not recommended routinely, nor in cases with EEG appearances typical of sporadic CJD, but may be useful in suspect cases in which the clinical features are compatible with vCJD and MRI does not show bilateral pulvinar high signal.
[e] spongiform change and extensive PrP deposition with florid plaques, throughout the cerebrum and cerebellum.

abnormalities have a high sensitivity and specificity for the diagnosis of vCJD and are included in the diagnostic criteria.

Invasive diagnostic procedures such as brain biopsy remain controversial. In many countries brain biopsy is discouraged because the diagnosis of CJD can usually be made with some confidence on clinical grounds, the procedure does not alter patient management and it has risks. In other countries brain biopsy is carried out to allow confirmation of the diagnosis in life and to exclude potentially treatable disorders, for example cerebral vasculitis. Tonsil biopsy has been advocated as a diagnostic procedure in vCJD (Hill et al., 1997b) because, in contrast to sporadic and iatrogenic CJD, immunostaining for PrP is positive in lymphoreticular tissues, including tonsil. Although tonsil biopsy may allow more confidence in the diagnosis in life, the procedure has risks and is of no direct benefit to the patient.

Conclusion

Human prion diseases are rare, but these are devastating disorders for the patient and their family. Early diagnosis is an important objective as it is difficult for the doctor and the family to see a previously fit person deteriorate so rapidly without a diagnosis. In sporadic CJD the affected patient often loses awareness and insight fairly quickly, but a frank explanation of the nature of the illness and prognosis can be helpful to the relatives. Managing patients with CJD can be difficult because of the rapid development of

cumulative neurological deficits. Symptomatic treatment of distress and involuntary movements can be effective, but there is no treatment available for the underlying disease process. In view of the possibility that a large number of people may have been exposed to the BSE agent in the UK and in other countries an important scientific objective is the discovery of an effective prophylactic treatment for human prion diseases.

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Bacterial infections

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Infections of the central nervous system (CNS) are notable for rapid progression resulting in death or permanent damage in a very short time (Baraff et al., 1993; Grimwood et al., 1995). CNS infections share many distinct characteristics, which distinguish them from systemic infections. The CNS is confined anatomically within a bony casement which allows little room for expansion following inflammatory responses; the resulting increase in intracranial pressure may cause severe damage to the structures within. The CNS also lacks a well-developed conventional immune system to defend against offending pathogens, and thus infections are more difficult to eradicate than in the periphery. Because of the presence of the blood–brain barrier (BBB), delivery of antimicrobial agents in adequate concentrations is difficult. As vital tissues are involved, CNS infections can cause devastating sequelae, and in some cases may result in both neurological and medical emergencies. Understanding their pathophysiological mechanisms, neuroanatomical principles, clinical manifestations and neuroaradiological features is essential to providing effective treatment.

Infections can primarily occur either within the brain parenchyma or in the spaces between the different layers of the brain called meninges. Between the dura mater and the arachnoid lies the subdural space, through which the veins course from the brain surface to the venous sinuses. The dura mater is tightly bound to the inner table of skull, and hence intracranially the epidural space is a potential space; along the spinal column, the dura is separated from bone by fat and other structures. The subarachnoid space refers to the space between the pia mater and the arachnoid membrane which contains CSF and the medium-sized arteries supplying blood to the brain. CSF in the ventricles is in continuity with the CSF in the subarachnoid space through the foramina of Luschka and Magendie. The CSF is finally absorbed by the arachnoid granulations to drain into the venous sinuses.

Bacterial meningitis

Bacterial meningitis is an inflammatory response to infection of the pia-arachnoid and the CSF of the subarachnoid space. Since the subarachnoid space is continuous throughout the neuraxis, this inflammation extends throughout the subarachnoid space as well as ventricles. When there is accompanying obvious brain involvement, it is more appropriately called meningoencephalitis. Histologically, most meningitides include some parenchymal involvement, but when clinical signs of meningeal inflammation predominate one traditionally refers to the condition as meningitis. Knowledge of the anatomic details and CSF flow pathways is important to understand the pathophysiologic manifestations.

Historical background

Meningitis was first described in detail by Gaspard Vieusseux as malignant purpuric fever in 1805 following an outbreak in Switzerland. Following the introduction of lumbar puncture in 1891 by Quinke, the CSF changes associated with meningitis were recognized, and attempts made at treatment with CSF drainage and irrigation with a variety of fluids. Survival from bacterial meningitis improved following the development of horse antimeningococcal antiserum and its intrathecal and systemic administration by Simon Flexner during the first world war. However, a much more substantial impact on outcome followed the advent of antimicrobial therapy. Although sulfonamides were discovered in 1908, their antibiotic potential was not appreciated until 1932 with the discovery of sulfachrysoidine (Prontosil). The subsequent isolation of penicillin by Howard Florey in 1941 further improved survival from bacterial meningitis. Though the techniques of its administration and dosage

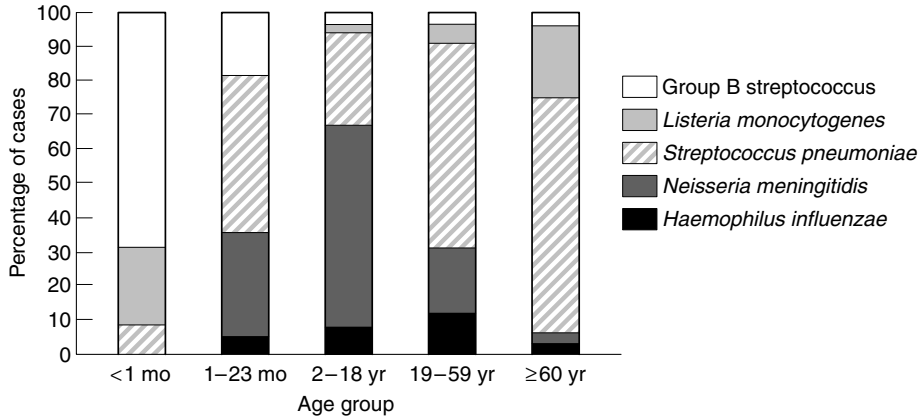

Fig. 106.1. Pathogenic agents for bacterial meningitis according to age group. (From Schuchat, 1997.)

have changed, and newer antibiotics have been developed, penicillin remained one of the most important drugs in the treatment of bacterial meningitis until the worldwide emergence of penicillin-resistant pneumococci in the 1990s. Further successes occurred in the last few decades with the synthesis of the third- and fourth-generation cephalosporins, and breakthroughs in immunizations against *Neisseria meningitidis* and *Hemophilus influenzae* type B.

Epidemiology

Bacterial meningitis is a fairly common problem, with an incidence varying between 4.6 and 10 per 100 000 people per year in US; it is much more common in developing countries. Until recently, the extremes of age were primarily involved, with the majority of cases occurring in children below 5 years. In a prospective laboratory-based surveillance project during 1986, covering a population of 34 million (thus representing 14% of US population), the overall incidences of the three most common organisms responsible for about 80% of cases of bacterial meningitis were 2.9, 1.35 and 1.0 per 100 000 population for *H. influenzae, N. meningitidis,* and *Streptococcus pneumoniae* (Wenger et al., 1990).

However, the most dramatic recent change in the epidemiology of bacterial meningitis has been a virtual disappearance of *H. influenzae* meningitis in populations immunized against this organism. Since the introduction of the *H. influenzae* type B conjugate vaccine, the common etiological agents are *S. pneumoniae* (47%), *N. meningitidis* (25%), *S. agalactiae* (group B streptococcus, 12%), *Listeria monocytogenes* (8%) and *H. influenzae* (7%) (Schuchat et al., 1997).

In addition, there was an overall decrease in the total number of cases of bacterial meningitis from 12 920 cases from these five common pathogens in 1986 to 5755 cases in 1995 (Schuchat et al. 1997). Apart from a 94% decrease in *H. influenzae* meningitis, there was also decrease in the number of cases secondary to *N. meningitidis* and group B streptococcus by 33% and 25% respectively. The median age of bacterial meningitis also changed from 15 months in 1986 to 25 years in 1995.

The organisms responsible for bacterial meningitis thus depend on the age of the patient (Fig. 106.1) and a number of other host factors. The relative frequency of each organism varies with geographic location (Sung et al., 1997) and race (Schuchat et al., 1997; McIntyre, 1998). Socioeconomic conditions also have a major impact on epidemiology of meningitis (Jones et al., 1997).

Pneumococcal meningitis is more common in adults over 30 years of age. A partial list of predisposing conditions include asplenic states (either physical or functional), multiple myeloma, immunoglobulin deficiency states, alcoholism, cirrhosis, and the Wiscott–Aldrich syndrome. It is also the most common organism responsible for recurrent meningitis in patients with history of prior head injury and residual CSF leak. There are 84 serotypes, of which about 14 cause disease in humans.

Meningococcal meningitis is most often encountered in children and young adults, and may occur in epidemics. Until 1946, meningococcal meningitis occurred in epidemics in the United States, but since then has been seen there only in local outbreaks, while still occurring in frequent epidemics in the developing countries, especially sub-Saharan Africa. However, clusters of meningococcal disease have been increasingly reported recently among adolescents and young adults in the US. Most of these clusters have

been associated with secondary schools and serogroup C strains (Gold, 1999). The use of serogroup C meningococcal vaccine can terminate such clusters (Gold, 1992), and guidelines to control such outbreaks are available (ACIP, 1997). Hot and dry climate, respiratory infections damaging the host defences, shifting antigenicity of the group A meningococcus, and blocking IgA antibodies induced by cross-reacting gram-negative enteric bacilli are some of the factors responsible for epidemics. There are 13 major serogroups, of which A, B, C, W, and Y most commonly cause meningitis. Serogroups A and C are commonly isolated in epidemics, and groups B, W, and Y occur in endemic or sporadic cases. Recently, serogroup C has been reported to be replacing serogroup B strains in certain endemic areas (Ashton et al., 1991). Serogroup B also is seen with sporadic cases, and serogroup Y is in addition associated with pneumonia. Nasopharyngeal carriage provides the usual reservoir of the organism, and such colonization serves as the portal of entry for the organism. Infection is more common with individuals having deficiencies in the terminal complement components (C5 to C8) and properdin. Antibodies to surface antigens of the bacteria are the major determinants of natural immunity (Griffiths et al., 1987; Jones et al., 1998).

Group B streptococci are an important cause of neonatal meningitis, accounting for approximately 70% of cases. They cause meningitis less frequently in adults, accounting for an overall incidence of 13% of bacterial meningitis of all age groups (Schuchat et al., 1997) (see Fig. 106.1). In early-onset cases (<7 days after birth), the organism is acquired from the mother's genital tract during delivery, whereas the source of the late onset is unclear (Spach & Jackson, 1999).

H. influenzae was the commonest organism responsible for meningitis in children between six months and six years of age until the introduction of the vaccine; more than 90% of cases were due to the capsular type B strains. Non-typable strains (NTHi) are responsible for recurrent meningitis and infections in non-immunized children. Nasopharyngeal colonization is a common preceding event prior to systemic invasion. It is not an typical isolate in patients older than 6 years, unless there is a predisposing condition increasing the risk of infection with encapsulated organisms.

L. monocytogenes infection is more likely in neonates, the elderly, alcoholic patients, and other immunocompromised adults (Khayr et al., 1992). However, there may not be an obvious predisposing condition in up to 30% of patients.

Gram-negative bacilli constitute the other major group of organisms producing meningitis in the neonatal period. Aerobic gram-negative bacillary meningitis is uncommon except at the extremes of age, but appears to be increasing in incidence. In one study, these organisms were responsible for about 33% of cases of nosocomial meningitis, but only 3% of the community-acquired episodes (Durand et al., 1993). The most common gram-negative bacilli isolated are *Escherichia coli, Klebsiella pneumoniae* and *Pseudomonas* species. *Pseudomonas*, *Serratia marcesens*, and *Flavobacterium* are common in patients on mechanical ventilation, presumably related to their tendency to first colonize the upper airway.

Staphylococcus epidermidis meningitis is found in patients with CSF shunts, indwelling catheters, endocarditis, following head trauma, and after neurosurgical procedures.

Anaerobic bacteria are rarely associated with meningitis, and their isolation from CSF should suggest intraventricular rupture of a brain abscess or meningitis occurring in the context of a subdural empyema.

Myobacterium tuberculosis, *Treponema pallidum*, *Nocardia* species, *Actinomyces* species, and cysticercosis usually produce chronic meningitides, but on occasion may present as an acute meningitis.

Unlike brain abscess, polymicrobial bacterial meningitis is unusual, accounting for less than 1% of cases.

Crowding, as seen commonly in military barracks, households in developing countries, and daycare or chronic care facilities, was independently associated with a higher risk of bacterial meningitis in a population-based case-control study of *H. influenzae* (Fraser et al., 1974). Breastfeeding was protective in preventing bacterial meningitis in young infants. Close contacts of patients with *H. influenzae* and meningococcal meningitis have a 500-fold increased risk of developing the disease for the first 30 days after contact.

Cigarette smoking was recently demonstrated to increase the risk of bacterial meningitis in general, and meningococcal carriage and disease in particular (Bredfeldt et al., 1995; Caugant et al., 1994; Dagan et al., 1992; Davies et al., 1996; Kremastinou et al., 1994; Stanwell-Smith et al., 1994). It is not clear whether smoking increases risk by increasing transmission between contacts or by damaging mucosa.

Pathogenesis

In recent years, our understanding of the pathogenesis of bacterial meningitis has increased dramatically, especially with the identification of some of the inflammatory and neurotoxic mediators involved in the processes leading to neuronal injury (Tauber et al., 1997; Tunkel & Scheld,

1993). These developments suggest widening the traditional therapeutic approaches from eradication of the bacterial pathogen with antibiotics and prevention with vaccines to attenuation of the detrimental effects of the host defences.

Bacteria reach CNS in three ways: via the blood, via contiguous sites, or by direct implantation (traumatic or iatrogenic). Most cases of bacterial meningitis occur as a result of hematogenous spread.

The pathogenesis of bacterial meningitis involves four phases: (i) invasion of the host by the bacteria (Fig. 106.2, see colour plate section) with subsequent infection of CNS; (ii) replication and induction of inflammation by bacteria within the CSF; (iii) progression of inflammation with associated pathophysiologic alterations; and (iv) production of tissue damage.

Bacterial invasion and CNS infection

Four sequential steps are involved in the process of bacterial pathogens reaching the CSF (Quagliarello et al., 1992; Tunkel et al., 1990):

Nasopharyngeal colonization

Most bacterial pathogens initially colonize the nasopharyngeal mucosa before they invade the host. They are usually acquired either from an asymptomatic carrier or from a patient through infected airborne droplets. The host's defence mechanisms responsible for preventing this colonization of bacteria include: local presence of IgA, ciliary clearance mechanisms, and the integrity of the mucosal membranes. The majority of isolates of the three classically common organisms secrete IgA proteases that cleave IgA in the hinge region (Wani et al., 1996), thus facilitating bacterial adhesion to the epithelium. *H. influenzae* and *N. meningitidis* also cause injury to the ciliated epithelial cells, resulting in ciliostasis and selective adherence to non-ciliated epithelial cells in nasopharyngeal organ cultures. Pili on meningococci and *H. influenzae* help them to adhere to mucosal surfaces and are responsible for their binding (Quagliarello et al., 1992). Although the nasopharynx is the usual portal of entry of the common organisms causing meningitis, any source of infection that results in bacteremia can potentially infect the meninges.

Nasopharyngeal epithelial cell invasion and entry into blood

Meningococci enter non-ciliated epithelial cells by an endocytic process and move to the abluminal side (basolateral side) by a transcellular route within membrane-bound vacuoles. *H. influenzae,* in contrast, break the apical tight junctions of the columnar epithelial cells and traverse through an intercellular route (Stephens & Farley, 1991). The mechanism of further transport from subepithelial layers into the bloodstream is unknown. Sequential switching of phase-variable surface components may be a prerequisite for the microorganism to adapt to the changes of environment between the mucosal surface, intra- or intercellular spaces, and the blood stream (de Vries et al., 1996).

Survival in the blood

Opsonized phagocytosis, specific antibodies, and complement activation are the principal mechanisms by which reticuloendothelial system normally clears bacterial pathogens from the blood. The role of antibody is exemplified by the protection afforded by the breastfeeding and peak age-specific incidence of meningitis which occurs at age 6–8 months, when the antibodies are at their lowest level, as passively acquired maternal IgG antibodies disappear (Wenger et al., 1990). The importance of antibody is further highlighted by the recent observation of more than 95% reduction in incidence of *H. influenzae* type b meningitis after the introduction of conjugate vaccine, which induces anticapsular antibody titres. If there has been prior infection or exposure to an organism, the classical complement pathway is primarily involved in eliminating the organism by opsono-phagocytosis mediated by the specific antibodies. In the absence of such prior exposure, bacteria must evade the alternative complement pathway to allow their intravascular survival; this is primarily achieved by the capsular polysaccharide, which also protects bacteria from circulating antibodies and neutrophil phagocytosis (Kim et al., 1992). The importance of the complement system is underscored by the predisposition to pneumococcal infections in patients with absent functional spleens, as in sickle cell disease or following splenectomy; and the predisposition to meningococcal infections in patients with defective terminal complement components (Quagliarello, 1992; Virji, 1996). The characteristics of the polysaccharide capsule of meningeal pathogens that reduce activation of the alternate complement system include presence of sialic acid, which is also present in human cells. Hence, the capsules resemble host cell surfaces, and thus evade complement activation.

Capsules also impede C3 convertase-mediated activation of the alternate complement cascade via a low binding affinity for serum protein B, which contributes to C3 convertase activity, or via a high binding affinity for serum protein H, which promotes decay of C3b complexes (Tunkel & Scheld, 1993). Bacteria also survive if there is a defect in the host defence system. These may include T-cell

deficiency, B-cell deficiency, terminal complement deficiency, and alternate complement pathway deficiency.

Transport across BBB and entry into CSF

The CNS is relatively protected from systemic influences by the BBB, which maintains homeostasis of the CNS microenvironment through selective restriction of the entry of macromolecules, cells, and pathogens. The BBB is formed by tight junctions between capillary endothelial cells, a pericyte-derived basal membrane, and the astrocytic foot processes investing the capillaries. However, many essential substances are transported across the barrier through non-specific diffusion, specific facilitated diffusion, and energy-dependent carrier-mediated transport. Early studies on an infant rat model suggested that dural venous sinuses were the major route of CNS invasion. Recent studies suggest that a non-specific sterile focal inflammation above the cribriform plate facilitates CNS invasion at this site. Experimental studies demonstrate the choroid plexus as the portal of entry due to its high blood flow (200 ml/g/min) and fenestrated capillaries. A high-grade bacteremia could also alter the capillary tight junctions. Three factors may be responsible for the organisms' neurotropism and CSF entry: (i) bacteremia of sustained duration and magnitude; (ii) adhesion to critical BBB components (mediating CNS invasion); and (iii) transfer within macrophages or other phagocytic cells (entering CNS by normal cellular trafficking pathways). Recent work suggests a complex interplay between endothelial cells and microbial gene products to orchestrate the traversal of bacteria across the BBB (Ring & Tuomanen, 1997). The initial step in this process is attachment of the pathogen to receptors located on endothelial cells. Following attachment, bacteria adopt one of the several strategies to cross the BBB, which include (i) paracellular passage by disruption of the intercellular endothelial connections or endothelial injury (Patrick et al., 1992; Arditi et al., 1995); (ii) transcellular transport by active or passive trancytosis; and (iii) invasion within white cells during diapedesis. Pneumococci appear to invade both through transcellular and paracellular pathways (Ring et al., 1998).

As mentioned earlier, infections may reach CNS by extension from contiguous sites like the paranasal sinuses, middle ear, or mastoid processes through compromised integrity of barriers around the brain. Finally, organisms may spread to CNS by direct implantation via a CSF communication that occurs following head trauma (either accidentally or iatrogenically through neurosurgical procedures), through congenital causes like myelomeningocele, congenital dermal sinus and by neoplastic destruction of skull bone.

Bacterial replication and induction of inflammation

Survival and replication within CSF is enhanced because typical host defence mechanisms are virtually absent in CSF, as neutrophils, plasma cells, complement components and immunoglobulins are significantly excluded by the BBB. In one study, CSF opsonic activity was undetectable in 50% of patients with bacterial meningitis (Simberkoff et al., 1980); this impedes phagocytosis by leptomeningeal macrophages and recruited peripheral granulocytes (Richardson, 1996). Bacteria can efficiently multiply within the CSF (Small et al., 1986). Induction of inflammation within the subarachnoid space occurs following invasion and replication of the bacterial pathogen in the CSF, which is primarily responsible for pathophysiological consequences that result in the clinical syndrome.

The cell wall of gram-positive organisms and the endotoxins (lipopolysaccharides) of gram-negative organisms are primarily responsible for stimulating subarachnoid inflammation; teichoic acid and peptidoglycan, the major cell-wall components, have a key role (Tuomanen et al., 1985). Intracisternal inoculation of either *H. influenzae* type B polysaccharide or *H. influenzae* outer membrane induces meningeal inflammation in animal experiments (Mustafa et al., 1989; Wispelwey et al., 1989). Release of various inflammatory mediators like interleukin 1 (IL-1) and tumour necrosis factor α (TNFα), and possibly prostaglandins, appear to be responsible for the initiation of inflammatory responses. Direct inoculation of IL-1 and TNFα into CSF of rats or rabbits induces meningeal inflammation (Quagliarello et al., 1992; Ramilo et al., 1990; Tunkel et al., 1990). Cytokines are released from meningeal macrophages, glial cells, ependymal cells, recruited inflammatory cells, and brain microvascular endothelial cells. Increased CSF concentrations of TNFα, IL-1, IL-6, IL-8, and IL-10 are characteristic of bacterial meningitis. These cytokines are proinflammatory, except for IL-10, which down-regulates the production of TNFα and other proinflammatory cytokines (Arvin et al., 1996; Tunkel et al., 1990). TNFα is a relatively specific marker for bacterial meningitis, as it is not released in viral meningitis. It is a glycoprotein produced by lymphocytes, NK cells, astrocytes and microglial cells. Experimental administration of TNFα into the CSF as well as intracerebrally results in pathophysiologic changes characteristic of bacterial meningitis (Tureen, 1995; Rosenberg et al., 1995; Glabinski, 1998). Antibiotic therapy causes additional rapid lysis of pathogens resulting in higher TNFα concentrations with initiation of antimicrobial treatment. IL-1 released in the CNS by

mononuclear phagocytes, glial cells and endothelial cells, has proinflammatory actions independent of but synergistic with TNFα (Quagliarello et al., 1992). Both IL-1 and TNFα induce other secondary cytokines like IL-6, IL-8, and IL-10 (Waage et al., 1998). Though there is evidence that IL-6 and IL-8 levels are increased in bacterial meningitis, and that they have proinflammatory effects, their presence is not strongly correlated with other indices of meningeal inflammation or with severity of the disease (Rusconi et al., 1991). IL-1 and TNFα cause secretion of adhesion molecules on endothelial cells and neutrophils, which helps migration of neutrophils into CSF.

Progression of inflammation

A CSF neutrophilic pleocytosis is a hallmark of acute subarachnoid inflammation. However, neutrophil movement into the CSF is complicated, yet a crucial step in the pathogenesis of bacterial meningitis. The initial step in this process is margination and adhesion of neutrophils to vascular endothelial cells, followed by transmigration through the vessel wall. Three families of adhesion molecules may mediate these interactions, including the immunoglobulin superfamily (e.g. ICAM-1 and ICAM-2), the integrin family, and the selectin family. A three-phase model was proposed by Quagliarello and Scheld in 1992 to explain neutrophil migration into the CSF. The first phase, lasting 1–2 hours, involves release of IL-1 and TNFα into the CSF in response to bacterial pathogen replication or lysis. The cytokines then interact with the surface membranes of endothelial cells, generating local production of thrombin and leading to expression of selectin molecules (ELAM-1 and CD62), which in turn enhance neutrophil endothelial cell binding. Subsequently, IL-8 is released by prolonged cytokine stimulation, which replaces the initial selectin-mediated neutrophil binding with an integrin-mediated neutrophil binding to endothelial intercellular adhesion molecules (ICAMs), and finally leading to neutrophil diapedesis through vessel walls along a chemotactic gradient into the CSF. In the final phase, cytokine activation of neutrophils results in their degranulation and release of leukotrienes, platelet-activating factor, prostaglandins, and and toxic oxygen metabolites, which damage the BBB by opening tight junctions.

Support for the role of these adhesion molecules is found in experimental models of meningitis, where systemic administration of monoclonal antibody (IB4) against the CD11/CD18 family of receptors results in absence of CSF pleocytosis and this is more effective when dexamethasone is administered along with the antibody. Corticosteroids reduce the release of cytokines into CSF, and reduce release of vasoactive substances from neutrophils directly into the CSF.

Recent work also has shown a correlation of high levels of IL-1 and IL-6 with high cerebral blood flow velocities (Fassbender et al., 1996). Nitric oxide also appears to have a significant role in pathogenesis of bacterial meningitis. Increased concentration of NO in CSF is shown to cause cerebral edema (Destache et al., 1998; Pfister & Scheld, 1997). Animal studies suggest that induction of NO synthase occurs within meningeal vessels and within cells of CSF; the production of NO appears to reduce cerebral ischemia (Leib et al., 1998a).

Reactive oxygen species play an important role in the pathophysiology of bacterial meningitis. Increased formation of ROS occur during inflammatory processes stimulated by bacterial products, phagocytosis, and TNFα. Inhibition of the effects of ROS by free radical scavengers prevented BBB breakdown, providing neuronal protection (Koedel & Pfister, 1997; Leib et al., 1998b). Vascular endothelial cell activation, cerebral inflammation, ischemia/reperfusion injury, neuronal apoptosis, and excitotoxic neuronal injury are the processes linked to the generation of ROS most likely to be important in meningitis. The harmful effects of NO are mediated through its role in generating a CSF pleocytosis, altering BBB permeability, inducing intracranial hypertension, producing brain edema, and influencing cerebral metabolism (Buster et al., 1995; Koedel et al., 1995; Leib et al., 1998b; Tureen, 1995). Despite these observations, there is evidence that use of NO inhibitors in meningitis may have deleterious effects (Leib et al., 1998a). This may reflect varying effects on the constitutive and inducible forms of NO synthase, or the need for NO-induced vasodilation as a protective mechanism against meningitis-induced vasculopathy.

Matrix metalloproteinases belong to a family of zinc-dependent endopeptidases; their release is induced by TNFα, and they appear to be involved in the pathogenesis of bacterial meningitis through BBB breakdown, extravasation of inflammatory cells into the CNS and glial and neuronal death (Paul et al., 1997; Sporer et al., 1998).

By the end of the first week of infection, neutrophils are replaced by macrophages, derived from meningeal histiocytes. Further infiltration of subependymal tissues and perivascular spaces by PMNs and lymphocytes occurs. Interference with normal CSF flow, and its resorption at the arachnoid granulations, by the inflammatory exudate may result in the blockage of pathways of flow and drainage. Cerebral edema and failure of CSF resorption result in dangerously elevated ICP. Cranial and spinal nerve deficits, focal neurological deficits, seizures, encephalopathy, and

subdural effusions are commonly recognized complications of meningitis.

Development of neuronal damage

The main abnormal processes involved in neuronal injury are: (i) alteration of the BBB; (ii) raised intracranial pressure; (iii) alterations in cerebral blood flow; and (iv) direct neurotoxicity. Increased permeability of the BBB results in vasogenic edema, as well as entry of potentially harmful molecules from the blood stream which may have a direct harmful effects on brain parenchyma or alter the brain's microenvironment. Dynamic changes in CBF are marked in meningitis, with early increased blood flow followed by its reduction in the late phases (Koedel et al., 1995; Leib et al., 1998a,b). Inadequate cerebral blood flow results from increased metabolism, seizures, and reduced cerebral blood flow secondary to disturbed autoregulation (Tureen et al., 1990) and systemic hypotension. Direct neurotoxicity is likely secondary to TNFα, ROS, NO, cerebral ischemia, and EAAs (Tauber et al., 1997; Leib et al., 1996), rather than by the direct spread of bacteria into the brain. In an infant rat model of neonatal meningitis, kynurenic acid, a nonselective inhibitor of EAAs attenuated brain injury, strengthening the role of EAAs (Leib et al., 1998a,b). In addition, neutrophils, by tracking along Virchow–Robin spaces, damage small vessels, infiltrate and damage cortex.

Peroxynitrate, which is a highly cytotoxic product of the reaction of superoxide and NO, appears to interfere with mitochondrial function (Beckman & Koppenol, 1996). Its inhibition appears to have a neuroprotective effect (Tureen et al., 1998).

One of the major pathophysiologic changes of bacterial meningitis is brain edema (and the consequent increase in ICP). The types of edema produced include (i) vasogenic edema, which occurs as a result of separation of intercellular tight junctions; this is correlated by penetration of marker protein across BBB; (ii) cytotoxic edema, due to alteration of cell membranes secondary to hypoxia and toxins released by bacteria and neutrophils, leading to increased intracellular water content; (iii) increased CSF volume secondary to increased CSF outflow resistance both within the CSF pathways and at the arachnoid granulations by the exudate (Quagliarello et al., 1992; Scheld et al., 1980); (iv) hypotonicity of extracellular fluid in the presence of increased permeability of BBB, reflecting either the syndrome of inappropriate antidiuretic hormone effect (Kaplan & Feigin, 1978) or cerebral salt wasting; (v) interstitial edema either secondary to increased CSF production or its outflow resistance; and (vi) increased blood volume in the brain from hyperemia or venous congestion (Tureen et al., 1996).

Pathology

Neurological sequelae from bacterial meningitis fall into three categories; (i) cranial nerve deficits, primarily sensorineural deafness; (ii) obstructive hydrocephalus; and (iii) parenchymal brain damage leading to focal neurological deficits in the form of deafness, blindness, seizures, and mental retardation in children. The main pathological features of bacterial meningitis involve inflammation of the subarachnoid space, disorders of the cerebral vasculature, and parenchymal brain damage.

The hallmark of meningitis is subarachnoid space exudate, most abundant in the cisterns at the base of the brain and over the convexities in the Rolandic and Sylvian fissures (See Fig. 106.2, see colour plate section). Initially, inflammatory cells are confined to the exudate, but during the subsequent 2 to 3 days they are also seen within the walls of the small and medium vessels (Cairns & Russell, 1946). The presence of subintimal inflammatory cells is unique to meningeal infections. Meningeal veins become distended and develop mural infection, which may be complicated by focal necrosis of the vessel wall, mural thrombus formation in the lumen, or involvement of the dural sinuses. Hemorrhagic cortical infarction may result from cortical venous and dural sinus thrombosis. Toxic effects of the inflammatory mediators and bacterial pathogen on the hair cells of the inner ear are likely responsible for deafness associated with bacterial meningitis (Blank et al., 1994).

Treatment

Management of bacterial meningitis involves rapid diagnosis, quick institution of antibiotic therapy, and monitoring for and treatment of associated systemic and neurological complications. Though many physicians believe in the importance of avoiding any delay in instituting antimicrobial therapy in bacterial meningitis, an analysis of prior studies did not reveal a good correlation between the duration of symptoms and the clinical outcome in at least half of these studies (Radetsky, 1992). However, the study of Aronin and colleagues (1998) provides strong evidence that treatment delay adversely affects outcome. Therefore, time must not be wasted before starting antibiotic therapy. Though experimental evidence showed explosive inflammatory enhancement following antibiotic therapy due to bacteriolysis, recent animal studies revealed lesser amounts of bacterial endotoxin compared to bacteria not exposed to antibiotics

(Friedland, 1993). Furthermore, delaying antibiotic treatment would facilitate bacterial spread to brain parenchyma and other sites. If a delay in obtaining the CSF sample is expected, as when imaging is requested prior to the lumbar puncture, empiric antibiotic therapy should be initiated immediately. As knowledge about a specific causative pathogen and its susceptibility is not available at the initial evaluation, one must choose appropriate antibiotic empirically based on the information from the initial evaluation. Age, patient risk factors, and regional antibiotic resistances help in the empiric choice of antibiotics. In view of the increase in penicillin-resistant *S. pneumoniae*, empiric antibiotic regimens usually include vancomycin when this pathogen is suspected. The antibiotic regimen can be modified after a specific organism and its susceptibilities are identified. For many years penicillin, chloramphenicol, and ampicillin were the traditional drugs against most of the pathogens. However, several events in the last decade or so necessitated modification of initial empiric antibiotic therapy.

A few general guidelines are important in the treatment of bacterial meningitis. (i) Antibiotic treatment in CNS infections is unique in that high doses of antimicrobials are usually needed to cross the BBB and achieve therapeutic levels in the CSF and brain. This is also important because effective drug concentrations in vivo are substantially higher than the minimal bactericidal concentrations in vitro (Tauber, 1984; Tunkel et al. 1990). Possible reasons for these observations are enhanced degree of protein binding (Sande, 1978), reduced antibiotic efficacy in the acidic environment of purulent CSF (Strausbaugh & Sande, 1978), and a reduced bacterial growth rate in the milieu of the CSF (Ernst, 1983). Fortunately, the increased permeability of the BBB that contributes to pathophysiology of meningitis also increases permeability for some antibiotics. Lipid solubility, protein binding, molecular size, degree of inflammation and capillary and choroid plexus efflux pumps are some of the determinants of drug penetration into the CSF (Andes, 1999). (ii) Antibiotic therapy should be initiated very early in the disease course, as permanent neurologic damage and even death can rapidly occur in patients with meningitis. Hence the importance of a rapid diagnosis, or of empiric treatment if a lumbar puncture must be delayed, cannot be overemphasized. (iii) Antibiotic regimens should include agents which are bactericidal in the CSF (Scheld & Sande, 1983). Suggested regimens for community-acquired meningitis in an immunocompetent host: third-generation cephalosporin and vascomysin. If immunodeficiency is suspected (diabetes, renal impairment or alcoholism), then ampicillin should be added (Schuchat et al., 1997). (iv) The duration of antibiotic treatment is generally empirical, but depends on the specific bacterial pathogen and should be individualized based on clinical and laboratory responses. In some cases, acute phase reactants like ESR and CRP are suggested as indices to guide the duration of treatment (Saez-Llorens, 1993). (v) Knowledge of the pharmacodynamics of the drugs is also important. Aminoglycosides and quinolones have a prolonged postantibiotic effect and concentration-dependent activity in serum that allows for once or twice-daily dosing (Craig, 1998). In contrast, β-lactam antibiotics and vancomycin show concentration-independent activity and no postantibiotic effect in serum, explaining the reason for these drugs to be given at more frequent intervals (Craig, 1995).

Since 1988, significant interest has been focused in the use of corticosteroids in bacterial meningitis (Lebel, 1988). However, the issue remains controversial. A meta-analysis of randomized, controlled trials of use of dexamethasone in childhood meningitis published between 1988 and 1996 did not show a definite benefit from the use of dexamethasone in preventing neurological deficits other than hearing loss (McIntyre et al., 1997). However, there were no uniform criteria for evaluating neurologic deficits (other than hearing loss) in this analysis. Also, in most of these studies, *H. influenzae* was the commonest organism, which now is very uncommon; and most studies were performed prior to penicillin resistant *S. pneumoniae* (Spach & Jackson, 1999). There are few data regarding the use of dexamethasone in meningitis in adults. There is also some concern from experimental studies regarding the potential for dexamethasone to interfere with the penetration and bactericidal activity of some antibiotics (Paris, 1994; Bonadio, 1996). However, some still favour the use of dexamethasone, especially in children above two months of age and in adults where gram positive organisms and increased intracranial pressure are present (Quagliarello & Scheld, 1997).

Chemoprophylaxis of household and close contacts of bacterial meningitis patients is warranted in infections secondary to *N. meningitidis* and *H. influenzae*.

Future directions

With the encouragement from the success of Hib vaccine, future efforts would likely focus on the development of vaccines for other pathogens. This is especially important for *S. pneumoniae*, as it is the most common organism for bacterial meningitis currently and also for the growing concern over spreading drug resistant strains. The preliminary data on the use of new conjugated *S. pneumoniae* vaccine is encouraging (Black et al., 1998).

Brain abscess

Brain abscess is a focal intracerebral suppuration with an historically high morbidity and mortality. Until the late nineteenth century, it was a uniformly fatal condition. Major breakthroughs in neuroimaging, stereotactic brain biopsy, and newer antibiotics have led to improved care and outcomes of this once devastating condition (Gonzalez-Garcia, 1999).

Pathophysiology

The brain is protected from blood-borne pathogens by the BBB and its abundant blood supply. Underlying brain pathologies like intracerebral hematoma, infarction, and tumour sometimes predispose development of brain abscess. Common pathogens reach brain by spread from contiguous sites like the paranasal sinuses, middle ear, mastoid air cells and teeth, presumably through invasion via valveless emissary veins draining these regions, draining into venous system of the brain. Surprisingly, brain abscess formation is not common following penetrating brain injuries (Saba, 1995), but hematogenous spread of pathogens from distant sources may occur. In about 20–30%, no identifiable source can be found, and these are termed *cryptogenic* brain abscesses.

Based on information from experimental models of brain abscess, supplemented by CT scanning, four stages of brain abscess can be identified; an early cerebritis stage (1–3 days), characterized by focal area of inflammation and edema, visualized as a hypodense lesion on the CT; a late cerebritis stage (4–9 days), with expansion of cerebritis and development of central necrosis; an early capsular stage (10–14 days), where peripheral gliosis and fibrosis is beginning to form a capsule seen as a ring-enhancing lesion with peripheral edema on CT scan; and a late capsular stage (beyond 14 days), with the formation of a discrete abscess with a well-formed capsule surrounded by edema.

Diagnosis

The clinical manifestation of a brain abscess depends upon the size, location, offending pathogen, and the underlying predispositions. Headache is the most common symptom, which has no distinguishing features. It is poorly localized and of acute to subacute onset; an abrupt onset is much less common. However, abrupt worsening of headache suggests rupture of the abscess into the ventricular system, which is commonly associated with signs of meningeal irritation and a fatal course (Zeidman et al., 1995). With increasing size of the abscess and the associated surrounding edema, symptoms of raised intracranial pressure develop in the form of nausea, vomiting, increasing headache, and worsening level of consciousness. Papilledema, if present, suggests significantly raised ICP.

Contrary to general expectation, fever is a presenting symptom in less than half of patients (Mathisen, 1984; Chun et al., 1986). In more than one-third of patients there are focal neurological signs based on the location of the abscess. Fluctuating mental status suggests a poor prognosis (Seydoux & Francioli, 1992). Presence of infection in contiguous sites not only serves as a clue to the diagnosis but also to the location of the brain abscess.

The diagnosis of brain abscess can be very difficult, in view of the fact that in addition to the non-specific clinical presentation, routine laboratory data (peripheral leukocyte count, sedimentation rate, blood cultures) are frequently normal. Lumbar puncture is contraindicated in view of potential brain herniation, the CSF analysis is often normal, and a microbiological diagnosis can rarely be made from the CSF. The diagnosis depends on clinical suspicion and cerebral imaging. CT and MRI techniques help not only in the diagnosis of cerebral abscess but also in its staging. Contrast-enhanced CT or, preferably, MRI is mandatory. Ring-enhancing lesions evolve with progression of the abscess formation, with surrounding edema (Fig. 106.3, see colour plate section). Though ring enhancement usually suggests formation of capsule, this appearance can also be seen in the cerebritis stage. To differentiate this, a delayed scan about 30–60 min later, showing filling in of the central hypodense area by the contrast suggests the cerebritis stage with no central necrosis (Enzmann et al., 1979). Once ring enhancement is seen, the differential diagnosis includes all the conditions that produce ring-enhancing lesions. However, there is no radiographical sign which can reliably distinguish an abscess from a rapidly growing tumour, underscoring the need for histologic and microbiologic diagnoses. MRI achieves better resolution than CT scan (Haimes et al., 1989). T_1-weighted images with contrast show hypointense centre with ring enhancement. On T_2-weighted sequences, abscess appears as hyperintense with hypointense periphery formed by capsule, and surrounding edema as hyperintense area mainly involving the white matter.

Microbiology and therapy

With the advent of modern imaging techniques aiding in early diagnosis, and with newer antibiotics and improved surgical techniques, the morbidity and mortality of the brain abscess has improved significantly in recent years.

Management of brain abscess is both medical and surgical (Fig. 106.4, see colour plate section). Most often brain abscesses are caused by multiple pathogens. The common organisms include viridans streptococci, anaerobic bacteria, *Staphylococcus aureus*, and sometimes facultatively anaerobic gram-negative bacteria. Empirical antibiotic treatment should be started for suspected pathogens based on infection in contiguous sites or a distant focus. Brain abscesses formed secondary to sinus infections are usually caused by viridans streptococci and anaerobic bacteria. The empiric antibiotic regimen should hence include a third generation cephalosporin or cefepime (if *Pseudomonas aeruginosa* is a concern) and metronidazole. In case of otitic source, coverage for *P. aeruginosa* and *Enterobacteriaceae* should be included in the antibiotic regimen. Penetrating brain injury, as in the case of trauma or surgery, is usually associated with *Staphylococcus* species, and hence an antistaphylococcal penicillin or vancomycin may be indicated. In addition, these patients benefit from prophylactic antibiotics (Patir et al., 1995). In contaminated wounds, *Clostridium* species and facultative gram-negative organisms are usually associated with the other pathogens.

Similar rules as to those for bacterial meningitis apply to brain abscess in antibiotic dosing, based on the drug's ability to penetrate the BBB and its bactericidal potency. In addition, antibiotics need to penetrate into the abscess cavity; however, limited information in this regard is currently available. Although penicillin seems to penetrate into the abscess, it may be inactivated in pus (Gortvai et al., 1996). Conversely, although CSF levels of vancomycin reach only 10% of the serum levels, it appears to have a high penetration into the brain abscess (Levy et al., 1986). Metronidazole, cefotaxime, its active metabolite desacetylcefotaxime, and ceftazidime, have favourable pharmacokinetic features with good penetration both into CSF and brain abscess (Ingham & Selkon, 1982; Sjolin et al., 1991; Yamamoto et al., 1993; Green et al., 1989). The other third-generation cephalosporins (e.g. ceftriaxone and ceftizoxime), meropenem, and some quinolones also appear to be effective antibiotic agents in brain abscess.

The duration of the antibiotic treatment is generally 6–8 weeks, though the size of the abscess, microbial features, surgical drainage, and both clinical and radiological responses may aid in individualizing the duration of therapy. A small area of enhancement is not surprising even after adequate treatment (Whelan & Hilal, 1980).

Operative treatment

The brain may on occasion constitute one of the exceptions to the general rule that abscesses should always be drained. This may be true in some cases where brain abscesses are small (<2 cm) and difficult to safely reach in clinically stable patients who are poor candidates for surgery. Disadvantages with this conservative approach include prolonged antibiotic treatment, risk of clinical deterioration, and the risk intraventricular rupture. Some authors believe that late epilepsy is more common in patients who do not have at least an aspiration of a suspected abscess.

A major change in the trends of operative management of brain abscess has been a shift from an open craniotomy and drainage to a closed drainage, commonly through stereotactic technique (Mampalam & Rosenblum, 1988; Lunsford, 1987; Skrap et al., 1996). However, the stereotactic drainage has a disadvantage in that it requires time for planning and hence may not be feasible in emergency situations. This technique is more useful in abscesses involving deeper structures, where precision is very important. The alternative freehand procedure, which also requires CT guidance and use of scalp markers, can be done in the emergency setting with an accuracy of 4–5 mm. The role of open drainage is now limited to multiloculated abscesses in which closed drainage procedures have failed, and in cases of abscesses secondary to resistant organisms. Intracavitary administration of antibiotics may be helpful in some situations with large, poorly responding abscesses (Broggi et al., 1985; Gentile et al., 1988), but this remains controversial. Management of intraventricular rupture of brain abscess involves open craniotomy with an external drainage procedure and is associated with significant mortality (>80%). The role of corticosteroids as adjunctive treatment is controversial, but in general, these agents have not been shown to be effective in altering morbidity (Yang, 1981; Chun et al., 1986; Seydoux & Francoli, 1992). Adjunctive treatment includes treatment of brain edema (for which steroids may be useful) and anticonvulsant drugs for seizures. Poor prognosticators include severe neurological deficits and shorter duration of symptoms (Seydoux & Francoli, 1992). Stereotactic needle aspiration might help as a diagnostic aid to obtain material for gram stain and culture as well as therapeutic drainage in selected cases. Not uncommonly, serial imaging is indicated to decide the timing for surgical drainage as well as for monitoring the response to medical therapy.

Epidural abscess

The epidural space is between the dura mater and the overlying skull or the vertebral column. As the dura forms the inner periosteal layer of the skull, infection within this

potential space in the cranium is almost always associated with osteomyelitis. Unlike that in the cranium, the spinal dura mater is separated from the vertebral column by an epidural space filled with fat, vascular and loose areolar tissue. Due to anatomical reasons, infection within this space, first described by Morgagni in the eighteenth century (Gellin, 1997), can spread longitudinally along the vertebral column and thus cause cord compression.

Intracranial epidural abscess is identical to intracranial subdural empyema in etiology, pathogenesis and microbiology (Silverberg & Di Nubile, 1985). Hence this discussion will be restricted to spinal epidural abscess.

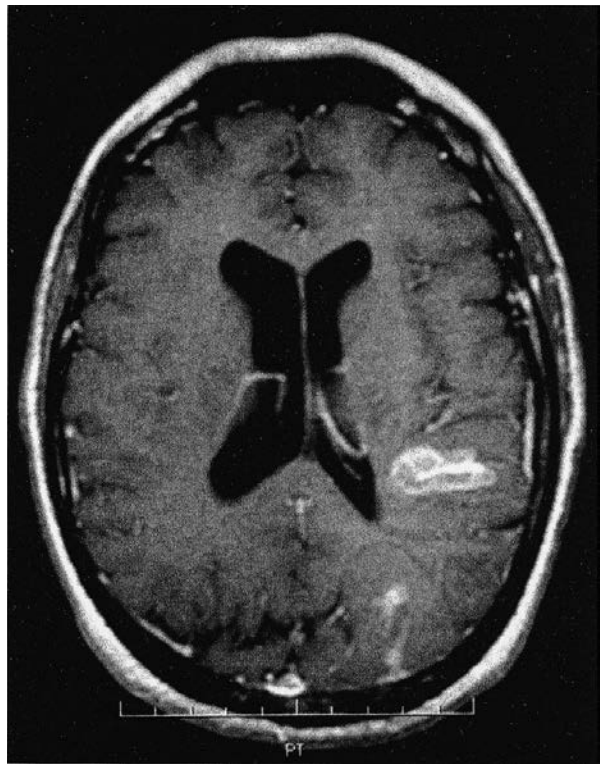

Fig. 106.5 (For (*a*), see colour plate section) (*b*) Contrast-enhanced MRI scan illustrates septic embolization in subacute bacterial endocarditis. (Figure courtesy of Dr Justin C. McArthur.)

Etiology and pathogenesis

Spinal epidural abscess can be acute or chronic and forms either by spread of infection from the vertebral column or by hematogenous spread from distant foci (Baker et al., 1975; Danner & Hartman, 1987). Chronic forms usually follow contiguous osteomyelitis of the vertebral column. Intravenous drug abuse is becoming a common etiological factor (Nussbaum et al., 1992). Though back surgery, lumbar puncture, and epidural anesthesia are recognized as possible precipitating events (Shintani et al., 1992), short-term epidural analgesia is not considered a major risk (Burstal et al., 1998), unlike chronic epidural analgesia (Smitt et al., 1998).

Microbiology

S. aureus is responsible for 60–90% of all cases of epidural abscess (Nussbaum et al., 1992); the remainder are caused by streptococci and gram-negative bacteria. A polymicrobial etiology is seen in only 10% of cases (Nussbaum et al., 1992; Danner & Hartman 1987).

Pathology

The majority (50–80%) of abscesses occur near the thoracic cord, followed by lumbar and cervical regions (Brock & Bleck, 1992; Baker et al., 1975), although in children the lumbar and cervical regions are more frequently involved. An abscess can occur on any side in relation to the spinal cord. Associated discitis or vertebral osteomyelitis, detectable by MRI, occurs in almost all cases. Granulation tissue containing loculated pus is the pathologic feature of an acute abscess, whereas, prominent fibrotic component is seen mainly with chronic cases. An abscess extends along the length of the cord, usually for about four or more segments (Baker et al., 1975) and may result in cord necrosis secondary to both direct pressure and vascular compression (Baker et al., 1975). Occasionally infection can spread into the subarachnoid space (Darouiche et al., 1992).

Clinical features

A spinal epidural abscess may present acutely or insidiously. Initially there is focal vertebral pain, followed by radicular pain along the involved nerve roots, and finally signs of spinal cord compression (Darouiche et al., 1992). Chronic epidural abscess may mimic epidural tumour in its presentation and lacks fever that usually accompanies the acute infections.

Diagnosis

Diagnosis of epidural abscess should be suspected in any patient with localized back pain, with or without radicular pain, occurring in a setting of infection (local or elsewhere). Nuchal rigidity and focal tenderness to percussion

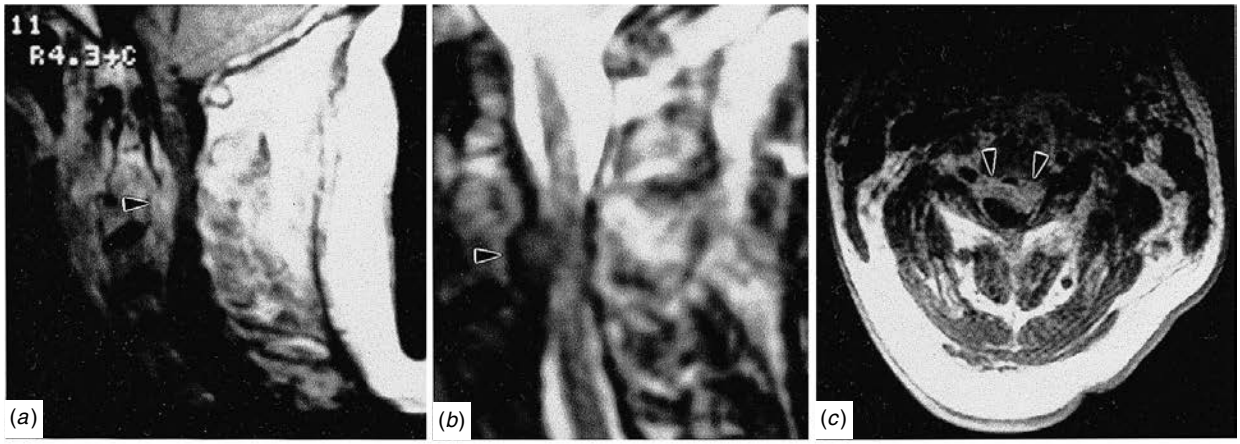

Fig. 106.6. Spinal epidural abscess: composite MRI scans showing (*a*) sagittal T_1-weighted contrast study with enhancing abscess (arrowhead) anterior to the spinal cord at C2; (*b*) T_2-weighted images showing cord compression from large anterior collection (arrowhead); (*c*) contrast-enhanced axial image showing enhancing abscess (arrowheads) deforming spinal cord. (Figure courtesy of Dr Justin C. McArthur.)

almost always follow the above signs, especially in an acute abscess. MRI is the first procedure of choice, and delay should be avoided in attempting to initially obtain plain films (Bleck, 1995) (See Figs. 106.5, for (*a*), see colour plate section, 106.6). Lumbar puncture is contraindicated for the risk of spreading of the infection into subarachnoid space.

Therapy

Epidural abscess is a surgical emergency. Delay in diagnosis or treatment results in permanent cord damage. Immediate surgical decompression and drainage is mandatory. Endoscopic surgical techniques are possible alternatives to open drainage in the future (Roselli et al., 1998). Patients with local pain alone and a small lesion might be managed with percutaneous CT-guided aspiration for a microbiologic diagnosis if close observation is assured. Antibiotic coverage should begin prior to surgery, either with nafcillin or vancomycin, and with the addition of a third generation cephalosporin in diabetic patients or those with a history of recent gram-negative infection elsewhere. In contrast to the other CNS infections, choice of antibiotics need not depend on the BBB permeability. Occasionally, antibiotic treatment alone might successfully treat the infection in cases of early abscess with minimal signs (Nordberg & Mark, 1998), but this should not be considered a standard treatment. Antibiotic coverage is indicated for about 3–4 weeks or 8–10 weeks in case of associated local osteomyelitis (Bleck & Greenlee, 2000c). A short course of corticosteroids may help with evidence of acute cord compression. Spinal stabilization procedures may be required in case of bony destruction. Good prognosis is seen in early institution of treatment prior to the onset of radicular treatment in addition to younger age (Khanna et al., 1996), with about overall neurological recovery in about 50% (Baker et al., 1975; Danner & Hartman, 1987).

Subdural empyema

The cranial subdural space is a potential space between the two outer layers of the meninges, the dura mater and the arachnoid. It is divided into multiple anatomical compartments by the falx cerebri, the tentorium, the base of the brain, and the foramen magnum, which confine infection within the space to these compartments. Although subdural empyema was first described by Sir Richard Bright in 1836 (Bleck, 1992), detailed clinicopathologic descriptions were only reported in the 1940s (Kubic & Adams, 1943; Courville, 1944). They account for 13–23% of intracranial bacterial infections (Harris et al., 1987; Mauser & Tulleken, 1984; Gallagher et al., 1998). Spinal subdural empyema is rare and usually metastatic.

Etiology and pathogenesis

Subdural infection, like brain abscess, usually develops in extension from contiguous sites via emissary veins or by extension from osteomyelitis of the skull (Brock & Bleck, 1992). In a majority of these latter cases, sinus infection is

the primary source (Dolan & Chowdhury, 1995). Rarely, it occurs through hematogenous spread from distant focus; in infants, it can be a complication of bacterial meningitis. The most frequently isolated organisms are aerobic streptococci or staphylococci; in a minority of cases, *S. pneumoniae, H. influenzae*, or other gram-negative bacteria are responsible. Unusual organisms such as *Salmonella* may be involved in immunocompromised patients (Aliaga et al., 1997; Parkers et al., 1995).

Pathology

Infection may involve any of the compartments of the subdural space, based on the source of the infection. Extension of the infection into the subarachnoid space is not common, but a focal inflammatory reaction is frequently present. However, focal osteomyelitis or epidural abscess is seen in about 50% of cases. Infection can also spread through septic thrombosis of veins into either the venous sinuses or to the cortical veins, resulting in hemorrhagic infarction and superficial brain abscess formation. Subdural empyema and the associated cerebral edema may result in rapid increases in ICP, unless the empyema is immediately surgically drained.

Clinical

Most cases present with fever, signs of raised ICP, and signs of meningeal irritation over a background of associated sinus or ear infection. Focal neurological deficits, alteration of consciousness, and seizures occur early in the course, with rapid worsening leading to signs of brain herniation and death, unless treated promptly. Rarely, the presentation may be more insidious, especially following craniotomy or with prior use of antibiotics. Fever, meningeal signs and focal neurological deficits should make one suspect this diagnosis. MRI with gadolinium contrast is superior to contrast CT scanning in the diagnosis of subdural empyema (Campbell & Zimmerman, 1994; Conlon et al., 1996). As with brain abscess, lumbar puncture is contraindicated in subdural empyema secondary to risk of herniation and in addition, CSF changes are non-specific.

Therapy

Surgery is the mainstay of the treatment of subdural empyema. Early subdural empyemas, deemed by some too small to be surgically drained, are occasionally managed with antibiotics, but in our experience this is rarely successful. The clinical state of the patient should direct the choice of therapy, as imaging techniques can sometimes underestimate the actual volume of the empyema. Open craniotomy is the preferred approach for drainage. In early cases however, some authors believe that burr hole drainage may be sufficient (Ak et al., 1996). The collected purulent material should be processed to identify the organism. Treatment of the infection in contiguous sites is important. Antibiotic therapy should be given at least for 3 weeks.

Prognosis

Permanent neurological sequelae rapidly result with any delay in the treatment, and often occur no matter how rapidly the diagnosis is made and treatment commenced. Mortality also depends on the clinical state at the time of presentation, the age of the patient, and coexistent immunosuppression.

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Parasitic disease

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Neurocysticercosis

Life cycle of *Taenia solium*

The infection caused by the complex Taeniasis/cysticercosis in humans represents a rather peculiar phylogenetic encounter between *Taenia solium*, the most evolved cestode parasite (order cyclophyllidea, family taeniidae) (Willms, 1992) and human, the most evolved mammal (order primates, family hominidae). Both protagonists are endowed for survival with sophisticated biological mechanisms. In fact, rather than being another infection, cysticercosis is the transplant of the embryo of *Taenia solium*, into the tissues of the intermediate host (pork and humans) where it hatches in the intestine and is transported, by the blood stream, to tissues to become a larva. For the cycle to be completed a human must ingest, undisturbed and intact, a cysticercus whose size is between 0.5 and 1 cm diameter. The unique source of this larva is undercooked pork meat; it is truly amazing to observe that the cyst survives not only the cooking process but also the powerful masticatory movements and the fast intestinal passage. Once within the digestive tract, the metacestode (larva), measuring between 1 and 2 mm evaginates from the cyst and strongly attaches itself to the intestinal wall with the aid of its four suckers and a double chain of hooks. Two months later, a cestode measuring 2–4 metres long has developed; thereafter, every day, a few mature progglotides spontaneously detach, each containing several thousand fertilized eggs, which in turn will pollute areas with deficient sanitary installations and inadequate disposal of human feces. When contaminated food is ingested either by pigs or humans, cysticercosis develops in these new hosts. In a strict sense, only cysticercosis in pigs and taeniasis in humans are favourable for the perpetuation of the parasite; cysticercosis in humans is a failed attempt, since cannibalism would be the only possibility for a cysticercus in human muscle or brain to develop to the cestode stage in the intestine of another human. Nonetheless, neurocysticercosis (NCC) is the most frequent and severe parasitic disease of the nervous system of humans.

The presence of a whole cyst larva within the brain provokes a far more complicated immune response of rejection or tolerance than would be the case for other less complex infectious agents (Del Bruto et al., 1998). A cysticercus is an intermediate stage of the organism, with its own nervous system (Fig. 107.1, see colour plate section), capable of active mechanisms of immune-evasion. The host, in dealing with this parasite may also produce an unpredictable immune response, which varies in immunocompetent individuals, from a hyperimmune response with fast elimination of the parasite to a remarkable tolerance in which the cysticercus survives in the brain for several years, with membranes that may grow to a very large size of 10–15 cm diameter.

Clinical characteristics of neurocysticercosis

Most cysticerci (around 80%) lodge in the brain parenchyma; the second location is meninges (around 18%); far less frequent are the ventricles, eye, and spinal cord (around 2% of all cases). As would be expected, clinical symptomatology may include a wide variety of syndromes dependent on the location and number of lesions (Castillo et al., 1996; Salgado et al., 1997), in fact, almost any neurological sign can be caused by NCC (Pitella, 1997). In this regard, its clinical expression is similar to that of multiple sclerosis where severity and clinical manifestations depend on number and location of lesions. Clinical signs of NCC are so varied that in neurological wards of endemic countries the diagnosis of NCC is entertained as a possibility at initial consultation in one-third of all neurological patients, regardless of their specific symptomatology (Del Brutto et al., 1998).

Some syndromes are associated with the two most frequent locations of parasites. In parenchymal cysticercosis epilepsy is conspicuous (Del Brutto et al., 1994); while in meningeal cysticercosis hydrocephalus is common (Estañol et al., 1986). These disorders are so closely related with NCC that in endemic areas the main causes of late-onset epilepsy and of hydrocephalus in adults are parenchymal and meningeal cysticercosis, respectively (Medina et al., 1990). As the main age for presenting symptoms of NCC is between 20 and 40 years, in any adult who presents a seizure or has hydrocephalus the diagnosis of NCC must be strongly suspected. Brain cysticercosis is far more frequent in adults than in children with an approximate ratio of 8/1. Thus, these two disorders, epilepsy and hydrocephalus, whose etiology in children might be due to several causes, in adults are usually related to NCC (Medina et al., 1990; Monteiro et al., 1991). In addition, a wide variety of neurological signs can also be present, the more frequent being motor and sensory disturbances, cranial nerve dysfunction due to basal arachnoiditis, persistent vascular headache due to cysticercotic vasculitis (Rodríguez-Carbajal et al., 1989); tumour-like syndromes due to giant cysts or clumps of cysts (Ramina & Hunhevicz, 1986); psychiatric syndromes due to scattered cysts in brain parenchyma; small and large brain infarctions due to vasculitis; and encephalitis due to diffuse brain edema.

Table 107.1. Cysticercosis classification

I	Brain parenchyma
	1 Cysts
	2 Colloid cysts
	3 Granulomas
	4 Calcifications
	A Single
	B Multiple
	C Racemose
	D Edema
	E Infarction
	F Inflammation
II	Subarachnoid space
	1 Cysts in cortical sulci
	2 Cysts in basal cisterns
	3 Arachnoiditis
	A Inflammation
	B. Hydrocephalus
	C Fibrosis
III	Ventricular system
	1 Lateral ventricles
	2 3rd and 4th ventricles
	A Hydrocephalus
	B Ependymitis
IV	Spinal canal
	1 Intramedullary
	2 Subarachnoid
	A Single
	B Multiple
	C Inflammation
	D Fibrosis
V	Ocular cysticercosis
	1 Vitreous cavity
	2 Subretinal
VI	Extraneural cysticercosis
	1 Muscular
	2 Systemic

Source: From Salgado et al. (1997) with permission.

Diagnosis of NCC

The clinical possibility of NCC might be suspected in a large number of patients, however, the only way to confirm the diagnosis is with the aid of neuroimaging studies, computed tomography (CT) and magnetic resonance (MR); as well as with the analysis of cerebrospinal fluid (CSF), including immunodiagnostic assays (either immunoblot, ELISA or complement fixation) (Table 107.1; Salgado et al., 1997; Téllez-Girón et al., 1987). Each of these diagnostic studies has advantages and limitations in the complex picture of NCC (Spina-Franca et al., 1993).

The main advantage of CT is the reliable localization of cysts, granulomas and calcifications (Chandy et al., 1989), the last two are the most frequent remnant lesions left by parenchymal cysticercosis (Chayasirisobhon et al., 1999); its relatively low cost makes it the study of choice for screening of NCC cases. Limitations of CT include low definition for visualization of cysticerci located at the base of the skull, fourth ventricle, eye and spinal cord. Besides, it has a lower image resolution than that achieved by MR for the analysis of perilesional histological abnormalities such as inflammation, edema and fibrosis (Salgado et al., 1997).

The main advantages of MR are the detection of NCC lesions (see Fig. 107.2, see colour plate section) in the areas mentioned above where CT has limitations, also the high resolution of MR allows a precise characterization of cyst viability according to the characteristics of fluid contents (viable cysts susceptible to cysticidal therapy are those whose fluid has image intensity similar to that of ventricular CSF, it changes to hyperintense soon after successful cysticidal therapy) (Martinez et al., 1989; Salgado et al., 1997). MR also provides detailed information on tissular abnormalities around cysticerci. The main disadvantages of MR are its higher cost and the difficulty in detecting granulomas and calcifications (Salgado et al., 1997).

The main advantages of CSF analysis are: the quantifica-

tion sof the inflammatory response in the subarachnoid space (increased cell and protein contents); the search for common, although non-specific findings (eosinophils and pleocytosis of mononuclear cells) and the accessibility for performing immunodiagnosis of NCC, which is particularly valuable in cases of hydrocephalus, vasculitis or chronic arachnoiditis that are not accompanied by specific features of NCC on imaging studies (such as cysts or granulomas). The main limitations of CSF analysis are the obvious difficulties posed by the need to carry out lumbar puncture, and those cases of parenchymal brain cysticercosis without inflammatory reaction in the subarachnoid space in which the immunodiagnostic tests might be negative even in the presence of active forms of NCC demonstrated by imaging studies. This feature makes the sensitivity of immunodiagnostic tests in CSF highly dependent on the presence of inflammation signs (increased cells and proteins) in CSF. Thus, in cases of NCC with inflammatory signs in CSF the sensitivity of ELISA and immuno-blot is high, around 95%; but decreases to about 50% when the CSF has no signs of inflammation. Nevertheless, specificity in both instances is good (around 98%). Therefore, immunodiagnostic tests in CSF are of great help when the interpretation of results is made within the context of the cytochemical results and imaging studies (Chang et al., 1988). In contrast with CSF, immunodiagnostic tests practiced in serum are unreliable for NCC diagnosis (Ramos-Kuri et al., 1992); there is a high frequency of false-positives (30%) in healthy individuals from endemic areas who have been in contact with the parasite but have not developed the disease or who have cross-reacting antibodies due to other parasitic diseases or who have muscle cysticercosis (Larralde et al., 1989). Also, false-negative results in tests on serum from NCC patients are frequent (20%) in cases of a single cysticercus in brain parenchyma with little or no evidence by imaging studies of inflammatory reaction around the parasite. More important, immunodiagnostic studies are usually negative in patients with epilepsy secondary to granulomas and calcifications without active forms of the disease (Rajshekhar, 1991); this is a very frequent presentation of NCC (over 30% of all cases).

Comprehensive treatment of NCC

Different pathological processes may participate in the clinical picture of NCC, each must be treated accordingly (Del Brutto et al., 1998). Some are due directly to the presence and growth of the parasite, some to the intensity of the inflammatory reaction developed by the host, some to the neurological disturbances induced by the tissue lesion, while others are due to the mechanical obstruction of the CSF transit and absorption. Therefore, treatment must be individualized, the independent therapeutic approaches are: (i) treatment with cysticidal drugs, (ii) anti-inflammatory treatment, (iii) symptomatic treatment and (iv) surgical treatment.

Treatment with cysticidals

Albendazole (ALB) and Praziquantel (PZQ) are highly effective cysticidal drugs; both are remarkably atoxic and have a good pharmacological profile (Cruz et al., 1991; Kim, 1999; Sotelo et al., 1990; Takayanagui & Jardin, 1992). Fast destruction of parenchymal cysticerci after a single course is obtained in 75–85% with ALB and in 65–75% with PZQ. In cases of cysts resistant to an initial course with either drug, the use of the alternative drug increases its effectiveness. In this way; destruction of more than 95% of viable parasites can be achieved, as shown by imaging studies, with the sequential use of ALB and if necessary with PZQ, or vice versa. The drug scheme of ALB that has been validated in most studies is 15 mg/kg/day during 1 week (Cruz et al., 1995; Sotelo & Jung, 1998); the drug is administered every 12 hours. ALB is effective against cysticerci located almost anywhere; brain parenchyma, muscle, subarachnoid space, ventricles and even within the eye (Lozano-Elizondo & Barbosa-Horta, 1990; Puri & Grover, 1998). In the latter, when the cyst is located in the vitreous body ALB kills the parasite, which has to be excised by surgery, in contrast, when the cyst is subretinal the parasite is destroyed and the debris are removed by the endogenous immune mechanisms which prevent the damage induced by surgical extraction.

Pharmacological studies have delineated two schemes of PZQ therapy, the 'traditional' lasts 2 weeks at doses of 50 mg/kg/day administered every 8 hours (Leblanc et al., 1986; Robles et al., 1987; Wadia et al., 1988): alternatively, a brief scheme of a single day has recently been designed (Corona et al., 1996); PZQ is given at a total dose of 75 mg/kg divided in three doses of 25 mg administering one every 2 hours (e.g. at 7, 9 and 11 am) on the same day. The pharmacodynamic foundation for this design is that the drug is promptly absorbed in the gastrointestinal tract; it reaches its maximum peak of plasma levels with cysticidal efficacy within two hours, decreasing soon afterwards. With the traditional scheme, high plasma and CSF contents of PZQ are achieved only for brief and sporadic moments during treatment (Overbosch et al., 1987); with the new scheme, high plasma contents of PZQ are obtained 2 hours after the first dose, and an additional dose maintains this level and a third one 2 hours later keeps the drug level higher, so that a lasting plateau of about 5–6 hours of high plasma and CSF contents of PZQ is obtained. This scheme has shown in initial clinical

studies to be as effective as the two week scheme (Del Brutto et al., 1999; Rajshekhar, 1991), with the additional advantage of being 10 times less expensive, 10 times lower total dose and 15 times shorter duration. Also, patients are treated at the outpatient clinic and the adherence to treatment can be supervised. Moreover, it has been recently demonstrated that plasma levels of PZQ are greatly increased when it is administered jointly with cimetidine (Jung et al., 1997) and with a high carbohydrate diet (Castro et al., 2000), these circumstances could further improve its therapeutic efficacy. The only drawback of PZQ is that it is less efficacious than ALB in the treatment of parenchymal and subarachnoid cysticercosis and it is not effective in ventricular and ocular cysticercosis.

Some early studies challenged cysticidal therapy arguing that in some cases the presence of the parasites in the brain causes discrete symptomatology (usually epilepsy) that can be managed with symptomatic therapy and that cysticidal treatment may prompt unwanted symptoms (Moodley & Moosa, 1989). In our experience cysticidal treatment should be given to all patients with active forms of the disease for the following reasons (Sotelo & Jung, 1998): (i) the drug treatment is highly effective, atoxic, brief and inexpensive; being so convenient there is no reason to leave to its natural course the presence of live parasites within the brain. Even in cases when they look clinically 'harmless', chronic fibrosis and astrogliosis develop in the surrounding area, becoming the principal source of long-term refractory epilepsy (Del Brutto et al., 1992; Gupta et al., 1999). Furthermore, cysticerci left untreated leave, as seen by prospective imaging studies, a remnant granuloma (Nash & Patronas, 1999; Sheth et al., 1998), whereas most cysticerci successfully eliminated by cysticidals disappear without the development of remnant granulomas (Ramos-Kuri et al., 1992); (ii) Secondary reactions are prevented by adequate steroid therapy; (iii) although at any given moment the symptomatology caused by the parasite might be mild, the natural course will follow two possible ways, either the cysticercus will grow over the years to reach a giant size of 15–20 cm long or it will spontaneously die, eliciting an acute immune reaction that is supposedly avoided by withholding the drug treatment (Caparros-Lefebvre et al., 1997); (iv) recent studies have suggested that the chronic presence of NCC may induce hematological or neurological malignancies in humans (Herrera et al., 1999).

Anti-inflammatory treatment

Inflammation, with various degrees of intensity is the conspicuous accompaniment of cysticercosis. In many cases it is responsible for neurological damage, rather than the parasite itself (Joubert, 1990). The inflammatory reaction may last years in the subarachnoid space or brain parenchyma causing pachymeningitis and calcified granulomas. Inflammation is the cause of vasculitis that may induce brain infarctions and obstruction of CSF absorption by the arachnoid villi (Del Brutto, 1992), with development of hydrocephalus. Acute exacerbation of inflammation is also the result of the parasite death, which may occur spontaneously or be mediated by the immune reaction, or by cysticidal treatment. Two schemes of anti-inflammatory therapy are used either for acute or for chronic inflammation. Treatment is based mostly on steroids, usually dexamethasone, aided in severe cases by immunosupressants suds as azathioprine or methotrexate. No studies have been reported with the use of selective immunosupressants such as cyclosporin.

Acute anti-inflammatory treatment is used mostly in two instances; as adjuvant of cysticidal treatment and as treatment of brain edema in cases of cysticercotic encephalitis. Cysticidal treatment may be accompanied by a brief period of exacerbation of neurological symptomatology such as headache, nausea, vomiting and occasionally seizures; this picture is caused by the acute destruction of parasites, it usually starts on the second day of treatment and spontaneously disappears two or three days later. These reactions may even be taken as a reliable predictor of successful treatment. Nevertheless, nowadays with the new pharmacological schemes these disturbances are prevented and in a great majority of cases the cysticidal treatment is uneventful, minimizing the anxiety by the practicing physician of clinical disturbances elicited by the cysticidal treatment. As dexamethasone increases the plasma levels of ALB by 50%, its addition favours the pharmacodynamics of treatment (Jung et al., 1990). Administration of 20 mg of oral dexamethasone once a day during the first 4 days of ALB therapy prevents secondary reactions in most patients, the other four days ALB is administered alone. In cases of retinal or ventricular cysticercosis treated with ALB longer courses of dexamethasone and retroocular steroids are used.

Dexamethasone interferes with the metabolism of PZQ, lowering its plasma levels by 50%. Therefore, in the traditional scheme of two weeks PZQ therapy the use of dexamethasone may be reserved as immediate therapy for those cases that present headache or secondary reactions. It can be assumed that when physical complaints develop, the parasites have already been affected, so, at this time 20 mg of IM dexamethasone are given. With this measure the symptoms abate a few minutes after the injection of dexamethasone. With the new scheme of a single day PZQ therapy the rationale for steroid administration is differ-

ent: subsequent to the three consecutive administrations of PZQ, the cysticidal effect lasts about 5 hours during the morning and disappears by the afternoon, when the plasma levels of PZQ drop. At this time, the parasites have already been targeted and it is the proper time for anti-inflammatory therapy, 20 mg of oral dexamethasone early in the afternoon and the next two days will prevent acute inflammatory reactions and clinical disturbances.

In many NCC patients chronic anti-inflammatory treatment is necessary, this is particularly important in arachnoiditis where activated immune cells and cell-mediators are distributed throughout the CNS by the CSF circulation producing widespread damage which can persist for several years. This has been called the 'malignant' form of NCC with a mortality rate of 50% within 2 years of diagnosis (Estañol et al., 1986). In these cases, sustained anti-inflammatory treatment is particularly important. Good results have been obtained with 50 mg of prednisone in a single oral dose administered three times a week (e.g. Monday, Wednesday and Friday). This schedule can be maintained for years minimizing the effects secondary to the chronic therapy with steroids (Suastegui-Roman et al., 1996). Follow-up should be made with periodic CSF analysis aiming to lessen the inflammatory signs.

Symptomatic treatment

Seizures secondary to cysticercosis must be managed according to the standard guidelines for treatment of epileptic disorders (Del Brutto et al., 1998). Some features of epilepsy are common in NCC patients: partial seizures with or without secondary generalization are more frequent than generalized seizures. In endemic areas it is common to find previously asymptomatic young adults, who have late-onset epilepsy secondary to a single calcified granuloma in brain parenchyma. This feature indicates that a cysticercus may lodge in the brain remaining alive for an undetermined period; afterwards, it dies either spontaneously or secondary to the endogenous immune response and a granulomatous scar develops which, in turn, becomes calcified over the years. All these events may be clinically silent; later, at any given time epilepsy develops without any evidence of active NCC. In many such cases, seizures are difficult to control with antiepileptic drugs (Del Brutto et al., 1998; Pradhan et al., 2000), in contrast with seizures secondary to live cysts that usually respond well to treatment (Vazquez & Sotelo, 1992). Therefore, every attempt should be made to prevent the development of granuloma as sequelae to the death of the parasite (Pradhan et al., 2000), cysticidal therapy must be administered soon after the diagnosis of NCC.

Symptomatic treatment should be individually designed according to each of the many clinical manifestations of NCC such as vascular headache, vertigo, psychiatric disturbances etc. Also, rehabilitation programs for neurological sequelae must be designed for diplopia, paresis, etc. (Del Brutto et al., 1998).

Surgical treatment

Nowadays, surgery has been limited mostly to the few cases of cysts refractory to cysticidal treatment: to ventricular shunting for treatment of hydrocephalus, and to ocular cysticercosis (Del Brutto et al., 1998).

Cerebral malaria

Cerebral malaria (CM) is the most severe complication of *Plasmodium falciparum* infections, the only species of plasmodia with CNS involvement (Hamer & Wyler, 1993). Severe *P. falciparum* malaria is one of the most lethal parasitic infections. It is responsible for more than a million deaths yearly in African children (Newton & Krishna, 1998). It is estimated that the syndrome causes death in 20–50% of all cases, infected children and adolescents being at high risk in endemic areas (Roman & Senanayake, 1992).

The pathogenesis of CM is caused by the sequestration of parasitized red blood cells in the cerebral microvasculature. Knobs, which appear on the membrane of infected erythrocytes, adhere to the vascular endothelium causing obstruction of small blood vessels (Aikawa et al., 1990; Turner, 1997). It is still unclear, however, how entrapment and clogging of small blood vessels result in the clinical expressions of cerebral dysfunction. A major line of inquiry has been the study of inflammatory cytokines such as tumour necrosis factor (TNF) which are overproduced in sepsis and infectious diseases, and which in turn induce widespread endothelial cell activation as well as focal endothelial cell damage and necrosis. It has been suggested that the local production of TNF by cerebral endothelial cells activated by infected erythrocytes, triggers the production of nitric oxide, which leads to cerebrovascular dilatation, increased cerebrospinal fluid pressure and defective neurotransmission (Clark et al., 1992, 1997).

Clinical manifestations of CM include altered cognitive functions, behavioural changes and hallucinations; major motor seizures and occasionally hemiparesis, Babinski sign, tremors, myoclonus and choreiform movements. Hypoglycemia is a frequent finding in severe cases and may aggravate manifestations of CM. In children, the febrile convulsions may be difficult to distinguish from

CM. Neurological sequelae have been described in patients recovered from the disease, but have not been widely documented, they appear to be more frequent in children than in adults (Nguyen et al., 1996).

Diagnosis of malaria is established by identification of parasitized erythrocytes on Giemsa stained blood smears. These should be prepared only fresh from finger or earlobe pricks and examined by trained personnel. In all cases of suspected falciparum malaria, it is recommended that a number of slides be prepared during the day until infected red blood cells are identified. In highly endemic areas, efforts should be made to quantify the parasitemia in order to administer the best possible supportive treatment.

P. falciparum malaria is a medical emergency! Treatment should be instituted immediately in order to avoid complications such as CM. Specific antimalarial treatment should consider the geographic area where the patient acquired the infection, since chloroquine and fansidar resistant strains are widespread in all regions. Chloroquine resistance has not been reported in: Dominican Republic, Haiti, Central America west of the Panama Canal and the Middle East. Fansidar resistant strains have been documented in Brazil, Panama, Vietnam, Kampuchea, Myanmar, Thailand, East Africa, Papua New Guinea, Vanuatu and Irian Java.

Updated information on the risk for malaria by country as well as appropriate preventive measures are available through the Centers for Disease Control in the US (Tel. 404 639 1610) 24 hours a day.

Laboratory results in acute malaria include: anemia (normocytic normochromic), thrombocytopenia, decreased lymphocyte and neutrophil counts, and hypoglycemia (Perrin et al., 1982).

Prognosis of CM continues to be poor. Current treatment includes injectable quinine in doses that vary from 10 to 20 mg/kg every 8 h (van der Torn et al., 1998); in distant areas with difficulties for medical implementation oral mefloquine in a single dose of 25 mg/kg through a nasogastric tube seems a good alternative (Di Perri et al., 1999). Addition of allopurinol (4 mg/kg every 8 h during 5 days) enhances the therapeutic effect of quinine (Sarma et al., 1998). There is evidence that activated microglia plays an important role on the pathogenesis of CM; acute adjuvant immunosuppressive and anti-inflammatory treatment similar to that used for other parasitic diseases, such as NCC should be evaluated.

African trypanosomiasis or sleeping sickness

Two species of trypanosomes cause sleeping sickness: *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*. Transmission of the infection occurs in focal areas of sub-Saharan Africa by the tse-tse fly (*Glossina*), which inhabits riverbanks and highly humid areas (Kurzoe, 1993). CNS involvement usually manifests itself several months after the mosquito bite, which produces a trypanosomal chancre at the site of the mosquito bite. The organism spreads slowly from the site of infection and eventually to bloodstream, lymphatics and other interstitial spaces, where the parasites continue to multiply. Hallmark of the infection are the recurring waves of parasitemia, which last for months or years, and are the result of antigenic variation encoded in the genome of these parasites. Each episode of parasitemia increases until enough serum antibodies area are produced to cause a sharp drop in the number of parasites. Parasites that have different surface antigens variants (Borst & Rudenko, 1994) escape destruction by the first wave of antibodies, duplicate and produce a new parasitemia wave. The CNS becomes infected after months or years, however, the pathogenesis of cerebral trypanosomiasis is not well understood. Signs and symptoms are pleomorphic and may include: personality changes, loss of concentration, persistent headaches, seizures, motor deficits (tremors, choreoathetosis, ataxia) and eventually coma. A rather unique feature of the disease is the daytime somnolence, due to disruption of normal circadian sleep and wakefulness patterns (Buguet et al., 1993).

Definitive diagnosis of the disease is made by observation of trypanosomes in blood, CSF or lymphatic fluid. The morphological characteristics can be established on Giemsa or Wright stained slides. Since neurological disease caused by African trypanosomes is almost always fatal, it is recommended that the CSF be examined in all patients.

Treatment should be administered as early as possible, before the CNS becomes infected. The recommended drugs are: pentamidine isothionate, Suramin, Melarsoprol and Effornithine. All of them are toxic and expert assistance should be sought before prescribing treatment, and can be obtained from the Centers for Disease Control and Prevention in Atlanta, GA.

Other protozoan infections with CNS involvement

Toxoplasma gondii

Congenital toxoplasmosis is a consequence of maternal infection with oocysts during the first and second trimester of pregnancy. Oocysts are transmitted in households from infected cats, which harbour the sexual stages in the intestine (contaminated litter boxes) and infected raw meat (beef, lamb and pork).

Naegleria fowleri

N. fowleri is a free-living ameba, and when the trophozoite is aspired into the nasal cavity can penetrate the nasal mucosa, enter the submucosal nerve plexus and gain access to the CNS, a pathway that has been demonstrated experimentally in mice (Jarolim et al., 2000) *Naegleria* is found worldwide in fresh water bodies and soil.

In the CNS the amebas cause acute meningo-encephalitis (AME), with fulminating necrosis of the meninges and brain; most documented cases have been fatal (Carter, 1968; John, 1982). The disease is rare and difficult to diagnose because of the short period between onset and the clinical picture of meningo-encephalitis, a time lapse of 72 h. The course of AME is dramatic at onset with intense headache, fever of 39–40 °C and anorexia. Later symptoms include nausea, vomiting and signs of meningeal irritation. Patients are confused and irritable and may present convulsions before falling into coma. The disease is typically seen in children and adolescents who have been swimming in freshwater lakes, pools, streams, ponds and hot spring waters in which the temperature is high.

No satisfactory treatment has been found for *Naegleria*. High doses of amphotericin B (1–15 mg/kg for 6 days) have been reported to cure a few cases.

Helminth parasites with CNS involvement

All helminthic infections with tissue migrating larval stages are potentially capable of inducing CNS disease. In practice, only a few need be taken into account when considering differential diagnosis. Eosinophilic meningitis is a frequent finding in gnathostomosis and angiostrongilodosis, both acquired by ingesting raw seafood.

Gnathostoma spinigerum is a disease contracted in countries where raw freshwater fish is routinely consumed (Japan, Thailand, China, Philippines, Korea, Malaysia, India, Vietnam, Taiwan, Bangladesh and Myanmar). In America cases have been documented in Mexico, Ecuador and Colombia. The larval stage in infected fish can traverse the intestinal wall of humans and migrate to various tissues, more often inducing the clinical entity of cutaneous larva migrans. In Thailand, a number of cases of eosinophilic meningo-encephalitis have been reported (Puri & Grover, 1998). Diagnosis can be established in suspected cases by ELISA using adult worm antigen (Diaz Camacho et al., 1998). Eosinophilia is also frequent in these nematode infections. The antihelminthic albendazole has been used for treatment of cutaneous gnthostomosis, although results have not always been satisfactory.

Other helminthic infections associated with eosinophilic meningitis are *Angiostrongylus cantonensis*, a rat lungworm that is acquired by ingestion of raw fish, snails and molluscs. It is endemic in the Far East, Pacific Islands and Hawaii.

Schistosoma, *Paragonimus westermanni* and *Strongyloides* infections should also be considered in patients with persistent meningeal signs in the absence of eosinophilia, particularly when they have a history of travel to endemic areas and present specific manifestations of helminth infections outside the CNS.

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108

Lyme disease

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In the mid-1970s several dozen patients living near Lyme Connecticut developed an illness, initially misdiagnosed as juvenile rheumatoid arthritis, and subsequently called Lyme arthritis (Steere et al., 1977). It was renamed Lyme disease when its systemic nature was appreciated. In retrospect, skin and neurological manifestations of Lyme disease had been described in Europe for decades, and had even been recognized as antibiotic responsive (Coyle, 2000). Lyme disease is a multisystem infection due to the spirochete *Borrelia burgdorferi*. This spirochete, named after its discoverer Willy Burgdorfer, is present in hard body ticks of the *Ixodes ricinus* family (Burgdorfer, 1984). *Ixodes* ticks feed on a variety of hosts, including humans. Virtually all transmissions occur through tick bite, although there have been rare congenital cases. To date, there have been no documented blood transfusion cases (McQuiston et al., 2000). Lyme disease is one of the major emerging pathogen infections. It has generated significant publicity and controversy, and has become a focus of interest for both lay action groups and the popular press.

Spirochetal infection

B. burgdorferi is a spirochete. Spirochetes are gram negative bacteria that belong to a distinct eubacterial phylum (Benach & Coleman, 1993; Reik, 1987). They are flexible cells with a helical configuration, excessive length to diameter ratios of up to 100 to one, and flagella that lie between inner and outer cell membranes. These endoflagella convey motility properties. Of the four recognized human spirochetal infections which cause neurological disease, all show frequent central nervous system (CNS) seeding during the spirochetemic stage (Table 108.1). CNS infection may be inapparent, or associated with clinical disease. Spirochetes can also persist silently within the CNS, only to cause late neurologic problems months to years after initial infection. These spirochetal disorders have a number of features in common (Table 108.2). The shared features provide guidelines to think about Lyme disease.

Organism

Borrelia spirochetes have coils which are spaced irregularly 2 to 4 micrometres (μm) apart (Benach & Coleman, 1993). *B. burgdorferi* is easy to culture from ticks, but difficult to culture from patients. The spirochete is 11 to 39 mcm long. It consists of a central protoplasmic cylinder, with seven to 12 attached periplasmic flagella, surrounded by an outer cellular membrane and covered by a carbohydrate-containing slime layer (Rosa, 1997). The *B. burgdorferi* genome has been completely sequenced, including its 12 linear and nine circular plasmids (Casjens et al., 2000; Fraser et al., 1997). *B. burgdorferi* shows significant genetic diversity (Mathiesen et al., 1997). Although there are at least ten genospecies in the *B. burgdorferi sensu lato* complex, only three are well documented to cause Lyme disease (Table 108.3). *B. burgdorferi* gene expression varies depending on whether the spirochete is in the tick vector, the host, or the test tube. Organisms can clearly adapt rapidly. Environmental triggers, such as ambient temperature or exposure to a blood meal, change gene expression. The fact that genes can change, with differential antigen expression, probably influences pathogenicity. Recent studies support strain differences in organotropism and virulence, and there are likely to be neurotropic and neurovirulent strains. *B. burgdorferi* is quite heterogeneous, with differences in protein expression, plasmids, and DNA between organisms. Variable major protein-like (Vmp) sequences have recently been described in *B. burgdorferi*, which could be involved in antigenic variation similar to that described in relapsing fever.

Table 108.1. Human spirochetal infections which cause neurological disease

Genus	Spirochete	Disease	Transmission	CNS seeding	Culture
Treponema	*T. pallidum*	Syphilis	Sexual contact	Up to 40%	Not possible
Leptospira	*L. interrogans*	Leptospirosis	Animal exposure	Up to 90%	High yield
Borrelia	*Borrelia* species (multiple)	Relapsing fever	Tick (endemic), or louse (epidemic) bite	Up to 50%	Low yield (but easily visualized)
Borrelia	*B. burgdorferi*	Lyme disease	Tick bite	Up to 40%	Low yield (not easily visualized)

Table 108.2. Shared properties of spirochetal infections

Skin or mucous membrane entry portal
Neurotropic and neurovirulent spirochete strains
Frequent CNS invasion during spirochetemia
Clinical disease stages, separated by quiescent periods
Broad clinical spectrum
Causes chronic persistent infection
Produces vasculopathy
Jarisch Herxheimer reaction may occur with initiation of antibiotics

Table 108.3. *B. burgdorferi sensu lato complex*

	Associated with Lyme disease
Genospecies	*Comment*
B. burgdorferi sensu stricto	North America; less so Eurasia Less genetic diversity Neurologic, dermatologic, rheumatologic disease
B. afzelii	Eurasia More genetic diversity Dermatological disease
B. garinii	Eurasia More genetic diversity Neurologic disease
	Not associated with Lyme disease
	B. andersonii *B. bissetti* *B. japonica* *B. lusitaniae* *B. tanukii* *B. turdae* *B. valaisana*

B. burgdorferi is a very tissue-tropic organism. Spirochetes do not tend to float free within body fluids, which probably explains the low culture and polymerase chain reaction (PCR) yield from cerebrospinal fluid (CSF). They will bind to endothelium, to platelets via integrins, and to most mammalian cells via glycosaminoglycans. In the host *B. burgdorferi* is often associated with extracellular matrix collagen fibres. This may involve the spirochete-specific decorin binding proteins A and B. In vivo, *B. burgdorferi* is always extracellular. Intracellular localization has only been described in vitro, and is therefore of uncertain significance.

Epidemiology

Lyme disease represents 96% of the vector-borne infection in the United States. It is also the most common vector-borne infection in Europe (Githeko et al., 2000). *B. burgdorferi* is the most common CNS bacterial pathogen in Sweden, and is an important pathogen in Germany, Austria, and Switzerland. A central feature of Lyme disease is that it is a highly focal disorder, geographically restricted to areas where the tick vector is found. In the United States *Ixodes scapularis* (Northeast, mid-Atlantic, and upper Midwest) and *I. pacificus* (upper Pacific coastal region) are the main vectors. *I. ricinus* is the major vector in Europe, and *I. persulcatus* in eastern Europe/Asia. *Ixodes* ticks have a two year, three stage (larva, nymph, adult) life cycle, and only feed a total of three times. These ticks are very small and easy to miss, and their bite is painless (Shapiro & Gerber, 2000). They will feed to repletion, and can remain attached for days. Infected ticks probably need to feed for 24 hours or longer to passage spirochetes (Sood et al., 1997). Within endemic areas, in the Northeast and Midwest, 30% or more of ticks may be infected. Even within these areas, small geographic differences may be associated with extreme variations in the number of infected ticks. The infection rate is much lower ($\leq$5%) for

Table 108.4. Lyme disease stages

Stage	Syndromes	Comments
Early local infection	Erythema migrans (EM) Flu-like illness with seroconversion	Occurs within 1 month of infection EM is the major Lyme disease syndrome, and the only pathognomonic clinical marker Flu-like syndrome may reflect dissemination
Early disseminated infection	Multifocal EM, lymphocytoma cutis (LC) Arthralgias, myalgias, brief arthritis/myositis Conduction block, myopericarditis, pancarditis Conjunctivitis Meningitis/meningoencephalitis, cranial neuropathy, acute painful radiculoneuritis	Occurs within 3 months of infection LC occurs outside North America Cardiac involvement has become rare Ocular involvement is uncommon
Late stage infection	Acrodermatitis chronica atrophicans (ACA) Oligoarticular arthritis, chronic arthritis Uveitis, keratitis Encephalopathy, chronic polyradiculoneuropathy, encephalomyelitis	Occurs 3 months or longer after infection ACA occurs outside North America Arthritis is more common in North America Ocular involvement is very uncommon

I. pacificus in the West, with a consequent lower number of Lyme disease cases from this region. Although ticks have a limited number of preferred hosts, they can feed on over 100 different species. Humans are accidental hosts, and in temperate climates are most likely to be bitten by questing nymphs during late spring and early summer.

Lyme disease occurs in over 50 countries worldwide (Shapiro & Gerber, 2000). In the United States cases have been reported from 49 states and the District of Columbia (Orloski et al., 2000). However, most are confined to 100 counties in 10 states. Over 90% of cases come from ten states: New York, Connecticut, Pennsylvania, New Jersey, Wisconsin, Rhode Island, Maryland, Massachusetts, Minnesota and Delaware. Although more than 160 000 cases have been reported to the Centers for Disease Control and Prevention (CDC), this is probably a significant underestimate. The incidence approximates 5 cases per 100 000 population; in endemic areas 1 to 3% of the population area are affected each year. Lyme disease-like cases have been reported in the South (Barbour, 1996; Kirkland et al., 1997). Although the tick vector is present, *B. burgdorferi* has not been documented within resident ticks. A different tick, *Amblyomma americanum* (the Lone Star tick), carries a presumptive new species, *B. lonestarii* sp. nov. It is possible that this slightly different spirochete is a cause of mimicking disease.

Lyme disease affects both genders and all ages, with peaks in children (ages 5 to 9) and middle-aged adults (ages 45 to 54). The major epidemiologic risk factor is time spent out of doors, either on a recreational or vocational basis. In temperate climates most cases cluster from June to August, but infection can occur all year round.

Clinical presentation

Infection with *B. burgdorferi* does not necessarily lead to disease. Asymptomatic infection occurs in perhaps 20 to 30% of cases. Subclinical disease may reflect non-pathogenic strains, ineffective inoculum, or efficient host immunity. Clinical illness occurs in stages, with suggestive organ-specific syndromes (Table 108.4). Target organs in Lyme disease are the skin, joint, heart, eye, and nervous system (Steere, 1989).

The only pathognomonic clinical syndrome is erythema migrans (EM). This early local infection marker occurs in up to 90% of patients, and is the major Lyme disease syndrome. It occurs one to 30 (typically 7 to 10 days) after tick bite. Spirochetes are present in the skin, particularly at the leading edge, so that punch biopsies of skin have a high yield on culture, stain and PCR studies. Important features to look for are expansion of the rash over days, large size (typically inches), and common accompanying symptoms (arthralgias, myalgias, headache, stiff neck, palpitations, malaise, fever, chills) (Nadelman & Wormser, 1998). A rash which occurs within 24 hours of a tick bite, or which clears spontaneously within 48 hours, is not EM. Flu-like illness has been associated with seroconversion, and probably represent early dissemination. A helpful diagnostic clue is that respira-

tory and gastrointestinal symptoms occur in less than 10% of these patients.

B. burgdorferi disseminates within days to weeks in blood, and possibly skin and lymphatics. Early dissemination is associated with multiple EM lesions, as well as characteristic musculoskeletal, cardiac, ocular, and neurologic syndromes. Migratory joint and muscle pains are more common than frank joint swelling at this stage. Involvement of the temporomandibular joint is a suggestive feature. High-degree heart block, the characteristic cardiac finding, is becoming very unusual. This may reflect more effective early antibiotic regimens.

Late stage infection occurs after months to years. Migratory oligoarticular or monoarticular large joint arthritis (tenosynovitis with swelling) is a particularly suggestive feature, especially when accompanied by Baker's cysts, while small joint involvement is seen in less than 10% of patients (Nadelman & Wormser, 1998; Steere, 1997). Approximately 10% of patients develop chronic Lyme arthritis unresponsive to antibiotics. This relates to genetic susceptibility, and is likely an immune-mediated phenomenon (see pathophysiology section below). Two skin manifestations, lymphocytoma cutis (LC), which consists of a collection of plasma cells within the earlobe, nipple or scrotum, and acrodermatitis chronica atrophicans (ACA), a sclerotic skin lesion particularly common in elderly women, are virtually confined to European cases. This probably reflects genospecies and strain differences between North America and Europe.

Congenital infection

Congenital infection is rare, and there is no identifiable congenital Lyme disease syndrome (Silver, 1997). Individual reports suggest perinatal transmission can lead to preterm delivery, fetal death, and fetal malformations, but epidemiologic studies indicate a very low risk. In one study of 19 maternal infections, in whom only 13 received antibiotics, the transmission rate was zero (Markowitz, 1986). In a European study of EM during pregnancy, patients were treated with ceftriaxone or penicillin, and no adverse fetal outcome was found (Maraspin, 1996). In population surveys, there is no difference in fetal outcomes between seropositive and seronegative mothers.

Neurological manifestations

Neurological involvement can occur at all stages of Lyme disease and can involve any part of the neuraxis (Table 108.5). (Belman et al., 1993, 1997; Coyle, 2000; Garcia-Monco & Benach, 1997; Haass, 1998; Halperin et al., 1987, 1990; Logigian, 1990; Logigian & Steere, 1992; Luft et al., 1992; Pachman & Steere, 1985). Spirochetes can invade the CNS quickly; a proportion of EM patients have CNS seeding. Since many EM patients experience some headache and stiff neck, this is probably most consistent with a pre-meningitis phase. Early dissemination is associated with three characteristic syndromes. Meningitis/meningoencephalitis appears to be the most common early neurologic syndrome in North America. It is an aseptic meningitis, and can occur along with EM. Aseptic meningitis with facial nerve or radicular involvement should suggest Lyme meningitis. CSF shows mononuclear pleocytosis (typically 100 to 200 WBC/mm^3, range 5 to 4000 WBC/mm^3) with elevated protein, normal glucose, and intrathecal organism-specific antibody production in up to 60% of North American meningitis cases and essentially all European cases. Lyme-related cranial neuropathy involves the facial nerve in most cases. About one-third of patients have bilateral involvement. Most Lyme-related facial nerve palsies, unlike idiopathic Bell's palsy, occur during summer time and are accompanied by a multisymptom complex (fatigue, arthralgias, myalgias, headache, stiff neck, cognitive difficulties). Most patients have abnormal CSF consistent with CNS involvement. Other cranial nerves (such as the optic and oculomotor nerves) are occasionally involved. Acute painful radiculoneuritis (lymphocytic meningoradiculitis, or Bannworths' syndrome) is the most common European neurologic manifestation. Patients frequently begin with intrascapular pain, radiating down the spine or into extremities. Patients develop asymmetric dermatomal and myotomal abnormalities. Meningeal features are subtle, yet these patients show the most inflammatory CSF changes.

The most common late stage neurologic syndrome in North America is Lyme encephalopathy. This involves rather subtle cognitive deficits in memory, concentration, and processing speed. CSF changes are not marked, and parameters may be normal. Neuroimaging shows cerebral blood flow disturbances on brain SPECT. Lyme encephalopathy is most consistent with CNS infection. Chronic polyradiculoneuropathy is an axonal process. Patients may experience subtle paresthesias, occasional shooting pains, numbness, and restless legs. CSF is normal, unless there is associated encephalopathy. Examination suggests mild polyneuropathy or radiculoneuropathy. In Europe, late stage ACA is often accompanied by a distal sensory polyneuropathy (Kindstrand et al., 1997). Chronic progressive encephalomyelitis has been reported mainly in Europe. There is parenchymal brain or spinal cord involvement,

Table 108.5. Neurologic manifestations of Lyme disease

Stage	Characteristic syndromes	Comments
Early local infection	Asymptomatic Non-specific symptoms	CNS invasion can occur with normal CSF (premeningitis phase)
Early disseminated infection	Meningitis, meningoencephalitis	Clinical features may be subtle Can see associated facial nerve, radicular involvement Spontaneous resolution, occasional chronic meningitis
	Cranial neuropathy	Over 80% involve facial nerve, one-third bilateral, accompanied by multisymptom complex Spontaneous resolution
	Acute painful radiculoneuritis	Most common neurological syndrome in Europe Very inflammatory CSF Spontaneous resolution
Late stage infection	Encephalopathy	Subtle memory, attention, processing abnormalities Abnormalities may include low grade CSF changes, cerebral blood flow disturbances Does not spontaneously resolve
	Polyradiculoneuropathy	Axonal process Subtle clinical and laboratory abnormalities CSF generally normal Does not spontaneously resolve
	Encephalomyelitis	Abnormal CSF Does not spontaneously resolve
Stage	Unusual syndromes	Comments
Late stage infection	Cerebrovascular disease	Includes vasculitis, transient ischemic attacks and hemorrhagic strokes Abnormal CSF
	Intracranial hypertension	Age restricted (children, adolescents) Abnormal CSF
	Psychiatric disease	Reflects encephalomyelitis Abnormal CSF
	Myositis, myopathy	Muscle infection Unifocal or multifocal

with a variety of clinical syndromes that can mimic multiple sclerosis, brain tumour, myelopathy, or degenerative syndromes. This is the most uncommon of the well-defined neurologic syndromes.

A number of unusual syndromes have been related to *B. burgdorferi* infection. They include psychiatric syndromes, cerebrovascular disease, or age-related intracranial hypertension syndrome, and myositis/myopathy (Coyle, 2000). Rare cases of dementia, normal pressure hydrocephalus, and motor neuron disease have been attributed to Lyme disease. Important clues are that these syndromes are associated with inflammatory CSF, and they improve after antibiotic therapy.

Diagnosis

Diagnosis of neurologic Lyme disease is complicated by the lack of a readily available active infection assay. Culture is not helpful. Although Lyme disease is ultimately a clinical diagnosis, it should be supported by laboratory data. The single exception is EM. With typical features, and endemic area exposure, no confirmatory laboratory testing is needed (Nichol et al., 1998; Tugwell et al., 1997). The American Academy of Neurology has provided a Practice Parameter Guideline to diagnose neurologic Lyme disease (Table 108.6) (American Academy of Neurology Quality Standards Subcommittee, 1996; Halperin et al.,

Table 108.6. American Academy of Neurology Practice Guidelines for diagnosis of neurological Lyme disease[a,b]

Exposure to appropriate ticks in area where Lyme disease occurs
One or more of the following:
– Skin manifestation (EM, or histopathologically proven LC or ACA)
– Immunologic evidence of *B. burgdorferi* exposure
– Detectable *B. burgdorferi* (by culture, histology, or PCR)
One or more specified disorders, no other etiology, possible additional testing (such as CSF evaluation for suspected CNS infection)
– Causally related disease
Lymphocytic meningitis +/− cranial neuropathy, painful radiculoneuritis, or both
Encephalomyelitis
Peripheral neuropathy
– Causally related syndrome
Encephalopathy

Notes:

[a] American Academy of Neurology Quality Standards Subcommittee, 1996.

[b] Halperin et al., 1996.

Table 108.7. Diagnosis of neurological Lyme disease

History
Endemic area exposure
– Outdoor activities
– Tick exposure (strain, geographic origin, attachment, blood engorgement)
History of EM-like rash or flu-like illness prior to neurological syndrome
Extraneural involvement
– Target organ involvement (skin, musculoskeletal, cardiac, ocular)
– Systemic symptoms (fatigue, myalgias, arthralgias, palpitations)
Characteristic neurological syndrome
Laboratory
Blood studies
– Specific (anti-*B. burgdorferi* antibodies)
– Nonspecific (↑ acute phase reactants and liver enzymes early, anticardiolipin IgM antibodies)
CSF
– specific (intrathecal anti-*B. burgdorferi* antibodies, culture, PCR)
– Non-specific (cell count, protein, glucose, cytology, VDRL, oligoclonal bands, IgG index)
Neuroimaging
– MRI (yield ≤25%; variable pattern)
– Brain SPECT
Electrophysiologic
– Nerve conduction tests, electromyography
Neurocognitive testing

1996). Both clinical and laboratory features can be used to support a diagnosis of neurologic Lyme disease (Table 108.7).

The single most used laboratory test is serology. Positive serology, if accurate, documents prior exposure to *B. burgdorferi* but not active infection. Following an antibody titre is not helpful in Lyme disease, since high titres may remain for years in treated and recovered individuals. Intrathecal antibody production can also persist for months to years. A proportion of recovered Lyme disease patients will even show persistent IgM reactivity, but the significance of this finding remains unknown.

Current CDC recommendations involve a two tier test system to evaluate antibodies. Screening serology (typically ELISA, using sonicated spirochetes as the antigen target) is used first. If positive or borderline, a second more specific immunoblot test is performed. Lyme serology is only standardized to the extent that positive IgM and IgG immunoblots need to show two of three (p23, 39, 41) and five of nine (p18, 21, 28, 30, 39, 41, 58, 66, 93) possible bands, respectively. First tier tests are not standardized, antigen targets are not standardized, and use of monoclonal antibodies and recombinant proteins are not required. Because spirochetes contain a number of immunodominant non-unique antigens, under optimal conditions the screening ELISA has a false-positive rate of at least 5%. There is great variability between laboratories with regard to sensitivity and specificity of Lyme serology tests. Second generation antibody tests have been developed, which do use recombinant and chimeric proteins. Chimeric proteins consist of epitopes of selected recombinant proteins, which have been joined together to provide multiple reaction sites. A recently approved office-based rapid detection assay (PreVue *B. burgdorferi* antibody detection assay, Wampole Laboratories, NJ) measures reaction to a chimeric protein; positive samples produce an immunostripe stain within a few minutes. Alternative antibody tests based on detection of neoantigens (spirochetal proteins only expressed in the host) are also under development. It is likely that both ELISA and immunoblot assays to detect anti-*B. burgdorferi* antibodies will be improved in the next few years, using recombinant/chimeric technology and automated readout.

CSF is abnormal in most neurologic Lyme patients. Intrathecal organism-specific antibody production can be

considered diagnostic for CNS infection. PCR assays have been somewhat disappointing, since the positivity rate in obvious neurological cases is no more than 40% (Luft et al., 1992; Nocton et al., 1996). This probably reflects the paucity of spirochetes in CSF. Abnormalities such as mononuclear pleocytosis, increased protein, monoclonal or oligoclonal bands, or intrathecal IgG production are helpful to document CNS involvement, but are not diagnostic. In fact, oligoclonal bands and intrathecal IgG antibody production are seen in a minority of neurologic Lyme disease patients in North America, in contrast to European patients. Electrophysiological tests, which suggest a multifocal axonal radiculoneuropathy are also helpful to support a diagnosis of neurologic Lyme disease, but are not diagnostic.

Neurocognitive function tests (to document objective deficits) and brain SPECT (to document multifocal cerebral blood flow disturbances) are suggestive of late Lyme encephalopathy. These abnormalities, along with any CSF disturbances, should improve following antibiotic treatment (Logigian et al., 1999).

There are certain experimental tests for diagnosis, that include special ways to culture spirochetes or to detect antigens in urine (the Lyme urine antigen tests or LUAT). These are not widely accepted, and there have been issues with regard to reproducibility of results. The LUAT test in particular uses no parameter to assure specificity, and becomes positive with concurrent urinary tract infection. Such tests should never be used in isolation to support a diagnosis of Lyme disease.

Treatment

Early local infection (EM) is treated with doxycycline (100 mg po BID), amoxicillin (500 mg po TID), or cefuroxime axetil (500 mg po BID) for at least two weeks (Nadelman & Wormser, 1998). Doxycycline is preferred because it also treats ehrlichia, a potential tick copathogen. This antibiotic cannot be used in young children under age 8 however, because of dental discolouration and bone problems. Side effects include gastrointestinal upset and photosensitivity.

Most extraneural disseminated Lyme disease syndromes also respond to doxycycline given for several weeks (Dattwyler et al., 1997). Although definitive randomized controlled trial data is lacking to specify the optimal treatment of neurological Lyme disease, expert consensus panels recommend the third generation cephalosporin ceftriaxone, at 2g QD for 2 to 4 weeks (Wormser et al., 2000). This is frequently used on an outpatient basis, since it is given intravenously once a day over 30 to 60 minutes. Anecdotal reports indicate it can be delivered over as short a time frame as ten minutes. The drug is basically well tolerated. Pseudomembraneous colitis is unusual; to avoid this problem patients are often placed on acidophilus (*Lactobacillus* species) from health food stores or from yogurt. One to 10 billion viable organisms need to be consumed, divided over a TID or QID schedule. Gall bladder disease, due to drug sludge, is another very unusual complication. Biliary pseudolithiasis is more likely in young women and children. Alternative regimens to ceftriaxone include intravenous cefotaxime (2 g TID), penicillin (at 18 to 24 million units) or doxycycline (200 mg BID or twice the usual dose to give higher CSF levels). Most patients respond to appropriate treatment. Late stage infection patients may continue to note improvement months after treatment has stopped.

With regard to the pregnant patient, both oral amoxicillin or ceftriaxone can be used safely. With a term pregnancy, cefotaxime is usually substituted for ceftriaxone. It does not involve biliary excretion, and does not carry a risk for jaundice in the newborn.

In certain cases patients continue to complain of symptoms (such as fatigue, arthralgias, myalgias, headache) after treatment for Lyme disease (Asch et al., 1994; Bujak & Weinstein, 1996; Gaudino et al., 1997; Seltzer, 2000; Shadick et al., 1994). They are sometimes diagnosed as 'chronic Lyme disease', and treated with extended combination antibiotics. There are no accepted criteria for this diagnosis. It is likely that a number of etiologies might explain persistent post-treatment problems (persistent *B. burgdorferi* infection, infection with another tick agent, postinfectious immune/inflammatory process, slow recovery, alternative diagnosis, reinfection, fixed damage, hypochondriasis). Several prospective studies have attempted to evaluate these patients, to address whether or not they have an antibiotic-responsive syndrome. The National Institute of Allergy and Infectious Disease (NIAID) funded a 5-year contract to analyse antibiotic responsiveness in seropositive and seronegative patients with persistent symptoms following a well documented history of treated Lyme disease. Patients received 30 days of intravenous ceftriaxone, followed by 60 days of oral doxycycline. At a recent preplanned interim analysis, after 131 patients had been entered, the independent Data Safety and Monitoring Board recommended termination of the treatment component. They recommended no further patient entry, since no significant benefit of antibiotic treatment had been found. In another recently completed NIAID-funded study of chronic Lyme disease patients with persistent fatigue, four weeks of ceftriaxone compared to placebo treatment

was associated with a significant improvement in fatigue at six months. However, there were no CSF or other biologic markers of treatment response, and no evidence for true persistent infection.

Prevention

Because Lyme disease involves exposure to an environmental source, preventive strategies such as daily body checks, protective clothing, and use of tick repellants have been tried. Although prophylactic antibiotics are often used following tick bite (Fix et al., 1998), prospective randomized double blind trials have failed to document a benefit over watchful waiting (Agger & Case, 1997; Costello et al., 1989; Shapiro et al., 1992). In a recent meta-analysis involving over 600 patients with tick bite, antibiotic prophylaxis was not found to be of benefit (Warshafsky et al., 1996). One study did suggest that with a high risk of Lyme disease after tick bite (>0.036), prophylactic doxycycline therapy should be considered (Magid et al., 1992).

A prophylactic monovalent vaccine (LYMErix, SmithKline Beecham), which uses recombinant lipidated outer surface protein A (OspA), is now available (Steere et al., 1998; Steigbigel & Benach, 1998). It is given at 0, 1, and 12 months, with 50% protection after the second dose and 80% protection after the third dose. There are several areas of concern about the current vaccine. Protection depends on generation of specific anti-OspA antibodies, which kill spirochetes within the feeding tick. Protective antibodies do not persist, so that frequent booster shots will be necessary. These may involve annual booster shots (Thanassi & Schoen, 2000). Patients become seropositive on current antibody tests, and can even show multiple bands on immunoblot. There is also a concern that the vaccine may result in an immune-mediated arthritis in genetically susceptible individuals (see below). Second generation multivalent vaccines are currently being evaluated.

Prognosis

For the most part, neurological Lyme disease has an excellent prognosis. Early disseminated syndromes get better on their own, and improve within 3 to 5 days of starting antibiotics. Radicular pain can improve within hours. Overall 85% of Lyme-related facial nerve palsies improve, while 70% show complete recovery (Smouha et al., 1997). A minority of patients (about 7%) may show development of new abnormalities (such as facial nerve palsy) during treatment, but this does not appear to reflect therapeutic failure since they ultimately do well. Late stage neurological syndromes do not resolve spontaneously. Treatment prevents worsening, and generally results in clinical and laboratory improvement over months. Patients may be left with residual problems, however.

Pathophysiology

Lyme disease produces a wide array of neurological problems in the setting of a limited number of organisms and pathological damage. Lyme disease neuropathology is not marked. There is low grade meningeal and perivascular mononuclear inflammation, but little tissue destruction. Late infection can produce obliterative vasculopathy, and rare patients show prominent demyelination or granulomatous tissue changes (Coyle, 2000; Oksi et al., 1996). The occasional visualized spirochete is always extracellular. These have never been visualized in peripheral nerve, although a recent study reported PCR reactivity in a sural nerve biopsy (Maimone et al., 1997). Peripheral nerve biopsies show axonal damage, with perivascular inflammation (Vallat et al., 1987). The pathology suggests that indirect mechanisms are likely to be important in the pathogenesis of neurological disease.

B. burgdorferi produces a number of immune and inflammatory abnormalities in the host (Coyle, 2000; Garcia-Monco & Benach, 1997; Hu & Klempner, 1997; Sigal, 1997). Spirochete outer surface (Osp) proteins induce inflammatory responses. Organisms bind to endothelial cells, up-regulate adhesion molecules, and induce local chemokine production. They cross endothelium through intercellular openings, or by transcytotic mechanisms, to penetrate multiple organs. They also bind to platelets, red blood cells, plasminogen, and glycosphingolipids on the surface of neurons, astrocytes, oligodendrocytes, and Schwann cells. In culture, *B. burgdorferi* injures both astrocytes and oligodendrocytes. Several different *B. burgdorferi* strains are neurotropic, and can invade the CNS (Wilske et al., 1996).

Chronic Lyme arthritis is now believed to be an immune-mediated syndrome (Gross et al., 1998a). It occurs in approximately 10% of Lyme arthritis patients. They are HLA-DR4 (DRB1*0401) positive, have an antibiotic unresponsive arthritis, and have PCR negative synovial fluid (Gross et al., 1998b). Patients show a strong cellular and humoral immune response to OspA. OspA reactive CD4+T helper 1 (TH1) cells within the joint release damaging proinflammatory cytokines, and inflammatory arthritis parallels the TH1: TH2 ratio within synovial fluid. OspA shows molecular mimicry with

human lymphocyte functional antigen-type 1 (LFA-1), an integrin receptor and adhesion molecule found primarily on T-cells. It binds to intercellular adhesion molecule-type 1 (ICAM-1). Both LFA-1 and ICAM-1 are overexpressed in inflammatory tissue.

B. burgdorferi can cause a vasculopathy similar to endarteritis obliterans. It produces cytokine changes. Proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumour necrosis factor-α (TNF-α), are elevated in the joints of arthritis patients (Yin et al., 1997). Cloned T-cell lines from synovial fluid and blood of Lyme arthritis patients secrete interferon-γ (IFN-γ) when exposed to *B. burgdorferi*. Mononuclear cells from neurologic Lyme disease patients also preferentially secrete IFN-γ when exposed to *B. burgdorferi* Osp proteins (Ekerfelt et al., 1997), particularly CSF cells. The antagonistic anti-inflammatory/regulatory cytokine, IL-4, is down-regulated. Neurological patients show increased levels of IL-1 and TNF-α in CSF. Soluble IL-2 receptors are increased in both CSF and blood, and decrease after treatment (Nilsson et al., 1994). IL-12 production is increased in monocytes collected from patients with longstanding Lyme disease, which favours TH1 cell production (Pohl-Koppe et al., 1998). In a recent study *B.burgdorferi* induced TH1 cells which produce IL-17, another potent inflammatory cytokine (Infante-Duarte et al., 2000). Overall, the cytokine data suggests an imbalance of the TH1:TH2 CD4+T cell ratio in Lyme disease, with TH1 cells predominant in late infection. This would favour cell-mediated immunity and inflammatory cytokine production, and is consistent with the concept that humoral immunity is protective in *B. burgdorferi* infection.

There are a number of potential pathogenetic factors in addition to cytokines. *B. burgdorferi* induces neurotoxins such as nitric oxide and quinolinic acid, an NMDA receptor antagonist and excitotoxin which is elevated in the CSF of neurological patients. Antibodies and immune complexes also appear to have some role. *B. burgdorferi* is B-cell mitogenic. Infection can result in autoreactive antibodies to cardiolipin and acidic gangliosides (GM1, asialo-GM1), anticardiolipin IgM, antiaxonal IgM, antibodies to myelin and myelin components, antineuronal antibodies, antibodies to heat shock protein, and antibodies to a 46kD protein which crossreacts with myosin (Coyle, 2000; Sigal, 1997; Yu et al., 1997). *B. burgdorferi* specific immune complexes have been reported in both serum and CSF, and may correlate with disease activity (Coyle et al., 1990; Schutzer et al., 1990). CSF T-cells from neurological patients react to cardiolipin as well as a variety of neural antigens, including myelin and galactocerebroside (Wang et al., 1996). In summary, a number of these indirect mechanisms could contribute to neurologic manifestations of infection.

There are many animal models of Lyme disease, but none truly mimic human disease. In some animals infection causes no obvious disease, while in others selected organs are involved. In some models infection spontaneously clears, in others infection clears with antibiotics, while in still others antibiotics contain but never clear infection (Foley et al., 1995; Goodman et al., 1991; Straubinger et al., 1997). The best animal model for neurological Lyme disease is in rhesus monkey primates (England et al., 1997a,b; Pachner et al., 1995a,b; Philipp et al., 1997; Roberts et al., 1995). They can be infected by tick bite, and go on to develop neurologic involvement. CSF pleocytosis occurs within 5 weeks of inoculation, and CSF is PCR positive. CSF pleocytosis and PCR positivity may wax and wane. Within three months of infection there is peripheral nerve involvement which persists at least 2 years. Infected monkeys show chronic meningeal inflammation. For unclear reasons, CNS and PNS tissues remain culture negative. This model remains under investigation.

Dual infections

Ixodid ticks carry other bacterial, parasitic, and viral pathogens. Patients can be coinfected with *B. burgdorferi*, and one or more other agents through a tick bite (Mitchell et al., 1996; Nadelman et al., 1997; Persing, 1997; Walker et al., 1996). Coinfection has been associated with more prolonged spirochetemia, more severe clinical illness, and a poorer therapeutic response. It is estimated that 4 to 30% of Lyme disease patients are dually infected with a parasite or a rickettsia-like bacterium. *Babesia microti* is a parasitic infection which can cause a malaria-like illness. It can also cause chronic infection, with fatigue, episodic fever, and chills (Krause et al., 1998). Patients who are coinfected with *B. burgdorferi* and babesia are more likely to experience fatigue, headache, sweats, chills, anorexia, emotional lability, nausea, conjunctivitis, and splenomegaly (Krause et al., 1996). They are 13 times more likely to be symptomatic for months, and three times more likely to be PCR positive in blood for circulating *B. burgdorferi* DNA. The antibiotic treatment for babesia is entirely different than that for *B. burgdorferi*. However, in a retrospective cohort study of Lyme disease patients with subclinical babesia infection, long-term outcome was not adversely affected (Wang et al., 2000). A recent study found that treatment over 1 week with atovaquone (750 mg BID) plus azithromycin (500 mg, followed by 250 mg QD) for babesiosis was not only as effective as conventional therapy (clindamycin plus

quinine), but was much better tolerated (Krause et al., 2000).

Ehrlichiae are obligate intracellular gram-negative like bacteria, which resemble rickettesiae. They show a marked tropism for leukocytes and platelets. Originally recognized to cause veterinary diseases, they are capable of producing chronic infection. The agent of human granulocyctic ehrlichiosis (HGE), an *E. equi-E. phagocyctophila*-like agent, infects Ixodid ticks (Dumler, 1997; Wallace et al., 1998). It responds well to tetracycline agents such as doxycycline. Patients infected with Lyme disease and HGE also appear to have worse clinical syndromes.

Coinfection may contribute to persistent post-treatment symptoms. A patient treated for Lyme disease could have persistent problems due to an unrecognized and untreated babesia or ehrlichia infection. In addition, there are likely to be other as yet unrecognized tick-borne pathogens. Although a tick borne flavivirus has been reported in North American Ixodid ticks, no clinical syndrome has been recognized to date. In Europe tick borne encephalitis virus causes a severe infection; fortunately, an effective vaccine is available.

There are some helpful clues to suspect an alternative tick pathogen. Both babesiosis and HGE increase alanine aminotransferase, and produce thrombocytopenia. These are unusual in Lyme disease, and should suggest the possibility of dual infection. Both of these alternate infections appear to be immunosuppressive, which could explain a more severe clinical illness. In endemic areas tick copathogen exposure should be considered when evaluating for Lyme disease. The simplest way to screen for exposure is to look for an antibody response, although PCR, culture, and peripheral smears and stains are available as well.

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Neurosyphilis

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Venereal syphilis is a chronic systemic infection caused by the spirochete *Treponema pallidum* and distinguished clinically by three stages: (i) a local primary lesion with regional lymphadenopathy; (ii) a secondary bacteremic stage with disseminated mucocutaneous lesions; and (iii) a tertiary stage of skin, bone, and visceral involvement that develops after a latent period lasting years.

Epidemiology

Treponema pallidum is an obligate human parasite with no animal or environmental reservoir that is nearly always transmitted sexually through contact with infectious mucocutaneous lesions. Transmission can occur also via non-sexual personal contact, accidental direct inoculation, blood transfusion, needle sharing, or transplacentally (Stamm, 1999).

The disease was first identified in Europe when an epidemic of severe infection overran the continent at the end of the fifteenth century, coinciding with the return of Columbus from the West Indies. Because of this, syphilis was believed to be a New World illness communicated to Europe by Columbus's returning sailors. But the infection likely was already present in the Old World, unrecognized and mistaken for leprosy (Hackett, 1963; Hollander, 1981; Sparling, 1999).

In the next five centuries, syphilis spread worldwide, becoming so common that its prevalence reached 5 to 10% in general autopsy series by the first half of the twentieth century (Sparling, 1999). Following the introduction of penicillin and the initiation of public health programmes in the late 1940s, however, the number of new cases fell by over 90% throughout the developed world. In the USA, for example, the incidence peaked in 1947 at 76 primary and secondary cases per 100 000 population and declined to a nadir of 2.6 per 100 000 in 1998 (Aral & Holmes, 1999; Centers for Disease Control and Prevention, 1999). In the developing world, however, syphilis remains common, and there is now an explosive outbreak in Eastern Europe and parts of the former USSR (Aral & Holmes, 1999).

Etiology

Treponema pallidum is a small (below the limit of resolution of the light microscope), motile, flagellated, spiral bacterium 6–20 μm long and 0.1–0.2 μm wide. It stains poorly with aniline dyes but can be stained by silver impregnation or visualized by either dark field or phase contrast microscopy. It lacks a capsule. Like gram-negative bacteria, it has an outer membrane, inner membrane, and a thin cell wall composed of peptidoglycan. Unlike gram-negative bacteria, the outer membrane lacks lipopolysaccharide and contains only rare integral membrane proteins, few of which are surface exposed ($<$100 particles/μm^2 compared to 6000–10 000/μm^2 in *Escherichia coli*) (Norris, 1993; Stamm, 1999).

T. pallidum is a fastidious organism that cannot be grown in culture. Capable of DNA, RNA, and protein synthesis, the spirochete can use both glucose and pyruvate as energy sources. But it lacks a complete Krebs cycle and depends on its host for at least some of its nutritional requirements (Stamm, 1999). Both the fastidious nature of the organism and its host dependence probably relate to its small genome: *T. pallidum*'s single circular chromosome of about 1000 kilobase pairs is one of the smallest prokaryotic genomes known (Norris, 1993).

Pathogenesis and pathophysiology

T. pallidum rapidly penetrates intact mucous membranes or abraded skin, attaches to host cells, and then prolife-

rates. Within hours, the proliferating treponemes migrate to local lymph nodes, enter the blood stream, and disseminate. Days to weeks later, a primary lesion or chancre develops at the site of inoculation. Spirochetes are present in the chancre in and between epithelial, endothelial, and phagocytic cells and fibroblasts; and there is accompanying perivasculitis, capillary endothelial proliferation, and obliterative endarteritis of the small vessels. The chancre heals spontaneously in weeks as cell mediated immunity develops: the treponemes are cleared via phagocytosis by activated macrophages facilitated by opsonizing antibodies (Stamm, 1999).

Not all of the organisms are cleared, however, and some survive to cause chronic infection. How they do so is still a matter of debate. Candidate mechanisms include localization inside cells or in immunoprotective niches like the CNS, the presence of a subpopulation resistant to phagocytosis, premature down-regulation of the local immune response, or an antigenically inert surface secondary to either a coat of host serum proteins or the paucity of treponemal outer membrane proteins. Evidence at present favours the last (Stamm, 1999).

Whatever the mechanism, proliferation and dissemination of the surviving organisms results in secondary syphilis. The onset is usually about 6 weeks after the chancre heals. Constitutional symptoms, generalized lymphadenopathy, and disseminated skin lesions are typical. Treponemes are present in the skin lesions, again accompanied by small vessel perivasculitis and endarteritis obliterans. Other abnormalities include the presence of spirochetes in the CSF and aqueous humor, granulomatous iritis, immune-complex glomerulonephritis, and infiltration of the liver by lymphocytes and neutrophils (Stamm, 1999).

These secondary lesions subside in turn, without treatment and within weeks, as the treponemes are eliminated via immune mechanisms. Latent syphilis follows. Then infection is detected only by serologic tests. The organisms are still present, however, especially in the spleen and lymph nodes; and they can still seed the blood stream and cause mucocutaneous relapse. Among untreated patients, 25% have one or more such relapses, 90% of them during the first year after infection (early latent syphilis). Late latency (>1 year after infection) brings relative immunity to relapse and increasing resistance to reinfection. Even then, intermittent spirochetemia still occurs. So transplacental transmission is possible while venereal transmission is not (Stamm, 1999).

Late latent syphilis probably never is cured spontaneously. Untreated, it has only two possible outcomes: lifelong inapparent infection or progression to late (tertiary) syphilis. Before penicillin, tertiary syphilis developed in about a third of those infected, most often years after latency began: cardiovascular syphilis in 10%, neurosyphilis in 6.5%, and gumma in 16% (Clark & Danbolt, 1964). Now rare, likely due to its sensitivity to low doses of penicillin or other antibiotics, gumma is a granulomatous lesion that results from a hypersensitivity response to *T. pallidum* antigens. Obliterative endarteritis of CNS vessels and the vasa vasorum of the ascending aorta and direct invasion of the CNS parenchyma underlie the other late manifestations.

Clinical manifestations

General clinical features

Early localized (primary) syphilis (Fig. 109.1)

The typical chancre begins as a painless papule that ulcerates to form a 1–2 cm clear-based sore with an indurated margin, then heals spontaneously within 3–6 weeks. Chancres are located most commonly on the penis of heterosexual men; on the labia, fourchette, or cervix of women; and on the penis or in the mouth, anus, or rectum of homosexual men. Accompanying regional adenopathy is common, usually developing about a week after the chancre. Multiple lesions are frequent (Musher, 1999).

Early disseminated (secondary) syphilis

The skin lesions of secondary syphilis develop 4–10 weeks after the appearance of the chancre. An evanescent macular rash occurs first, followed within days by a symmetric papular eruption. The red or red–brown papules, 0.5–2 cm in diameter, are present on the trunk, face, scalp, and limbs, including the palms and soles. In warm, moist, intertriginous areas where skin breakdown occurs, the lesions enlarge to become raised grey–white or pink infectious condyloma lata. Involvement of the mucous membranes results in greyish areas of superficial erosion with surrounding erythema (mucous patches). When the hair follicles are affected, alopecia results (Musher, 1999).

Generalized, non-tender lymphadenopathy frequently accompanies the rash as do systemic symptoms. These include malaise, sore throat, anorexia, weight loss, fever, myalgias, pruritis, headache, and meningismus. Abnormal liver function tests are also frequent (20% of cases), but symptomatic hepatitis is rare. Other, less common features are arthritis, gastritis, iridocyclitis, the nephrotic syndrome, periostitis, and proctitis (Musher, 1999).

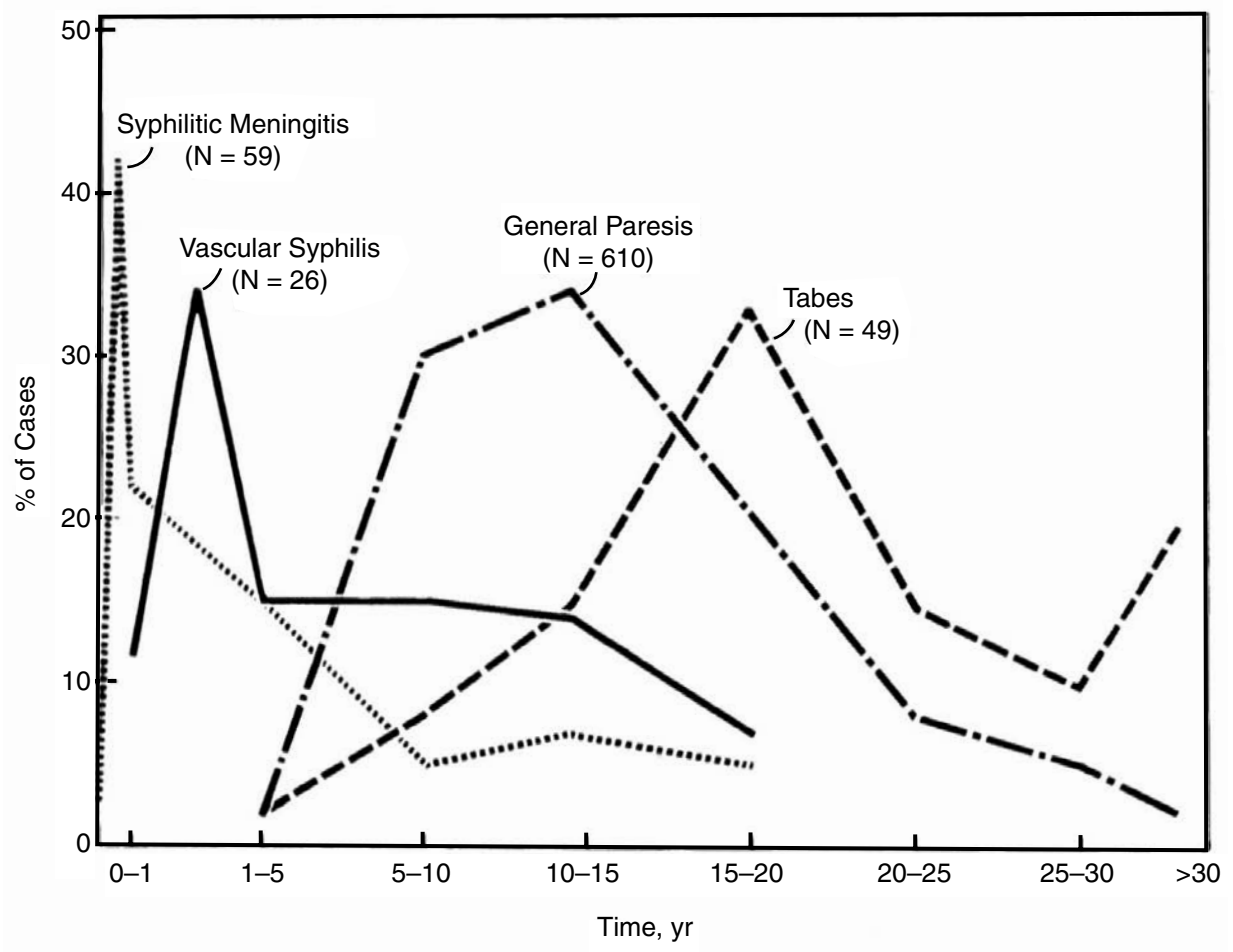

Fig. 109.1. Timing of neurological complications of syphilis.

Latent syphilis

The signs and symptoms of untreated secondary syphilis resolve spontaneously after 3–12 weeks. Then latency begins. The patient is asymptomatic and the physical examination normal (Musher, 1999).

Late (tertiary) syphilis

The disease is only relatively quiescent during latency, however. Ongoing and slowly progressive inflammation that begins then is followed years later by aortitis, gummata, and neurosyphilis (Table 109.1).

The consequences of aortitis are valvular insufficiency, aneurysm, and coronary ostial narrowing, their symptoms beginning 15–30 years after infection (Swartz et al., 1999). The symptoms of gumma/gummata, single or multiple destructive angiocentric granulomas with central necrosis and surrounding perivasculitis, usually start earlier, within 15 years of infection (range, 1–46 years). Remissions and recurrences (up to 7) are common (25–33% of patients). Gummata most commonly involve the skin (70%), mucosa (10%), and bone (10%). But any organ can be involved, including the liver, stomach, and CNS (Aral & Holmes, 1999; Swartz et al., 1999). However, most tertiary CNS abnormalities, meningovascular syphilis, general paresis, and tabes dorsalis, are the result of chronic syphilitic meningitis.

Neurosyphilis

Early syphilis

Treponemal invasion of the CNS probably occurs in the majority of patients with syphilis, usually within the first year after infection and almost always within the first two. Among patients with primary or secondary syphilis, up to 43% and 58% respectively have CSF abnormalities (Hook, 1997; Jaffe & Kabins, 1982; Mills, 1927; Moore & Faupel, 1928; Swartz et al., 1999 Zenker & Rolfs, 1990). Considering

Table 109.1. Time to development of symptomatic neurosyphilis

	Time of onset (latency)	
Type of neurosyphilis	Usual	Range
Acute syphilitic meningitis	<2 yr	2 mos–20 years
Meningovascular syphilis	5–10 yrs	mos to 12 yrs
Gummatous neurosyphilis	<15 yrs	1–46 yrs
General paresis	15–20 yrs	1–40 yrs
Tabes dorsalis	20–25 yrs	3–47 yrs

also that *T. pallidum* has been isolated from otherwise completely normal CSF (Chesney & Kemp, 1924; Lukehart et al., 1988), the frequency of CNS invasion in early syphilis is likely even higher. Among the CSF abnormalities described, pleocytosis (usually <100 lymphocytes/mm^3) is most common, increased protein or globulins less so, and positive serology the least (Hahn & Clark, 1946).

Acute syphilitic meningitis

No CNS signs or symptoms aside from a mild headache accompany these early CSF changes in most cases, but in 1–2%, symptomatic meningitis develops, usually within 2 years of infection. The onset is subacute, and the most common symptoms are headache, nausea, and vomiting (91%). Meningismus is slightly less routine (59%), and fever is present in less than half. Cranial nerve palsies are also frequent (45%) and often multiple. The vestibulocochlear, facial and oculomotor nerves are involved most often (in that order), and papilledema and optic perineuritis are common as well (Figs. 109.2, 109.3, see colour plate section). Hydrocephalus is present in about a third of cases, resulting either from meningeal adhesions in the posterior fossa or the basal cisterns. Seizures, hemiparesis, aphasia, other focal signs, and mental changes are less typical but do occur occasionally (Hook, 1997; Merritt, 1940; Merritt et al., 1946; Merritt & Moore, 1935; Swartz et al., 1999).

The CSF cell count is always increased (up to 2000 cells/mm^3, mainly lymphocytes). Other CSF changes include abnormal colloidal gold curves in 96%, increased protein (up to 380 mg/dl) in 90%, positive serology in 86%, increased pressure (up to 520 mm CSF) in 65%, and hypoglycorrhachia (as low as 18 mg/dl) in 45% (Merritt, 1940; Merritt et al., 1946; Swartz et al., 1999). Increased globulins and oligoclonal bands of IgG may be present (Bayne et al., 1986). CT and MR imaging with contrast may show meningeal enhancement (Katz et al., 1993).

Even untreated, the outcome is often favourable and spontaneous recovery likely. But cranial nerve palsies can be permanent, and progressive CNS disease can follow. Penicillin therapy is curative: the meningeal symptoms clear within days (Bayne et al., 1986).

Asymptomatic neurosyphilis

The prevalence of CSF abnormalities in untreated syphilis peaks 8–10 months after infection begins, then falls gradually (Hahn & Clark, 1946). After 2 years, 20–30% of patients still have abnormal spinal fluids, and further spontaneous reversion is rare. The CSF abnormalities that remain reflect chronic CNS infections that is not advanced enough to show symptoms (asymptomatic neurosyphilis). But these persisting changes are harbingers of symptomatic neurosyphilis, the risk of its development proportional to the initial degree of CSF abnormality (Hahn & Clark, 1946; Hook, 1997; Jaffe & Kabins, 1992). A normal CSF after 2 years on the other hand, virtually guarantees that neurosyphilis will not develop (Lukehart et al., 1988; Merritt, 1940; Moore & Hopkins, 1930).

Those affected show no definite signs of neurosyphilis, but they are not always asymptomatic. As many as 22% of them complain of headache, insomnia, giddiness, nervousness, rheumatic pains, or weakness. Minor neurologic abnormalities are also frequent: up to 28% have abnormal pupils, sluggish light reflexes, or slight deep tendon reflex abnormalities; and 8% have aortitis (Merritt et al., 1946; Moore & Hopkins, 1930).

The CSF is always abnormal. The abnormalities include pleocytosis in 40% (usually <100 cells/mm^3), increased protein in 41% (up to 100 mg/dl), increased globulins in 82%, and positive serology in 84% (Merritt et al., 1946).

Among untreated patients, the number with asymptomatic neurosyphilis declines over time as CNS infection progresses and symptomatic neurosyphilis develops. Symptomatic CNS disease is probably inevitable whenever patients with asymptomatic neurosyphilis live long enough. For example, in one study of asymptomatic neurosyphilitics, all already infected for 10–20 years when their CSF was first examined, 26 of 30 developed clinical neurosyphilis during the next 5–10 years (Hahn & Clark, 1946).

Meningovascular syphilis

Meningovascular syphilis typically develops 5–10 years after infection (range, months to 12 years; average, 7 years). Overall, it comprises about 15% of cases of symptomatic neurosyphilis (Holmes et al., 1984; Hook, 1997; Merritt et al., 1946).

A combination of meningitis and arteritis distinguishes

its pathology. Lymphocytic and plasmacytic infiltration of the leptomeninges and perivascular spaces and diffuse meningeal thickening, opacification, and fibrosis are typical and most marked over the convexities and in the basal cisterns. When the fibrosis is severe, cranial nerves can be compressed and CSF flow obstructed. Accompanying arteritis results in thrombosis and parenchymal ischemia and infarction. The walls of large and medium-sized arteries are infiltrated by inflammatory cells, their muscularis and elastica destroyed, and their intima thickened by fibroblastic proliferation (Heubner's arteritis). In small arteries, proliferation of endothelial and adventitial cells similarly causes narrowing or obliteration of the lumen (Nissl–Alzheimer arteritis) but their walls are not infiltrated. The arteries most often involved are the cortical branches of the middle cerebral and those at the base of the brain, especially the lenticulostriates. Similar pathological changes, either generalized or patchy, and usually more marked posteriorly, can affect the spinal dura, leptomeninges, and arteries. The clinical consequences are cord compression, meningomyelitis, radiculitis, and cord infarction (Holmes et al., 1984; Hook, 1997; Merritt et al., 1946).

The illness begins insidiously with diffuse cerebral and meningeal symptoms. Headache, dizziness, insomnia, irritability, difficulty concentrating, impaired memory, apathy, and emotional lability are most common. Dementia, psychosis, convulsions, optic atrophy, reflex iridoplegia, and cranial nerve palsies (most often nerves VII, VIII, V, IX, and X, in that order) are possible also. Weeks to months later, progressive arteritis results in cerebral infarction. The onset can be apoplectic (75%) or subacute (25%) and is sometimes preceded by premonitory transient focal symptoms. Typically (90% of cases), a single vessel is involved clinically, usually a branch of the middle cerebral (60%) or the basilar (12%). Hemiplegia or hemiparesis is the most frequent sign (83%), followed by aphasia (31%), hemianesthesia (14%), cerebellar ataxia (10%), and hemianopia (7%). As many as 14% may have convulsions in addition (Holmes et al., 1984; Hook, 1997; Johns et al., 1987b; Merritt et al., 1946).

Meningomyelitis, usually thoracic, begins with leg weakness or paresthesias and progresses to paraparesis, incontinence, girdle and leg pains, and impaired position and vibratory sense in the legs. If spinal artery thrombosis supervenes, spinal cord infarction is the outcome. Radiculitis causes segmental deficits: focal amyotrophy, fasciculation, and reflex loss with anterior, and dermatomal pain and sensory loss with posterior root involvement (syphilitic meningopolyradiculitis), asymmetric, areflexic leg weakness and sensory loss ensue when multiple roots are involved (Lanska et al., 1988; Feraru et al., 1990). Inflammation and thickening of the cervical dura (pachymeningitis cervicalis hypertrophica) result first in radicular pain, followed by segmental amyotrophy and then progressive paraparesis and sensory loss (Merritt et al., 1946).

The CSF is probably always abnormal in meningovascular syphilis. Typical changes are lymphocytic pleocytosis (usually 11–100 cells/mm^3), increased protein (usually 45–260 mg/dl, but higher in cases with spinal subarachnoid block), increased globulins, and positive serology (81%). The CSF pressure is routinely normal. Both CT and MR images generally show areas of abnormality consistent with infarction, and may show meningeal enhancement if contrast is given; but the changes are not specific (Berry et al., 1987; Gordon et al., 1994; Harris et al., 1997; Holmes et al., 1984; Johns et al., 1987a; Kaplan et al., 1981). Changes on cerebral angiograms, similarly non-specific, indicate vasculitis. These include local areas of concentric constriction, beading, and spasm of arteries (Harris et al., 1997; Simon, 1985). In one case of meningomyelitis, an area of increased signal intensity was present on T_2-weighted MR images of the mid-thoracic cord (Strom & Schnek, 1991).

The response to penicillin is usually good: treatment halts progression, meningeal symptoms resolve, and focal deficits may improve. But residual disability is common, and mental changes may be permanent (Holmes et al., 1984; Kaplan et al., 1981; Kase, 1988; Perdrup et al., 1981).

Gummatous neurosyphilis

Nervous system gummata arise from the meninges in areas of especially intense local inflammation. They are characterized histologically by an area of central necrosis surrounded by histiocytes, epithelioid cells, lymphocytes, and plasma cells plus a few foreign body giant cells (Kaplan et al., 1981; Merritt et al., 1946). Treponemes can be demonstrated within them by silver stains or immunofluorescence (Horowitz et al., 1994). Over time, the inflammation subsides spontaneously and is replaced by proliferating connective tissue. Non-specific scarring is the result.

Small gummata are frequent in meningovascular syphilis but generally cause no symptoms. Larger symptomatic ones, though rare, can arise any time during the illness. Usually durally based and up to several centimetres in size, they compress and invade the underlying brain or spinal cord. Cerebral gummata are located routinely over the brain convexity or at its base (where they occur as small tumours along arteries and cranial nerves). Their signs and symptoms are non-specific and reflect only lesion size and location (Eltomey et al., 1984; Kaplan et al., 1981). Spinal cord gummata are most often cervical. They mimic rapidly

growing tumours and cause root pains, paresthesias, spastic paraparesis, incontinence, and sensory loss below the level of the lesion (Merritt et al., 1946).

The frequency of CSF anomalies in gummatous neurosyphilis is not known; but pleocytosis, increased protein (especially when spinal cord gummata cause subarachnoid block), and positive serology are typical (Hook, 1997; Merritt et al., 1946). Neuroimaging abnormalities are not specific. Reported CT findings include both high- and low-density mass lesions, with or without surrounding edema, that are usually durally based and extra-axial. Following contrast infusion, both diffuse and ring-like enhancement are possible (Eltomey et al., 1984; Horowitz et al., 1994; Harris et al., 1997; Madsen et al., 1987). The MR appearance similarly is not diagnostic. Gummata are either hypo- or iso-intense on T_1 images and hyperintense on T_2 images. They enhance with gadolinium (Harris et al., 1997). Angiography normally shows an avascular mass with a contiguous zone of arteritis (Eltomey et al., 1984; Harris et al., 1997; Kaplan et al., 1981; Tonelli et al., 1989).

Because gummatous neurosyphilis is rare and its radiologic appearance non-specific, diagnosis usually requires biopsy: positive serology can only provide a clue. If gumma is diagnosed and penicillin prescribed, the lesion generally regresses (Kaplan et al., 1981).

General paresis

General paresis develops in about 40% of patients with symptomatic neurosyphilis, usually beginning 15–20 years (range, 1–40) after infection. Men are affected 4–7 times more often than women (Hook, 1997; Merritt et al., 1946; Swartz et al., 1999).

Chronic spirochetal meningoencephalitis is the cause. In the usual case, both frontal and temporal lobes are atrophied. Less often, there is striking focal cerebral atrophy, frequently unilateral (Lissauer's form). The meninges are cloudy and thickened, especially those overlying the areas of atrophy. The ventricles are dilated and their surface is covered by fine granulations (granular ependymitis). Underlying microscopic changes include round cell infiltration of the leptomeninges and perivascular spaces, Heubner's and Nissl-Alzheimer arteritis, loss of neurons, proliferation of astrocytes and microglia, the appearance of rod cells, deposition of iron pigment in blood vessel and rod cells, and demyelination of cortical and subcortical fibres. Spirochetes are present in the walls of blood vessels and inside microglia and astrocytes in the cerebral grey matter, basal ganglia, cerebellum, brain stem, and spinal cord (Merritt et al., 1946).

The illness begins insidiously with subtle changes in cognition and personality. Impaired concentration, forgetfulness, faulty judgement, poor hygiene, and changes in mood are common. Without treatment, the mental symptoms progress. Ultimately, they can mimic almost any psychiatric syndrome. Simple dementia is most frequent; but grandiose, manic, depressed and agitated, and paranoid types are all recognized. With further progression, dementia is inevitable in every case, regardless of the initiating symptoms. Neurologic signs develop later than mental symptoms. Seizures; tremors of the tongue, face, and fingers; pupillary abnormalities, especially Argyll Robertson pupils; and dysarthria are routine. Focal signs are less typical. They occur regularly only in Lissauer's form where they often appear suddenly (apoplectiform attacks). Then, hemiplegia and aphasia are most common. Clonus and Babinski signs appear later still. Eventually the patient becomes bedridden and incontinent and dies within 4–5 years of symptom onset (average, 2.5) (Hook, 1997; Merritt et al., 1946; Swartz et al., 1999).

The CSF is abnormal in 100% of untreated cases. Typical changes include lymphocytic pleocytosis of 10–100 cells/mm^3, increased protein (usually, 45–100 mg/dl), increased globulins, and strongly positive serology (Dewhurst, 1969; Hook, 1997). Reported CT abnormalities include frontal and temporal atrophy and bilateral symmetrical areas of white matter hypodensity (Kulla et al., 1984; Zifko et al., 1996). Similar areas of atrophy are depicted by MRI and can be accompanied by increased signal intensity in the hippocampi and frontal lobes on T_2-weighted images (subcortical gliosis) or signal loss in the basal ganglia (from iron deposition) (Zifko et al., 1996). Lissauer's form appears on CT as a low-density mass lesion with either diffuse or gyral enhancement. On MRI, the lesion's intensity is low on T_1-weighted and high on T_2-weighted images (Ito et al., 1990; Kulla et al., 1984; Nitrini et al., 1988).

Penicillin therapy reliably normalizes the CSF and arrests the disease, but complete cure is possible only when symptoms are of recent onset (months). The deficits of patients with disease of longer duration improve only partially or not at all (Perdrup et al., 1981).

Tabes dorsalis

Tabes dorsalis also develops in about 40% of patients with symptomatic neurosyphilis, its symptoms beginning from 3 to 47 years after infection (average latency, 21 years) (Fischer et al., 1976; Hook, 1997; Swartz et al., 1999). Clinical features of other forms of neurosyphilis may be present simultaneously, especially general paresis (taboparesis). Men are affected 4–6 times as often as women (Merritt et al., 1946).

Degeneration of the posterior roots and columns of the

spinal cord defines the gross pathology. The posterior columns are shrunken, primarily the fasciculus gracilis, the overlying arachnoid is opaque and thickened, and the lumbar and lower thoracic dorsal roots are atrophied. In early cases, inflammatory cell infiltration of the leptomeninges and dorsal roots and accompanying destruction of myelinated nerve fibres are the underlying microscopic changes. In older, 'burnt-out' cases, inflammation is either less conspicuous or entirely absent. Ultimately, few intact fibres remain in the lumbar posterior roots, the dorsal root entry zone and tract of Lissauer atrophy, and the central processes of the dorsal root ganglion cells degenerate. Secondary shrinkage and gliosis of the posterior columns follow. Sensory ganglia are not affected. The cranial nerves, on the other hand, often are, especially nerves II, III, V, and VIII. The microscopic changes are similar: arachnoidal inflammation and adhesions and nerve fibre loss are characteristic (Hook, 1997; Merritt et al., 1946).

The onset is insidious and the course progressive. Pains, paresthesias, sensory loss, and ataxia dominate the picture. The pains and paresthesias generally come first. Sudden, severe, stabbing, paroxysmal pains that last mere seconds (lightning pains) are most common (present in 75% of cases). These affect mainly the legs, less often the back, arms and face. Repeated salvos, lasting minutes to days, separated by pain-free intervals are typical. The individual pains either recur in the same spot or migrate. Paresthesias, also waxing and waning, are present in 25%. These include numbness, tingling, tightness, coldness, hypersensitivity to touch, and aching of the legs and trunk; deadness of the soles of the feet; and girdle sensations on the trunk (Hook, 1997; Merrick et al., 1946; Swartz et al., 1999).

Less often (10–15% of cases), probably when posterior root inflammation irritates visceral afferent fibres, reflex spasm of visceral smooth muscles causes paroxysms of pain that can last for days (tabetic or visceral crises). Gastric crises with epigastric pain and vomiting are most common. Less frequent are rectal crises with tenesmus; intestinal with colic and intermittent diarrhea and constipation; laryngeal with throat pain, hoarseness, stridor, and dyspnea; and vesical with pain and strangury (Hook, 1997; Merritt et al., 1946; Swartz et al., 1999).

Sensory loss develops later. Early on, sensitivity to pain and touch is lost from the nose and cheeks, the ulnar surface of the forearms, around the nipples, and the peroneal surface of the legs (Hitzig's zones). Later, first vibratory and then position sense and deep pain sensibility are impaired in the legs and then in the arms. Next, Romberg's test becomes positive and locomotor ataxia develops. The gait is wide based and foot slapping, the steps are uneven and uncertain, and the head and eyes are positioned to watch the feet. When the cervical roots are affected, clumsiness and pseudoathetosis of the arms, hands, and fingers result (Hook, 1997; Merritt et al., 1946; Swartz et al., 1999).

Deafferentation also leads to muscular hypotonia and loss of the knee and ankle jerks. The hypotonia in turn causes hyperextensibility and injury of anesthetic joints. With repeated injury, painless degenerative arthropathy (Charcot's joints) develops (7% of patients), usually in the knee, ankle, hip, shoulder, elbow, wrist, or spine in that order. Similarly, painless perforating ulcers (mal perforans) may form at pressure points on the sole of the foot when the anesthetic tissue is injured during walking. Also caused by deafferentation are impotence, anesthesia of the genitalia, bladder hypotonia, urinary retention and dribbling incontinence, and constipation (Hook, 1997; Merritt et al., 1946; Swartz et al., 1999).

Common results of cranial nerve involvement include optic atrophy (20% of patients), oculomotor palsies (20–25%, usually of nerve III), hearing loss, sometimes sudden (28%), and zones of facial hypalgesia. Pupillary abnormalities are nearly universal (94%), especially Argyll Robertson pupils (present in about 50%) (Merritt et al., 1946).

CSF abnormalities tend to decrease with increased duration of the disease: the fluid can be normal in 'burnt-out' cases. Overall, 47% of patients have pleocytosis (usually <100 cells/mm^3, mostly lymphocytes), 53% increased protein (up to 250 mg/dl, usually <100), 75% abnormal globulins, and 72% reactive serology (Hook, 1997; Merritt et al., 1946; Swartz et al., 1999). Electrodiagnostic testing yields normal sensory and motor nerve conduction velocities and F waves, but H reflexes are absent and somatosensory evoked potentials abnormal (Donofrio & Walker, 1987).

Penicillin clears the CSF and arrests the course in about 50% of cases when treatment is begun early. In advanced cases, symptoms may worsen in spite of treatment, probably because of continuing fibroblastic proliferation around posterior roots (Kofman, 1956; Perdrup et al., 1981; Swartz et al., 1999). Sensory loss and hypotonia generally do not improve, hence Charcot joints and mal perforans can still develop after treatment. Lightning pains and visceral crises often continue. Carbamazepine may relieve the lightning pains (Ekbom, 1972) and atropine and phenothiazines the visceral crises. Charcot joints are treated by bracing or fusion.

Changes in neurosyphilis in the antibiotic era

Cases of late syphilis have declined steadily in the USA in the last five decades in spite of relatively constant rates of

primary and secondary disease during most of this period (Sparling, 1999). Almost certainly, antibiotic therapy has been responsible for the decline.

As regards neurosyphilis in particular, some observers believe that antibiotics have modified more than its frequency. They maintain that partially effective and often incidental (prescribed for other infections) antibiotic treatment has altered its clinical features as well (Hook, 1997). Kofman (1956) suggested this possibility first. In a study of 177 neurosyphilitics, he described many monosymptomatic cases and formes frustes; a result, he felt, of arrested illness progression and fixation of neurologic deficit at an early stage following penicillin therapy. Hooshmand et al. (1972) reached similar conclusions: their patients with neurosyphilis seldom suffered from classical paresis, tabes, or meningovascular syphilis. Instead, their disease was more often monosymptomatic or atypical or its diagnosis incidental; and the accompanying CSF abnormalities were less striking than those described earlier (as others: Burke & Schaberg, 1985; Dewhurst, 1969, have noted also). But because Hooshmand et al. (1972) relied heavily on non-standard tests (CSF-FTA) for diagnosis, their conclusions likely are not valid. Indeed, in several more recent series of patients with neurosyphilis, the presenting clinical features were no different than those reported in the pre-antibiotic era (Fischer et al., 1976; Luxon et al., 1979; Perdrup et al., 1981).

Neurosyphilis and HIV infection

More recently still, the HIV epidemic has altered the epidemiology and natural history of syphilis further. HIV infection increases the risk for syphilis (and vice versa); and coinfection with the virus can modify the clinical manifestations of syphilis, its serologic reactions, its response to treatment, and the appearance of its complications (Hook, 1997). In the USA, the nature of neurosyphilis has been affected in particular as nearly 50% of neurosyphilitics are now coinfected with HIV-1 (Katz & Berger, 1989; Musher et al., 1990; Berger, 1991).

The principal change in neurosyphilis related to coinfection is an increase in the relative frequencies of meningitis and meningovascular disease (Burke & Schaberg, 1985; Johns et al., 1987a; Katz et al., 1993; Musher, 1999; Stamm, 1999), possibly because most coinfected patients die of AIDS before they can develop tabes or paresis. But the latencies of syphilitic meningitis and meningovascular syphilis are shorter in addition, especially in those HIV patients who relapse with neurosyphilis following conventional benzathine penicillin G therapy for early disease (Johns et al., 1987a; Musher, 1999; Musher et al., 1990). In the pre-antibiotic era, patients treated for early syphilis relapsed neurologically in the same manner if their arsenical treatment was either inadequate or interrupted (Merritt et al., 1946; Musher & Baughn, 1984; Nichols & Hough, 1913). While penicillin therapy of syphilis is more effective than was arsenical, it is not always curative: natural immune mechanisms work with the antibiotic in arresting the disease (Musher et al., 1990; Musher & Baughn, 1984; Tramont, 1987). Hence both inadequate treatment and host immunocompromise can have the same outcome, early meningitis and meningovascular syphilis.

HIV-infected patients are living longer now because of newer antiretroviral therapies. Whether the number of cases of tabes and general paresis among them will increase as a result remains to be seen, they still may not survive long enough. It is worth noting though that, in the past, inadequate arsenical treatment shortened the latency of tabes (Merritt et al., 1946) just as it did that of meningovascular syphilis.

Diagnosis

Laboratory diagnosis

Because *Treponema pallidum* cannot be cultured routinely, the laboratory diagnosis of syphilis depends on serologic tests. Two types of antibodies are measured ordinarily: non-specific, non-treponemal antibodies (reagins) that react with lipoidal antigens, either of *T. pallidum* itself or formed through its interaction with the host, and treponemal antibodies that react with specific *T. pallidum* antigens (Musher, 1999; Simon, 1985).

Reagins usually are measured by flocculation tests: a precipitate forms when antibody-containing syphilitic serum is added to a suspension of cardiolipin–lecithin antigen. A number of such tests are available. Laboratories in the USA commonly use either the rapid plasma reagin (RPR) test or the Venereal Disease Reference Laboratory (VDRL) test. The RPR can be automated to screen large numbers of samples, but it cannot be quantified. While the VDRL can be (the titres reflect disease activity and the response to treatment), it takes longer to perform. Regardless of the exact non-treponemal test used, however, as many as 20–40% of all positive results are falsely positive. The tests are also insensitive: they are non-reactive in up to 25% of cases of late neurosyphilis (Fishman, 1992; Simon, 1985).

The tests for treponemal antibodies are more sensitive and more specific. Several are available. Among these, the fluorescent treponemal antibody-absorption (FTA-Abs) test is performed most often (in the USA). The test almost invariably is reactive in late syphilis and seldom falsely positive

(<2%, and then usually only borderline). But it cannot be quantified, and it remains positive for life despite successful treatment, so its results do not reflect disease activity. Consequently the FTA-Abs test is used most often to confirm the specificity of a positive non-treponemal test or to evaluate seronegative patients with suspected tertiary syphilis. If the serum FTA-Abs is negative, neurosyphilis is ruled out (Fishman, 1992; Simon, 1985).

Among the others, the *T. pallidum* microhemagglutination (MHA-TP) assay is easier to perform than the FTA-Abs as it requires no fluorescence microscopy and is automated. Like the FTA-Abs (which it eventually could replace), the MHA-TP is more sensitive and specific than the VDRL. Unfortunately, its reactivity similarly persists after treatment (Musher, 1999; Simon, 1985).

These serological tests have been applied to spinal fluid as well. The non-treponemal tests are most useful. A positive CSF VDRL test is definite evidence of neurosyphilis (Fishman, 1992), unless the fluid is visibly contaminated by blood, at serum VDRL titres of 1:256 or less, contamination sufficient to make the CSF tests reactive always results in a perceptibly bloody mixture (Izzat et al., 1971). But CSF reagin tests are negative in up to 30% of patients with neurosyphilis (Fishman, 1992; Merritt et al., 1946). Tests for CSF antitreponemal antibodies are more sensitive, yet the antibodies detected are usually derived from serum, and their presence represents only a dilute serum sample (Jaffe et al., 1978). Consequently, there is no basis for applying these tests to CSF in clinical practice (Davis & Schmitt, 1989; Hook, 1997; Lukehart et al., 1988).

Clinical diagnosis

The diagnosis is straightforward in typical cases with reactive serum and CSF reagin tests and compatible CSF abnormalities. But both serum and CSF non-treponemal tests can be negative in neurosyphilis (Jaffe et al., 1978). Hence, all patients whose neurologic abnormalities suggest neurosyphilis should be tested by serum FTA-Abs or MHA-TP and then CSF examination if the serum test is positive. The diagnosis is established and treatment should be prescribed if a reactive CSF (pleocytosis, increased protein or IgG, or reactive VDRL test) is present (Burke & Schaberg, 1985).

CSF reactivity is the best measure of disease activity in neurosyphilis, and patients with fixed deficits due to inactive disease do not improve with antibiotic therapy (Simon, 1985). Therefore, patients with consonant neurological abnormalities, reactive serum treponemal tests, and normal CSF should be considered for treatment only if their deficits are progressive and no cause other than syphilis can be identified.

Table 109.2. Antibiotic therapy of neurosyphilis[a]

IV penicillin G, $18\times10^6-24\times10^6$ units/day ($3\times10^6-4\times10^6$ units every 4 hours), for 10–14 days[b]
or
IM procaine penicillin, 2.4×10^6 units/day, plus oral probenecid, 500 mg 4 times/day, each for 10–14 days[b]

Notes:

[a] from Centers for Disease Control and Prevention (1998).

[b] benzathine penicillin, 2.4×10^6 units IM, may be given at the end of either regimen to achieve a total of 3 weeks of therapy.

Treatment

Penicillin is the treatment of choice for all stages of syphilis. For neurosyphilis, the Centers for Disease Control and Prevention (CDC) (1998) recommend 10–14 days of therapy with either IV aqueous crystalline penicillin G or IM procaine penicillin plus oral probenecid (Table 109.2). For other forms of late syphilis, the recommended treatment is longer, 3 weekly injections of benzathine penicillin G (BPG). Because the duration may be as important as the intensity of antibiotic therapy, some experts in the field prescribe BPG at the end of these regimens for neurosyphilis to achieve a comparable total treatment span. Alternatives to penicillin have not been evaluated in large scale clinical trials, and published data supporting their use are minimal. Hence, the CDC recommend desensitizing penicillin-allergic neurosyphilis patients and treating them with penicillin. Some experts give IV ceftriaxone, 1 gm daily for 3 weeks instead (Swartz et al., 1999).

Changes in the CSF best reflect the efficacy of treatment, so the fluid should be examined weekly during treatment and every 3–6 months thereafter for 2 years (Simon, 1985). The cell count should fall during treatment. By 6 months, the count should be normal and the protein level falling. The VDRL titre usually falls too, but the test may remain reactive at low titre. Persistent or recurrent pleocytosis warrants retreatment (with more intensive therapy if possible). A normal CSF at 1 year indicates cure, and relapse is rare after 2 years (Dattner et al., 1951). Once the CSF is normal, no further clinical response to antibiotics should be expected. Fixed neurological deficits will remain and may even progress, especially the deficits in tabes and optic atrophy (Hook, 1997; Kofman, 1956).

A Jarisch–Herxheimer reaction, caused by the release of cytokines during phagocytosis of dead spirochetes, can complicate the first 24 hours of penicillin therapy (2% of

cases) (Zenker & Rolfs, 1990). Usually mild the symptoms (fever, headache, myalgia, and other systemic complaints) are easily managed with bedrest and antipyretics, but neither antipyretics nor corticosteroids prevent the reaction (Zenker & Rolfs, 1989). More severe reactions leading to irreversible progression of neurological deficit occur rarely (<1%).

HIV-infected patients with neurosyphilis may be at increased risk for treatment failure (Feraru et al., 1990; Gordon et al., 1994; Katz et al., 1993), though the increase is probably small. A recent trial comparing i.v. penicillin regimens with ceftriaxone showed a high rate of treatment failure (Marra et al., 2000). But no systematic studies provide a scientific basis for routinely treating coinfected patients differently than those who are HIV negative. Hence, the CDC (1998) recommend the same penicillin regimens for both. Follow-up must be meticulous, however, with regular CSF examination. If the CSF fails to clear, more prolonged treatment is indicated.

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Tuberculosis

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Despite the availability of curative therapy and a widely used vaccine, tuberculosis is one of the greatest threats to human health and continues to cause enormous suffering, disability and death. Infections with *Mycobacterium tuberculosis* cause a wide array of clinical manifestations, ranging from asymptomatic latent infection to disseminated and fulminant disease. Tuberculosis is generally regarded as a respiratory infection, but early in *M. tuberculosis* infection the organism is hematogenously disseminated and takes up residence in a number of organs, including the central nervous system. Tuberculosis affects the central nervous system in three principal ways: tuberculous meningitis, tuberculomas of the brain and spinal cord, and vertebral tuberculosis, or Pott's disease, an infection of vertebrae and paraspinous areas that can lead to destabilization of the spinal cord with potentially devastating neurological consequences. The purpose of this chapter is to describe the neurologic manifestations of tuberculosis and discuss its diagnosis and management.

Epidemiology

Tuberculosis remains a global problem with 8 million new cases per year and approximately 2 million deaths. Twenty-two countries account for 80% of all tuberculosis cases, and the case rate in developing countries is approximately sevenfold higher than in industrialized nations. Globally, increasing rates of HIV-related tuberculosis have been noted in areas where tuberculosis infection is endemic and HIV is epidemic. Tuberculosis is the most common opportunistic infection in people with HIV, and more HIV-infected individuals die from tuberculosis than any other cause. In many countries where HIV is not prevalent, tuberculosis remains a common cause of disability and death, primarily affecting young adults.

M. tuberculosis epidemiology can be divided into two components based on the natural history of the organism in humans: latent infection with *M. tuberculosis*, which is acquired from infectious cases of tuberculosis, and tuberculosis disease, which results from either primary or remote progression of a latent infection to clinical illness. Risk factors for acquiring tuberculosis infection include close contact with an infectious case, often in the same household or workplace, or exposure to air shared by infectious tuberculosis patients, such as in health care facilities or in public places in high prevalence communities. Socioeconomic factors associated with tuberculosis infection generally reflect an increased likelihood of exposure to others with active disease. Risk factors for developing active tuberculosis disease include recent infection, large inoculum, and impaired cellular immunity, such as with HIV infection or pharmacological immunosuppression. Cases of tuberculosis, not surprisingly, share epidemiological characteristics with tuberculosis infection, as the latter is required before the former can occur.

Most tuberculosis involves the lung, but between 15 and 50% can involve extrapulmonary sites, depending on the clinical setting. Tuberculous meningitis (TM) is the most common central nervous system manifestation of tuberculosis. The Centers for Disease Control and Prevention report that the proportion of extrapulmonary tuberculosis cases due to TM remained relatively stable between 1969 (4.7% of cases) and 1997 (5.2% of cases) (Farer et al., 1979; Rieder et al., 1990). TM is five times more likely to occur in children under the age of 15 than in adults, and substantially more common in HIV-infected patients than in immunocompetent adults (Rieder et al., 1990). Although TM accounts for only a small fraction of all cases of tuberculosis, it is a devastating form of the disease and is uniformly fatal if left untreated.

In developed countries, extrapulmonary tuberculosis has a disproportionately high incidence in non-whites as compared to whites (Ogawa et al., 1987). This is particularly important as non-whites make up an increasing proportion of urban populations. Further, in the United States, blacks and other racial and ethnic minorities have a case rate of extrapulmonary tuberculosis that is 5 times that for whites. In one study of population from in the Southwestern United States, the Native American population was overrepresented with 32% of all cases of extrapulmonary tuberculosis but only 8% of the population at large (Davis et al., 1993). HIV-infected persons with tuberculosis are more likely to have at least one extrapulmonary site of disease than HIV-uninfected patients (Chaisson et al., 1987). In a study of 2205 tuberculosis patients in Spain, 10% of the HIV-infected patients had *M. tuberculosis* isolated from their cerebrospinal fluid, compared to only 2% of the non-HIV-infected patients with culture-proven tuberculosis (Berenguer et al., 1992).

Pathogenesis

M. tuberculosis is transmitted via respiratory secretions with the acid-fast bacilli trapped in droplet nuclei that are the ideal vehicle for deposition into the alveoli. Those organisms that are not cleared by ciliary action in the bronchial tree are deposited in the alveoli. There, alveolar macrophages engulf the invading bacilli through a process of phagocytosis and the organisms are transported into intracellular holding spaces, or phagosomes. Ordinarily, an invading organism would be killed in the phagosome, as toxic chemicals, enzymes and cellular mechanisms to decrease the intraphagosomal pH would be introduced. *M. tuberculosis* is able to effectively prevent these processes and multiply intracellularly in macrophages. Some infected macrophages are then transported to the regional lymph nodes of the lung. In both the site of primary infection and the lymph node, the macrophages recruit and activate helper T-cells. Activated T-cells release cytokines such as IL-2 and IFN-α that, in turn, activate macrophages, cytotoxic T-cells and natural killer cells. Recruited T-cells and activated macrophages form a ring of inflammatory defenses around the central zone of infected macrophages, tubercle bacilli, and cellular debris. Some macrophages also die as a result of infection with *M. tuberculosis* and release bacteria and bacterial products that attract other lymphocytes to the site. A delayed type hypersensitivity inflammatory response is induced and eventually produces an inflammatory lesion called a granuloma. Histologically, granulomas consist of a central area of 'cheesy' necrosis, where the acid-fast bacilli can be seen, surrounded by macrophages, giant cells, hyaline and a ring of lymphocytes that have been recruited to the area (Fig. 110.1, see colour plate section). Therefore, containment of the mycobacteria in granulomas is contingent upon functioning cell-mediated immunity in the host. For this reason, patients infected with HIV and who have defective cell-mediated immunity are poorly equipped to handle tuberculosis.

At the time of the primary infection, there is also bloodborne spread of the organism to remote sites in the body including bone, joints, vertebral bodies, kidneys and the central nervous system. The majority of patients will control the infection both in the lung and at extrapulmonary sites through the formation of granulomas and will not develop disease. Patients who effectively wall off bacilli in granulomas are said to have latent disease that may lie dormant for many decades before reactivating. Despite the effective immune response, small numbers of viable bacilli remain. Immunosuppression with steroids, chemotherapy, or HIV infection as well as senescence can also precipitate reactivation as the immune mechanisms that keep the infection in check are disrupted and weakened.

In the 1930s, it was thought that TM was the direct and immediate result of miliary tuberculosis, a disseminated form of disease (Auerbach, 1951). The famous tuberculosis pathologist, Arnold Rich, first presented evidence of 'Rich foci', older lesions in the meninges that predated the miliary disease and that could cause diffuse infection of the meninges (Rich & McCordock, 1933). Further evidence that these CNS foci likely implanted at the time of primary bacillemia, was presented by MacGregor and Green in 1935 (MacGregor & Green, 1937). These caseous foci were found in 78 of 88 cases of TM. These tuberculous foci were found within the meninges, brain, and rarely in the adjacent bone or spinal cord. These lesions presumably rupture into the subarachnoid space, setting up the inflammatory response leading to TM. Therefore, meningitis usually develops as the result of reactivation of a latent focus in the CNS. TM can also occur in conjunction with miliary disease especially in children who are particularly susceptible to hematogenous spread of tuberculosis after primary infection. Likewise, adults can acquire meningeal disease during bacillemia of miliary disease, but this is not the usual pathogenesis of meningeal infection. Rarely, invasion into the spinal canal from a paraspinous or vertebral focus can also be the source. Rare cases of skull fracture leading to disruption of the blood–brain barrier can also lead to TM.

As inflammation progresses in the meninges and leptomeninges, hydrocephalus almost invariably occurs as a result of tuberculous exudates acutely, and later as a result

of an adhesive leptomeningitis. In most patients, the hydrocephalus is communicating and secondary to blockage of the basal cisterns. In the minority of patients, the hydrocephalus is non-communicating as the blockage occurs at the level of the foramina of the IVth ventricle. Gross pathological studies of TM patients have shown that narrowing and block of the aqueduct occurs as a result of brainstem meningeal exudates exerting circumferential pressure (Dastur et al., 1970). In general, the degree of hydrocephalus correlates with the duration of illness (Lorber, 1951; Foltz & Sheehy, 1956; Bharucha et al., 1969; Tandon et al., 1975). Children are more likely than adults to develop hydrocephalus (Dastur et al., 1970; Tandon et al., 1975). This may be due to the ability of the larger ventricular system in adults to accommodate the increased CSF, and the fully myelinated adult brain to resist stretch (Bhargava et al., 1982).

Hydrocephalus alone cannot account for the high mortality associated with this disease, however. Studies on the MRI appearance of infected patients' brains correlated with pathologic studies and reveal ischemic lesions in the basal ganglia and diencephalons (Dastur & Lalitha, 1973). Vasculitis develops in vessels traversing through the basal exudates with subsequent inflammation, spasm, constriction, and thrombosis. The 'tuberculous zone' was defined in one study of cerebral infarctions as the zone fed by the medial striate, thalamotuberal and the thalamoperforating arteries (Hsieh et al., 1992). In one MRI study of 27 patients, 20 patients had supratentorial lesions, 10 of whom also had brainstem ischemic lesions. All patients had evidence of ventricular dilatation (Schoeman et al., 1988). Arteritis of the subarachnoid space vessels and occlusion of the penetrating arteries extraparenchymally result in cerebral infarction or vascular lesions in 17–53% of patients examined by CT (Bhargava et al., 1982; Bullock & Welchman, 1982; Bonafe et al., 1985; Kingsley et al., 1987; Teoh et al., 1989).

Clinical presentation

The clinical spectrum of TM has historically been separated into three stages, defined by the Medical Research Council in 1948 (Medical Research Council, 1948). In Stage 1 disease, patients can have a long (>3 month) prodrome, although the most common length of time with symptoms is generally 3 weeks. Non-specific symptoms such as fever, malaise, and headache predominate. In this stage, patients are conscious and rational, but may have signs of meningismus. Focal neurologic signs are absent and there cannot be any signs of hydrocephalus in order to be classified Stage 1 disease. Some studies have found the general appearance of patients to be misleading, with only a minority presenting with significant weight loss, generalized lymphadenopathy, or hepatosplenomegaly (Barrett-Connor, 1967). Because of the non-specific clinical signs and symptoms of Stage 1, and the insidious neurological symptoms in the setting of tuberculous toxemia, diagnosis is often delayed (Kennedy & Fallon, 1979).

Stage 2 is notable for the development of single cranial nerve impairment (ptosis or facial paralysis) due to progressive basilar disease, paresis, and focal seizures. Kernig and Brudzinski signs have been noted as well as hyperactive deep tendon reflexes (Lincoln & Kirmse, 1950). Unusual focal neurologic signs such as internuclear ophthalmoplegia have been reported (Sandyk & Brennan, 1984). Prominent signs include alterations in mentation, behavioural change, impaired cognitive ability, and often increasing stupor. Worsening chronic headache, and persistent fever may also be features of this stage of disease.

In Stage 3, patients are comatose (Glasgow coma scale $\leq$8) or stuporous and often have multiple cranial nerve palsies, complete hemiplegia, or paraplegia. Seizures have also been described both in this stage and in Stage 2. By this stage, hydrocephalus is common and chronic inflammation in the enclosed space of the skull may result in significant intracranial hypertension.

Fever, headache, changes in mentation, and meningismus are present in the majority of patients in most large studies, although no one single sign or symptom has any reliable degree of sensitivity or specificity (Ogawa et al., 1987; Davis et al., 1993; Kent et al., 1993; Watson et al., 1993; Verdon et al., 1996). Children can be especially difficult to diagnose as symptoms such as fever, vomiting, drowsiness, or irritablity are commonly seen in many minor viral illnesses (Lincoln & Kirmse, 1950). Several atypical presentations of disease have been described in the literature. Behavioural abnormalities including social withdrawal, personality change, cognitive change, and memory decline can make the diagnosis difficult to differentiate from other causes of dementia or psychiatric disease. By the same token, a clinical picture indistinguishable from acute pyogenic meningitis has also been described. Although signs and symptoms of meningeal irritation are seen in the majority of cases, they can be predated or superseded by focal neurologic signs, signs of hydrocephalus, or obtundation (Udani & Dastur, 1970; Leonard & Des Prez, 1990).

A syndrome of transient, spontaneously remitting TM or 'serous meningitis' has also been described. In 1922, Cramer and Bickel published 48 cases of TM spontaneously cured in the era before anti-tuberculous therapy

Table 110.1. Diagnostic contribution of chest X-ray, tuberculin skin test, and clinical evidence of miliary disease in patients with tuberculous meningitis

Years of study	CXR evidence of TB	Tuberculin	Evidence of miliary disease	Reference
1958–1966	12/21(57%)	7/16(44%)	7/21(33%)	Barrett-Connor (1967)
1966–1974	11/19(58%)	6/14(43%)	4/19(21%)	Haas et al. (1977)
1968–1983	14/45(31%)	17/34(50%)	7/45(16%)	Ogawa et al. (1987)
1978–1989	12/22(55%)	8/17(47%)	7/22(32%)	Watson et al. (1993)
1960–1976	22/52(42%)	20/24(83%)	14/50(28%)	Kennedy & Fallon (1979)
1970–1990	29/54(53%)	23/36(64%)	2/48(4%)	Davis et al. (1993)
1953–1975	50/77(65%)	34/61(56%)	18/79(23%)	Delage & Dusseault (1979)
1961–1984	104/199(52%)			Humphries et al. (1990)
1960–1990	24/59 (41%)	18/40(45%)	9/58(16%)	Kent et al. (1993)
1981–1984	3/10(30%)	0/10		Bishburg et al. (1986)
1985–1990	29/56(52%)	12/36(33%)		Berenguer et al. (1992)
1986–1991	23/31(74%)		12–/31(39%)	Dube et al. (1992)
1982–1993	20/46(43%)	10/32(31%)	6/46(13%)	Verdon et al. (1996)
1983–1994	21/31(68%)	8/13(62%)	4/31(13%)	Yechoor et al. (1996)
1966–1967		13/23(57%)		O'Toole et al. (1969)

(Cramer & Bickel, 1922). Presumably, small foci in the meninges brought there by transient bacillemia are contained by the immune system after a mild inflammatory response in the spinal fluid. Even in this early report, the authors note that such contained disease can often be a harbinger for future fatal tuberculosis with several patients in their series later admitted with pulmonary tuberculosis. In 1937, MacGregor and Green sectioned 112 brains showing old tuberculomas in the CNS, 20 with no evidence of meningitis in the face of florid pulmonary disease (MacGregor & Green, 1937). Subsequently, other sporadic case reports have appeared in the literature suggesting that some cases of 'aseptic meningitis' could be due to tuberculosis that is subsequently contained (Edmond & McKendrick, 1973; Zinneman & Hall, 1976).

Diagnosis

The diagnosis of TM (Table 110.1) rests on a constellation of findings that, together, are highly suggestive of the diagnosis. Because of the high morbidity and mortality associated with this disease despite treatment, the diagnosis of TM should be entertained in any patient with subacute meningitis. A history of recent exposure to an active case of tuberculosis can be helpful, although only a minority of patients in most large series could establish an epidemiologic link with an infectious case. Also, patients who are members of high risk groups such as HIV-infected, injection drug users, alcoholics, and some racial groups (Native American, African American) may be more likely to have TM. The tuberculin skin test is only positive in 31–64% of patients with TM, illustrating the limited sensitivity of this test. The tuberculin test is most helpful in children who develop TM in the course of primary disease. In one study of pediatric TM patients, 85% of the children were reported to be tuberculin positive (Lincoln & Kirmse, 1950). Up to one-third of patients had evidence of miliary disease either by CXR, biopsy of a remote site, or autopsy evidence. Chest X-ray, however, may be more helpful and should be performed on any patient suspected of having TM, as 30–74% of patients showed evidence of tuberculosis on a chest film. Finally, funduscopic evidence of choroidal tubercles may also be present and may be helpful in the enigmatic case.

Other more routine laboratory tests again are nonspecific and may show evidence of an elevated peripheral white blood cell count, anemia, elevated sedimentation rate; all consistent with subacute or chronic infection. None of these parameters have enough sensitivity or specificity to recommend them as definitive diagnostic tests. Hyponatremia, postulated to be secondary to the syndrome of inappropriate secretion of antidiuretic hormone, has been noted in a few studies. Davis et al., describe 79% of their cohort of 54 patients in the Southwestern United States with serum sodium $<$135 mEq/l in the first week of hospitalization, 68% with $<$130 mEq/l, and 45% with $<$125 mEq/L (Davis et al., 1993). In another urban study in the

US, 11 of 45 patients (24%) were noted to be hyponatremic during their hospital course (Ogawa et al., 1987). In an Australian study, 50% of patients were noted to have a serum sodium <130 mEq/l (Kent et al., 1993).

Examination of the cerebrospinal fluid is mandatory although elevated opening pressures and the possibility of a non-communicating hydrocephalus should be borne in mind. In one study, a 65% mortality rate was attributable in large part to 35% of patients who herniated after undergoing lumbar puncture (O'Toole et al., 1969). The CSF is clear early in disease and often becomes cloudy or turbid with chronicity. If the CSF if allowed to stand, a pellicle may form at the surface that can often be smear positive. Pleocytosis is generally present with a large range from none to over one thousand white blood cells. Greater than 50% of the cells are usually lymphocytes in 48–93% of the cohorts reviewed. Early in disease polymorphonuclear cell predominance has been reported, but usually changes to lymphocyte pleocytosis in a repeat tap several days later. Elevated protein is reported in the majority of patients in the range of 100–500 mg/dl. Nevertheless, more than a quarter of patients can have proteins less than 100 mg/dl (Iseman, 2000). Very high proteins >1000 mg/dl are rare and occur in patients with non-communicating hydrocephalus or long-standing disease with inflammation. Low CSF glucose <45 mg/dl is seen in 43–88% of patients. In some studies, a declining CSF glucose was used as evidence for a probable diagnosis of TM (Lincoln & Kirmse, 1950; Davis et al., 1993). In a paper by Kumar et al., they found five independent predictors of TM in a study with 110 cases of TM, 94 non-tuberculous meningitis patients, and 28 indeterminate patients: prodromal state >7 days, optic atrophy on fundal examination, focal deficit, abnormal movements, and CSF pleocytosis with <50% polymorphs. If three or more of these criteria were present, specificity was 98.3% (Kumar et al., 1999). The differential diagnosis of a lymphocytic pleocytosis, elevated protein, low glucose CSF profile includes the other causes of a granulomatous basilar meningitis including fungal infection, syphilis, and neurobrucellosis, as well as brain abscess.

A positive acid-fast stain of the cerebrospinal fluid combined with a positive CSF culture is the best way to diagnose TM. Because of the relative paucity of organisms in the CSF and the length of time required to grow *M. tuberculosis*, repeated CSF examinations of large volumes (10–15 ml) may be necessary to secure a diagnosis. The wide variability (4–87%) in the percentage of patients in different cohorts reported to have positive CSF smears is the result of variable technique and tenacity. Kennedy et al., report 87% of all patients had at least one CSF smear with acid fast bacilli. In this study, patients had up to 4 CSF samples sent to the laboratory with 37% of patients positive on sample 1, 25% positive on sample 2, 19% positive on sample 3 and 6% positive on sample 4. In addition, samples were concentrated by centrifugation with 0.02 ml of centrifuged deposit of CSF allowed to dry on an area not to exceed 1 cm in diameter, and with 500 high power fields examined with a 50x oil-immersion objective. The CSF culture positivity rate was also high (83%) with cultures held a minimum of 8 weeks (Kennedy & Fallon, 1979).

Alternative tests for the diagnosis of TM lack in sensitivity and specificity in a disease where diagnosis and treatment delay have profound consequences for subsequent morbidity and mortality. Polymerase chain reaction (PCR) amplifying the IS6110 insertion sequence has an overall sensitivity of <65% with slightly higher sensitivities among probable cases. False positivity rates are as high as 9%. ELISA, immune complex, and antibody immunoassays have similarly low sensitivity and specificity. Adenosine deaminase has been touted to have high sensitivity (100%), high specificity (99%), in addition to good discriminating power for TM and neurobrucellosis with levels >10 IU/L (Ribera et al., 1987; Lopez-Cortes et al., 1995). Subsequent reports showing unacceptable overlap between TM and other pyogenic causes of meningitis have shed doubt on the initial encouraging studies (Donald et al., 1987; Chawla et al., 1991).

The newer radiographical modalities such as CT and MRI have enabled clinicians to see more of the pathologic changes associated with TM. CT and MRI abnormalities are present in the majority of patients, although there are no pathognomonic changes. As described above, the finding of hydrocephalus and ventricular dilatation alone are relatively good prognostic signs. In a study by Bhargava et al. Of 60 cases of TM, only 3 patients had a normal CT scan, with 87% of pediatric patients showing evidence of hydrocephalus and only 12% of adults. The degree of basilar enhancement or evidence of inflammatory exudates is a harbinger for the formation of arteritis and ultimately ischemic injury (Bhargava et al., 1982). Therefore the presence of both meningeal and parenchymal disease with basilar enhancement is associated with the worst prognosis (Jinkins, 1991). Arteriography of patients who have evidence of basilar enhancement by CT often reveals vascular irregularity of the medium and large vessels of the basal subarachnoid cisterns. In one study of MR on 27 children with TM, MR was found to be superior in identifying both supratentorial (basal ganglia and diencephalic) lesions as well as brainstem parenchymal signal abnormalities, an area poorly examined by CT. In terms of prognostic staging, however, these authors concluded that no radiologic finding was a more superior prognostic indica-

Table 110.2. Overall mortality in tuberculous meningitis series

Years of study	Country	Stage 1	Stage 2	Stage 3	Mortality	Reference
1958–1966	Miami, USA	5(24%)	12(57%)	4(19%)	33%	Barrett-Connor (1967)
1966–1974	Detroit, USA	6(32%)	9(47%)	4(21%)	42%	Haas et al. (1977)
1968–1983	NYC, USA	11(24%)	25(56%)	9(20%)	31%	Ogawa et al. (1987)
1960–1976	Glasgow, Scotland	10(19%)	30(58%)	11(21%)	15%	Kennedy & Fallon (1979)
1970–1990	New Mexico, USA	12(23%)	32(53%)	10(14%)	31%	Davis et al. (1993)
1953–1975	Montreal, Canada	17(22%)	23(29%)	35(44%)	38%	Delage & Dusseault (1979)
1961–1984	Hong Kong	50(25%)	77(39%)	72(36%)	7%	Humphries et al. (1990)
1960–1990	Victoria, Australia	25(43%)	25(43%)	8(14%)	7%	Kent et al. (1993)
1981–1984	Newark, USA	3/10(30%)	7/10(70%)	0/10	57%	Bishburg et al. (1986)
1985–1990	Madrid, Spain	13/37(35%)	24/37(65%)	0/37	27%	Berenguer et al. (1992)
1982–1993	Paris, France	8(17%)	11(23%)	29(60%)	65%	Verdon et al. (1996)
1983–1994	Texas, USA		24/31(77%)	3/31(10%)	43%	Yechoor et al. (1996)
1966–1967	Calcutta, India	1(4%)	14(61%)	8(35%)	65%	O'Toole et al. (1969)
1982–1987	Cairo, Egypt	8(5%)	62(39%)	90(56%)	43%	Girgis et al. (1983)
1967–1970	Cali, Columbia			25(25%)	52%	Eschobar et al. (1975)

tor than the clinical stage of disease on admission in patients with TM (Schoeman et al., 1988). The differential diagnosis of the radiologic appearance of TM can include brain abscess, neurocyticercosis, tumour and the other causes of basilar meningitis listed above.

Prognostic factors

Table 110.2 illustrates that the proportion of patients in worse stages of disease at the time of admission predicts subsequent overall mortality in most studies (Haas et al., 1977; Delage & Dusseault, 1979; Ogawa et al., 1987; Humphries et al., 1990; Kent et al., 1993). Age >40 (or >60 (Kent et al., 1993), >50 (Delage & Dusseault, 1979)) is significantly associated with increased mortality (Haas et al., 1977; Delage & Dusseault, 1979; Ogawa et al., 1987). Likewise, the other extreme of age (<3) is also associated with a worse prognosis (Medical Research Council, 1948; Freiman & Geefhuysen, 1970). In developed countries as the incidence of pulmonary tuberculosis in young persons decreases, it is the elderly who carry latent disease and have a higher than average risk for reactivation. In one study by Ogawa et al., 16% of the cases were in persons older than 65. The mortality in this group was 57% as compared with 31% overall. Delaying treatment more than 1 week after admission also often correlated with a longer duration of symptoms and generally portended a worse prognosis (Haas et al., 1977; Kennedy & Fallon, 1979; Verdon et al., 1996). These risk factors for increased mortality are listed in Table 110.3.

Table 110.3. Risk factors associated with mortality in tuberculous meningitis

Risk factor
Age >50, <3
Stage 3 Disease/coma
Delaying treatment
Very high CSF protein
Multiple cranial nerve deficits

Presentation and outcome in HIV-infected persons

Patients with HIV infection are more likely to reactivate latent disease, more likely to contract primary tuberculosis, and also more at risk for developing extrapulmonary disease. In data from San Francisco, 60% of the AIDS group had at least one extrapulmonary site of involvement, as compared to only 28% of the non-AIDS patients (Chaisson et al., 1987). Other studies have shown an increased predilection to the development of TM in particular (Bishburg et al., 1986; Fertel & Pitchenik, 1989). In the largest series comparing HIV-infected to non-infected from Spain, HIV-seropositive patients were five times more likely to have central nervous system involvement. In their series, it was the most frequently identified meningeal pathogen and was the AIDS-defining oppor-

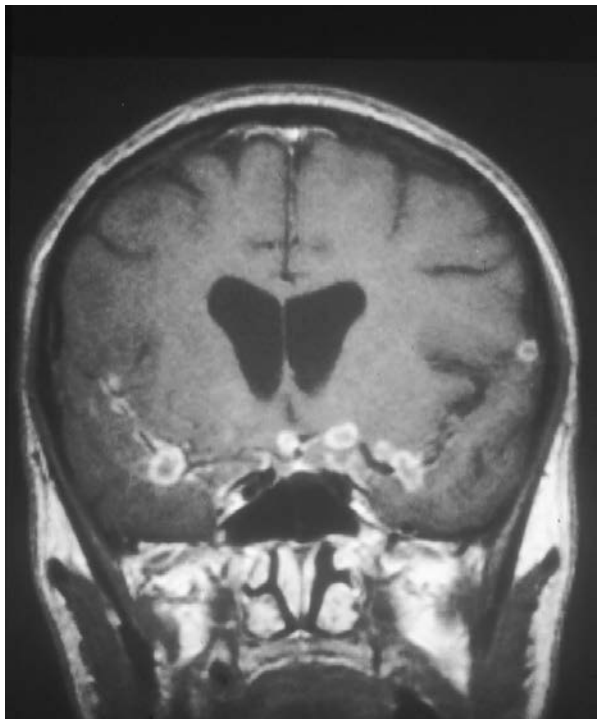

Fig. 110.2. Coronal T_1-weighted contrast-enhanced MRI scan in TB meningitis. Numerous basal tuberculous foci are identified. (Courtesy of Dr R.T. Johnson.)

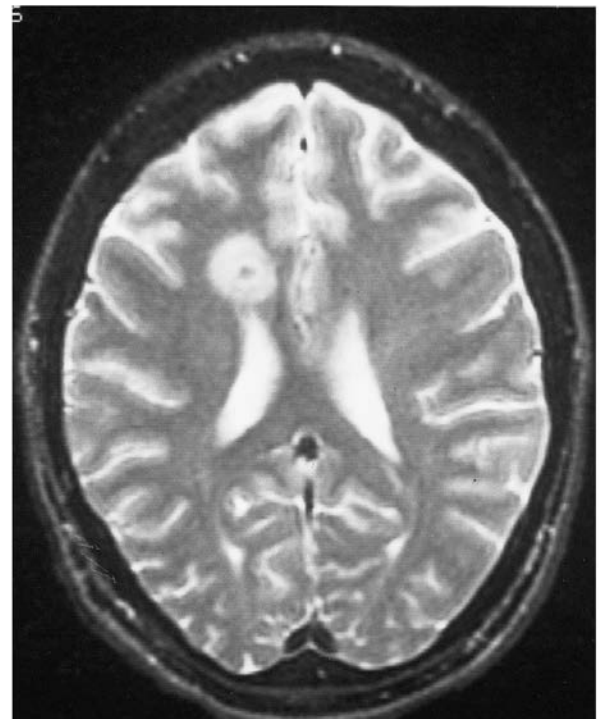

Fig. 110.3. Axial T_2-weighted cranial MRI scan showing right frontal tuberculoma with surrounding edema. (Courtesy of Dr J.C. McArthur.)

tunistic infection in the majority of the seropositive patients (Berenguer et al., 1992). In general, the clinical presentation of patients with HIV does not differ markedly from those who are seronegative. Some have noted a trend towards more patients presenting with normal CSF protein, perhaps due to less inflammatory response in those with immune compromise (Berenguer et al., 1992). In a study by Yechoor et al., with 20 HIV-infected patients, a higher percentage of patients with Stage 2 and 3 disease was noted (87%) with an overall mortality of 65% (Yechoor et al., 1996). Prognostic factors for the HIV-infected include stage of disease on admission, delay in diagnosis and the institution of therapy, and lower CD4 counts (Berenguer et al., 1992; Dube et al., 1992; Yechoor et al., 1996). One small study from Los Angeles showed that intracerebral mass lesions were more common in the HIV-infected group (60% vs. 14%), although the presence of such lesions did not correlate with mortality or focal neurological findings (Dube et al., 1992). Another cohort of ten AIDS patients, nine of whom were intravenous drug users, found eight cases of TM with intracranial mass lesions (tuberculomas, see below) (Bishburg et al., 1986).

Tuberculomas

In neuropathological studies, tubercles in the brain deposited during hematogenous dissemination of disease result in intraparenchymal caseous foci. They are often multiple and have been reported to be more common in patients under 30 years of age (Loizou & Anderson, 1982). These foci do not cause frank meningitis unless they erode into the subarachnoid space (Fig. 110.2), and if small, may be silent clinically. The vigour of the immune response to such lesions determines whether there will be inflammation (cerebritis) or areas of abscess (Rich & McCordock, 1933). CT scanning has greatly enhanced the clinician's ability to diagnose such intraparenchymal lesions. Tuberculomas typically are rounded or lobulated in appearance and following contrast enhancement can show either a solid or radiolucent centre with irregular wall thickness (Fig. 110.3). Moderate surrounding edema is usually noted with contrast enhancement (Jinkins, 1991). By MR, lesions greater than 2 cm generally show a T_2 hypointense wall with T_2 hyperintensity of the surrounding area consistent with edema. The contents of the granulomatous mass is generally inhomogenous as would be expected with

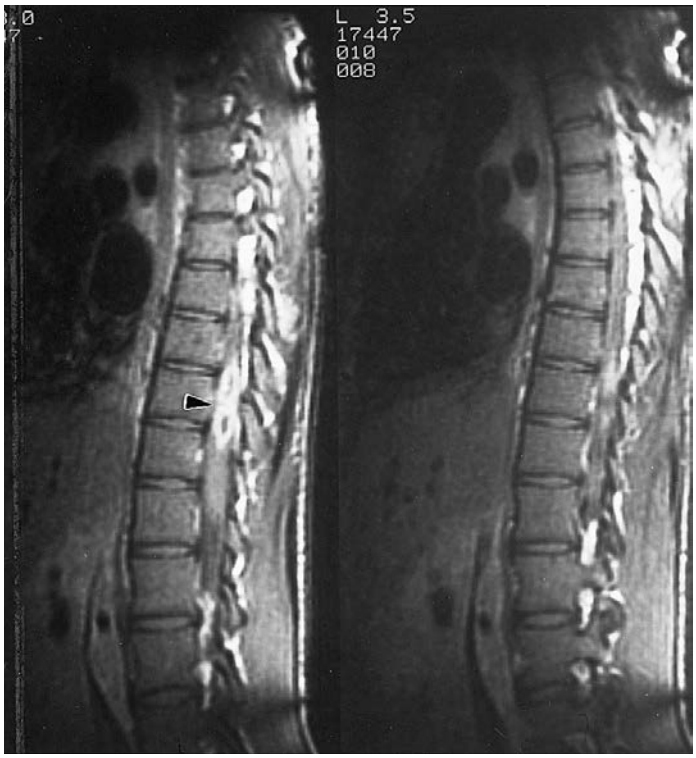

Fig. 110.4. Sagittal spine MRI scan showing large area of intramedullary tuberculous involvement at T10–12. (Courtesy of Dr J.C. McArthur.)

caseous necrosis. Smaller lesions in an early stage of evolution are less likely to be encapsulated and are usually T_2 hypointense, with hyperintense spots (Schoeman et al., 1988). Older lesions that often have microscopic or macroscopic calcification can appear as a high-attenuation area with little enhancement (Loizou & Anderson, 1982). The differential diagnosis of the CT tuberculoma lesion includes gliomas, metastases, meningiomas, abscesses, cysticercosis, coccidioidomycosis and tuberous sclerosis (Rodriguez et al., 1978; Witham et al., 1979). Intramedullary tuberculomas are uncommon, estimated to occur 50 times less frequently than intracranial tuberculomas (Fig. 110.4).

Tuberculomas are seen more often in the developing world where there are more cases of extrapulmonary disease overall (Lalitha & Dastur, 1980; Loizou & Anderson, 1982; Dastur, 1983). As noted above, the increasing prevalence of HIV in the developed world and in the developing world may result in an increase in the numbers of TM as well as of tuberculomas. Diagnosis in the HIV-infected and in areas where tuberculoma is unusual epidemiologically may necessitate needle biopsy for definitive diagnosis. Cerebral angiograms can be helpful in differentiating tumour masses from tuberculomas as tuberculosis rarely causes tumour blush secondary to an absence of increased vascularity. Tuberculomas respond well to medical treatment with antituberculous antibiotics so that surgery is rarely necessary (Harder et al., 1983). Surgical intervention is best reserved for cases with obstructive hydrocephalus (often with very large lesions), or brainstem compression as it may be complicated by severe, fatal meningitis (Tandon & Bhargava, 1985).

With treatment, tuberculomas can paradoxically worsen before they recede, or appear in cases where no lesions were seen by CT or MR (Lees et al., 1980; Loizou & Anderson, 1982; Chambers et al., 1984; Chang et al., 1986; Shepard et al., 1986; Teoh et al., 1987; Watson et al., 1993) There are numerous reports in the literature of paradoxical worsening. In general, these cases should be medically managed and in cases where surrounding edema is severe and symptomatic, systemic corticosteroids may be useful (Harder et al., 1983; Leonard & Des Prez, 1990; Watson et al., 1993)

Vertebral tuberculosis

Bone and joint tuberculosis may affect a number of areas, but vertebral tuberculosis (Pott's disease) is the most common form, accounting for almost one-half of cases. Hematogenous seeding of the anterior portion of vertebral bone during initial infection sets the stage for later development of Pott's disease. Infection grows initially within the anterior vertebral body, then may spread to the disk space and to paraspinous tissues. Destruction of the vertebral body causes wedging and eventual collapse. Patients usually complain of back pain, with constitutional symptoms less prominent. Neurologic impairment is a late complication, but delays in diagnosis are common and many patients experience neurological sequelae. Imaging studies of the spine reveal anterior wedging, collapse of vertebrae and paraspinous abscesses most often. The diagnosis is established with bone biopsy or curettage, or by culture of the drainage from a paraspinous abscess.

Treatment

Treatment of tuberculosis requires the use of multiple agents active against the infecting strain; when only one active drug is given, selection of innately drug-resistant clones can occur, resulting in the emergence of drug-resistant disease. The current standard regimen to treat pulmonary tuberculosis is isoniazid and rifampin given for 6 months, with pyrazinamide and ethambutol or streptomycin given during the first 2 months. Standard dosages of

Table 110.4(*a*). Dosage recommendation for the inital treatment of tuberculosis in children and adults

	Daily dose		Twice-weekly dose		Thrice-weekly	
Drugs	Children	Adults	Children	Adults	Children	Adults
Isoniazid, mg/kg	10–20 Max 300 mg	5 Max 300 mg	20–40 Max 900 mg	15 Max 900 mg	20–40 Max 900 mg	15 Max 900 mg
Rifampin, mg/kg	10–20 Max 600 mg	10 Max 600 mg	10–20 Max 600 mg	10 Max 600 mg	10–20 Max 600 mg	10 Max 600 mg
Pyrazinamide, mg/kg	15–30 Max 2 g	15–30 Max 2 g	50–70 Max 4 g	50–70 Max 3.5 g	50–60 Max 3.5 g	50–60 Max 3.5 g
Ethambutol, mg/kg[1]	15–25 Max 1.5 g	15–25 Max 1.5 g	50 Max 4 g	50 Max 4 g	25–30	25–30
Streptomycin, mg/kg	20–40 Max 1.0 g	15 Max 1.0 g	25–30 Max 1.5 g	25–30 Max 1.5 g	25–30 Max 1.5 g	25–30 Max 1.5 g

Table 110.4(*b*). Chemotherapy in tuberculous meningitis

Antibiotic	Recommended dose	CSF penetration (no inflam.)	CSF penetration with TM	Clinical efficacy
Isoniazid	5 mg/ kg, usual maximum 300 mg daily; doses of 10 mg/kg/d–20 mg/ kg/d sometimes used in CNS disease	++	(Elmendorf et al., 1952; Barclay et al., 1953; Fletcher, 1953; Lanier et al., 1958; Donald et al., 1992)	Documented (Clark et al., 1952)
Pyrazinamide	20–30 mg/kg/d	++	(Ellard et al., 1987; Donald & Seifart, 1988)	No proven efficacy, but important sterilizing drug in pulmonary TB
Ethionamide	10–15mg/kg/d	++		Only 5x the MIC at peak concentration with rapid elimination
Ethambutol	25 mg/kg/d	+	(Place et al., 1969; Bobrowitz, 1972)	Static drug at non-toxic doses with no proven efficacy in TM
Streptomycin	22 mg/kg TIW 15 mg/kg/d 1 gm qd (adults)	±	(McDermott et al., 1947; Bunn, 1948; Lincoln & Kirmse, 1950; Illingsworth & Lorber, 1951; Perry, 1952)	Some limited efficacy in early studies even when used as monoRx. 8th nerve toxicity
Rifampin	10 mg/kg/d, maximum dose 600 mg daily, some experts recommend up to 750 mg daily for CNS disease	±	(D'Oliveira, 1972; Sippel et al., 1974)	Important sterilizing drug in pulmonary TB, 5–25% of serum levels only, ?additional benefit with increased doses

the first line antituberculous agents are given in Table 110.4(*a*). When treating pulmonary and some extrapulmonary forms of tuberculosis, intermittent therapy with higher doses of most agents is frequently employed, usually after an initial 2–8 weeks of daily therapy. Treatment of neurological forms of tuberculosis is usually given daily throughout treatment because the drug levels achieved in cerebrospinal fluid may be marginally adequate. Moreover, treatment of neurological tuberculosis generally requires more prolonged therapy, usually 12 months, as described below. Drug-resistant tuberculosis may require prolonged therapy, as well, depending on the drugs to which the isolate is resistant. All patients being treated for tuberculosis should have cultures taken to confirm the

diagnosis, and susceptibility testing of the initial isolate should be performed to rule out drug-resistance.

Since the advent of chemotherapy for TM, the mortality has changed remarkably little. Streptomycin was the first antituberculous drug produce, and it brought about remarkable remissions of tuberculous meningitis. Many patients experienced relapses with streptomycin-resistant organisms, however, dampening the initial enthusiasm for antibiotic therapy. Subsequently, landmark studies by the British Medical Research Council and the US Public Health Service verified the efficacy of combination therapy against tuberculosis, and multidrug treatment became the rule. Isoniazid became the mainstay of therapy in the early 1950s, and later ethambutol, pyrazinamide (PZA) and rifampin were added to the repertoire of antituberculosis agents. Although the development of these latter drugs was critically important for the therapy of most forms of tuberculosis, their availability did not change mortality in TM compared to streptomycin or isoniazid.

Treatment of central nervous system tuberculosis is complicated by the difficulty of delivering adequate concentrations of antimicrobial agents to the site of infection. Penetration through the blood–brain barrier with uninflamed meninges depends on the molecular weight, ionization, protein binding, and, to a lesser extent, to the lipid solubility of the antimicrobial compound. Isoniazid, PZA, and ethionamide have the best CSF levels among the antituberculosis arsenal. In contrast, rifampin, streptomycin, and ethambutol have poor CSF penetration unless there is meningeal inflammation, and even in that setting, rifampin achieves only 5–25% of the serum levels (Holdiness, 1985; Ellard et al., 1993).

The treatment of TM, therefore, should begin with at least four drugs, usually isoniazid, rifampin, PZA and ethambutol. Drug dosages used in TM are shown in Table 110.4(*b*). Isoniazid is the cornerstone of any regimen unless there is known or suspected resistance, because its good CSF penetration results in drug exposures (area under the curve) in CSF similar to that in serum. The dose of isoniazid for tuberculosis is generally 5 mg/kg/day, with a maximum daily dosage of 300 mg. In central nervous system tuberculosis, however, some authorities recommend increasing the dosage to 10 mg/kg per day to assure adequate drug levels in cerebrospinal fluid. At this dosage, the isoniazid concentration in the CSF 12–14 hours after a dose still exceeds the MIC for *M. tuberculosis*. In areas where there is a high prevalence of multidrug resistant tuberculosis a dosage of 20 mg/kg may allow for coverage of moderately resistant *M. tuberculosis* strains by achieving slightly higher CSF concentrations, even in patients who are rapid acetylators of this agent (Donald et al., 1992). Although the number of tubercle bacilli in the CSF in TM is several orders of magnitude lower than that in a pulmonary cavity, at least two other active drugs should be added to the regimen to prevent the selection of drug resistance. Isoniazid (INH) eliminates only actively dividing bacilli, and drugs with known activity against dormant and semidormant organisms are also required. PZA and rifampin probably contribute to sterilization of the meninges in TM, though firm evidence of this is lacking (Fox & Mitchison, 1975; Jindani et al., 1980). PZA is a small molecule that is uncharged, not protein bound and lipophilic and consequently has good CSF penetration (Ellard et al., 1987). Data from studies of pulmonary tuberculosis show a better tuberculocidal effect with the addition of this agent to isoniazid and rifampin, and this drug should be included in the first 2 months of treatment for TM. Some experts continue PZA throughout the course of treatment for TM, especially in severely ill patients. Increased doses of rifampin should be considered given the poor CSF penetration of this agent, but liver function tests should be monitored closely. In a study by Ramachandran et al., the incidence of jaundice was related to high dosages of both INH and rifampin; at INH doses of 20 mg/kg with rifampin doses of 12 mg/kg, 39% of patients developed jaundice, while at a dosage of INH 12 mg/kg jaundice occurred in 16% of patients. Moreover, when rifampin was given only twice weekly only 5% of patients developed jaundice (Ramachandran et al., 1986).

Several alternatives exist for the fourth drug in combination with INH, rifampin and PZA. Streptomycin showed initial efficacy when used as monotherapy in the 1940s and 1950s and may be a reasonable alternative. In the extensive experience at National Jewish Center in Denver, a thrice weekly regimen of streptomycin is given with daily isoniazid, rifampin and PZA in order to minimize eighth cranial nerve toxicity (Iseman, 2000). Ethambutol may be a reasonable alternative as it showed some efficacy in combination with INH in a small trial of patients with TM, although it does not have good CSF penetration (Bobrowitz, 1972). Alternatively, ethionamide may be an attractive alternative, especially for the pediatric patient, as it has better CSF penetration, no ocular toxicity, and may be better tolerated from a gastrointestinal standpoint (Ellard et al., 1993; Iseman, 2000). Twelve months of therapy is likely required for TM, although 9 months may be adequate in patients with a rapid initial improvement with therapy. Overall, those who present with Stage 3 disease are least likely to benefit from chemotherapy, as the mortality in the moribund patient at presentation is high and has not changed since the advent of antituberculous drugs.

Table 110.5. Studies examining adjunctive corticosteroid (CS) therapy in TM[a]

Year	# Pts (#CS)	Antibiotic regimen	Steroid regimen	Comments	Ref
1955	12(6)	INH/S	Cortisone 100mg/day, ACTH during taper	Faster recovery 2–3 days vs. 7–10 days, less neuro sequelae 0/6 vs. 4/6 controls	Ashby & Grant (1955)
1952–8	33(16)	INH/S/PAS	IM cortisone, then PO prednisone (34 day mean)	3/16 steroid Rx'ed died vs 9/17 controls	Voljavec & Corpe (1960)
	37(19)	INH/S/PAS	Hydrocortisone, 300mg/d× 14 d, ACTH (days11–14)	No difference in CSF parameters, death or neuro sequelae	Lepper & Spies (1963)
1966–7	23(11)	INH/S	Dexamethasone 9 mg/d, 4 wk taper	Faster drop in CSF pressure with fewer herniations in steroid Rx'ed, CSF gluc, prot, WBS count all improved faster with steroids	O'Toole et al. (1969)
1967–70	99(52)	INH/S/PAS	Prednisone 1 or 10 mg/kg/ day, 30 day taper	22/52 steroid Rx'ed died vs. 23/47 controls died, no difference in sequelae	Escobar et al. (1975)
1979–82	136(66)	INH/S/Eth	Dexamethasone 8–12 mg/day×21 d	No significant difference in survival or ocular complications, less optic atrophy in steroid Rx'ed	Girgis et al. (1983)
1982–7	160(75)	INH/S/Eth	Dexamethasone 12 mg/day, taper over 6 wks	Faster improvement in CSF parameters in steroid Rx'ed, significantly decreased mortality 43% vs. 59%, and neuro sequelae (4/10 steroid Rx'ed vs. 6/13)	Girgis et al. (1991)
1955–77	445(339)	INH/S/PAS (345) Kan/INH (80) Kan/INH/PAS(20)	Prednisone 30–40 mg/day, after one month, 2 month taper	Reduction in mortality in steroid Rx'ed in Stage 2 and 3 disease	Shaw et al. (1984)
1991–2	47(24)	RIF/INH/PZA	Dexamethasone 16 mg/day, p.o. dexamethasone 8 mg/day ×21 days, 14 day taper	Trend towards better outcome with mild sequelae, no survival difference	Kumarvelu et al. (1994)

Note:

[a] Adapted from table in Dooley et al. (1997).

Steroid therapy in TM

There are eight published studies in the literature examining the impact of steroids in TM (Ashby & Grant, 1955; Kumar et al., 1994; Shaw et al., 1984; Voljavec & Corpe, 1960; Lepper & Spies, 1963; O'Toole et al., 1969; Escobar et al., 1975; Girgis et al., 1983, 1991). They are summarized in Table 110.5. There are methodologic flaws in all, but taken together, there is likely some benefit to the administration of corticosteroids (Dooley et al., 1997). Patients with intermediate disease are most likely to benefit based on the two trials that stratified patients by stage of disease at presentation. Interestingly, drowsy rather than comatose patients were more likely to benefit, those with single cranial nerve paresis, or hemiparesis were also found to have better outcomes (Voljavec & Corpe, 1960; Girgis et al., 1991). Studies testing steroid regimens longer than 4 weeks were more likely to demonstrate significant benefit (Ashby & Grant, 1955; Voljavec & Corpe, 1960; Escobar et al., 1975; Girgis et al., 1991). The mechanisms of action resulting in lower mortality seems to be in the alleviation of cerebral edema, decrease in arachnoiditis with concomitant relief of hydrocephalus, increased intracranial pressure, and cranial nerve palsies. Relief of spinal cord blockage or non-communicating hydrocephalus secondary to inflammation could also occur. One potential concern with the initiation of steroids is an unfavourable decrease in the CSF penetration of antituberculous drugs. In one study, however, steroid therapy did not significantly alter the CSF pharmacokinetics of chemotherapy (Kaojarern et al., 1991).

The treatment of CNS tuberculomas requires prolonged courses of antituberculous drugs. Surgery is usually only indicated for establishing the diagnosis or managing impending neurologic catastrophes such as herniation. Penetration of drugs into tuberculomas is limited, and the time to a clinical response may be prolonged. During the course of treatment for tuberculomas, masses are frequently noted to increase in size and generally follow an erratic course. The majority of lesions are improved after 6 months of therapy, and most have resolved after 12–15 months.

Pott's disease is usually diagnosed by biopsy of a vertebra or paraspinous abscess, and debridement is often required. Surgical intervention to stabilize the spine is needed in a minority of cases. The optimal surgical management of Pott's disease is controversial, but one study found that patients given early surgical treatment had fewer long-term deformities and neurologic sequelae than those treated conservatively. Antimicrobial therapy for Pott's disease is the same as for pulmonary tuberculosis, but the duration of treatment is extended to 9–12 months. Previously, most patients with Pott's disease were treated for 18 months, but a controlled trial of 9 vs. 18 months of therapy found no differences in outcomes with the longer course.

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Part XV

Trauma and toxic disorders

111

Head trauma

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Traumatic brain injury (TBI) is one of the leading causes of morbidity and mortality in children and young adults throughout the world. Substantial progress has been made in reducing death and improving outcome for this little recognized epidemic since the 1980s. Nonetheless, over 50 000 US citizens die annually as a consequence of TBI and 80 000–90 000 survivors experience substantial long-term disability. In this chapter, we will discuss recent epidemiologic studies, diagnosis and management of TBI and describe ongoing efforts in bench and translational research.

Trends in TBI (Thurman et al., 1999)

The Centers for Disease Control and Prevention (CDC) began the development of a multi-state surveillance system for TBI in 1989 in response to a Federal Interagency Head Injury Task Force report that identified a need for better information on TBI. Prior to this, data was derived from hospital-based clinical case series in geographically restricted epidemiological studies. Consequently, the ability to broadly generalize findings from these early efforts was limited. Prior to 1990, estimates of hospital admissions for TBI in the US were about 500 000 per year, with an incidence ranging from 132 to 367 per 100 000, depending on the region studied. With the onset of the CDC study, a much broader and more representative analysis began which now includes 15 states (Thurman et al., 1999). These include states with rural populations (Alaska, Arkansas, Minnesota and Nebraska), major cities (New York, California) and broad racial representation. Guidelines were established to define TBI: craniocerebral trauma due to blunt or penetrating trauma to the head resulting in decreased level of consciousness, amnesia, other neurologic or neuropsychologic abnormalities, skull fracture, diagnosed intracranial lesions or death. As a result of these efforts, a more accurate representation of TBI in the US may now be described (see Figs. 11.1, 11.2).

Recent data show that 230 000 people are hospitalized and survive TBI with over 80 000 of these individuals sustaining long-term disability. The hospital admission number is substantially reduced from prior decades when over 500 000 patients per year were hospitalized. This is probably a consequence of improved and readily available technology (CT scan) which can screen for intracranial pathology as well as changing criteria for hospital admission. About 50 000 die from TBI, which is 30% of all traumatic deaths. Adolescents, young adults and the elderly are most at risk, with a male:female rate of 2:1. The age and gender profile is unchanged from prior studies but the death rate has decreased, from 24.7 per 100 000 to 19.8 per 100 000. There has been a substantial shift in the cause of death from transportation to firearms due to improvement in vehicle safety, more stringent drinking and driving laws, increased seat belt use and other safety measures (helmets, child seats). Firearms became the leading cause of TBI-related death in 1990, with two-thirds of these firearm-induced deaths due to suicide. Given the restriction on firearms, transportation accidents remain outside the US the leading cause of death due to TBI.

Estimates of TBI-induced long-term disability are based on hospital discharge data combined with an estimate of severity using the Abbreviated Injury Scale included as part of the discharge data. Using this information, a prevalence of 5.3 million US citizens (2% of the population) live with TBI-related disability. The incidence of TBI-related disability is estimated at 80 000 individuals. Less information is available on the age, gender or ethnicity of this population. Economic analysis of the annual cost of TBI-related disability ranges from $4.5 billion in direct expenditure (medical care and services) to $20.6 billion in injury-related work loss and disability. Thus, while much progress

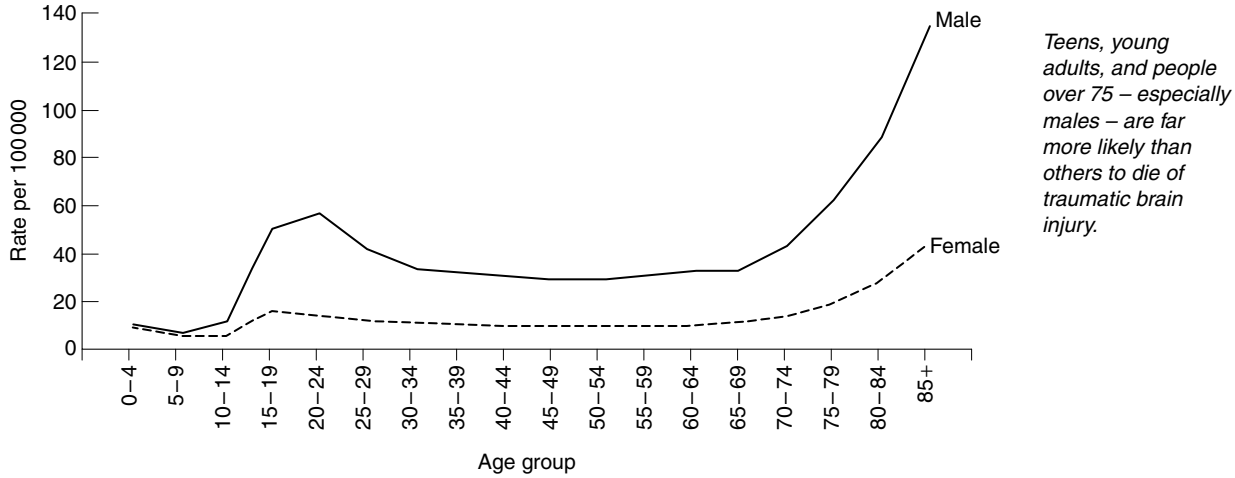

Fig. 111.1. TBI death rates by age and gender (permission: Traumatic Brain Injury in the United States: A Report to Congress, Division of Acute Care, Rehabilitation Research, and Disability, Prevention, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, US Department of Health and Human Services, December 1999).

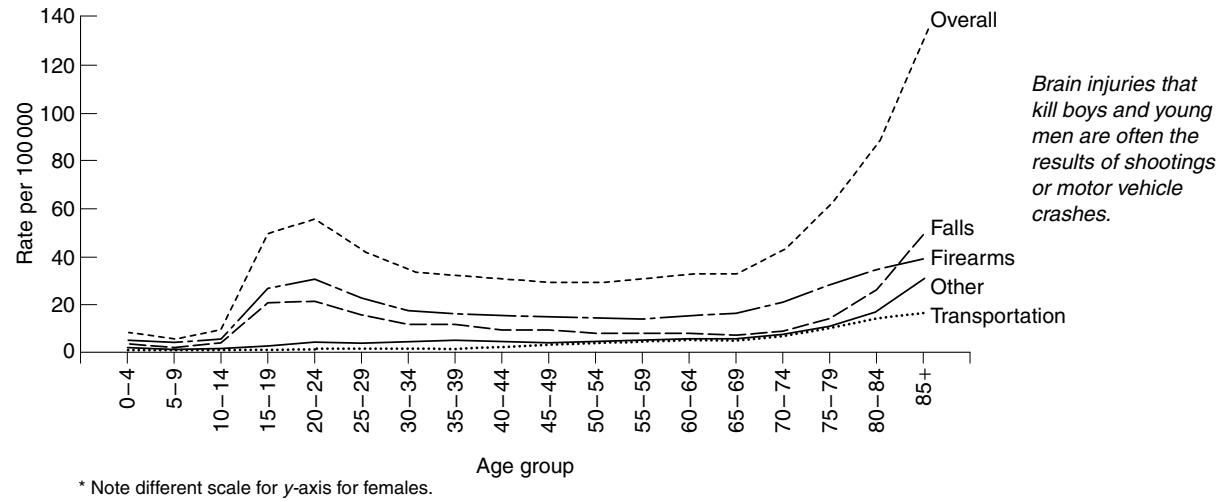

Fig. 111.2. TBI related deaths by cause (permission: Traumatic Brain Injury in the United States: a Report to Congress, Division of Acute Care, Rehabilitation Research, and Disability, Prevention, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, US Department of Health and Human Services, December 1999).

has been made in reducing death and disability from TBI, much more remains to be accomplished.

Medical and surgical management of TBI (Bullock et al., 1996)

A system of classification of TBI into three grades: minor, moderate and severe was established by Teasdale and Jennett in 1974. This schema, known as the Glasgow Coma Scale, has demonstrated persistence because of its ease of administration, high interobserver reliability and utility for grading severity and predicting outcome (see Fig. 111.3).

The summation of these individual scores ranges from 3–15, with severe TBI classified as less than or equal to 8, moderate 9–12 and minor as 13–15.

Motor Score:	
Obey verbal commands	6
Localize to painful stimuli	5
Withdrawal to painful stimuli	4
Flexion (decorticate) posturing to painful stimuli	3
Extension (decerebrate) posturing to painful stimuli	2
No motor response	1
Verbal Score:	
Oriented and conversing	5
Conversing but disoriented	4
Inappropriate words	3
Incomprehensible sounds	2
No verbal response	1
Intubated	T
Eye Score:	
Open spontaneously	4
Open to verbal stimuli	3
Open to painful stimuli	2
No eye opening	1
Total Score:	**3-15**

Fig. 111.3. Glasgow Coma Scale.

In the field

Treatment of TBI begins with resuscitation in the field by trained paramedics or emergency medical technicians. Following the initial insult, the brain is susceptible to a variety of secondary insults that will compromise neurological outcome. These insults can occur within minutes of injury and may include expanding hematomas or brain edema causing raised intracranial pressure, hypoxia due to ventilatory compromise or hypotension due to hemorrhagic shock. These events must be recognized and reversed to optimize long-term recovery potential.

Traditionally, ambulance services attempted to transfer the trauma patient as rapidly as possible from the injury scene to the emergency room. However, a significant number of patients with severe TBI experience at least one episode of hypotension (systolic blood pressure $<$90 mm Hg) or hypoxia ($PaO_2 < 60$ mm Hg), according to data from the Traumatic Coma Data Bank (Marshall et al., 1991). Mortality increased 150% in those patients with an episode of hypotension, compared to patients without hypotension. Pathological studies of brains of humans dying from TBI but with no recorded episodes of hypotension identified ischemic lesions in 40% of these patients (Adams et al., 1982). Therefore, even minor ischemia may have adverse consequences on a traumatically injured brain. Consequently, there has been an emphasis on resuscitation in the field including intubation for airway control and intravenous fluids for maintaining adequate volume. The notion of keeping the brain-injured patient in a relative state of dehydration to avoid brain edema is no longer supported by the literature or in practice (Bullock, 1996).

There are several studies demonstrating the importance of an organized trauma system to improving outcome from

TBI. In a prospective study, Colohan et al. (1989) compared outcome after severe TBI in two very different environments, Charlottesville, Virginia and Delhi, India. The mortality rates of the most severely injured patients, those with GCS 3 or 4 were similar at both centres. However, the mortality of patients with GCS 5 was 12.5% in Delhi as opposed to 4% in Charlottesville. The difference was attributed to prehospital systems, with <3% of patients in Delhi receiving prehospital care by trained professionals compared to >85% of patients in Charlottesville receiving field resuscitation by paramedics. Further, transport time to definitive care was substantially different, with only 7% of patients in Delhi being admitted to a hospital within 1 hour compared to 50% in Charlottesville. Further, air transport where possible has reduced anticipated mortality by as much as 52% (Baxt & Moody, 1983).

In the emergency room

After transport to a facility capable of managing trauma, patients undergo an overall evaluation to determine the basics of life support and to identify and prioritize treatment of all injuries. For example, 10% of patient with severe TBI have a concomitant spine fracture (O'Malley & Ross, 1988). Further chest, abdominal, pelvis or extremity injuries may result in hemorrhagic shock that must be corrected. The American College of Surgeons has developed the Advanced Trauma Life Support (ATLS) course curriculum for physicians to provide a rational and standardized trauma care. Standards have been developed by the ACS Committee on Trauma that specify how trauma systems should be organized and these have been adapted by many states. Patients are evaluated according to a simple mnemonic in the primary survey: airway, breathing, circulation, disability and exposure/environment control. The first three efforts are directed at preventing or correcting hypotension and hypoxia, the fourth effort categorizes the neurological disability and the fifth concentrates on exposing for a complete examination and avoiding or correcting hypothermia. The GCS is performed as part of the Disability exam, along with pupillary examination for dilated or asymmetric pupils. Even when there has been pharmacological paralysis as a measure for intubation, the pupillary exam is reliable. The severity of the TBI is graded as previously described, and appropriate measures undertaken.

For moderate (GCS 9–12) and severe (GCS 3–8) TBI an emergency computed tomographic (CT) scan is mandatory after hemodynamic stabilization. The use of CT has revolutionized management of TBI, giving physicians the ability to rapidly and accurately diagnose hematomas, cerebral edema, infarction or hydrocephalus. Skull radiographs play virtually no role in assessment of patients with blunt trauma demonstrating a moderate or severe TBI. In cases of penetrating injury, skull radiographs may help in localizing metal or bone fragments. Use of skull films in minor TBI (GCS 13–15) has been evaluated. The presence of a skull fracture significantly increases the risk of an important intracranial hemorrhage. However, with the widespread availability of CT scanners, the cost efficacy of skull films is difficult to rationalize. In a prospective study at an inner city level 1 trauma centre, the presence of one or more of seven simple clinical findings (headache, vomiting, age >60 years, drug or alcohol intoxication, deficits in short term memory, physical evidence of trauma above the clavicles, and seizure) was 100% sensitive in predicting a positive finding on CT scan in patients with minor TBI (Haydel et al., 2000). The completion of the CT scan now provides the physician with definitive treatment of the brain injury.

In the hospital: minor TBI (Stein & Ross, 1990)

This category comprises the majority of patients, as many as 350 000 annually in the United States. At a minimum, all of these patients will have had a loss of consciousness, but many may not require hospitalization. For those patients with a GCS of 15 in the emergency room and a normal CT scan, discharge from the emergency room to a reasonable home environment is safe. There is controversy as to indications for CT scan in patients who have had transient loss of consciousness only, but Stein has shown in 1538 patients with mild TBI, 209 (13.5%) had an abnormal scan (Stein & Ross, 1990). As comparison, Duus reported a series of 1876 patients with mild TBI in whom 27 (1.4%) underwent CT scan due to clinical deterioration (Duus et al., 1993). Of those patients scanned, 9 had an intracranial hematoma. With the cost of CT scan being lower than that of hospital admission for a single day observation, a strong argument may be made for more frequent utilization of CT scan. Consideration must be made for those patients with signs of alcohol or drug intoxication, as these will impair an accurate neurological examination. A low threshold for obtaining a CT scan must be maintained for this population who are also likely to be frequent patients in the emergency soom.

In the hospital: moderate/severe TBI (Bullock et al., 1996)

Literature based guidelines for treatment of severe TBI have been published and represent the most recent

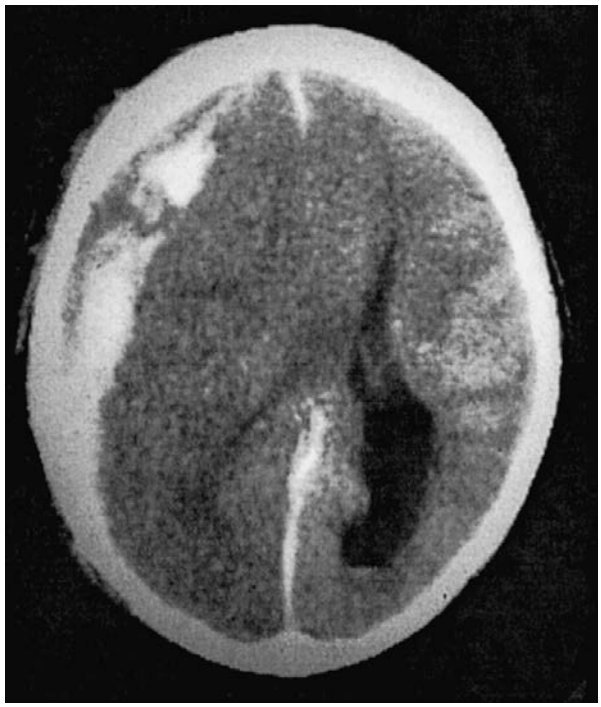

Fig. 111.4. Acute subdural hematoma: CT scan shows blood extending over the convexity of the brain causing compression of the ipsilateral ventricle and shift (herniation) of the brain.

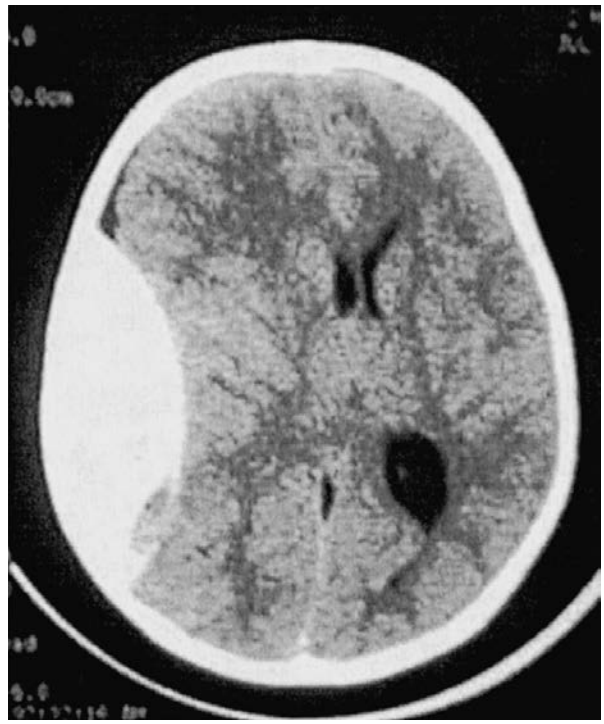

Fig. 111.5. Acute epidural hematoma: In this entity blood between the skull and the dura expands to cause brain shift, creating a secondary injury due to herniation.

attempt at standardizing the care of these patients (Bullock et al., 1996). Patients with these injuries are admitted to a nursing unit with the capacity to perform frequent neurological examinations in addition to invasive monitoring, ventilatory and blood pressure support. Alternatively, if the patient has a significant subdural or extradural hematoma detected by the initial CT scan, the patient will be taken to the operating room for evacuation of the clot. Acute subdural hematoma (Fig. 111.4) is often associated with underlying brain injury, as may be anticipated with a force strong enough to tear veins over the surface of the brain. Consequently, outcome after severe TBI with acute subdural hematoma is worse than with extradural hematoma. In extradural hematomas (Fig. 111.5) a blood clot forms between the calvarium and the dura, often due to a torn meningeal artery. Patients with this entity are often initially alert but deteriorate into coma as a consequence of mass effect causing a herniation syndrome. Drainage of the clot frequently has dramatic positive results on neurologic outcome.

In the intensive care unit, patients are monitored for adequate blood pressure and oxygenation. Patients with a severe TBI should undergo placement of an intracranial pressure (ICP) monitor to determine and treat raised intracranial pressure. The efficacy of this modality has not been prospectively tested, but is commonly accepted. There are several modalities for decreasing intracranial pressure, including drainage of cerebrospinal fluid, dehydration using intravenous mannitol or decreasing intracranial blood volume using hyperventilation. To understand the importance of lowering the intracranial pressure in a patient with severe TBI, one must understand intracranial compliance and consequences of raised ICP.

The brain rests within a closed vault, with the components being brain, CSF and blood. When a blood clot accumulates or cerebral edema occurs, the brain accommodates by shifting CSF out of the intracranial compartment into the spinal subarachnoid space. Since the total CSF volume of the adult head is about 75 cm^3, a blood clot of this size could theoretically be accommodated without substantial pressure on the brain. At this point the brain has no more compliance for the clot volume and the ICP begins to rise. The effect of this is twofold. First, the blood pressure must rise to maintain cerebral circulation. This reflex is known as the Cushing reflex and is associated with bradycardia. Secondly, the brain shifts by moving underneath the

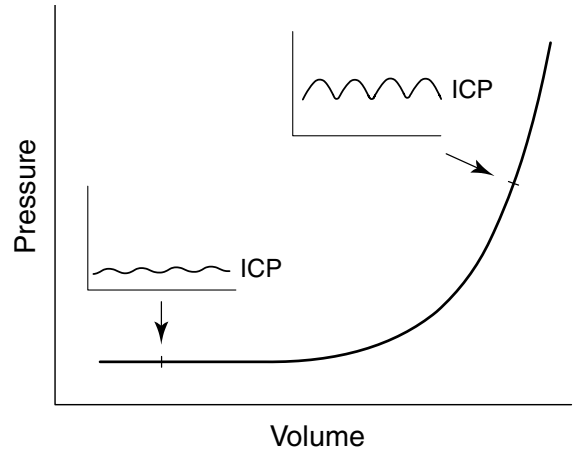

Fig. 111.6. Pressure–volume curve that reflects the ability of the brain to accommodate an expanding intracranial lesion. As the volume increases, the brain loses its compliance and intracranial pressure may rise abruptly.

falx, or through the tentorium or foramen magnum. These shifts, known as herniation, compress blood vessels and brain tissue leading to infarction and, if untreated, death or severe disability. While small increases in volume may cause substantial rises in ICP, conversely small decreases in volume may have substantial effect on lowering ICP (Fig. 111.6).

Drainage of CSF through a catheter placed into a ventricle may be a very effective way of both lowering ICP as well as being useful as a pressure monitoring device. Risks include a 1% risk of intracerebral hemorrhage as a consequence of catheter placement and a risk of infection ranging from 3–7% (Narayan et al., 1982). Otherwise, a fibreoptic monitor can be placed into the subarachnoid space or into the brain parenchyma. The osmotic diuretic mannitol rapidly lowers ICP when given intravenously. While it does lower water content within the brain, it is more probable that its effects are caused by acutely raising cerebral blood flow through volume expansion which decreases blood viscosity permitting cerebral vasoconstriction and lowering ICP (Mendelow et al., 1985; Muizelaar et al., 1984). Its effectiveness is lost as serum osmolarity rises beyond 320 mOsm. Bolus doses of 0.5 to 1 mg/kg may be given, a Foley catheter must be in place due to the diuretic effect, and fluids must be replaced to avoid hypotension due to hypovolemia. Hyperventilation decreases raised ICP through cerebral vasoconstriction. For each 1mm Hg decrease in pCO_2, the cerebral blood flow drops 2.5%. Consequently, hyperventilation must be used with caution. Aggressive hyperventilation (pCO_2 >25 mm Hg) clearly results in cerebral ischemia in the traumatically injured brain and is associated with poor outcome (Muizelaar et al., 1991). The guidelines for treatment of severe brain injury indicate that a pCO_2 between 30–35 mm Hg is optimal for ICP control without the adverse consequences of lowered cerebral blood flow.

Other medical strategies include the short-term use of dilantin for seizure prophylaxis. Several prospective, double-blind, placebo-controlled randomized studies have shown that use of an anticonvulsant longer than 1 week after TBI is not able to prevent seizures and may have some detrimental psychomotor effects (Temkin et al., 1990). Seizure control in the initial period after injury is important to prevent raised ICP as a consequence of airway compromise or increased cerebral blood flow. Barbiturates have been used to lower ICP by decreasing CBF (through reducing cerebral metabolism). However, barbiturates may also cause hypotension and consequently their use is recommended only in hemodynamically stable patients in whom other measures have failed. The use of glucocorticoids remains controversial. Several prospective randomized studies failed to find efficacy but a meta-analysis by Alderson and Roberts concluded that while there was not significant beneficial effect, there was a modest positive trend towards better outcome (Alderson & Roberts, 1997; Newell et al., 1998). A large multicentre European trial is under way to re-evaluate the efficacy of glucocorticoids.

Research in traumatic brain injury

The biomechanics of experimental TBI (Melvin, 1994) Numerous studies have evaluated the response of the skull and the underlying brain tissue to direct impact loading (Melvin, 1994). In response to relatively large impact forces, the skull deforms only slightly before fracturing due to its inherent mechanical properties. For forces distributed over very small areas, the fracture tolerance decreases and its nature changes from a linear to a penetrating or comminuted depressed fracture. The local depression, or inbending, of the skull from dynamic contact forces causes stress waves to propagate through the skull in all directions from the point of impact. These waves travel and meet at points on the skull remote from impact and they consequently cause skull fracture remote from the impact site (Got et al., 1993).

The local distortion of the skull without fracture can also transiently deform the underlying brain tissue and create pressure gradients throughout the neuraxis. Work with experimental biomechanical models has indicated that the rate and amount of local skull displacement are important predictors of the magnitude of pressure underneath,

and distant to, the impact site (Lee & Advani, 1975; Liu et al., 1975). Due to the apparent association between skull displacement and intracranial pressure, several studies have utilized mechanical impedance methods to reveal that the characteristic driving force frequency is an important parameter in assessing the magnitude of intracranial pressures caused solely by bending of the skull (Gurdjian, 1975). Short duration impact forces (<2 ms) generated pressure disturbances only if the skull was allowed to accelerate.

Despite the observations that the contact effects from impact forces can produce skull bending and intracranial pressure changes, the resulting brain injuries caused by these mechanical events appear to be restricted to focal lesions such as surface cerebral contusions, intracerebral hematomas, subdural hematomas, and epidural hematomas. Negative intracranial pressure changes have also been hypothesized to be significant factors in producing cerebral contusions at the sites of impact (Ommaya et al., 1994). An intracerebral hematoma may be viewed as a more extensive form of cerebral contusions related to negative pressures larger in magnitude than those required to cause cerebral contusions. A subdural hematoma due to local contact may occur when a skull fracture compromises the vascular network beneath the fracture site. Similarly, an epidural hematoma is not associated at all with intracranial pressure increases in 85% of cases, but is thought to occur when underlying dural vessels are torn as a result of skull fracture. In the remaining 15% of cases, fracture is not observed.

Impact or impulsive loading creates different mechanical effects (e.g. acceleration) on brain tissue. Brain lesions produced by inertial forces can be quite different, therefore, from those injuries due to contact. Two forms of acceleration, translational and rotational, form the basis for most biomechanical studies aimed at defining mechanisms and biomechanics of brain injury. Translational acceleration produces an intracranial pressure gradient and movement of the brain relative to the inner surface of the skull, the magnitude of which depends directly on the level of translational acceleration (Hayashi, 1969). In comparison, rotational acceleration produces widespread and significant tissue strains throughout the brain. The amount of shear strain is related not only to the amount of rotational acceleration, but also to the presence of intracranial dural compartments (e.g. falx, tentorium cerebri) and direction of motion.

In all, the intracranial pressure changes and brain motions due to translational accelerations have been linked most extensively to lesions such as coup and contrecoup contusions, intracerebral hematomas, subdural hematoma, and histological lesions in the brainstem region. Other lesions, however, such as diffuse axonal injury and gliding contusions, cannot be explained by the effects of translational acceleration.

Evidence for the importance of rotational acceleration in brain injury first appeared in experimental studies, and was soon followed with several theoretical or computational studies. Indeed, with the exception of epidural hematoma and injuries associated with skull fracture, rotational acceleration can produce every major form of brain injury. Using photoelastic gelatin skulls subjected to rapid rotation without impact, Holbourn (1943) reported that areas of high maximum shear stress coincided with brain lesions identifiable at autopsy. In contrast to the translational acceleration motions and pressures, these areas of high strain were throughout the brain and depended more on the geometric characteristics of the skull. Additional mathematical studies, complemented with experimental studies, have shown significant intracranial motions can occur for a range of rotational accelerations, and these motions are relatively unaffected by adding translational accelerations to these loading conditions (Meaney et al., 1993). Moreover, physical modelling studies indicate that regions of the brain experiencing large strains during rotational accelerations may differ depending upon the direction and orientation of acceleration (Margulies et al., 1990; Meaney et al., 1993). Currently, sophisticated finite element models of the brain (Willinger et al., 1992) are being used to understand the response of the brain to impact loading, and will assist in further delineating the effects of rotational acceleration on several forms of brain injury.

Experimental models of TBI play an important role in evaluating and understanding the complex physiologic, behavioural and histopathologic changes associated with TBI. Many of the preclinical models of TBI have been designed to mimic closely the clinical sequelae of human TBI. However, since human TBI is very much a heterogeneous disease, no single animal model of TBI can mimic the whole spectrum of clinical TBI. Rather, the concurrent use of a number of distinct yet complementary models is necessary to reliably reproduce the whole range of injury severity and characteristic features observed upon clinical and postmortem examination of TBI patients (Gennarelli, 1994; McIntosh et al., 1998a). Intensive experimental research over the past decades employing these preclinical models has contributed to our knowledge of these sequelae after TBI (Teasdale et al., 1999). The new understanding of these processes prompted the development of several novel diagnostic and treatment strategies, which are either now part of clinical standard practice or are under intense

preclinical and clinical investigation (McIntosh et al., 1998b).

Current concepts on the pathobiology of TBI

Brain trauma and neurodegenerative disease

(Graham et al., 1995)

Convincing epidemiological studies have implicated head injury as a risk factor for Alzheimer's disease (Mortimer et al., 1991; Gualtieri & Cox, 1991; Clinton et al., 1991). Brain damage associated with dementia pugilistica (punch-drunk syndrome) and associated memory loss and Parkinson-like symptoms include diffuse beta-amyloid (Aβ) deposits and neurofibrillary tangles (Roberts et al., 1991; Geddes et al., 1996), pathological hallmarks of Alzheimer's disease that have also been identified and associated with brain trauma. In experimental animal models, up-regulation of β-amyloid precursor protein (β-APP) has been reported to occur within hours following experimental TBI and is associated with axonal damage. This increased expression of β-APP has been observed following weight-drop brain injury (Lewen et al., 1995) and lateral FP brain injury in rats (Pierce et al., 1996, 1998). Laboratory studies of brain injury in rodents, however, have been unable to find evidence for diffuse or senile neuritic β-AP plaque deposits. Using transgenic mice which overexpress human β-APP twofold, recent studies have failed to note any evidence of Aβ plaques or worsened behavioural outcome after CCI brain injury (Murai et al., 1998). However, a subsequent study employing a strain of transgenic mice that overexpressed mutant human β-APP ten-fold showed evidence of exacerbated neuronal cell loss in vulnerable hippocampal regions, significantly impaired cognitive scores and increased regional concentrations of Aβ 1–42 with no evidence of amyloid plaque formation (Smith et al., 1998).

Diffuse Aβ plaques have also been reported in head-injured patients who died 6–18 days following brain trauma (Roberts et al., 1991). Subsequent studies employing larger series of patients showed that in 152 head injured patients, with survival times between 4 hours and 2.5 years, 30% of cases showed Aβ deposits. No correlation was observed between Aβ deposits and cerebral contusions, intracranial hematoma, ischemic brain damage, brain swelling or the pathology of raised intracranial pressure, suggesting that the deposition of this peptide may represent a consequence of the acute phase response of neurons to stress in susceptible individuals (Roberts et al., 1994; Graham et al., 1995). Conversely, other studies have been unable to detect any significant increase in Aβ deposits following human head injury (Adle-Biassette et al., 1996). Still other clinical studies have associated immunohistochemical detection of β-APP expression with the topography of axonal injury in head-injured patients (Gentleman et al., 1993).

Cytoskeleton-related neurodegenerative pathology

(Yaghmai & Povlischock, 1992; Smith et al., 1999)

In addition to amyloid plaques, Alzheimer's disease is characterized by neurofibrillary tangles, composed of hyperphosphorylation tau protein, which is believed to contribute to reduced binding to microtubules, with subsequent microtubule destabilization and disruption of axonal transport (Trojanowski et al., 1993). Neurofibrillary tangles in brains from ex-boxers also immunolabel for tau, suggesting tau pathology may be a feature of dementia pugilistica-associated neurodegeneration as well (Tokuda et al., 1991). In brain-injured humans, cleaved forms of tau proteins are markedly elevated in the CSF (Zemlan et al., 1999). Although little is known about alterations in tau in the traumatically injured brain, there is some indication that phosphorylated tau may accumulate in injured axons and cell bodies following experimental TBI (Kanayama et al., 1996; Smith et al., 1999). In addition, increased tau immunoreactivity has been observed in oligodendrocytes in the acute posttraumatic period following TBI in humans (Irving et al., 1996).

Many aspects of the neurofilament (NF) alterations, which accompany neurodegenerative diseases, are also present in the pathology of TBI. Increased NF immunoreactivity in axonal swellings, indicative of NF protein accumulation, is a well-established consequence of traumatic axonal injury (Yaghmai & Povlishock, 1992; Grady et al., 1993). This disruption of the neurofilamentous cytoskeleton and loss of NF proteins occurs in regions of grey and white matter following TBI (Posmantur et al., 1996; Saatman et al., 1998), although a transient increase in neurofilament immunoreactivity in injured neurons has been reported after brain injury of moderate severity in rats. Abnormal phosphorylation of NF proteins in neuronal cell bodies (Kanayama et al., 1996) and dephosphorylation of NF proteins in axons (Yaghmai & Povlishock, 1992) has been reported to occur after experimental TBI, paralleling changes in NF phosphorylation observed after axotomy and nerve crush (Rosenfeld et al., 1987). While it is not well appreciated how the neurofilament cytoskeleton contributes to the morbidity or mortality of TBI, transgenic mice expressing a NF fusion protein and exhibiting perikaryal NF accumulation subjected to experimental lateral fluid percussion brain injury had greater initial neuromotor dysfunction, slower recovery of function, and larger cortical lesions than their wild-type littermates after

TBI (Nakamura et al., 1999). Together, these data suggest that the study of neurodegenerative disease may provide great insight into the mechanisms and treatment of cytoskeletal pathology-associated TBI.

Calcium-mediated cytoskeleton proteolysis (McIntosh et al., 1998b; Doppenberg & Bullock, 1997)

Alterations in brain Ca^{2+} homeostasis (Maxwell et al., 1995; McIntosh et al., 1997) and receptors/channels associated with Ca^{2+} entry (voltage sensitive channels or ionophore-associated glutamate receptors such as *N*-methyl-D-aspartate-NMDA receptors) have been associated with regional cerebral edema, vasospasm, and delayed cell death. Traumatic, ischemic, or anoxic injury to neurons is associated with widespread neuronal depolarization (including the induction of cortical spreading depression) and releases excitatory amino acid neurotransmitters such as glutamate, leading to the opening of NMDA receptor-associated ion channels and influx of Ca^{2+} (Faden et al., 1989; Katayama et al., 1990). Marked post-traumatic increases in Ca^{2+} have been documented using ^{45}Ca-autoradiography and indirectly via cytochemical evidence for redistribution of membrane pump calcium-ATPase and ecto- Ca^{2+}-ATPase activity, and Ca^{2+} influx in myelinated nerve fibres of the guinea-pig optic nerve after stretch (Maxwell et al., 1995) and the analysis of calcium-mediated gene expression (McIntosh et al., 1997). Ca^{2+} channel blockers and competitive and non-competitive NMDA receptor antagonists have been shown to be efficacious in the treatment of experimental TBI (see McIntosh et al., 1998b for review), but to date have been disappointing in human studies (Doppenberg & Bullock, 1997).

Pathological elevations in intracellular Ca^{2+} after TBI can precipitate an attack on the lipid bilayer cell membrane via the activation of calcium-dependent phospholipases and generation of reactive oxygen species (ROS) (McIntosh et al., 1998b). These ROS cause direct peroxidative destruction of the cell membrane, oxidize cellular proteins and nucleic acids, and destroy the cerebral vasculature. Calcium can also activate non-lysosomal cysteine protease calpain, which can degrade a wide range of cytoskeletal protein substrates, including spectrin, microtubulin, microtubule-associated proteins MAP-1B, MAP-2, and the neurofilament protein family. The activation of calpain can be determined by direct detection of autolyzed calpain or indirectly via detection of calpain-specific proteolytic fragments. Several recent studies have documented both acute calpain activation and regional calpain-induced cytoskeletal proteolysis following experimental TBI (Saatman et al., 1996). Both the neuronal and axonal cytoskeletons appear to be vulnerable to calpain-induced proteolysis (Saatman et al., 1996) in laboratory models of brain injury and in human TBI (McCracken et al., 1999), and therapeutic strategies to block or antagonize the proteolytic effects of calpain on the cytoarchitecture of the cell have proven effective by attenuating both posttraumatic motor and cognitive deficits (Posmantur et al., 1996; Saatman et al., 1996).

Inflammation and cytokines: is TBI an inflammatory disease?

A great deal of recent attention has been paid to the potentially deleterious (and paradoxically beneficial) role of postinjury inflammation in mediating delayed neuronal damage following brain trauma. Alterations in blood-borne immunocompetent cells have been found in head-injured patients (Quattrocchi et al., 1992a,b), and since the blood–brain barrier is remarkably leaky in the acute post-traumatic period, entry into the brain of circulating immunocompetent cells may influence on neuronal survival and death. Infiltration and accumulation of polymorphonuclear leukocytes (PMNLs) into brain parenchyma has been associated with the development of posttraumatic edema (Schoettle et al., 1990), while pharmacological depletion of PMNL has been shown to improve outcome following experimental brain injury in rats. More recently, the infiltration of PMNLs into brain parenchyma has been documented in the acute (first 3 days) post-traumatic period following human head injury.

Head injury and programmed cell death pathways (Smith et al., 2000)

While necrotic cell death has been extensively documented after both clinical and experimental TBI, brain injury also appears to activate other pathological cell death cascades, including programmed cell death (PCD). Unlike necrosis, PCD involves the initiation and active expression of transcription and translation-dependent pathways in which apoptosis is regarded as the primary hallmark. Although necrosis and apoptosis have been more traditionally considered as distinct mechanisms, it may be possible to consider them to be part of the same continuum of cell death, particularly within the context of traumatic CNS injury. Using a combination of terminal deoxynucleotidyl transferase (TdT)-mediated biotinylated deoxyuridine trisphosphate (dUTP) nick end labelling (TUNEL) histochemistry with electron microscopy and DNA gel electrophoresis, it has been possible to identify apoptotic cells

after experimental lateral fluid percussion brain injury in the rat (Rink et al., 1995). These observations have been extended by demonstrating regional and temporal differences in apoptotic cell death cascades in astrocytes, oligodendrocytes and neurons some months after experimental traumatic brain injury in a number of TBI models (Yakovlev et al., 1997; Conti et al., 1998), and by the presence of apoptotic, TUNEL-positive neurons and oligodendrocytes in the tissue of surface contusions of human head-injured patients (Smith et al., 2000).

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Environmental toxins and neurological disease

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Toxic chemicals and natural products in the environment contribute to the burden of neurological disease. For this reason, research on environmental neurotoxins can increase our ability to identify and control preventable causes of these often incurable diseases. Several reviews have catalogued lists of chemicals and agents associated with human neurotoxicity, including solvents, metals, pesticides, and natural toxins of marine origin (OTA, 1990; NRC, 1992; IOM, 1991; Morris, 1999). Many toxic chemicals in the workplace, especially solvents and narcotizing agents, are regulated on the basis of their neurotoxic effects (OTA, 1990). Many biocides, including insecticides, fungicides, and rodenticides were deliberately designed to be neurotoxic to pest organisms (OTA, 1990). However, target sites in the nervous system are largely conserved across species, and desirable lethal effects in pests may engender undesirable neurotoxicity in humans.

The effects of both acute and chronic exposures to many neurotoxins have been well studied. However, there is at present considerable uncertainty about the role of neurotoxins in the long latency neurodegenerative diseases, such as Parkinsonism, dementia or progressive neuropathies. Recent epidemiological studies strongly suggest associations between certain pesticides and increased risks of Parkinsonism, and between chronic exposures to certain solvents and dementias of the non-Alzheimer type (Feldman, 1999). Detecting chemical etiologies of these neurological diseases is difficult, for two reasons: epidemiological resources and data on patterns of neurological disease incidence and prevalence are very limited, and there are few animal models of acquired neurological disease.

In this chapter, we discuss examples of neurotoxic agents associated with human disease and neurological impairments. We have selected examples that illustrate the importance of understanding differences in the effects of high dose acute exposures from the effects of low dose chronic exposures. In addition, for many neurotoxins the route of exposure and the age or developmental stage of the exposed individual determines the type of neurotoxic insult. In some cases, toxic agents by themselves damage the nervous system, while in other cases, these agents probably interact with host susceptibility factors, including genetics, to induce disease or to hasten the onset or increase the severity of disease.

Lead

The heavy metal lead may be the single most significant cause of neurotoxicity in human populations worldwide. Because of its long history of human use, especially its relatively recent use in automotive fuels, lead levels in human populations are significantly elevated, by orders of magnitude, over 'natural' levels in preindustrial or remote societies (Silbergeld & Nash, 2000). Residues from past uses continue to provide exposure sources, such as lead in soils from gasoline fallout, lead in paint in old housing, and lead in plumbing in some older water systems (Silbergeld, 1997).

The neurotoxicity of lead was well understood by early medical writers, including its effects on the central and peripheral nervous system (Hamilton, 1925; Lin-fu, 1985). In the eighteenth and nineteenth centuries, Ramazzini, Tanquerel des Planches, and Oliver all described neuropsychiatric problems in lead workers, along with weakened neuromuscular function (lead palsy). These writers

* Neuropathic disorders due to environmental or industrial use agents with neurotoxic properties (acrylamide, arsenic, hexacarbons, organophosphates and others) may be found in the text and tables of Chapter 66.

Table 112.1 Meta-analysis, studies of the lead IQ relationsip

References	Year	*n*	Effect size	Power to detect small effect	*P*<
Perino et al.	1974	80	0.6	0.2	0.025
Needleman et al.	1979	73	0.35	0.47	0.015
Yule et al.	1981	82	0.573	0.42	0.021
Winneke et al.	1983	115	0.351	0.25	0.4
Harvey et al.	1984	48		0	
Shapiro & Maracek	1984	193	0.46	0.48	0.025
Lansdown et al.	1986	162	0.07	0.48	0.66
Hansen et al.	1987	82	0.5	0.34	0.0005
Hawk et al.	1986	75	0.64	0.25	0.0004
Schroeder et al.	1985	104	0.5	0.33	0.005
Fulton et al.	1987	501	0.4	0.52	0.003
Hatzakis et al.	1987	509	0.4	0.52	0.00065

Notes:
Sum $x = 109.13$
$P = 2.97 \times 10^{-12}$
Source: Table from Silbergeld (1997). See Needleman et al. (1990) for original citations.

noted that lead neurotoxicity was associated with both acute, high dose exposures, and also, insidiously, with low dose chronic exposures. When the manufacture of tetraethyllead began in the 1920s to supply antiknock additives to gasoline, florid neuropsychiatric symptoms, and deaths, were encountered by workers at DuPont's Deepwater facility in New Jersey (Rosner & Markowitz, 1985).

In the late nineteenth century, physicians noted that children were also, and possibly especially, at risk of lead neurotoxicity. Lockhart Gibson, in 1897, first described painted surfaces as a hazard to young children (Gibson, 1904); Oliver in 1914 referred to lead as a 'race poison' because of its abortifacient effects, fetotoxicity, and adverse effects on mental development of young children (Oliver, 1914). The often fatal effects of lead 'encephalitis' were frequently reported from large cities in the US throughout the 1920s and 1930s (Silbergeld, 1997). In 1943, Byers and Lord first reported that mental retardation and behavioural problems persisted in young children exposed to levels below those causing frank or acute encephalopathy (Byers & Lord, 1943; Silbergeld, 1997).

Starting in the 1970s, with new emphasis on environmental health in the USA through the creation of the Environmental Protection Agency, clinicians and researchers began to focus on understanding the nature of lead neurotoxicity in children. Some of the first indications that early lead exposure, at what were considered 'subclinincal' exposures, was associated with persistent and significant neurotoxic effects in children came from prospective studies of children's development in which some subjects became lead exposed during the study (Silbergeld, 1997). Over the next 20 years, a body of epidemiological and toxicological research produced an extraordinarily convergent literature on the nature of chronic, low dose lead neurotoxicity in young children (Rice & Silbergeld, 1996). The functional manifestations of chronic, low level lead toxicity in young children involve decrements in cognitive function, problems in sustained attention, and behavioural problems involving aggression and social behaviours. A meta-analysis of the effects of lead on cognitive performance was conducted by Needleman and coworkers, as shown in Table 112.1.

Many of the neurotoxic effects of lead appear to persist and may possibly be amplified years after lead exposure ceases (Needleman et al., 1990). Lead toxicity may recur as internal lead stores change over aging, as reported for postmenopausal women (Nash et al., 1998).

Mechanistic research has provided information on how lead affects the peripheral nervous system, the development of the CNS, and the functional manifestations of cognitive impairments, inattention, and aggressiveness (Rice & Silbergeld, 1996). The consensus of this research can be summarized as follows: lead interferes with neuronal signaling, at the level of transmitter release and receptor transduction, largely related to those processes requiring calcium (such as voltage-dependent transmitter release, calmodulin-regulated signal transduction, and synaptic strengthening). In the developing brain this interference

with intercellular signalling affects the neuromorphology of development, since firing supports wiring at this stage. A recent study found that relatively low dose lead exposure induces significant alterations in specific cortical nuclei within the somatosensory areas of the rat brain (Wilson et al., 2000). Cory Slechta and colleagues have reported persistent changes in NMDA and dopaminergic pathways in the midbrain and cortex of lead-exposed rodents (Cory-Slechta et al., 1996a,b, 1997, 1998; Cory-Slechta, 1997).

Lead is also neurotoxic for adults. Several reviews and meta-analyses of lead neurotoxicity in adults demonstrate consistent impairments in certain performance tasks requiring attention and appropriate motor function.

Because of the ubiquity of lead exposures in the biosphere and its continued uses in many countries, lead will continue to be a major neurotoxin of public health significance. Excess exposures are reported in many developing countries, especially in India and other regions where lead is still used in gasoline, in workers and families involved in or living near cottage industries (Jamaica; Manila), in persons using lead compounds as traditional medicines and in low-fired pottery glazes (Silbergeld, 1995). Vigilance is especially necessary to identify lead exposures, by means of blood lead screening, prior to the induction of characteristic symptoms. This is because such symptoms usually appear at exposures associated with severe and persistent neurological damage and because as with many neurotoxins these symptoms are not unique to lead.

Manganese

Manganese (Mn) neurotoxicity poses a major challenge since, contrary to many other toxic substances such as lead and mercury, which are not required by normal biological processes, Mn is an essential element, particularly for nervous system development. Both deficiency and overload can result in neurological disorders.

The normal daily requirement for Mn is obtained through food intake. Approximately 3–5% of dietary intake is absorbed, and subjected to homeostatic control through the hepatic portal system. The principal route of excretion is in feces. Most absorbed Mn is transported in plasma bound to a gamma globulin, probably transferrin. The biological half-life of Mn in the body is about 37 days, but in brain, which Mn readily accesses, the half-life is two to three times longer.

Recent studies have shown that, when hepatic control mechanisms are damaged through liver dysfunction or bypassed during parenteral nutrition, blood manganese levels (MnB) increase (Andersen et al., 1999). Magnetic resonance imaging (MRI) of patients with these conditions indicates subsequent dose-related build-up of Mn in the basal ganglia, particularly in the pallidum; some patients, but not all, display neurological symptomatology (Krieger et al., 1995; Hauser et al., 1996; Pomier-Layrargues et al., 1995; Bertinet et al., 2000).

The risk for overexposure to Mn through inhalation of airborne Mn was first demonstrated in workplace studies. Airborne Mn enters the lungs and the small, 'respirable' particles are absorbed through the alveoli, thereby bypassing the hepatic control mechanisms. Animal studies suggest that there may be a further mechanism of Mn uptake in the brain through the olfactory epithelium (Tjalve et al., 1996; Tjalve & Henriksson, 1999; Gianutsos et al., 1997; Vitarella et al., 2000).

Occupational exposures include manganese ore mining, manganese alloy production, welding (particularly soft-steel), dry alkaline battery manufacture, and manganese oxide and salt production, as well as work with agrochemicals containing manganese such as the fungicides maneb and mancozeb. These fungicides serve as seed protectants and foliar fungicides on a wide variety of small fruits and vegetables as well as banana plantations. Registered uses for these fungicides have been reduced in North America, but they are still used extensively in developing countries,

Neurologic damage in Mn exposed workers was first documented in 1837 by Couper, who described a condition resembling Parkinsonism in five pyrolusite mill workers who inhaled manganese oxide (Couper, 1837). Since that time, hundreds of cases of manganism, characterized by exytrapyramidal dysfunction and neuropsychiatric symptomatology, have been reported among industrial workers and miners throughout the world (Cook et al., 1974; Mena et al., 1967; Wang et al., 1989; Cotzias, 1958; WHO, 1981). Although manganism bears many similarities to Parkinsonism, it differs in clinical presentation and neuropathology (Calne et al., 1994; Pal et al., 1999). Within several months symptoms can progress to include posture and gait dysfunction, a characteristic dazed facial expression (masque manganigue), spasmodic laughing, and generally slow and clumsy movements. In the final stages of disease, disorders of walking become more severe; the inability to walk backwards due to severe retropulsion is a diagnostic feature (Huang et al., 1989). The characteristic neuropathology of manganism is degeneration of the basal ganglia, principally the medial segment of the globus pallidus and the substantia nigra pars compacta, although other areas of the brain may be affected (Larsen et al., 1979; Yamada et al., 1986; Newland et al., 1989). Manganism is a progressive disorder and neurodegeneration can continue even after

the cessation of exposure (Huang et al., 1998; Meco et al., 1994; Nelson et al., 1993). Active workers, without clinical disease, can display preclinical signs and symptoms of manganism (Tanaka & Lieben, 1969; Ferraz et al., 1988; Schuler et al., 1957). Recent studies have shown a consistent profile of nervous system deficits among Mn-exposed workers, involving poorer hand–eye coordination, motor slowing, increased tremor, reduced response speed, olfactory enhancement, mood changes, diminished libido, and some memory and intellectual deficits (Iregren, 1994, 1999; Mergler & Baldwin, 1997). In workers with long-term exposure to Mn, prolactin levels are increased (Smargiassi & Mutti, 1999) and MRI results shown Mn accumulation in the palladium (Lucchini et al., 1999).

Concern about environmental exposure to Mn has increased over the past years with the use of an organo-manganese gasoline additive, methylcyclopentadienyl manganese tricarbonyl (MMT). Introduced in Canada in 1976, MMT utilization in that country increased substantially until it completely replaced tetraethyl lead by 1990. Canadian studies show that atmospheric concentrations of Mn increase with traffic density, and in areas with high traffic density they can surpass the US EPA reference concentration (RfC) of 0.05 $\mu g/m^3$ for respirable Mn (Zayed et al., 1999). MMT is now approved for use in Argentina, Australia, Bulgaria, Russia, the United States, France and conditionally in New Zealand. Nevertheless, because of the lack of adequate information on its toxicological properties and possible health effects, gasoline manufacturers in some countries have been hesitant to use MMT.

There have been few studies on the effects of environmental exposures to Mn. In Japan, an episode of 16 cases of Mn poisoning resulted in four deaths, due to high levels of Mn in drinking water (20–30 mg Mn/l) from contaminated wells around which 300 dry cells had been buried (Kawamura et al., 1940). Two community studies have been carried out in areas with high levels of Mn in well water. The first, performed in Greece (Kondakis et al., 1989) among men and women aged 50 years and over, showed a progressively increasing prevalance of subclinical Parkinsonian symptoms with increasing Mn concentrations in drinking water, ranging from 0.004–0.015 mg/l in the lowest group to 1.80–2.39 mg Mn/l in the highest group. Older people appeared to be more susceptible to the effects of manganese. However, a second study compared two cohorts from rural Northern Germany, exposed to well water with high (mean of 0.300 mgMn/l, range of 0.300 to 2.106) or low manganese content (less than 0.050 mgMn/l) for up to 40 years. These authors found no neurological deficits associated with Mn exposure, and conclude that Mn in drinking water is not a risk factor (Vieregge et al., 1995).

Two reports from China describe a study of 92 children aged 11–13 years who lived in an area with moderately high Mn levels in drinking water (0.24–0.35 mg/l) due to extensive field irrigation with sewage products (He et al., 1994; Zhang et al., 1995). Neurobehavioural performance of the exposed children was significantly lower, and negative correlations between Mn in hair and most endpoints were reported. These results are consistent with an earlier reports of higher hair Mn levels in learning disabled than in normal children (Collipp et al., 1983).

A recent community based study, carried out in Canada, examined the neurotoxic effects of manganese from various environmental sources (Mergler et al., 1999; Bowler et al., 1999; Hudnell, 1999; Baldwin et al., 1999; Beuter et al., 1999). The highest levels of airborne Mn were observed downwind of the site of a former Mn alloy production plant and in the region of highest traffic density. Although blood Mn concentrations were lower than those observed among Mn exposed workers, it was significantly higher in the region with higher airborne Mn. Blood Mn (MnB) was higher among women than men, increased with consumption of cereals and leafy vegetables and paralleled airborne MnB levels in areas with higher airborne Mn (Baldwin et al., 1999). Higher MnB levels were associated with poorer performance on tasks involving coordinated movements of the upper limbs and changes in tremor parameters; among men, increasing MnB was significantly correlated to poorer postural stability, slower learning and recall and depressed near visual contrast sensitivity (Hudnell, 1999; Mergler et al., 1999; Beuter et al., 1999). An age-Mn interaction was observed, with poorest performance among those >50 years in the higher MnB category (>7.5 $\mu g/l$) (Mergler et al., 1999; Beuter et al., 1999). Mood states likewise showed an age–Mn interaction for men (Bowler et al., 1999).

Overall, the results of the studies on Mn neurotoxicity suggest that, depending on the intensity and duration of exposure, nervous system deterioration is on a continuum of dysfunction. Mn metabolism is complex and appears to be sex related. Manganese may accelerate the aging process, which would have important consequences for the onset of neurodegenerative disorders and the well-being of the elderly.

Aquatic neurotoxins (Table 112.2)

Potent neurotoxins can be secreted by harmful algal blooms (HABs), the devastating result of toxic-producing bacteria, algae, or dinoflagellates. All are single-celled eukaryotic organisms which flourish in marine and estua-

Table 112.2. Marine neurotoxins – source, exposures and toxicity

Toxin	Source (organism)	Exposures	Toxicity
CTX	*Gambierdiscus toxicus*	Via consumption of fish, especially carnivorous	GI; paresthesias; motor dysfunction; low mortality
STX	*Gonyaulax Alexandrinum* spp.	Via shellfish (red tide)	GI; paresthesias; motor flaccidity; apnea; neuropathy; moderate mortality
TTX	Unknown	Via fish, amphibians, shellfish	GI; paresthesias, bulbar and motor sign; apnea; high mortality
Brevetoxins	*Gymnodinium breve*	Via shellfish	GI; paresthesia; rhinorrhea; bronchospasm; low mortality
Domoic acid	*Nitzschia pungens*	Via shellfish and crabs	GI; paresthesia; neuropathy; seizure; soma; amnesia; low mortality
Okadaic acid	*Diophysis* spp.	Via shellfish	GI; diarrhea; nausea; chills; no mortality
Pfiesteria toxin	*Pfiesteria piscicida* (?)	Contact with water	Paresthesias; amnesia; psychological disturbances; impaired psychometric function; no mortality

Source: Taken from Silbergeld et al. (2000).

rine environments. Increasing awareness of HABs as a major health threat has spurred research on these harmful aquatic micro-organisms, and increased regulation of the seafood industry (Morris, 1999). HABs have been responsible for massive fish kills, alterations in marine habitats, and severe human illness through ingestion of affected fish and shellfish (Silbergeld et al., 2000). The production of toxins, both water and lipid soluble, has been demonstrated for approximately 60 of the over 2000 known dinoflagellate species. Toxic blooms along the coastal United States afflict hundreds of Americans annually; in countries with poor surveillance and response measures incidence rates are much higher (Morris, 1999). These events can constitute serious public health problems, in addition to deleterious effects on the environment. The occurrence of HABs is poorly predicted, either temporally or geographically, with existing methods. Thus, prevention of harmful effects depends on strict surveillance of marine environments, routine screening of seafood, and rapid response when an outbreak occurs.

Paralytic shellfish poisoning (PSP)

Paralytic shellfish poisoning results from the consumption of shellfish that bioaccumulate saxitoxins, fast-acting sodium channel blockers, produced by dinoflagellates such as *Alexandrium tamarensis* and *Alexandrium catenella*. Effects are primarily neurological, including paresthesias, ataxia, dysarthria, and confusion within an hour of ingesting contaminated shellfish. Death, due to respiratory paralysis, can occur in severe exposures. In Alaska between 1973 and 1992, PSP was responsible for 117 illnesses and one death (Gessner & Middaugh, 1995). The estimated cost of a single outbreak of paralytic shellfish poisoning in Maine was estimated to be $6 million in medical costs and lost productivity (Shumway et al., 1988).

Neurotoxic shellfish poisoning (NSP)

The brevetoxins, produced by the dinoflagellate *Karenia brevis* (formerly *Gymnodinium breve*) are the cause of neurotoxic shellfish poisoning, characterized by gastrointestinal symptoms, cramping, nausea, diarrhea, and vomiting (Hughes & Merson, 1976). Aerosolization of the brevetoxins can cause illness following inhalation, including respiratory stress and eye irritation. In 1987–1988 a bloom in North Carolina lasting several months affected 48 persons with symptoms severe enough to seek medical attention, and cost the coastal community an estimated $25 million in lost seafood and tourist revenue (Tester & Fowler, 1990). On the southwest coast of Florida, where blooms occur annually, this NSP was responsible for the deaths of 150 manatees in 1996.

Ciguatera poisoning

Ciguatera poisoning results from the consumption of predatory coral fish which accumulate toxins produced by the coral-associated dinoflagellate *Gambierdiscus toxicus*. These toxins are heat stable, and thus not inactivated by cooking fish. They bioaccumulate through the food chain, so that the larger predatory fish are the most toxic. Affected

individuals suffer gastrointestinal pains, including nausea, cramping, vomiting, and diarrhea, as well as neurological symptoms that include paresthesis, pain and weakness of the limbs, paradoxical temperature dysesthesia (cold feels hot), and 'aching teeth' (Morris, 1999). Acute toxicity may result in coma and, in severe cases, death. In Miami between 1972–1976, 129 cases of ciguatera poisoning were reported to local Health Departments (annual incidence of 5 cases/100 000 population/year) (Lawrence et al., 1980). In the South Pacific 219 cases/100 000 population were reported in 1987; the high incidence makes development of a seafood industry impossible, although the local population still eats local catch ((Glaziou & Legrand, 1994).

Amnesic shellfish poisoning (ASP)

In 1987 a dramatic new shellfish poisoning was first described in Prince Edward Island (Perl et al., 1990a,b). Following consumption of mussels, patients suffered acute gastrointestinal pain, nausea, diarrhea, and headache. But most disturbing of all, severely afflicted patients suffered permanent memory disturbances, profound loss of anterograde memory, neuronal degeneration in the hippocampus and amygdala, seizures, and, in several cases, death. The toxin responsible, domoic acid, is produced by the diatom *Pseudonitzschia*, and has been shown to act as an excitatory neurotoxin, irreversibly binding to glutamate receptors (specifically the MK801 and NMDA receptors), inducing excitotoxic neuronal death. In the spring of 1998, domoic acid was demonstrated to be the cause of severe neurologic symptoms and deaths in Californian sea lions following ingestion of contaminated anchovies (Lefebvre et al., 1999) confirming an ongoing need for monitoring of diatom and algal blooms, regular screening of fish and shellfish for toxicity, physician awareness, and public health surveillance systems.

Pfiesteria piscicida

The recent recognition of *Pfiesteria piscicida* as a neurotoxic dinoflagellate with severe human health effects provides an example where astute clinicians working closely with public health officials were able to limit toxic exposure and prevent further injury (Silbergeld et al., 2000). Although estimated to be at least several thousand years old, current thinking is that *P. piscicida* is usually present as a non-toxic predator, feeding on bacteria or algae. It was first introduced to researchers as an unknown contaminant of aquacultures in North Carolina in 1988 (Smith & Music, 1998; Glasgow et al., 1995). In 1991 it was associated with a fish kill event involving over 1 million Atlantic Menhaden in the Pamlico River, North Carolina (Smith & Music, 1998). Subsequently, other estuaries and outdoor aquaculture facilities in North Carolina suffered *P. piscicida*-associated fish kill events (1991–1993); in the summer of 1996 the organism was detected in the Chesapeake Bay (Morris, 1998). It was identified as the causative agent of both fish kill events and a novel human health syndrome in Maryland's Chesapeake Bay in 1997 (Silbergeld et al., 2000; Glasgow et al., 1995; Levin et al., 1999; Matuszak et al., 1997). *Pfiesteria* is ubiquitous in estuarine waters along the Eastern coast of the USA, from Florida to Delaware, mainly in its non-toxic forms, and research efforts are currently under way to better define/predict the environmental conditions (temperature, salinity, nutrient-load, pH, etc.) which 'trigger' production of toxins.

From an environmental and human health perspective, *Pfiesteria* came on like a lion, effecting swift and dramatic damage, both in terms of fish kills, and in terms of wreaking severe, long-lasting neurological damage. Lab researchers, watermen, and recreationists were affected, making it a hazard of great concern to the general public (Faith & Miller, 2000; Silbergeld et al., 2000; Burkholder, 1999; Fleming et al., 1999). Lab researchers exposed to toxic *Pfiesteria* culture by skin contact and inhalation of aerosolized toxin experienced neurocognitive impairments and emotional disturbances, in addition to gastrointestinal pain, respiratory stress, eye irritation, and localized dermatitis (Glasgow et al., 1995). Although the severely affected underwent clinical tests, which included electroencephalogram, MRI, and PET analysis, no site of organic damage could be determined. Neuropsychological examinations of Maryland watermen who reported to physicians during and immediately following a large fish kill event in 1997 revealed common symptoms of fatigue, confusion, headaches, and some respiratory irritation. Skin rashes were spotted in areas coinciding with water contact. All reports coincided with fish-kill events. Epidemiological studies following the investigation of the 1997 oubreak in Maryland resulted in a defined symptomatology correlated with a dose-dependent exposure to *Pfiesteria piscicida*. Of the people exposed at high doses many suffered neurological symptoms (confusion, disorientation, difficulty concentrating on a task, forgetfulness), headache, muscle/leg cramps, and skin lesions. These watermen showed dose-dependent deficits in performance on neuropsychological examination, particularly in tasks requiring divided attention, new learning, and memory (Grattan, 1998; Grattan et al., 1998a,b). Interestingly, tests for possible respiratory, immunogenic, or other physiological dysfunction proved negative.

The isolation and characterization of the precise toxin, or toxins, produced by *P. piscicida* has been difficult.

Evidence suggests that the fish kill event signals the final outcome of toxicity, at which time the toxic agent may no longer be present. Several reporter gene assays have recently been developed with the hope that screening water for presence of toxic organisms may be a rapid, routine procedure (Fairey et al., 1999). In addition, gene-screen assays have been developed to detect the organism based on a species-specific sequence of the small-subunit (18S) rRNA (Oldach et al., 1998). A reliable screen for the presence of toxin in biological samples (urine or sera) is needed for diagnostic certainty. Mounting evidence of the dramatic neurotoxicity of *P. piscicida* is based on observation of neurobehavioural changes and death in exposed fish, and impaired learning and memory formation in rats following ingestion and injection of toxic culture (Levin et al., 1999). Cytotoxicity has been demonstrated in vitro, in both piscine- and mammalian-derived cell lines. Media from toxic aquaculture samples can induce alterations in the transcription of regulatory proteins (Fairey et al., 1999). Recent studies suggest that *pfiesteria* toxins may act as antagonists at the *N*-methyl-D-aspartate (NMDA) receptor (El-Nabawi et al., 2000) which is known to be involved in learning and memory formation.

Role of clinicians in identifying an outbreak

The role of clinicians in the identification of toxic exposures cannot be overstated. Clinical practitioners are relied upon to identify alterations in the normal patterns of diseases. Increases in the number or severity of cases and/or clustering of cases by occupation or geographic location may suggest an environmental etiology. Recognizing changes in the patterns of disease is made difficult by the paucity of information available on the background incidence and prevalence of many major neurological diseases. Characterization of neurological effects of an environmental exposure is made more difficult by the range of individual reactions to an exposure, complicated by gender, age, dose, and confounding factors like smoking, diet, and general health. If disease progression is slow, onset of clinical symptoms may be months or even years after exposure. All these complications point to the need for careful and complete documentation of clinical observations, and data collection through formal surveillance systems. The documentation of an exposure and occupational history, including possible exposure sources such as hobbies, self-medication, eating habits, and recent travel history, is critical. The sharing of information between physicians other health professionals, existing disease surveillance systems, and public health departments facilitates the rapid formation of a case definition and development of a case series. The public health response is crucial in limiting or preventing a disease outbreak.

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Alcohol neurotoxicity

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Alcoholism and alcohol abuse

Alcoholism is a chronic disease characterized by addiction to ethanol; the alcoholic craves and consumes alcoholic beverages without apparent satiation. Alcoholics are remarkably tolerant to the intoxicating effects of ethanol. When drinking is discontinued, however, they exhibit the neurological symptoms and signs of alcohol withdrawal; this is considered to be evidence of physical dependence on ethanol. Addiction to ethanol also occurs as a secondary complication in patients with specific neuropsychiatric disorders, but the vast majority of alcoholics do not have an antecedent history of major psychiatric disease; they are considered to have primary alcoholism. Alcohol abuse is characterized by prodigious drinking without evidence of physical dependence upon withdrawal. Such individuals continue to drink excessively, sometimes as binge drinkers for several days at a time, despite considerable personal socioeconomic hardship and serious medical complications.

Epidemiology

Almost two-thirds of Americans older than 14 years of age drink alcoholic beverages. The per capita ethanol consumption in this group is the equivalent of nearly 90 gallons of beer, 31 gallons of wine, or 10 gallons of whisky per year (*Seventh Special Report to the US Congress on Alcohol and Health, 1990*). However, only 7% of Americans are heavy drinkers. This small group accounts for approximately 50% of the alcohol consumed in the USA and probably most of the socioeconomic and medical complications of alcoholism and alcohol abuse. These alcohol-related complications are not trivial; in 1990, the annual cost to US society is estimated to have been $136 billion (*Seventh Special Report to the US Congress on Alcohol and Health, 1990*). The prevalence of alcoholic disorders among hospitalized patients is about 25%.

Clinical pharmacology of ethanol

Ethanol is rapidly and completely absorbed from the gastrointestinal tract into the circulation within minutes after drinking (Goldstein, 1983). It is then widely distributed to all organs and fluid compartments in the body, readily equilibrates into total body water, and intercalates into biologic membranes. Ninety to 98% of ethanol is removed by metabolism in the liver, and the remainder is excreted by the kidneys, lungs and skin. An important rate-limiting step in ethanol metabolism is oxidation to acetaldehyde by alcohol dehydrogenase in the liver. Acetaldehyde is then converted to acetate by aldehyde dehydrogenase, a metabolic step with significant clinical ramifications.

Ethanol intoxication

Clinical features

Because of the solubility properties of ethanol, it readily crosses the blood–brain barrier and its uptake into the brain is limited primarily by cerebral blood flow and capillary perfusion. Therefore, within a short time after drinking, the concentration of ethanol in the brain is nearly identical to the level of ethanol in the blood. In non-alcoholics, rising blood alcohol levels of 50–150 mg/dl are associated with symptoms of intoxication. Symptoms vary directly with the rate of drinking and are more severe when the blood alcohol concentration is rising than when it is falling (Goldstein, 1983).

Table 113.1. Acute ethanol intoxication

Blood ethanol levels (mg/dl)	Symptoms and signs	
	Sporadic drinkers	Chronic drinkers
50–100	Euphoria Gregariousness Incoordination	Minimal or no effect
100–200	Slurred speech Truncal ataxia Labile mood Drowsiness Nausea Impaired cognition	Sobriety or incoordination Euphoria
200–300	Lethargy Combativeness Stupor Incoherent speech Vomiting	Mild emotional and motor changes
300–400	Coma	Drowsiness
>500	Respiratory depression Death	Lethargy Stupor Coma

Many of the effects of acute ethanol intoxication are indicated in Table 113.1. Most individuals feel euphoric, lose social inhibition, and manifest expansive, sometimes garrulous behaviour; others may become gloomy, belligerent, or even explosively combative. Some people do not experience euphoria but instead become sleepy after moderate drinking; they rarely abuse alcohol. With continued drinking, cerebellar and vestibular function deteriorates and at higher blood ethanol levels the findings of central nervous system (CNS) depression predominate. Progressive lethargy leads to hyporeflexia, hypotension, depression of the brainstem respiratory centre, and coma without focal signs. In non-alcoholics, fatalities may occur at 500 mg/dl, usually because of respiratory depression with ventilatory acidosis and hypotension. Alcoholics are more resistant to ethanol than non-alcoholics (Johnson et al., 1982; Lindblad & Olsson, 1976; Urso et al., 1981; Watanabe et al., 1985).

Acute tolerance

A slow rise in blood ethanol levels produces less intoxication than a more rapid rise to the same concentrations. Moreover, intoxication may not always be present when blood ethanol concentrations are elevated (see Table 113.1). Tolerance to ethanol may develop during a single bout of drinking (Goldstein, 1983; Victor & Adams, 1953) and is characterized by a reduced intoxicating response to ethanol. Indeed, subjects can become sober at blood ethanol levels higher than those at which intoxication first developed (Mirsky et al., 1941). This phenomenon is known as acute tolerance and appears to be due primarily to adaptive CNS changes.

Chronic tolerance

The magnitude of increased tolerance to ethanol in chronic alcoholics is not often appreciated. Chronic alcoholics have increased resistance to the intoxicating effects of ethanol and can appear to be sober or merely drowsy at blood alcohol levels of 400–500 mg/dl (Urso et al., 1981), concentrations that are severely intoxicating or even fatal in naïve individuals (see Table 113.1). This is known as chronic tolerance. A serum ethanol level of 1510 mg/dl was documented in an ambulatory chronic alcoholic, who had stopped drinking 3 days earlier (Lindblad & Olsson, 1976). Despite legal definitions of intoxication at blood alcohol levels above 80–100 mg/dl, a single blood ethanol determination may not accurately measure the extent of drunkenness (Urso et al., 1981).

Alcoholic blackouts

Alcoholic blackouts sometimes complicate acute alcohol intoxication during excessive drinking. These episodes can occur in alcoholics or sporadic drinkers and are characterized by hours of amnesia without impaired consciousness. The patient reports an inability to remember new events, but has no difficulty with long-term memory or immediate recall. These symptoms resemble the syndrome of transient global amnesia.

Evaluation and management of acute ethanol intoxication

Severe acute alcohol intoxication can be fatal and is a medical emergency. The airway must be evaluated immediately if the patient is stuporous and unable to walk. Masked hypoventilation, accumulating secretions, and coma are all indications for endotracheal intubation and assisted ventilation. If the blood alcohol level is too low to account for the patient's obtundation or if improvement does not occur as expected, it is necessary to search for other causes, such as hypoglycemia, meningitis, subdural hematoma, and hepatic encephalopathy. Evidence of head trauma or focal or lateralizing neurologic signs suggests an

urgent intracranial pathologic condition. Gastric lavage may be performed if obtundation is due to recent and substantial alcohol ingestion but only after endotracheal intubation. Thiamine (100 mg) should be given parenterally to each patient to prevent or treat Wernicke's encephalopathy (see later), followed by daily thiamine and multivitamins.

Intoxicated patients without serious medical problems, who have adequate vital signs and acceptable mental status can be observed until they become sober. However, it is important to search for commonly associated complications, such as hypoglycemia, ketoacidosis, hypokalemia, hypophosphatemia, hypomagnesemia and anemia.

Alcohol withdrawal syndrome

Ethanol is a CNS depressant. The nervous system appears to adapt to chronic ethanol exposure through neural mechanisms that counteract alcohol's depressant effects. When drinking is abruptly reduced or discontinued, these adaptive changes appear to persist unopposed by ethanol and a hyperexcitable *ethanol withdrawal* syndrome develops (Porter et al., 1990). It is considered to be evidence of physical dependence on ethanol. The clinical features of the ethanol withdrawal syndrome consist of several characteristic abnormalities that vary in severity (Victor & Adams, 1953). These include tremulousness, disordered perceptions, convulsions, and delirium tremens (Table 113.2). The same general medical evaluation and treatment of the ethanol withdrawal syndrome should be followed as for acute ethanol intoxication (described earlier).

Table 113.2. Alcohol withdrawal syndrome

Time	Clinical features
8 h	Onset of tremors, anxiety, irritability, nausea, vomiting
24 h	Increasing tremors, hyperexcitability, insomnia
12–48 h	Hallucinations, grand mal seizures
2–5 d	Delirium tremens
	Profound confusion
	Delusions
	Vivid hallucinations
	Agitation
	Autonomic nervous system hyperactivity

Tremulousness and disordered perceptions

Tremor, the earliest, most common, and most apparent symptom, begins about 6–8 hours after the last drink, usually the morning after an overnight abstinence (morning shakes). The tremor is diffuse, rapid and coarse in amplitude and resembles other accentuated physiological tremors. It is often accompanied by irritability, nausea and vomiting. The patient usually senses an inner tremulousness even when tremor is not severe. Self-treatment is commonly a morning drink to 'quiet the nerves', and the drinking is continued for the rest of the day. If drinking is not resumed, tremor becomes much more intense by 24–36 hours later and is exacerbated by motor activity or stress. It can be so severe as to interfere with walking, eating or speech. Accompanying symptoms and signs of sympathetic hyperactivity are also apparent.

The patient is increasingly anxious, easily startled by minor stimuli, and complains of insomnia and anorexia. Increased sweating, facial flushing, mydrasis, tachycardia, mild hypertension and hyperreflexia occur. Although most abnormalities subside in a few days, increased arousal and anxiety may persist for 2 weeks. Elevated levels of norepinephrine and its metabolites have been measured in the blood and cerebrospinal fluid of patients during the withdrawal syndrome (Hawley et al., 1981).

Disordered perceptions may parallel the development of tremor and sympathetic hyperactivity. They become most pronounced at 24–36 hours and clear in a few days. Ordinary visual, auditory and tactile experiences become distorted and are misinterpreted. Vivid nightmares interfere with sleep.

Alcoholics undergoing withdrawal can develop isolated and more prolonged auditory hallucinations (alcoholic hallucinosis) despite being alert, oriented, and without memory deficits. Because auditory hallucinations can persist for weeks after other manifestations of ethanol withdrawal improve, these symptoms may be confused with acute schizophrenia. However, alcoholic hallucinosis is easily distinguished by its close association with ethanol withdrawal; symptoms usually subside in weeks to months.

Management of ethanol withdrawal tremors and disordered perceptions

Benzodiazepines are quite effective in the management of ethanol withdrawal tremors and disordered perceptions. The goal of treatment is to suppress symptoms and produce mild sedation; drug dosage is adjusted to the severity of the withdrawal syndrome. Patients with mild tremulousness and few associated symptoms usually respond to 5–20 mg diazepam orally every 4–6 hours. Dosage is then reduced on successive days or increased if symptoms of ethanol withdrawal return. If symptoms are

severe, diazepam is used intravenously; some patients may require extraordinarily high doses to achieve mild sedation. When the symptoms of ethanol withdrawal have been suppressed, it is necessary to avoid oversedation and the danger of respiratory depression by carefully titrating the dose of diazepam to just keep the patient calm.

Ethanol withdrawal convulsions

A small percentage of alcoholics (approximately 12% of hospitalized patients) develop generalized tonic–clonic convulsions, most often within 6–24 hours after they reduce or discontinue ethanol consumption (Victor & Adams, 1953). Ethanol withdrawal convulsions are usually associated with a history of chronic daily consumption, but binge drinking can also be followed by withdrawal seizures. Normally, generalized tonic–clonic seizures are observed. Focal seizures are rare and should always suggest a focal lesion and an additional diagnosis. Alcoholics who have seizures during one episode of ethanol withdrawal are likely to have convulsions again when alcohol withdrawal is repeated. Status epilepticus occurs in only about 3% of cases; although, ethanol withdrawal accounts for about 15% of all patients who present with status epilepticus (Aminoff & Simon, 1980).

Evaluation and management of ethanol withdrawal convulsions

Ethanol withdrawal seizures usually are brief and self-limited. A complete evaluation for a convulsive disorder is indicated if there is a clinical suspicion of trauma or other CNS disorder, if there are focal seizures, or if the seizure disorder or postictal state is prolonged. Typical ethanol withdrawal convulsions do not require specific anticonvulsant therapy. Benzodiazepines (diazepam, loraxepam and chlordiazepoxide) are effective in patients with repeated seizures. Controlled studies indicate that phenylhydantoin does not prevent recurrent seizures in these patients (Alldredge et al., 1989). Phenobarbitol may also be effective although controlled trials have not compared this drug to benzodiazepines. It also poses a greater risk of respiratory depression due to the long half life and possible additivity if combined with ethanol. Status epilepticus from any cause is a medical emergency and requires immediate treatment in the same way as status from other causes. Alcoholics are at particular risk for multiple other causes of status (hyponatremia, hypoglycemia, meningitis, other drug ingestions, history of head trauma, or occult head trauma). Approximately one third of alcoholics experiencing withdrawal seizures go on to have delirium tremens.

Delirium tremens

Delirium tremens is the most alarming manifestation of the ethanol withdrawal syndrome. It is characterized by agitated arousal, global confusion and disorientation, insomnia, and vivid, often threatening hallucinations and delusions. Signs of sympathetic hyperactivity include tremor, mydriasis, tachycardia, fever, and intense diaphoresis. In contrast to the early appearance of tremulousness and disordered perceptions, and seizures, delirium tremens develops abruptly within 2–5 days of abstinence. This is often a surprising development in unrecognized alcoholics who have been admitted to the hospital for other reasons. These patients are terrified by their hallucinations and can be combative, destructive, and dangerous. Episodes of delirium tremens last 1–3 days and may end as abruptly as they begin.

Evaluation and management of delirium tremens

Delirium tremens requires hospitalization and vigorous emergency treatment. It may be difficult to distinguish delirium tremens from an acute psychosis when there are no signs of sympathetic hyperactivity. However, the diagnosis is usually suggested by the evolution of symptoms in a chronic alcoholic who is undergoing withdrawal. The differential diagnosis includes alcoholic hypoglycemia; overdose with anticholingergic agents; intoxication with amphetamines, cocaine, or phencyclidine piperdine; encephalitis; meningitis; thyrotoxicosis; and withdrawal from other sedating drugs. Seizures are unusual in delirium tremens and should be evaluated promptly because of the possibility of meningitis or other diagnoses. The major threat to life derives from associated illness or injuries, hyperthermia, and dehydration with circulatory collapse.

The goal of treatment is to control behaviour and suppress symptoms without excessive sedation and danger to the patient. A variety of sedatives, neuroleptics, and sympatholytic drugs have been given to patients with delirium tremens, usually in uncontrolled trials. Benzodiazepines are the mainstay of therapy, and 5–10 mg diazepam is given intravenously every 10–15 minutes until the patient is calm, followed by 5–10 mg every 1–4 hours as needed. Doses of 200 mg are not usual during the first few hours, and some patients may need up to 1200 mg in the first 3–4 days of treatment to maintain calm. Special care must be taken to support fluid and electrolyte balance and hypoglycemia; volume depletion accompanying delirium tremens may cause circulatory collapse, and fluid losses can require replacement of 4–10 l in the first day. Hypomagnesemia is frequent and can be treated with 1 g i.v. every 6 hours for the first 24 hours in patients with normal renal function.

Cellular pathophysiology of ethanol intoxication, tolerance, and physical dependence

Unlike most drugs of abuse, ethanol does not appear to act through a single major molecular target in the brain. Historically, it was thought that ethanol (and other agents capable of inducing anesthesia) acted through a disruption of membrane fluidity. More recent studies have demonstrated clearly that specific proteins mediate effects of ethanol on neural excitability (Diamond & Gordon, 1997; Chandler et al., 1998). Targets of ethanol include major ligand-gated channels such as the $GABA_A$ and NMDA receptors, voltage-gated Ca^{2+} and K^+ channels, neuropeptides and second messenger systems. The determination of the mechanisms of action of ethanol on a molecular level has provided the basis for a directed approach to the development of therapeutics to treat alcoholism and alcoholic neurological disorders.

NMDA receptors

In multiple electrophysiological preparations, ethanol antagonizes NMDA receptors at physiological doses (Lovinger et al., 1989; Hoffman et al., 1989). This is consistent with the neurodepressant behavioural effects of ethanol. Ethanol sensitivity of NMDA receptors varies with subunit composition. This is supported by brain regional differences in ethanol sensitivity and by recombinant expression systems showing variability with different expressed subunit combinations. Acute tolerance to the inhibitory effect of ethanol on NMDA receptor function is observed at the cellular level. There is gradual recovery of the initial induced depression in NMDA-mediated EPSPs in the hippocampal CA1 region. The tolerance may be mediated through a non-receptor tyrosine kinase, Fyn (Miyakawa et al., 1997). Fyn deficient mice (fyn-/fyn-) are defective in acute tolerance to ethanol and are hypersensitive to the intoxicating effects of the drug. The observed ethanol-induced increase in tyrosine phosphorylation of the NR2B subunit of the NMDA receptor is not observed in fyn-/fyn- mice.

$GABA_A$ receptors

In addition to antagonizing excitatory glutamatergic neurotransmission, ethanol also enhances inhibitory GABAergic neurotransmission (Suzdak et al., 1986; Allan & Harris, 1987; Mehta & Ticku, 1988). Potentiating effects of ethanol are well demonstrated in vitro and are again dependent on subunit composition. A proposed 'hydrophobic binding pocket' of ethanol has been defined in the $GABA_A$ receptor by chimeric receptor studies (Mihic et al., 1997). A specific role for the γ subunit of the $GABA_A$ receptor has been proposed from studies of clonal cell lines. One form of the γ subunit (γ21) has a phosphorylation site for PKC and phosphorylation of this site in vitro modulates ethanol sensitivity of the receptor. Mutant mice lacking the PKC-γ are relatively resistant to the effects of ethanol on behaviour and on $GABA_A$ receptors.

Clinically, ethanol shows cross tolerance with other compounds acting on the $GABA_A$ receptor such as benzodiazepines and barbituates. Benzodiazepine receptor inverse agonists interfere with ethanol intoxication but are not clinicaly useful as they act as convulsants. The use of benzodiazepines to treat alcohol withdrawal is descibed above.

Calcium channels

Acutely ethanol has been shown to inhibit N, T and L-type Ca^{2+} channels (Twombly et al., 1990; Wang et al., 1991). With more prolonged ethanol exposure there is a secondary increase in apparent channel number as measured with labelled antagonists (Dolin & Little, 1989). Such increases have also been demonstrated in alcohol-dependent animals (Little, 1991). The increase in Ca^{2+} channel number has been shown to reflect ethanol-induced increases in PKC isoenzymes and PKC-mediated phosphorylation (Messing et al., 1990, 1991). These findings of elevated channel number are consistent with the observed increases in depolarization induced Ca^{2+} influx in cells chronically exposed to ethanol. Up-regulation of Ca^{2+} channels persists for approximately 16 hours after cessation of ethanol exposure (Diamond & Gordon, 1997). This correlates with the time period for withdrawal seizure risk in alcoholics stopping ethanol consumption. Enhanced Ca^{2+} channel activity would stimulate neurotransmitter release and NMDA receptor activation, plausible mechanisms for hyperexcitability and seizure induction. Furthermore, Ca^{2+} channel blockers have been shown to reduce withdrawal seizures as well as withdrawal tremors and mortality in human alcoholics.

Potassium channels

Ethanol interactions with K^+ channels may also contribute to the observed physiological effects of the drug (Weight, 1992; Anantharam et al., 1992). An activating effect of ethanol at physiological doses on the BK class of voltage and Ca^{2+} activated K^+ channels has been demonstrated in vitro (Dopico et al., 1998, 1999). The potentiation persists

when the channel is reconstituted in lipid bilayers, suggesting a possible direct effect of ethanol on the channel (Chu et al., 1998). Potentiation of K^+ channels would depress neural activity, consistent with the depressant behavioural effects of ethanol. Ethanol activation of the G-protein-activated, inwardly rectifying K^+ (GIRK) channel has also been demonstrated in vitro (Lewohl et al., 1999). The effect appears independent of G proteins or second messangers. *Weaver* (*wv*) mutant mice, have a mutation in the GIRK2 channel and are hyposensitive to ethanol-induced analgesia.

Neuropeptide Y

Recent studies have demonstrated an important role of the peptidergic neurotransmitter, neuropeptide Y (NPY), in drinking behaviour and mammalian responses to alcohol. NPY is a widely expressed neuropeptide with particularly high levels in cerebral cortex, basal ganglia, hypothalamus and amygdala. NPY acts through multiple G protein-coupled receptors. NPY knockout mice show substantially increased ethanol consumption, a preference for ethanol over water, and less sensitivity to the sedative effects of ethanol (Thiele et al., 1998). Conversely, mice overexpressing NPY show increased sensitivity to ethanol and drink less than controls. Furthermore, P rats which were bred for elevated ethanol preference have a QTL with a substantial effect on alcohol behaviour that was mapped to a region containing the precursor of NPY (Carr et al., 1998). Therapeutics related to human drinking behaviour may emerge from further pharmacological characterizations of NPY receptors.

Adenosine

Adenosine is a global inhibitory neuromodulator in the nervous system, acting through A1, A2 and other receptor subtypes. Adenosine acts presynaptically to inhibit the release of excitatory neurotransmitters and postsynaptically to diminish the response of dopamine and acetylcholine receptors. The extracellular concentration of adenosine increases with neural activity and inhibitors of adenosine uptake potentiate cellular responses to adenosine, suggesting that physiologic effects are terminated, in part by reuptake into the cell.

Adenosine appears to mediate acute ethanol-induced ataxia in rodents; adenosine receptor agonists increase ethanol-induced intoxication and antagonists diminish this response. Sensitivity to adenosine agonists correlates with acute sensitivity to alcohol in mice bred selectively for differential responses to ethanol. There is also cross-tolerance between ethanol and adenosine agonists. In cell culture systems ethanol inhibits adenosine reuptake via a specific nucleoside transporter (ENT-1) thereby increasing extracellular adenosine that activates adenosine A2 receptors. This increases cAMP levels, resulting in activation and translocation of cAMP-dependent protein kinase (PKA) into the nucleus, increasing cAMP-dependent gene expression. This suggests that adenosine plays a role in acute responses to ethanol and, perhaps, the development of chronic alcohol-related behaviours such as craving, tolerance and dependence (Diamond & Gordon, 1997). It is possible that specific adenosinergic agents can be developed to modify acute and chronic alcohol-related behaviours and neurological complications.

Protein kinase signalling

PKA and protein kinase C (PKC) play major roles in regulating and mediating neural responses to ethanol (Diamond & Gordon, 1997). Ethanol increases cAMP levels in many biological preparations, resulting in activation of PKA. This can involve adenosinergic mechanisms, as described above. In cultured cells ethanol causes PKA to translocate into the nucleus where it remains as long as ethanol is present (Dohrman et al., 1996). This results in phosphorylation of the cAMP response element-binding protein (CREB) and sustained increases in cAMP dependent gene expression. These kinds of molecular events are known to regulate neuronal function and may contribute to such long-term alcoholic neuroadaptive behaviours as craving, tolerance and dependence. It is of interest, therefore, that mice genetically engineered with diminished PKA activity in the striatum have reduced sensitivity to ethanol intoxication and exhibit excessive drinking behaviour (Thiele et al., 2000). Taken together, these findings suggest that ethanol-induced activation of cAMP and PKA signalling appears to modulate many of the short-term and prolonged effects of ethanol in the nervous system.

Ethanol also increases the activity and translocation of a few PKC isozymes. In PC-12 cells an ethanol-dependent increase in epsilon PKC is required for ethanol-induced neurite outgrowth, a process associated with neuronal plasticity. Mice lacking PKC epsilon are more sensitive to ethanol intoxication and drink 75% less alcohol than wild-type littermates (Hodge et al., 1999). This suggests that, in contrast to PKA, normally functioning PKC epsilon in the brain might enable excessive alcohol consumption. Most important, the discovery that mice lacking PKC epsilon drink less raises the possibility that drugs designed to inhibit PKC epsilon might be effective in reversing excessive drinking.

Clinical observations in young adults with a genetic risk for alcoholism (see below) suggest that individuals with a diminished intoxicating response to alcohol more often develop alcoholism in the future (Schuckit, 1994). This is consistent with observations made in genetically engineered mice who drink excessively; often they are less sensitive to acute intoxication (Schuckit, 2000). By contrast, animals with increased sensitivity to alcohol intoxication are often less likely to drink excessively. Current concepts suggest that phosphorylation regulates alcohol sensitivity of many membrane proteins that are selective targets for ethanol in the brain. Experimental findings in animal models suggest that PKA and PKC epsilon may function as homeostatic mechanisms to regulate sensitivity to ethanol intoxication and the development of excessive drinking afterwards. It is possible, therefore, that drugs designed to selectively modify protein kinase activities, including PKA and PKC signalling, may become novel and effective therapies for alcoholism and alcohol-related behaviours.

Genetics of alcoholism

There is evidence that genetic factors play a role in alcoholism. A genetically transmitted susceptibility for alcoholism has been demonstrated in family, twin and adoption studies (Ball & Murray, 1994; Begleiter & Kissin, 1995). Genes that influence the risk for alcoholism have not yet been identified. As with many complex behavioural traits, the identification is complicated by the probable multigenic nature of the disorder and the difficulties in defining and distinguishing between the different phenotypic forms of alcohol dependence and alcohol abuse.

Many biochemical and physiological measurements have been evaluated as possible relevant phenotypic markers. One that has emerged as likely to be significant is the 'low level of response to alcohol'. The level of response (LR) is an objective and subjective measure of the response to the intoxicating effects of alcohol as determined at specific blood alcohol concentrations. Objective measurements include electrophysiological and hormonal measures. Individuals with a low LR have an increased risk of alcoholism (Schuckit, 1994). Low LRs have been observed at an elevated frequency in studies of 700 children of alcoholics. A longitudinal study of 435 sons of alcoholics demonstrated that a low LR is a significant predictor of later alcohol abuse or dependence (Schuckit & Smith, 1996). Groups identified as having a relatively higher risk for alcoholism, such as Native Americans, tend to show low LRs, while other groups identified as having relatively lower risks of alcoholism (Jews and certain Asian groups) have higher LRs.

The LR to alcohol appears to be genetically influenced. In humans, the LR is more similar in first degree relatives than unrelated individuals. The LR is also more similar in identical twin pairs than fraternal twin pairs. Studies in animals have identified a QTL associated with the LR.

Another potentially useful marker of increased risk of alcoholism is the lower amplitude P3 on the event-related potential paradigm. Approximately one-third of offspring of alcoholics have a low amplitude P3. Small P3 amplitudes are observed in alcoholics after extended abstinence. There is controversy however as to whether or not a low amplitude P3 more directly reflects Anti Social Personality Disorder (see below) or related disorders found in a subset of alcoholics.

Alcoholism emerges with greatly increased frequency in patients with certain specific neuropsychiatric disorders. Nearly two out of three patients with the antisocial personality disorder are alcoholic. Twenty percent of all alcoholics meet the criteria for this disorder. Antisocial personality disorder and alcoholism appear to coexist in many families and are often inherited together.

Particular alleles of genes encoding alcohol metabolizing enzymes also affect the risk of alcoholism. Alcohol is metabolized to acetaldehyde by alcohol dehydrogenase (ADH). Acetaldehyde is metabolized by ALDH. Asian individuals who are homozygous for the ALDH 2-2, 2-2 allele lack the low Km form of ALDH and produce high levels of acetaldehyde. These individuals are at extremely low risk of alcoholism. Such individuals experience an alcoholic flush reaction from the very high levels of acetaldehyde. Shortly after drinking, there is vasodilation, facial flushing, hot sensations, tachycardia and hypotension. Heterozygotes for the 2-2 allele also have a lower risk for alcoholism. In the case of ADH, certain alleles (ADH 2-2, 2-3, 3-1) are associated with more rapid production of acetaldehyde and deceased risk of alcoholism. In these later cases, however, it is not clear that the reduced risk relates to an obvious aversive reaction as in the ALDH homozygotes.

Treatment of alcoholism

Medications have recently emerged from clinical trials as effective in the treatment of alcoholism. The opiate antagonist, naltrexone, has been approved by the Food and Drug Administration for the treatment of alcohol dependence. In several studies, recently abstinent alcoholics who were treated for 12 weeks with naltrexone (50 mg/day) showed reduced relapse rates and greater periods of maintenance

Table 113.3. Alcoholic neurologic disorders

Wernicke's encephalopathy
Korsakoff's amnestic syndrome
Alcoholic dementia
Marchiafava–Bignami disease
Alcoholic cerebellar degeneration
Central pontine myelinolysis
Alcoholic neuropathy
Alcoholic myopathy
Fetal alcohol syndrome

of abstinence. The effect of naltrexone on relapse was however small to moderate (20–25% difference between medication and placebo groups) and not all studies have demonstrated significant effects. Larger multisite trials with naltrexone are ongoing.

European studies have demonstrated effectiveness of the drug, acamprosate, in the treatment of alcoholism. Three thousand alcoholics were treated in seven multicentre trials in Europe. Effects were significant but again small to moderate changes were observed. Acamprosate is thought to act through modulation of NMDA receptor function. Acamprosate is in use for the treatment of alcoholism in Europe but awaits FDA approval in the US. Additional acamprosate studies are ongoing in the US.

Alcoholic neurologic disorders

The alcoholic neurologic disorders complicate alcoholism and alcohol abuse (Table 113.3). These major syndromes do not develop in all alcoholics, however, and it is not understood why some patients manifest one or several of the disorders and other patients are relatively spared. Many clinicians consider malnutrition to be of primary importance in the pathogenesis of many of these syndromes (Victor & Adams, 1961).

Alcoholics often obtain as much as 50% of their calories from ethanol, and some develop serious nutritional deficiencies, particularly for protein, thiamine, folate, and pyridoxine. However, evidence suggests that genetic factors also contribute to the diverse toxicity of ethanol (Devor et al., 1988).

The transition between reversible metabolic effects of ethanol and the development of alcoholic organ damage in the brain or elsewhere is not understood. Studies of alcoholics with skeletal myopathy and cardiomyopathy suggest that a lifetime ethanol consumption threshold is exceeded before significant damage develops (Diamond, 1989; Urvano-Marquez et al., 1989). Evidence suggests several possibilities to account for the potential neurotoxicity of ethanol. Ethanol can be an exogenous substrate for specific enzymes, thus leading to the accumulation of potentially toxic abnormal products. These include phosphatidylethanol (Alling et al., 1984; Kobayashi & Kanfer, 1987; Mueller et al., 1988), a product of phospholipase D activity, and fatty acid ethyl esters (Bora et al., 1989; Laposata et al., 1987), products of synthase activity.

Acetaldehyde, a product of alcohol dehydrogenase, is another potential toxin. Acetaldehyde can react with diverse proteins to form acetaldehyde–protein adducts (Behrens et al., 1988; Lin & Lumeng, 1989).

Prolonged ethanol-induced changes in receptor-stimulated second-messenger production and ion channel function could also be cytotoxic (Diamond, 1989), particularly for ordinarily non-proliferating organs, such as brain, muscle and liver.

Table 113.4. Conditions associated with Wernicke's encephalopathy

Chronic alcoholism
Starvation
Systemic diseases
Malignancy
Hepatic failure
Disseminated tuberculosis
Uremia
Persistent vomiting
Hyperemesis gravidarum
Gastric malignancy
Gastritis
Intestinal obstruction
Digitalis intoxication
Inadequate parenteral nutrition
Chronic hemodialysis

Wernicke's encephalopathy

Wernicke's encephalopathy develops most commonly in chronic alcoholics but also occurs in other conditions (Table 113.4). A clinical triad of ataxia, ophthalmoplegia, and global confusion is characteristic (Victor et al., 1989), although Wernicke's encephalophathy should be suspected in any poorly nourished patient with a confusional state of recent onset. The major clinical manifestations are summarized in Table 113.5. Patients first complain of diplopia or difficulty with balance. Horizontal nystagmus on lateral

Table 113.5. Major clinical manifestations of Wernicke's disease

Abrupt onset
Encephalopathy, opthalmoplegia, gait ataxia
Confusion, apathy, sleepiness
Horizontal and vertical nystagmus
Lateral rectus palsies
Conjugate gaze defects
Reactive pupils

gaze is almost always demonstrable, vertical nystagmus is less frequent, and rotary nystagmus is rare. Bilateral, usually asymmetric lateral rectus palsies may develop rapidly, and defects in conjugate gaze are common. Ptosis and internuclear ophthalmoplegia occur rarely. There may be decreased pupillary reactions to light, but failure to respond to light should suggest an alternative or additional diagnosis. Mild-to-severe cerebellar truncal ataxia occurs in nearly all patients, tremor and limb ataxia are found less often, and speech is rarely affected.

An acute confusional state with inattention, disorientation, and sleepiness is common in patients with Wernicke's encephalopathy. Patients may sometimes be agitated, but most patients exhibit apathy and indifference. Amnesia and an inability to form new memories is observed. Pathologic studies have indicated that obtundation and coma can be important features in clinically unrecognized cases of Wernicke's encephalopathy (Harper, 1983; Harper et al., 1986; Torvik et al., 1982). Therefore, it is necessary to consider this diagnosis in all patients with unexplained stupor or coma. Fever should prompt a search for concomitant infection.

A peripheral neuropathy often coexists with Wernicke's encephalopathy. Hypothermia and hypotension may also be observed.

Pathophysiology

Wernicke's encephalopathy is the only alcohol-related neurological disorder that can be corrected by a specific vitamin – thiamine. Thiamine (vitamin B1) is absorbed in the small intestine and is transported into brain by a saturable energy-dependent transport system. A series of phosphorylation reactions produces thiamine pyrophosphate, a required cofactor in carbohydrate and amino acid metabolism. Four principal thiamine-dependent enzymes are pyruvate dehydrogenase, α-ketoglutaric dehydrogenase, transketolase, and branched chain α-keto acid dehydrogenase. Evidence suggests that functional thiamine deficiency in alcoholics may result from combination of inadequate diet, impaired intestinal absorption, and, perhaps, a genetically determined abnormality of transketolase (Blass & Gibson, 1977; Mukherjee et al., 1986, 1987). Such individuals would be at greater risk to develop functional thiamine deficiency when thiamine levels in the diet are compromised. However, the precise role of thiamine deficiency in the pathogenesis of the characteristic brain lesions in Wernicke's encephalopathy is poorly understood.

Evaluation and management

The diagnosis of Wernicke's encephalopathy is usually suggested by the clinical triad of ataxia, ophthalmoplegia, and confusion in an alcoholic as well as by the response to thiamine treatment. Although there are no antemortem laboratory tests that unequivocally establish the diagnosis, evidence suggests that magnetic resonance imaging (MRI) may be valuable in mild or unusual cases.

Management of Wernicke's encephalopathy requires hospitalization (mortality rate 10–20%) and prompt treatment with thiamine. 100 mg of thiamine is given parenterally because intestinal absorption is impaired in malnourished alcoholics. Thiamine treatment should be started before beginning intravenous glucose or oral feeding; carbohydrates administered before thiamine can precipitate or worsen the encephalopathy. Recovery begins promptly. Oral treatment with thiamine (50 mg) should be started after several days of IV thiamine. Ophthalmoplegia and gaze palsies begin to resolve during the first day. Nystagmus, gait ataxia, and confusion may improve within days to weeks. However, residual nystagmus and cerebellar truncal ataxia may persist after the patient recovers from the acute episode. Nearly all patients with Wernicke's encephalopathy recover from the global confusional state, but many are left with a residual disorder of memory, Korsakoff's amnestic syndrome.

Korsakoff's amnestic syndrome

A characteristic defect in forming new memories (anterograde amnesia) and in recalling established memories (retrograde amnesia) occurs with Korsakoff's amnestic syndrome. Recent memories tend to be most severely affected, and patients are usually disoriented for place and time. Patients often have well preserved distant memories. Immediate recall is intact, but patients are unable to remember the same information several minutes later. Imaging studies are consistent with pathologic findings, which suggest that lesions in the dorsal medial nucleus of the thalamus are probably responsible for the memory

deficits (Shimamura et al., 1988). Korsakoff's patients often show a lack of appreciation of their deficit. The patients may exhibit confabulation or make-up stories to compensate for their impaired recall. Other aspects of cognitive function, including arousal, language, praxis and judgement, are unaffected.

All patients should be given thiamine to treat coexistent Wernicke's encephalophy or to prevent further memory loss. About 20% of patients with Korsakoff's syndrome recover completely, but more than one-half show little or no change. Recovery may be delayed for 1–3 months. The transition between the reversible metabolic disorder of Wernicke's encephalopathy and the development of permanent neurological deficits in Korsakoff's syndrome is not well understood. However, calorie-containing ethanol appears to be an important contributing factor. Calorie-deprived prisoners of war who developed Wernicke's encephalopathy rarely exhibited the irreversible amnestic syndrome. Alcohol may be required with malnutrition to produce the syndrome.

Alcoholic dementia

Most alcoholics have cognitive deficits on psychometric evaluation. Alcoholics also tend to develop cerebral atrophy that increases with age and that can be visualized on CT scans and MRI of the brain. Symmetric enlargement of the lateral ventricles and an increase in the size of the cerebral sulci and the width of interhemispheric and sylvian fissures have been described. These structural changes may improve if drinking is discontinued (Carlen et al., 1986; Schroth et al., 1988). The structural abnormalities, however, correlate poorly with specific cognitive deficencies (Carlen et al., 1981). The specific mechanisms underlying alcoholic dementia are not known. Experimental studies have demonstrated that ethanol exposure leads to altered dendritic morphology in the hippocampus and neuronal loss (Durand et al., 1989; Ferrer et al., 1989).

Marchiafava–Bignami disease

This rare condition affects mainly individuals who have a long history of alcoholism. The clinical features are quite variable. Patients may present with seizures and coma or may follow a subacute progressive course with agitation or apathy, hallucinations, and emotional disorders until stupor and coma supervene. Clinical signs are non-specific but often suggest bilateral frontal lobe involvement with later spasticity and rigidity. Recovery is rare. Patients may not progress with abstinence and nutritional supplementation, but remain demented. Symmetric demyelination of the corpus callosum and anterior commissure can be seen on MRI and CT scans (Kawamura et al., 1985). Adjacent white matter regions are less frequently involved. The etiology is unknown, and there is no specific treatment.

Alcoholic cerebellar degeneration

Cerebellar degeneration occurs frequently in chronic alcoholics. Pathologically, the cerebellar findings are highly similar to those observed in Wernicke's encephalopathy. The disorder may reflect a history of Wernicke's encephalopathy. The patients are usually long-standing alcoholics. Affected patients usually complain of progressive unsteadiness and difficulty in walking. Abnormalities of gait and station are the most common findings, and truncal ataxia may be mild or severe. Limb ataxia, particularly of the lower extremities, may also be observed. Dysarthria and nystagmus are less common. Often, the cerebellar syndrome develops rapidly over a period of several weeks or months and then remains stable. The disorder sometimes develops more slowly, but exacerbation occurs during binge drinking or intercurrent illness. CT scans and MRI studies may confirm cerebellar vermis atrophy. Affected patients should discontinue drinking and be treated with thiamine and multivitamins.

Central pontine myelinolysis

Central pontine myelinolysis (CPM) is a rare disorder encountered in alcoholics and in other settings such as patients with electrolyte disorders, liver disease, malnutrition, anorexia, burns, cancer, Addison's disease, sepsis, and Wilson's disease. CPM results from rapid correction of hyponatremia rather than from a toxic effect of ethanol.

Alcoholic neuropathy

Polyneuropathy is quite common among alcoholic patients (Mills et al., 1986). Complaints include parasthesias, dysasthesias, weakness and ataxia. Symptoms usually begin insidiously in the distal lower extremities and progress proximally. On examination, decreased vibration sense is typically observed. Light touch, pain and temperature sensation may also be impaired. Absent or diminished reflexes are common. Distal weakness is also frequently seen. Rarely are there autonomic or cranial nerve findings. Alcoholic polyneuropathy is characterized primarily by axonal degeneration. Segmental demyelination is, however, also described. NCS can be used to demonstrate a primarily axonal process. Treatment includes

abstinence and nutritional supplementation (including thiamine). Improvement sometimes occurs. Dysesthesias are treated with agents used for other forms of neuropathic pain (including tricyclics and anticonvulsants).

An unusual form of alcoholic neuropathy has been described that evolves within several days and results in severe weakness, hyporeflexia and sensory loss (Wohrle et al., 1998). It may be confused with Guillian–Barré syndrome. Unlike GBS, however, there is not respiratory muscle involvement or bulbar signs. CSF protein is also normal or only mildly elevated. Electrophysiological and pathological studies reveal primarily an axonal process. Recovery typically occurs over several months.

Alcoholic myopathy

Acute alcoholic myopathy

Acute alcoholic myopathy is a dramatic and life-threatening disorder that occurs in alcoholics, often after several days of heavy binge drinking (Haller & Knochel, 1984). Symptoms begin abruptly with pain, cramps, tenderness, proximal weakness, and swelling of the muscles. Muscle involvement can be generalized or asymmetric. Weakness is typically proximal. There may be arrhythmias because of cardiac involvement and electrolyte abnormalities. CHF may occur. Creatine kinase activity in blood is elevated, and muscle biopsy shows necrotic changes in muscle fibres. Myoglobinuria is a frequent complication and may lead to hyperkalemia, renal failure and death. Arrhythmias may be observed on the electrocardiogram. The electromyogram usually shows evidence of mypopathic changes. Recovery generally occurs within weeks of abstinence but may be incomplete with a residual proximal muscle weakness and cardiac conduction abnormalities.

Chronic alcoholic myopathy

A chronic, typically painless, syndrome of proximal muscle weakness and atrophy may evolve gradually in alcoholics. The myopathy can be mild or severe and affects legs more often than arms. Muscle biopsy reveals Type II fibre involvement. Improvement usually occurs between 2 and 3 months after drinking is discontinued.

Fetal alcohol syndrome

Alcoholic mothers who drink heavily throughout pregnancy can give birth to infants with intrauterine growth retardation, dysmorphic features, microcephaly, and neurological abnormalities (Rosett & Weiner, 1984). The dysmorphic features include short palpebral fissures, midfacial hypoplasia, thinned upper lip vermilion, diminished or absent philtrum, and a low nasal bridge. The disorder is known as fetal alcohol syndrome, but some investigators consider these features to be ungrouped congenital anomalies (Kalter & Warkany, 1983). Moreover, malnutrition, tobacco, and concomitant drug abuse frequently complicate maternal alcoholism and can also adversely affect the developing fetus. Infants with fetal alcohol syndrome may show hypotonia, poor sucking, tremulousness, irritability, and seizures. Older children exhibit mental retardation, hyperactivity and learning disabilities. The incidence of this syndrome in the offspring of alcoholic mothers ranges from 2.5–40% and is about 0.25% of all live births (Rosett & Weiner, 1984).

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Neurological consequences of drug abuse

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There are two kinds of drug dependence. 'Psychic dependence' is compulsive recreational use of a substance to produce pleasure or to avoid discomfort. 'Physical dependence' is an adaptive state in which cessation of drug use (or administration of an antagonist) causes intense physical discomfort. 'Tolerance' is the need for ever larger doses of a drug to achieve the desired effect or to avoid withdrawal symptoms. 'Sensitization' ('reverse tolerance') is a lowered threshold for certain drug effects following repeated use. The term 'addiction' refers to psychic dependence. The term 'drug abuse' refers to the perception that recreational use of a substance, licit or illicit, is harmful (Brust, 1993).

Pathophysiological aspects of drug addiction, including intended effects, are discussed in Chapter 30. This chapter addresses, first, clinical features of overdose and withdrawal and, second, other neurological complications encountered in recreational substance users. Alcohol is discussed in Chapter 113.

Drugs of dependence

Opiates

Of the many opiates available in the United States (Table 114.1), heroin (diacetylmorphine) is the most popular urban street drug. Before the 1980s it was usually taken parenterally, but ready availability of cheap potent heroin, plus fear of AIDS, have more recently favoured snorting or smoking. The drug is highly addicting, and tolerance in daily users leads to the need for huge doses. Many users, however, take heroin only occasionally, and erratic use combined with variably potent street mixtures carries considerable risk for overdose (Brust, 1993).

Acting at different types of receptors in many areas of the central and peripheral nervous systems, opiates produce

Table 114.1. Opiates

Agonist
Powdered opium
Tincture of opium (laudanum)
Camphorated tincture of opium (paregoric)
Morphine
Heroin (legally available only for investigational use)
Methadone (Dolophine, etc.)
Fentanyl (Sublimaze)
Oxymorphone (Numorphan)
Hydromorphone (Dilaudid)
Codeine
Oxycodone (in mixtures, e.g. Percodan, Percocet)
Levorphanol (Levodromoran)
Meperidine (pethidine, Demerol, etc.)
Diphenoxylate (in Lomotil)
Loperamide (Imodium)
Dextromethorphan (Robitussin)
Propoxyphene (Darvon)
Apomorphine
Tramadol (Ultram)
Mixed agonist–antagonist/partial agonist
Levallorphan (Lorfan)
Nalorphine (Naline)
Pentazocine (Talwin)
Butorphanol (Stadol)
Nalbuphine (Nubain)
Buprenorphine (Buprenex)
Cyclazocine (for investigational use only)
Antagonist
Nalmefene (Revex)
Naloxone (Narcan)
Naltrexone (Trexan)

diverse effects. In intended dosage heroin causes analgesia, drowsiness, and euphoria; injected or smoked heroin produces an ecstatic 'rush' followed by either a dreamlike 'nodding' or increased psychomotor activity ('drive'). Other effects include nausea and vomiting, miosis, dryness of the mouth, pruritis, sweating, suppression of the cough reflex, constipation, hypothermia, respiratory depression, and postural hypotension.

Overdose causes coma, pinpoint pupils, and respiratory depression. Miosis may be so marked that the light reflex, which opiates do not interrupt, may be difficult to discern. On the other hand, anoxia–ischemia or hypothermia can produce large and unreactive pupils. Further confusing the picture are the effects of concomitantly administered drugs. Heroin is frequently taken with cocaine or amphetamine ('speedball'), and heroin addicts often abuse ethanol. Signs of overdose from one agent may therefore coexist with signs of overdose or withdrawal from another agent. For example, seizures in a heroin user may be the combined result of cocaine toxicity, ethanol withdrawal, anoxia, and the opiate's own ability to lower seizure threshold.

Treatment of overdose begins with attention to apnea or shock (Nelson, 1998). Opiates depress brainstem carbon dioxide sensitivity, and so oxygen is administered cautiously. Hypotension usually responds to correction of hypoxia and administration of fluids; vasopressors or plasma expanders are rarely needed. In some patients heroin causes pulmonary edema, which vigorous fluid administration can aggravate.

Patients with respiratory depression are given naloxone, 2 mg intravenously (or, if veins are unavailable, intramuscularly or subcutaneously). If signs persist, boluses of 2 to 4 mg are repeated up to a total of 20 mg. Higher doses may be required for propoxyphene, pentazocine, nalbuphine, butorphanol, buprenorphine or diphenoxylate, but failure to respond to 20 mg suggests the presence of additional drugs, anoxic–ischemic brain damage, or an alternative diagnosis.

Patients with depressed sensorium but normal respirations receive smaller doses of naloxone to avoid precipitating withdrawal signs: 0.4 to 0.8 mg are given, and if there is no response, 2-mg doses are repeated every 2 to 3 minutes.

Maximal effects occur 2 to 3 minutes after intravenous naloxone but only about 15 minutes after intramuscular or subcutaneous naloxone. Because of vomiting, some emergency medicine physicians perform endotracheal intubation before giving naloxone. Too much naloxone can precipitate opiate withdrawal. On the other hand, naloxone is shorter acting than most opiate agonists, and patients who seem to have fully recovered can slip back into coma and apnea. Hospitalization and close observation are required for at least 24 hours with heroin and 72 hours with methadone, during which time it may be necessary to give naloxone in repeated doses or as a continuous infusion.

Physical dependence develops rapidly in daily heroin users, and symptoms and signs develop within hours of withdrawal (Khanzian & McKenna, 1979). Unlike withdrawal from ethanol or sedatives, the opiate abstinence syndrome does not include seizures, hallucinosis, or delirium and in adults is rarely life threatening. Rather, there are irritability, weakness, lacrimation, rhinorrhea, sweating alternating with chills and piloerection, myalgia, nausea, vomiting, diarrhea, abdominal cramps, hot flashes, fever, rhonchi, rales, tachypnea, tachycardia, and hypertension. Symptoms can resemble a severe case of 'the flu', with drug craving disproportionate to other symptoms. With heroin, symptoms peak at 24 to 72 hours and last a week or two. With methadone, symptoms peak at about a week and last up to 3 months. Opiate withdrawal symptoms are promptly relieved by oral methadone 20 mg once or twice daily, with subsequent dosage titrated to symptoms.

By contrast, opiate abstinence in newborns exposed in utero is often severe or even fatal. Tremor, jitteriness, muscle hypertonia, screaming, lacrimation, tachypnea, tachycardia, vomiting, and diarrhea can progress to myoclonus or convulsions (although seizures can be difficult to tell from jitteriness and if present might be secondary to barbiturate or ethanol withdrawal). Mortality is as high as 90% without treatment, which includes either methadone or another opiate such as paregoric (Kandall et al., 1983). Symptoms resemble those associated with neonatal hypoglycemia, sepsis, meningitis, hypocalcemia, or intracranial hemorrhage, any of which might coexist.

Overdose of other opiates has special features. Meperidine, through its metabolite normeperidine, causes tremor, myoclonus, and seizures (Hershey, 1983). Fentanyl and its many 'designer drug' analogs produce acute muscular rigidity, which further impairs ventilation (Henderson, 1988). Propoxyphene causes naloxone-resistant cardiotoxicity and seizures (Young, 1983). Pentazocine, sometimes taken parenterally with antihistamine or methylphenidate, causes psychosis (Sandoval & Wand, 1969).

Psychostimulants

Psychostimulant drugs include amphetamine and related agents, as well as cocaine (Table 114.2). Their major CNS effects are the result of indirect dopamine agonism, causing psychic symptoms through actions within the

Table 114.2. Amphetamines and related agents

Amphetamine (Adderall, Biphetamine)
Dextroamphetamine (Dexedrine)
Methamphetamine (methedrine, Desoxyn, Fetamin, 'speed', 'ice')
Ephedrine
Pseudoephedrine
Phenmetrazine (Preludin)
Methylphenidate (Ritalin)
Pemoline (Cylert)
Diethylpropion (Tenuate, Tepanil)
Benzphetamine (Didrex)
Chlorphentermine (Pre-Sate)
Phendimetrazine (Plegine, Bontril, Phenzine, Prelu-Z)
Phentermine (Ionamin, Wilpo, Adipex, Fastin)
Phenylpropanolamine (Propadrine, and in decongestants, e.g. Ornade, Comtrex, and in diet pills, e.g. Dex-a-Diet, Dexatrim, Maxi-Slim, Vita-Slim)
Propylhexedrine (Benzedrex)
Tuaminoheptane (Tuamine)
Naphazoline (Privine)
Tetrahydrozoline (Tyzine)
Oxymetazoline (Afrin)
Phenylephrine
Xylometazoline (Otrivin)
Cyclopentamine (Clopane)
Fenfluramine (Pondimin) (withdrawn)
Dexfenfluramine (Redux) (withdrawn)
Methylenedimethoxymethamphetamine ('ecstasy', 'Adam')
Methylenedimethoxyethamphetamine ('Eve')

limbic 'reward system' (see Chapter 30) and abnormal movements through actions within nigrostriatal circuits of the basal ganglia. Amphetamine-like agents release dopamine at synaptic endings through a dopamine transporter; cocaine blocks dopamine re-uptake through the same transporter (Hyman, 1996). Peripherally, similar actions affect norepinephrine nerve endings. Amphetamine-like drugs and cocaine therefore produce similar syndromes of overdose and withdrawal, although the symptoms and signs of cocaine overdose tend to be shorter lived.

Dextroamphetamine and methamphetamine are taken orally or parenterally, and crystalline methamphetamine ('ice') is smoked. Cocaine hydrochloride is either snorted or injected; its alkaloidal form ('free-base' or 'crack') is smoked (Cho, 1990). Less often used recreationally are decongestants such as phenylpropanolamine, ephedrine and propylhexadrine, some of which are sold as 'legal stimulants' (Lake & Quirk, 1984). The 'designer amphetamine' methylenedioxymethamphetamine ('ecstasy'), popular among college students, has both psychostimulant and LSD-like hallucinogenic properties (Bost, 1988). Increased international travel has led to the appearance in Europe and North America of lesser known psychostimulants such as khat, a shrub widely used in East Africa and the Arabian peninsula (Kalix, 1990).

Injectors or smokers of methamphetamine or cocaine often take the drug daily in huge doses, for psychic dependence and tolerance to euphoria are rapidly acquired. During the course of repeated administration, users may be continuously awake and gradually undergo mood changes, which progress to paranoia or frank psychosis with auditory and visual hallucinations. Violent behaviour can result in suicide or homicide. Abnormal movements progress from stereotypic activity, bruxism, and tremor to dystonia and choreoathetosis. The appearance of psychosis and abnormal movements with repeated use is an example of sensitization ('reverse tolerance').

More acute overdose causes excitement, confusion, headache, chest pain, tachycardia, hypertension, sweating, mydriasis, and then delirium, cardiac arrhythmia (including ventricular tachycardia and ventricular fibrillation), fever (sometimes over 109 °F), myoclonus, seizures, coma, shock, and death. There may be myoglobinuria, disseminated intravascular coagulation, or intracranial hemorrhage. Especially with cocaine, peripheral vasoconstriction causes myocardial infarction, aortic dissection, and gastrointestinal infarction or perforation (Derlet & Albertson, 1989; Ruttenber et al., 1997).

Treatment of psychostimulant overdose includes temperature control, fluid replacement, sedation and oxygen. Benzodiazepines are preferable to neuroleptics, which lower seizure threshold and cause hypotension, hypothermia, cardiac arrhythmia, and acute dystonia. Very high doses of a benzodiazepine may be necessary, e.g. diazepam 100 mg in the first 30 minutes. If seizures do not respond to benzodiazepine administration, barbiturates are preferred to phenytoin. Hypertension usually responds to sedation, but if sustained or dangerous is treated with an alpha-blocker (e.g. nitroprusside). (Beta-blockers may result in unopposed alpha-agonism and paradoxical worsening of hypertension.) Conversely, hypotension requires blood pressure support, and close ventilatory and cardiac monitoring are essential. Metabolic acidosis can be severe, requiring large doses of bicarbonate; although urinary acidification increases cocaine and amphetamine excretion, it is contraindicated in such a setting. Recovery from cocaine intoxication usually occurs within a few hours and is complete unless there has been anoxic-ischemic brain damage. Signs of amphetamine poisoning tend to be more prolonged, and in some cases hemodialysis may be appropriate (Goldfrank & Hoffman, 1991; Chiang, 1998).

Psychostimulant withdrawal causes fatigue, hunger, depression, and drug craving. There is little in the way of objective signs, but suicidal ideation may require hospitalization.

Barbiturates and other sedatives

Sedative drugs include barbiturates, benzodiazepines, and a variety of other agents (Table 114.3). Although they differ in many of their properties, most resemble ethanol in their sedative affects and withdrawal symptoms. They are partially cross-tolerant with ethanol and with each other.

Barbiturate overdose is most often the result of a suicide attempt or accidental ingestion by children. Recreational use usually involves short-acting agents such as secobarbital, taken orally or parenterally. Tolerance develops rapidly to euphoria and sedation but less so to respiratory depression, and so small increments in dosage can be dangerous. Ethanol, moreover, can aggravate the effects of barbiturates.

Overdose causes coma and respiratory depression progressing to apnea (Gary & Tresznewsky, 1983). Hypotension is more often secondary to hypoxia than to direct medullary depression. Treatment begins with respiratory support and oxygen. If only a few hours have elapsed since ingestion, induced emesis or gastric lavage is performed. Activated charcoal and a cathartic are administered, and if hypotension does not respond to artificial ventilation, it may be necessary to use volume expansion or pressors, and metabolic acidosis may require correction. Urinary alkalization hastens the excretion of long-acting barbiturates such as phenobarbital. Hemodialysis is also more effective with long-acting agents. CNS stimulant drugs are contraindicated.

As noted in Chapter 30, barbiturates and ethanol cause similar withdrawal syndromes, including tremor, hallucinations, seizures, and delirium tremens (Wikler, 1968). Symptoms can last weeks, and cardiovascular collapse can be fatal. Mild barbiturate withdrawal symptoms can be treated with titrated doses of a short-acting barbiturate. Seizures are appropriately treated with phenobarbital. Hallucinations are also treated with a barbiturate, for neuroleptics lower seizure threshold. Delirium tremens is a medical emergency requiring sedation (appropriately with a barbiturate, although, as with alcohol delirium tremens and in contrast to opiate withdrawal, administration of the offending agent does not reverse symptoms once full-blown delirium tremens is present). Cooling, correction of fluid and electrolyte imbalance, and close cardiac monitoring are best performed in an intensive care unit.

Table 114.3. Sedatives

Barbiturates
Amobarbital (Amytal)
Aprobarbital (Alurate)
Barbital (in Plexonal)
Butalbital (Sandoptal, and in mixtures, e.g. Amaphen, Fiorinal, Plexonal, Repan)
Hexobarbital (Sombulex)
Mephobarbital (Mebaral)
Methohexital (Brevital)
Pentobarbital (Nembutal)
Phenobarbital (Luminal, etc. and in mixtures, e.g. Donnatal)
Primidone (Mysoline)
Secobarbital (Seconal)
Talbutal (Lotusate)
Thiamylal (Surital)
Thiopental (Pentothal)

Benzodiazepines
Alprozolam (Xanax)
Bromazepan (Lectopam)
Chlorazepate (Tranxene)
Chlordiazepoxide (Librium)
Diazepam (Valium)
Flunitriazepam (Rohypnol) (illegal in the US)
Flurazepam (Dalmane)
Halazepam (Paxipam)
Lorazepam (Ativan)
Nitrazepam (Mogadon)
Oxazepam (Serax)
Oxazolam (Serenal)
Prazepam (Verstran, Centrax)
Temazepam (Cerepax, Levanxol)
Triazolam (Halcion)

Others
Bromide
Buspirone (Buspar)
Chloral hydrate (Noctec)
Chlormezanone (Trancopal)
Ethchlorvynol (Placidyl)
Glutethimide (Doriden)
Hydroxyzine (Atarax, Vistaril)
Meprobamate (Miltown, Equanil)
Methaqualone (Qualude, Sopor) (withdrawn)
Methyprylon (Noludar)
Paraldehyde (withdrawn)
Zolpidem (Ambien)

The abuse potential of benzodiazepines is less than that of barbiturates, but illicit use does occur (probably more often to treat pre-existing symptoms than to obtain a 'high'). Benzodiazepine overdose is much less likely than barbiturate overdose to depress respiration. Flumazenil reverses the sedative effects of benzodiazepines (and of zolpidem), but symptoms tend to return within 30 to 60 minutes, and withdrawal symptoms can be precipitated (Geller et al., 1991).

Benzodiazepine abstinence symptoms, usually limited to anxiety and tremor, are often difficult to tell from those symptoms for which the drug was being taken in the first place. Seizures, hallucinations, and delirium can follow abrupt withdrawal from short-acting agents (du Bard, 1979).

Non-barbiturate, non-benzodiazepine sedatives also cause coma and respiratory depression in overdose and tremor, seizures, or delirium in withdrawal. Some also have characteristic features of their own. Overdose with methaqualone (no longer marketed in the United States) causes delirium, hallucinations, myoclonus, seizures, papilledema, and congestive heart failure (Wetli, 1983). Glutethimide and methyprylon can cause severe circulatory failure, and with its anticholinergic properties glutethimide causes dilated unreactive pupils, ileus, and atonic bladder. As a street drug glutethimide is often injected parenterally combined with codeine ('hits', 'loads') (Bender et al., 1988). Ethchlorvynol causes hypotension, pulmonary edema, and prolonged coma; exchange transfusion and hemoperfusion with Amberlite resin can be used to treat ethchlorvynol poisoning (Lynn et al., 1979). Bromide salts (no longer present in over-the-counter sleeping pills) cause a skin rash; treatment of overdose includes sodium chloride and diuresis.

Increasingly popular during the 1990s, gamma-hydroxybutyrate (GHB) is readily synthesized from the industrial solvent gamma-hydroxybutyrolactone (Chin et al., 1992). Taken for its sedative and euphoric properties, GHB (and the illegal benzodiazepine flunitrazepam) are particularly implicated as 'date rape' drugs. GHB overdose causes coma and respiratory depression, which tend to be short lived, requiring supportive treatment, but fatalities have occurred. Withdrawal symptoms consist of tremor, anxiety and insomnia.

Marijuana

The most widely used illicit drug in the United States, marijuana consists of leaves and tops of the hemp plant *cannabis sativa*, which contains numerous cannabinoid compounds. Delta-9-tetrahydrocannabinol (Δ-9-THC), the principal psychoactive ingredient, causes euphoria and drowsiness. Hashish, derived from the plant resin, has high concentrations of Δ-9-THC. Cannabinoid compounds act at specific receptors in the central and peripheral nervous systems, and endogenous ligands for these receptors have been identified, yet the mechanisms of cannabinoid compounds' multiple actions – convulsant, anticonvulsant, hyperthermic, hypothermic, analgesic, bronchodilating – are uncertain (Brust, 1999).

Marijuana and hashish are usually smoked but can be eaten. Acute adverse effects are infrequent, and fatal overdose has never been convincingly described. (Marijuana users are, however, over-represented in traffic and other accidents.) Often accompanying the intended dreamy euphoria are jocularity, disinhibition, depersonalization, subjective time slowing, conjunctival injection, tachycardia, and postural hypotension (Heishman et al., 1990). High doses cause auditory or visual hallucinations, confusion, anxiety, and psychotic depression or excitement, and conventional doses can cause paranoia, delusions, depression, or panic ('freaking out') (Weil, 1970). 'Flashbacks' consist of the spontaneous reappearance, weeks or months after using marijuana, of hallucinations or other symptoms associated with earlier use. Adverse reactions usually last a few hours and require no more than calm reassurance; benzodiazepine therapy can be used for severe cases, which should raise suspicion of concomitant use of another drug such as phencyclidine.

Tolerance develops to marijuana's cardiovascular and perhaps to its depressant behavioural effects, but there may be 'reverse tolerance' for excitement or psychosis. Addiction occurs, but symptoms of physical dependence – jitteriness, anorexia, and headache – tend to be mild.

Hallucinogens

Hallucinogenic plants are used ritualistically or recreationally around the world; most often encountered in North America are mushrooms containing psilocin and psilocybin, peyote cactus containing mescaline, and the synthetic ergot d-lysergic acid diethylamide (LSD), which during the 1990s became increasingly popular among American adolescents (Table 114.4). Taken orally, these substances produce similar effects and are cross-tolerant with one another (Jacobs, 1987; Schwartz & Smith 1988).

Acute effects of hallucinogens are perceptual (distortions and hallucinations, usually visual and elaborately formed), somatic (dizziness, tremor, paresthesias, hyperthermia, piloerection, mydriasis with preserved light reflex, tachycardia, hypertension), and psychological (depersonalization, altered mood, derealization, autism,

Table 114.4. Hallucinogens abused in the United States

Mescaline (peyote cactus)
Psilocybin and psilocin (*Psilocybe*, *Penaelous*, and *Conocybe* mushrooms)
D-lysergic acid diethylamide (LSD)
Dimethyltryptamine (DMT)
Diethyltryptamine (DET)
Dimethoxymethylamphetamine (DOM, 'STP')
Dimethoxyethylamphetamine (DOET)
Methylenedioxyamphetamine
D-lyseric acid amide (morning glory seeds)
Myristicin (nutmeg)
Nepetalactone (catnip)

mystical elation), and it is the latter that pose potential danger (Hollister, 1984). 'Bad trips', with panic or marked paranoia, can lead to accidents, self-mutilation, suicide, or homicide. Such symptoms can spontaneously recur as flashbacks weeks or months after original use (Hatrick & Dewhurst, 1970). Adverse reactions usually clear within 24 hours and can be managed with talking down or benzodiazepine therapy. (Neuroleptics can paradoxically exacerbate symptoms.) Death directly attributable to LSD has not been described, but severe hypertension may require treatment with an alpha blocker or direct vasodilator, and hyperthermia, which in the presence of agitation can cause myoglobinuria, may require cooling.

Tolerance develops to LSD's effects, but physical dependence does not seem to occur.

Inhalants

Inhalation of volatile substances to achieve euphoria is popular among American children and adolescents, who sniff a wide variety of products with many constituents (Table 114.5). Substances are usually sniffed from a saturated rag, a plastic bag, directly from the container, or from a heated frying pan, sometimes for hours at a time daily over years. Nitrous oxide is obtained from whipped cream canisters, and butyl or amyl nitrite from 'room odorizers'.

Acute effects, including toxicity, are remarkably similar among different agents (Morton, 1987). Moderate doses produce euphoria and ataxia resembling ethanol intoxication, with similar propensity to accidents or violence. Higher doses cause psychosis with delusions and hallucinations, as well as cyanosis, seizures, and coma (Ramsey et al., 1989). Aspiration of vomitus and asphyxiation by plastic bags can be fatal; unexplained sudden death is probably due to cardiac arrhythmia, and respiratory depression can occur. Acute lead encephalopathy has followed gasoline sniffing, and nitrous oxide sniffers have died from brain anoxia. Nitrite sniffing causes methemoglobinemia, but syncope tends to prevent inhalation of a life-threatening amount (Brust, 1993).

Table 114.5. Substances commonly abused as inhalants

Aerosols (refrigerants, frying pan sprays, antitussives, bronchodilators, deodorants, hair sprays, shampoos, antiseptics)
Lacquers, paints, enamels, and lacquer and paint thinners
Lighter fluids
Fingernail polish removers
Cleaning fluids (spots, shoes, wigs)
Airplane model cements
Furniture polishes
Household cements
Plastic (polystyrene) cements
Rubber, tyre-patching, or tube repair cements
Gasoline
Anesthetics (ether, nitrous oxide, halothane, trichlorethylene)
'Room fresheners' (nitrites)

Acute symptoms tend to clear within a few hours, and treatment includes respiratory and cardiac monitoring. Tolerance develops, but there is no predictable abstinence syndrome other than craving.

Phencyclidine

Developed as an anesthetic and withdrawn because it causes psychosis, phencyclidine ('PCP', 'angel dust') blocks *N*-methyl-D-aspartate receptor excitatory neurotransmission. The drug can be eaten, snorted, or injected but is most often smoked, sprinkled on tobacco or marijuana (Thombs, 1989). A number of PCP congeners sold as street drugs, including the anesthetic ketamine, may give negative results on toxicological testing for PCP.

Low doses of PCP cause euphoria or dysphoria, emotional liability, a sense of numbness, and sensory distortions. Higher doses produce agitation, confusion, bizarre behaviour, synesthesias, and analgesia and then psychosis with both negative and positive features of schizophrenia, including paranoia with auditory hallucinations and stuporous catatonia (McCarron et al., 1981a,b). Somatic signs include burst-like horizontal and vertical nystagmus, miosis, ataxia, myoclonus, fever, sweating, tachycardia and hypertension. Anesthetic doses produce seizures, coma

with extensor posturing, respiratory depression and hypotension. Myoglobinuria occurs, and malignant hyperthermia may cause liver necrosis. Death can be the result of direct overdose, accidents, violence or suicide. Recovery can take days, during which time even mild stimuli may provoke agitated or violent behaviour.

Very little active drug is excreted through the kidney, and so diuresis is ineffectual; although acidification increases PCP excretion, myoglobinuria contraindicates such treatment. Gastroenteric recirculation favours intermittent gastric lavage, and a cathartic and activated charcoal prevent absorption. Severe hypertension, which can appear days after drug intake, may require alpha-blockade or direct vasodilatation. Seizures are treated with a benzodiazepine or phenytoin.

Agitation or psychosis (which can emerge as the patient comes out of stupor or coma) does not respond to 'talking down'. Although benzodiazepines prolong PCP's half-life and can aggravate its depressant actions, they are preferable to neuroleptics, which lower seizure threshold, are hypotensive, and cause a malignant neuroleptic syndrome with myoglobinuria, and, through anticholinergic actions, aggravate delirium. Symptoms of overdose last hours to days, and sometimes psychosis outlasts other symptoms and signs; in such a situation, a trial of neuroleptic therapy is appropriate.

Tolerance develops to PCP's effects, but physical dependence and withdrawal symptoms, other than craving, are not encountered.

Anticholinergics

The recreational use of anticholinergic agents includes ingestion of the plant *Datura stramonium*, popular among American adolescents, as well as the use of antiparkinsonian drugs, antiasthmatic inhalers, and tricyclic antidepressants (especially amitriptyline). Symptoms and signs include euphoria, excitement, delirium, hallucinations, dilated unreactive pupils, dysphagia, urinary retention, dry flushed skin, high fever, hypertension, tachypnea, and tachycardia (Mikolich et al., 1975). Severe poisoning causes myoclonus, seizures, extensor posturing, coma, respiratory failure, shock and death. Delusions and hallucinations can be prominent during recovery.

Symptoms last hours to days. Treatment includes physostigmine 1 to 3 mg intravenously at 30 minute to 2 hour intervals (unless intraventricular conduction delay is suspected), plus gastric lavage (the drug delays gastric emptying), cooling, bladder catheterization, respiratory and cardiac monitoring, and, if necessary, anticonvulsants, Neuroleptics, which have anticholinergic actions, are contraindicated; benzodiazepines can be used cautiously for agitation.

A withdrawal syndrome is not described.

Neurological complications

Trauma

Acute intoxication from any of the above drugs, as well as ethanol, can result in accidents or violent behaviour, including suicide. Overprescribing of sedatives is a common cause of falls in the elderly. Cerebral or spinal cord injury must always be considered in intoxicated subjects, who may be difficult to examine or to image. Trauma among illicit drug users, however, is more often related to the drug's illegal status, i.e. either involving crimes committed to obtain the drug or reflecting the business practices of drug traffickers (Goldstein, 1985). Prior to the AIDS epidemic violence accounted for nearly half of all fatalities among New York city heroin addicts, and a surge of violent crime in American cities accompanied the 'crack' cocaine epidemic of the 1980s and 1990s.

Infection

An array of local and systemic infections affect parenteral users of any drug. Frequently encountered are local abscesses, pyomyositis, cellulitis, pneumonia, sepsis, endophthalmitis, chorioretinitis, episcleritis, fasciitis, osteomyelitis, and pyogenic arthritis (Richter, 1993). Infections frequently affect the central or peripheral nervous systems. Endocarditis, bacterial or fungal, leads to meningitis, cerebral infarction, diffuse vasculitis, abscess (brain, subdural, or epidural, including the spinal cord), or subarachnoid hemorrhage from rupture of a septic ('mycotic') aneurysm (Gattell et al., 1984). Mycotic aneurysms in parenteral drug users have occurred on the carotid, subclavian and pulmonary arteries.

Infectious hepatitis can cause encephalopathy or, because of deranged clotting, hemorrhagic stroke. Vertebral osteomyelitis or disc infection can cause radiculopathy or myelopathy. Tetanus, seen especially in subcutaneous injectors of heroin, tends to be severe (Brust & Richter, 1974). Botulism occurs at injection sites or, among cocaine snorters, in the nasal sinuses (Kudrow et al., 1988). Malaria has affected heroin users in endemic areas (Gonzalez-Garcia et al., 1986).

As of 2000, in the United States non-homosexual parenteral drug abusers accounted for 26% of adult and

adolescent cases of acquired immunodeficiency syndrome (AIDS) reported to the Centers for Disease Control and Prevention (and nearly half of reported women with AIDS). Male homosexual drug abusers represented another 6%, and heterosexual contact with a parenteral drug abuser another 4%. Over half of the 8000 American children less than 13 years of age with AIDS have had a mother who either abused drugs or who had sex with a drug abuser (HIV/AIDS Surveillance Report, 2000). Nearly two-thirds of patients receiving methadone maintenance therapy in New York City are seropositive for human immunodeficiency virus (HIV) (DesJarlais et al., 1989).

Parenteral drug abusers develop the same neurological complications of AIDS as do those with other risk factors (Malouf et al., 1990). They are particularly susceptible to tuberculosis (including drug-resistant strains) and syphilis (Friedman et al., 1996). Because of promiscuity and associated sexually transmitted diseases, non-parenteral cocaine users are also at increased risk for HIV infection. Heroin and cocaine are themselves immunosuppressant, yet HIV-seropositive users do not seem to be more susceptible to the development of AIDS.

Parenteral drug abusers are also subject to infection with human T-cell lymphotrophic retrovirus (HTLV) type I or type II, and a number of cases of associated myelopathy have been reported (Jacobson et al., 1993).

Seizures

As noted, seizures can be a feature of drug toxicity (e.g. psychostimulants) or drug withdrawal (e.g. sedatives) (Earnest, 1993; Alldredge et al., 1989). With amphetamine-like agents, seizures are usually accompanied by other signs of overdose. With cocaine, however, seizures can occur without other symptoms and signs (Pascual-Leone et al., 1990). Animal studies demonstrate a 'kindling' pattern at initially subconvulsant doses; the difference between amphetamine and cocaine epileptogenicity might be related to cocaine's local anesthetic properties (Karler et al., 1989). Seizures have also occurred following ingestion of phenylpropanolamine in recommended dosage for weight reduction (Mueller & Solow, 1982).

In animals, opiates can be proconvulsant or anticonvulsant depending on receptor specificity and seizure model (Ng et al., 1990). Opiate agonists lower seizure threshold in humans, but seizures are an uncommon feature of heroin overdose, and an alternative cause should always be sought. Meperidine, however, readily causes myoclonus and seizures through the proconvulsant properties of its metabolite normeperidine (Hershey, 1983). Seizures are also frequently seen in injectors of the mixed agonist-antagonist pentazocine combined with the antihistamine tripelennamine ('Ts and blues'); both drugs are proconvulsant (Caplan et al., 1982).

As with ethanol, seizures associated with barbiturate or benzodiazepine withdrawal tend to be single or clustered, but status epilepticus can occur. Seizures as a toxic effect are described with methaqualone (which is sometimes combined with an antihistamine) and with glutethimide (which has anticholinergic properties) (Hoaken, 1975).

As a blocker at NMDA receptors, phencyclidine would be expected to have anticonvulsant properties, yet seizures and myoclonus are often encountered at high doses (McCarron et al., 1981a,b).

A case-control study found that marijuana was protective against the development of new onset seizures. In animals, the non-psychoactive cannabinoid, cannabidiol, is anticonvulsant, and limited studies suggest it can reduce seizure frequency in human epileptics (Ng et al., 1990).

Stroke

Many illicit drug users also abuse tobacco and ethanol, increasing their risk for ischemic and hemorrhagic stroke. (Low-to-moderate doses of ethanol protect against both myocardial infarction and ischemic stroke, but heavy doses increase risk, and even low doses of ethanol increase risk of hemorrhagic stroke.) Systemic complications of parenteral drug abuse, for example, hepatitis, endocarditis, or AIDS, also predispose to stroke. Heroin nephropathy causes uremia, bleeding, and hemorrhagic stroke (Brust, 1998).

Heroin has caused ischemic stroke without such intermediary conditions or other evident risk factors (Brust & Richter, 1976). In some reported cases, angiographic changes were consistent with cerebral vasculitis, and laboratory abnormalities, e.g. blood eosinophilia, hypergammaglobulinemia, positive Coombs test, suggested hypersensitivity. Other possible mechanisms are systemic hypotension following overdose and embolization of injected foreign material. Stroke in injectors of pentazocine and tripelennamine ('Ts and blues') has resulted from embolization of particulate material passing through secondary pulmonary arteriovenous shunts (Caplan et al., 1982). Possibly vascular in origin is heroin myelopathy, in which acute paraparesis, sensory loss, and urinary retention follow injection, sometimes after a period of abstinence (Goodhart et al., 1982).

Intracerebral hemorrhage, often associated with fever and acute hypertension, affects users of amphetamine-like drugs. Ischemic stroke in amphetamine or methampheta-

mine users has reportedly been a feature of systemic and central nervous system vasculitis resembling polyarteritis nodosa (Citron et al., 1970). Small vessel vasculitis more typical of hypersensitivity angiitis has also caused ischemic stroke. Although reported cases are often based on non-specific angiographic 'beading', cerebral vasculitis has been demonstrated in animals receiving repeated doses of methamphetamine over weeks or months (Brust, 1997).

Stroke in cocaine users can be secondary to drug-induced cardiac arrhythmia, myocardial infarction, or cardiomyopathy. In many cases, however, neither cardiac disease, infection, nor other risk factor is apparent (Sloan et al., 1998). Of the more than 400 cocaine-related strokes reported to date, about half were ischemic and half hemorrhagic. Strokes have occurred with both cocaine hydrochloride and alkaloidal 'crack' (Levine et al., 1990). Ischemic strokes include transient ischemic attacks and infarction of the cerebrum, thalamus, brainstem, spinal cord, and retina. Of those patients with hemorrhagic stroke who underwent cerebral angiography, about half harboured saccular aneurysms or vascular malformations. A plausible mechanism for hemorrhagic stroke is surges of systemic hypertension. Some ischemic strokes might be the result of direct cerebral vasoconstriction induced by the drug. Most autopsies have failed to show cerebral vasculitis, and when present, it was mild (round cell infiltration without vessel wall necrosis). Contributory might be cocaine effects on platelets and clotting factors and the ability of the drug to accelerate atherosclerosis (Brust, 1998).

LSD and phencyclidine are vasoconstrictive, and occlusive and hemorrhagic stroke have followed their use (Lieberman et al., 1974). In the case of phencyclidine acute elevation of blood pressure and intracerebral hemorrhage have occurred a few days after using the drug (Eastman & Cohen, 1975).

Altered mentation

Illicit drug users are at risk for altered mentation, including dementia, by indirect mechanisms such as concomitant ethanol abuse, malnutrition, head trauma, and infection, especially HIV. Less clear is whether the drugs themselves cause lasting cognitive or behavioural change. Predrug mental status is nearly always uncertain, and many drug users are self-medicating pre-existing psychiatric conditions, for example, cocaine for depression. The weight of evidence is against chronic mental abnormality secondary to opiates, marijuana, or hallucinogens (Weinrieb & O'Brien, 1993).

Controversial is whether repeated use of psychostimulants predisposes to lasting depression, a proposed mechanism for which would be perturbation of dopaminergic circuits in the mesolimbic 'reward circuit'. Cerebral atrophy and irregularly decreased cerebral blood flow are described in chronic cocaine users, and studies using controls have shown abnormalities on psychometric testing; a proposed mechanism is repeated widespread cerebral vasoconstriction and ischemia (Pascual-Leone et al., 1991; Holman et al., 1991). In a careful prospective analysis, however, chronic exposure to cocaine was associated with neuropsychological impairment, yet there was no correlation with brain volume loss when subjects with additional substance abuse were excluded (Langendorf et al., 2000).

Chronic barbiturate abuse is associated with psychological and social deterioration, including paranoia and suicide, but in contrast to ethanol abuse, CT results do not differ from controls (Allgulander et al., 1984).

Behavioural changes and EEG abnormalities are described in sniffers of halogenated hydrocarbons, but causality is unproven (Chadwick & Anderson, 1989). More convincing is persistent encephalopathy following chronic toluene exposure; autopsies on such patients reveal widespread loss of CNS myelin (Filley et al., 1990).

Memory disturbance, word-finding difficulty, loss of impulse control, and symptoms suggesting schizophrenia are common among users of phencyclidine, but as with other drugs, cause versus effect is uncertain (Fauman et al., 1976).

Fetal effects

The effects of illicit drugs on intrauterine development are similarly confounded by ethanol and tobacco use, malnutrition, inadequate prenatal care, and incompetent parenting (Chiriboga, 1993). Infants exposed in utero to heroin (or methadone) are reportedly small for gestational age, at risk for respiratory distress, and cognitively impaired later in life; other studies, however, have failed to identify long-term developmental or cognitive sequelae when correcting for other risk factors (Strauss & Reynolds, 1983). Low birth weight and later cognitive impairment do follow intrauterine opiate exposure in animals (Kirby, 1979).

In utero marijuana exposure is associated with decreased birth weight and length (Zuckerman et al., 1989; Frank et al., 1990). Whether such exposure causes cognitive or behavioural abnormalities in either humans or animals is controversial.

Cocaine exposure has reportedly caused absuptio placentae, decreased birthweight, a variety of congenital

anomalies, microcephaly, perinatal stroke, and developmental delay. A prospective study found diffuse or axial hypertonia in cocaine-exposed neonates compared to controls, and this 'spastic tetraparesis' cleared by 24 months of age, with no differences between groups in mental or motor development (Chiriboga et al., 1999). Animal studies, however, offer evidence that cocaine damages fetuses, perhaps by decreasing placental blood flow; in one study impaired learning occurred in the absence of evident brain malformation (Church et al., 1988).

Miscellaneous effects

Guillain–Barré polyneuropathy and brachial and lumbosacral plexopathy, probably immunologic in origin, are described in heroin users (Shafer, 1993). (Brachial plexopathy has also resulted from compression by a subclavian infected aneurysm.)

Sniffers of glues containing n-hexane are at risk for severe sensorimotor polyneuropathy, which can result in quadriplegia over a few weeks, with incomplete improvement upon removal of the toxin (Procop et al., 1974). Nerve biopsy reveals distention of axons by masses of neurofilaments and secondary demyelination.

Myeloneuropathy clinically and pathologically indistinguishable from combined systems disease of cobalamin deficiency affects sniffers of nitrous oxide, which oxidizes cobalamin. Anemia is usually absent, and serum cobalamin levels are usually normal (Heyer et al., 1986).

Severe irreversible parkinsonism developed in Californians exposed to a meperidine analog contaminated with 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine, a metabolite of which is toxic to neurons in the substantia nigra. Levodopa relieved symptoms, which in some cases were of life-threatening severity, but treatment had to be continued indefinitely, and levodopa-induced dyskinesias were common (Langston, 1985). Moreover, delayed parkinsonism has developed in previously asymptomatic subjects exposed to small doses of the drug.

Smoking the vapour of heroin heated on metal foil ('chasing the dragon') resulted in cerebral and cerebellar spongiform leukoencephalopathy in European and North American users. Dementia, ataxia, quadriparesis and blindness progressed to death in several cases; in others there was incomplete improvement. The mechanism of damage is unclear; elevated lactate in white matter suggests mitochondrial dysfunction (Kriegstein et al., 1999).

A man who took large parenteral doses of heroin containing quinine developed blindness. His vision improved when he resumed using heroin without quinine (Brust & Richter, 1971).

Dystonia and chorea lasting days or weeks occur in chronic cocaine users, and cocaine can precipitate symptoms in patients with Tourette's syndrome (Factor et al., 1988). Opsoclonus is also reported in cocaine users.

Marijuana inhibits luteinizing and follicle-stimulating hormone, causing erectile dysfunction and sterility in men and menstrual irregularity in women. Symptoms are reversible with abstinence (Powell & Fuller, 1983).

In addition to cerebral leukoencephalopathy, toluene sniffers develop cerebellar white matter degeneration and ataxia (Kelly, 1975).

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Part XVI

Degenerative disorders

115

Genetically engineered models of neurodegenerative disorders

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The neurodegenerative diseases (Table 115.1) represent some of the greatest challenges for basic science and clinical medicine because of their prevalence, cost, complex biochemistries and pathologies, lack of mechanism-based treatments, and impacts on individuals, caregivers, and society at large (Price et al., 1998a,b; Wong et al., 1998; Hardy & Gwinn-Hardy, 1998; Dunnett & Bjorklund, 1999; Lee & Trojanowski, 1999; Lin et al., 1999; Yamamoto et al., 2000). This heterogeneous group of age-associated, chronic, illnesses, including Alzheimer's disease (AD), Parkinson's Disease (PD), motor neuron diseases (MND), the trinucleotide repeat diseases, and the prion disorders, are usually characterized by: genetic risk factors; onset within certain age ranges; progressive courses; well-defined clinical syndromes; evidence of dysfunction/death of specific populations of neurons; specific pathological and biochemical abnormalities; and presence, in many instances, of intra- or extracellular protein aggregates (Burright et al., 1995; Mangiarini et al., 1996; Robitaille et al., 1997; Davies et al., 1997; Becher et al., 1998; Price et al., 1998a,b; Wong et al., 1998; Hardy & Gwinn-Hardy, 1998; Goedert et al., 1998; Schilling et al., 1999; Selkoe, 1999; Cleveland, 1999; Lin et al., 1999; Lansbury, 1999; Zoghbi & Orr, 1999). At present, only symptomatic treatments are available and there are no mechanism-based therapies. The vast majority of patients with these various disorders become severely disabled and die of intercurrent illnesses. However, recent research, particularly in animal models, has begun to provide new insights into the mechanisms of these disorders and has identified new targets for therapy (*see also* Chapter 15).

Over the past few years, genetic studies have provided major clues as to pathogeneses of these illnesses. For some of these diseases, the cause is always due to genetic abnormalities (Table 115.2). For example, the trinucleotide repeat diseases (i.e. the autosomal dominant spinocerebellar ataxias, SCA and Huntington's disease, HD) are always associated with expanded CAG repeats in specific genes and all cases of autosomal recessive infantile and childhood spinal muscular atrophy (SMA) are caused by mutations/deletions of both alleles of the gene encoding survival motor neuron (SMN). In other instances, the illness can be familial or putatively sporadic. The majority of cases of AD, ALS, and PD are considered to be sporadic because most affected individuals do not exhibit obvious Mendelian patterns of inheritance. However, perhaps 5–10% of cases of AD, PD, and amyotrophic lateral sclerosis (ALS) have positive family histories, distinct patterns of inheritance, and mutations of specific genes (Price et al., 1998a,b; Wong et al., 1998; Hardy & Gwinn-Hardy, 1998) (Table 115.2). For example, familial ALS (FALS), AD (FAD), and PD (FPD) as well as frontotemporal dementia with Parkinsonism (FTD-P) show autosomal dominant inheritance: some cases of FALS are linked to mutations in the superoxide dismutase 1 (*SOD1*) gene (Wong et al., 1998; Andersen et al., 2000); subsets of cases of FAD are caused

Table 115.1. Neurodegenerative diseases

Chronic, progressive neurological disorders
Sporadic and/or familial
Autosomal dominant, recessive, X-linked, allele-associated
Clinical manifestations reflect involvement of subsets of cells (selective vulnerability)
Often associated with intra- or extracellular aggregates, degeneration of synapses and axons, and evidence of cell dysfunction/death
Significant causes of morbidity and mortality
With rare exceptions, no effective therapies
Associated with enormous costs to society
New opportunities for mechanism-based therapies

Table 115.2. Autosomal dominant neurodegenerative diseases and transgenic models

Disease	Mutant gene	Intracellular or extracellular aggregates	Aggregate component	Transgene in models
FAD	APP PS1 PS2	Extracellular amyloid	Aβ	Mutant APP and PS1
FALS	SOD1	Cytoplasmic inclusions	SOD1	Mutant SOD1
FTDP-17	Tau	Tangle-like structures	tau	Mutant tau
PD	α-syn	Lewy bodies Lewy neurites	α-syn	wt (or mutant)α-syn
Prion	PrP	Amyloid-like material	PrP^{SC}	mutant PrP
HD	huntingtin	Intranuclear inclusions	huntingtin	huntingtin (expanded repeat)
SCA-1	ataxin-1	Intranuclear inclusions	ataxin-1	ataxin-1 (expanded repeat)
SCA-3	ataxin-3	Intranuclear inclusions	ataxin-3	ataxin-3(expanded repeat)
DRPLA	atrophin-1	Intranuclear inclusions	atrophin-1	atrophin-1 (expanded repeat)

by mutant genes encoding the amyloid precursor protein (APP), presenilins 1 (PS1) or presenilin 2 (PS2) (Price et al., 1998a,b; St. George-Hyslop, 1999) (Fig. 115.1); some individuals with FPD are linked to missense mutations in α-synuclein (*α-syn*); and cases of FTD-P linked to chromosome 17 are associated with either intronic or exonic mutations in *tau*. Some individuals with autosomal recessive parkinsonism have mutations/deletions in *parkin*. Often, patients within each of these familial illnesses exhibit clinical and pathological features that are difficult to distinguish from those manifestations occurring in cases of sporadic disease.

The identification of mutations in specific genes causing each of these neurodegenerative diseases has provided new opportunities to investigate the molecular participants in disease processes and to explore pathogenic mechanisms in model systems. To investigate the biochemical pathways whereby mutant gene products impact, directly or indirectly, on the functions of neural cells, investigators have increasingly used transfection, transgenic, and gene targeting methods to introduce mutant genes or ablate genes in both in vitro and in vivo model systems (Table 115.2). Genetically engineered animal models allow investigations of the in vivo consequences of mutations or deletion of genes and determination of the biochemical pathways/mechanisms leading to dysfunction/death of affected populations of neural cells. Transgenic mice overexpressing mutant genes are of great value in the autosomal dominant genetic neurodegenerative disorders in which the mutant proteins do not exhibit reductions in their normal functions, but instead often acquire toxic properties or participate indirectly in the formation of toxic products (Price et al., 1998a,b; Wong et al., 1998; Hardy & Gwinn-Hardy, 1998; Goedert et al., 1998; Schilling et al., 1999; Selkoe, 1999; Cleveland, 1999; Zoghbi & Orr, 1999). The autosomal recessive diseases, which are associated with absence of the encoded protein (loss of function), can often be modelled by gene targeting strategies. In models of both groups of disorders, knocking out or overexpressing some of the genes that influence the pathways leading to disease have proved to be extremely valuable strategies (Fig. 115.1). In concert, these approaches have begun to provide information critical for the identification of new targets for mechanism-based treatments, which, if successful in model systems, can be rapidly introduced into clinical trials for these once intractable and mysterious diseases of the central nervous system (CNS).

In this review we focus on the familial forms of two of these diseases, AD and MND, to illustrate the ways new approaches are providing insights into these illnesses. For these two prototypes of the inherited neurodegenerative disorders, we discuss: the nature of clinical syndromes/neuropathology; the genetics and biochemistry of specific gene products; the value of genetically engineered models; issues critical to the understanding of the selective vulnerability of neurons and the pathogenesis of cell dysfunction/death in one of these diseases (AD); and experimental therapeutics. Our ultimate goal is to indicate how the information from different approaches is leading to new understanding of the susceptibilities of neurons to disease and the mechanisms leading to cell pathology, to identification of new therapeutic targets, and to

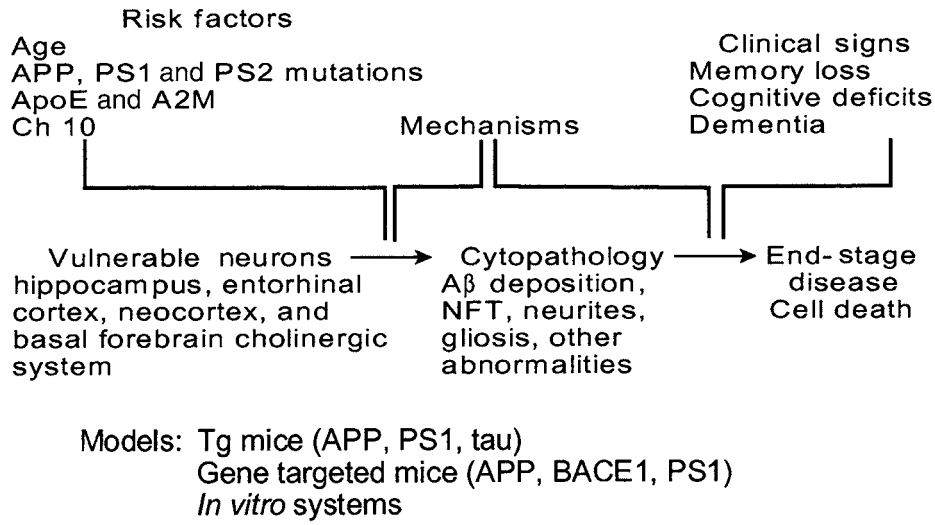

Fig. 115.1. Interactions of various risk or susceptibility factors with vulnerable populations of neurons that are responsible for memory and higher cognitive functions. The brains of individuals with Alzheimer's disease develop Aβ deposits, tangles, neurites, etc. These pathologies involving critical neuronal circuits lead to the clinical signs. In transgenic models, mutant genes linked to FAD are introduced and reproduced in the amyloid pathology seen in human subjects. Gene-targeted mice are valuable for understanding the functions of specific gene products and for defining, in the case of the secretases, the participation of specific proteins in pathogenic processes. For example, BACE1, is a key secretase in amyloidogenesis and an excellent therapeutic target.

design/testing of novel treatments for these tragic human illnesses.

Clinical signs/neuropathology

In this section, we define briefly some of clinical-pathological features of AD and MNDs that reflect the selective dysfunction/death of specific subsets of nerve cells.

Alzheimer's disease (AD)

In 1907, Alois Alzheimer described a middle-aged woman whose first complaints were increased suspicion of her husband's behaviour, followed by impairments in memory, orientation and cognition. Approximately 5 years after the onset of illness, an autopsy disclosed the now-recognized classical pathology of AD: neurofibrillary tangles and senile plaques in the neocortex and hippocampus.

In the majority of individuals with AD, the initial manifestations appear during the seventh decade, but the condition may develop in mid-life; in these instances, there may be a family history. In both the sporadic and familial forms of AD, patients have difficulties with memory, problem solving, language, calculation, visual–spatial perceptions, judgment, and behaviour; some patients develop psychotic symptoms, such as hallucinations and delusions. Mental functions and activities of daily living become progressively impaired. The accuracy of clinical diagnoses of specific causes of dementia, particularly AD, has greatly improved during the past two decades. Early diagnosis will be particularly important as mechanism based treatments become available.

Five million people in the United States now suffer from dementia. Because of increased life expectancy and post-World War II baby boom, the elderly, the population at risk for AD, is the fastest growing segment of our society. During the next 25 years, the number of people with AD in the United States will triple, as will the cost. Thus, AD is one of society's major public health problems.

As occurs in many other neurodegenerative diseases, AD involves the brain (and not other organs) and certain populations of neurons are selectively vulnerable (Table 115.1, Fig. 115.1). Thus, the clinical signs of AD are the consequence of the selective degeneration of nerve cells in those brain regions/neural circuits critical for memory, cognitive performance, and personality (Albert, 1996; Price & Sisodia, 1998; Mesulam, 1999). Dysfunction/death of neurons in the cortex, hippocampus, amygdala, basal forebrain cholinergic system, and brainstem monoaminergic nuclei leads to reduced numbers of generic and transmitter specific synaptic markers in target fields (Whitehouse et al., 1982; Francis et al., 1994; Sze et al., 1997; Price & Sisodia, 1998; Masliah, 1998); the disruption of synaptic communication in affected regions/circuits leads to memory/cognitive impairments and, finally, severe dementia (Morrison & Hof, 1997; Price & Sisodia, 1998).

Another feature of AD, shared with other neurodegenerative diseases (Tables 115.1–115.2), is the presence of characteristic protein aggregates, which in AD can be intracellular or extracellular. Within many affected neurons, aberrant tau immunoreactivity exists in: neurofibrillary tangles (NFTs), inclusions located within cell bodies and proximal dendrites; neuropil threads, which are usually within dendrites; and dystrophic neurites, filamentous swellings of distal axons/terminals (usually seen in proximity to Aβ deposits) (Price & Sisodia, 1998; Goedert et al., 1998; Delacourte et al., 1998; Price & Morris, 1999). Each of these cytoskeletal abnormalities reflects the intracellular accumulation of poorly soluble paired helical filaments (PHF), which are composed principally of hyperphosphorylated isoforms of tau, a low molecular weight microtubule-binding protein (Goedert et al., 1998; Delacourte et al., 1998). It is hypothesized that perturbations related to hyperphosphorylated tau are associated with disturbances in intracellular transport. Since nerve cells have complex geometries, they rely on transport systems to deliver critical constituents to the proper parts of the cell. Impairments of these transport processes compromises the functions and viability of neurons.

The extracellular aggregates in AD are abnormal accumulations of an amyloid peptide, termed Aβ, a 4kD α-pleated sheet amyloid peptide, derived by α- and γ-secretase cleavages of the amyloid precursor protein (APP) (Fig. 115.2, see colour plate section). Levels of Aβ are elevated in brain and Aβ monomers form oligomers and multimers which assemble into protofilaments and then fibrils (Price & Sisodia, 1998; Selkoe, 1999; Lansbury, 1999). Eventually, Aβ fibrils are deposited as the amyloid cores of neuritic or senile plaques, which are complex structures also containing dystrophic neurites, astrocytes, and microglia. Plaques are preferentially localized to cortex, hippocampus, and amygdala. As outlined below, the levels and distributions of APP and its cleavage enzymes in neurons are principal determinants leading to the selective appearance of Aβ in brain. Significantly, Aβ42 is thought to be particularly toxic to nerve cells and their processes. It is hypothesized that, at least in cases of FAD linked to mutant genes implicated in promoting amyloidogenesis, toxic Aβ peptides accumulate near synapses, and, in ways not yet clear, impair transsynaptic communication, and, ultimately, synaptic connections between neurons and their targets (other nerve cells). In parallel, subtle, possibly age-related, independent changes occur in the neuronal cytoskeleton whereby damaged nerve cells, responding to Aβ-mediated injury to its terminal fields, starts to hyperphosphorylate tau. Eventually, microtubule stability becomes compromised and intracellular transport processes are impaired; cell geometry is altered, particularly synapses and dendrites, and the cell is incapable of performing its normal functions for a significant interval before a death program kills the cell.

Motor neuron diseases

Amyotrophic lateral sclerosis (ALS)

The most common adult-onset motor neuron disease, ALS manifests as weakness/muscle atrophy and spastic paralysis, which are the result of the selective involvement of lower and upper motor neurons, respectively (Rowland, 1994; Wong et al., 1998). In ALS, the pathology of lower motor neurons evolves through a progression of stages: chromatolysis or loss of Nissl substance; alterations of the cytoskeleton, particularly neurofilaments; atrophy of dendrites and cell body; and, finally, apoptosis (Martin, 1999). Chromatolytic neurons often accumulate phosphorylated neurofilament and ubiquitin immunoreactivities in cell bodies; similarly, in FALS, caused by the presence of mutant SOD1, neurons exhibit SOD1 and ubiquitin immunoreactive cytoplasmic aggregates. The roles of these inclusions are unclear, but the presence of ubiquitin immunoreactivity suggests that these inclusions contain specific proteins destined for degradation, presumably, in part, via the proteosomal pathway. It is not known whether components within these aggregates sequester essential molecules needed for the biology of motor neurons or whether the malfolded proteins can perform aberrant catalytic reactions. In the majority of cases of ALS, neurofilamentous swellings are identified in proximal axonal segments (Carpenter, 1968; Chou, 1992; Hirano, 1996; Wong et al., 1998; Martin, 1999; Ince, 2000). Motor axons become disconnected from the muscles and begin to undergo Wallerian degeneration. Over time, cell bodies shrink and dendrites are attenuated. In the late stages, there is evidence of cell death manifest by: TUNEL labelling of some neurons; internucleosomal DNA fragments (laddering); conversion of DFF 45 to DFF 40 (the latter is the active form of enzyme that cleaves DNA into fragments); activation of caspase 1 and 3; and alterations in the distributions of Bax and Bcl_2, pro- and anti-apoptotic proteins, respectively, in the soluble and membranous (mitochondrial) compartments (Wyss-Coray et al., 1995; Martin, 1999).

This series of observations on motor neurons in ALS has been interpreted to signify that early biochemical changes impact on cell size/metabolism, the cytoskeleton, and attempts to degrade proteins via the ubiquitin–proteosomal pathway. Subsequently, cell shape is altered: proximal axons are enlarged (with accumulated neurofilaments); and dendritic arbors shrink (perhaps with attendant alter-

ations in synaptic inputs). Both the axonal and dendritic lesions could have functional consequences (impairments in conduction by axons and in integration of inputs by dendrites, respectively). Axons begin to 'die back' in peripheral motor nerves and corticospinal tracts and there is denervation of target fields (muscle and motor neurons, respectively). At this stage, trophic support from muscle and, possibly, from other cells is compromised. The neurons die utilizing the same molecular pathways that are associated with apoptosis in other cells. Ultimately, the numbers of motor neurons in brainstem nuclei and spinal cord are reduced and there is a loss of large pyramidal neurons in motor cortex; clinical signs are most closely linked to the disconnection of terminals from targets.

Spinal muscular atrophy (SMA) of infancy and childhood

Characterized by early-onset of muscle weakness and atrophy (Crawford & Pardo, 1996), this autosomal recessive disease, caused by homozygous deletion/conversion of SMN (Lefebvre et al., 1995, 1997; DiDonato et al., 1997; Pellizzoni et al., 1999; Monani et al., 1999), is classified as Type I, II, and III on the basis of age of onset and degree of functional disabilities. The incidence of Type I SMA (Werdnig–Hoffmann disease) is estimated at ~1:10 000 live births with a carrier rate frequency between 1:50 and 1:80. Infants with Type 1 SMA become weak prior to six months of age; ~30% of individuals show reduced fetal movements in utero, and these infants develop respiratory and bulbar difficulties and die before 2 years of age. Type-II SMA is usually recognized before the first birthday; these children are never able to walk independently. Type-III SMA begins in early childhood; affected individuals have milder degrees of disability.

The characteristic neuropathological features of SMA are: chromatolysis and accumulations of phosphorylated neurofilaments in cell bodies of motor neurons; degeneration of motor roots leading to denervation of skeletal muscle; evidence of apoptosis of large motor neurons in the spinal cord and brainstem; and reduced numbers of motor neurons. Relatively spared are cranial nerve nuclei III, IV, and VI as well as motor neurons of the phrenic nerve (which innervates the diaphragm) and Onuf's nucleus (which innervates the male genitalia and anal sphincters). Upper motor neurons do not appear to be affected. Because of the relative paucity of cases of SMA well studied by modern methods, it will probably be necessary to extrapolate, for the moment, from analyses of mouse models of SMA to understand the sequence and mechanisms of pathology.

Table 115.3. Treatment strategies

Inhibit formation of toxic Aβ (inhibitors of BACE1 and γ-secretase)
Promote clearance of Aβ (Aβ immunization)
Cholinomimetics (cholinesterase inhibition)
Suppress inflammation/oxidative injury (COX inhibition, Vitamin E)
Ameliorate synaptic/axonal degeneration (?)
Attenuate tau abnormalities (? target kinases)
Promote cell viability (trophic factors)
Prevent cell death (caspase inhibitors)
Replace neurons or other essential cells (stem cells)

Genetics and biochemistry

In this section, we review the genes and aspects of the biology of the gene products implicated in several of the familial forms of AD and MND inherited in a Mendelian fashion.

Mutant genes implicated in familial Alzheimer's disease (FAD)

In some individuals, particularly those with early-onset AD, the illness may be inherited as an autosomal dominant with mutations in three different genes: *APP*; *PS1*; and *PS2* (Price et al., 1998b; Hardy & Gwinn-Hardy, 1998; Selkoe, 1999) (Table 115.3).

APP

Encoded by a gene on chromosome 21, APP is expressed in many cells/tissues, but is particularly abundant in neurons. This type 1 transmembrane protein is cleaved endoproteolytically by an enzyme, β-site APP cleaving enzyme 1 (BACE1) (Sinha et al., 1999; Yan et al., 1999; Vassar et al., 1999; Hussain et al., 1999; Lin et al., 2000), and by an activity termed 'γ-secretase', which, in concert, generate the N- and C-termini of the Aβ peptide, respectively (Price et al., 1998b; Selkoe, 1999) (Fig. 115.2, see colour plate section). The levels and distributions of APP and the pro-amyloidogenic cleavage enzymes, particularly BACE1, in neurons are principal determinants leading to formation of Aβ in brain (see below). The formation of Aβ 1–40, 42 is precluded by the endoproteolytic cleavage of APP within the Aβ sequence by: 'γ-secretase', now thought to be either tumour necrosis factor (TNF) α converting enzyme (TACE) or a disintegrin and metalloproteinase 10 (ADAM 10), both members of the family of 'sheddases' (Sisodia, 1992); and by BACE2, a protease sharing features with BACE1, but

cleaving APP at different sites (i.e. within the Aβ domain). 'α-Secretase', cuts between residues 16 and 17 of Aβ, while BACE2 cleaves after residues 19 and 20 of Aβ. These different endoproteolytic cleavages generate various C-terminal peptides and can release the ectodomain of APP from the cell (Selkoe, 1999) (Fig. 115.3, see colour plate section).

A variety of APP mutations, including APPswe (a double mutation at the N-terminus of Aβ) and APP-717 (near the C-terminus of Aβ), have been reported in cases of FAD (Goate et al., 1991; Mullan et al., 1992) (Fig. 115.2, see colour plate section). These mutations, strikingly situated near several secretase cleavage sites, are pro-amyloidogenic and cells that express mutant APP show aberrant APP processing: the APPswe mutation, which enhances BACE1 cleavage, is associated with elevated levels of Aβ; the APP 717 mutations, which impact on γ-secretase activity, lead to a higher secreted fraction of longer Aβ peptides (Aβ42) relative to cells that express wild-type APP (Citron et al., 1992; Suzuki et al., 1994; Price et al., 1998b; Selkoe, 1999).

PS1 and *PS2*

Localized to chromosomes 14 (PS1) and 1 (PS2) respectively, these genes encode highly homologous 43- to 50-kD proteins with: multiple transmembrane (TM) domains (Sherrington et al., 1995); and, oriented towards cytoplasm, an hydrophilic acidic 'loop' region, an N-terminal domain, and a C-terminal domain (Doan et al., 1996). PS1 is synthesized as an ~42- to 43-kD polypeptide, but the preponderant PS1-related species that accumulate in vitro and in vivo are ~27- to 28-kD N-terminal and ~16- to 17-kD C-terminal derivatives (Thinakaran et al., 1996; Lee et al., 1996; Podlisny et al., 1997). These fragments accumulate/associate in a 1:1 stochiometry, and they are stable, tightly regulated, and saturable. *PS* genes are widely expressed at low abundance in the CNS. PS1 influences APP processing: cells from *PS1* mutants secrete increased levels of Aβ42; and cells from *PS1* knockouts secrete reduced levels of Aβ. It is not clear whether PS1 itself acts as an aspartyl protease (i.e. γ-secretase), functions as a co-factor critical for the activity of γ-secretase, or exerts its influence by playing a role in trafficking of APP to the proper compartment for γ-secretase cleavage (De Strooper et al., 1998; Naruse et al., 1998; Wolfe et al., 1999). Consistent with the concept that PS1 may act as an aspartyl protease or may be a critical co-factor essential for the activity of γ-secretase are several observations: cells in which the *PS1* gene has been targeted show decreased levels of secretion of Aβ (see below); PS1 is isolated with γ-secretase under specific detergent soluble conditions; substitutions of aspartate residues at D257 in transmembrane 6 (although now possibly controversial) and at D385 in transmembrane 7 reduce secretion of Aβ and final cleavage of Notch1 in vitro; and PS1 is selectively crosslinked or photoaffinity labelled by γ-secretase transition state inhibitors. Alternatively, PS1 may play a critical role trafficking APP, γ-secretase, and other elements of the catalytic complex into the proper compartments for ultimate Aβ42 cleavage.

The *PS1* gene has been reported to harbour >50 different FAD mutations in >80 families, whereas only a small number of mutations have been found in PS2-linked families (Hardy, 1997; Cruts et al., 1998). The vast majority of the abnormalities in *PS* genes are missense mutations that result in single amino acid substitutions; however, a mutation that deletes exon 9 from *PS1* has been identified in several different FAD families. In general, the various *PS* mutations appear to influence γ-secretase activity and increase the levels of the Aβ 42 peptide.

Motor neuron diseases

Familial amyotrophic lateral sclerosis (FALS)

Approximately 10% of cases of ALS are familial, and, in the majority of these cases, the disease is inherited in an autosomal dominant pattern (Brown, 1997; Andersen et al., 2000). Approximately 15–20% of patients with autosomal dominant FALS (i.e. ~2% of cases of ALS) have mutations in the gene that encodes cytosolic Cu/Zn superoxide dismutase (SOD1) (Table 115.2)(Rosen et al., 1993; Deng et al., 1993), a 153 residue enzyme that, as a homodimer, catalyzes the conversion of $\cdot O^-_2$ to O_2 and H_2O_2 (Fridovich, 1986; Stadtman, 1992). SOD1 is on the front line of free radical scavenging.

To date, ~90 different missense mutations and more than one frame shift mutation have been identified in the *SOD1* gene (Wong & Borchelt, 1995; Andersen et al., 2000); these mutations are scattered throughout the protein and are not preferentially localized near the active site or the dimer interface. The phenotypes associated with different mutations may show some clinical differences, but all mutations result in motor neuron disease (Cudkowicz et al., 1998).

A variety of in vivo and in vitro studies have demonstrated that the mutant enzyme causes selective neuronal degeneration through a gain of toxic property rather than a loss of SOD1 activity; these observations are consistent with the finding that SOD1-linked FALS is inherited as an autosomal dominant. While some FALS SOD1 mutants show reduced enzymatic activities, others retain nearly wild type levels and mutant SOD1 subunits do not appear to alter the metabolism/activity of wild type SOD1 in a dominant negative fashion. Moreover, as described below, transgenic mice expressing different FALS SOD1 mutants

exhibit progressive motor neuron disease resembling the illness occurring in cases of ALS. Mice deficient in SOD1 do not develop a motor neuron disease-like phenotype. Crossing SOD1 mutant mice to mice overexpressing wild-type SOD1 or to SOD -/- mice does not influence disease in the progeny (Bruijn et al., 1998). Taken together, these results are consistent with the view that mutant SOD1 causes disease through a gain of neurotoxic property.

Other chromosomal loci have been linked to FALS showing autosomal dominant, autosomal recessive, or X-linked inheritance patterns (Brown & Chan, 2000; Andersen et al., 2000), but space constraints do not permit their discussion here. Deletion/insertion mutations in the KSP repeat motif of the NF-H tail domain have been identified in 10 of 1047 patients with sporadic ALS and in 1 of 295 FALS patients. Although these genetic alterations may represent risk factors, there is little direct evidence that mutations of NF genes are a primary cause of ALS.

Spinal muscular atrophy

Genetic studies have mapped SMA Type I, II, and III to a single highly complex genetic locus on chromosome 5q11.2–q13.3 (Roy et al., 1995; Lefebvre et al., 1995). The genomic organization of this region is polymorphic and complex, with numerous repeated DNA elements that occur in different orientations on chromosomes from different individuals. In this region, investigators initially identified two SMA candidate genes: survival motor neuron (*SMN*) and neuronal apoptosis inhibitory protein (*NAIP*) (Roy et al., 1995; Lefebvre et al., 1995). *SMN1* is now recognized as the SMA-determining gene with *NAIP* possibly playing a role in modifying the severity of the disease. The *SMN1* gene, encoding a 294-amino acid polypeptide (32 kD), lies in the telomeric portion of chromosome 5q11.2–q13.3 and a homologous copy of *SMN1*, termed *SMN2*, is located in a more centromeric position. Whereas, the two ~20-kb genes encode identical proteins, they can be differentiated by single-strand conformational polymorphism analysis or by RT-PCR, because of differences in the transcripts at two nucleotides in exons 7 and 8. Transcripts encoded by the two genes are subjected to alternative modes of post-transcriptional processing; *SMN1* produces full-length RNA, whereas *SMN2* produces mainly transcripts lacking exon 7. Recently, it was demonstrated that exon 7 skipping is caused by a single nucleotide difference between the *SMN1* and *SMN2* gene (Monani et al., 1999). *SMN* is highly conserved between mice (one copy on chromosome 13) and humans (two copies), with 82% identity (Bergin et al., 1997; Pagliardini et al., 2000). *SMN* is expressed in large motor neurons, but it is also expressed in many other cells, with the highest levels seen in the hippocampus and cerebellum.

SMN, a member of a multiprotein complex is involved in small nuclear ribonucleoprotein (snRNP) biogenesis and pre-mRNA splicing (Liu et al., 1997). SMN is present in the nucleus associated with small intranuclear structures termed 'gem bodies' for Gemini of coiled bodies, which are closely associated with, but distinct from, coiled bodies (Liu & Dreyfuss, 1996). Because of the similarity between gems and coiled bodies, it is suggested that gems and SMN might play roles in the processing of small nuclear RNAs. In the cytoplasm, the SMN complex is associated with snRNP Sm core proteins and is involved in spliceosomal snRNP assembly (Fischer et al., 1997). ('Sm' refers to Smith, which, in turn, refers to an antigenic site common to all snRNPs (small nuclear ribonucleoproteins). Sm proteins are proteins exhibiting the Smith antigen, an autoantibody target in lupus erythematosus.) A variety of methods have shown that SMN forms a stable heteromeric complex with a novel 32 kD protein termed Gemin2 (for components of gems 2), formerly called SIP1 (SMN-interacting protein-1). Gemin2 and SMN are present in a large stable complex (~300 kD) together with spliceosomal snRNP proteins (B, D1–3, and E) in both the nuclear and cytoplasmic fractions. SMN is physically associated with Sm proteins and functional studies reveal that Gemin2 plays an important role in the assembly of snRNPs. SMN also participates in the cytoplasmic assembly of snRNPs and is required for recycling of snRNPs in pre-mRNA splicing (Pellizzoni et al., 1998). More recently, other components of the SMN complex termed Gemin3 (a DEAD box protein with putative RNA helicase activity) (Charroux et al., 1999) and Gemin 4 have been identified (Charroux et al., 2000). Gemin3 colocalizes and interacts directly with SMN in gems and this interaction has been shown to be decreased in some SMA cases in which there is deficiency in snRNP regeneration activity. Gemin4 is associated with the SMN protein complex through direct interaction with Gemin3 and it is thought that Gemin4 functions as a cofactor for Gemin3. It is also shown that Gemin4 physically interacts with several Sm core proteins and is colocalized with SMN in the cytoplasm and in gems. It is proposed that the complex comprised of SMN, Gemin2, Gemin3, and Gemin4 represents an active functional unit that serves to bind substrates such as Sm proteins.

Mutations are present in nearly 100% of affected individuals, and the levels of SMN1 are different in cases of SMA (Crawford & Pardo, 1996; DiDonato et al., 1997; Lefebvre et al., 1997). Individuals with Type I SMA have the least amount of SMN in spinal motor neurons. Partial or complete deletions are detected in *SMN1* in over 95% of cases with other disabling mutations found in many of the remaining cases. Homozygous deletion of *SMN1* has not

been found in controls. *SMN2* has not been shown to be deleted in any affected individual, although it is deleted in 4% of normal controls. This finding suggests that embryos with homozygous deletion of the centromeric and telomeric copies of *SMN* are not viable; that such a deletion results in an embryonic lethal event is confirmed by gene targeting (Hsieh-Li et al., 2000; Monani et al., 2000). Levels of full-length SMN proteins govern whether the individual has SMA Type I, II or III, and *SMN2* is predicted to be able to partially substitute for *SMN1*. It is not clear why motor neurons are specifically vulnerable to reductions of this gene product.

These studies demonstrate that SMN is linked to several fundamental biochemical pathways and that SMN mutants occurring in SMA patients are defective in binding to Sm proteins because mutant SMN is incapable of forming large oligomers that are essential for high-affinity binding to spliceosomal snRNP Sm proteins. These findings further support the view that abnormalities of spliceosomal snRNP biogenesis and metabolism are directly involved in the pathogenesis of SMA.

Transgenic and gene targeted models

Models relevant to AD (Fig. 115.4, see colour plate section)

Transgenic models of Aβ amyloidogenesis

To attempt to generate animal models of Aβ amyloidogenesis and associated abnormalities, many groups have used cDNA or genomic constructs, to produce transgenic mice that express wild type APP, APP fragments, Aβ, and FAD-linked mutant APP and PS1 (Kammesheidt et al., 1992; Neve et al., 1992; Lamb et al., 1993; Buxbaum et al., 1993; Higgins et al., 1994; Moran et al., 1995; Hsiao et al., 1995; Games et al., 1995; LaFerla et al., 1995; Masliah et al., 1996; Hsiao et al., 1996; Borchelt et al., 1997; Nalbantoglu et al., 1997; Lamb et al., 1997; Irizarry et al., 1997). Some of the various lines of mutant APP mice, although they do not reproduce the full phenotype of AD, represent excellent models of Aβ amyloidosis and are of great value for testing causal effects of mutant genes, analyses of pathogenic pathways, determination of the molecules participating in Aβ amyloidogenesis, and identification of therapeutic targets. These models will be essential for testing a variety of therapeutic strategies, including the introduction/ablation of specific genes, administration of pharmacological agents (BACE1 and/or γ-secretase inhibitors), variants of protocols of Aβ vaccination or passive transfer of Aβ antibody, blockade of toxicity of Aβ oligomers on neurons (particularly synapses/synaptic interactions/axons), anti-fibrillogenic agents, anti-apoptotic agents, etc. (Table 115.3).

Reviewed below are selected examples of lines of mice expressing autosomal dominent FAD-linked mutant transgenes. We have not reviewed mouse models in which Apo E alleles have been introduced or ablated, nor have we attempted to review models in which tau is the transgene.

Mutant APP mice

Several different promoters have been used to drive the expression of APP minigenes that encode the FAD-linked APP mutants (swe and 717) in strains of mice. The pathology is influenced by the level of transgene product and the specific mutation. The brains of these mice have elevated levels of Aβ40 and Aβ42 as well as both diffuse Aβ deposits and mature neuritic plaques (dystrophic neurites displayed around an Aβ core) in amygdala, hippocampus, and cortex (Sotelo & Palay, 1971; Games et al., 1995; Masliah et al., 1996; Hsiao et al., 1996; Calhoun et al., 1999; Phinney et al., 1999). Some neurites contain hyperphosphorylated tau immunoreactivity; the degree of tau phosphorylation in neurons may increase with age, but accumulations of tangle-like structures in cell bodies are not evident. Astrocytes and microglia are clustered in and around plaques. There is relatively little evidence of neuronal loss in hippocampus. Some mice show abnormalities of synaptic transmission in hippocampal circuits that precedes the deposition of Aβ (Hsia et al., 1999). In some lines, mice may exhibit deficits in object recognition memory (related to the number of amyloid deposits in specific regions) and in alternation-spatial reference and working memory (related to reductions in synaptic density and hippocampal atrophy) (Dodart et al., 2000).

APPswe/PS1 mutant Tg mice

Transgenic mice that coexpress A246E HuPS1 and Mouse/Human-APPswe have elevated levels of Aβ in brain and develop numerous amyloid deposits in hippocampus and cortex (Borchelt et al., 1996, 1997). Associated with many of the Aβ deposits are dystrophic neurites that contain APP, PS1, and BACE1 immunoreactivities; thus, the key participants involved in amyloidosis are present locally at some of the sites of formation of Aβ. Reactive cells, astrocytes, and to a lesser extent, microglial cells, surround the amyloid and neurites. The presence of the PS1 mutations in mice with APP mutations accelerates the deposition of Aβ (as compared with mutant APP alone); in this respect, ΔE9 PS1 is more malignant than A246E PS1 (Borchelt et al., 1997).

Gene targeted mice relevant to AD

APP and APLP2 null mice

Homozygous *APP*-/- mice are viable and fertile, but they appear to have subtle decreases in locomotor activity and forelimb grip strength (Zheng et al., 1995). The absence of substantial phenotypes in *APP*-/- mice may be related to functional redundancy provided by homologous amyloid precurors-like proteins (APLP1 and APLP2), molecules expressed at high levels with developmental and cellular distributions similar to APP (Wasco et al., 1992, 1993; Slunt et al., 1994). Consistent with this idea are observations that *APLP2*-/- mice appear normal (von Koch et al., 1997), but mice with either both *APP* and *APLP2* targeted alleles or both *APLP1* and *APLP2* null alleles show significant postnatal lethality (von Koch et al., 1997; Heber et al., 2000).

PS1 and PS2 null mice

To examine the roles of PS1 in development, several groups have produced *PS1*-/- mice (Wong et al., 1997; Shen et al., 1997; De Strooper et al., 1998). Homozygous mutant mice fail to survive beyond the early postnatal period and show severe perturbations in the development of the axial skeleton and ribs (defects in somatogenesis). PS1 homologues interact with Notch1, a receptor protein involved in critical cell-fate decisions during development (Levitan & Greenwald, 1995), and cells lacking PS1 show reductions in proteolytic release of the Notch1 intracellular domain (NICD), a cleavage that is thought to be critical for Notch1 signalling (Struhl & Greenwald, 1999; Ye et al., 1999; Huppert et al., 2000). Several γ-secretase inhibitors block the proteolytic release of NICD, and it has been hypothesized that similar protease activities are involved in the transmembrane domain cleavage of Notch1 and APP. Substitutions in intramembranous aspartate residues 257 and 385, which appear to be critical for PS1 functions (Wolfe et al., 1999), inhibit generation of NICD and Aβ (Capell et al., 2000). This result is consistent with the view that PS1 differentially facilitates the final proteolytic cleavage of Notch1 pathway involved in the formation of NICD and the γ-secretase-mediated endoproteolysis of APP to generate Aβ. *PS1*-/- embryos also exhibit intraparenchymal hemorrhages, thin ventricular zones, and bilateral cerebral cavitation caused by loss of neurons (Shen et al., 1997). Both wild type and mutant human *PS1* transgenes rescue the spectrum of developmental defects in *PS1* null mice (Davis et al., 1998; Qian et al., 1998; Davis & Goodman, 1998). Thus, the FAD-linked PS1 variants retain sufficient normal function to allow normal mammalian embryonic development. With regard to the role of PS proteins in Aβ biology, mutations in *PS* genes increase formation of Aβ42, and ablation of *PS1* reduces secretion of Aβ. Significantly, as first reported by DeStrooper et al., and later by our group, cells from PS1-/- mice show selective reductions in the levels of γ-secretase cleavage products and levels of Aβ. This observation is a principal line of evidence that PS1 is either γ-secretase or a critical influence on this activity (see below).

Gene targeting of *PS2* is associated with viable fertile mice that develop age-associated mild pulmonary fibrosis and hemorrhage. There was little detectable evidence of APP processing. *PS1*+/−; *PS2*-/- survive in relatively good health, but *PS1*-/-; *PS2*-/- mice die midway through gestation with full Notch-1 deficiency (Herreman et al., 1999).

BACE1-/- mice

Gene targeting approaches (Cai et al., 2001; Luo et al., 2001; Roberds et al., 2001) have produced *BACE1* null mice that are viable and healthy, have no obvious phenotype or pathology, and are capable of successful mating. Importantly, the secretion of Aβ peptides is abolished in BACE1-deficient cortical neurons and Aβ peptides are not produced in brains of *BACE1* null mice. These results establish that BACE1 is the principal β-secretase required to cleave APP to generate the N-termini of Aβ and indicate that BACE1 is an excellent therapeutic target for drug development for AD (see below).

Transgenic and gene targeted models relevant to motor neuron diseases

A variety of experimental models of motor neuron disease have been described (Price et al., 1994; Elliott, 1999), but of greatest interest in the context of this review are genetically engineered models.

Transgenic models mutant SOD1 mice

Mice expressing a variety of mutant SOD1 develop progressive weakness and muscle atrophy (Gurney et al., 1994; Dal Canto & Gurney, 1994; Wong et al., 1995; Ripps et al., 1995; Chiu et al., 1995; Morrison et al., 1996, 1998; Tu et al., 1996; Bruijn et al., 1997; Dal Canto & Gurney, 1997; Kong & Xu, 1997; Borchelt et al., 1998; Williamson et al., 1998; Gurney, 2000). SOD1/ubiquitin immunoreactive cytoplasmic aggregates appear within motor nerve cells; dendrites and motor axons (both of which show swollen mitochondria) are irregularly enlarged; abnormal patterns of neurofilament immunoreactivities are seen in cell bodies/axons of motor neurons; motor axons undergo Wallerian degeneration; and, finally, neurons die.

The G37R SOD1 transgenic mice, which are similar to several other mutant lines, provide an excellent illustration of this disease in mice. G37R SOD1 accumulates to 3–12x levels of endogenous SOD1 in the spinal cord; the mutant

SOD1 retains full specific activity. The levels and nature of the mutant transgene product influence the age of onset; in general, higher levels of a given mutant are associated with earlier onset of clinical signs. Toxic SOD1 is transported anterograde in axons (Borchelt et al., 1998), and early on, it accumulates in axons where it is associated with structural pathology (Borchelt et al., 1998). Approximately 2–3 months before the appearance of clinical signs, SOD1 accumulates in irregular swollen intraparenchymal portions of motor axons, and axonal transport is abnormal as is the axonal cytoskeleton. Vacuoles, thought to represent degenerating mitochondria (Kong & Xu, 1997), are present in enlarged axons and in dendritic swellings, the latter reminiscent of changes seen in excitotoxicity, which has been suggested to play a role in ALS (Leigh & Meldrum, 1996; Rothstein, 1996; Shaw, 2000; Jackson & Rothstein, 2000)). The cell bodies of some neurons show SOD1 and ubiquitin-immunoreactive inclusions and phosphorylated NF-H immunoreactivities. Axonal and dendritic abnormalities (Wong et al., 1995; Zhang et al., 1997; Williamson & Cleveland, 1999), as well as intracellular aggregates, occur in animals without clinical signs. However, once Wallerian degeneration is obvious, the mice are usually weak. Eventually, the number of motor neurons is reduced, and astrocytes are increased in ventral horns.

The molecular mechanisms whereby mutant SOD1 causes selective motor neuron death have not yet been defined. It has been hypothesized that the toxic property of mutant SOD1 may be related to mutation-induced conformational changes in SOD1 that facilitate the interactions of the catalytic Cu with small molecules such as peroxynitrite or hydrogen peroxide to generate toxic free radicals that damage a variety of cell constituents important for the maintenance and survival of motor neurons. In this scenario, cell dysfunction/death could be initiated by aberrant oxidative chemistries catalyzed by the copper atom bound in the active site of mutant SOD1, especially after loss of zinc binding to SOD1. Two prominent proposed oxidative chemistries are copper dependent: (i) peroxidation to generate hydroxyl radical (Wiedau-Pazos et al., 1996); or (ii) nitration of tyrosines using peroxynitrite generated from reaction of nitric oxide with superoxide (Beckman et al., 1993; Estévez et al., 1999). However, there is no documentation of increased levels of nitrated proteins in mutant SOD1 mice as compared to controls, nor is disease progression in mutant mice influenced by lack of either the neuronal or endothelial nitric oxide synthase genes (Facchinetti et al., 1999). These results do not support a critical role for peroxynitrate or neuronal-derived nitric oxide in disease pathogenesis. With regard to peroxidase-mediated mechanisms, mutant SOD1 mice fail to show increased levels of hydroxyl radicals (or obvious oxidative damage) when compared to controls. Furthermore, the onset and progression of disease in mutant mice is independent of the levels of wild type SOD1 activities, results interpreted as inconsistent with either the peroxynitrite or the peroxidase hypotheses (Bruijn et al., 1998). As mentioned, it has been reported that the loss of zinc from either mutant or wild type SOD1 in cultured motor neurons can induce apoptosis following trophic factor withdrawal; the toxic effect requires Cu bound to SOD1 and production of endogeneous nitric oxide (Estévez et al., 1999). These results were interpreted to indicate that zinc-deficient SOD1 might play a role in disease through a nitric oxide-mediated mechanism involving Cu bound to SOD1. However, these aberrant Cu chemistries have not been demonstrated to occur in vivo, and the gene targeting experiments involving copper chaperone for SOD1 (CCS), which are described below, provide no support for the idea that Cu bound to mutant SOD1 mediates directly motor neuron degeneration in SOD1-linked FALS.

Gene targeted mice relevant to MND

SOD1-/- mice

While these animals do not develop an overt motor neuron disease, *SOD1-/-* mice show a distinct motor axonopathy as they age (Shefner et al., 1999). In addition, facial motor neurons lacking SOD1 are more susceptible to axotomy (Reaume et al., 1996)and *SOD1* null mice are more sensitive to paraquat exposure as compared to littermate controls (Huang et al., 1997; Ho et al., 1998). While the homozygous *SOD1* knockout male mice are fertile, the female *SOD1-/-* mice show reduced fertility due to abnormal development of follicles in ovaries (Matzuk et al., 1998; Ho et al., 1998).

CCS-/- mice

In its free form, copper is toxic and there is virtually no free copper in cells (Rae et al., 1999). Normally, copper is imported into cells by a plasma membrane bound copper transporter (Zhou & Gitschier, 1997; Kuo et al., 2001) and then selectively shuttled to intracellular target proteins by a series of specific copper chaperones. The delivery of Cu to specific proteins is mediated through distinct intracellular pathways of copper trafficking (Valentine & Gralla, 1997; Culotta et al., 1999). A family of soluble Cu chaperones is required to deliver Cu to specific intracellular metalloproteins (Lin & Cizewski Culotta, 1995; Glerum et al., 1996a,b; Klomp et al., 1997; Pufahl et al., 1997). Recently, the yeast Cu chaperone, termed lys7, or its mammalian homologue (CCS) was shown to be necessary to deliver copper to SOD1 in yeast (Culotta et al., 1997). CCS

is able to rescue the *lys7* null mutant and is shown to interact physically with SOD1 (Casareno et al., 1998; Rae et al., 1999). Biochemical and structural analysis of yeast CCS indicated that the insertion of Cu into SOD1 requires the interactions amongst three distinct domains of the copper chaperone: an Atx1p-like amino-terminal domain responsible for Cu uptake, an SOD1-like central domain functions in SOD1 recognition, and a carboxyl-terminal domain which is unique to copper chaperones and which mediates Cu incorporation into SOD1 (Lamb et al., 1999; Schmidt et al., 1999; Schmidt et al., 1999a,b). Inactivation of the *CCS* gene in mice has demonstrated that CCS is required for efficient copper incorporation into SOD1 in mammals and the phenotypes of the CCS *null* mice resemble those of the *SOD1* null mice (Wong et al., 2000).

SMN gene targeted mice

Smn−/− embryos died with massive cell death during the peri-implantation stage corresponding to the initiation of embryonic RNA transcription, precluding analysis of any postnatal phenotype (Schrank et al., 1997). These results are consistent with the view that SMN functions in essential cellular pathways, including the biogenesis of spliceosomal snRNPs and pre-mRNA splicing.

To test whether *SMN2* can complement the embryonic lethality of *Smn*−/− embryos and to generate a mouse model for SMA, several groups generated transgenic mice expressing human *SMN2* and crossbred them to *Smn*+/− mice to produce *SMN2* transgenic mice lacking mouse endogenous SMN (Hsieh-Li et al., 2000; Monani et al., 2000). These *Smn*−/−; *SMN2* mice have abnormalities in the spinal cord and skeletal muscles similar to those seen in cases of SMA, and the severity of the pathology correlates with the level of SMN polypeptide that retains the amino acids encoded by exon 7. These results demonstrate that *SMN2* can partially compensate for the endogenous mouse SMN and the variable phenotypes observed in the *Smn*−/−; *SMN2* mice recapitulate those seen in SMA Type I, II or III. These *Smn*−/−; *SMN2* mice exhibit several patterns of clinical signs: Type 1 mice, the most severe pathological form, do not develop furry hair and die before postnatal day 10; Type 2 mice are inactive and die between 2 to 4 weeks of age; and Type 3 mice survive and breed normally, and have short and enlarged tails. Furthermore, the level of full-length SMN protein in these *Smn*−/−; *SMN2* mice correlates with the severity of the disease. These studies strongly support the view that the level of intact SMN is the determining factor for severity of phenotypes in SMA. Interestingly, analysis of *Smn*+/− heterozygous knockout mice (Jablonka et al., 2000) disclose a ~50% reduction of SMN protein in the spinal cord which results in a progressive loss of motor neurons between birth and 6 months of age and the phenotype of these mice resembles SMA type III. In addition, a conditional deletion of the mouse *SMN* exon 7 directed to neurons resulted in a phenotype resembling SMA, suggesting that motor neurons are the primary target of the gene defect (Frugier et al., 2000). Taken together, these studies support the view that SMA is caused by insufficient level of SMN and the severity of the disease is dependent on the level of SMN generated from the *SMN2* gene. These mouse models of SMA will be useful in understanding disease mechanisms and for testing therapeutic strategies.

Investigations of genetically engineered models can provide important new information about selective vulnerability of neurons in specific diseases and for experimental therapeutics

Among the most challenging mysteries of neurodegenerative diseases is the identification of factors that render neurons particularly susceptible in specific diseases (principle of selective vulnerability). Recent research has begun to provide exciting new clues concerning the biological basis for these vulnerabilities, and this information has direct relevance to developing novel therapies. AD serves as an illustration of these principles. We hypothesize that the basis for the vulnerabilities of brain to AD are the levels and distributions of APP and its cleavage enzymes in neurons versus other cells, and that these enzymes are attractive targets for drug therapy.

Why do we think neurons are the principal source of Aβ? APP is one of the most abundant proteins in neurons, particularly as compared to other cells in other tissues. In nerve cells, APP is transported within axons by the fast anterograde system (Koo et al., 1990; Sisodia et al., 1993). For example, in peripheral sensory neurons of rodents, APP-695 is the predominant isoform; full-length APP-695 and, to a lesser extent, APP-751/770 are rapidly transported anterogradely in axons toward distal terminals (Koo et al., 1990; Sisodia et al., 1993). APP processing can occur in distal axons/terminals. Radiolabelling studies in the entorhinal cortex have shown that newly synthesized APP, principally APP-695, is transported via axons of the perforant pathway to accumulate at presynaptic terminals in the hippocampal formation (Buxbaum et al., 1998b). In the terminal fields of this pathway, soluble C-terminally truncated APP and amyloidogenic C-terminal fragments have been identified (Buxbaum et al., 1998b). Moreover, in mutant APP transgenic mice, APP, BACE1, and PS1, the key identified proteins in formation of amyloid, have been visualized in swollen

neurites in proximity to amyloid deposits. These observations are consistent with the idea that neurons and their processes, particularly, but not exclusively, axon terminals, are one source of the APP that gives rise to peptide species. Also consistent with this hypothesis are results of studies of a cross between APP −/ – mice and APP V717I mice, in which the transgene is driven by a neuron-specific promoter. In these APPV717I mice lacking endogenous mouse APP, Aβ is produced from neurons in many regions of brain. Significantly, although the *APP* transgene is not expressed around cerebral vessels, amyloid is deposited in the CNS vasculature (Calhoun et al., 1999). Hence, in this setting, neurons (the only cells expressing APP) appear to be a source of mobile Aβ that can accumulate in both the brain parenchyma and around vessels. This observation undercuts the argument that the Aβ in vessels is coming from the serum. Consistent with the concept that neurons are the major source of APP giving rise to Aβ are observations made by several groups, including scientists in our group, in which transection of the perforant pathways of mutant APP transgenic mice reduces the Aβ burden in the terminal fields of this input to hippocampus.

However, the presence of APP in neurons, although necessary, is not sufficient to explain why the brain and not other organs, such as the pancreas, are particularly vulnerable to Aβ amyloidogenesis. In our view, the patterns of APP cleavage enzymes in different cell populations are of equal importance. We believe that the cellular distributions, relative levels, and APP cleavage patterns of two β-secretases (BACE1 and BACE2) are the principal determinants of such vulnerability. Although both BACE1 (Asp2 or Memapsin2) and BACE2 (Asp1 or Memapsin1) are expressed ubiquitously, BACE1 mRNA levels are particularly high in brain and pancreas, whereas the levels of BACE2 mRNA are relatively low in all tissues, except in brain where it is nearly undetectable (Vassar et al., 1999; Bennett, 2000). We hypothesize that the ratios of BACE1: BACE2 in different cells/tissues profoundly influence the susceptibility to Aβ amyloidogenesis. In simple terms, the combination of abundant BACE1 in neurons coupled with low levels of BACE2 in these cells predisposes to amyloidosis in the brain. As indicated above, Aβ is generated by biochemical pathways involving the endoproteolytic cleavages carried out by BACE1, a type I transmembrane aspartyl protease (Sinha et al., 1999; Yan et al., 1999; Vassar et al., 1999), and by an activity termed 'γ-secretase', which generate the N- and C-termini of the Aβ peptide, respectively (Fig. 115.2, see colour plate section). Most importantly, BACE1 is the principal β-secretase necessary to cleave APP at the +1 and +11 sites of Aβ in neurons (Cai et al., 2001). In contrast, BACE2 cleaves APP more efficiently at residues +19 and +20 of APP compared to the +1 site of Aβ (Farzan et al., 2000). Significantly, levels of Aβ1–19 and Aβ1–20 are undetectable in brain. APP can also be cleaved endoproteolytically before residue +17 within the Aβ sequence by putative 'α-secretases', TACE (Buxbaum et al., 1998a) and ADAM10 (Lammich et al., 1999); significantly, +17 C-terminal products are relatively low in brain. These three cleavages within the Aβ domain of APP preclude the formation of Aβ 1– 40, 42. As BACE1 is the principal β-secretase in neurons and BACE2 may serve to limit the secretion of Aβ peptides, we hypothesize that BACE1 is a pro-amyloidogenic enzyme while BACE2 is an anti-amyloidogenic protease, and the relative levels of BACE1 and BACE2 are major determinants of Aβ amyloidosis. In this model, the secretion of Aβ peptides would be expected to be the highest in neurons/brain as compared to other cell types/organs because the neurons express high levels of BACE1 coupled with low expression of BACE2. If the ratio of the level of BACE1 to BACE2 is a critical factor that selectively predisposes the brain to Aβ amyloidosis, AD would be predicted to involve selectively the brain rather than other organs. Seemingly inconsistent with this hypothesis is a study showing a high level of BACE1 mRNA expression in the pancreas. However, it now appears that some of the pancreatic BACE1 mRNAs are alternatively spliced to generate a BACE1 isoform that is incapable of cleaving APP. Taken together with the observations that pancreas possesses low levels of BACE1 as well as low amounts of BACE1 activity (Sinha et al., 1999), these results are consistent with the view that a high ratio of the level of BACE1 to BACE2 activity leads to selective vulnerability to Aβ amyloidosis.

Thus, in concert with low activities of γ-secretases (TACE and ADAM10) and BACE2 in brain, the abundance of APP substrate and the activity of the pro-amyloidogenic BACE1 in neurons predisposes the brain to this type of amyloidosis. Finally, γ-secretase, which may be PS1 (or has its activity influenced by PS), is present in a relatively low level in brain and does not form Aβ without BACE1 cleavages. To test this hypothesis at the level of specific cell populations, it will be important to define the levels and distributions of BACE1 and BACE2 in specific brain regions/circuits/neurons using specific BACE1 and 2 antisera and to attempt to correlate these measures with the regional vulnerabilities to Aβ amyloidosis seen in AD.

Experimental therapeutics

Treatments of models of Aβ amyloidogenesis

Again, we use work on AD and model systems to illustrate the value of studies of transgenic and gene targeted mice for experimental treatments (Table 115.3). Although they do not model the full phenotype of AD, these mutant mice

represent excellent models of Aβ amyloidogenesis and are highly suitable for analyses of pathogenic pathways, determination of the molecular participants in amyloidogenesis, and identification of therapeutic targets. Moreover, they are invaluable for examining the effects of: introduction/ablation of specific genes; administration of pharmacological agents (secretase inhibitors); Aβ vaccination or passive transfer of Aβ antibody; reagents that interfere with Aβ (? oligomers) toxicity on neurons and their synapses; anti-fibrillogenic agents, etc. Several of these strategies are described below.

Secretase inhibition

The Aβ amyloidogenesis model has begun to be tested by a variety of approaches, including the use of transgenic and gene targeted mouse models. While both β- and γ-secretase activities represent therapeutic targets for the development of novel protease inhibitors for AD, the demonstrations that BACE1 is the principal β-secretase in cultured neurons (Cai et al., 2001) and in brain in vivo (Luo et al., 2001) provide excellent rationale for focusing on the design of novel therapeutics to inhibit BACE1 activity in brain. In contrast to *PS1*$-/-$ mice, the *BACE1*$-/-$ mice appear to be normal (Luo et al., 2001; Roberds et al., 2001). Most significantly, when mutant APP transgenic mice are crossed with *BACE1* null mice, the levels of Aβ are negligible in progeny lacking BACE1. Thus, not only do BACE1 deficient neurons fail to secrete Aβ but, APPswe transgenic mice lacking BACE1 do not generate Aβ peptides in brain (H. Cai et al., personal communication; Luo et al., 2001). These several observations suggest that it may be possible to develop inhibitors that are brain penetrant (i.e. can cross the blood–brain barrier), bind to the active sites of BACE1 to ameliorate Aβ deposition, and lack mechanism-based toxicity. The publication of the crystal structure of the protease domain of BACE1 associated with an eight-residue peptide inhibitor (Hong et al., 2000) should be of value in development of specific drugs designed to inhibit BACE1 activity. Moreover, lead compounds with potent BACE1 inhibition identified through high throughput screens can be further modified for efficacy and bioavailability and minimized for toxicity. These compounds can be tested in mutant APP transgenic mice to determine whether they ameliorate deposition in vivo and, if efficacious and nontoxic, they can be brought to clinical trials.

Although γ-secretase, which cleaves at the C-terminal portion of Aβ, has not yet been cloned, it has been shown that the PS1, which when mutated cause FAD (Sherrington et al., 1995), participates in the intramembraneous proteolysis of several proteins, including APP (De Strooper et al., 1998; Naruse et al., 1998) and Notch1 (De Strooper & König, 1999), and thus may be the putative γ-secretase or a critical cofactor for these cleavages. The demonstrations that PS1 co-fractionates with γ-secretase activity (Li et al., 2000b), that transition-state analogue inhibitors of γ-secretase can covalently label PS1 (Esler et al., 2000; Li et al., 2000c), and that two transmembrane aspartates appear to be required for γ-secretase activity (Wolfe et al., 1999) provide support for the view that PS1/2 may possess γ-secretase activity or that the PS are co-factors intimately influencing γ-secretase cleavages. Alternatively, PS1/2 may play a role in trafficking of APP or other molecules into proper compartments for processing (Naruse et al., 1998). Consistent with the idea that γ -secretase activity involves a multi-subunit catalytic complex is the recent identification of the type 1 transmembrane protein, nicastrin, which interacts with PS that are known to modulate both γ-secretase activity and Notch1 functions (Yu et al., 2000).

Because PS are involved in the proteolytic processing of Notch1 (to liberate the Notch intracellular domain which enters the nucleus to influence transcription) and are critical for Notch1 functions (Huppert et al., 2000), it is not surprising that *PS1* null mice have a phenotype resembling, to a lesser degree, that observed in the *Notch1* null mice (Wong et al., 1997; Shen et al., 1997). Thus, the design of therapeutics that inhibit γ-secretase and thus influence, at some level, Notch1 processing could have, in the adult, impact on some cell populations (hematopoetic cells, especially lymphocytes) that utilize Notch1 signaling for cell fate decisions (Hadland et al., 2001). In this case, it may be necessary to try to develop highly selective inhibitors that act principally on γ-secretase activities that cleave APP and have less inhibitory potency on Notch1 cleavage (Petit et al., 2001). Significantly, a newly developed γ-secretase inhibitor appears to reduce the levels of Aβ in APP mutant mice, and the compound is now in Phase 1 clinical trials. In the event that neither a γ-secretase nor a β-secretase inhibitor alone proves efficacious, a cocktail of γ- and β-secretase inhibitors might be developed to act in concert to reduce the burden of Aβ in AD.

Immunotherapy

Both Aβ immunization (with Freund's adjuvant) and passive transfer of Aβ antibodies reduce levels of Aβ and plaque burden in mutant APP transgenic mice in both prevention and treatment trials (Schenk et al., 1999; Bard et al., 2000; DeMattos et al., 2001) (Table 115.3). The mechanisms of enhanced clearance are not certain, but it has been suggested that a small amount of Aβ antibody reaches the brain, binds to Aβ peptides, promotes the disassembly of fibrils, and the Fc antibody domain attracts activated microglia to remove Aβ. It is also possible that antibody-mediated processes interfere with the toxicity of Aβ 42. Another possibility, not mutually exclusive with the

aforementioned, is that serum antibodies serve as a sink to draw the amyloid peptide from brain to circulation, thus changing the equilibrium of Aβ in different compartments and promoting removal from brain. Immunization appears to attenuate learning/behavioural deficits in at least two small cohorts of mutant APP mice (Janus et al., 2000; Morgan et al., 2000). Human Phase 1 trials are under way with Aβ and a safer adjuvant; the levels of antibody titre will be critical since these levels are predictive of amyloid clearance in mutant transgenic mice.

Editor's note These trials are on hold due to encephalitis -like side effects.

Treatments of models relevant to MND

A variety of mechanisms, including copper toxicity, protein misfolding, aggregation of critical components, alterations in the biology of neurofilaments, oxidation/nitration-mediated damage, excitotoxicity, calcium-related injury, and apoptosis are among the processes that have been suggested to play roles in ALS and FALS. As described above, in vivo and in vitro studies have demonstrated that the mutant enzyme causes selective neuronal degeneration through a gain of toxic property rather than a loss of SOD1 activity, consistent with some FALS pedigrees displaying an autosomal dominant pattern of inheritance.

Lines of mutant SOD1 mice have been used for pharmacological and 'genetic' therapeutic trials (Friedlander et al., 1997; Couillard-Després et al., 1998; Pasinelli et al., 1998; Klivenyi et al., 1999; Cleveland, 1999; Julien, 1999, 2001). Vitamin E and selenium modestly delay both the onset/progression of disease without affecting survival. In contrast, riluzole and gabapentin do not influence the onset/progression, but they do increase survival slightly (Gurney et al., 1996). Oral administration of D-penicillamine, a copper chelator, delays the onset of disease modestly (Hottinger et al., 1997). At present, treatment with creatine appears to have the most robust pharmacological impact on disease (Klivenyi et al., 1999); oral administration of creatine to G93A SOD1 mice resulted in a dose-dependent improvement in motor tasks and extended survival.

The effect of increasing or reducing the levels of SOD1 has been tested by mating mutant SOD1 mice with transgenic mice overexpressing wild-type SOD1 or by mating with SOD1$-/-$ mice. Neither of these genetic manipulations appeared to have a significant effect on the phenotype of mutant *SOD1* mice in these experiments (Bruijn et al., 1998) (The clinical course and pathology, including the presence of aggregates, which contain SOD1 and other unidentified components, are no different from those of mutant SOD1 transgenic mice.

Overexpression of *BCL-2* in these transgenic mice extends survival, but the presence of the gene does not change the progression of the disease (Kostic et al., 1997), while with overexpression of a dominant negative inhibitor of interleukin-1B converting enzyme (ICE), a cell death gene, produces a modest slowing of progression of disease (Friedlander et al., 1997).

The role of neurofilaments in SOD1 mutant mice was tested by cross-breeding to: (i) transgenic mice that accumulate NF-H-β-galactosidase fusion protein (NF-H-lacZ), a multivalent protein that crosslinks neurofilaments in neuronal perikarya and limits their export to axons (Eyer & Peterson, 1994); and (ii) transgenic mice expressing human NF-H subunits (Côté et al., 1993). In mutant SOD1 mice expressing NF-H-lacZ, NF are withheld from the axonal compartment, but there is no influence on disease (Eyer et al., 1998), implying that neither initiation nor progression of pathology requires an axonal NF cytoskeleton and that alterations in NF biology observed in some forms of motor neuron disease may be secondary responses (Eyer et al., 1998). By contrast, the expression of wild type human *NF-H* transgenes in the SOD1 mutant mice increases the mean life-span of the mice (Couillard-Després et al., 1998) and is associated with sparing of motor neurons (Couillard-Després et al., 1998; Julien, 1999). Similarly, mutant S*OD1: NF-L* $-/-$ mice show later onset and a slower progression (Williamson et al., 1998; Julien, 1999). The common properties shared by these compound transgenic mice are the reduced content of assembled neurofilaments in the axonal compartment and an increase in neurofilament proteins in cell bodies. How the distribution of neurofilaments in mutant SOD1 mice influences phenotype is not known.

To test the hypothesis that Cu bound to mutant SOD1 plays a key role in generating the toxic property in SOD1-linked FALS, multiple lines of mutant SOD1 mice were crossed with *CCS*$-/-$ mice. Metabolic ^{64}Cu labelling studies in mutant SOD1 mice lacking the CCS reveal that copper incorporation into wild type and mutant SOD1 is significantly diminished in the absence of the CCS. Motor neurons in mice lacking the CCS have an increased rate of death after facial nerve axotomy, a response previously documented for mice deficient in SOD1. Thus, CCS is necessary for efficient copper incorporation into SOD1 in motor neurons. However, while the absence of the CCS results in a significant reduction in the level of copper-loaded mutant SOD1, the onset, progression and pathology of motor neuron disease is not modified in mutant SOD1 mice. These results demonstrate that the CCS-dependent copper-loaded mutant SOD1 plays no role in the pathogenesis of mutant SOD1-induced motor neuron disease.

Although the molecular mechanisms underlying mutant SOD1-linked familial ALS remain unclear, several pathogenic mechanisms other than the copper hypothesis (Martin, 1999; Pasinelli et al., 2000; Li et al., 2000a) have been proposed. Mutant SOD1-containing aggregates have been implicated to participate in the pathogenesis of SOD1-linked FALS (Bruijn et al., 1998; Johnston et al., 2000; Beaulieu et al., 2000). While the role of aggregates in disease pathogenesis remains to be clarified, the identification of mutant SOD1-containing complexes as an early event in mutant SOD1 mice supports the importance of aggregates in the pathogenesis of SOD1-linked FALS.

In conclusion, this review of FAD and two inherited MND is intended to provide lessons for understanding other neurodegenerative diseases. Recent investigations of pathology of AD, of the genetics of FAD, of the biochemistry of APP processing (particularly the secretases involved), and of gene targeted and transgenic models have provided extraordinary new insights into the reasons why AD is a brain amyloidosis, the mechanisms of amyloidogenesis, and targets for mechanism-based therapies for this very common, devastating disease of the elderly. Of particular note are the discoveries that indicate BACE1 plays a key role in rendering neurons vulnerable to amyloidogenesis and that inhibition of this enzyme is an attractive treatment strategy.

Over the past several years, similar approaches have led to substantial progress in understanding the pathological and molecular processes that underlie MND. It was hypothesized that aberrant Cu chemistries generated neurotoxic radicals that damaged motor neurons, and that inhibiting this potential pathogenic pathway might have beneficial effects in FALS. Unfortunately, when the copper hypothesis was tested by targeting the gene encoding CCS and by crossing these mice with a series of mutant SOD1 mice, the outcome failed to confirm the hypothesis. Mutant SOD1 mice lacking the CCS did not incorporate Cu into wild type and mutant SOD1 in the absence of the CCS. However, the absence of Cu in SOD1 failed to modify the onset, progression and pathology of motor neuron disease in mutant SOD1 mice. These results demonstrate that the CCS-dependent copper-loaded mutant SOD1 plays little role in the pathogenesis of mutant SOD1-induced motor neuron disease, and that therapeutic attempts to inhibit aberrant Cu chemistries are not an attractive approach. The mechanisms that account for 'selective' neuronal degeneration in ALS and SMA are still uncertain and to date we have not sufficient information to develop mechanism-based therapies.

However, more generally, the identification of specific genes/proteins that are mutated/deleted in the inherited forms of neurodegenerative diseases has allowed investigators to create in vivo and in vitro model systems relevant to a wide variety of human neurological disorders. Genetically engineered mice (or other species, like Drosophila) that recapitulate some of the features of human diseases can provide important new information about the neurobiology of these diseases. The availability of new models will allow investigators to examine the molecular mechanisms by which mutant proteins cause selective dysfunction/death of motor neurons. Moreover, pathogenic hypotheses can be tested by experimental manipulations and by breeding mice carrying mutant genes to mice that express other transgenes or to gene-targeted mice. The results of these approaches should provide us with a better understanding of the pathogenic mechanisms of these diseases. In turn, this new knowledge should lead to the design of novel therapeutic strategies that can be tested in these animal models. Finally, it is highly likely that the discovery of genes linked to psychiatric diseases (affective disorders, schizophrenia, etc.) will allow the application of similar strategies to these devastating illnesses.

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Motor neuron disease

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The World Federation of Neurology classification of motor neurone diseases is based on heredity and presumed causes (De Jong, 1991). A simplified clinical classification is shown in Table 116.1. Motor neuron disease (MND, also referred to as amyotrophic lateral sclerosis (ALS)) is one of the commonest adult-onset neurodegenerative disorders with a worldwide incidence of 1–2 per 100 000. This chapter will review the clinical and pathological features of MND, current pathogenetic hypotheses and symptomatic therapy, as well as prospects for neuroprotective therapies.

Table 116.1. Clinical classification of motor neuron diseases

1	Sporadic motor neuron disease
	A Amyotrophic lateral sclerosis (ALS)
	B Progressive bulbar palsy (PBP)
	C Progressive muscular atrophy (PMA)
	D Primary lateral sclerosis (PLS)
2	Familial motor neuron disease
	A SOD_1 (Cu/Zn superoxide dismutase) related (20%)
	B Juvenile onset – autosomal recessive or autosomal dominant (linked to chromosome 2q, 9q or 15q)
	C Genetic locus unknown (80%)
	D Familial MND with fronto-temporal dementia (linked to chromosome 9q)
3	Other inherited forms of motor neuron degeneration, e.g. Kennedy's disease; Brown Vialetto van Laere syndrome; Spinal muscular atrophy
4	Western Pacific amyotrophic lateral sclerosis/parkinsonism/dementia complex
5	Juvenile onset MND with intracytoplasmic inclusions
6	Motor neuron diseases with definable causes, e.g. Postpolio syndrome; Heavy metal intoxication; Hexosaminidase-A deficiency

Clinical features of motor neuron disease

MND is a progressive neurodegenerative disorder involving primarily the motor neurons of the cerebral cortex, brainstem and spinal cord. The onset of symptoms in MND is often insidious and patients may not present to a neurologist until several months have elapsed. The disease is sporadic in 90% and familial, usually with an autosomal dominant mode of inheritance, in approximately 10% of cases. Twenty per cent of familial cases or two per cent of the MND population as a whole have a mutation in the gene on chromosome 21 encoding Cu/Zn superoxide dismutase (SOD1) (Rosen et al., 1993). The genetic alterations underlying the remaining 80% of cases of familial MND remain unknown.

Clinical variants

There are several clinical and pathological variants of sporadic MND. Approximately two-thirds of patients present with the amyotrophic lateral sclerosis (ALS) variant; 25% present with progressive bulbar palsy (PBP); 8% with progressive muscular atrophy (PMA) and 2% with primary lateral sclerosis (PLS) (Caroscio et al., 1984). Criteria have been developed for MND to allow clinicians and researchers to classify patients according to the level of certainty of the diagnosis (World Federation of Neurology El Escorial Criteria) (Brooks, 1994).

In the commonest ALS variant, there are signs of impairment of both upper and lower motor neurons with eventual involvement of both somatic and bulbar muscles. In progressive bulbar palsy, the initial symptoms begin in

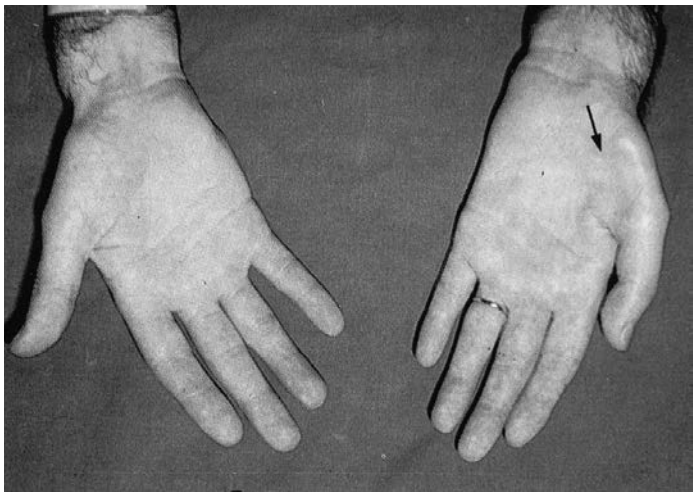

Fig. 116.1. Wasting of the thenar muscles (arrow) in a patient with ALS.

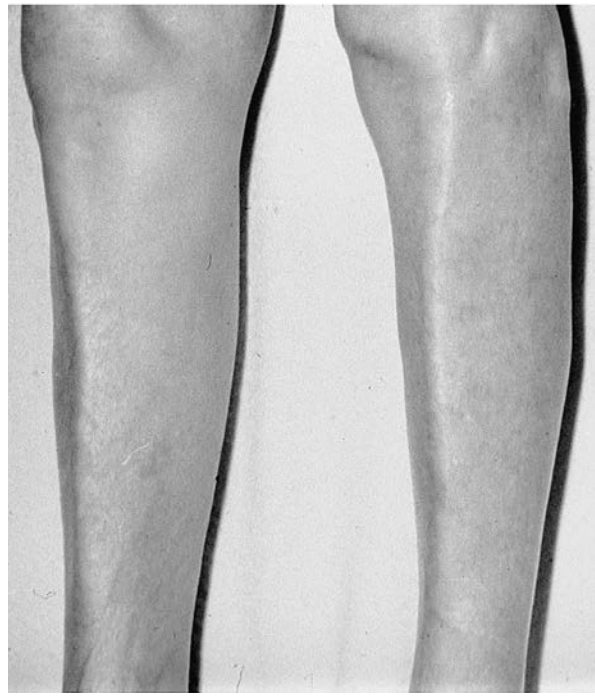

Fig. 116.2. Wasting of the anterior tibial compartment muscles in a patient with ALS.

muscles controlling speech and swallowing innervated by motor neuron groups in the pons and medulla. At presentation, there may be no clinical evidence of involvement outside the bulbar territory. In the progressive muscular atrophy variant, the initial symptoms are due to degeneration of lower motor neurons in the spinal cord, in the absence of clinical features indicating upper motor neuron or bulbar involvement. Primary lateral sclerosis is a relatively rare variant of MND. The patient presents with progressive upper motor dysfunction involving the limb and bulbar musculature, sometimes accompanied by alteration of sphincter function, in the absence of clinical or neurophysiological features of lower motor neuron pathology (Pringle et al., 1992). The PLS form of MND tends to progress more slowly than the other clinical variants. Lower motor neuron features may become apparent as long as 8 to 10 years after presentation.

Clinical features at diagnosis

Limb weakness

Upper limb symptoms are the presenting feature in 40–50% of patients, lower limb symptoms in approximately 25–40% and bulbar symptoms in 20–30% (Swash & Schwartz, 1995). Muscle weakness without sensory loss is the most frequent presenting feature, though occasionally the first complaint may be of muscle wasting, cramps or fasciculations. These early symptoms are usually asymmetrical and often involve only one limb. In patients with prominent upper motor neuron involvement presenting complaints may include stiffness, spasticity or ankle clonus.

Clinical examination of patients with MND will often reveal a rather characteristic pattern of limb involvement. Distally in the upper limb muscle weakness and wasting tends to be most severe in the thenar muscles, interossei and wrist and finger extensors, with relative sparing of the wrist and finger flexors (Fig. 116.1). A frequent early symptom is of difficulty in manipulating objects with the fingers of one hand. Proximally in the upper limb the biceps, deltoid and infraspinatus muscles tend to be affected first, with relative sparing of triceps. In the lower extremities weakness often initially involves hip flexion and ankle dorsiflexion. The calf and quadriceps muscles tend to be involved only later in the course of the disease. Common early lower limb symptoms include heaviness of one leg, unilateral foot drop or a tendency to trip (Fig. 116.2).

Tone and reflex abnormalities

Clinical evidence of upper motor neuron involvement is the rule in the commonest ALS variant of MND, though this may not be as functionally significant as the accompanying lower motor neuron features. The tendon reflexes are frequently brisk in the presence of significant wasting of

the limb musculature and extensor plantar reflexes may be present. Occasionally limb tone is severely increased and spasticity is an important cause of disability in some patients.

Fasciculation

Fasciculations are fine, rapid flickering movements of muscle due to spontaneous contractions of the fibres within a single motor unit. The cause of muscle fasciculation in MND is still debated. In general, the larger the muscle, the larger the size of the fasciculations, and they tend to be most readily observed in the bulky proximal limb muscles such as deltoid, biceps, triceps and quadriceps. Patients with MND will often be aware that their muscles are twitching, but do not usually find fasciculations painful or distressing.

Cramps

Muscle cramp is an sudden, involuntary and painful muscle contraction which is visible or palpable and which may be relieved by massage or stretching. In patients with MND muscle cramp is a frequent early complaint and is often observed during the clinical assessment of muscle power. Cramps may predate the onset of other symptoms in MND by several years (Fleet & Watson, 1986). Cramps are most commonly experienced in the lower limbs, but the hands, proximal upper limb muscles, neck, jaw, abdomen, chest and even the tongue may also be involved. The cause of cramp in MND is not well understood.

Fatigue

The neuromuscular junctions in muscles undergoing denervation and reinnervation are electrophysiologically unstable, which may cause fatigue following repeated muscle contraction. Fatiguability is a common symptom in MND and may occasionally be sufficiently pronounced so as to suggest a diagnosis of myasthenia gravis. The fatigue will often relate to specific activities, for example increasing dysarthria at the end of the day, or reduced ability to walk more than a certain distance without tiring. Fatigue may be demonstrated electrophysiologically in MND, using repetitive stimulation.

Bulbar dysfunction

The first evidence of bulbar involvement in MND is often an articulation problem due to weakness or spasticity of the tongue. Initial complaints include an inability to speak loudly or sing, a softening of the voice or slurring of speech. Hoarseness may result from paresis of vocal cord abduction. Weakness of palatal elevation may occur which imparts a nasal quality to the voice. Spasticity of the bulbar muscles leads to an effortful, tight quality to the speech and impairment of repetitive movements of the lips, tongue and pharynx. Progression to complete anarthria is common. Dysphagia is usually only noticed by the patient after the development of significant dysarthria. Particular problems include: weakness of lip closure allowing escape of oral contents; tongue weakness resulting in slowness and incoordination in the passage of the bolus from mouth to pharynx; weak palatal elevation causing nasal regurgitation of oral contents; pooling of material in the vallecula and pyriform recesses and impaired laryngeal elevation resulting in tracheal aspiration of swallowed material; spasticity of the cricopharyngeal sphincter hindering entry of the food bolus into the esophagus. Patients with bulbar MND frequently complain of drooling of saliva due to weakness of lip closure and dysphagia (Langton Hewer, 1995). Weakness of the facial and jaw muscles may also occur. Examination of the patient with bulbar dysfunction will frequently uncover a combination of upper and lower motor neuron signs. Facial weakness and reduced voluntary movement of the palate may be seen. The tongue often shows fasciculation, wasting and bilateral weakness, together with spasticity. The jaw jerk may be pathologically brisk.

Emotional problems

MND patients with upper motor neuron bulbar features may develop prominent emotional lability with inappropriate crying or laughter. Severe depression, however, appears to be surprisingly uncommon, occurring in 2.5% in one series of 40 patients (Houpt et al., 1977). While suicidal thoughts are common, particularly arising from the patient's fear of becoming a burden on the family, suicide attempts are uncommon (Ganzini et al., 1998).

Weight loss

Progressive muscle wasting and reduced caloric intake due to dysphagia or loss of appetite can cause progressive weight loss in patients with MND. Sometimes disproportionately severe weight loss occurs, a phenomenon which has been called MND cachexia and which is associated with a poor prognosis.

Neck weakness

Weakness of the neck extensor muscles may cause a tendency of the head to fall forwards. In more advanced disease, the head may adopt a completely flexed posture, resulting in limitation of the field of vision, interference with feeding and respiratory function and neck discomfort.

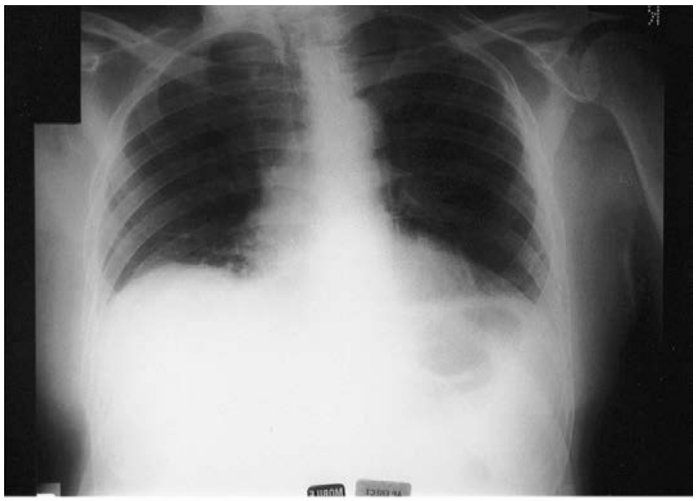

Fig. 116.3. Chest radiograph of a patient with ALS and respiratory failure showing raised hemidiaphragms bilaterally.

Respiratory symptoms

Up to 80% of patients with MND have a degree of impairment of respiratory function at the time of presentation, though this is seldom symptomatic (Schiffman & Belsh, 1993). In some patients diaphragmatic weakness is a relatively early feature, resulting in symptomatic breathlessness in the supine position (Fig. 116.3). A high frequency of sleep disordered breathing has also been reported in MND (Ferguson et al., 1996). On rare occasions, patients present with impending respiratory failure (Nightingale et al., 1982). As the initial manifestation of MND, this symptom is associated with a very grave prognosis. The symptoms of respiratory muscle weakness in MND include dyspnea on mild exertion or when lying flat; difficulty with coughing and talking; daytime somnolence; difficulty falling asleep, interrupted sleep, nightmares; morning headaches; nervousness, tremor, increased sweating, tachycardia and anorexia. When the vital capacity approaches 30–40% of the predicted value, there is a risk of sudden, life-threatening respiratory failure (Oppenheimer, 1993).

Sleep disturbance

Sleep disturbance is a common problem in patients with MND and may also have a significant impact on the well-being of the carer. Multiple factors may contribute to insomnia. Muscle weakness and the resultant impairment of mobility both reduces or prevents customary physical activities during the day and interferes with postural adjustments at night. Various types of pain may interfere with sleep including painful cramps, joint stiffness, and discomfort due to pressure effects or poor positioning. Anxiety and depression may also contribute to insomnia. Respiratory insufficiency with hypoxia and dyspnea may render the patient fearful of going to sleep.

Pain

Pain is not usually present in the early stages of MND, but is common in the later stages of the disease. One study of 42 patients reported that pain was a major feature in 64% (Newrick & Langton-Hewer, 1985). Saunders et al. (1981) evaluated 100 patients in a hospice setting and found that 45% had pain. The major identifiable problems were: stiffness of joints, muscle cramps, skin pressure, immobility requiring external help, severe spasticity and constipation.

Uncommon manifestations of MND

Dementia

Traditionally, it has been reported that patients with MND show preserved cognitive function. However, it has been estimated that dementia, typically of fronto-temporal lobe type, occurs in approximately 3% of patients and this may occasionally be the presenting feature of the disease (Hudson, 1981). MND patients with overt dementia frequently have a characteristic pattern of cognitive dysfunction, with prominent attentional deficits, particularly on tasks requiring sustained effort or the ability to shift from one thinking paradigm to another. Confrontation naming, verbal fluency, insight and judgement are also impaired. In contrast, verbal and non-verbal memory and spatial abilities are usually well preserved (Neary et al., 1990). Detailed neuro-psychological assessment in MND patients without overt dementia has shown that a mild degree of cognitive disturbance is more common than previously recognized, particularly in patients with prominent bulbar features (Rakowicz & Hodges, 1998).

Sensory impairment

Although sensory abnormalities are not usually considered a typical feature of the clinical spectrum of MND, patients may complain of sensory symptoms, particularly early in the disease. Objective signs of sensory impairment on examination, however, are virtually never found.

Autonomic function is generally preserved in MND. Normally, bowel and bladder control and ocular movements are preserved, unless the course of the disease is extended by respiratory support measures.

Disease progression and prognosis

In MND relentless progression of limb and bulbar weakness is the rule, ultimately producing severe disability.

Temporary stabilization sometimes occurs. Occasional cases have been described where the disease appears to remit (Tucker et al., 1991), but this is extremely rare. Limb weakness usually progresses to involve all four limbs. Early involvement of paravertebral muscles is unusual, but as the disease progresses weakness of trunk muscles and neck extensors is common. Significant diaphragmatic weakness usually occurs following the development of marked limb and/or bulbar weakness. Bulbar symptoms will eventually develop in approximately 80% of afflicted individuals. Speech difficulties may progress to anarthria. Dysphagia may also progress to a severe level, with the potential complications of dehydration, malnutrition and aspiration pneumonia.

Approximately 50% of patients with MND die within 3–4 years of the onset of symptoms, 20% live for 5 years, 10% live for 10 years and a few individuals live for as long as 20 years (Mulder, 1982). The cause of death in MND is usually respiratory failure, which may be accompanied by bronchpneumonia.

Investigation and differential diagnosis

The diagnosis of MND is essentially clinical, since there is no specific diagnostic test. The important features supporting the diagnosis are the presence of upper and lower motor neuron signs in a distribution extending beyond a discrete spinal level or peripheral nerve, usually with spontaneous fasciculation, and without sensory abnormalities. A number of specific investigations may be necessary to confidently exclude other diagnoses. Neurophysiological assessment is particularly useful. Evidence of denervation and reinnervation in muscles of at least two limbs, not corresponding to a single nerve root or peripheral nerve distribution, is strongly supportive of a diagnosis of MND. Motor conduction is normal or may be slightly slowed, with no evidence of conduction block, and with normal sensory conduction velocities. Neuroimaging may be advisable to exclude other intracranial or spinal disorders. Most biochemical investigations are normal. The blood creatine kinase level may be increased two–threefold in up to 50% of patients. The CSF protein is slightly elevated in a proportion of patients. Approximately 5% of MND patients have an IgG or IgM paraprotein band, though no causal association with motor neuron dysfunction has been demonstrated to date. Oligoclonal bands are also occasionally noted in the CSF of patients with MND (Younger et al., 1990).

The major conditions to be considered in the differential diagnosis of MND are listed in Table 116.2.

Table 116.2. Differential diagnosis of amyotrophic lateral sclerosis

Benign cramp/fasciculation syndrome
Degenerative spinal disease: radiculomyelopathy
Motor neuropathies, e.g. multifocal motor neuropathy with conduction block
Myasthenia gravis
Myopathies, e.g. inclusion body myopathy
Multifocal cerebrovascular disease
Postpoliomyelitis syndrome
Spinal muscular atrophy
Kennedy's disease (X-linked bulbospinal neuronopathy)
Syringomyelia/syringobulbia
Endocrine disease, e.g. hyperthyroidism, hyperparathyroidism
Heavy metal intoxication

Pathology of MND

The neurodegenerative process in MND is relatively selective for upper motor neurons, a proportion of which are represented by Betz cells in the fifth layer of the motor cortex, and for lower motor neurons in the ventral horn of the spinal cord and brainstem. Motor neurons innervating the extraocular muscles and those comprising Onuf's nucleus in the sacral spinal cord innervating the pelvic floor muscles, tend to remain unaffected, which correlates with the preservation of eye movements and control of bowel and bladder function in MND patients. However, the selective vulnerability of motor neurons to the disease process in MND is relative rather than absolute, and there is increasing evidence from pathological (Ince et al., 1998a,b) and clinical (Chari et al., 1996; Kew et al., 1993) studies that pathology outside the motor system can be found frequently and that MND is actually a multisystem disorder in which the motor system tends to be affected earliest and most severely. Experience from countries where clinical practice includes the use of respiratory support measures to prolong life to an advanced stage of disease has revealed very extensive multisystem pathological changes (Sasaki et al., 1992).

Gross pathological examination in MND may reveal atrophy of the precentral gyrus of the cerebrum, thin hypoglossal nerves and atrophied ventral roots emanating from the spinal cord. There may be shrinkage and sclerosis of the anterolateral tracts of the spinal cord. Microscopical examination reveals extensive loss of motor neurons with a degree of reactive gliosis in the ventral horns of the spinal cord and in the motor nuclei within the brainstem. There may be obvious depletion of Betz cells in layer V of the motor cortex.

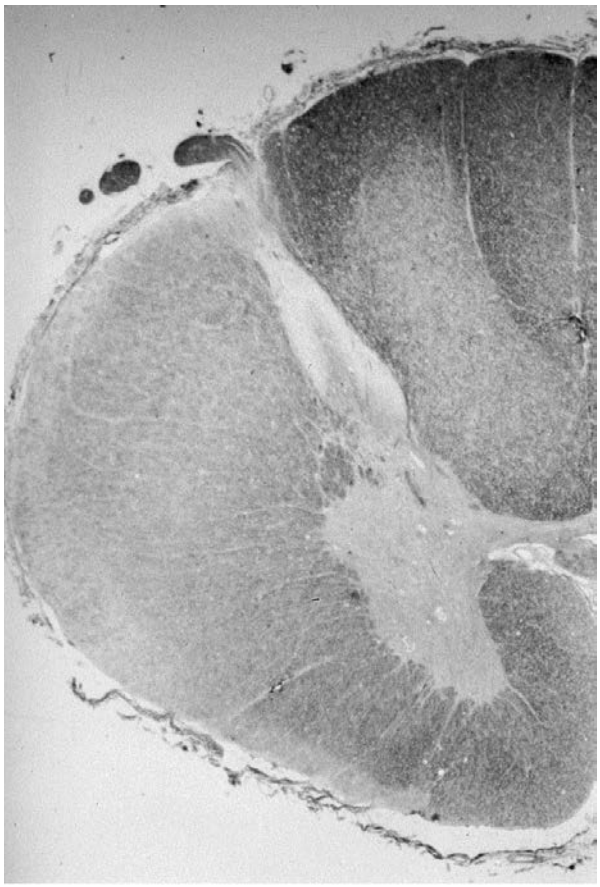

Fig. 116.4. Hemisection of the spinal cord from a patient with ALS showing depletion of anterior horn cells and degenerative changes affecting the corticospinal tract. This patient also has a degree of myelin pallor in the ascending dorsal column sensory tract.

There is demyelination and axonal loss affecting the crossed and uncrossed corticospinal tracts of the spinal cord. The anterolateral pathways of the spinal cord often show reduction in staining for myelin, in contrast to the usually preserved posterior columns (Fig. 116.4). However, degenerative changes are seen in the posterior column sensory pathways and in the ascending spinocerebellar tracts in some cases.

The degenerating motor neurons in MND contain characteristic ubiquitinated inclusion bodies (Leigh et al., 1988; Lowe et al., 1988). The inclusions may be hyaline, Lewy body-like or skein-like (Fig. 116.5(*a*), (*b*), see colour plate section). The main protein constituent of the fibrils comprising these inclusions is unknown. In some cases of SOD1-related familial MND dramatic hyaline conglomerate inclusions have been observed which demonstrate intense immunoreactivity for both phosphorylated and non-phosphorylated neurofilament epitopes (Ince et al., 1998a,b, see colour plate section) (Fig. 116.5(*c*)).

Death of lower motor neurons denervates muscle fibres, which may, in time, be reinnervated by collateral sprouts from the axons of surviving motor neurons. In the earlier stages of the disease this reinnervation compensates for the progressive loss of motor neurons. Histological studies of muscle in MND show the features of fatty infiltration of muscle and denervation atrophy, with groups of angular atrophic muscle fibres. Enzyme histochemistry shows muscle fibre type grouping. Axonal sprouting from residual intramuscular nerve fibres, and increased segmentation and volume of the motor end-plate have been reported.

Pathogenesis of MND

The primary pathogenetic processes underlying MND are likely to be multifactorial and the precise mechanisms underlying selective cell death in the disease are at present unknown. Current understanding of the neurodegenerative process in MND suggests that there may be a complex interplay between genetic factors, oxidative stress, toxic activation of glutamate receptors and damage to critical target proteins and organelles (Brown, 1995). The relative importance of these factors may vary in different subgroups of patients.

Genetic factors

MND is sporadic in 90% of cases and familial in 5 to 10% of cases. Familial cases usually show autosomal dominant inheritance, though autosomal recessive and X-linked inheritance may be seen in some pedigrees. Multiple abnormal gene products can set the scene for motor neuron degeneration (Table 116.3). A very important research advance came from the finding that 20% of families with autosomal dominant MND showed mutations in the gene on chromosome 21 which encodes the free radical scavenging enzyme Cu/Zn superoxide dismutase (SOD1) (Rosen et al., 1993). More than 90 different mutations, largely point mutations, have been described. SOD1 is a cytosolic metalloenzyme, with copper and zinc binding sites, whose major role is to catalyse the conversion of intracellular superoxide radicals to hydrogen peroxide, which is then eliminated by the action of other free radical scavenging enzymes. SOD1 is ubiquitously expressed in cells throughout the body. The reasons why motor neurons are selectively vulnerable to injury in the presence of SOD1 mutations are not yet clear, though one factor may be the high level of expression of this anti-oxidant defence protein by motor neurons.

Table 116.3. Genetic factors in amyotrophic lateral sclerosis

Autosomal dominant		Gene locus
Mutations in Cu/Zn superoxide dismutase		Chromosome 21
Juvenile-onset ALS	linked to	Chromosome 9q34
ALS with fronto-temporal dementia	linked to	Chromosome 9q21–q22
Gene unknown in approximately 80% of pedigrees		
Autosomal recessive		
Tunisian juvenile-onset ALS	linked to	Chromosome 2q 33–q35
Scandinavian ALS with D90A SOD1 mutation		Chromosome 21
Juvenile-onset ALS	linked to	Chromosome 15q15–q21
X-linked		
X- linked dominant (single family)	linked to	Chromosome X centromere
Possible genetic risk factors for ALS (non-Mendelian inheritance)		
Deletions or insertions in KSP repeat region of neurofilament heavy subunit gene		Chromosome 22q12
Excitatory amino acid transporter gene (EAAT2)		Chromosome 11p13
Survival motor neuron (SMN) gene		Chromosome 5q13
Neuronal apoptosis inhibitory protein (NAIP)		Chromosome 5q13
Apolipoprotein E e4		Chromosome 19q13
Cytochrome c oxidase subunit 1		Mitochondrial
AP endonuclease		Chromosome 14q11–q12
Mn superoxide dismutase		Chromosome 6q25

The pathways leading to cell death of motor neurons in the presence of SOD1 mutations have not yet been fully elucidated, though there is a compelling body of evidence that the mutant SOD1 protein exerts its deleterious effects through a toxic gain of function rather than a loss of function. Several hypotheses have been formulated to explain this toxic gain of function (Brown, 1995; Cookson & Shaw, 1999). The most favoured suggestions include the possibility that the mutant SOD1 protein may cause alteration in the handling of intracellular free radicals resulting in oxidative stress or may cause the formation of toxic intracellular protein aggregates.

The genetic alterations underlying the remaining 80% of cases of autosomal dominant MND at present remain unknown. Linkage analysis has revealed that chromosomes 2q, 9q and 15q may harbour mutations associated with rare forms of juvenile-onset MND (Hentati et al., 1994; Chance et al., 1998; Anderson et al., 2000). Familial MND with frontotemporal dementia has recently been linked to chromosome 9q21–q22 (Hosler et al., 2000).

There have been isolated reports of rare genetic abnormalities found in sporadic cases of MND. Deletions or insertions in the KSP repeat region of the gene encoding the neurofilament heavy protein, which is a major component of the neuronal cytoskeleton have been described (Figlewicz et al., 1994; Tomkins et al., 1998). Isolated mutations have also been described in subunit 1 of the cytochrome c oxidase subunit, which is an important component of the mitochondrial respiratory chain (Comi et al., 1998) and in the AP endonuclease enzyme (Tomkins et al., 2000), which has a key role in the repair of oxidative damage to DNA. It has also been suggested that the apolipoprotein e4 genotype is a risk factor for the development of bulbar onset MND (Al Chalabi et al., 1996), though not all research groups have been able to confirm this finding. Other studies have indicated that mutations in the glutamate re-uptake transporter protein EAAT2, in the SMN (survival motor neuron) and NAIP (neuronal apoptosis inhibitory protein) genes may occasionally be found in patients with ALS or pure lower motor neuron syndromes. It has also been suggested that a polymorphism in the mitochondrial targeting sequence of Mn superoxide dismutase may be over-represented in cases of sporadic MND (for review see Andersen et al., 2000).

The possibility of hereditary factors protecting against the development of motor neuron degeneration has also been postulated. In Finland the D90A SOD1 mutation results in MND only when homozygously expressed, whereas in other parts of the world this mutation results in ALS in heterozygotes. This has led to the hypothesis that a

coinherited neuroprotective factor may be present in the Finnish patients (Anderson et al., 1996).

Glutamatergic toxicity

Glutamate is the major excitatory neurotransmitter in the human nervous system, with a widespread distribution. Motor neurons are activated by stimulation of cell surface glutamate receptors and the excitatory signal is terminated by active removal of glutamate from the synaptic cleft by transporter proteins which are largely located on perisynaptic glial cells. It is known that excessive stimulation of neuronal glutamate receptors (excitotoxicity) can injure neurones by mechanisms which include derangement of intracellular calcium homeostasis and excessive free radical production. A body of circumstantial evidence has implicated glutamate-mediated toxicity as a contributory factor to motor neuron injury (Shaw & Ince, 1997; Jackson & Rothstein, 2000). Antiglutamate therapy has some effect in prolonging survival in human patients (Lacomblez et al., 1996) and in a transgenic mouse model of familial MND (Gurney et al., 1996). The key findings are that the expression and function of the major glial glutamate re-uptake transporter protein EAAT2 (excitatory amino acid transporter 2) may be impaired in MND and that extracellular and CSF levels of glutamate may be abnormal in at least a proportion of MND patients (Rothstein et al., 1992, 1995; Shaw et al., 1995a). In addition, both PET (positron emission tomography) scanning studies and transcranial magnetic stimulation of the motor cortex in patients with MND have indicated that there is hyperexcitability of the motor system (Kew et al., 1993; Mills, 1995). Recently the presence of abnormally spliced RNA transcripts for the EAAT2 protein was reported in the motor system and CSF of patients with MND, and it was suggested that a specific defect of RNA processing may be important in disease pathogenesis (Lin et al., 1998). However, other groups have been unable to confirm that these alternatively spliced RNA transcripts are disease specific (Meyer et al., 1999).

Oxidative stress

The effects of oxidative stress within non-replicating cells such as neurones may be cumulative, and injury by free radical species is a major potential cause of the age-related deterioration in neuronal function occurring in neurodegenerative diseases. There is particular interest in the role of oxidative stress in MND given that mutations in the SOD1 gene, which encodes an enzyme crucial for cellular antioxidant defence, underlie some cases of familial MND as described above (Cookson & Shaw, 1999; Robberecht, 2000). Studies of human postmortem CNS tissue have demonstrated the presence of biochemical changes to proteins and DNA, which represent the effects of free radical damage and these changes are more pronounced in MND cases compared to controls (Shaw et al., 1995b; Ferrante et al., 1997). Other postmortem neurochemical changes, including altered expression of components of the intracellular antioxidant defence systems, have been interpreted to indicate an attempted compensatory response to the presence of oxidative stress during the course of MND (Sillevis-Smitt et al., 1994; Shaw et al., 1997). Fibroblasts cultured from the skin of patients with both familial and sporadic MND show increased sensitivity to oxidative insults compared to those from control cases (Aguirre et al., 1998). Recent studies of CSF from MND patients compared to controls have shown an increase in 4-hydroxynonenal (Smith et al., 1998) and 3-nitrotyrosine (Toghi et al., 1999), which may both reflect abnormal free radical metabolism.

Derangement of intracellular calcium homeostasis

Calcium plays a fundamental role in many normal cellular processes including neuronal excitability and regulation of intracellular second messenger systems. Intracellular calcium homeostasis is inextricably linked with other potential mechanisms underlying degeneration of motor neurons, including glutamatergic toxicity, oxidative stress and mitochondrial dysfunction. Activation of cell surface glutamate receptors is a major route for calcium entry into neurons. Both *N*-methyl-D-aspartate (NMDA) and AMPA receptors lacking the GluR2 subunit have calcium permeable ion channels. In addition, depolarization of a neuron by activation of glutamate receptors may lead to a secondary influx of calcium resulting from activation of voltage-gated calcium channels. Sustained elevation of intracellular calcium resulting from glutamate receptor activation can eventually lead to neuronal injury due to excessive activation of several enzyme cascades and the generation of free radicals (Siesjo, 1994). Mitochondria act as an important intracellular store for calcium. It has been suggested that the permeability transition pore in the mitochondrial membrane may act as a calcium release channel involved in calcium homeostasis in the cell (Bernardi & Petronilli, 1996).

The possibility that spinal motor neurons may be particularly vulnerable to calcium-mediated injury is suggested by the observations that this cell population appears to lack the expression of the Ca^{2+} buffering proteins parvalbumin and calbindin D28K (Ince et al., 1993), while expressing abundant calpain II, a calcium-activated prote-

olytic enzyme. Motor neuron groups such as the oculomotor neurons which are less vulnerable to pathology in MND do express parvalbumin. In addition, the expression of calcium-permeable AMPA receptors by human motor neurons (Williams et al., 1997) may be a further factor contributing to the vulnerability of this cell group to calcium-mediated toxic processes.

Siklos et al. reported in muscle biopsies from patients with MND, increased calcium, increased mitochondrial volume and increased numbers of synaptic vesicles in the motor axon terminals (Siklos et al., 1996). In a subsequent study the same group have demonstrated, using the oxalate–pyroantimonate technique and ultrastructural examination, that motor neurons of transgenic mice with a G93A SOD1 mutation exhibit alterations in intracellular calcium (Siklos et al., 1998). The cell bodies and proximal dendrites of spinal motor neurons showed small vacuoles filled with calcium, whereas these changes were not observed in oculomotor neurons. The authors concluded that the free radical-mediated stress induced by mutant SOD1 appeared to induce deleterious changes in intracellular calcium distribution in motor neuron populations lacking calbindin D28K and/or parvalbumin.

Cytoskeletal protein defects

Neurofilament proteins form a major component of the cytoskeleton of neurons and have significant roles in the maintenance of cell shape and axonal calibre as well as in axonal transport. Neurofilaments are the most abundant structural proteins in large cells with long axons, like motor neurons. Neurofilaments are composed of three subunit polypeptides: neurofilament light NF-L (MW 68 kDa); neurofilament medium NF-M (MW 150 kDa) and neurofilament heavy NF-H (MW 200 kDa), assembled in a 6:2:1 ratio to form macromolecular filaments. NF-L makes up the core of the neurofilament, while NF-M and NF-H are arranged around this core and contribute to the side arms radiating from the filament. Neurofilament subunits are assembled in the motor neuron perikaryon and are transported down the axon by slow axonal transport. Under normal circumstances there is progressive phosphorylation as the neurofilament proteins are transported down the axon.

Neurofilament proteins are of considerable interest in MND as potential cellular targets for injury. The abnormal assembly and accumulation of neurofilaments in the perikaryon and proximal axons of motor neurons is a characteristic feature of the pathology of MND (Hirano, 1991). Consensus agreement has not been reached as to whether phosphorylated neurofilaments are increased in cell bodies of surviving motor neurons in MND. Ubiquitinated inclusions with compact or Lewy body-like morphology in surviving motor neurons in MND may show immunoreactivity for neurofilament epitopes. In some cases of SOD1-related familial MND, large argyrophilic hyaline conglomerate inclusions expressing both phosphorylated and non-phosphorylated neurofilament epitopes, have been observed in the cell bodies and axons of motor neurons (Ince et al., 1998a,b). The importance of neurofilaments in the normal health of motor neurons is emphasized by the finding that occasional cases of sporadic MND have deletions or insertions in the KSP repeat region of the neurofilament heavy gene (Figlewicz et al., 1994; Tomkins et al., 1998). In addition, motor neuron pathological changes develop in transgenic mice overexpressing NF-L or NF-H subunits (Xu et al., 1993; Cote et al., 1993) or in mice expressing mutations in the NF-L gene (Lee et al., 1994). These in vivo models demonstrate that disruption of neurofilament assembly can selectively injure motor neurons.

Transgenic mice which carry mutations in the human SOD1 gene also show neuropathological changes affecting neurofilament organization. The G93A mutant transgenic mouse develops neurofilamentous spheroids within motor neurons (Tu et al., 1996) and reductions in axonal neurofilament content and in the rate of axonal transport have also been observed (Zhang et al., 1997).

Mitochondrial dysfunction

Important functions of mitochondria relevant to the pathogenesis of neurodegenerative diseases include the synthesis of ATP, buffering of intracellular calcium, generation of intracellular free radicals and initiation of apoptosis. Mitochondria have been shown to be particularly susceptible to free radical damage at both protein and DNA levels and free radicals are known to inhibit the activities of specific mitochondrial enzymes (Zhang et al., 1990). Changes in mitochondrial function have been suggested as an important factor contributing to age-related neurodegenerative diseases. A significant factor contibuting to the age-related decline in mitochondrial function is the effect of accumulating mutations in the mitochondrial genome (Linnane et al., 1989).

The evidence that mitochondrial dysfunction may contribute to motor neuron injury in MND (Beal, 2000; Menzies et al., 2000) can be summarized as follows.

Structural changes in mitochondria

Ultrastructural studies have shown abnormal mitochondrial morphology in muscle, intramuscular nerves and

liver as well as within spinal cord motor neurons (Nakano et al., 1987; Okamoto et al., 1990; Sasaki & Iwata, 1996).

Alteration in the activity of mitochondrial respiratory chain enzymes

Increases in the activities of complex I and/or complex II/III, suggested to represent a compensatory mechanism for oxidative damage, have been reported in the frontal cortex of patients with SOD1 related familial ALS (Browne et al., 1998). Fujita and coworkers reported a decrease in complex IV activity in the spinal cord ventral horn in MND cases (Fujita et al., 1996). Borthwick and colleagues, using a histochemical technique, reported reduced complex IV activity in individual spinal motor neurons from MND cases (Borthwick et al., 1999). Complex IV deficiency has also been reported in muscle from sporadic MND cases (Vielhaber et al., 2000). One patient has been described with an MND phenotype and severe deficiency of muscle complex IV, which was due to a microdeletion in subunit 1 of cytochrome c oxidase (complex IV) (Comi et al., 1998).

Alterations in the mitochondrial genome

Veilhaber and colleagues (2000) screened the mtDNA in skeletal muscle from 17 MND patients and found one patient with multiple mtDNA deletions and a further 13 patients showed total mtDNA levels below those of control cases. Dhaliwal and Grewal (2000) measured levels of the so-called common deletion, a 4977 base pair deletion of mtDNA previously shown to be increased in the brain of aged individuals. The levels of the common deletion were higher in the motor compared to temporal cortex and an average of 11-fold higher in MND cases compared to controls.

Evidence from cellular and animal experimental models

A neuronal cell line transfected to express mutant SOD1 has been reported to show loss of mitochondrial membrane potential, together with an increase in cytosolic calcium concentration, suggesting a reduction in the ability of the mitochondria in these cells to sequester calcium (Carri et al., 1997). Studies in transgenic mouse models of SOD1-related ALS have shown that one of the very early features of motor neuron injury, occurring before the animals develop clinical evidence of motor neuron dysfunction, is the appearance of abnormal mitochondria (Wong et al., 1995). The mitochondria are initially noted to be dilated, with disorganized cristae and fractured outer membranes, with the eventual formation of vacuolar structures. Therapeutic effects of compounds which have an effect on mitochondrial function have also begun to be investigated in the SOD1 transgenic mouse models. Creatine buffers energy levels within the cell, maintains ATP levels and stabilizes mitochondrial creatine kinase which inhibits opening of the mitochondrial permeability transition pore. Administration of creatine to G93A transgenic mice improved motor function and extended survival in a dose-dependent manner, as well as causing a reduction in biochemical indices of oxidative damage in the spinal cord (Klivenyi et al., 1999).

Other pathogenetic hypotheses in ALS

These include the potential contributions of viral infection, exogenous toxins and immune-mediated mechanisms which have been reviewed elsewhere (Strong, 2000; Appel et al., 2000). There is emerging evidence that, following initiation of cellular injury in MND, the motor neurons may eventually die by a programmed cell death pathway or apoptosis (for review see Sathasivam et al., 2000).

Management of MND

General aspects of management

The main roles of the neurologist in the care of patients with MND are to: (i) establish the diagnosis; (ii) manage symptomatic therapy; (iii) coordinate paramedical services and the provision of aids and appliances quickly once the patient has need of them. The timing of discussion and the provision of these measures is very important: too early can be as bad for the morale of the patient as too late; (iv) educate and counsel patients and their families as appropriate for the stage of the disease. This is particularly important in MND where the patient may not have time to adapt to one level of disability before new problems have to be faced; (v) offer patients the opportunity to participate in therapeutic trials or clinical research projects where possible.

There is a growing tendency in the United Kingdom and other countries for patients with MND to be managed in specialist clinics, with input from nursing staff with specialist training. Other paramedical staff whose expertise may be of great value in the care of MND patients include the physiotherapist, the occupational therapist, the speech therapist, the dietician, the social worker and the orthotist. The coordinated action of multiple health care professionals within a multidisciplinary team can lessen the difficulties experienced by patients with MND and by their carers and families.

Table 116.4. Symptom control in amyotrophic lateral sclerosis

Symptom	Therapies
1 Cramp	Quinine sulphate (baclofen, diazepam, phenytoin)
2 Fatigue	Occasionally pyridostigmine
3 Spasticity	Baclofen, diazepam, tizanidine
4 Dysphagia	Nutritional supplements, liquid thickeners, PEG
5 Drooling	Hyoscine patches, atropine, amitriptyline, suction machine, parotid gland irradiation
6 Constipation	Ispaghula, methyl cellulose, lactulose, glycerol suppositories
7 Emotional lability	Amitriptyline, imipramine (L-dopa preparations)
8 Depression	Tricyclic agents or serotonin reuptake inhibitors
9 Insomnia	Address underlying cause, fluorazepam, diphenhydramine
10 Pain	Address underlying cause + analgesia
11 Dyspnea	Antibiotics for aspiration pneumonia, chest physiotherapy, sublingual lorazepam for acute attacks of dyspnea. Consider NIPPV in selected patients. Morphine for end-stage respiratory distress

Medical aspects of symptom control in MND (Table 116.4)

Symptomatic therapy aimed at alleviating the distressing symptoms, which often arise during the course of MND, can do much to improve the quality of life for the patient. Many of the symptomatic therapies currently recommended by clinicians have not been assessed in rigorous controlled trials. The evidence base for many of these therapies has recently been reviewed by an American Academy of Neurology task force (Miller et al., 1999).

Cramps

Painful muscle cramps are common in MND, particularly in the early stages of the disease. This symptom often responds to quinine sulfate in a dose of 200–400 mg per day. Other therapies which can be useful in alleviating cramp include phenytoin, baclofen and diazepam.

Weakness and fatigue

There is little that can be done pharmacologically to alleviate weakness in MND. A variety of aids and appliances may help to maximize mobility and function including foot-drop splints, walking frames, wheelchairs, mobile arm supports, supporting collars. Fatigue is a common symptom and patients may obtain temporary benefit from anticholinesterase medication such as pyridostigmine, although the beneficial effect is likely to recede within a few months.

Spasticity

The use of muscle relaxants to treat spasticity may be helpful in some patients. However, many patients are intolerant of such therapy, because reduction of tone in the limbs may increase the sensation of weakness and reduce mobility. If spasmolytic therapy is required, baclofen, tizanidine or a benzodiazepine such as diazepam may be used.

Dysarthria

Decreasing the speed of speech and the use of key words and short phrases may improve intelligibility. When speech becomes unintelligible, communication aids of varying sophistication may be required.

Dysphagia

In early dysphagia, alteration in food consistency may suffice to maintain adequate nutrition. If the patient is continuing to lose weight, then nutritional supplements of liquid or semisolid consistency may be helpful. The insertion of a PEG (percutaneous endoscopic gastrostomy) tube should be considered when the following problems are apparent: (i) continuing weight loss (more than 20% of the normal body weight); (ii) dehydration; (iii) aspiration with resultant respiratory infections; (iv) meal times have become intolerable due to frequent choking spells. PEG feeding represents one of the major advances in symptomatic care for patients with MND. After PEG placement many patients report great relief and increased well-being, though as yet no large-scale quality of life studies have been conducted. Whether early PEG placement results in increased duration of survival has not yet been convincingly demonstrated (Mazzini et al., 1995). The PEG procedure should not be postponed until the patient has severely compromised respiratory function. At this stage in the disease the patient may develop respiratory failure following the procedure.

Drooling of saliva

The mainstay of therapy is the use of anticholinergic medication. The most commonly used medications are amitriptyline, atropine and hyoscine skin patches. A portable suction device which can be used to remove pools of saliva may be useful. Carbocysteine or propranolol are sometimes recommended to reduce the viscosity of secretions (Borascio & Volz, 1997). If pharmacological agents do not successfully control salivation problems, then staged, low-dose parotid irradiation may be considered.

Constipation

Constipation may be a major and distressing problem in MND. Contributory factors include inability to adequately perform a Valsalva manoeuvre due to weakness of the abdominal muscles, spasticity of the pelvic floor muscles, immobility, dehydration, dietary alterations with reduced fibre intake and medication including anticholinergics and opiates. Severe constipation and abdominal distension may exacerbate respiratory dysfunction. Potential remedies include increasing dietary fluid and fibre intake, adjustment of constipating medication and administration of laxative preparations.

Emotional and psychological problems

Emotional lability often reponds to amitriptyline or imipramine therapy. L-dopa preparations and serotonin reuptake inhibitors may also be of benefit (Borascio & Volz, 1997). Antidepressant or anxiolytic therapy may be required for some patients. The psychological state of patients with MND has been shown to correlate with survival (McDonald et al., 1994) and it is therefore important that clinically significant mood changes should be looked for and treated.

Sleep disturbance

The management of sleep disturbance in patients with MND depends on assessment of the underlying cause. Attention to sleeping position, a pressure relieving mattress or an electrically powered bed may be helpful. Pain management may be required. A night time prescription of amitriptyline may be helpful, both for its sedative and antidepressant actions. Care should be taken in prescribing sedative medication to patients with MND as respiratory depression may occur. Diphenhydramine is a sedative preparation well tolerated by older individuals, which has the added benefit of reducing muscle cramps.

Pain

Effort should be made to establish the site and reason for the patient's pain. This may prove a challenge in the late stages of the disease with its attendant communication difficulties. Non-steroidal anti-inflammatory agents and physiotherapy will help to control pain arising from joint stiffness. Pharmacological agents may be employed to alleviate cramps, spasticity and constipation, as described above. Analgesic agents of increasing potency may be required in the later stages of the disease.

Respiratory failure

The management of the respiratory complications of MND include the following general measures. Attention should be given to the detection and prevention of aspiration pneumonia. Antiobiotic therapy should be used at the first indication of a chest infection. Chest physiotherapy and postural drainage should be used when the patient has difficulty in clearing secretions from the chest. Patients will breathe more comfortably during sleep if placed in an upright position. When patients experience bouts of severe dyspnea, accompanied by extreme anxiety or panic, a small dose of lorazepam (0.5–1 mg) sublingually may be helpful (Borascio & Volz, 1997). If breathlessness causes distress during the later stages of the disease, the use of small amounts of morphine will be useful. Depression of respiration can usually be avoided if the initial dose is small and increments are gradual (Saunders et al., 1981).

Assisted ventilation, coupled with appropriate nutritional support, could theoretically extend the patient's life indefinitely, and the implications of initiating such respiratory support must be clearly thought through and discussed for each patient. Full 24-hour intermittent positive pressure ventilation via a tracheostomy, is an option that is only rarely chosen by fully informed patients. The costs, in terms both of financial resources and the caregiver support required, are substantial. Non-invasive intermittent positive pressure ventilation (NIPPV) via a mask is the most practical form of assisted ventilation which may be considered (Fig. 116.6). Use of ventilatory support during sleep may lead to subjective improvement in sleep, resolution of morning headache and improvement in exercise tolerance, mobility, respiratory function and fatigue during the day (Howard et al., 1989). Controlled trials of this form of therapy with attention to quality of life parameters are warranted.

Terminal care

The aim of medical intervention in the terminal phase of the disease is to ensure that the patient is comfortable. Morphine therapy should be administered as required to alleviate discomfort or distress. This can be given via the PEG, by subcutaneous or intravenous injection or via a

Table 116.5. Recent clinical trials of potential neuroprotective therapies in motor neuron disease

Antiglutamate agents	Neurotrophic factors
Riluzole	Ciliary neurotrophic factor (CNTF)
Gabapentin	Insulin-like growth factor 1 (IGF-1)
Lamotrigine	Brain derived neurotrophic factor (BDNF)
	Glial-derived neurotrophic factor (GDNF)
	SR57746A/Xaliproden (neurotrophic-like effects), currently being assessed
Antioxidant therapy	
N-acetyl cysteine	

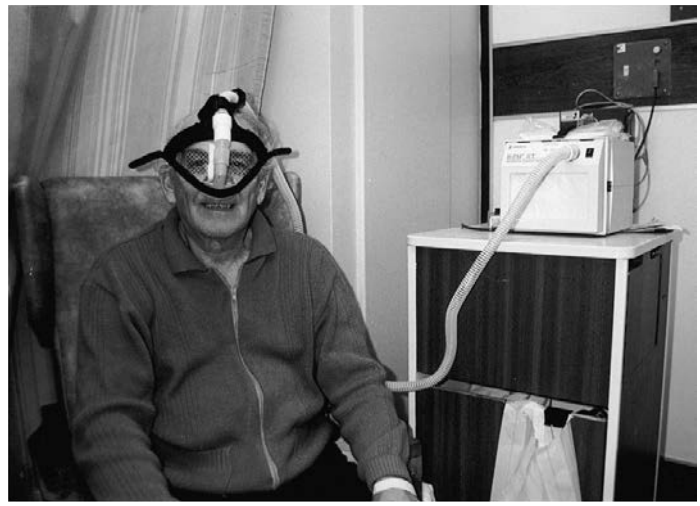

Fig. 116.6. Non-invasive respiratory support (NIPPV) in a patient with ALS.

nebuliser. Diazepam or chlorpromazine may be given to alleviate anxiety.

Neuroprotective therapy aimed at slowing clinical and pathological progression in MND

There is no therapy currently available, which has a dramatic effect in slowing disease progression in MND. However, some small steps have been made towards this ultimate goal in the last few years. A detailed critique of all the recent therapeutic trials (Meininger & Salachas, 2000) is beyond the scope of this chapter, and only the key results will be highlighted (Table 116.5).

Antiglutamate therapy

Several trials of antiglutamate therapy have taken place. Riluzole is a sodium channel blocker which inhibits glutamate release, and has several other potentially neuroprotective effects. Two double-blind, placebo-controlled clinical trials of riluzole have been carried out in more than 1100 patients with MND (Bensimon et al., 1994; Lacomblez et al., 1996). The results of both studies showed a statistically significant, though modest, benefit in prolonging survival and the drug has been licensed for use in MND. Riluzole therapy is relatively expensive (approximately £3700 per patient per year) and the average survival benefit to be expected is modest, but against this must be weighed the arguments that the patient population requiring the drug is relatively small, and that these patients are facing a lethal disease, for which no other therapy is available. At present it is unknown whether the modest overall therapeutic effect of riluzole conceals responders and non-responders.

Gabapentin, an anticonvulsant drug with antiglutamate activity, was evaluated in MND in a pilot therapeutic trial (Miller et al., 1996a,b) which showed a trend indicating potential slowing in the rate of decline of limb strength. Unfortunately, this positive trend was not replicated in a further trial, using higher doses of gabapentin.

Antioxidant therapy

No large-scale trials of antioxidant therapy have yet been conducted in MND. An under-powered trial of *N*-acetylcysteine therapy in 110 patients showed a trend towards improved survival in patients with limb-onset disease, which just failed to reach statistical significance ($P = 0.06$) (Louwerse et al., 1995). In the G93A SOD1 transgenic mouse model of MND, the anti-oxidant vitamin E, delays the onset of the disease, though does not influence disease duration (Gurney et al., 1996). The effect in human patients is unproven, though many patients are empirically prescribed vitamin E, because of the emerging evidence that free radicals may contribute to motor neuron injury.

Neurotrophic factors

Multiple neurotrophic factors contribute to the health and survival of motor neurons and exert neuroprotective effects in experimental paradigms and animal models of motor neuron injury. Several neurotrophic factors, administered by subcutaneous injection, have been assessed in recent trials, so far with rather disappointing results. Ciliary neurotrophic factor (CNTF) showed no therapeutic benefit, when administered by this route in MND, and actually appeared to have a detrimental effect in the high dose group (Miller et al., 1996a,b). In the USA recombinant human insulin-like growth factor 1 (IGF-1), in a trial

involving 266 patients, slowed progression of functional impairment and the decline in health-related quality of life (Lai et al., 1997). A similar trial conducted in Europe failed, however, to replicate this result and IGF-1 has not been licensed for use in MND. A trial of subcutaneously administered brain-derived neurotrophic factor (BDNF) showed no significant benefit and a further trial of glial-derived neurotrophic factor (GDNF) administered by the intraventricular route has been aborted. Concern has been expressed about the half-life and access to motor neurons of neurotrophic factors administered by the subcutaneous route and BDNF is currently being evaluated administered by continuous intrathecal delivery.

In conclusion, in several ways MND is a disease which is uniquely challenging to medical and health care professionals. Rapidly progressive disability, without periods of remission, and usually in the presence of preserved intellectual function, make MND a particularly difficult disease for patients and their families to face. A nihilistic approach from medical attendants can add to the distress and suffering of these families. There is much that can be done during the course of the disease to alleviate symptoms, maximise functional independence and to provide counselling and support. A coordinated, multidisciplinary approach is the best way of managing the disease, with the development of links between hospital-based, community and palliative-care personnel. At the present time drug therapies are becoming available which may have a modest effect in slowing the progression of MND and prolonging survival. Quality of life issues will be important in the evaluation of the place in management of these new neuroprotective therapies.

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The hereditary ataxias

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The hereditary ataxias are a group of disorders characterized by motor incoordination resulting from dysfunction of the cerebellum and its connections. Although these diseases are easily recognizable due to the obvious cerebellar dysfunction, distinguishing among them is no easy matter. On the one hand, there is a great deal of clinical overlap between genetically heterogeneous diseases; on the other, the manifestations of any given genetic ataxia are protean. Today, although we as clinicians might wish to believe otherwise, we feel forced to conclude that in most instances, once a general diagnosis of hereditary ataxia has been made, determining the specific type relies more on genetic testing than on clinical criteria. Genetic testing, because of its specificity, is a powerful tool; if positive, the diagnosis is irrefutable. This might suggest that the role of the neurologist has been circumscribed, but this is really not the case. Rather, we must take on new responsibilities. Not only must we become familiar with the scientific, ethical, and statistical implications of genetic testing, but we must also learn how best to counsel our patients, an activity previously limited to geneticists in tertiary health-care centres.

The hereditary ataxias fall into two main classes. The first group of ataxias result from enzyme defects and can be either intermittent (e.g. when caused by defects in intermediary metabolism) or chronic (e.g. ataxia telangiectasia, caused by deficiency in DNA repair). These ataxias are inherited in an autosomal recessive or X-linked manner and are typically present in childhood. The second group, consisting of the progressive degenerative ataxias, do not appear to be caused by catalytic abnormalities. They can be further divided based on the mode of inheritance: the autosomal recessive ataxias, of which Friedreich's ataxia is by far the most common; the relatively large group of autosomal dominant inherited ataxias; the rare X-linked ataxias; and, finally, those resulting from defects in mitochondrial function. In this chapter we discuss the genetics of hereditary ataxias within this broad framework, focusing on the chronic degenerative ataxias and their differential diagnosis.

Ataxias resulting from specific enzyme defects: the metabolic ataxias

This heterogenous group of ataxias are best viewed as a subset of inborn errors of metabolism. The cerebellar dysfunction stems from specific enzyme defects that result in either toxic by-products or a deficiency in metabolites that affect neuronal function. The dissection of metabolic pathways in the early half of the twentieth century has played an important role in suggesting candidate enzymes in cloning strategies. This is in contrast to the degenerative ataxias, for which positional cloning, a more time-consuming process, was needed to identify genes encoding novel proteins whose functions are still to be unveiled.

Like most disorders resulting from catalytic deficiencies, the metabolic ataxias tend to be recessive, since the presence of half the complement of enzymatic activity in heterozygotes is sufficient for most metabolic activities to proceed. Because metabolic pathways lie at the root of several housekeeping functions, the resulting ataxia is just one component of a complex clinical phenotype. It is this clinical picture, taken as whole, that usually betrays the underlying metabolic defect. These ataxias are best managed by pediatricians familiar with metabolic derangements and their ramifications. For the clinical neurologist we present only a brief outline. These ataxias can be divided into one of two groups (see Table 117.1). The first group comprises those ataxias that present intermittently when the biochemical abnormalities are at their worst; the second category is characterized by a more chronic and progressive ataxia induced by specific enzyme deficiencies.

Table 117.1. Genetics of inherited ataxias with known enzyme defects

Disease	Chromosomal localization	Enzyme/protein deficiency
I Intermittent ataxias		
Hyperammonemias and aminoacidurias		
OTC deficiency	Xp21.1	Ornithine transcarbamylase
Citrullinemia	9q34	Arginosuccinate synthetase
Arginase deficiency	6q23	Arginase
Arginosuccinaciduria	7cen-q11.2	Arginosuccinate lyase
Hyperornithemia–hyperammonemia–homocitrullinuria syndrome	13q14	Mitochondrial ornithine transporter
Hartnup disease	11q13	–
Isovaleric acidemia	15q14–q15	Isovaleric Acid CoA dehydrogenase
Disorders of pyruvate and lactate metabolism		
Pyruvate dehydrogenase complex	Xp22.2–p22.1	E1-alpha subunit of PDH complex (most common)
Pyruvate carboxylase deficiency	11q13.4–q13.5	Holocarboxylase synthetase
II Progressive ataxias from metabolic insufficiency		
Hexosaminidase deficiency – GM2 gangliosidosis (Tay Sachs disease)	Genetically heterogenous	Hexosaminidase A, B or S isozymes
Niemann Pick	11p15.4–15.1	Acid sphingomyelinase
Niemann Pick type C	18q11–q12	NPC1
Cerebrotendinous xanthomatosis	2q33–qter	Mitochondrial sterol 27 hydroxylase
Metachromatic leukodystrophy	22q13.31–qter	Arylsulfatase A
Adrenoleukodystrophy	Xq28	Adrenoleukodystrophy protein
Abetalipoproteinemia	4q22–q24	Microsomal triglyceride transfer protein
Hypobetalipoproteinemia	2p24	ApoB
Ataxia with Vitamin E deficiency	8q13.1–q13.3	Alpha-tocopherol transfer protein
Lesch–Nyhan syndrome	Xq26–q27.2	Hypoxanthine–guanine phosphoribosyltransferase
Wilson disease	13q14.3–q21.1	ATP7B protein
Ceroid lipofuscinosis	Several variants	Multiple gene products
X-linked ataxia, ichthyosis and tapetoretinal dystrophy	Xpter-p22.32	Arylsulfatase C
III Progressive ataxia associated with defective DNA repair mechanisms		
Ataxia telangiectasia	11q2.3	ATM kinase
Xeroderma pigmentosa	Several variants	Multiple
Cockayne syndrome	Several variants	Multiple

The intermittent ataxias result chiefly from deficits of urea cycle enzymes or disorders of pyruvate and lactate metabolism. In all of these conditions, affected infants usually display mental retardation and developmental delay. It is, however, important to distinguish between these subtypes, since some of the supportive measures aimed at preserving biochemical homeostasis differ. Inheritance of urea cycle deficits is autosomal recessive, with the notable exception of the X-linked and relatively common ornithine transcarbamylase deficiency (OTC) (Xp21.1). Ataxias seen in the aminoacidurias, such as intermittent branched-chain ketoaciduria and isovaleric acidemia, are usually diagnosed by the characteristic odour of the urine of these infants. Hartnup disease, another aminoaciduria that results in ataxia, is caused by a defect in renal and intestinal transport of amino acids. Because of the associated niacin deficiency, other features of pellagra such as dermatitis and mental confusion are often seen. Treatment of the aminoacidurias consists of a dietary protein modification so as to counter the protein loss, along with nicotinamide supplementation.

Pyruvate dehydrogenase deficiency, a less common form of metabolic intermittent ataxia, is most often caused by a mutation in the E1 alpha subunit of the pyruvate dehydrogenase enzyme (Xp22.2–p22.1) (Dahl et al., 1992). This condition is characterized by lactic acidosis, seizures, mental retardation and spasticity. Biotin responsive multiple carboxylase deficiency, another autosomal recessive ataxia, is caused by a variety of mutations in the holocarboxylase synthetase (*HLCS*) gene at locus 21q22 and characterized by seizures, myoclonus and nystagmus (Aoki et al., 1999; Dupuis et al., 1996).

Metabolic ataxias are usually diagnosed by screening biochemical tests when the neurological abnormalities are first noticed. If the family history is positive, it is even possible to diagnose OTC deficiency and several of the hyperammonemias from blood samples taken in utero. Pyruvate dehydrogenase deficiency can, in addition, be corroborated by a relatively simple biochemical assay on cultured fibroblasts. Despite the identification of individual gene defects, genetic testing is impractical at present because of the large number of mutations in the relevant genes. This scenario is certain to change with the development of low-cost and high-throughput DNA sequencing of genes, especially since diagnosis determines key management decisions.

Progressive metabolic ataxias, much like the intermittent ataxias, can also be caused by a variety of gene defects. Unlike the intermittent ataxias, however, these diseases usually present in later childhood or adolescence and the persistence of the biochemical abnormalities explains the progressive nature of the symptoms. These diseases can mimic the degenerative hereditary ataxias, although most of these diseases have characteristic clinical pictures and hallmark diagnostic tests. For instance, Niemann–Pick is characterized by foamy storage cells in bone marrow. When accompanied by the typical supranuclear gaze palsy, the diagnosis is virtually certain. Adrenoleukodystrophy is often suspected when X-linked inheritance is confirmed, and there are elevated levels of very long chain fatty acids in the blood. Although there is no cure for a number of these ataxic syndromes, there is a growing list of ataxias for which specific measures can be taken to at least halt progression (Table 117.2). As a consequence, efforts to develop cheap genetic tests are gaining centre-stage. Wilson's disease or hepatolenticular degeneration, characterized by copper overload, is probably the best known. Although the disease was described by Kinnier Wilson in 1911, the relevant gene, *ATP7B*, encoding a copper transporting ATPase, was discovered only in the last decade (Tanzi et al., 1993). This gene maps to13q14.3–q21.1. Because there are at least 25 different disease-causing mutations in a gene that occupies 80kb of genomic DNA, genetic testing is currently not possible and diagnosis rests on clinical tests, including the demonstration of Kayser–Fleischer rings and characteristic liver biopsy findings (Thomas et al., 1995). Medical management consists of instituting a diet low in copper, along with zinc that reduces copper absorption from the gut and the chelating agent, D-penicillamine. Other pharmacological agents include triethylenetetramine dihydrochloride (Trientine) and ammonium tetrathiomolybdate, both of value when penicillamine is not tolerated because of occasional toxicity.

Vitamin E deficiency induced by mutations in the alpha tocopherol transfer protein (8q13.1–q13.3) can present as a slowly progressive ataxia syndrome with neuropathy (Gotoda et al., 1995; Ouachchi et al., 1995). Hypovitaminosis E can also occur as part of abetalipoproteinemia, also known as Bassen–Kornzweig disease or acanthocytosis because of the presence of acanthocytes in peripheral blood smear evaluations. Characterized by hypocholesterolemia, hypolipidemia and reduction of fat soluble vitamins A, D, E and K, this ataxia is inherited in an autosomal recessive fashion. Patients often suffer from pigmentary retinopathy from the coexisting deficiency of vitamin A. Mutations in the microsomal triglyceride transfer protein (MTP) that result in an inability to form the apoB peptide of LDL and VLDL cause this syndrome (Sharp et al., 1993). Recently, genetic defects in the apoB gene itself have been identified to cause a virtually indistinguishable ataxic syndrome. Oral supplementation with vitamin E in high doses is effective in slowing down the progression in all these vitamin E deficient states (Martinello et al., 1998).

Cholestenolosis or cerebrotendinous xanthomatosis (CTX) is a relatively rare cause of progressive ataxia. Caused by any one of a variety of defects (missense, nonsense and frameshift) in the mitochondrial 27 hydroxylase gene (locus 2q33–qter), CTX is characterized by autosomal recessive ataxia, neuropathy, cataracts, and achilles tendon xanthomas (Leitersdorf et al., 1993). Magnetic resonance imaging reveals cerebral atrophy and evidence of demyelination. The diagnosis is confirmed by elevated serum cholestanol in the face of normal cholesterol. There is some evidence to suggest that treatment with chenodeoxycholic acid slows progression of the disease (van Heijst et al., 1998).

Refsum disease is yet another treatable ataxia caused by an enzyme deficiency, in this case a deficiency of phytanoyl-CoA hydroxylase that maps to locus 10pter–p11.2. Refsum should be suspected in any autosomal recessive ataxia presenting with the triad of ichthyosis, retinitis pigmentosa and neuropathy (Jansen et al., 1997; Mihalik et al., 1997). Toxicity as a result of the elevation of phytanic acid

Table 117.2. Treatable hereditary ataxias

Disorder	Metabolic abnormality	Clinical features	Treatment
Bassen Kornzweig syndrome	Abetalipoproteinemia	Acanthocytosis, retinitis pigmentosa, fat malabsorption	Vitamin E
Ataxia with isolated vitamin E deficiency (AVED)	Deficiency of alpha-tocopherol transfer protein	Progressive ataxic syndrome	Vitamin E
Hartnup disease	Tryptophan malabsorption	Pellagra rash, intermittent ataxia	Niacin
Mitochondrial complex defects	Complexes I, III, IV	Encephalomyelopathy	Riboflavin, CoQ10, dichloroacetate
Multiple carboxylase deficiency	Biotinidase deficiency	Alopecia, recurrent infections, variable organic aciduria	Biotin
Pyruvate dehydrogenase deficiency	Block in pyruvate metabolism	Lactic acidosis, ataxia	Ketogenic diet, chloroacetate
Refsum disease	Phytanic acid, alpha hydroxylase	Retinitis pigmentosa, cardiomyopathy, hypertrophic neuropathy, ichthyosis	Dietary restriction of phytanic acid
Urea cycle defects	Urea cycle enzymes	Hyperammonemia	Protein restriction, arginine, benzoate, alpha ketoacids

can be minimized by avoiding food containing this substance or its precursors.

Progressive ataxias associated with defective DNA repair

Although caused by known enzymatic defects, these autosomal recessive disorders are usually separated from the metabolic ataxias because they result from a specific inability to repair DNA damage. As might be expected, all of these closely related conditions, ataxia telangiectasia, xeroderma pigmentosum and Cockayne syndrome, are characterized by wide-ranging deficits in organ systems most vulnerable to the fell effects of genome instability.

Ataxia telangiectasia (AT)

AT is the most common of the three, appears in early childhood as growth retardation, hypotonia and diminished reflexes. As the disease progresses, children develop ataxia along with oculomotor apraxia, nystagmus and peripheral neuropathy (Stell et al., 1989). The hallmark telangiectases usually develop by the age of 7 and are most often seen in the conjunctiva of the eyes and in exposed areas of the skin. In the absence of telangiectases, either early in the course of the disease or in atypical cases, AT can be difficult to distinguish clinically from other chronic ataxic syndromes (Maserati et al., 1988). If ataxia develops early, it may be misdiagnosed as an ataxic variety of cerebral palsy; when the onset is delayed, it is most often mistaken for Friedreich's ataxia.

Apart from neurodegeneration, growth retardation and gonadal dysfunction, this disease is also characterized by a tendency to develop cancer and immune function defects. The malignancies typically affect the lymphoreticular system, but there is also a predisposition to cancers of the breast, skin and stomach. Infections resulting from deficiency in both cellular and humoral immunity typically affect the airway and are often life threatening. Other features of AT contributing to morbidity include glucose intolerance because of peripheral insulin resistance and the associated complications of diabetes. Since cloning the *AT* gene, it has been realized that abnormalities in even one copy of the gene might predispose heterozygotes to an increased incidence of cancer, particularly of the breast although this is a matter of still some dispute (Angele & Hall, 2000).

Of diagnostic importance are the low levels of IgA and IgE, a testimony to the defects in humoral immunity. In addition, deficient cellular immunity is reflected in anergy to intradermal injections of a battery of test antigens, which has been of some diagnostic value in the past. Another suggestive feature seen in more than 90% of patients is the elevation of serum alpha-fetoprotein levels (Waldmann & McIntire, 1972).

Both the central and peripheral nervous systems are involved in AT. The central nervous system pathology is

more severe, with cerebellar atrophy and loss of Purkinje cells, whereas the peripheral nervous system involvement is characterized by Schwann cell abnormalities. In line with deficits in the immune system, the thymus is characteristically hypoplastic, with fewer lymphocytes and absent Hassall's corpuscles (Peterson et al., 1964).

AT is difficult to treat and has an especially poor prognosis because of its multisystem involvement. There is no specific treatment for the ataxic syndrome. Most therapies are directed at treatment of infections and malignancies. Diagnostic tests involving X-rays and ionizing radiation should be kept to a minimum, to avoid causing iatrogenic somatic mutations and malignancies. Treatment of malignancies is complicated by the fact that these patients cannot tolerate conventional doses of radiation therapy. Despite the best supportive measures, most patients die in their third decade.

The *AT* gene was mapped to chromosome 11q22.3 in 1988 and the gene was finally cloned in 1995 (Gatti et al., 1988; Savitsky et al., 1995). The gene product, ATM or ataxia telangiectasis mutant, is a protein ubiquitously expressed in all tissues of the body and belongs to a family of important protein kinases called inositol-3 kinases (Brown et al., 1997). The ATM kinase, in particular, appears to play a key role in cell cycle progression. Overwhelming evidence suggests that ATM is involved in a surveillance mechanism designed to stall progression of the cell cycle if and when there is detectable DNA damage. This supervisory function of ATM offers the cell an opportunity to repair the damage rather than bequeath inappropriate genetic information to daughter cells. In the absence of this checkpoint, cells build up somatic mutations and increase their risk of becoming cancerous (Dasika et al., 1999).

The major mechanistic steps in ATM pathogenesis are only now coming to light. It appears that in response to double-stranded DNA damage, the ATM kinase interacts directly with, and phosphorylates, the tumour suppressor protein p53 (Khanna et al., 1998), a transcriptional activator of genes that cause cell cycle arrest or apoptosis. More recently, ATM has been shown to phosphorylate another tumour suppressor, Brca1, one of the genes implicated in breast cancer (Cortez et al., 1999). This interaction may explain how ATM predisposes patients and heterozygotes to breast cancer. Mouse models of the disease promise to increase our understanding of the molecular mechanisms of pathogenesis (Barlow et al., 1996). This is an exciting area of scientific research at the crossroads of tumour biology, cell cycle research and neurodegeneration (Canman & Lim, 1998; Rotman & Shiloh, 1998).

A disease very similar to AT, known as the Aicardi variant, was in the past separated from AT by the lack of telangiectasia and severe limitation in vertical eye movements. This disease is now known to share the same genetics as AT. There is, however, at least one disorder that closely mirrors AT but results from a defect in a gene other than ATM. Called ataxia–telangiectasia-like-disorder (ATLD), this disorder is caused by a mutation in the gene hMRE11 encoding a protein involved in the DNA repair complex of which AT is another component (Stewart et al., 1999).

Xeroderma pigmentosum (XP) has an incidence of approximately 1 in a million. This disease is characterized by a range of cutaneous lesions varying from mild freckling to xerosis, erythema, bullae, telangiectasia, actinic keratosis and skin malignancies. Most of these lesions occur around the eyes and eyelids. The eyes are also threatened by an increased incidence of keratitis, opacification of the cornea, iritis with synechia formation, and malignant melanoma of the choroid. The neurological features of xeroderma pigmentosa consist of progressive cognitive decline, sensorineural deafness, peripheral neuropathy and choreoathetosis. As with AT, XP is characterized by an increased risk of neoplasms (Kraemer et al., 1984). Oral administration of retinoic acid has been shown to be helpful in preventing skin cancer (Kraemer et al., 1988).

At a molecular level, XP constitutes a genetically heterogenous group of disorders characterized by defects in genes encoding proteins involved in excision repair (Lehmann et al., 1994). There are several complementation groups based on functional studies using fibroblasts derived from human patients. Patients in the same complementation group have a similar constellation of symptoms with variable neurological involvement that can range from severe to none at all. Ultraviolet-sensitive chinese hamster cells have also been successfully used to identify genes involved in excision repair. Because some of these genes were named by both of these methods, there is an unfortunate redundancy in the nomenclature.

Cockayne syndrome (CS) is a rare disorder (Nance & Berry, 1992). Although the clinical phenotype shows some overlap with XP in deafness and ataxia, patients with CS also show characteristic retinal degeneration and early aging without displaying a tendency to develop cancer. Pathologically, there is evidence for demyelination in the central nervous system and basal ganglia calcification, both of which are detected in imaging studies. Like XP, CS is genetically heterogenous, with several complementation groups. In fact, there are a few patients with a mixed XP–CS phenotype. The key defect in most cases appears to be insufficiency of transcription or transcription-translation coupled repair, a phenomenon that pertains to excision repair of DNA that must precede the transcription of active genes (van Gool et al., 1997).

Table 117.3. Genetics of chronic progressive hereditary ataxias

					Repeat lengths	
Disease	Gene	Chromosome	Protein	Mutation	Normal	Disease
Friedreich's ataxia	X 25	9q13.1–21.1	Frataxin	GAA repeat expansion in intron 1 of the gene	7–34	>100
SCA1	SCA1	6p23	Ataxin-1	CAG repeat in coding region of gene	6–44[a]	36–121
SCA2	SCA2	12q24.1	Ataxin-2	CAG repeat in coding region of gene	15–31	36–82
SCA3 (Machado Joseph disease)	SCA3, MJD1	14q32.1	Ataxin-3	CAG repeats in coding region of gene	12–40	55–84
SCA4	SCA4	16q22.1				
SCA5	SCA5	11p11–11q11				
SCA6	SCA6	19p13	Alpha-1A voltage-dependent calcium channel subunit	CAG repeat in coding region of gene	4–18	21–33
SCA7	SCA7	3p12–13	Ataxin-7	CAG repeat in coding region of gene	4–35	37–306
SCA8	SCA8	13q21	None	CTG repeat in the 3′ terminal exon (antisense)	16–37	110–<250?
SCA10	SCA10	22q13ter	–	Pentanucleotide repeat in intron	extremely large ATTCT expansions in disease	
SCA11	SCA11	15q14–q21	–	–	–	
SCA12	SCA12	5q31–33	Protein phosphatase 2A	CAG repeat in 5′ UTR	7–28	66–78
SCA13	SCA13	19q13.3–q13.4	–	–		
SCA14	SCA14	19qter–q13.4	–	–		
DRPLA	DRPLA	12q	Atrophin-1	CAG repeat in coding region of gene	6–35	49–88

Notes:
34–100 can be premutations (see text).
[a] Alleles with 21 or more repeats are interrupted by 1–3 (CAT) units; disease alleles contain pure CAG tracts.

Degenerative ataxias not caused by specific enzyme deficiencies

In the past, the degenerative ataxias were distinguished from the previous group by the paucity of knowledge regarding the causative mechanisms and the lack of correspondence to clear-cut enzyme deficiencies. Nonetheless, major strides have been made in the last decade in understanding their molecular basis (Table 117.3). Surprisingly, several of these ataxias appear to result from a common mutational mechanism: a repeat expansion within the disease-causing gene (Zoghbi & Orr, 2000). When the repeat expansion occurs in the coding region of the gene, it causes an expanded polyglutamine repeat in the resulting protein. This family comprises dentatorubropallidoluysian atrophy (DRPLA), spinocerebellar ataxias (SCAs) 1, 2, 3, 6 and 7. The family of ataxic disorders characterized by a repeat expansion in the noncoding region of the gene consists of the trinucleotide disorders Friedreich's ataxia and the spinocerebellar ataxias 8 and 12, a pentanucleotide repeat disorder (SCA10), and a dodecamer repeat disorder (Baltic myoclonus).

The expanded repeats, whether in the coding or noncoding region, show repeat instability, with a tendency to expand in germline transmission. For the afflicted family, this unfortunately results in the phenomenon of 'anticipation', an earlier disease onset and a progressively worse phenotype with each subsequent generation. All trinucleotide repeat disorders that cause ataxia are autosomal dominant with the exception of Friedreich's ataxia, which is inherited in an autosomal recessive manner. Besides the triplet repeat diseases, there are a few other genetic conditions that present with similar ataxic syndromes; although

most are quite rare, they are discussed in the differential diagnosis to make the list comprehensive.

The autosomal recessive cerebellar ataxias

Friedreich's ataxia

Friedreich's ataxia (FRDA) is the most common autosomal recessive spinocerebellar ataxia, with a prevalence rate of 1 to 2 per 100 000. In the typical case, symptoms begin in late childhood or adolescence. The neurological phenotype is characterized by the cerebellar features of ataxia, scanning speech and nystagmus. In addition, eye movements tend to be sluggish, the gait is disorganized and lurching, and patients demonstrate signs of motor and sensory neuropathy. Because of the motor neuropathy, especially in the later stages of the illness, the distal extremities become weak and wasted while sensory neuropathy causes loss of vibration sense and proprioception. Early evidence for sensorimotor neuropathy can be elicited clinically by absent ankle reflexes and impairments on electrophysiological tests. These constitute the core features of the diagnosis (Harding, 1984).

Other noteworthy neurological features include incontinence, visual disturbance because of optic atrophy and, rarely, deafness from degeneration of cochlear neurons. Occasionally extrapyramidal involvement in the form of choreiform movements may be seen. Besides involvement of the nervous system, patients with FRDA often have musculoskeletal abnormalities such as scoliosis, kyphoscoliosis and pes cavus. Often this requires orthopedic intervention. Cardiac pathology is another hallmark of the disease and usually results from muscular subaortic stenosis and hypertrophic cardiomyopathy. In the later stages, a dilated form of cardiomyopathy with wall motion abnormalities replaces the earlier hypertrophic picture. In the early stages of the disease, however, a wide range of abnormal ECG findings have been observed: T wave abnormalities, deep Q waves, low QRS complexes, and the more obvious heart block. Thus all patients should be closely followed by yearly ECGs and chest X-rays. Although there is variability in the progression of the disease, the mean age of death is in the fourth decade (Hewer, 1968). Death occurs because of cardiac complications or bulbar dysfunction. As in AT, approximately one-fourth of the patients with Friedreich's ataxia develop glucose intolerance and diabetes that increases morbidity.

Since discovery of the gene and the availability of genetic testing, we are beginning to appreciate atypical presentations of FRDA, which can present as early as infancy and should be suspected when delay in achieving motor milestones is associated with skeletal abnormalities. This early onset phenotype tends to be associated with a worse prognosis than typical Friedreich's. Surprisingly, FRDA can also present much later in life, even beyond the age of 40, in a so-called 'very late onset FRDA' (Bidichandani et al., 2000; Palau et al., 1995). Since several of the cardinal features of FRDA are milder in this instance, with a preservation of reflexes, this variant was bracketed into a separate category in the pregenetic era: 'autosomal recessive ataxia with preserved reflexes'.

In the past, the diagnosis of FRDA was primarily a clinical one, resting on the aforementioned signs and symptoms and supported by only a few ancillary tests. Electrophysiologic testing provides additional evidence for motor and sensory axonal neuropathy, whereas ECG findings present supportive evidence relating to the cardiac manifestations of the disease. MRI scans in FRDA often show evidence of spinal cord and cerebellar atrophy. Today, the only necessary diagnostic test is genetic, and it should be performed in all recessive, chronic ataxic syndromes.

FRDA is caused by a GAA repeat expansion in the first intron of the gene called *frataxin* or *X25*. This gene is located on chromosome 9q13 (Campuzano et al., 1996). Most normal individuals carry alleles ranging from 7 to 34 GAA repeats, while patients with the disease have alleles with a tract of over 100 repeats. Tract sizes that vary between 34 and 100 do not result in disease, but are further divided based on whether or not they are interrupted by non-GAA repeats. If interrupted, they are considered non-pathological, because the interruption stabilizes the repeat against expansions in subsequent generations. On the other hand, uninterrupted repeat tracts with 34 to100 GAAs are considered to be pre-mutations, since without the stabilizing influence of the interruption they can expand to over 300 repeats in just a single generation (Cossee et al., 1997). The unstable repeats tend to expand in paternal transmission, and can expand or contract in maternal transmission. Because of the recessive nature of the disease, with a requirement for two expanded alleles, there is no anticipation. Nonetheless, disease severity and onset of disease correlate with repeat length. This is not just confined to the neurological phenotype, but also holds true for the glucose intolerance and the skeletal and cardiac abnormalities as well (Filla et al., 1996; Monros et al., 1997).

As might be expected from its recessive genetics, Friedreich's ataxia is caused by a loss of function of the gene product, frataxin. The intronic repeat expansion results in a reduced expression of the messenger RNA encoding this

210 amino acid protein. That Friedreich's is caused by a loss of function mechanism is supported by the observation that a Friedreich's phenotype can also be seen in patients carrying only one expanded allele of frataxin, provided their second allele is inactive due to a point mutation (Bartolo et al., 1998). This situation might be more common than currently recognized, since most genetic tests search for expansions and not for other types of mutations.

Recent research has aimed to delineate the function of frataxin and explain why its loss should result in such widespread and profound pathology. It appears that frataxin is a mitochondrial protein, expressed at particularly high levels in tissues undergoing degeneration such as the brain, heart and pancreas (Campuzano et al., 1996; Koutnikova et al., 1997; Puccio & Koenig, 2000). Studies of the yeast frataxin homologue suggest that this protein is involved in the normal efflux of iron from mitochondria (Babcock et al., 1997). Inactivation of the protein causes iron to accumulate in the mitochondria, which in turn might disrupt mitochondrial respiratory chain function, resulting in oxidative stress (Radisky et al., 1999). In humans, iron deposits have been found in the myocardium of FA patients (Rotig et al., 1997). This raises the intriguing possibility that chelating agents and antioxidants might reverse pathology (Rustin et al., 1999).

Differential diagnosis of recessive progressive hereditary ataxias

As mentioned earlier, atypical cases of AT can be misdiagnosed as FRDA until the disease progression tilts the spectrum of symptoms towards the one or the other. Another autosomal dominant condition with a better prognosis, hereditary motor and sensory neuropathy type I (HMSN I), can also mimic FRDA because of areflexia and a sensory ataxia. Nerve conduction tests in HMSN I, however, usually reflect an underlying dysmyelination as opposed to the axonal pathology of FRDA.

Harding separated 'hereditary ataxia with retained tendon reflexes' from Friedreich's ataxia as a distinct clinical entity (Harding, 1981). Recent genotype–phenotype correlations, however, indicate that this disorder actually represents a milder variant of Friedreich's in which the repeat size is relatively small. There are autosomal recessive cerebellar ataxias that can mimic FRDA but have a distinct genetic basis. Most are rare, but they can occur at higher rates in isolated pockets of the world because of consanguinous marriages. One such disorder is autosomal recessive spastic ataxia of Charlevoix–Saguenay, named after the region in Quebec where it was first described. The recently cloned gene, mapping to chromosome 13q11 (Engert et al., 2000), encodes a large protein with a predicted molecular weight of 437 kDa that shares some homology to molecular chaperones, proteins that play a role in protein misfolding. This is intriguing, since protein misfolding appears to play a central role in the polyglutamine-induced autosomal dominant ataxias, as will be discussed later in this chapter.

Infantile onset spinocerebellar ataxia is another geographically isolated condition (Koskinen et al., 1994). Recently identified as an autosomal recessive ataxia in the North Carelia province of Finland, this ataxia maps to 10q24 (Nikali et al., 1997). It is characterized by early-onset ataxia with ophthalmoplegia and hearing loss. In addition, affected infants have EEG abnormalities and seizures.

Wolfram syndrome, characterized by diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD) (4p16), can also present with ataxia. It is now known to be caused by a mutation in a transmembrane protein expressed predominantly in the pancreas and the brain (Strom et al., 1998). Among the cerebellar ataxias yet to be genetically characterized are Marinesco–Sjögren's syndrome, characterized by cerebellar ataxia, congenital cataracts, impaired physical growth, mental deficiency, myopathy and skeletal abnormalities, and Matthews Rundle syndrome with ataxia and hypogonadism. In passing it should be mentioned that the term Ramsay Hunt syndrome was used in the past to describe ataxia combined with myoclonus. This syndrome is actually not a distinct disease entity; its combination of symptoms can be seen in some of the storage disorders described above, particularly sialidosis, and in some of the ataxias due to defects in mitochondrial function (described below). Myoclonus is also a hallmark of the autosomal recessive Baltic myoclonus of Unverricht–Lundberg, in which the underlying defect is in the gene encoding the protease inhibitor cystatin B (Pennacchio et al., 1996). Surprisingly, in most instances this is also a repeat disorder, but it is a dodecamer repeat in the gene's promoter (Lalioti et al., 1997).

The autosomal dominant hereditary ataxias

The autosomal dominant cerebellar ataxias have an interesting history. They were first recognized by Marie in 1893 as a syndrome distinct from FRDA because of their autosomal dominant pattern of inheritance (Marie, 1893). Gordon Holmes rightly recognized Marie's ataxia or the 'hereditary olivo-pontocerebellar atrophies' as a clinically

Table 117.4. Correlation between Harding's clinical classification and genetic classification

Harding's classification	Genetic typing
ADCAI: Ataxia with ophthalmoplegia, optic atrophy, dementia or extrapyramidal features	SCA1, SCA2, SCA3, SCA4, SCA12, possibly DRPLA
ADCAII: Ataxia with pigmentary maculopathy with or without ophthalmoplegia or extrapyramidal features	SCA7
ADCAIII: Relatively pure ataxia	SCA5, SCA6, SCA8, SCA10, SCA11, SCA13, SCA14

Table 117.5. A few differentiating features of the autosomal dominant spinocerebellar ataxias

AD spinocerebellar ataxia	Distinguishing features
SCA1	Relatively nondescript spinocerebellar ataxia with neuropathy and pyramidal signs
SCA2	Slow saccades, myoclonus, areflexia
SCA3	Bulging eyes, fasciolingual fasciculations, extrapyramidal signs
SCA4	Sensory neuropathy
SCA5	Slow course despite early onset
SCA6	Very late onset, mild, apparently sporadic onset
SCA7	Macular degeneration
SCA8	Mild
SCA9	Unassigned
SCA10	Generalized or complex partial seizures
SCA11	Mild
SCA12	Tremor, dementia
SCA13	Mental retardation
SCA14	Sometimes myoclonus
DRPLA	Chorea, seizures, myoclonus

and pathologically heterogenous group (Holmes, 1907). Since this observation, numerous classifications have been proposed to sort individual members of the group by clinical presentation, the most recent being proposed by Anita Harding in 1984 (Harding, 1984). She divided these ataxias into three distinct groups called autosomal dominant cerebellar ataxia types I, II and III.

Over the last several years, however, a new classification based on the genetic loci of the spinocerebellar ataxias (SCA) has gained wide acceptance. These disorders have been numbered based on their order of identification: SCA1 through 14, with a locus for SCA9 yet to be assigned. We have tried to correlate the older Harding classification with this genetic nomenclature for the sake of smoothing the transition between systems, but because of the broad overlap of clinical features and phenotypic variations within each disorder, such a correspondence is difficult to achieve in clinical practice (Tables 117.4 and 117.5). As mentioned earlier, several of the SCAs are nucleotide repeat disorders and therefore present with the common findings of anticipation and increased severity correlating to the size of the nucleotide expansions within the relevant gene.

SCA1 was the first dominantly inherited ataxia gene to be linked to a locus (6p22–23) (Zoghbi et al., 1989). It is characterized by progressive cerebellar ataxia, dysarthria, and bulbar dysfunction that results in death. Other accompaniments include hyperreflexia, increased tone and extensor plantar responses. Occasionally, the peripheral nervous system involvement can obscure these upper motor neuron findings and lead to wasting of the extremities and generalized fasciculations. Oculomotor signs include nystagmus, lid retraction and slowing of saccades. Atypical features include chorea, dystonia and bladder incontinence. The disease most often presents in the third decade of life, but can appear as early as age 6 or as late as the 70s. It was this clinical feature that led to a targeted search for trinucleotide repeat expansions, known to be the defect in causing anticipation in other neurological conditions. The natural history of this disease is also variable, with an earlier onset forecasting an accelerated progression. The mean duration of the illness ranges from nine to sixteen years.

SCA1 is caused by a CAG repeat expansion in the coding region of the gene *SCA1* encoding the protein ataxin-1 (Orr et al., 1993). At the time of this writing, the normal function of ataxin-1 remains unknown. Immunolocalization studies show that mutant ataxin-1 aggregates into single ubiquitin-positive nuclear inclusions (NI) that are approximately 2 microns in size (Skinner et al., 1997). NIs have been noted in other glutamine repeat diseases as well. These inclusions often contain not only the relevant disease-causing protein, but they also stain positive for chaperones and components of the ubiquitin–proteasomal pathway, which

are both instrumental in protein clearance. Recent work suggests that ataxin-1 tends to accumulate in SCA1, probably because of an altered conformation induced by the polyglutamine tract. Ubiquitination and proteosomal degradation probably represent a cellular protective response: interventions to prevent these processes in SCA1 and other polyglutamine diseases only increase neuronal toxicity (Chai et al., 1999; Cummings et al., 1999; Saudou et al., 1998). Based on these findings, strategies aimed at improving protein folding or clearance are gaining centre stage.

SCA2 distinguishes itself from SCA1 by the clinical feature of slow saccadic eye movements in afflicted patients. Genetically, however, it was set apart from SCA1 when its locus (12q23–24) was identified (Auburger et al., 1990; Orozco et al., 1990). The *SCA2* gene encodes a protein called ataxin-2 that contains structural elements that appear to be important in RNA splicing. Disease-causing alleles contain 36–63 repeats, whereas healthy people harbour 15–31 repeats. Like SCA1, SCA2 is also characterized by variable features. Some patients display tremors, some complain of severe muscle cramps, some occasionally suffer incontinence. When *SCA2* alleles contain more than 200 repeats, the disease can present as early as infancy with hypotonia, developmental delay, dysphagia and retinitis pigmentosa (Babovic-Vuksanovic et al., 1998). The genetic background may be relevant, since atypical features are seen in geographically distinct families: mental deterioration in an Italian family (Babovic-Vuksanovic et al., 1998; Malandrini et al., 1998), chorea and dystonia in families from Tunis and Martinique (Belal et al., 1994; Dürr et al., 1995).

SCA3 or Machado–Joseph disease (MJD) is probably the most common of the autosomal dominant spinocerebellar ataxias and also has a broad clinical spectrum. The disease initially linked to the spinocerebellar ataxia 3 locus was not recognized as an MJD variant, since the initial SCA3 patients did not exhibit the extrapyramidal syndrome which was then thought to be characteristic of the MJD syndrome. Only when linkage analysis assigned both of these ataxic syndromes to the same genetic locus on the long arm of chromosome 14 (14q24.3–q32) did it become clear that they were one and the same disease (Kawaguchi et al., 1994). *SCA3* encodes the 42 kDa ataxin-3, a predominantly cytoplasmic protein, which is the smallest polyglutamine disease protein. The glutamine tract is close to the C terminal of the molecule.

Besides ataxia, clinical features in SCA3 include slow saccades and saccadic pursuit. Other features include lid retraction that gives the impression of a persistent stare, and signs of brainstem dysfunction including dysarthria, difficulty in swallowing, poor cough and tongue fasciculations. Because of peripheral nervous system involvement, the neurological examination usually shows a mix of upper and lower motor neuron findings. Thus tone can range from hypotonia to significant rigidity and reflexes can be exaggerated or absent. The plantar response tends to be extensor. The common extrapyramidal features include rigidity and dystonia. In the past MJD had been classified into three subtypes: type I, when spasticity was the major sign without significant ataxia; type II when ataxia occurred on its own; and type III when ataxia was accompanied by peripheral neuropathy. This classification formalizes the phenotypic variability that we now know is most likely contributed by genetic background and polyglutamine length.

SCA4 has no features that distinguish it from the other ataxias, except perhaps for an exaggerated sensory axonal neuropathy that results in absent reflexes. Otherwise, it is almost a purely cerebellar syndrome with little in the way of brainstem dysfunction. The gene, which maps to 16q22.1, has yet to be identified.

SCA5 and 6 are both characterized by an almost pure cerebellar syndrome. SCA5, in particular, is a relatively mild syndrome with a slow progression. In SCA6, there is occasional horizontal and vertical nystagmus and abnormal vestibulo-ocular reflex (Gomez et al., 1997). Both diseases begin in the third decade, and MRI examinations on affected patients show cerebellar atrophy. The CAG tract in SCA6 is the shortest polyglutamine repeat length of all the SCAs: 21–33 repeats in the disease state, with normal alleles less than 18 (Zhuchenko et al., 1997). Moreover, SCA6 is unique among the dominant ataxias in that its gene encodes a protein with a known function: the P/Q type calcium channel alpha-1a subunit. Intriguingly, this gene has been implicated in episodic ataxia type 2 and familial hemiplegic migraine, although the mutational mechanisms are distinct (Ophoff et al., 1996). Nonetheless, compromise of the function of the calcium channel might be central to all three, since there is some overlap of symptoms. Like episodic ataxia, SCA6 can present with intermittent ataxia in the early stages, and all three conditions (SCA6, EA2 and familial hemiplegic migraine) often involve cerebellar atrophy.

Among the spinocerebellar ataxias, SCA7 has perhaps the most variable expression. With childhood onset, the usual features of ataxia are accompanied by seizures, myoclonus, and cardiac involvement. In adults, ataxia develops along with oculomotor abnormalities. In both childhood and adult cases, visual loss from pigmentary macular degeneration is almost invariable, and can precede the ataxic syndrome. Since this sets it apart from the other autosomal dominant ataxias, defects in colour vision and

electroretinogram abnormalities might suggest the diagnosis in early cases (Gouw et al., 1995). SCA7 is a glutamine repeat disorder mapping to chromosome 3p12–p21.1. Expanded alleles have repeats between 38 and 306; normal alleles range from 7 to 17. Another notable feature of SCA7 is the remarkable intergenerational instability, with expansion particularly likely upon paternal transmission (David et al., 1997; Stevanin et al., 1998). As in SCA2, it is the expanded allele that contributes to the severe infantile phenotype (Benton et al., 1998).

SCA8 is difficult to distinguish clinically from the other SCAs, yet it is the only SCA with a possibly novel mechanism of pathogenesis for triplet repeat disorders. The repeat expansion in this case occurs in a CTG tract in the non-coding region of the relevant gene. Data suggest that the *SCA8* gene might encode an antisense RNA that regulates the levels of a neighboring messenger RNA (Koob et al., 1999). This hypothesis has recently become a point of dispute, since the expansion has been seen in normal individuals as well and might simply represent a polymorphism in linkage disequilibrium with the disease-causing mutation.

In SCA10, seizures coexist with spinocerebellar ataxia, and this ataxia appears to be more common among Mexicans. This spinocerebellar ataxia at locus 22q13–qter, is a repeat disorder with anticipation, although in this case the repeat is an intronic expansion of a pentanucleotide ATTCT (Matsuura et al., 1999, 2000; Zu et al., 1999).

SCA11 is a relatively mild ataxia assigned to locus 15q14–q21, but little is known about disease pathogenesis (Worth et al., 1999). SCA12 is a trinucleotide repeat disorder caused by a CAG trinucleotide expansion in the 5′ UTR of a gene encoding a brain-specific regulatory subunit of protein-phosphatase 2A (Holmes et al., 1999). This ataxia is often complicated by tremors and dementia in the later stages of disease progression. SCA13 is a childhood-onset ataxia with associated features of mental retardation and developmental delay (Herman-Bert et al., 2000). SCA14, a novel ataxia identified in Japan, causes older patients to display ataxia whereas those with a younger age at onset frequently display myoclonus (Yamashita et al., 2000). The genes responsible for SCA 13 and 14 are unknown, but both diseases appear to map to distinct loci on the long arm of chromosome 19.

Based on this brief summary of the known autosomal dominant spinocerebellar diseases and their phenotypes, it should not be misconstrued that all genes contributing to dominant spinocerebellar ataxia have been identified. Only 60–70% of patients have mutations in the known loci. This situation is likely to change and on-line resources such as the Online Mendelian Inheritance in Man (www.OMIM.org) provide an excellent means for keeping track of advances in this area.

Besides the numbered spinocerebellar ataxias, there are other autosomal dominant conditions that result in ataxias. Dentatorubropallidoluysian atrophy (DRPLA) is relatively common in Japan, and should be suspected when ataxia and rigidity are accompanied by choreoathetosis, myoclonic epilepsy and dementia. Other features include hyper-reflexia and slowing of saccades. Caused by an expanded CAG repeat, anticipation is more common with paternal transmission. The relevant protein encoded by the *DRPLA* gene (locus 12p) is called atrophin-1. This is a cytoplasmic protein with a molecular weight of 125 kDa (Nagafuchi et al., 1994; Onodera et al., 1995). Calcification of the basal ganglia and leukodystrophic changes are often seen on imaging studies. Haw–River syndrome is a variant of DRPLA, without the characteristic myoclonic epilepsy, and is seen in a few families of African–American descent in North Carolina (Burke et al., 1994).

Another class of diseases that may resemble the spinocerebellar ataxias are the prion disorders with mutations in the prion or *PRNP* gene. Of these, Gerstmann–Straussler–Scheinker disease (GSS), particularly the ataxic variant, is the most likely to mimic a spinocerebellar syndrome. GSS is diagnosed when autosomal dominant ataxia coexists with cognitive and motor decline alongside pathological findings of prion protein-containing amyloid plaques. Unlike those afflicted with the other SCAs, GSS patients often complain of altered sensation or even pain in their legs; moreover, they rather rapidly develop cognitive decline and EEG changes, similar to the more common variants of prion diseases such as Creutzfeldt–Jakob Disease (CJD). GSS represents a group of at least six mutations in the *PRNP* gene, with the ataxic variant caused by a proline to leucine missense mutation at codon 102 (Dohura et al., 1989; Hsiao et al., 1989; Prusiner & Hsiao, 1994).

Diagnostic studies in the autosomal dominant spinocerebellar ataxias

In all autosomal dominant ataxias, neuroimaging studies by MRI and computerized axial tomography (CAT) mirror the clinical and pathological phenotypes of each of the spinocerebellar ataxias. Cerebellar atrophy is the most commonly reported finding, along with enlargement of the fourth ventricle. The relative degrees of degeneration vary, with SCA2 patients showing the most atrophy and those with SCA5 and 6 the least. Brainstem atrophy, which one would expect to be almost universal, can be minimal in SCA3 and DRPLA, and is rare in SCA6. On the other hand,

it is quite characteristic of SCA1, 2 and 7. Cerebral atrophy and compensatory enlargement of the lateral ventricles can be seen in DRPLA, SCA2 and the infantile variant of SCA7. But one of the chief advantages of imaging is to help exclude other causes of ataxia such as posterior fossa lesions, tumours, or demyelinating conditions such as multiple sclerosis.

More expensive imaging studies such as magnetic resonance spectroscopy and positron emission tomography (PET) scanning are sensitive markers for deterioration and show abnormalities beyond the structural changes revealed by MRI scans. Their utility in diagnosing these diseases, however, is controversial and at the moment these modalities should be reserved for research rather than diagnosis.

Most spinocerebellar ataxias cause defects in nerve conduction, especially SCA4. The predominant axonal neuropathy affects mainly sensory neurons, and sural nerve action potentials are commonly absent. Nerve conduction abnormalities, however, are rarely helpful in determining the genetic subclass of the ataxia. On the other hand, visual-evoked potentials can be helpful to suggest SCA7, while interictal electroencephalograph (EEG) abnormalities might suggest DRPLA. Although seizures are common in SCA10, interictal EEGs are typically normal.

Genetic testing is the only definitive diagnostic test. The Harding clinical classification and the few differentiating features (Tables 117.4 and 117.5) may help in suggesting likely candidates for a step-wise screen. More often, blood is sent out to test for mutations in a battery of genes. So far, this list includes SCA1, 2, 3, 6, 7, 8 and DRPLA, but it is likely to increase. Once again, on-line resources, e.g. www.geneclinics.org, are extremely informative.

Episodic ataxias

There are two varieties of dominantly inherited episodic ataxias called episodic ataxia type 1 (EA1) and 2 (EA2). Both of these diseases begin in late childhood or adolescence and respond to treatment with acetazolamide.

Patients with EA1 show short episodes of ataxia rarely lasting beyond a few minutes. Ataxic spells sometimes are induced by exercise and may be accompanied by myokymia in the hands and face. Pathology is minimal, with mild atrophy of anterior cerebellar vermis. The genetic basis for EA1 is the presence of point mutations in a voltage-gated potassium channel gene, *KCNA1*, located on chromosome 12p13 (Browne et al., 1994; Scheffer et al., 1998).

In EA2 the attacks are longer, lasting usually for a few hours or even days. Moreover, these episodes appear to result in cumulative damage, as patients often go on to develop cerebellar symptoms and atrophy. Subtle cerebellar signs such as nystagmus and mild clumsiness should therefore tilt the diagnosis towards EA2 rather than EA1. As mentioned in the context of SCA6, EA2 is caused by mutations in the α-$_{1A}$ subunit of the calcium channel gene, the gene involved in SCA6 and also familial hemiplegic migraine. Known mutations in EA2 include a frameshift mutation in the coding region of the channel itself and a substitution in a conserved region of an intron that may affect splicing of the gene (Ophoff et al., 1996).

The episodic ataxias are difficult to diagnose in children, from whom a history can be difficult to elicit. Diseases that can mimic this syndrome (apart from the metabolic ataxias mentioned earlier) include the non-hereditary causes of ataxia such as posterior fossa masses, basilar migraine, seizures, benign paroxysmal vertigo and the accidental ingestion of toxins.

X-linked ataxias

Besides adrenomyeloneuropathy, which can present as an ataxic syndrome, there are a few X-linked progressive ataxias. These can be almost purely cerebellar syndromes (Lutz et al., 1989; Spira et al., 1979) or associated with a wider spectrum of signs such as anemia, deafness, spasticity or dementia (Apak et al., 1989; Arts et al., 1993; Farlow et al., 1987; Raskind et al., 1991). In most instances the genetic loci are still unknown, with the exception of an early onset X-linked ataxia that is characterized by deafness and loss of vision and links to locus Xq21.2–q24 (Kremer et al., 1996).

Mitochondrial ataxias

Mitochondrial deficits can present with a progressive or intermittent ataxia. For instance, Leigh's syndrome, a genetically heterogeneous syndrome caused by mutations in several genes affecting mitochondrial function, often presents with an intermittent ataxia and a necrotizing encephalitis not unlike that seen in thiamine deficiency. An MRI scan is informative in revealing characteristic subcortical necrotic lesions.

Leigh's syndrome is also often accompanied by cardiomyopathy, presumably because of mitochondrial energy failure in cardiac muscle. Ataxia and myoclonus can also be seen in other defects of the mitochondrial genome. Both larger deletions and duplications characteristic of Kearns–Sayre syndrome and maternally inherited point mutations in mitochondrial genes encoding tRNA, the

MELAS (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes) and MERRF (myoclonic epilepsy with ragged red fibres) have been associated with the ataxic phenotype.

Genetic testing in the hereditary ataxias

Genetic testing is the only definitive way to pinpoint the nature of a hereditary ataxia. Because of the expense of such testing, a detailed history of the patient and his or her family, in addition to a thorough clinical examination, should be used to guide the selection of molecular tests. In the case of ataxias resulting from catalytic insufficiency, it is still relatively difficult to test for genetic mutations in large genes, where a variety of mutations can produce a similar picture. In these instances the biochemical sequelae of the disease form the basis for most diagnostic tests. Automated and high throughput screening should make genetic testing more feasible in the future. This would be an especially fortunate situation, since so many of these diseases are amenable to therapeutic intervention.

In the case of the progressive degenerative ataxias caused by nucleotide repeat expansions, the situation is diametrically opposite. It is already possible to provide genetic tests of high specificity and sensitivity, but there is little in the way of therapeutic intervention. For patients presenting with symptoms, these tests are diagnostic and exclude further search for other causes of ataxia. If the test result is positive, patients should be counselled not just with regard to their own prognosis but also about the implications for family members (present and future) and their risk for the disease. Several neurology departments and physicians have created helpful web page links to support groups such as the National Ataxia Foundation (www.ataxia.org) and non-profit organizations such as www.wemove.org, that help patients and families to understand and cope with their disease.

Genetic testing of asymptomatic family members for diseases for which there is no therapeutic intervention is debatable. Such testing should be performed only after the implications are explained. For instance, if the grandchild of a patient with autosomal ataxia tests positive, the intermediate generation must be a carrier, even if this person did not submit to testing. Ethical norms should be scrupulously followed, especially with regard to respecting the right of the individual to make the decision for themselves about whether to know or keep their status in the dark. Confidentiality is an extremely important issue in the present climate of managed care, when insurance companies might discriminate based on this information. Genetic testing of asymptomatic children should be avoided.

In conclusion, a decade ago, it would have been difficult to predict the rapid advances that have taken place in our understanding of the genetics of hereditary ataxias. This progress has not been confined to the identification of the genetic basis of individual diseases; we have begun to sort out candidate pathways in pathogenesis using tools from the growing armamentarium offered by present day molecular biology and genomics. The development of animal models, in particular, is now recognized as a notable first step in hypothesis testing. The various species, mice, *Drosophila*, *C. elegans* and yeast, offer powerful, complementary tools for elucidating complex pathways at the level of the whole organism. In the prevailing climate of combinatorial chemistry and rational drug design, we anticipate high-throughput screens for chemical modifiers using simple animal models. Using such techniques pharmaceutical companies could identify candidate agents that could then be tested as therapeutic agents first in animal models and then in the human patient.

For the patient, there is reason for hope, even though the desired outcome of actual therapies remains years in the future. Genomics and web-based dissemination of information have already wrought changes in the way patients view their illnesses. They are better informed about the genetics of transmission and disease prognosis and are therefore in a better position to plan their lives. In return, they are often more willing to provide blood samples for DNA analyses and enrol in the clinical trials that are crucial for our collective progress.

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Huntington's disease

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History

George Huntington saw his first cases of HD when he was about 8 years old, while accompanying his father and grandfather on their medical rounds in East Hampton, Long Island. His longitudinal experience with several families of patients, as part of a three-generation family of physicians, was crucial to his famously concise and accurate account of the disease that now bears his name (Huntington, 1872). As William Osler commented in his paper reporting two additional families with HD (Osler, 1893), 'In the whole range of descriptive nosology there is not, to my knowledge, an instance in which a disease has been so accurately and fully delineated in so few words.' George Huntington's description over a century ago identified the key aspects of the disease, an adult onset hereditary disorder progressing inexorably to death, and characterized by abnormal movements, as well as cognitive and emotional changes. The pathologic changes in the corpus striatum and cerebral cortex were later described by Meynert, Alzheimer and Hunt in the early part of the twentieth century.

The discovery of the CAG repeat expansion mutation in the gene *huntingtin* in 1993 greatly facilitated the application of modern molecular and cellular techniques to the study of HD. The consequent development of biochemical, cellular and animal models of the disorder has led to new insights into its pathogenesis. The hope is that these approaches will foster the development of rational therapeutics in the near future.

Clinical course

HD can be described as a triad of motor, cognitive, and emotional disturbances (Folstein, 1989; Harper, 1996; Penney et al., 1990; Ross et al., 1997). Onset is usually insidious, and may occur at any time from childhood to old age, though mid-life onset is most common. Early complaints include clumsiness, difficulty with balance, and jerky movements or tremor. Death occurs an average of 15 to 20 years after the appearance of symptoms, with some patients dying earlier from falls or suicide and others surviving for 30 to 40 years (Fig. 118.1).

The most striking movement disorder of HD consists of abnormal involuntary movements. Chorea or choreoathetosis, continuous and irregular jerky or writhing motions, are the clinical manifestation most frequently associated with Huntington disease. While most commonly present in the limb and trunk, movements may also include motor tics or chorea involving respiratory, laryngeal, pharyngeal, oral or nasal musculature.

Though chorea is often the most obvious feature of HD on superficial examination of typical patients, incoordination and other disturbances of voluntary movement are in fact more highly correlated with functional disability and the extent of brain pathology. These disturbances include abnormal eye movements, such as slow, hypometric saccades and catchy smooth pursuit movements; uncoordinated, arrhythmic, and slow fine motor movements; dysphasia and dysarthria; dysdiadochokinesis; and a characteristic gait disturbance, consisting of a writhing, dancing walk.

The nature of motor impairment in HD has recently been evaluated with the assistance of sophisticated robotic methods to quantify movement irregularities (Smith et al., 2000). Patients with HD displayed impaired error correction, especially toward the ends of movements, and increased movement jerkiness. The impaired error correction was seen both in response to internally generated errors and externally imposed errors. Most striking, an impairment in error correction could be observed seven to

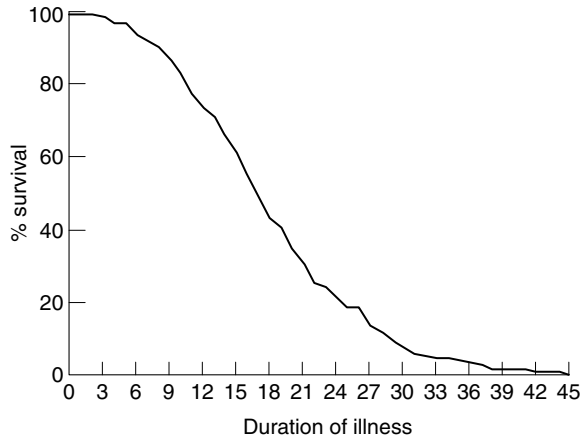

Fig. 118.1. HD survival curve. Percentage of patients surviving as a function of years since disease onset. The curve is derived from 163 patients enrolled in the Baltimore Huntington's Disease Center with a record of both age at disease onset and age at death. (Reprinted with permission from Lippincott, Williams and Wilkins; Ross et al., 1997).

ten years prior to expected onset in presymptomatic gene-positive individuals. These methods promise to improve our understanding of motor control abnormalities in HD, and may provide sensitive measures of movement abnormalities useful long before the onset of clinically diagnosable disease. In addition, it is possible that some of the cognitive deficits of HD can be conceived of as a kind of cognitive error correction abnormality, perhaps leading to improved understanding of cognitive dysfunction as well.

Chorea may plateau, and even decrease, in the later stages of the disease, but disturbances in voluntary movement continue to progress. In late stage HD, patients are often akinetic and largely non-verbal, and may have severe rigidity and joint contractures. At this point, they may have few involuntary movements except for occasional movements of the entire body, resembling myoclonic jerks, when disturbed. Difficulties with swallowing commonly lead to death, either directly from suffocation or aspiration or indirectly from starvation.

When HD begins in childhood or adolescence (juvenile onset HD), the presentation is often somewhat different, with bradykinesia, rigidity and dystonia but minimal chorea. Involuntary movements may take the form of tremors, and patients may develop seizures and myoclonus.

The cognitive disorder of HD is distinctive. In contrast to patients with Alzheimer's disease (AD), patients with HD seem to have more trouble with retrieval than storage of memories. They are more apt than AD patients to recognize words from a previously memorized list or to respond to other cues to help them recall information. This distinction has led to the classification of HD as a 'subcortical dementia' (Brandt et al., 1988). Early in the course of HD, aphasia and agnosia are usually much less obvious than in the cortical dementias such as Alzheimer's disease, while deficits in cognitive speed and flexibility are more common. Cognitive losses accumulate progressively. Deficits in memory, visuospatial abilities, and judgement develop, and late-stage HD patients demonstrate profound global impairment similar to patients with late-stage AD, though their paucity of speech can make assessment difficult.

The emotional disorders of HD can be very disruptive to patients and families, and may be the first signs of the disorder. The behavioural expression of these symptoms may include aggressive outbursts, impulsiveness, social withdrawal, and suicide (which was recognized by George Huntington as an important feature of the disorder). Yet the psychiatric manifestations of HD are the most amenable to treatment (Rosenblatt et al., 1999).

Affective (mood) disorder is extremely common. Epidemiological and phenomenological evidence indicates that affective disorder in HD is a function of the brain disease itself, rather than a reaction to changes in life circumstance (Penney et al., 1990; Folstein, 1989). HD-related major depression resembles the idiopathic form of major depression. Prominent symptoms include feelings of worthlessness or guilt, self-blame, changes in sleep and appetite, anxiety, anhedonia, loss of energy, hopelessness, and diurnal variation of mood with more severe symptoms in the morning. Delusions and hallucinations, when present, tend to be mood congruent: delusions of poverty, illness, or guilt; auditory hallucinations of derogatory or threatening voices. The diagnosis of major depression may be more difficult in patients with advanced disease, but is often signalled by a departure from baseline levels of activity or functional capacity.

Apathy and irritability are other common symptoms. Irritability and aggression may occur in patients without a prior history of a short temper, but are more common in patients who have had these traits lifelong. Apathy may become evident at any time in the course of the disease. Once present, it tends to persist or worsen. Irritability can coexist with apathy. Either apathy or irritability may exist independently or as part of an affective syndrome.

HD patients occasionally develop classic obsessive–compulsive disorder (OCD), with typical symptoms such as fear of contamination or excessive hand-washing. More commonly, however, patients may display perseverative preoccupation with particular ideas or plans, obtaining

cigarettes, getting a refill of coffee, etc., and become irritable when these requests are not honoured. Rarely, patients develop a schizophrenia-like syndrome, with prominent delusions, hallucinations, and/or thought disorder in the absence of an abnormal mood.

In summary, adult-onset HD falls roughly into three stages. Early in the disease, manifestations include subtle changes in coordination, minor involuntary movements, difficulty thinking through problems, and, often, a depressed or irritable mood. In the middle stage chorea usually becomes prominent, and difficulty with voluntary motor activities becomes more evident with worsening dysarthria and dysphagia. As cognitive deficits increase, the patient becomes unable to hold a job or carry out most household responsibilities. Patients with late-stage disease may have severe chorea, but are often rigid and bradykinetic. They are largely non-verbal and bedridden with a more global dementia, although retaining a significant degree of comprehension.

Differential diagnosis of HD

While the clinical diagnosis of HD is straightforward in a patient with a known family history, typical choreiform movements, and cognitive dysfunction, diagnosis may be more difficult in patients with uncharacteristic presentations or a lack of family history (Harper, 1996). For instance, patients may present with very little chorea or with movements that are predominantly athetoid, dystonic or even tic-like. Occasional patients (particularly with late onset) may have only subtle movement abnormality and relatively little cognitive disorder (Harper, 1996). Recent genetic modelling studies have suggested the possibility that late onset HD may be underdiagnosed (Falush et al., 2000). Fortunately, with the availability of the HD gene test, it is now possible to definitively establish the diagnosis of HD, even in patients with no family history or an atypical presentation. Most patients thought to have HD on clinical examination, but who do not have the HD mutation have atypical features, more characteristic of spinocerebellar ataxias or other multisystem atrophies.

HD is now recognized as one of a family of related neurodegenerative disorders caused by expansions of triplet repeats, in many cases CAG encoding glutamine (Zoghbi & Orr, 2000; Margolis et al., 1999). The diseases share a number of clinical features, especially ataxia and dementia, and can be confused with each other. Many of them affect an overlapping set of brain regions, including cerebral cortex, basal ganglia, certain brainstem nuclei, and cerebellar Purkinje cells or deep cerebellar output nuclei.

Dentato-rubral and pallido-luysian atrophy (DRPLA), MIM 125370 involves degeneration in the dentate nucleus of the cerebellum, red nucleus, globus pallidus and subthalamic nucleus, and cerebral cortex and other brainstem nuclei. Cases with adult onset can be phenotypically very similar to HD, despite the different pattern of pathology. Cases with juvenile onset, rather than having the rigid bradykinetic presentation often seen with HD, tend to be mobile, but ataxic and incoordinated, and prone to seizures which can be difficult to control. While extremely rare in the US and Europe, it is more common in Japan.

Other disorders that can be mistaken for HD include SCA3 or Machado-Joseph disease (MIM 109150) and SCA2. Like HD and DRPLA, these are both polyglutamine expansion diseases. They are characterized by degeneration in the cerebellum as well as brainstem regions and less degeneration in the basal ganglia.

Some families have an HD-like disorder but do not have any of the known triplet repeat expansions. We have followed one such family in our clinic for a number of years (Rosenblatt et al., 1998). Affected individuals from this pedigree have chorea or dystonia, rigidity, hyperreflexia, incoordination, ataxia, dementia, psychiatric syndromes, and weight loss (Margolis et al., 2001). All affected individuals and none of the unaffected individuals have a novel CTG expansion in a variably spliced exon of junctophilin 3 (Holmes et al., 2001). At least six other unrelated pedigrees, all with HD-like phenotype, have the same mutation. Thus, this appears to be a rare HD-like disorder, tentatively named HD-like 2.

A variety of other diseases may also present with HD-like symptoms (see Table 118.1), including Wilson's disease, Creutzfeldt–Jakob disease, forms of ceroid neuronal lipofuscinoses, chorea with red blood cell acanthocytosis, hereditary non-progressive chorea, paroxysmal choreoathetosis, mitochondrial disorders, corticobasal degeneration, basal ganglia calcification, forms of hereditary dystonia, Sydenham's chorea, vitamin E deficiency, and cerebral vascular disease (Harper, 1996, Ross et al., 1997).

Genetics

The mutation that causes HD was identified in 1993 (Group HDCR, 1993). The mutation proved to be an expansion of a CAG repeat in a gene termed *IT15* or *huntingtin*, the third CAG expansion mutation discovered (Zoghbi & Orr, 2000; Ross, 1995). The human and mouse gene both

Table 118.1. Selected Mendelian disorders in the differential diagnosis of HD

Disease	Inheritance	Distinctive features	Gene	Mutation
DRPLA	AD	Very HD-like	Atrophin-1	CAG expansion
SCA2	AD	Cerebellar signs	Ataxin-2	CAG expansion
SCA3	AD	Cerebellar signs	Ataxin-3	CAG expansion
Familial CJD	AD	Seizures common	Prion	Multiple
HD-like 2	AD	Very HD-like	Junctophilin-3	CTG expansion
Benign hereditary chorea	AD (AR form?)	Non-progressive	Linkage to 14q	Unknown
Choreoacanthocytosis	AR	Hemotologic findings	Chorein	Multiple
Wilson's disease	AR	Liver disease, low ceruloplasmin	ATP7B	Multiple
Neuronal ceroid lipofuscinosis (multiple forms)	AR, some AD	Lipoprotein deposits	Multiple	Multiple
Paroxysmal choreoathetosis (multiple forms)	AD	Episodic	Linkage to 2q, 1p, 16	Unknown
Familial basal ganglia calcification	AD, AR	Imaging findings	Unknown	Unknown

contain 67 exons. The human gene is located on chromosome 4p16.3, spans a genomic region of over 200 kb and is transcribed into two versions of mRNA, varying only in the length of the 3' untranslated regions. The open reading frame encodes a protein of about 350 kDa with no strong homology to known proteins (HDCR Group, 1993).

CAG repeats with fewer than 27 triplets in the HD gene are within the normal range. The rare repeats with 27 to 35 triplets are considered of intermediate length, prone to expansion but not in themselves of sufficient length to produce the disease phenotype. Repeats with 36 or more triplets are considered expansions. Within the expanded range, there is a striking correlation between the length of the triplet repeat expansion and the age of onset with longer repeats yielding earlier age of onset (Duyao et al., 1993). Most patients with adult onset have repeat lengths between 40 and 50 triplets, while most patients with juvenile onset have 60 or more CAG units. Overall, the length of the CAG repeat explains approximately 50–60% of the variance of the age of onset. However, especially for the adult onset cases, there is a wide range of variability in the age of onset, and thus triplet repeat length is not very useful for predicting age of onset for individual patients.

HD was previously considered to be 100% penetrant. However, with the discovery of the triplet repeat expansion mutation, it is now clear that penetrance (currently defined as the presence of signs or symptoms of HD by the age of 65) is less than 100% in individuals carrying an allele with 36 to 39 triplets (Rubinsztein et al., 1996). Since alleles with 36–39 triplets are uncommon, the frequency of non-penetrance is difficult to estimate reliably, but may be close to 50% for repeats with 36 or 37 triplets.

Anticipation, the phenomenon of decreasing age of onset and increasing disease severity in successive generations, has long been recognized in HD, and known to be selective for paternal transmission (Duyao et al., 1993, Ranen et al., 1995). There is no significant change from parent to child in the age of onset in maternal transmission, but a mean advance of eight years in paternal transmission. In addition, a great majority of cases with juvenile onset, arguably a more severe form of HD, arise from paternal transmission. Two features of the molecular genetics of HD explain the phenomenon of anticipation. First, age of HD onset is inversely correlated with repeat length. Second, the length of the expanded triplet repeat is unstable in vertical transmission. Paternal alleles more frequently expand then contract during transmission, while maternal alleles have an equal probability of expanding and contracting. Instability increases as repeat length increases. The net result, driven by paternal transmissions, is a skew toward earlier ages of onset in successive generations of a family.

While the length of the CAG repeat has a striking influence on age of onset, it appears to have much less influence on the rate of clinical progression. The rate of progression may be more rapid in cases with longer repeats (Aylward et al., 1997), but this is not a universal finding (Kieburtz et al., 1994). On postmortem examination, pathological changes in cases with longer triplet repeats were more advanced than in cases with the same

duration of illness but shorter repeats, providing support for a correlation between repeat length and rate of progression (Furtado et al., 1996). However, longitudinal studies of large numbers of patients are likely to be necessary to demonstrate the effect conclusively, and it appears to be relatively small. This raises the possibility that factors affecting age of onset and rate of progression may be different; thus different treatments may be required to delay onset in presymptomatic mutation positive individuals and slow progression in patients with the disease.

Furthermore, the rate of progression of HD is itself probably not constant. In a large study of patients from the multicentre Huntington Study Group database (Marder et al., 2000), the rate of change of functional capacity was relatively rapid early in the course, but slower later in the course. While this finding may reflect floor effects of the measurement instrument, an actual change in the rate of disease progression may be present, since the rate of change stabilized or even slightly increased very late in the illness. This change in the rate of decline of functional capacity can be contrasted with apparent relatively steady decline in the volume of the striatum as assessed by structural MRI studies (Aylward et al., 2000).

The genetics of HD provides some important clues about disease pathogenesis. Most prominently, there is strong evidence supporting a toxic gain-of-function of the mutated gene product. First, HD, like all the other polyglutamine repeat disorders, has a dominant mode of inheritance, which is typically the result of gain-of-function mechanisms rather than loss-of-function mechanisms. Secondly, the age of onset for homozygotes for the HD mutation generally is not markedly less than the age of onset for cases with only one copy of comparable repeat length (Wexler et al., 1987) (though this is not necessarily the case in the other glutamine repeat diseases). Thirdly, no cases of HD or related polyglutamine disorders have been identified with deletions or point mutations in any of the causative genes. In contrast, the fragile X phenotype can be caused by a triplet repeat expansion leading to impaired transcription, a deletion, or a point mutation; all three types of mutations result in loss of normal protein function. Consistent with this gain-of-function model, mice with targeted deletions of the HD gene, resulting in very low levels of HD gene expression, have developmental abnormalities rather than a progressive neurological disorder. As discussed below, however, other mouse models indicate that loss-of-function could play some role in HD pathogenesis.

The genetics of HD also suggests that toxicity increases as a function of the length of the glutamine repeat, with a threshold effect at 35–40 glutamines, strikingly similar to the other glutamine expansion diseases. In addition, genetic evidence demonstrates that factors other than repeat length must also influence the age of disease onset; the quantitative nature of these relationships should facilitate efforts to find these factors. Statistical genetic analyses have already suggested two genes (GluR6 and CA150) that may play a small role in modifying HD age of onset (MacDonald et al., 1999; Rubinsztein et al., 1997; Holbert et al., 2001).

Neuropathology

The neuropathology of HD (Figs. 118.2 and 118.3, see colour plate section) is notable for selective atrophy and neuronal loss (Vonsattel et al., 1985; Ross, 1995). The most prominent atrophy is found in the caudate nucleus and putamen (which together comprise the corpus striatum within the basal ganglia). Striatal atrophy leads to marked dilatation of the lateral ventricles. In addition, there is overall atrophy of the brain. Total brain weight is reduced by 25 to 30% in advanced cases, reflecting atrophy of the cerebral cortex and underlying white matter, the basal ganglia, and other brain regions.

Within the striatum, atrophy begins in dorsal and medial regions, and progressive loss of neurons occurs in ventral and lateral regions as the disease progresses. There is severe loss of medium spiny projection neurons, especially those synthesizing enkephalin and GABA (Richfield et al., 1995) but relative preservation of large and medium aspiny interneurons (Kowall et al., 1987). Neuronal loss is accompanied by reactive astrocytosis (gliosis). Other areas of the basal ganglia, especially the globus pallidus and subthalamic nucleus, also become atrophic, though less than the striatum. A 0–4 rating scale of gross and microscopic neurodegeneration, based primarily on changes in the caudate and putamen, has been used to semiquantitatively grade the severity of HD (Vonsattel et al., 1985). Cases with more severe neurodegeneration have greater clinical impairment prior to death, and tend to have longer expanded repeats (Furtado et al., 1996; Myers et al., 1988).

Later in the course of the disease, the cerebral cortex also undergoes atrophy. Large cortical neurons appear to be most severely affected, and there is laminar specificity, with greatest loss in layer VI and significant loss in layers III and V. The neurons lost in the greatest numbers appear to project to the thalamus, rather than to the striatum. In addition, the extent of cortical degeneration does not closely correlate with the severity of striatal degeneration.

Thus the loss of neurons in the cortex does not appear to arise simply from retrograde changes beginning in the striatum.

Within the striatum, the surviving neurons often appear to be undergoing regenerative or plastic changes (Graveland et al., 1993). These neurons in HD cases have more dendrites, more long recurved dendrites, greater density and larger size of dendritic spines, and greater somatic area compared to neurons from control brains. A complete understanding of the pathogenesis of HD will need to encompass an explanation for these regenerative changes as well as neuronal death and brain atrophy.

The severity of many of the clinical symptoms of HD is correlated with pathology in the basal ganglia and cerebral cortex. The motor changes are believed to stem from interruption of a set of neuronal circuits interconnecting the cerebral cortex, the basal ganglia, and the thalamus. The involuntary and voluntary movement abnormalities in HD may arise from early degeneration of specific populations of medium spiny neurons. Changes in the basal ganglia also likely underlie the early and relatively mild 'subcortical' cognitive changes seen in HD. The more severe global dementia seen late in the illness may relate to the later widespread loss of neurons in the cerebral cortex.

Occasional cases arise of individuals with clinically diagnosed HD but no discernible cell loss at autopsy. These have been termed 'grade zero' in the Vonsattel severity scale (Vonsattel et al., 1985), since there is little or no appreciable gliosis or neuronal loss. Therefore, it is possible that symptoms in these patients arise more from functional changes than actual neuronal loss. In fact, it may be the case that many of the early signs and symptoms of HD relate more to neuronal dysfunction than neuronal loss.

In severe cases, degeneration is also observed in other regions of the brain, including the brain stem, the cerebellum, and hypothalamic regions, including the lateral tuberal nucleus, the amygdala and portions of the thalamus. The relationship between these changes and clinical features is not clear.

The characteristic pathology of HD consists of intranuclear neuronal inclusion bodies (Fig. 118.3). Studies of human postmortem HD brain tissue using antibodies directed at the N-terminus of huntingtin have revealed small intranuclear inclusions present in neurons but not in glia (DiFiglia et al., 1997; Becher et al., 1998). While present in other brain regions, inclusions are most abundant in the cortex and the caudate. The density of inclusions is significantly correlated with the length of the CAG repeat. However, the neurons containing the inclusions are not necessarily the ones which suffer the most severe degeneration (Gutekunst el al., 1999).

The inclusions cannot be detected by antibodies directed at internal epitopes of huntingtin, suggesting that huntingtin within the inclusions is truncated. However, it is also possible that it is misfolded in a way such that internal epitopes are hidden. The inclusions can be detected with antibodies to ubiquitin, a tag for proteins undergoing proteolytic degradation. This could mean that huntingtin within inclusions has been targeted for degradation but cannot be removed by proteolysis. Ultrastructural analyses of the inclusions indicate that they are composed of a mixture of granules, straight and tortuous filaments, and masses of parallel and randomly oriented fibrils, not enclosed by an intracellular membrane. Similar inclusions were originally detected in transgenic mouse models of HD (Davies et al., 1997).

In addition, huntingtin has been found in aggregates in dystrophic neurites in HD brains (DiFiglia et al., 1997). These were present predominantly in cortical layers V and VI and appeared to be contained within neurofilament-labelled axonal processes. Such dystrophic neurites may reflect dysfunction of retrograde axonal transport. In adult-onset cases the intranuclear inclusions are less prominent than in juvenile-onset cases, but the neuritic aggregates are more prominent.

Neurotoxic models of HD

Before the discovery of the genetic etiology of HD, animal models of HD had been generated using neurotoxins. Injections of NMDA receptor agonists, such as quinolinic acid, into the striatum induce HD-like pathology, with loss of medium spiny projection neurons and sparing of cholinergic and NADPH diaphorase neurons (Beal et al., 1986). Peripheral injections into rodents or primates of several mitochondrial toxins, including 3-nitroproprionic acid (3–NPA), also reproduce aspects of striatal pathology found in HD (Beal et al., 1993). Other metabolic poisons cause preferential toxicity in different regions of the brain, often those regions affected in other glutamine repeat diseases.

These neurotoxin experiments suggest several pathways that could be involved in HD cell death. For instance, both excitotoxicity and metabolic poisoning may be mediated, in part, by damage from free radicals. Also, neurotoxic stimuli can give rise to apoptosis, a form of cell death under control of cellular machinery that plays an essential role in normal development. The process is triggered by a group of aspartate proteases termed caspases, and GAPDH and

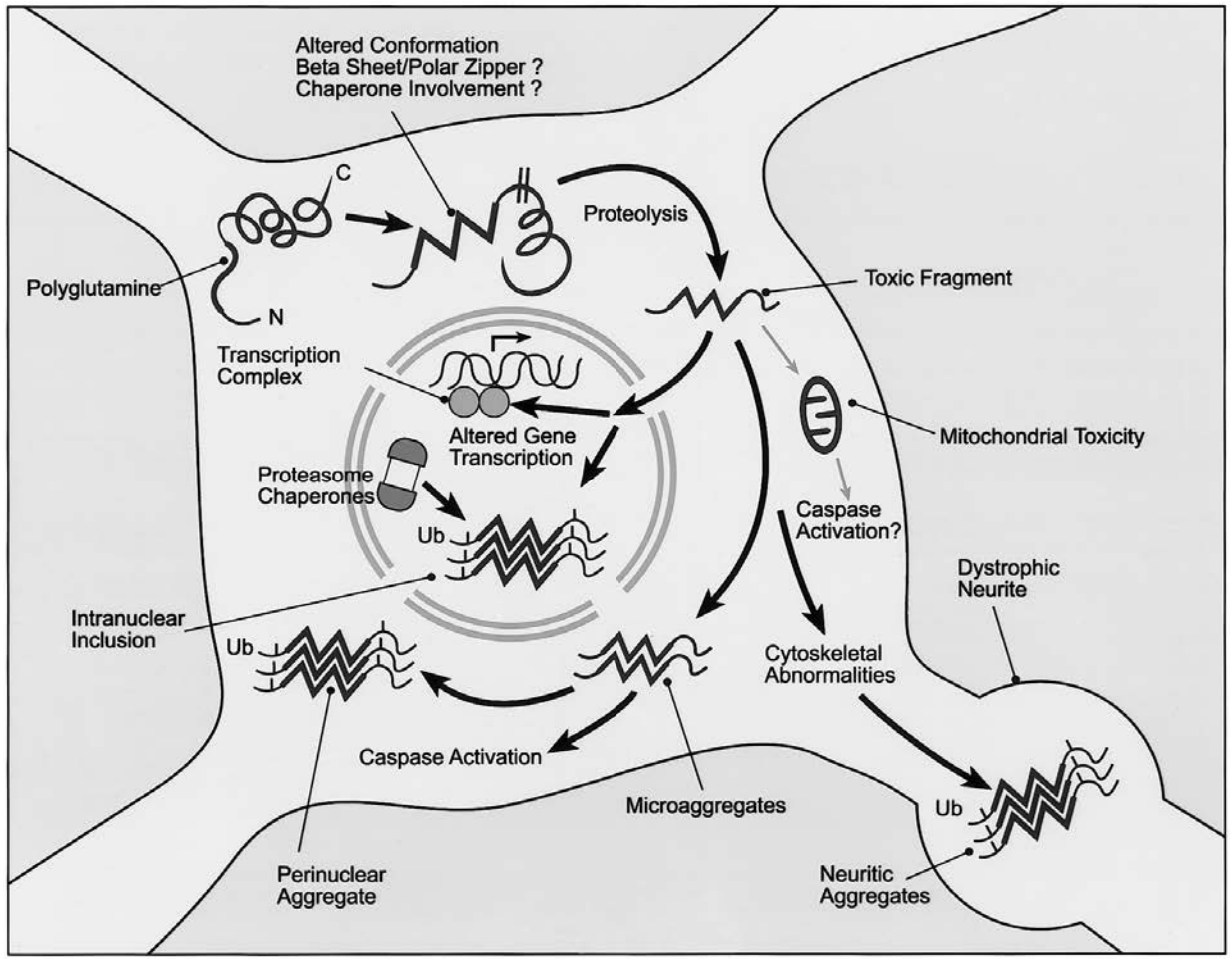

Fig. 118.4. A model of HD pathogenesis. We propose that HD pathogenesis begins with altered conformation of the protein containing the expanded polyglutamine repeat. Proteolysis generates a fragment that leads to toxicity through several pathways. Nuclear importation may lead to altered gene transcription with a detrimental effect on cell survival. Inclusions also form in the nucleus but may not be a major cause of cell death. Huntingtin fragments may interfere with mitochondrial energy metabolism, either directly, or more likely indirectly, perhaps via altered gene transcription. Microaggregation of the fragment may lead to caspase activation and the consequent initiation of cell death pathways. Fragments may be transported into neurites, interfering with cytoskeletal function. Toxicity may also be mediated by the full-length huntingtin protein with the expanded repeat. As discussed in the text, many of the steps remain speculative.

other metabolic enzymes may also serve as initiating factors.

Studies of subjects with HD have yielded results consistent with some of these neurotoxicologic mechanisms. For instance, NMR spectroscopy suggests the presence of metabolic compromise within neurons (Koroshetz et al., 1997). Marked biochemical defects of mitochondrial complex II and complex III activity, and moderate defects of complex IV activity, have been detected in mitochondria isolated from the brain tissue of individuals with HD. Evidence of free radical activation is also present in HD postmortem tissue (Gu et al., 1996).

The huntingtin protein and aggregation

The protein product of the *HD* gene, or huntingtin, is widely expressed in both the brain and peripheral tissues (Sharp et al., 1995; Di Figlia et al., 1995). The CAG repeat, even when expanded, is translated into polyglutamine (Trottier et al., 1995). Immunocytochemical and subcellular fractionation studies indicate that huntingtin is present in neuronal perikarya, dendrites and terminals, with a generally cytoplasmic localization. Huntingtin has not been consistently detected in the nucleus, though it is possible that it cycles through the nucleus without normally accu-

mulating there. The protein appears to associate with cytoskeletal elements and intracellular vesicles, with enrichment in endosomal compartments and Golgi complex membranes, and it is detected at all stages of embryonic and postnatal brain development.

The presence of the glutamine repeat with huntingtin provides some hints about its normal function. Many proteins contain stretches of polyglutamine, and such tracts are more common than repeats of other amino acids. Proteins containing glutamine repeats often appear to have a role in the regulation of development and neurogenesis, and a number of proteins with glutamine repeats are transcription factors. Glutamine-rich regions may function as factor interaction domains in transcription factors, but it is unclear if glutamine repeats serve this or more specialized functions. The lengths of glutamine repeats tend to vary considerably in homologous genes from different species; mouse huntingtin has only seven consecutive glutamines and the puffer fish homologue has only four. This may reflect a tolerance for repeat length variation in the normal function of huntingtin or species specific variations in huntingtin function modulated by repeat length.

One hypothesis for the role of glutamine repeats in human disease is based on the 'polar zipper' model proposed by Perutz (1999). He suggested that two antiparallel beta strands of polyglutamine can be linked together by hydrogen bonds between their main chain and side chain amides, forming beta sheets and potentially leading to protein aggregation and precipitation. Circular dichroism, electron microscopic and X-ray diffraction studies of synthetic peptides provide in vitro evidence supporting the formation of beta strands and possibly beta sheets by glutamine repeats. Alternatively, it has been suggested that the covalent modification of glutamines via an isopeptide linkage to lysine by the enzyme transglutaminase could lead to an insoluble precipitate of proteins containing long stretches of glutamine.

In support of the idea that huntingtin by itself can aggregate, an in vitro filter assay has been used to demonstrate that a small portion (exon 1 only) of the huntingtin protein with an expanded glutamine repeat can aggregate to form amyloid-like fibrils (Scherzinger et al., 1999). These fibrils show green birefringence when stained with Congo red and viewed by polarized light microscopy, consistent with the presence of amyloid. Aggregation does not occur if the polyglutamine repeat is of normal length. The kinetics and concentration dependence of huntingtin aggregation show many of the features of seeded polymerization (Lansbury, 1997), a process which has been implicated in the protein aggregation characteristic of several neurodegenerative diseases.

Aggregation in vitro only occurs if a huntingtin fragment with an expansion of typical length is first cleaved from the carrier protein to which it was fused during synthesis for the assay. The implication, consistent with cell and mouse models described below, is that generation of a proteolytic fragment of HD may be an important step in HD pathogenesis. Consensus cleavage sites for caspase-3 exist at approximately position 513 and 530 of huntingtin, and huntingtin can be cleaved by purified caspase-3, caspase-6, caspase-8. However, other cleavage events may also take place.

To obtain additional clues about the normal function of huntingtin and HD pathogenesis, an intensive effort has been devoted to finding proteins that interact with huntingtin. Interactors of particular interest include HIP1, HAP1, GAPDH, and SH3GL3 (Gusella & MacDonald, 1998). Some of these proteins are directly or indirectly associated with microtubule motor proteins and intracellular vesicles, suggesting a role for huntingtin in cytoskeletal function or vesicular transport. The interaction of huntingtin and other proteins containing glutamine repeats with the metabolic enzyme GAPDH is of potential significance given the possible role of GAPDH in apoptosis. Huntingtin also interacts with the nuclear corepressor protein (NCoR), and the strength of the interaction correlates with the length of the huntingtin glutamine repeat (Boutell et al., 1999). This interaction suggests that huntingtin may have some role in transcriptional regulation.

Cell and animal models

The development of cell models has facilitated research into the pathogenesis of HD, and has generally supported the gain of function model. Huntingtin has been introduced into cells through transient transfection, or by engineering cell lines that stably express huntingtin. In general, short truncations of huntingtin containing the expanded polyglutamine appear to be much more toxic than full-length huntingtin, and more liable to aggregate (Hackam et al., 1998; Cooper et al., 1998). However, aggregate formation and cellular toxicity can be disassociated, suggesting that cell toxicity is not related in a simple way to aggregation (Saudou et al., 1998). Elimination of caspase cleavage sites may reduce the toxicity of mutant huntingtin (Zoghbi & Orr, 2000; Wellington & Hayden, 2000; Sanchez et al., 1999). The cell death in these cell models does not correspond to all characteristics of apoptosis, but can be decreased or blocked in several models with caspase inhibitors (Moulder et al., 1999; Saudou et al., 1998).

A role for nuclear localization of the mutant huntingtin protein in huntingtin toxicity has been suggested, but is

still not proven. Transfection of primary neurons with constructs incorporating a nuclear export signal diminished toxicity, while the addition of nuclear localization signals appeared to enhance toxicity (Peters et al., 1999; Saudou et al., 1998). However, other studies have suggested that both the nucleus and cytoplasm can be the site of pathogenesis.

Transgenic mouse models have provided additional evidence for the gain-of-function hypothesis of HD pathogenesis. The first mouse model of HD was constructed using exon 1 of huntingtin with a very long expanded repeat. These animals developed progressive neurological deficits strikingly similar to HD, including incoordination, abnormal involuntary movements, seizures, and weight loss. However, unlike in HD patients, neuronal cell loss was not prominent. These mice also developed intranuclear inclusions containing the truncated huntingtin transgene product, but not the full-length endogenous huntingtin protein (Davies et al., 1997). The intranuclear inclusions are present at the time, and perhaps before, the animals have neurologic signs or brain or body weight loss. As in HD patient postmortem material, the intranuclear inclusions are clearly distinct from the nucleolus, and no membrane separates them from the rest of the nucleus.

Several other transgenic HD mouse models have been constructed, using various forms of the huntingtin protein, each with an expanded repeat. A truncated N-terminal fragment of huntingtin driven by the prion protein promoter resulted in mice with progressive hypoactivity, incoordination, and weight loss. Neuropathologically, the brains have intranuclear inclusions and neuritic aggregates, and moderate neuronal degeneration (Schilling et al., 1999). A transgene consisting of a full-length huntingtin cDNA driven by the CMV promoter resulted in a line of mice with a rather different phenotype, characterized by early weight gain and hyperactivity followed later by hypoactivity. These mice have both intranuclear inclusions and some loss of neurons (Reddy et al., 1998)

A promising mouse model of HD involves the use of YAC constructs, so that the transgene consists of the entire human *HD* gene with an expanded repeat, including the human *HD* promotor and all introns. These mice develop neurological signs and electrophysiologic abnormalities, and have a shortened life-span (Hodgson et al., 1999). Pathological investigation of a single founder with a long repeat revealed striking evidence of selective striatal neurodegeneration and nuclear localization of N-terminal epitopes of huntingtin in striatal neurons. If these initial results are confirmed and extended to mice with longer repeat lengths or higher levels of expression, these mice may prove to be the best model of the human disease yet generated.

A model with conditional inactivation of Huntington has recently provided evidence that loss of function of huntingtin may also yield a neurodegenerative phenotype (Dragatsis et al., 2000). Mice were generated in which huntingtin expression could be deleted using the Cre/loxP system with Cre-recombinase under the control of the CaM Kinase II promotor. With this strategy, mice develop to adulthood with normal levels of huntingtin expression, and then forebrain huntingtin expression can be reduced by 90% or more. These mice have neurological abnormalities, including limb clasping that is somewhat similar to that of some of the transgenic models. They also have neuronal degeneration in both grey matter and white matter. The distribution of degeneration is different from HD, with degeneration in lateral cortical grey and white matter. Another study has indicated that there is a loss of function contribution to cell death in the testis in vivo (Leavitt et al., 2001). These data raise the possibility that loss of function may contribute to the HD phenotype. Presumably a dominant negative effect would be required to explain why only one mutant allele can cause the HD phenotype, since heterozygous knockout animals are essentially normal. In light of this data, it is puzzling why the homozygous mutant patients described in Venezuela (Wexler et al., 1987) have a phenotype so similar to that of the heterozygous mutant patients. Overall, the role of loss-of-function in HD pathogenesis remains an open question.

Another approach to model HD is to insert the CAG expansion into the endogenous mouse *huntingtin* gene, as a so-called 'knockin', thus avoiding the confounding factor of the presence of the human transgene. So far, mice generated using this strategy may need to have a very long repeat to develop a robust behavioural and pathological phenotype (Wheeler et al., 2000; Lin et al., 2001). There is evidence of translocation of huntingtin into the nucleus, selectively in striatal neurons. Thus, these mice may provide a model for studying early stages of HD pathogenesis. Study of another similar knockin model has revealed N-terminal fragments of huntingtin, enriched in cell nuclei and migrating at 40 kDa on Western blots, consistent with a role for proteolytic processing and nuclear transport of mutant huntingtin.

The difficulties in generating a mouse knockin model with a phenotype may be overcome by making a very long polyglutamine insert. Mice with a 150 triplet CAG repeat exhibit late onset neurological and neuroanatomical abnormalities consistent with HD, including gait and other motor abnormalities as well as intranuclear inclusions and gliosis (Lin et al., 2001). They do not appear to have substantial loss of neurons. However, the gliosis appears to be selective to the striatum, suggesting that this model may

also address early pathogenic events in striatal neurons.

The construction of an inducible mouse model of HD has yielded additional insight into HD pathogenesis (Yamamoto et al., 2000). A transgene containing exon 1 of *huntingtin* with an expanded glutamine repeat was inserted using the tet-off system, such that the timing of transgene expression could be controlled by the presence or absence of an antibiotic in the animals' food. With the transgene on, mice developed neurological signs and neuropathologic changes including nuclear inclusions. Remarkably, when the expression of *huntingtin* was turned off, these abnormalities partially reversed. This suggests that the brain may have more restorative and plastic ability than previously appreciated. Thus, if the pathological changes of HD could be halted, substantial repair may be possible.

Invertebrate models offer the potential of using powerful genetic techniques to search for genetic factors that enhance or suppress an experimentally induced phenotype. Several drosophila models of polyglutamine-induced neurodegeneration have been generated (Warrick et al., 1999; Kazemi-Esfarjani & Benser, 2000), with many of the same features of neuronal degeneration observed in mammalian cell models and mouse models. Genetic screens have been used to demonstrate that molecular chaperones such as HDJ1 and HSP70 can suppress the phenotype (Kazemi-Esfarjani & Benser, 2000). *C. elegans* models may prove to be of similar value.

Current models of polyglutamine pathogenesis

A model for HD pathogenesis is depicted in Fig. 118.4. Several of the steps are speculative and the data supporting the model are at times conflicting. Here, we highlight areas of uncertainty and recent hypotheses.

Many lines of evidence indicate that the initial step in pathogenesis is a conformational change in the region of the protein with the expanded polyglutamine repeat. Proteolytic cleavage of huntingtin may be the next step; however, evidence for proteolytic cleavage of huntingtin remains indirect. The fact that nuclear inclusions can be labelled by antibodies against N-terminal epitopes of huntingtin, but not antibodies against internal or C-terminal epitopes, is consistent with proteolytic cleavage, but could also result from masking of epitopes. In addition, details of the cleavage, including whether it is processive or endoproteolytic and where in the cell it may occur, are uncertain. The figure shows the cleavage event in the cytoplasm, but this is speculative. It is equally possible that the full-length protein may be transported into the nucleus.

Another uncertainty is the role of aggregation. Abnormal

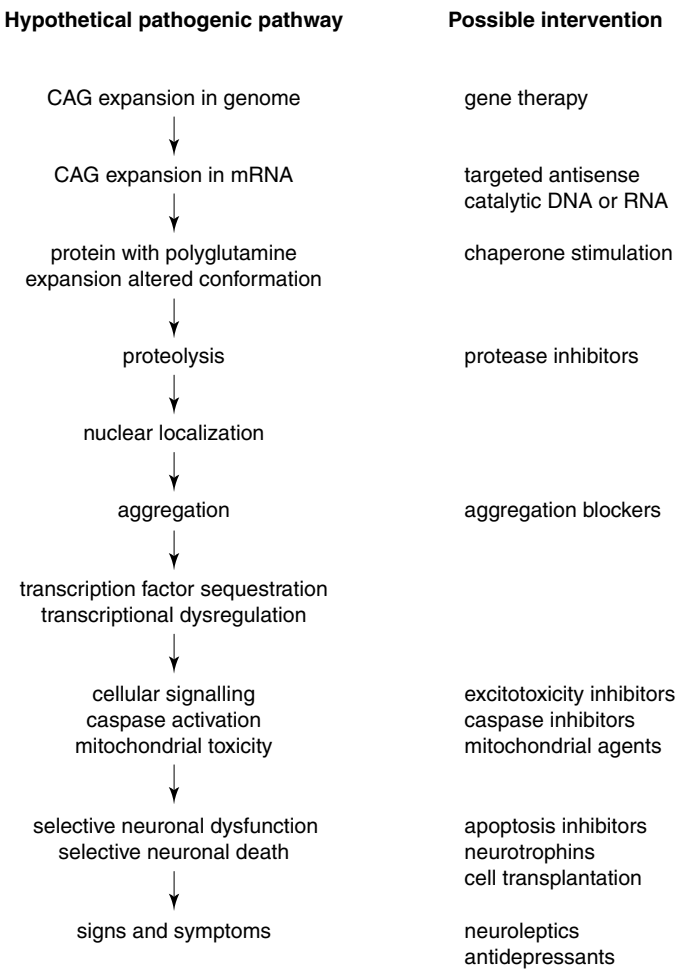

Fig. 118.5. Approaches to HD therapy. Possible interventions at different stages of a model of HD pathogenesis. While the figure depicts a linear process, it is likely that some steps are actually parallel rather than in series, and that each step may not be equally important in leading to the disease phenotype. The role of aggregation, in particular, remains uncertain. The therapeutic approaches include accepted treatments (e.g. neuroleptics, antidepressants), agents in clinical trials (e.g. excitotoxic inhibitors), agents under active preclinical investigation (e.g. aggregation blockers, caspase inhibitors, cell transplantation), and agents that are presently speculative (e.g. gene therapy).

conformation appears to be a necessary step in pathogenesis. However, the large inclusion bodies visible by light microscopy appear to represent a downstream event, an epiphenomenon, or even a protective reaction, and therefore may not be directly tied to pathogenesis. An earlier step is likely to involve abnormal interactions between mutant huntingtin and other cellular proteins, including other proteins with short polyglutamine repeats. The result

may be the sequestration of proteins that normally contain short polyglutamine repeats. An example of such protein is CREB binding protein (CBP); an important transcriptional regulator; sequestration of this and similar proteins could have marked effects on neuronal function and survival (Nucifora et al., 2001, in press).

Recent evidence has pointed toward a role for abnormalities of gene transcription in huntingtin pathogenesis (Cha et al., 2000). In the exon-1 mouse model, decreases in transcription of a number of neurotransmitter receptors is an early event (Cha et al., 1998). A gene expression screen using gene chip technology revealed that while the expression of most genes is unchanged, a subset show significant changes. Most of these are decreases (Luthi-Carter et al., 2000). Many of the gene products with decreased expression are involved in neuronal signalling pathways or intracellular calcium regulation, suggesting that these pathways may be involved in pathogenesis. However, it is also possible that they represent compensatory responses.

The mechanism of such changes in gene transcription is still uncertain. Interference with co-activator function mediated by CBP is one possibility (Nucifora et al., 2001). Another possibility is alteration of p53 mediated transcription (Steffan et al., 2000; Sawa, 2001), which could also explain mitochondria dysfunction, since a number of p53-regulated gene products have mitochondria functions. A common downstream mechanism could be abnormal histone acetylation (Nucifora et al., 2001; McCampbell et al., 2000, 2001; Steffan et al., 2001).

The relative importance of nuclear and cytoplasmic events also remains unclear. In our model, the location of mutant huntingtin in the nucleus leads to altered gene transcription. However, mutant huntingtin could act also within the cytoplasm to interfere with proteins that might otherwise be imported into the nucleus (Nucifora et al., 2001). Furthermore, toxicity might also arise from the interaction of mutant huntingtin with cytoplasmic molecules, including microtubules or microtubule motors, caspase adaptors, and other proteins.

Symptomatic treatments

There are no currently accepted specific treatments to slow the rate of clinical progression of HD (Penney et al., 1990; Rosenblatt et al., 1999). However, symptomatic management of both movement and emotional disturbance is currently possible. A detailed handbook of HD treatment options has been prepared by Rosenblatt and colleagues (Rosenblatt et al., 1999).

Dopamine receptor blocking agents such as haloperidol can be quite effective inhibitors of chorea, especially early in the illness. Dosage should be kept as low as possible. The starting dose of 1–2 mg a day of haloperidol may prove sufficient for some patients. If not, the dose can be increased slowly. Most patients will get benefits at doses of about 2–5 mg a day, though occasional patients have some beneficial effect up to 10 mg a day or more. Side effects of stiffness, rigidity, bradykinesia and sedation may severely limit effectiveness of this class of medicines. In addition, these agents are of no benefit for incoordination and ataxia (unless caused by chorea), which are more disabling than chorea for most patients.

Occasionally patients, especially those with juvenile onset, may have focal dystonia that may improve with botulinum toxin injections. In addition, for some juvenile onset patients, the rigidity and bradykinesia is so prominent that dopamine agonists such as L-DOPA may be tried, though they are rarely of any marked benefit.

Depression in HD can be treated much as idiopathic major depression, and should be sought out actively. It should not be assumed that patients who are discouraged or demoralized have an understandable reaction to their illness. Most patients with HD are able to carry on in remarkably good spirits even in the face of a disabling progressive illness. Bipolar disorder is less common than unipolar depression, but does occur in HD, and can be treated successfully with lithium or anti-convulsant mood stabilizing agents. A bipolar type 2 phenotype, with periods of depression and brief periods of hypomania, appears to be more common than classic bipolar 1 disorder. This may or may not require mood stabilizers, depending on the extent of the hypomania. Bipolar type 2 may respond better to anti-convulsant mood stabilizers than to lithium.

Other emotional features may also be prominent in HD. Whenever possible, non-pharmacologic intervention should be tried for behavioral manifestations of HD. Patients may have so-called catastrophic reactions, brief periods of emotional upset when confronted by unexpected events or unpredictable changes in their environment. Family and caretakers should be counselled to give patients advance warning of changes in plan or schedule. They should also be counselled that patients may forget, and may need frequent reminders.

Some patients have obsessive–compulsive features and these may be treated with serotonin-selective reuptake blockers. Occasional patients have delusions in the absence of mood changes, and these can be treated with neuroleptics, especially the newer ‘atypical’ agents. A common problem is irritability in the absence of mood

changes. This may respond to serotonin selective reuptake inhibitors, anticonvulsant mood stabilizers, or neuroleptics. Apathy and loss of interest in the patient's surroundings can be a difficult problem. However, one should search carefully for an affective disorder before concluding that pure apathy is the problem.

Towards rational therapeutics

Recent biochemical, cell and animal studies are beginning to suggest approaches for development of rational therapy for the progress of the disease itself (Fig. 118.5). The first generation of agents designed to slow the progression, or delay the onset, of HD have emerged from neurotoxicologic models of HD. A major multicentred trial has evaluated the CARE-HD Study (Coenzyme Q and Remacemide Evaluation in Huntington's Disease) Coenzyme Q (a mitochondrial cofactor) and remacemide (a glutamate receptor antagonist), both of which have efficacy in neurotoxicological mouse models. The CARE-HD Study was the first major multicentre HD drug trial, and involves 340 patients treated for 30 months under the sponsorship of the Huntington Study Group (Huntington Study Group, 2001). Neither drug has a significant effect on the primary outcome measure, though post hoc analysis suggested the possibility that Co-EnzymeQ might have had a modest effect. Neurotoxicologic models have also led to smaller trials of other agents, including vitamin E, idebenone, and lamotrigine. No clear efficacy has been demonstrated for any of these drugs (Shoulson et al., 1989; Kieburtz et al., 1996; Feigin et al., 1996; Ranen et al., 1996; Peyser et al., 1995).

Another approach to HD therapeutics involves transplantation, either of fetal striatal cells or of cells secreting growth factors (Boucoud-Levi et al., 2000; Freeman et al., 2000). These methods have met with, at best, limited success so far, but may have promise for the future. Stem cells, if they can be differentiated into striatal neurons in a controlled fashion, might have great potential as therapeutic agents. Gene therapy is likely to be very difficult, given that HD appears to have predominantly a gain-of-function genetic mechanism. Catalytic DNA or RNA may conceivably be used to decrease huntingtin levels (Yen et al., 1999); however, it may be dangerous to decrease levels too much.

A screen for therapeutic agents that may alter polyglutamine aggregation is currently in progress using the filter aggregation assay developed by Wanker and colleagues. Early results indicate that congo red and related dyes that intercalate into beta sheets (Heiser et al., 2000) and members of the heat shock protein/chaperone family can reduce aggregation. The effect of these agents in animal or cell models of HD is unknown, and even if effective, it is unclear if these agents would themselves be suitable therapeutic compounds. Based on these results with histone acetylation, histone de-acetylation inhibitors may appear to be good candidates (McCampbell et al., 2001; Steffan et al., 2001). New compounds may emerge based on those already shown to be effective in vitro, or entirely new classes of useful agents may be discovered with further screening.

Mouse models are now in active use to test therapeutic compounds. Based on work in cells, the role of caspase inhibitors on disease progression has been investigated. Caspase inhibition led to a modest but significant beneficial effect in the exon-1 HD transgenic mouse model (Ona et al., 1999). A genetic cross of these transgenic mice with a line of mice over-expressing a caspase-1 dominant negative construct (and hence deficient in caspase-1 activity) also suggested that caspase inhibition can slow disease progress. Creatine, chosen based on its effect in neurotoxicologic models of neuronal cell death, also has a significant effect on disease progression in the exon-1 HD transgenic mouse (Ferrante et al., 2000). Minocycline, which has shown some efficacy in ischemic models, also has a beneficial effect on this mouse line (Chen et al., 2000). Cystamine has also been reported to be of benefit (Karpuj et al., 2002). The magnitude of the effect on disease progression observed in these studies is significant but modest. A similar effect can be induced by altering the environment in which the mice are raised (van Dellen et al., 2000). It is possible that a combination of several of these agents may have enhanced effectiveness. Also, most of the agents tested so far have been targeted at relatively downstream points in the presumed pathogenetic pathway. Agents targeted at earlier steps in the pathogenetic pathway may be more effective. As the pathogenesis of HD is unravelled, development of rational and effective therapeutics should become possible.

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Progressive cerebral degeneration of childhood

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The progressive cerebral degenerations of childhood are a heterogeneous group of disorders characterized by the loss of previously acquired skills during development. They stand in contrast to the static encephalopathies, mental retardation, cerebral palsy, and autism. The causes of both progressive and static disorders are varied and include infectious, inflammatory, neoplastic, and vascular etiologies, this chapter will, however, deal only with those that result from genetic mechanisms. The importance of these disorders even with this restriction is emphasized by the series of Dyken and Krawiecki which found that genetic neurodegenerative conditions made up approximately 15% of admissions to pediatric neurology services in two institutions over a 10-year period (Dyken & Krawiecki, 1983).

General comments on evaluation

The evaluation of degeneration results in special difficulties when presenting in childhood. For the young child, the early findings may be subtle and may be mistaken for normal variation or static difficulties such as mental retardation or cerebral palsy. It is only when evaluated over time, or with a clear presentation, will the diagnosis be uncovered. It is not difficult to suspect a particular disorder when all the characteristic symptoms and signs are present – the challenge comes in doing this early in the course (Clarke, 1997).

Once the suspicion has arisen that one is dealing with a progressive condition, the evaluator must cope with a seemingly endless list of disorders (Dyken & Krawiecki, 1983). Compounding this difficulty, disease classification by biochemical abnormality, typical for these disorders, usually does not serve the purpose of clinicians. This type of designation allows one to determine the appropriate biochemical test, but does not easily direct the clinical diagnosis. Algorithms and computerized database programs have been developed to assist the clinician. When appropriately used they may be of significant benefit, however, one must recognize that the symptom complex does not appear all at once, but evolves. A knowledge of the course of disease and timing of the evolution of signs is therefore useful (Clarke, 1997).

These challenges aside, it is to be emphasized that presently there is the ability to make a diagnosis in many of the conditions which previously either were simply clinical descriptions or required invasive pathologic investigation. There are now morphological, biochemical, and genetic tools available that allow diagnosis to be made. Neuroimaging can demonstrate important alterations in the brain. This is particularly important in the evaluation of leukodystrophies, destructive disorders of myelin, but will also show abnormalities of the cerebral cortex, basal ganglia, or cerebellum. The addition of magnetic resonance spectroscopy can demonstrate changes in the concentration of certain molecules. Biochemically, by sampling with spectroscopy or directly by examining tissues, one can confirm the presence and composition of stored material or document the absence of specific enzyme activity. Diagnosis by genetic means has been the latest in the diagnostic methods and is extremely important in those disorders that do not have an easily measured biochemical assay. Examples of the latter include myotonic dystrophy and Huntington disease, which lack the classic storage material.

The purpose of the diagnosis should be clear. While therapy is ultimately hoped for, as will be seen, this is a rarity in these conditions. Instead, one of the main reasons must be to give clear genetic information and some guidance of the course of the illness. Once a diagnosis is obtained, the clinician must be certain that the family is

informed of the availability of carrier testing, recurrence risk, and the availability of prenatal testing when available.

Neonatal encephalopathies

Disorders that present in the newborn period are not typically seen as disorders of degeneration, but there are an important group of disorders that have their onset in this period and have progressive cerebral effects (Table 119.1). Deterioration in the level of alertness, irritability, seizures, liver dysfunction, and feeding intolerance may be initial clues, but also share features with other conditions such as intracerebral hemorrhage or infections. A level of vigilance is essential whenever evaluating newborns because institution of appropriate therapy may not only be life saving but result in a normal outcome. The institution of newborn screening with therapy has been one of the triumphs of genetic medicine.

The evaluation of the newborn infant with encephalopathy is one instance where rapid, inclusive testing is indicated. While the details of the acute illness may be non-specific, the events of the pregnancy, delivery, and the interval before onset of illness should be determined. The family medical history should always be reviewed and may be informative. The emphasis is on neonatal deaths and other children with either mental retardation or other perceived static difficulties. Laboratory evaluation of the acid–base balance including bicarbonate, lactate and pyruvate; ammonia; glucose; hepatic function; calcium; phosphorous; magnesium; amino and organic acid; carnitine; and urine for reducing substances should be performed in all infants presenting with acute encephalopathy. In addition, the infant with altered consciousness requires evaluation of cerebrospinal fluid, neuroimaging and EEG.

As can be seen, there are many disorders that can present in this age group. Three categorical examples will be presented: disorders of amino and organic acids, peroxisomal disorders, and disorders of glucose transporters.

Table 119.1. Neonatal metabolic disorders

Urea cycle disorders
N-acetylglutamate synthetase (NAGS)
carbamylphosphate synthetase (CPS)
ornithine transcarbamylase (OTC)
argininosuccinate synthetase
argininosuccinate lyase
arginase
Hyperornithemia–hyperammonemia–homocitrullinuria (HHH)
Non-ketotic hyperglycinemia
Maple syrup urine disease: branched chain alpha keto acid dehydrogenase
Isovaleric acidemia: isovaleryl-CoA dehydrogenase
Proprionic acidemia
Methylmalonic acidemia
Sulfite oxidase deficiency and molybdenum cofactor deficiency
Neonatal mitochondrial encephalopathies
Disorders of pyruvate metabolism
Pyruvate dehydrogenase complex deficiency
Pyruvate carboxylase deficiency
Respiratory chain disorders
Defects in mitochondrial fatty acid oxidation
Holocarboxylase synthetase deficiency
Peroxisomal disorders
Zellweger syndrome
Rhizomelic chondrodysplasia punctata
Multifunctional enzyme deficiency (bifunctional enzyme deficiency)

Disorders of amino and organic acid metabolism

Neurological manifestations are especially common in this group of disorders and may present with life-threatening encephalopathy, e.g. urea cycle disorders or more insidiously, e.g. phenylketonuria. Features seen include progressive neurological symptoms of ataxia, myoclonus, extrapyramidal symptoms, metabolic stroke and macrocephaly. Many of these conditions are diagnosed by the examination of plasma amino acids and urine amino and organic acids. It is important to emphasize assessment of the clinical setting and the use of ancillary studies. Disorders that result from the inability to handle certain types of amino acids may not present until the infant has been on full feeds and toxic levels of metabolites have accumulated. Specific measurements such as cerebrospinal fluid amino acid levels in non-ketotic hyperglycinemia may be required and are indicated in the evaluation of neonatal seizures (Lyon et al. 1996).

The final method of diagnosis, availability of prenatal testing in future pregnancies, and treatment will rest on the specific diagnosis. Certain circumstances such as phenylketonuria or maple syrup urine disease (disorder of branched chain amino acid catabolism) are the paradigm for inborn errors of metabolism and respond to a diet restricting specific amino acids which cannot be catabolized. Unfortunately, not all disorders even within this group are amenable to such manipulations.

Disorders of peroxisome

Peroxisomal disorders can be divided into two broad categories, those that involve single enzyme dysfunction and those that affect peroxisome biogenesis. Peroxisomal diseases can present at a variety of ages, but the newborn presentation is particularly common, but still often underdiagnosed.

Zellweger syndrome and the related neonatal adrenoleukodystrophy and infantile Refsum disease are disorders of peroxisome assembly or biogenesis. The affected newborn presents with hypotonia, characteristic craniofacial features, and may develop seizures in the first days of life. Children often have evidence of liver dysfunction, skeletal stippling, renal cysts, and ophthalmologic findings such as cataracts and glaucoma. If not already evident at birth, there is progressive visual and hearing loss. Survival beyond the second year of life is unusual for those with the severest form of the disease. Neonatal adrenoleukodystrophy and infantile Refsum disease are now known to be phenotypic variations of the more severe Zellweger syndrome. They are characterized by somewhat milder clinical features and longer survival. Multiple biochemical abnormalities secondary to the inability to assemble peroxisomes are seen in affected children. These include defects in the beta oxidation of very long chain fatty acids, defects in plasmalogen synthesis, abnormalities in phytanic acid oxidation, and pipecolic acid metabolism. These abnormalities may be seen in a variety of tissues including blood, fibroblasts, and liver as well as amniocytes and chorionic villi cells, which allow prenatal diagnosis.

Peroxisome assembly disorders are caused by genetic defects in PEX genes and the altering of their proteins, peroxins, which are necessary for the importation of targeted proteins into the peroxisomes. It has now been determined that disorders of peroxisomal assembly are genetically heterogeneous and defects in ten PEX genes have been identified. The largest group of abnormalities is in PEX1, a AAA-type ATPase involved in the import of targeted proteins (Raymond, 1999).

While the specific genes are varied, all forms to date are autosomal recessive and prenatal diagnosis is available using biochemical assay for subsequent pregnancies. There is presently no curative therapy, but appropriate symptomatic treatment is indicated.

Single enzyme disorders include the X-linked adrenoleukodystrophy (ALD), acyl-CoA oxidase deficiency and peroxisomal multifunctional enzyme, all defects in very long chain fatty acid beta oxidation. The X-linked form of adrenoleukodystrophy does not present in the newborn and is discussed in the chapter on leukodystrophies (Chapter 100). However, the other two typically present in the neonatal period with hypotonia and seizures and are progressive in their course. The multifunctional enzyme defect results in very profound hypotonia and progressively severe seizures often resistant to therapy. Death occurs typically at 9 months. Acyl CoA oxidase appears initially to be more mild in presentation, and the children may gain some developmental milestones before the onset of regression after the first year or two of life. Initial diagnosis of these disorders is made by the demonstration of abnormalities in very long chain fatty acid levels in plasma and subsequently confirmed by the demonstration of a defect in very long chain fatty acid oxidation and confirmation of the specific defect in fibroblasts (Watkins et al., 1995). Prenatal testing is available using the biochemical assay of beta oxidation. There is no curative therapy available for either defect.

Disorders of glucose transporters

De Vivo and his associates have reported children who presented in infancy with severe seizures, acquired microcephaly, mental retardation and motor delays (De Vivo et al., 1991). Diagnosis rests on low glucose concentrations in the cerebrospinal fluid with normal blood glucose levels. The impaired glucose is due to a defect in the glucose transporter responsible for the facilitative diffusion of glucose across the blood–brain endothelial barrier. The transporter designated GLUT1 belongs to a family of closely related glucose transporters. Wang et al. (2000) described 15 children who presented with typical features of heterozygous mutations in the GLUT1 gene (Wang et al., 2000). The type of mutations varied, but the resultant deficiency in the transporter reduced cerebrospinal fluid glucose concentrations and erythrocyte glucose transporter activities in the patients.

The use of the ketogenic diet as a supply of alternative fuel for the brain has been therapeutic. Ketone bodies, which use a different transport mechanism prevent the neurological damage seen in the untreated condition. Seizures resolve and there is normal brain growth in treated children (De Vivo et al., 1991).

Progressive encephalopathies of childhood

These diagnoses come into consideration when there is neurological regression or arrest of development. There may be additional clues such as familial recurrence, non-neurological abnormalities including retinal and other

ophthalmological abnormalities, and the presence of a particular neurological sign as in the acoustic startle seen in Tay–Sachs disease. It is traditional to distinguish leukodystrophies from polioencephalopathies by the characterization that progressive white matter destruction presents with the early onset of spasticity and that encephalopathies present with seizures. Unfortunately, there are too many exceptions for this to be a useful rule. Many cerebral diseases involve both grey and white matter, and seizures may be the presenting sign of certain white matter disorders. Rather than rely on clinical means for the type of disorder, magnetic resonance imaging is extremely useful for determining the areas of involvement and should be performed in any child with evidence of a progressive condition.

Non-neurological abnormalities are extremely important in the evaluation and therefore warrant a careful search for their presence. Inclusions in certain cell types including leukocytes, histiocytes, and fibroblasts may be noted. The finding of storage material should prompt an appropriate search. Electron microscopy for ultrastructural details may be diagnostic (Ceuterick-de Groote & Martin, 1998; Ceuterick & Martin, 1992). Other features that the child should be examined for include unexplained failure to thrive, skeletal changes, changes of skin and hair, and pulmonary involvement. Specific craniofacial features may be seen in the peroxisomal disorders and progressive coarsening noted in certain mucopolysaccharidoses. The presence of liver and spleen enlargement in certain storage disorders, cardiomegaly in Pompe disease and mitochondrial conditions, and liver or kidney cysts in peroxisomal disorders are other examples.

Lysosomal storage disorders

This group of disorders are characterized by the accumulation of storage material in the autophagocytic vacuoles, the lysosome. Based on the storage material, lysosomal disorders may be separated into sphingolipidoses, mucopolysaccharidoses, glycopeptide, glycogen storage disorders, lipid storage, peptide abnormalities, transport defects, and multiple enzyme disorders (abnormalities of targeting) (Hopwood & Brooks, 1997). Several of these disorders are especially important in the evaluation of the child with cerebral degeneration. A complete discussion of this large group is not possible, but specific examples will be highlighted including Tay–Sachs disease, Niemann–Pick type C, neuronal ceroid lipofuscinosis, and the mucopolysaccharidoses that affect the nervous system directly (Table 119.2).

Sphingolipidoses: Tay–Sachs disease

Tay–Sachs or infantile GM_2 gangliosidosis is an early infantile degeneration with megalencephaly and blindness. It is seen predominantly in Ashkenazi Jewish children and in certain other populations including French Canadians. The incidence is reported to be 1/112 000 of live births in the general population and 1/3900 in the Jewish population.

The infant, normal at birth, develops an exaggerated startle to sounds at 4 months. There is quick extension of the arms and legs followed by few clonic jerks, blinking with a startled look and neck extension. No adaptation occurs. This needs to be distinguished from seizures which occur later in the disease. While this may be seen in other conditions, it is nearly always present in this disorder. Deterioration is usually not seen until 6 months of age. The affected child loses the ability to roll over, is unable to sit, spontaneous vocalization stops, and then loses head control. Axial hypotonia and spasticity develops. With further progression, there is development of seizures, tonic–clonic as well as minor motor, and unusual laughing spells. The EEG changes and hypsarrhythmia may occur. It eventually becomes obvious that the child is blind and pendular nystagmus, evidence of early visual loss, may develop. A bilateral cherry red spot is seen in the majority. This is a large conspicuous grey circular zone of retinal degeneration, in the centre of which is the contrasting red macula (Lyon et al., 1996).

A late feature is an increase in the head circumference. This may not be seen until the second year of life and actual separation of the sutures may occur. This is a true enlargement of the brain secondary to stored neuronal material and is not secondary to hydrocephalus. There is no visceral or skeletal involvement; no peripheral nerve involvement; no abnormalities found in the bone marrow or leukocytes; and no abnormal excretion of oligosaccharides. The disease is relentlessly progressive and usually fatal between 3 and 5 years of age (Lyon et al., 1996).

There is an accumulation of GM_2 gangliosides and related glycolipids in neurons and other organs. Normally the hydrolysis of gangliosides is accomplished by the action of two structurally related lysosomal enzymes hexosaminidase A and hexosaminidase B with the involvement of GM_2 activator protein. Hexosaminidase A is composed of two subunits, α and β, encoded on chromosome 15 and chromosome 5, respectively. Hexosaminidase B contains only beta subunits ($\beta\beta$). The activator protein is also encoded on chromosome 5 and is necessary for the degradation of GM_2 ganglioside by hexosaminidase A. Mutations at any one of the gene loci can result in the accu-

Table 119.2. Selected lysosomal storage disorders

Clinical syndrome	Enzyme abnormality	Accumulated material
GM1 gangliosidoses	β-galactosidase	GM1 gangliosides, galactosyl oligosaccharides, keratan sulfate
Tay-Sachs (Variant B)	Hexosaminidase A (α-subunit)	GM2 gangliosides
Sandhoff (Variant O)	Hexosaminidase A and B (β-subunit)	GM2 gangliosides, other sphingoglycolipids and glycoproteins with terminal β-hexosamine residues including globosides and GA2 glycolipids
GM2 gangliosidosis (Variant AB)	GM2 activator protein	GM2 gangliosides
Krabbe	Galactosylceramidase (galactocerebroside beta-galactosidase)	Galactosylceramide, galactosylsphingosine (psychosine)
Gaucher	β-glucosidase (glucocerebrosidase)	Glucoceramide globosides (glucosylceramide)
Metachromatic leukodystrophy	Arylsulfatase A	Sulfatides
Farbers	Acid ceramidase	Ceramide
Niemann–Pick type A and B	Sphingomyelinase	Sphingomyelin
Niemann–Pick type C	Niemann–Pick C1 protein	Unesterified cholesterol
MPS I (Hurler Disease)	α-L-iduronidase	Dermatan sulfate Heparan sulfate
MPS II (Hunter Disease)	Iduronate 2-sulfatase	Dermatan sulfate Heparan sulfate
MPS III (Sanfilippo Disease)		
Type A	Heparan *N*-sulphatase	Heparan sulfate
Type B	α-*N*-acetylglucosaminidase (NAGLU)	Heparan sulfate
Type C	Acetyl CoA: α-glucosamine *N*-acetyl transferase	Heparan sulfate
Type D	*N*-acetylgalactosamine-6-sulfatase	Heparan sulfate
Infantile NCL (Santavuori–Haltia Disease)	Palmitoyl-protein thioesterase (PPT1)	Palmitoylated proteins
Late infantile NCL (Jansky–Bielschowsky Disease)	Tripeptidyl-peptidase I precursor (TPP-I) (Pepstatin-insensitive carboxypeptidase)	Subunit c of mitochondrial ATP synthase
Juvenile NCL	CLN3 protein (Battenin)	Unknown

mulation of GM_2. Three varieties have been reported. Defects in the α subunit give rise to defective hexosaminidase A and Tay–Sachs and other later onset variants. Defects in the β subunit result in a defect in both hexosaminidase A and B and gives rise to the Sandhoff disease. Activator protein deficiency or the AB variant, because there are normal levels of hexosaminidase A and B, also can result in a similar accumulation (Lyon et al., 1996).

Diagnosis requires the demonstration of a deficiency of hexosaminidase A with normal or elevated levels of hexosaminidase B. Enzymatic studies can be performed on leukocytes using artificial compounds or the natural GM_2 gangliosides as substrates. Heterozygotes can be detected by assays of hexosaminidase A in serum, leukocytes, or cultured fibroblasts. The carrier frequency is 1/31 in the Jewish population compared to 1/167 in the general population (Petersen et al., 1983). This has led to widespread screening programmes in this population, which in conjunction with available prenatal testing has resulted in a decreased incidence of disease.

There presently is no known treatment, but recent studies of the compound *N*-butyldeoxynojirimycin in the Tay–Sachs mouse has raised the potential for therapy. The treatment of Tay–Sachs mice with *N*-butyldeoxynojirimycin prevented the accumulation of GM_2 in the brain. This agent appears to act by interfering in the synthesis of GM_2 and other glycosphingolipids (Platt et al., 1997).

Defects in lysosomal lipid metabolism

Niemann–Pick Type C

The Niemann–Pick disorders are characterized by the accumulation of sphingomyelin in reticuloendothelial cells and other cell types throughout the body. Features of the condition are progressive neurologic deterioration, hepatosplenomegaly and retarded growth. Early on in the description of the disorder, it appeared that there were different presentations and four varieties were labelled A, B, C and D. Group A and B patients clearly had a defect in sphingomyelinase leading to accumulation of sphingomyelin. The enigma was that while sphingomyelinase levels were low in type C, they were not absent. It has subsequently been determined that type A and B are allelic and are a separate disorder from type C. Niemann–Pick type C is not a primary defect in sphingomyelinase (Vanier & Suzuki, 1996). While type A is more common than the others, the recent understanding of the biochemical mechanism of type C has given new insights into lysosomal lipid metabolism and it will be discussed.

To state that Niemann–Pick type C is variable in presentation is an understatement. The disease may present from the perinatal period through adulthood. Neurological and visceral manifestations are important but appear to be indefinite in severity and timing. Liver involvement may be present prenatally or in the neonatal period. Cholestatic jaundice is present in about half of the cases. This typically spontaneously resolves, but has been reported to result in liver failure. Neurological findings consist of ataxia, dysarthria, progressive dementia, cataplexy, seizures, dystonia, and a supranuclear vertical gaze palsy. When presenting early on, there is delayed motor development and hypotonia followed by pyramidal signs (Vanier & Suzuki, 1996).

The presentations that have been described are based on the age of onset and presenting signs. There is a late infantile/juvenile form, severe infantile form, adult presentation, and finally a rapidly fatal neonatal form characterized by cholestatic liver failure (Fink et al., 1989; Vanier & Suzuki, 1996). The late infantile and juvenile forms are the most common presentation and are characterized as a slowly progressive disease. Children are initially normal, then develop neurological abnormalities with loss of previously acquired speech, the appearance of mild intellectual impairment, supranuclear vertical gaze palsy, ataxia and later associated with dementia and variably seizures and extrapyramidal deficits.

Biochemically, there are elevated levels of sphingomyelin in the liver and spleen with normal total sphingomyelinase activity. However, by isoelectric focusing sphingomyelinase activity in the acidic range was markedly reduced. These findings led to the confusion concerning the classification of this disorder. Pentchev et al. (1985) subsequently demonstrated that there was a major block in cholesterol esterification and an accumulation of unesterified cholesterol in cells (Pentchev et al., 1985). The gene subsequently labelled NPC located on 18q11–q12 was identified. The translated protein has similarity to the putative sterol-sensing regions of SREBP cleavage activating protein and 3-hydroxy-3-methylglutaryl coenzyme A reductase (Carstea et al., 1997).

Nerve cells demonstrate not only storage of cholesterol but also neurofibrillary tangles containing paired helical filaments similar to the tangles present in Alzheimer's disease and other disorders, but this does distinguish it from other forms of Niemann–Pick. Auer et al. (1995) demonstrated tau protein in Western blots from brain tissue in five cases of Niemann–Pick type C (Auer et al., 1995). The NPC mouse showed that the terminal fields of axons and dendrites are the earliest sites of degeneration and occur well before the appearance of a neurological phenotype.

The clinical diagnosis is not difficult when faced with typical findings, but atypical presentations are not rare and will present problems. It is estimated that 10% of cases will not have overt organomegaly. Foam cells and sea-blue histiocytes, which may be present in bone marrow, are nonspecific and may be lacking. Ultrastructural analysis of biopsies may demonstrate storage in a variety of tissues, but false-negatives are reported (Vanier & Suzuki, 1996).

Diagnosis depends on the demonstration of lysosomal accumulation of unesterified cholesterol in cultured fibroblasts as shown by a characteristic pattern of intense perinuclear fluorescence after staining with filipin, a probe that forms complexes with unesterified cholesterol, and abnormal intracellular cholesterol homeostasis as defined by impaired LDL-induced cholesterol homeostasis (Vanier & Suzuki, 1996).

No strict correlation has been noted between the severity of alteration in intracellular cholesterol homeostasis and the clinical phenotype. Provided marked abnormalities have been demonstrated in the first affected individual, similar tests for prenatal detection of affected fetuses using cultured chorionic villi cells or amniocytes can be performed. Since some heterozygotes may show significant alterations, prior studies of parents are advised (Vanier & Suzuki, 1996).

No specific treatment is available. Bone marrow transplantation has not, to date, been evaluated and liver transplantation did not influence the course of the neurological deterioration (Gartner et al., 1986). Combined transplantation did not have a beneficial effect on neurological deterioration in animal models (Vanier & Suzuki, 1996).

Neuronal ceroid lipofuscinosis (NCL)

Neuronal ceroid lipofuscinosis encompasses a group of lysosomal diseases with defects in different aspects of lysosomal protein catabolism. All are inherited in an autosomal recessive fashion with an overall frequency of 1 in 12 500 births. The terms neuronal ceroid lipofuscinosis and Batten disease are now used interchangeably. They are delineated by seizures, retinal disease, visual loss, cognitive impairment and motor decline. There are presently defined an infantile form, late infantile, juvenile, and adult. There are also variants recognized that have ultrastructural features of one form, but an atypical clinical presentation (Boustany, 1996).

Infantile NCL (Haltia–Santavouri disease)

Primarily a Finnish disease, infantile NCL is characterized by normal initial development and then psychomotor retardation with onset between 8 and 18 months, hypotonia, myoclonus, progressive microcephaly and blindness. Vision begins to deteriorate at 12 months and there are obvious retinal changes by 2 years. Infants become microcephalic by 2 years of age. By age 3, they are bedridden, blind, spastic with frequent myoclonic jerks. On ultrastructural analysis, lysosomes contain granular, osmiophilic deposits referred to as GROD (Boustany, 1996).

Late infantile NCL

Early development proceeds in a normal fashion with attainment of walking, talking, and other motor skills at the appropriate age (Boustany et al., 1988). Children then develop ataxia, hypotonia, drop attacks, and tonic–clonic seizures around three years of age (Boustany, 1992). Visual deterioration secondary to tapetoretinal degeneration follows at age 4 and the child then enters a period of rapid deterioration. By age 5, the child is mute, bedridden with frequent seizures. An enlarged amplitude is seen on visual-evoked potentials. The typical ultrastructural abnormalities on skin biopsy are curvilinear or C-shaped structures enclosed within lysosomal membranes (Carpenter et al., 1977). The typical profile is also seen in a variety of tissues including smooth muscle, macrophages, endothelial cells, Schwann cells, mast cells, pericytes and eccrine duct cells. Pathologically, the brain is extremely atrophic with extensive narrowing of the cortical layers and cerebellar atrophy. Microscopically, there is nearly complete depletion of the neuronal elements with gliosis and total loss of Purkinje and granular cells in the cerebellum. The remaining cells are distended with granular autofluorescent lipopigment.

Juvenile NCL

The first symptom to appear is deteriorating vision secondary to retinitis pigmentosa at the ages of 4–6 years. Macular degeneration evolves with time, and the electroretinogram and visual-evoked potentials become flat. Around age 10, there is cognitive decline, poor school performance, decreased attention span and deteriorating speech. Children then develop seizures although the EEG is usually abnormal prior to this showing runs of spike-wave. Speech develops a monotonous cadence with perseveration and echolalia. In their teenage years, patients develop rigidity and tremor (Boustany, 1996).

Vacuolated peripheral lymphocytes help distinguish this type from others (Schwendemann, 1976). The other distinctive feature is the lesser amount of storage material with a higher incidence of fingerprint profiles. Vacuoles in cells appear enclosed by a limiting membrane. Osmiophilic inclusions resembling smudged fingerprint impressions associated with lipid-like droplets are considered a hallmark. Curvilinear profiles are seen as well. Various tissues may be examined including suction rectal biopsies (Rapola et al., 1984).

All discerned forms of NCL are autosomal recessive. The elucidation of the molecular biology has assisted the understanding of NCL categories. The gene for INCL was assigned to chromosome 1p32 and then determined to code for palmitoyl-protein thioesterase (PPT1), an enzyme that modifies proteins by removing fatty acid groups from S-acetylated proteins (Vesa et al., 1995). The accumulation of undigested substrates leads to the formation of neuronal storage bodies that are associated with the clinical symptoms. There have been variant phenotypes associated with PPT1 mutations. The gene responsible for late infantile NCL is *CLN2*, which encodes for a tripeptidylpeptidase (Ezaki et al., 1999; Liu et al., 1998; Rawlings & Barrett, 1999; Sleat et al., 1997; Sohar et al., 1999). The juvenile form is secondary to mutations in CLN3 which appears to be involved in the maintenance of the appropriate pH in the intracellular vacuolar compartments essential for normal cell function (Golabek et al., 2000). The predominant mutation is a 1.02 kb genomic deletion that accounts for nearly 85% of the disease alleles (Munroe et al., 1997). This deleted portion causes a frameshift and subsequent premature stop codon resulting in a truncated protein, which cannot move out of the endoplasmic reticulum (Haskell et al., 2000; Jarvela et al., 1999).

Mucopolysaccharidoses (MPS)

MPS are a clinically, biochemically and genetically heterogeneous group of disorders of lysosomal glycosaminoglycan metabolism. Abnormal systemic accumulation of partially degraded glycosaminoglycan fragments is present in nearly all tissues (Lyon et al., 1996; Whitley,

1996). Each disorder results from deficiency of an enzyme required in the sequential process of catabolism. These compounds are large complex heteropolysaccharide molecules derived from extracellular components chiefly connective tissue proteoglycans. After endocytosis into the lysosome, the series of enzymes removes monosaccharide and sulfate groups from the non-reducing end of the molecule (Whitley, 1996).

Deficiency of any of the ten enzymes results in a disorder in this group with accumulation of their substrates. The compounds that accumulate include heparan sulfate, dermatan sulfate, keratan sulfate and the chondroitin sulfates. In affected patients they are synthesized in the normal fashion and become integral components of connective tissue. The accumulation of heparan sulfate is associated with the nervous system involvement which is seen in Hurler, Hunter, Sanfilippo, and Sly disease. Injury, however, may be secondary to an associated accumulation of gangliosides. Diagnosis of the mucopolysaccharidoses rests on the demonstration of specific enzymatic abnormalities. Screening for this group of disorders may be performed by examining the urine for mucopolysaccharides (Lyon et al., 1996).

Hurler syndrome is an autosomal recessive disorder caused by a deficiency of alpha-L-iduronidase. There is coarsening of facial features, hepatosplenomegaly, skeletal manifestations, and progressive neurologic deterioration. Severe disease presents around the first 12 months of life. Lumbar kyphosis and recurrent upper respiratory infections are the most common presenting findings (Cleary & Wraith, 1995). The course is characterized by early, progressive airway issues including obstructive sleep apnea and eventually neurological deterioration with loss of motor and language skills. The progressive dementia is sometimes associated with frank hydrocephalus, which may benefit from shunting. Combined hearing loss is common. There are also ophthalmological abnormalities including photophobia, progressive corneal clouding, a retinal pigmentary dystrophy, optic nerve swelling and glaucoma. Other organ systems are also involved and there is pulmonary and cardiovascular disease, skeletal changes with dysostosis multiplex, hepatosplenomegaly, skin thickening and hirsutism. Progressive respiratory and cardiac failure are the underlying cause of death.

The only X-linked recessive disorder among the MPS, Hunter syndrome is secondary to a deficiency of the lysosomal enzyme iduronate-2-sulfatase. It shares several features in common with the more common Hurler syndrome and, in boys, the early differentiation between the two often relies solely on enzyme determination. There are stiff joints, short stature, hepatosplenomegaly, and coarse facial features (Young & Harper, 1983). There is the insidious onset of dementia between 4 and 8 years of age, then mental age levels off and behavioural problems become manifest. Unlike Hurler syndrome, there is no corneal clouding. Cervical cord compression may occur secondary to pachymeningitis or a stenotic cervical canal. Conductive and sensorineural hearing loss occur. Bone marrow therapy has been attempted, but has not been curative.

Sanfilippo syndrome is secondary to the accumulation of heparan sulfate and there is marked urinary excretion of heparan sulfate. There are four types identified depending on the enzyme abnormality: type A: heparan *N*-sulfatase; type B: alpha-*N*-acetylglucosaminidase (NAGLU); type C: acetyl-CoA: alpha glucosaminide *N*-acetyltransferase; type D: *N*-acetylglucosamine 6-sulfatase (Lyon et al., 1996). Neurological deterioration which is the primary manifestation of this disorder is first noted between 4 and 6 years. Behavioural problems are often the initial feature and sleep disturbances, aggression, hyperactivity and difficulties with attention are particularly common (Cleary & Wraith, 1993). Motor activities remain intact until late in the course of the disease. Speech may, or may not, be acquired, but if so it is eventually lost. Seizures occur in approximately 40% of individuals (van de Kamp et al., 1981).

Sly syndrome is a rare condition secondary to β-glucuronidase deficiency with accumulation of the β-linked glucuronic acid residues: dermatan sulfate, heparan sulfate and chondroitin sulfate. It is characterized by short stature, hepatosplenomegaly, progressive dysostosis multiplex, intellectual impairment; and mental retardation marked by speech delay. It is variable in presentation and course (Lyon et al., 1996).

Therapy for the MPS has been limited. Bone marrow transplantation has been used as therapy in Hurler disease in early affected individuals (Whitley, 1996). It has not been effective in Hunter or Sanfilippo disease. There are presently ongoing investigations of lysosomal enzyme infusions and gene therapy in appropriate animal models for most of the lysosomal storage diseases.

Other categories of neurodegenerative disease

As noted, not all the degenerative conditions presenting in childhood are lysosomal storage diseases. In addition to the lysosomal diseases, there are mitochondrial, peroxisomal, abnormalities of copper metabolism, disorders of amino and organic acid, as well as other single gene disorders for which the molecular defect may or may not be

known. In addition, while the majority of the chapter has focused on disorders affecting cortical neuronal function, it is obvious that there are other presentations for degenerative disorders presenting in childhood and these will be briefly touched upon.

Progressive myoclonic epilepsies

While it is recognized that many of the disorders discussed in this chapter may make their initial presentation through seizures, the progressive myoclonic epilepsies are sufficiently distinct to warrant some additional comments. This group is characterized by the combination of seizures with myoclonus or polymyoclonus (Lyon et al., 1996). The list of progressive myoclonus epilepsy include Unverricht–Lundborg or Baltic myoclonus, Lafora disease, Alpers disease, Sialidosis type 1 (cherry red spot-myoclonus), NCL, MERRF, and dentatorubro-pallidoluysian atrophy (DRPLA). There are also other disorders which may have this as a feature, these include Gaucher disease, Krabbe and certain other diseases both genetic as well as infectious. The pattern of inheritance when clear may provide useful information. While the majority are recessive, the importance of recognizing the dominantly inherited DRPLA or maternal inheritance seen in the mitochondrial disorder, MERRF, should be readily apparent.

Disorders affecting the basal ganglia

The extrapyramidal signs of athetosis, chorea, dystonia, and rigidity characterize this group. Dementia and seizures may accompany the other findings. Included are juvenile Huntington disease, which often presents with rigidity and seizures. When presenting in childhood, it is usually secondary to paternal inheritance and anticipation, the earlier, more severe presentation of disease secondary to expansion of the triplet repeats causing disease. The other disorder which should be considered with this presentation is Wilson disease. This is particularly important because both liver and brain symptoms may be treated or more accurately prevented if recognized early and treatment instituted. Other disorders are the familial dystonias including Dopa-responsive dystonia, Hallevorden–Spatz and the choreas including chorea–acanthocytosis.

Disorders associated with strokes

While it is traditional to think of cellular degeneration as the archetype of progressive disorders, it must be recognized that as in the adult multiple infarctions can result in progressive neurologic disease. Homocystinuria, Fabry disease, sickle cell disease, hereditary coagulopathies, pseudoxanthoma elastica, and others can result in loss of neurological function and should be considered in the child who presents with a vascular event. Appropriate testing of the child with a cerebrovascular event will depend on the nature of the event, distribution, and associated findings. Evaluation will include hematological and coagulation studies, amino acids, liver function and appropriate imaging of the vasculature.

Disorders that may have regressive component

There are disorders which appear to combine a regressive period as well as a static phase. Certain previously acquired skills are lost and there is no further progress made, but the relentlessly progressive degeneration seen, for instance, in the lysosomal disorders does not occur. Specific examples of this include Rett syndrome, which is due to a defect in MECP2 gene and the expanding congenital disorders of glycosylation (CDG) previously labelled carbohydrate deficient glycoprotein disorders. The latter are diagnosed by examination of the electrophoretic pattern of transferrins (Aebi et al., 1999; Matthijs, 2000).

In conclusion, tremendous progress has been made in the diagnosis and understanding of the pathogenesis of many of the disorders that result in cerebral degeneration in childhood. It is also apparent that therapies are presently markedly inadequate for many of these disorders. The promise of gene therapy has yet to be fulfilled, but complete pessimism is also inappropriate when dealing with affected individuals and their families. As previously stated, these children deserve an appropriate evaluation and continued therapy to maintain function and comfort.

For most of the disorders covered in this chapter, there are family support organizations with most maintaining webpages. With this access to information, families are often surprised and sometimes resentful that a busy physician does not have complete information on new developments. Caretakers should be aware of these resources and must certainly maintain some familiarity with new developments when dealing with a particular disorder. However, it is also important to maintain balance and explain the difference between research and practical clinical therapies.

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Mitochondrial encephalomyopathies

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This chapter deals with those mitochondrial disorders due to defects of the mitochondrial respiratory chain and oxidative phosphorylation (MITOX) system. Although usually referred to as mitochondrial encephalomyopathies, they often involve multiple systems and their mode of manifestation is protean. Thus, the MITOX diseases are a diverse group and this is also reflected at the molecular genetic level, because the respiratory chain is under dual genetic control, with thirteen proteins encoded by mitochondrial DNA (mtDNA) and all others encoded by nuclear DNA (nDNA). A variety of causative mutations have been identified in both the mitochondrial and nuclear genomes (Table 120.1). The spectrum of the primary mitochondrial disorders has complicated an estimation of their frequency in the general population. However, studies from three Northern European regions with homogeneous health systems and limited migration have come up with similar estimates. A study from western Sweden suggested that mitochondrial diseases (defined by clinical, morphological, biochemical, and molecular criteria) affect 1 in 11 000 preschool children (Darin et al., 2001), whereas a study from northeastern England found that mtDNA mutations cause disease in 6.57/100 000 adults (Chinnery et al., 2000). The third study focused on a specific mtDNA mutation (the A3243G MELAS mutation) and estimated that it has a frequency of at least 16.3/100 000 in the population of Northern Ostrobothnia, a region of northern Finland (Majamaa et al., 1998). Thus, defects of the respiratory chain may be amongst the commoner of the genetic causes of neurological disease.

Table 120.1. Genetic classification of respiratory chain defects

Defects of mtDNA
Mutations in genes affecting mitochondrial protein synthesis
(tRNA, rRNA, rearrangements)
Mutations in protein-coding genes
Multisystemic (LHON; NARP/MILS)
Tissue-specific (exercise intolerance/myoglobinuria)
Defects of nDNA
Mutations in genes encoding respiratory chain subunits
Complex I; Complex II
Mutations in genes encoding ancillary proteins
Complex IV (SURF1; SCO2; COX10; SCO1)
Defects of intergenomic signalling
mtDNA depletion
AR-PEO with multiple mtDNA deletions
(ARCO; MNGIE)
AD-PEO with multiple mtDNA deletions

Notes:
Abbreviations: LHON, Leber's hereditary optic neuropathy; NARP, neuropathy, ataxia, retinitis pigmentosa; MILS, maternally inherited Leigh syndrome; AR, autosomal recessive; AD, autosomal dominant; PEO, progressive external ophthalmoplegia; ARCO, autosomal recessive cardiomyopathy and ophthalmoplegia; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy.

Mitochondrial biogenesis and biochemistry

Mitochondria are ubiquitous in mammalian cells, their number varying from one cell type to another in accordance with the aerobic metabolic demands of the host tissue. Thus brain, skeletal muscle, and cardiac muscle have particularly high concentrations of mitochondria. Each mitochondrion contains 2–10 molecules of mtDNA. MtDNA is a circular, double-stranded molecule 16.6 kilobases in length (Fig. 120.1). It encodes two ribosomal RNAs (rRNA), 22 transfer RNAs (tRNA) and 13 proteins, all of

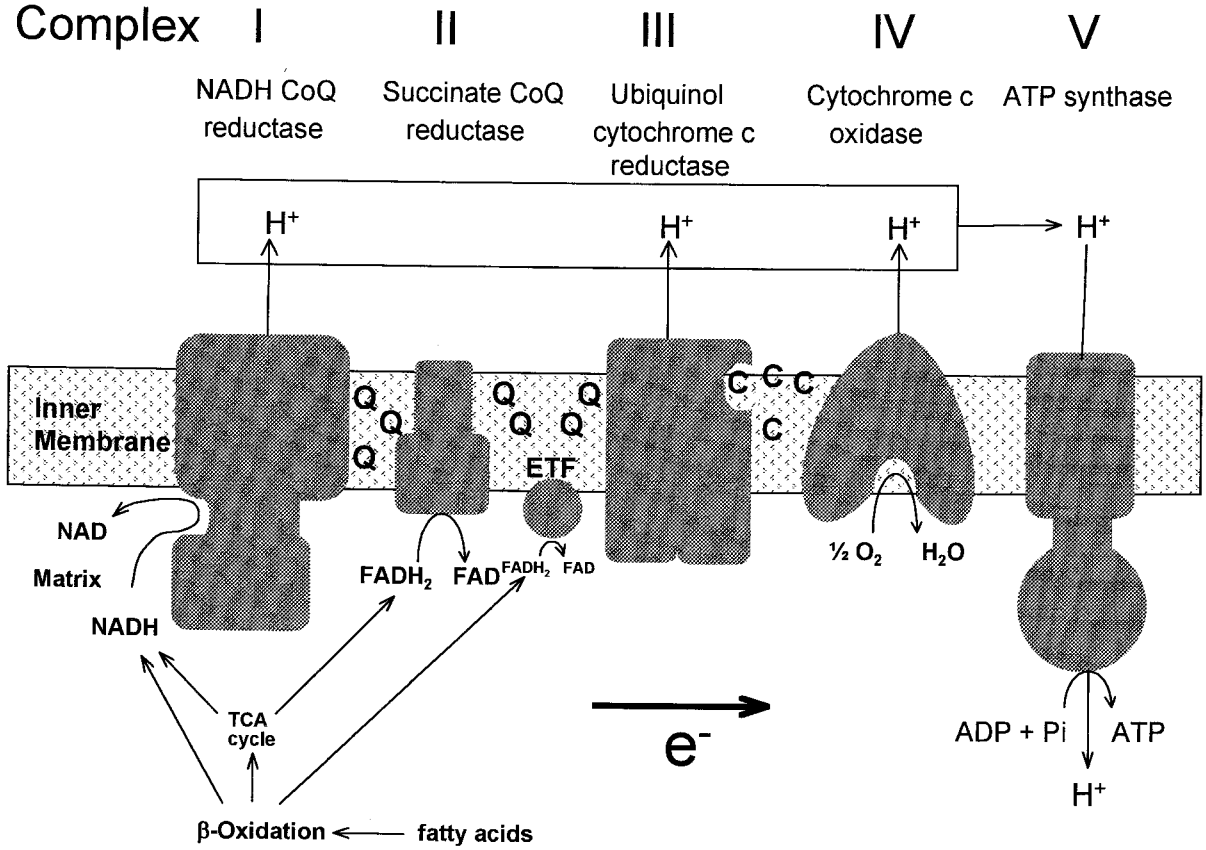

Fig. 120.1. The mitochondrial respiratory chain and oxidative phosphorylation system (NADH = the reduced form of nicotinamide–adenine dinucleotide; CoQ = ubiquinone; ATP = adenosine triphosphate; NAD = nicotinamide-adenine dinucleotide; TCA = tricarboxylic acid cycle; $FADH_2$ = the reduced form of flavin adenine dinucleotide; FAD = flavin adenine dinucleotide; ETF = electron transfer flavoprotein; e = electron; ADP = adenosine diphosphate; Pi = inorganic phosphate). (Reprinted with permission from Cooper & Clark, 1994).

them subunits of various complexes in the respiratory chain (Fig. 120.2). Mitochondria are slaves of the nucleus, and MtDNA is dependent upon nuclear encoded factors for its transcription, translation, replication and repair. The MITOX system comprises five multi-subunit complexes located in the inner mitochondrial membrane. Complex I is the largest of these and has seven subunits encoded by mtDNA. It is responsible for the reduction of NAD-linked substrates such as pyruvate, malate, glutamate and β-hydroxybutyrate and the passage of electrons to ubiquinone (coenzyme $Q_{10,}$ CoQ_{10}). Complex II, otherwise known as succinate dehydrogenase (SDH), is the only component of the MITOX system that is entirely encoded by nuclear genes and is not only part of the respiratory chain but also of the Krebs citric acid cycle. It is responsible for the reduction of FAD-linked substrates such as succinate and feeds reducing equivalents to ubiquinone. Cytochrome *b* is the only mtDNA-encoded subunit of complex III. This complex receives electrons from ubiquinone and shuttles these to complex IV (cytochrome oxidase) via cytochrome *c*. Cytochrome oxidase (COX) has three components encoded by mtDNA (COI, COII, COIII) and is responsible for the reduction of oxygen. Complexes I, III, and IV pump protons out across the inner mitochondrial membrane thereby creating an electrochemical gradient, which is used by complex V (ATPase) to generate ATP from ADP. The MITOX system therefore constitutes the most important component of oxidative phosphorylation, and mtDNA, in turn, devotes all its protein-coding genes to the production of subunits of this system. It is not surprising, therefore, that mutations in the mitochondrial genome result in deficits of oxidative phosphorylation and ATP production.

MtDNA is exclusively inherited through the maternal line. Thus, mtDNA is passed from the mother to all offspring and

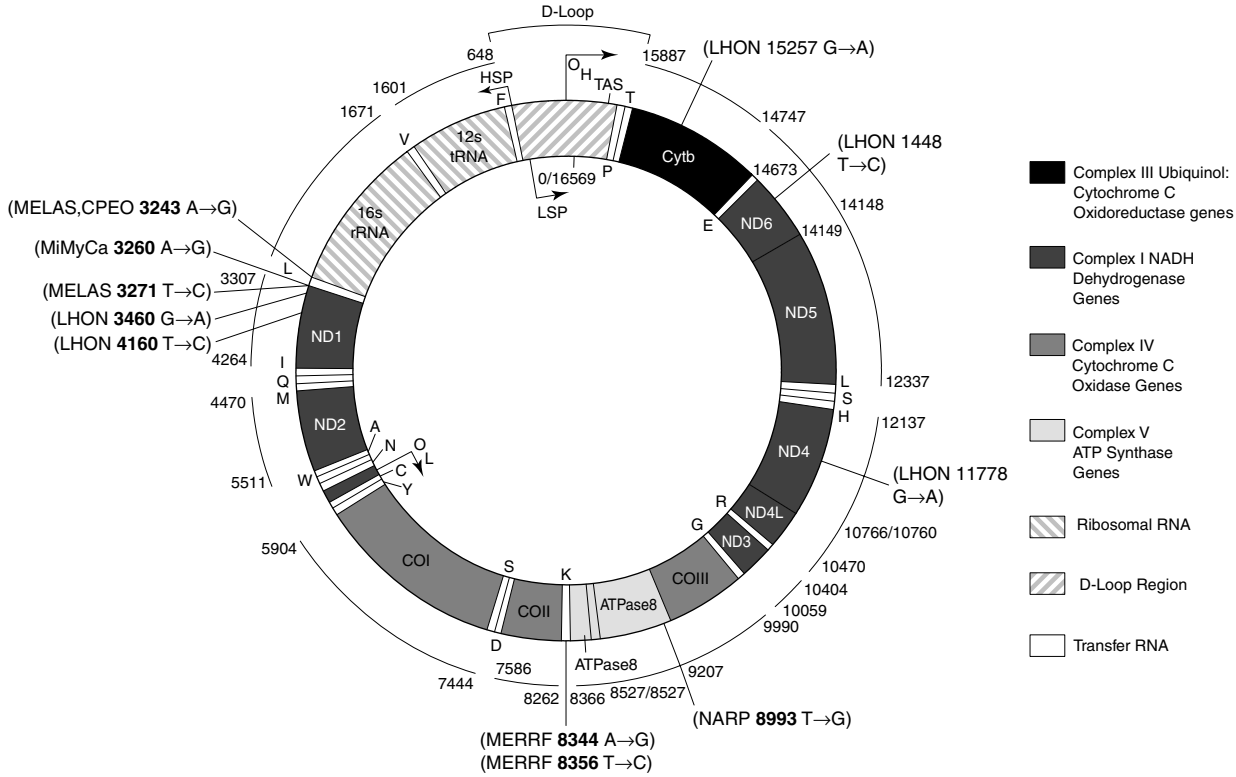

Fig. 120.2. Human mtDNA. O_H and O_L are the origins of heavy and light strand replication respectively. The more common mtDNA mutations associated with mitochrondrial encephalomyopathies are shown. (NADH = the reduced form of nicotinamide-adenine dinucleotide; ATP = adenosine triphosphate) (Reprinted with permission from Rahman & Schapira, 1999).

subsequently through the female line. Primary mtDNA mutations therefore exhibit maternal inheritance, although it is important to note that a maternal history is available in less than half of patients who are subsequently identified as having a mtDNA mutation. For instance, the vast majority of patients with single deletions in mtDNA manifest as sporadic cases, and only about 40% of patients with the G11778A mutation of mtDNA associated with Leber's hereditary optic neuropathy have a maternal history. The absence of such a history, particularly in patients with mtDNA point mutations, is usually either due to the development of a spontaneous mutation, or to the presence of oligosymptomatic family members. Secondary mutations of mtDNA can result from a primary nuclear mutation: these are multiple mtDNA deletions or mtDNA depletion. Multiple mtDNA deletions have been associated with autosomal recessively inherited myoneurogastrointestinal encephalopathy (MNGIE) and with autosomal dominant chronic progressive external ophthalmoplegia (CPEO) (see below).

Despite the wide variation of clinical manifestations of the mitochondrial disorders, the majority of patients can be grouped into one of a number of phenotypes according to their predominant features. Such grouping remains useful at both the clinical and, to some extent, the molecular genetic levels as there are broad generalizations that can be applied to such groups. Whilst such simplification is pragmatic, it must be recognized that a significant number of patients occupy 'overlap' syndromes. In addition, a given phenotype may be caused by a variety of molecular genetic mutations and a single mutation may give rise to a number of different phenotypes. In describing the main phenotypes of MITOX disorders, we will follow the genetic classification in Table 120.1.

Defects of mtDNA

Mutations in genes affecting mitochondrial protein synthesis

These include single mtDNA deletions (which always encompass one or more tRNA genes), and point mutations in rRNA or tRNA genes. These mutations are usually associated with multisystem disorders, lactic acidosis, and

massive mitochondrial proliferation resulting in the 'ragged-red' appearance of fibres in the muscle biopsy (Engel and Cunnigham, 1963). Histochemical studies have shown that RRFs react intensely with the succinate dehydrogenase (SDH) stain, but weakly or not at all with the cytochrome c oxidase (COX) stain. This is in agreement with the fact that SDH is entirely encoded by nDNA (and is therefore unaffected by mtDNA mutations), whereas 3 of the 13 subunits of COX are encoded by mtDNA.

Chronic progressive external ophthalmoplegia

Chronic progressive external ophthalmoplegia (CPEO) is probably the commonest manifestation of the mitochondrial myopathies. Patients may develop features from early to late adulthood and symptoms usually include slowly progressive bilateral, usually symmetrical ptosis and ophthalmoplegia involving all directions of gaze. Diplopia is relatively uncommon. Approximately 5–10% of patients may present with unilateral ptosis, around 66% have a salt and pepper retinopathy and 50% have an associated proximal limb myopathy characterized by muscle weakness and fatigue.

Kearns–Sayre syndrome (KSS) is a subset of CPEO, which involves the development of ptosis and ophthalmoplegia before the age of 20, together with the presence of a salt and pepper retinopathy and one of the following: cardiac conduction defect (heart block), elevated CSF protein or ataxia (Rowland, 1992). Additional encephalopathic features may most commonly develop in the KSS subgroup and include deafness and dementia. Seizures are distinctly uncommon and usually related to electrolyte disturbances, as may occur in hypoparathyroidism, one of several endocrine disorders often associated with KSS.

The prognosis for patients with CPEO and purely myopathic features is good. Life span is usually normal and clinical features translate to only mild or moderate functional disability. Such patients rarely become dependent on a wheelchair. The prognosis for patients with KSS is less good. Cardiac conduction defects are an important cause of death in these patients. Thus, regular cardiac evaluation may allow identification of patients in need of a pacemaker. Progression with the development of severe ataxia, diabetes mellitus, cognitive impairment and metabolic acidosis results in a shortened life-span with most patients not surviving beyond age 30.

Diagnosis is based upon the characteristic morphological features and the identification of mtDNA deletions in skeletal muscle. The great majority of patients with CPEO or KSS are sporadic. Males with a mtDNA deletion will not pass on the disorder. Mothers have a relatively low risk of passage to offspring, which is estimated at around 5%.

Accurate family history is important in the differential diagnosis of CPEO. Whereas sporadic cases are most likely due to single large-scale deletions of mtDNA, maternally inherited cases are usually attributable to the A3243G MELAS mutation in one of its several phenotypic variations (Moraes et al., 1993b), and, more rarely, to the A8344G MERRF mutation. About a dozen other point mutations in tRNA genes have been associated with CPEO, although many of these patients were sporadic and the mutations were identified only after Southern blot analysis excluded the presence of mtDNA rearrangements. The autosomal dominant and recessive forms of CPEO are described below.

Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)

The clinical features of MELAS may manifest at any age from early adolescence to late adulthood, although the great majority of patients present before age 40. The initial clinical presentation may involve myopathy or encephalopathy, an endocrine disturbance such as non-insulin dependent diabetes mellitus, or an oligosymptomatic feature such as sensorineural deafness. Acute presentations may involve seizures or stroke-like episodes causing hemianopia, hemianesthesia or hemiplegia. On examination, patients are frequently of short stature with generalized muscle thinning but no focal wasting. As mentioned above, ophthalmoplegia may be a presenting sign. The myopathy usually comprises a proximal muscle weakness with premature fatigue. There may be ataxia, cognitive impairment, and sensorineural deafness. Additional neurological deficits may relate to stroke-like episodes: in this setting, movement disorders, particularly dystonia, may occur.

In many patients, initial manifestation may be oligosymptomatic but they invariably progress to additional features typical of the full syndrome. Neurological problems may accrue as a consequence of stroke-like episodes. These appear particularly to involve the parieto-occipital region. MELAS is an important differential diagnosis in young-onset stroke. The progressive course of MELAS is punctuated by episodes often involving headache, nausea, vomiting, seizures and/or strokes, usually in association with lactic acidosis. Acute deterioration may occur in the context of intercurrent illnesses such as infection. Treatment is supportive, with appropriate and gradual correction of the acidosis (bicarbonate is commonly used but a double-blind trial of dichloroacetate is currently under way), and treatment of seizures with anticonvulsants, avoiding sodium valproate, if possible, due to its interaction with mitochondrial metabolism (Silva et al., 1997; Tein

et al., 1993). There have been anecdotal reports of patients with intractable seizures responding to steroids although the pathophysiological basis of this is unclear. Steroids, however, are not recommended in the long-term management of these patients.

The etiology of the stroke-like episodes remains unclear. They do not characteristically follow specific vascular territories. Abnormal mitochondria staining strongly positive for SDH have been observed in the endothelial cells of intracerebral small blood vessels. It is likely that the pathogenesis of these episodes involves abnormal vascular tone, decreased blood flow and abnormal oxidative metabolism resulting in an area of cerebral damage consequent upon both vascular and metabolic deficits.

The diagnosis of MELAS rests upon the clinical manifestations, supported by abnormal muscle morphology (characteristically, RRFs in patients with typical MELAS are COX-positive) and/or the identification of the relevant mitochondrial DNA mutation in blood or other accessible tissues (hair follicles, urinary sediment, cultured skin fibroblasts).

The prognosis for patients with MELAS depends upon the extent and severity of their tissue dysfunction. Life span is invariably shortened. The development of seizures and recurrent stroke-like episodes are poor prognostic indicators. Common causes of death include cardiopulmonary failure, status epilepticus, aspiration pneumonia or intestinal obstruction.

MELAS is usually due to a mtDNA point mutation, most frequently an A-to-G substitution at nt-3243 in the $tRNA^{Leu(UUR)}$ gene (Goto et al., 1990). However, a total of 11 point mutations (plus one microdeletion) have been associated with the MELAS phenotype: five of these are in the $tRNA^{Leu(UUR)}$ gene (Goto et al., 1991, 1994; Morten et al., 1993; Nishino et al., 1996), four in other tRNA genes (Hanna et al., 1998a; Manfredi et al., 1996; Nakamura et al., 1995; Taylor et al., 1996), and, rather surprisingly, two are in protein-coding genes (De Coo et al., 1999; Manfredi et al., 1995; Santorelli et al., 1995). Point mutations are invariably systemically distributed and the transmission rate of the most common mutation (A3243G) is relatively high, particularly when a woman has a high mutation load in blood (>40%).

Myoclonic epilepsy with ragged red fibres (MERRF)

The predominant clinical features of MERRF are myoclonus, ataxia and seizures. Myoclonus is often the presenting symptom and may be precipitated by action, noise or photic stimulation. However, these patients may also experience drop attacks, focal seizures and generalized tonic–clonic epilepsy. Skeletal muscle involvement is usually relatively mild. Some patients may have ophthalmoplegia and ptosis, deafness, sensorimotor axonal peripheral neuropathy and lipomas. Patients may manifest from early childhood to late adulthood.

The diagnosis of MERRF rests upon identification of the characteristic morphological changes in skeletal muscle biopsy and/or identification of a specific mtDNA mutation in blood or muscle.

Prognosis is intermediate between CPEO and MELAS. Seizures are controlled with standard anticonvulsant therapy, avoiding sodium valproate. As a generalization, there is a closer correlation between the level of mutation in muscle and clinical outcome in MERRF. The most frequent mutation identified is the A8344G in the $tRNA^{Lys}$ gene (Shoffner et al., 1990), but two other mutations in the same gene have been associated with MERRF (Ozawa et al., 1997; Shtilbahns et al., 2000; Silvestri et al., 1992). The proportion of mutation in the blood also gives some guide as to risk of transmission. Those mothers with <30% mutation have a <5% chance of transmission.

Leigh syndrome

Leigh syndrome (LS) most frequently presents in infancy or early childhood with generalized spasticity, somnolence, blindness and deafness. Progression is usually rapid and prognosis poor, particularly in the early-onset cases. Less severe forms of LS can involve hypotonia, failure to thrive, respiratory abnormalities, ophthalmoplegia, seizures and lactic acidosis.

Diagnosis is often suggested by neuroimaging, which demonstrates bilateral symmetrical abnormalities in the brainstem, including low T1, high T2 signal changes on magnetic resonance imaging.

Lactic acidosis is frequent. Changes on muscle biopsy are rarely typical of mitochondrial myopathy (there are no RRF, SDH-hyperintense, or isolated COX-negative fibres), but diffuse COX deficiency can be seen histochemically in patients with nuclear defects of complex IV. Mutations affecting both nuclear and mitochondrial genomes have been identified in LS. As mentioned above, the T8893G mutation, when present in high mutation load, may cause this disorder. Other mtDNA mutations in transfer RNAs have also been identified, including the common A8344G MERRF mutation (Howell et al., 1996; Santorelli et al., 1998), the rarer G8363A MERRF mutation (Shtilbahns et al., 2000), and the common A3243G MELAS mutation (Koga et al., 2000; Vilarinho et al., 1999). Nuclear gene mutations affecting subunits of complex I and complex IV are discussed below. The prognosis for LS is poor, with most infantile-onset cases dying in early childhood, and rare patients surviving beyond adolescence.

Table 120.2. Patients with pure myopathy (without ophthalmoplegia) and point mutations in tRNA genes of mtDNA

Gene	Base change	Clinical features	Family history	References
$tRNA^{Leu(UUR)}$	T3250C	Respiratory/SIDS	+	Goto et al. (1992); Ogle et al. (1997)
	A3302G	Respiratory	+	Bindoff et al. (1993)
	A3288G	Respiratory	+	Hadjigeorgiou et al. (1999)
$tRNA^{Pro}$	G15990A	Myopathy	−	Moraes et al. (1993a)
$tRNA^{Phe}$	T618C	Respiratory	+	Kleinle et al. (1998)
$tRNA^{Trp}$	G5521A	Ptosis	+	Silvestri et al. (1998)
$tRNA^{Met}$	U4409C	'Dystrophy'	−	Vissing et al. (1998)
$tRNA^{Leu(CUN)}$	A12320G	Ptosis	−	Weber et al. (1997)

Note:
SIDS = sudden infant death syndrome.

Cardiomyopathy

Cardiomyopathy may develop in many of the mitochondrial myopathies. Cardiac disease usually presents as conduction defects and is seen most frequently in KSS. However, isolated, usually hypertrophic cardiomyopathy has also been observed in patients with the A3243G MELAS mutation (Silvestri et al., 1998; Vilarinho et al., 1997), in patients with a variety of other tRNA mutations, especially involving $tRNA^{Ile}$ (DiMauro & Hirano, 1998), as well in patients with multiple mtDNA deletions (see below). A mutation in the 12S rRNA of mtDNA has also been identified in a family with maternally inherited cardiomyopathy (Santorelli et al., 1999). This mutation, A1555G, is also associated with aminoglycoside-induced deafness (Prezant et al., 1993).

Diabetes

Diabetes mellitus is a relatively frequent finding in patients with mitochondrial myopathy. Indeed, it is estimated that up to 1% of patients with non-insulin dependent diabetes mellitus are positive for the A3243G mutation (Kadowaki et al., 1994). As mentioned above, diabetes mellitus may be part of a multisystem involvement in mitochondrial disorders, for instance in MELAS and KSS. In addition, diabetes mellitus may occur in association with diabetes insipidus, optic atrophy and deafness (Wolfram's syndrome) and multiple mtDNA deletions (Barrientos et al., 1996). Diabetes mellitus may also occur in association with deafness alone (Remes et al., 1993; van den Ouweland et al., 1992).

Hematological disturbances

Besides CPEO and KSS, single mtDNA deletions can cause Pearson syndrome (PS), which is characterized by sideroblastic anemia and pancreatic failure (Rotig et al., 1990). This may be associated with diabetes mellitus, hepatic disease, de Toni Fanconi syndrome and lactic acidosis. Onset is usually in infancy and patients have single mtDNA deletions or duplications. These mutations are predominantly present in blood, but they are also systemically distributed throughout tissues. The great majority of cases are sporadic and most die in infancy or early childhood. Occasional survivors have been reported and interestingly these appear to develop features of KSS in later life (Larsson et al., 1990; McShane et al., 1991).

Myopathy

While mutations in tRNA genes are usually associated with multisystem disorders, in rare cases there is involvement of a single tissue, most commonly skeletal muscle. In Table 120.2, we have listed eight patients with pure myopathy, excluding progressive external ophthalmoplegia. It is noteworthy, and a useful diagnostic clue, that all three mutations in the $tRNA^{Leu(UUR)}$ affected preferentially respiratory muscles (Goto et al., 1992; Hadjigeorgiou et al., 1999; Ogle et al., 1997). It is also interesting that one such mutation was associated with dystrophic features in the muscle biopsy, although serum CK levels were normal (Vissing et al., 1998). Family history was negative in three of the eight patients with pure myopathy (Moraes et al., 1993a; Vissing et al., 1998; Weber et al., 1997), suggesting that the mutations in these patients occurred *de novo*. In most of the patients, the mutation was also present in blood or cultured skin fibroblasts, implying that the selective muscle involvement was due to 'skewed heteroplasmy', with preferential accumulation of the pathogenic mutation in skeletal muscle. In one patient, however, there was no evidence of the mutation in blood cells, cultured fibroblasts or cultured muscle, suggesting that this was a 'somatic mutation', which arose during embryogenesis in myogenic stem cells after germ-layer differentiation (Weber et al., 1997).

Exercise intolerance is a common complaint in patients with mitochondrial encephalomyopathies, but it is often overshadowed by other symptoms and signs. Only recently have we come to appreciate that exercise intolerance, myalgia, and myoglobinuria can be the sole presentation of respiratory chain defects. These are most commonly caused by mutations in protein-coding genes and are discussed below.

Mutations in protein-coding genes

Leber's hereditary optic neuropathy (LHON)

LHON is characterized by acute or subacute loss of vision with onset usually between 18 and 30 years and marked predominance in men. Typical ophthalmoscopic features are circumpapillary telangiectatic microangiopathy and pseudoedema of the optic disk. Associated features may include hyperreflexia, cerebellar ataxia, peripheral neuropathy, or cardiac conduction anomalies (pre-excitation syndrome).

Laboratory tests may show mild lactic acidosis and muscle biopsy is usually normal.

LHON is associated with three main mutations in complex I (NADH dehydrogenase, or ND) genes: G11778A in ND4 (Wallace et al., 1988), G3460A in ND1 (Huoponen et al., 1991), and T14484C in ND6 (Johns et al., 1992).

Neurogenic weakness, ataxia and retinitis pigmentosa (NARP)

The key features of NARP are peripheral neuropathy, ataxia and retinitis pigmentosa, often accompanied by seizures and dementia. Maternal inheritance is usually ascertainable.

Muscle biopsy may reveal neurogenic features but RRF and the other classic morphological changes of mitochondrial myopathy are not present. Diagnosis rests upon recognition of the clinical syndrome and lactic acidosis, when present. The most frequent mtDNA mutation causing NARP is the T8893G mutation in the ATPase 6 gene of complex V (Holt et al., 1990). The mutation is present in blood and the mutation load is usually >70%. When >90%, this mutation is most frequently associated with Leigh syndrome (Tatuch et al., 1992).

Prognosis is variable and there is perhaps a closer correlation with mutation load in the blood than in other mitochondrial disorders (White et al., 1999b). This also relates to the risk of transmission where rates are high with high mutation loads in the blood. Prenatal diagnosis has been performed in mothers with NARP, and fetuses aborted when a high mutation load has been identified in chorionic tissue (Harding et al., 1992; White et al., 1999a).

A milder phenotype often associated with the neuroradiological features of bilateral striatal necrosis (BSN) is associated with a T-to-C instead of a T-to-G mutation at the same nucleotide, 8993, of the ATPase 6 gene (De Meirleir et al., 1995; Santorelli et al., 1992).

Other encephalomyopathies

As mentioned above, three mutations in protein-coding genes were associated with the MELAS phenotype, one in the COX III gene (Manfredi et al., 1995), another in the ND5 gene (Pulkes et al., 1999; Santorelli et al., 1997), and the third in the cyt *b* gene (De Coo et al., 1999).

Besides the COX III gene mutation in the patient with MELAS, other mutations in COX genes have been associated with encephalomyopathies. A 5-bp microdeletion in the COX I gene was found in a 32-year-old man with early-onset motor neuron disease and a negative family history (Comi et al., 1998). A 36-year-old woman with exercise intolerance, proximal myopathy, lactic acidosis, and episodes of confusion after exercise had a stop-codon mutation in the COX III gene (Hanna et al., 1998b). A mother and son suffered from a multisystem disorder dominated by ataxia, dementia, optic atrophy, and pigmentary retinal degeneration: they harboured a heteroplasmic missense mutation in the COX II gene (Clark et al., 1999). A 22-year-old woman had a stormy lifelong clinical course characterized by sensorineural hearing loss, cataracts, myoclonic epilepsy, weakness, ataxia, and visual loss. Alone in her family, she harboured a heteroplasmic nonsense mutation in the COX I gene (Bruno et al., 1999).

Symmetrical lesions in the putamina, reminiscent of Leigh syndrome, were seen in an 11-year-old girl with spastic paraparesis, ophthalmoparesis, and mental retardation. She had a frame-shift mutation in the COX III gene and a negative family history (Tiranti et al., 2000).

Myopathy

Exercise intolerance (without myoglobinuria) was the predominant clinical feature in two sporadic patients with *complex I deficiency* and COX-positive RRF in their muscle biopsies. One had a nonsense mutation (G11832A) in the ND4 gene (Andreu et al., 1999b), the other (Bet et al., 1990) had an intragenic inversion of seven nucleotides within the ND1 gene, resulting in the alteration of three amino acids (Musumeci et al., 2000).

Nine patients with isolated *complex III deficiency* in muscle complained of exercise intolerance, but only two had myoglobinuria (Andreu et al., 1999a; DiMauro, 1999). All patients in whom muscle histochemistry was performed showed COX-positive RRF. The nine mutations in

Table 120.3. Mutations in nuclear DNA associated with respiratory chain defects

Complex	Gene	Clinical Features	References
I	NDUFS4	LS	van den Heuvel et al. (1998)
I	NDUFS7	LS	Triepels et al. (1999)
I	NDUFS8	LS	Loeffen et al. (1998)
I	NDUFV1	Leukodystrophy/Myoclonic epilepsy	Schuelke et al. (1999)
I	NDUFS4	LS-like	Petruzzella et al. (2001)
II	SDHA	LS	Bourgeron et al. (1995), Parfait et al. (2000)
IV	SURF1	LS	Zhu et al. (1998), Tiranti et al. (1998)
IV	SCO2	Cardioencephalomyopathy	Papadopoulou et al. (1999)
IV	COX10	Nephroencephalomyopathy	Valnot et al. (2000a)
IV	SCO1	Hepatoencephalomyopathy	Valnot et al. (2000b)

the cytochrome *b* gene were different from one another although, except for a single deletion, they were all G-to-A transitions. Most patients had no detectable mutant mtDNA in blood or fibroblasts, but one patient had low levels (0.7%) mutation in non-muscle tissues, suggesting skewed heteroplasmy (Keightley et al., 2000). Two other patients had pathogenic mutations in the cytochrome *b* gene. One was a 20-year-old man with signs of Parkinsonism and MELAS and an apparently *de novo* microdeletion (De Coo et al., 1999). The other was an infant girl who died of histiocytoid cardiomyopathy and in whose muscle complex III deficiency and decreased concentration of reducible cytochrome *b* had been documented (Papadimitriou et al., 1984). Molecular analysis has now revealed a missense mutation (G15498A) in the cytochrome *b* gene (Andreu et al., 2000).

The first mtDNA molecular defect identified in a patient with *complex IV (cytochrome c oxidase, COX) deficiency* was a 15-bp microdeletion in the COX III gene. The patient was a 16-year-old woman with recurrent myoglobinuria triggered by prolonged exercise or viral illness (Keightley et al., 1996). Between attacks, both physical and neurological exams were normal, as were routine laboratory tests, including serum creatine kinase (CK) and lactate. No tissue other than muscle was affected, and family history was entirely negative. Muscle biopsy showed many SDH-positive, COX-negative RRF and marked isolated COX deficiency. A nonsense mutation (G5920A) in the COX I gene of muscle mtDNA was identified in a 34-year-old man with lifelong exercise intolerance and recurrent myoglobinuria induced by intense or repetitive exercise (Karadimas et al., 2000). His muscle biopsy showed scattered COX-negative RRF and numerous COX-negative non-RRF, and isolated COX deficiency. The mutation was not present in blood or fibroblasts from the patient nor in blood from his asymptomatic mother and sister. Proximal weakness without myoglobinuria characterized the clinical picture of a 14-year-old boy with a missense mutation in the COX II gene: no one else in his family was similarly affected (Rahman et al., 1999).

Defects of nDNA

Leigh and Leigh-like syndromes

Considering that most proteins of the respiratory chain are encoded by nDNA and that proper assembly and functioning of respiratory chain complexes requires multiple ancillary nDNA-encoded factors, this relatively new area of investigation promises to yield exciting results. This prediction is borne out by the number of recent papers on the subject (Table 120.3). Most of the patients described thus far have had early-onset, multisystemic disorders that almost invariably involved the brain and often had the neuroradiological and neuropathological stigmata of LS (see above). This is not too surprising when we consider that two of the commonest causes of LS are complex I deficiency and complex IV (COX) deficiency, both inherited as autosomal recessive traits (DiMauro & De Vivo, 1996). The early onset of these disorders also comes as no surprise, as nuclear defects tend to be 'all-or-none', with very little residual activities of affected enzymes but sufficiently high residual activities in heterozygotes as to prevent disease expression in carrier patients or siblings. This contrasts with the 'rheostat effect' of heteroplasmy in mitochondrial genetics. For example, in NARP/MILS, almost homoplasmic levels of the T8993G mutation in the ATPase 6 gene of mtDNA cause LS, whereas slightly lower mutation loads (around 70%) cause the later-onset and milder NARP syndrome (see above).

Mutations in genes encoding respiratory chain subunits

Mutations have been identified in genes encoding subunits of complex I and complex II, but not (at least, not yet) in genes encoding subunits of complex III or complex IV.

The strategy used by the University of Nijmegen group to facilitate the identification of pathogenic mutations in the 'mare magnum' of the 34 nDNA-encoded subunits of complex I was to focus on those that have homologues in the much simpler complex I of yeast. In short order, they identified seven different mutations. Three of these affected NDUFV subunits in children with leukodystrophy and myoclonic epilepsy (Schuelke et al., 1999). The other four were found in families with autosomal recessive LS and involved NDUFS subunits (Loeffen et al., 1998; Triepels et al., 1999; van den Heuvel et al., 1998). A fifth mutation in the NUDFS4 gene was reported in a child with Leigh-like syndrome and cardiomyopathy (Petruzzella et al., 2001).

Complex II is composed of two subunits, both encoded by the nuclear genome. The first mutation in a nDNA-encoded respiratory chain protein was reported in 1995 in two sisters with LS: it affected the flavoprotein subunit of complex II (Bourgeron et al., 1995). Two more mutations, also affecting the flavoprotein subunit, were identified in a compound heterozygous patient with LS (Parfait et al., 2000).

Mutations in genes encoding ancillary proteins

Thorough searches for mutations in nuclear genes encoding COX subunits were fruitless (Adams et al., 1997; DiMauro et al., 1994). However, defects of COX have been associated with mutations in COX-assembly genes, in a sort of 'murder-by-proxy' mechanism. In yeast, there are at least 30 different complementation groups for COX assembly (Tzagoloff et al., 1975). Several of these genes have mammalian homologues (Petruzzella et al., 1998), and mutations in four of them have been identified in patients with COX deficiencies.

Numerous mutations were initially found in the *SURF1* gene (Tiranti et al., 1998; Zhu et al., 1998), which encodes a protein apparently involved in the early stages of COX assembly (Zeviani et al., 2000). Mutations in *SURF1* appear to be the most common cause of COX-deficient LS, although the frequency varies widely in different series (Sue et al., 2000) and remains to be established.

The second COX-assembly gene associated with COX deficiency and encephalomyopathy was *SCO2* (Papadopoulou et al., 1999). The SCO2 protein is required for the insertion of copper into the mtDNA-encoded subunits COX I and COX II, and mutations in *SCO2* are associated not with typical LS, but, rather, with hypertrophic cardiomyopathy and encephalopathy manifesting soon after birth (Jaksch et al., 2000; Papadopoulou et al., 1999; Sue et al., 2000). Comparative biochemical and histochemical studies showed that COX deficiency in muscle is more severe with *SCO2* than with *SURF1* mutations, whereas the opposite is true for COX deficiency in fibroblasts (Sue et al., 2000).

Mutations in the *COX10* gene have been associated with neurological features (hypotonia, myopathy, ataxia, seizures) and renal proximal tubulopathy (Valnot et al., 2000b). *COX10* encodes a heme A: farnesyltransferase that catalyses the conversion of protoheme to heme O. Heme O, in turn, is the precursor of heme A, which is the prosthetic group of the COX I subunit.

The latest COX-assembly culprit gene is *SCO1*: two mutations have been identified in a large family with fatal infantile hepatic failure and encephalopathy (Valnot et al., 2000a). This is an interesting counterpart to the clinical picture associated with *SCO2* mutations, where brain was also involved, but heart rather than liver was the 'target' organ. Both *SCO1* and *SCO2* genes are involved in copper insertion into the holoenzyme: the apparent 'tissue specificity' of mutations in each gene remains to be confirmed in more patients but raises interesting questions about differential tissue expression of distinct COX-assembly genes.

Although mutations have already been discovered in four COX-assembly genes, many patients with COX deficiency, manifesting as LS or as other multisystemic syndromes remain unexplained at the molecular level (Horvath et al., 2000; Sue et al., 2000). Based on recent developments, it seems safe to predict that many more mutations will be identified in the near future both in already known and in as yet unrecognized COX-assembly genes.

As mentioned above, no mutations have yet been described in nuclear genes encoding subunits of complex III, complex IV, or complex V. It has been suggested that mendelian, 'all-or-none', mutations might not be compatible with life because these complexes are arranged 'in series', with no alternative pathway. In contrast, mutations in subunits of complex I or complex II may be better tolerated because these complexes are arranged 'in parallel', both feeding electrons to CoQ10 (Sue & Schon, 2000).

Defects of intergenomic signalling

The dependence of the mitochondrial genome renders it vulnerable to defects in nuclear encoded proteins responsible for its replication and maintenance. Both autosomal dominant and autosomal recessive disorders associated with multiple mtDNA deletions have been described. In

addition, a quantitative defect of mtDNA (mtDNA depletion) has also been reported.

Mitochondrial DNA depletion: myopathy, hepatopathy and multisystem disorders

Onset of myopathy can be at or soon after birth, sometimes associated with renal dysfunction ('congenital myopathy'), or develop at about one year of age ('infantile myopathy') (Hirano & Vu, 2000; Moraes et al., 1991). There is lactic acidosis and serum creatine kinase is often elevated, an unusual feature of most other mitochondrial myopathies. Muscle biopsy may show RRF but most frequently is characterized by COX-negative fibres. It is important to remember that initial biopsies in children with infantile myopathy may show non-specific changes and mitochondrial abnormalities may become apparent only in later biopsies. Immunohistochemistry using anti-DNA antibodies has demonstrated reduced levels of mtDNA. Biochemical analysis usually demonstrates multiple respiratory chain defects. Cultured myoblasts from patients with mtDNA depletion may demonstrate this defect and this is most readily documented by immmunocytochemistry. Decreased mtDNA levels are identified by Southern blotting and comparison with an age-matched control tissue. Prognosis is poor, although patients with only moderate mtDNA depletion (>30% residual mtDNA) may survive and develop normally with resolution of the mtDNA depletion.

Hepatopathy can coexist with myopathy in the same family (Boustany et al., 1983; Moraes et al., 1991). It usually presents during the first year of life and progresses rapidly to intractable liver failure. Liver biopsies show mitochondrial proliferation and multiple respiratory chain defects.

The nuclear origin of mtDNA depletion has been documented in one patient whose enucleated fibroblasts were fused with a human cell line lacking mtDNA (rho^0). The resulting cybrids regained normal mtDNA concentration and respiratory chain function, showing that the nucleus of the rho^0 cell line had replaced the defective factor (or factors) in the mtDNA depleted cells (Bodnar et al., 1993). The molecular genetic defect in mtDNA depletion syndrome has not as yet been identified. It is likely however that, similar to Leigh's syndrome, the etiology of mtDNA depletion syndrome will prove to be heterogeneous at the molecular level.

Autosomal dominant CPEO syndrome

This was first described in an Italian pedigree which exhibited early adult onset of CPEO, ptosis, facial and limb weakness, bulbar symptoms, cataracts and early death (Zeviani et al., 1989). Additional families were described with features that included cardiomyopathy, neuropathy and ataxia. Lactic acidosis was common. Muscle biopsy demonstrated ragged-red and COX-negative fibres (Servidei et al., 1991). Three separate loci were identified on chromosomes 3, 4 and 10 (Kaukonen et al., 1996, 1999; Li et al., 1999; Suomalainen et al., 1995). However, the locus on chromosome 3 was recently excluded upon re-examination of the one small family on which it was based (Kaukonen et al., 2000). The chromosome 10-linked disease is due to a mutation in the adenine nucleotide translocator 1, which exchanges ADP and ATP across the inner mitochondrial membrane (Kaukonen et al., 2000). ANT-1 knockout mice developed a severe cardiac and skeletal myopathy (Graham et al., 1997). All gene loci have been associated with multiple mtDNA deletions.

Autosomal recessive cardiomyopathy/ophthalmoplegia (ARCO)

The association of CPEO and severe cardiomyopathy (requiring cardiac transplantation) has been reported in two families from the eastern area of the Arabian peninsula (Bohlega et al., 1996). One family was consanguineous. Muscle biopsies showed ragged-red COX-negative fibres, multiple respiratory chain enzyme defects, and multiple mtDNA deletions by Southern blot. The molecular etiology of ARCO remains unknown.

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)

This is an autosomal recessive disorder characterized by peripheral neuropathy, CPEO and gastrointestinal dysmotility (Bardosi et al., 1987; Hirano et al., 1994). Gastrointestinal symptoms may include recurrent nausea, vomiting and diarrhea and may result in cachexia. Onset is usually in late adolescence or early adulthood. Patients may have lactic acidosis. Muscle biopsy demonstrates ragged-red, COX-negative fibres against a background of neurogenic changes. Biochemical analysis demonstrates multiple respiratory chain defects, and mtDNA analysis demonstrates both multiple deletions and depletion. MNGIE is due to mutations in the thymidine phosphorylase gene and is associated with a severe reduction in the activity of this enzyme (Nishino et al., 1999, 2000). Consequently plasma thymidine levels are high. It has been suggested that an imbalance in the mitochondrial deoxynucleotide pools may result in impaired replication of mtDNA.

Investigations

As gleaned from the description of individual disorders, the laboratory investigation of patients suspected of

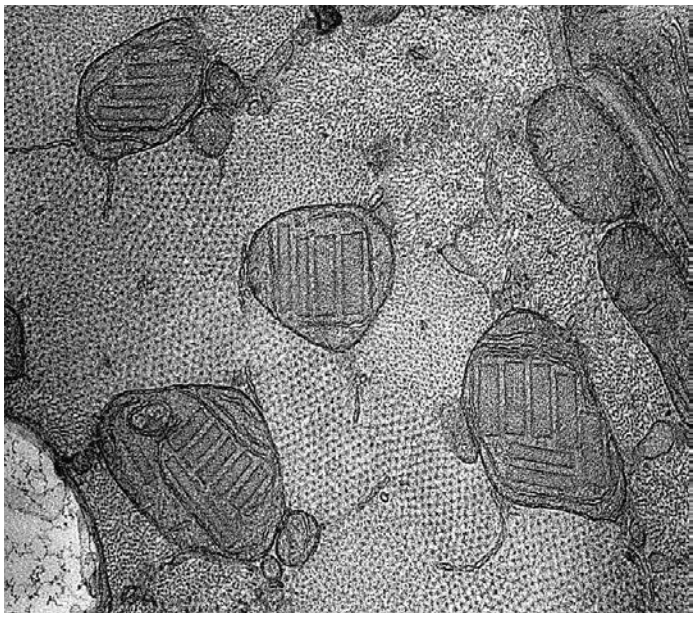

Fig. 120.4. Electron microscopy of a muscle biopsy from a patient with mitochondrial myopathy showing intramitochondrial paracrystalline inclusions.

having mitochondrial disorders includes hematological, biochemical, neurophysiological, radiological, morphological and molecular genetic analysis.

Hematological abnormalities are usually confined to the presence of sideroblastic anemia in Pearson syndrome. Routine biochemical investigations may demonstrate an elevated glucose in patients with diabetes mellitus. Appropriate endocrinological investigations are indicated in these cases and when thyroid or parathyroid abnormalities are suspected. Serum creatine kinase may be normal or modestly elevated, except in children with mtDNA depletion myopathy.

A resting lactic acidosis should raise suspicions of an underlying mitochondrial defect. If a patient is suspected of having a mitochondrial disorder but has a normal resting lactic acid level, he/she should undergo exercise testing, which may elevate the lactate level and also increase the lactate/pyruvate ratio. Increased lactate (and lactate/pyruvate ratios) in the CSF may be present in patients with CNS involvement, even when blood lactate is normal.

Nerve conduction studies may demonstrate a sensorimotor axonal peripheral neuropathy. Electromyography may be normal or show myopathic changes. Visual-evoked potentials may be abnormal in patients with optic atrophy and electroretinograms are abnormal in the majority of patients with pigmentary retinopathy. Electroencephalography may show a variety of abnormalities including epileptiform discharges and generalized slow waves indicative of an underlying encephalopathy.

Muscle biopsy is probably the most sensitive guide to the diagnosis of mitochondrial myopathy. The morphological hallmark of these disorders is the RRF. This is observed with the modified Gomori trichrome stain in which abnormal fibres exhibit central and peripheral accumulation of red staining material denoting increased aggregation of mitochondria. These same fibres stain strongly positive for SDH. This histochemical stain is more sensitive in detecting RRFs (Fig. 120.3(*a*), (*b*), see colour plate section). The SDH-positive fibres are often negative for COX staining in patients with mitochondrial DNA mutations affecting protein synthesis (Fig. 120.3(*c*), see colour plate section), except for the MELAS mutation (see above). Strongly SDH-positive fibres are also COX-positive in patients with protein-coding mtDNA mutations, except, of course, for mutations in COX genes. There may be a coexisting lipid storage myopathy due to carnitine deficiency, which may be secondary to the MITOX abnormality. Neurogenic changes may be seen in patients with a motor neuropathy. Electron microscopy may demonstrate intramitochondrial inclusions (Fig. 120.4).

The morphological changes, although sensitive in the diagnosis of mitochondrial myopathy, are not specific. Some patients may have a normal muscle biopsy but subsequently be shown to have abnormal biochemistry and mutations in mtDNA or nDNA. In particular, most patients with LS have normal muscle biopsies, including those with pyruvate dehydrogenase (PDH) deficiency, complex I deficiency, complex IV deficiency (except by COX histochemistry), and those with maternally inherited LS (MILS). On the other hand, scattered SDH-positive COX-negative fibres may be seen in patients over the age of 40 and can represent up to 5% of fibres in old age (Johnston et al., 1995). These mitochondrial changes are also observed in polymyositis and inclusion body myositis (IBM) (Santorelli et al., 1996).

The function of the mitochondrial respiratory chain and oxidative phosphorylation system may be analysed either in mitochondria freshly isolated from skeletal muscle or alternatively on muscle homogenates. The use of isolated mitochondria allows the application of polarography to assess oxygen consumption in response to specific substrates. This may allow a respiratory chain defect to be defined down to the individual complex. Individual respiratory chain enzyme assays on mitochondria or muscle homogenates may likewise enable individual respiratory chain complex deficiencies to be identified. More frequently, however, combined respiratory chain defects are

seen, particularly involving complexes I and IV. These combined deficiencies are often seen in mutations affecting mitochondrial protein synthesis as a whole, i.e. single or multiple deletions of mtDNA, mutations in tRNA or rRNA mtDNA genes and mtDNA depletion.

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Part XVII

Neurological manifestations of systemic conditions

121

Neurological aspects of pregnancy

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Introduction

Pregnancy often modifies the clinical expression of neurological disease. It also introduces concerns regarding the safety of treatment of the mother on the developing fetus. Management of problems of the central and peripheral nervous system (whether major or minor), therefore present the treating clinician with particular challenges.

This chapter will review some of the more important neurological diseases modified by, or affecting, pregnancy and some entities exclusively seen in pregnancy. A comprehensive review is beyond the scope of this chapter. The interested reader can consult a text on this subject (see references).

Sex differences in regional brain structure and function

Several mammalian and avian species have significant gender differences in brain morphology and connectivity, although the study of humans shows more subtle gender differences. Principal among them, are the findings on neuroimaging of the relatively larger callosal isthmus in females, and the decreased lateralization of brain activation in females measured by fMRI during phonological processing of particular tasks (Shaywitz et al., 1995; Witelson, 1991). Studies have only begun to appreciate the effects of sex and age on the differences of brain structure, and future studies with functional imaging may reveal other differences.

The effect of ovarian hormones on the nervous system

During menstruation and pregnancy, the nervous system is exposed to different absolute and relative levels of estrogen and progesterone. In the brain, estrogen may have both trophic and transmitter roles with receptors being present in the CA 1 and CA 3 regions of the hippocampus, locus ceruleus, raphe nuclei, central grey matter and cingulate gyrus, but even more so in the preoptic region. Estrogen can induce new NMDA-mediated synapse formation and dendritic spine formation particularly in the limbic system, magnified by the presence of progesterone (McEwen et al., 1997). Estrogen also induces choline acetyl transferase in the basal forebrain cholinergic regions and their secondary projections (Luine, 1985). Progesterone often appears to have an opposite effect on neuronal systems.

These hormones may influence the clinical expression of neurological problems such as migraine, epilepsy, brain tumours, autoimmune diseases and neuromuscular diseases. Accurately predicting how a particular disease will be clinically modified by hormones, or basing therapy on these presumed changes, remains in its infancy.

Migraine

Women have migraine more frequently than men by a factor of up to 3: 1 (Stewart et. al., 1992) with a peak incidence in those of childbearing age. Curiously, a high proportion of women become migraine-free during pregnancy, beginning in the third to fourth month of pregnancy (Vinken & Bruyn, 1968). Patients with catamenial migraine exacerbations are most likely to improve (Ratinahirana et al., 1990), particularly during the third and fourth trimester of pregnancy. About 50% show significant improvement (Maggioni et al., 1995), and about a sixth may report complete remission (Granella et al., 1993), possibly associated with the elevation of estrogen levels. Conversely, in some series, about a quarter of women fail to improve,

and several per cent may worsen (Somerville, 1972). There is no increased risk of complications from migraine during pregnancy, such as eclampsia, miscarriage or abortion, and children have no increased incidence of birth defects.

After birth, headaches may return within the first week, possibly due to withdrawal of estrogen and progesterone (Stein, 1981). Breast-feeding occasionally alleviates migraine. This is thought to be due to an effect of oxytocin on cerebral vasculature (Dooling & Sweeney, 1974).

Differential diagnosis

Since migraine typically improves after the first trimester, worsening, or severe headache persisting into the third trimester may signal a less benign process. Other causes of headache include tumours, intracranial hemorrhage, cerebral venous occlusion, and eclampsia. Pituitary tumours, meningiomas, choriocarcinoma tend to grow rapidly during pregnancy. Occlusive arterial disease peaks in the puerperium, presenting with migraine-like vision changes and worsening headache.

Investigation

With a history of typical migraine, laboratory and radiological investigation are rarely needed during pregnancy. Only with new onset, severe headache, particularly with neurological findings on clinical examination, or a sudden change in the chararacter of headache, should radiological testing be considered. Danger to fetal development is less after the first two trimesters of pregnancy. With head CT scanning, radiation exposure to the fetus is about 2 mrad. Scanning can be used to look for mass lesions or intracranial blood in the appropriate clinical context. Although the safety of head MRI during pregnancy has not been established, there are few data to suggest that it poses a significant fetal risk. With open MRI, previous restrictions on body size have been minimized.

Treatment

Identifying and removing trigger factors, psychophysiological techniques, and relaxation provide an alternative to pharmacotherapy. Drugs should be used when only absolutely necessary as many medications have teratogenic risk. Drugs should be particularly avoided in the first trimester and used only when absolutely necessary at their minimal effective doses. In the acute attack, acetaminophen, meperidine, dimenhydrinate and prednisone are regarded as safe, as may possibly be codeine and prochlorperazine (Koren et al., 1998). For prophylaxis, some regard propranolol as relatively safe, but the safety of amitriptyline and fluoxetine are less established. Most prophylaxis agents are in category 'C'. Low doses of beta-adrenergic blockers, valproic acid (Depakote®), serotonin reuptake inhibitors, tricyclic antidepressants, calcium channel blockers and gabapentin (Neurontin®) have been used safely particularly in late months of pregnancy, but there are reports of fetal and neonatal toxicity. Some beta-adrenergic blockers such as nadolol (Corgard®) and atenolol (Tenoretic®) have been reported to retard growth. With regard to tricyclic antidepressants, amitriptyline (Elavil®), nortriptyline (Aventyl®) and imipramine (Tofranil®) are in category 'D', because of reports of fetal malformations. Valproic acid (Depakote®; Depakene®) poses a risk for neural tube defects of 1% to 2%. The teratogenic risk for gabapentin (Neurontin®) is not known. Calcium channel blockers such as verapamil have not been reported to be teratogenic in animals; nonetheless most are in category 'B' and 'C'. The SSRI fluoxetine (Prozac®) poses a minor risk for anomalies and premature labour. However, five studies involving more than 450 pregnancies have shown no risk for birth defects (Robert, 1996). Nonsteroidal anti-inflammatory drugs (NSAIDs) are believed to be safe during the first two trimesters of pregnancy, but concerns that they may decrease the volume of amniotic fluid, or increase bleeding, limits their use during the third trimester. There are concerns about the use of indomethacin: after 32 weeks gestation, indomethacin may increase closure of the ductus arteriosus in the developing fetus, as well as reducing urine production. Although Fiorinal® which contains butalbital has an FDA safety category 'C' for pregnancy, the barbiturate butalbital may lead to neonatal barbiturate withdrawal problems, usually if the medication has been used for an extended period of time. For more severe headaches, narcotics are safe if used for brief periods. Codeine taking during the first two trimesters has been associated with hip dislocation, cleft palate, cardiopulmonary defects and inguinal hernias (Briggs et al., 1994) and is also FDA category 'C'. Propoxyphene may also be teratogenic. Most other narcotics are FDA category 'B'. Ergot alkaloids are contraindicated in pregnancy because of their effect on vasculature and consequent risk for abortion. To help abort migraine, antiemetic drugs have also been given in combination with NSAIDs. Medications in category C such as prochlorperazine (Compazine®), metoclopramide (Reglan®), or chlorpromazine (Thorazine®), are generally regarded as being safe if used occasionally and in low doses. Table 121.1 shows the FDA and TERIS risk categories for drugs taken during pregnancy. Table 121.2 shows medications for headache used in pregnancy.

Table 121.1. FDA and TERIS risk categories

FDA risk categories	TERIS risk rating	
Category A Controlled human studies show no risk	N	None
Category B No evidence of risk in humans, no controlled human studies	N-Min	None–minimal
Category C Risk to humans has not been ruled out	Min-S	Minimal–small
Category D Positive evidence of risks to humans from human and/or animal studies	S	Small
	S-Mod	Small–moderate
Category X Contraindicated in pregnancy	Mod	Moderate
	H	High
	U	Undetermined

Source: Adapted from Silberstein S. (1998). Remodelled with permission from Demos, New York, NY.
FDA, Food and Drug administration, USA; TERIS, a consensus assessment of known or suspected teratogens. (See Friedman & Polifka, 1994.)

Cerebrovascular diseases

The largest recent study of stroke during pregnancy is the Baltimore–Washington Cooperative Stroke Study, examining all strokes in women of child-bearing age in the region (Kittner et al., 1996). Comparing stroke and pregnancy with the first 6 weeks postpartum, the authors found a 2.5-fold increase in stroke during pregnancy and the postpartum period. Although ischemic stroke did not increase during pregnancy, it was nine times as likely in the first 6 weeks postpartum. This contrasts with a 2.5-fold increase in intracerebral hemorrhage (ICH) during pregnancy, but a 28-fold increase in the first 6 weeks postpartum. Thus, the overall stroke risk during this period is 8.1 per 100 000 pregnancies. These data are similar to those from the French study (Sharshar et al., 1995) which contained a greater number of women with eclampsia, and inclusion of African–Americans in the US study vs. predominantly Caucasians in the French study.

Looked at another way, a third of all strokes in women of child-bearing age are related to pregnancy, and 25% occur in the first week postpartum (Bickerstaff, 1975). Some studies show an incidence of one ischemic stroke per 3000 pregnancies (ten times the risk of young non-pregnant women) (Wiebers & Whisnant, 1985), but most occur in women younger than 30 years. The oral contraceptive pill increases the chance of ischemic stroke (Vessey & Doll, 1968). Patients, however, are mostly over 30 years of age, usually smoke cigarettes, and may have hypertension, diabetes and lipid abnormalities.

Most strokes involve the carotid artery but only three-quarters of angiograms show arterial occlusion. In pregnancy, there is a predilection for the middle cerebral artery territory (Cross et al., 1968). Conversely, the oral contraceptive pill is associated with occlusions of the vertebrobasilar artery in up to 40% of strokes (Bickerstaff, 1975).

Although a quarter of women with strokes have the clearly identifiable usual risk factors such as diabetes, hypertension or hyperlipidemia, half may have rare underlying conditions, and in 25%, no cause can be found. Causes of ischemic stroke in pregnancy are given in Table 121.3.

Investigation

Investigation may be done with head CT and head MRI, supplemented by cerebral angiography with abdominal shielding limiting the fetal exposure. The American College of Obstetricians and Gynecologists (ACOG) warns that women should be informed that fetal exposure to less than 5 rads of ionizing radiation has not been demonstrated to increase fetal abnormality (1995). Other tests such as transesophageal echocardiography can be safely performed during pregnancy, and may reveal valvular abnormalities, intramural clots and or patent foramen ovale. Magnetic resonance angiography now approaches the sensitivity and specificity of the more invasive standard angiography, and for some vascular problems, should be considered.

Hematological studies should include prothrombin and activated partial thromboplastin time (PT/INR; PTT); complete blood count with platelet count; fibrinogen, protein C and S, activated antithrombin III, factor V Leiden, prothrombin-gene mutation, and antiphospholipid antibody profile.

Table 121.2a. Abortive medications in the treatment of headache and migraine

	FDA	TERIS	Breast-feeding
Analgesics			
Aspirin	C[a]	N–Min	Caution
Acetaminophen	B	N	Compatible
Caffeine	B	N–Min	Compatible
NSAIDS			
Ibuprofen	B[a]	N–Min	Compatible
Indomethacin	B[a]	N	Compatible
Ketorolac	B[a]	U	Caution
Naproxen	B[a]	U	Compatible
Sedatives, hypnotics, and antihistamines			
Cyproheptadine	B	U	Contraindicated
Butalbital	C	N–Min	Caution
Neuroleptics/antiemetics			
Chlorpromazine	C	N–Min	Concern
Prochlorpromazine	C	N	Compatible
Promethazine	C	N	NA
Metoclopramide	B	N–Min	Concern
Corticosteroid			
Prednisone	B	N–Min	Compatible
Narcotics			
Codeine	C[b]	N–Min	Compatible
Meperidine	B[b]	N–Min	Compatible
Propoxyphene	C[b]	N–Min	Compatible
Ergotamines and serotonin agonists			
Ergotamine	X	Min	Contraindicated
Dihydroergotamine	X	U	Contraindicated
Sumatriptan	C	U	Caution
Zolmitriptan	C	U	Caution
Naratriptan	C	U	Caution
Rizatriptan	C	U	Caution

Notes:
[a] D if third trimester
[b] D if prolonged or at term
Source: Adapted from Silberstein (1998). Reproduced by permission from Demos, New York, NY.

Table 121.2b. Preventative medications in migraine

	FDA	TERIS	Breast-feeding
Beta-blockers			
Atenolol	C	U	Compatible
Metoprolol	B	U	Compatible
Nadolol	C	U	Compatible
Propranolol	C	U	Compatible
Calcium channel blockers			
Verapamil	C	U	Compatible
Diltiazem	C	U	Compatible
Tricyclic antidepressants			
Amitriptyline	D	N–Min	Concern
Nortriptyline	D	U	Concern
Desipramine	C	U	Concern
Imipramine	D	N–Min	Concern
Protriptyline	C	U	Concern
SSRIs			
Fluoxetine	B	N	Caution
Paroxetine	C	U	Concern
Sertraline	B	U	Concern
Antiepileptic drugs			
Valproic acid	D	S–Mod	Compatible
Gabapentin	C	U	Uncertain
Serotonin agonist			
Methysergide	D	U	Caution
MAOIs			
Phenelzine	C	U	Concern

Source: Adapted from Silberstein (1998). Reproduced with permission from Demos, New York, NY..

Table 121.3. Causes of stroke in pregnancy

Pre-eclampsia and eclampsia
Coagulopathies
Atherosclerosis
Antiphospholipid antibody
Hemocystinuria
Antithrombin III deficiency
Sickle cell anemia
Protein C and S deficiencies
Factor V Leiden deficiency
Thrombotic thrombocytopenic purpura (TTP)
Cardio-embolic disease
Rheumatic heart disease
Endocarditis
Paradoxical embolism via ASD or PFO
Postpartum cardiomyopathy
Carotid artery dissection

Treatment

When anticoagulation is indicated, heparin can be given as it does not cross the placenta, however it does have teratogenic properties if given in the first trimester. Coumadin is problematic as it does cross the placenta.

Indications for anticoagulation include deep vein thromboses, atrial fibrillation, peripartum cardiomegaly and hypercoagulable states.

Subarachnoid hemorrhage (SAH)

Subarachnoid hemorrhage may arise from arteriovenous malformations (AVMs), or aneurysms, and may account for 30% to 80% of maternal deaths from cerebral hemorrhage, the third most common cause of non-obstetric maternal death (Dias & Sekhar, 1990; Miller & Hinckley, 1970). Ruptures may occur at any time during pregnancy, but favour the last trimester and the first six weeks postpartum. The severe sudden-onset headache with meningismus and focal neurologic signs (such as intrinsic and extrinsic ocular palsies) suggest the diagnosis. Up to 50% of patients may have a sentinel bleed 7 to 10 days before the more catastrophic hemorrhage (Verweij et al., 1988). Predisposing causes for SAH include AVMs, aneurysms, moya-moya disease, Marfan syndrome, polycystic kidneys and fibromuscular dysplasia.

Diagnosis

Diagnosis is made with an unenhanced head CT scan, and IV contrast can outline an aneurysmal or vascular malformation source, but head MRI/MRA provides better resolution. If both imaging modalities fail to reveal evidence of blood, a spinal tap can be diagnostic.

Treatment

Current treatment favours early operation and ligation of the aneurysm, but treatment must be individualized and obstetric issues must be balanced against neurologic needs. Neurosurgical treatment can be combined with cesarian section if the fetus is viable. The optimal mode of delivery of the infant is still under contention, but vaginal delivery and cesarian section have been successfully performed.

Other causes of, or associations with, stroke

These include alcohol intoxication, intravenous and oral substance abuse (particularly with central stimulants such as amphetamine and cocaine), or following a vasculitic reaction or infection from intravenous drug use. Intracerebral and subarachnoid hemorrhage may result from the sudden hypertension after crack cocaine or following emboli from bacterial endocarditis.

Migraine only occasionally causes cerebral infarction and during pregnancy. Patients should be evaluated for antiphospholipid antibody syndrome.

Cardioembolic causes of stroke

Patent foramen ovale

Patent foramen ovale is associated with an increase in strokes in young women. When the right atrial pressure exceeds that in the left atrium, a right-to-left shunt allows an embolus to enter the cerebral circulation. Such reversals of pressure gradients occur with Valsalva manoeuvres. Forceps rotation and cesarian section favour thrombosis in the pelvic and leg veins during pregnancy and the puerperium, which may then paradoxically embolize to the brain. Diagnosis is made with transesophageal echocardiography and the microbubble test.

Atrial septal defects

Atrial septal defects (ASDs) are usually asymptomatic. Strokes may occur with right-to-left shunting via the defect or with cardiac dysrhythmias.

Atrial fibrillation

Atrial fibrillation and heart failure may occur after rheumatic heart disease with significant mortalities for the mother and fetus. Emboli occur in 10% to 23% of pregnant women with atrial fibrillation, and up to a 10% risk of cerebral embolus (Mendelson, 1956; Szekely & Snaith, 1961). When atrial fibrillation occurs during pregnancy, cardiac failure is frequent. Because of the embolic risk with atrial fibrillation, patients should be anticoagulated.

Mitral valve prolapse

Mitral valve prolapse affects 6% of women, but with a low risk for stroke. In patients with strokes or transient ischemic attacks, there is a three times increased risk of having mitral valve prolapse.

Arterial dissection

Vertebral and carotid artery dissections are rare, possibly triggered by vigorous neck movements during labour and delivery. Fibromuscular dysplasia is a rare underlying cause. Diagnosis is made by angiography, and anticoagulation is indicated.

Cerebral venous thrombosis (CVT)

CVT occurs in 1–2 per 10 000 childbirths, mostly in the puerperal period. Eighty percent occur in the second to

third weeks postpartum (Lanska & Kryscio, 1998). Dehydration would appear to be an important risk factor, but other causes are estrogen, vitamin K and coagulopathies. Frequently, primary thrombosis occurs in the superior sagittal sinus and lateral sinuses with secondary extension to the cortical veins.

CVT may be accompanied by seizures, focal weakness and lateralizing neurological signs (Ameri & Bousser, 1992). A persistent and often increasing headache lasting more than several days to a week engenders suspicion for this non-benign cause of headache. Common clinical features of CVT are focal weakness, seizures, decreased consciousness and papilledema. The differential diagnosis includes migraine, pseudotumour cerebri, arterial venous malformations, intracerebral hemorrhages, meningitis and late postpartum eclampsia.

Investigation

Unenhanced head CT may show single or multiple hemorrhages, and intravenous contrast may reveal the lack of enhancement of the blood within the cerebral sinuses: 'The empty delta sign'. Magnetic resonance imaging may show hyperdensities on T_1-weighted images, and older lesions on T_2-weighted images. Hematological studies indicated include those listed under investigation of stroke.

Treatment

Treatment remains controversial and balances the benefits of anticoagulation of a potentially extending thrombus, against the risk of bleeding from hemorrhagic infarction. The absence of hemorrhagic changes on unhanced head CT may favour the use of heparin, partially in the presence of other concurrent thrombotic diatheses, such as intercurrent pelvic or leg thrombophlebitis. Anticoagulation is usually given for up to 3 months using heparin (Einhaüpl et al., 1991) or low-molecular weight heparinoids. Intraclot thrombolysis with rtPA or prourokinase, or therapy combined with anticoagulation, have been tried (Frey et al., 1999). Treatment of blood pressure, hydration, raised intracranial pressure, and antiseizure drugs may be needed.

Outcome

Outcome after CVT has improved. Mortality can be as low as 5% to 10% with outcomes being better in the obstetric population (Cantù & Barinagarrementaria, 1993). Follow-up for periods of up to 63 months has revealed the absence of permanent sequelae in most patients (86% of 77 patients) (Preter et al., 1996). Seizures were recurrent in only 14% and no patient had recurrent CVTs.

Hemoglobinopathies

Twenty per cent of women with sickle cell disease may have a first trimester miscarriage and one-half will have a sickle cell crisis during pregnancy (Adams, 1957). Sickle cell trait does not significantly increase maternal morbidity. Stroke is thought to be produced by the sludging of the sickle cells in the small vessels resulting in thrombosis, or by affecting vessels supplying the brainstem. This process may also result in encephalopathy and seizures. If hemoglobin S constitutes less than 20% of the hemoglobin, cerebral angiography is generally safe (Keeling et al., 1980; Powars et al., 1986). Red cell exchange and exchange transfusions may be helpful although reactions may occur (Perry, 1990).

Thrombotic thrombocytopic purpura (TTP)

This multisystem disorder frequently presents with transient ischemic attacks and strokes (Wiebers, 1985; Upshaw et al., 1985). It mimics pre-eclampsia, but in contrast, there is a normal level of antithrombin III. Stroke risk increases with the duration of pregnancy and in the puerperium. If anticoagulation is not possible, low-dose aspirin may be used in the third trimester.

Amniotic fluid emboli

Amniotic fluid emboli usually occur after childbirth or abortions, and result in sudden shortness of breath, cyanosis or shock (Chatelain & Quirk, 1985). In women over age 30 years, a prolonged and traumatic labour is a predisposing factor with amniotic fluid entering via tears in the cervix, vagina or uterus. Seizures occur in 10% of patients and mortality is over 80% (Chatelain & Quirk, 1990; Mulder, 1985).

Fat emboli

Fractures of the long bones can result in embolization of fat, causing shortness of breath, encephalopathy and petechial eruptions. A fat embolism in itself is usually a self-limited disorder.

Air emboli

These may occur with the rupture of the membranes during labour, allowing air to enter the circulation, and resulting in shortness of breath, cyanosis, tachycardia, anxiety, and shock (Nelson, 1960). Hypoxia, convulsions, and death are frequent. Treatment relies on the rapid diagnosis and turning the patient on the left side to trap air in the right chambers of the heart, from where it can be aspirated (Muth & Shank, 2000). Up to 1% of maternal deaths can arise from venous air emboli (OSMACMH, 1972),

often introduced by poorly performed abortions (Nelson, 1960).

Epilepsy

Epilepsy is one of the more common neurologic diseases that can affect women of child-bearing years, and there is, therefore, a significant number of births involving women with epilepsy (0.3% to 0.5% of births). Women with epilepsy who become pregnant face several diagnostic and management problems. There are even challenges to becoming pregnant: fertility in women (and possibly men) is decreased. Furthermore, there are several interactions that can occur including the effect of seizures on the fetus, the effect of seizures on the course of pregnancy, the effect of pregnancy in altering seizure threshold and seizure control, and the influence of pregnancy on the pharmacokinetics and pharmaco-dynamics of antiepileptic drugs (AEDs). Antiepileptic drugs themselves have known teratogenic effects in the developing fetus and may enter breast milk in the postpartum period.

Pregnancy in patients with epilepsy is usually uneventful. However, about 25–30% of women will have a worsening frequency or severity of seizures during pregnancy (Morrell, 1997), particularly during the sixth and seventh months; most women have no significant change in frequency, and a few improve. In recent years, closer monitoring of epilepsy during pregnancy has improved seizure control. About 10% of pregnant women will have a complication during pregnancy. Up to 20% of babies will have a congenital anomaly, and 4% to 8% will have malformations, most frequently cardiac (2%); orofacial clefts (1.8%); skeletal anomalies (0.9%), and severe CNS malformations (0.7%) (Morrell, 1997). A maternal history of epilepsy confers twice the risk for epilepsy in the child than if the father has epilepsy. Epilepsy susceptibility may be transmitted by a mitochondrial gene or by imprinting of a nuclear gene from the mother. The most common genetic epilepsies are the idiopathic generalized epilepsies, and localization-related epilepsies such as benign rolandic epilepsy.

Women with epilepsy are more prone to miscarriage, spontaneous abortion, or preterm delivery, possibly related to the consequence of hypoxia and acidosis with tonic–clonic seizures, and the pulsatile release of luteinizing hormone (LH) that compromises implantation (Morrell, 1997). There is also a higher incidence of low birth-weight infants and fetal head growth retardation.

Causes of increased seizures during pregnancy include an increased volume of AED distribution and clearance, resulting in decreases in AED levels. Conversely, the fall in serum albumin, and competition for binding sites by sex steroids may increase the unbound (active) AED fraction. Poor adherence to taking AEDs may be caused by maternal fears that AEDs may damage the developing fetus, and it is therefore of great importance that women of childbearing age and pregnant women be counselled regarding these interactions, and the consequent deleterious effect of convulsions on the fetus.

Counselling should also include the teratogenic risks of AEDs such as congenital heart defects (atrial septal defects, tetralogy of Fallot, ventricular septal defects, pulmonary stenosis, patent ductus arteriosus, and coarctation of the aorta). There is a three- to four-fold increase in the incidence of these defects over the background rate. Neural tube defects may appear in 0.5% to 1% of children whose mothers take carbamazepine, and 1% to 2% of those on valproate (Omtzigt et al., 1992; Rosa 1991). Minor abnormalities such as epicanthal folds, nasal growth deficiency, abnormal ears, distal digital hypoplasia, and nail hypoplasia, low hairline and hypertelorism occur with phenobarbital, primidone, carbamazepine, phenytoin, and probably valproate, but many of these dysmorphic features may be outgrown after several years of life (Koch et al., 1992). The effects of the newer AEDs: felbamate, neurontin, lamotrigine, topiramate, oxcarbazepine, tiagabine, zonisamide and levetiracetam, are not known, but all have gained a category 'C' FDA classification.

AED polypharmacy significantly increases the risks for major and minor birth defects, reaching 20% in women on four or more AEDs (Oguni et al., 1992). Since neural tube defects rarely occur on valproate when taken in doses below 1 gram per day, more frequent dosing intervals and minimizing dosage may help. Neural tube defects may be detected by the 16th week of gestation with more than 95% sensitivity using maternal serum alpha fetoprotein and a level II ultrasound that can detect cardiac and neural tube malformations (ACOGPEB, 1996).

Folic acid deficiency contributes to neural tube defects, and folate supplementation is strongly advocated (400 μg to 4 mg/day). The optimal daily folate dose is not known, but folate should optimally be taken prior to pregnancy and particularly during the first 28 days of gestation.

During pregnancy, mothers should be seen monthly, at which time AED levels can be measured, particularly if convulsions increase. Oral or intramuscular vitamin K should be given in the last months of pregnancy to forestall the bleeding tendency in newborns produced by phenytoin and barbiturate exposure in utero. Infants should receive 1 mg of phytonadione after birth.

Although AEDs enter breast milk, most experts endorse breast-feeding.

Chorea gravidarum (Dike, 1998; Petri, 1998)

Chorea gravidarum by definition is peculiar to pregnancy. This rare condition represents the sudden appearance of chorea during pregnancy, often preceded by cognitive changes or emotional lability. Choreiform movements may be unilateral or involve the four limbs, and be severe enough to impair routine activities of daily living. Although previously a highly morbid condition leading to maternal death in 13% and fetal death in 50%, morbidity and mortality has markedly decreased to a few per cent. Up to a quarter of women, however, will relapse during subsequent pregnancies.

The most frequent causes are rheumatic fever and autoimmune disorders, with the chorea appearing in the first trimester and decreasing during the second and third trimesters. It is believed that many women have had Sydenham's chorea in childhood with consequent basal ganglia injury, which is reactivated during pregnancy in association with the hormonal changes. Increased striatal metabolism has been demonstrated using PET-fluorodeoxy-glucose imaging.

Symptomatic treatment with chlorpromazine (Thorazine®) can be used in the first trimester, but may cause sedation and orthostatic hypotension. Haloperidol (Haldol®) can be used after the first trimester (because of concerns of teratogenic limb deformity), because it is less sedating than chlorpromazine. Because of the frequent association of rheumatic heart disease, prophylactic antibiotics are advised during instrumentation and delivery to prevent endocarditis. Curiously, chorea resolves within hours of delivery.

A rarer cause of chorea gravidarum is seen in association with the antiphospholipid antibody syndrome (APS) or with systemic lupus erythematosus (SLE). Chorea gravidarum in this setting is usually a more morbid condition and treatment is directed at the underlying condition: steroid immunosuppression with SLE, and symptomatic treatment as outlined above. Treatment of antiphospholipid antibody syndrome during pregnancy involves low molecular weight or subcutaneous heparin, often in combination with steroids and antiplatelet agents. Some improvement has been obtained with corticosteroids. With SLE and APS, there is a greater probability of structural brain injury and chorea may persist after delivery.

Even rarer causes of chorea initially appearing during pregnancy are Wilson's disease and Huntington's chorea.

Eclampsia

Pre-eclampsia/eclampsia is a syndrome characterized by pregnancy-induced hypertension, proteinuria, and edema after the 20th week of pregnancy. This multisystem disorder may affect clotting, kidney and liver function, and the lungs. Neurological features include headache, visual hallucinations, blindness, confusion, seizures, and coma. The appearance of seizures signals the evolution of pre-eclampsia to eclampsia, but seizures may appear with few if any signs of pre-eclampsia. Many eclamptic seizures appear postpartum, and only at that time, may hypertension be noted. Pre-eclampsia affects 6% to 8% of pregnancies (Chesley, 1978) and is more frequent in black primigravidas and twin pregnancies, the poorly nourished, nulliparous women, and women over the age of 35, as well as in women who have had pre-eclampsia in previous pregnancies (Sibai, 1989, 1990).

The hypertension of pre-eclampsia/eclampsia may be mild, representing a rise of 30 millimetres Hg in systolic pressure, or 15 millimetres Hg in diastolic blood pressure above first trimester blood pressure readings (Committee ACOG, 1986). Antenatal history may be lacking, and an absolute blood pressure of 140/90 has been used to diagnose hypertension.

Unlike the frequently seen ankle edema in normal pregnancy, preeclamptic edema is more marked, and affects the face and hands. Proteinuria is determined by the repeated finding of 1+ proteinuria on two occasions six hours apart, or the presence of 300 mg of protein in a 24-hour urine collection (Committee ACOG, 1986).

Seizures may start focally but are usually noted once a generalized convulsion occurs. Most women will not have repeated seizures once the baby is delivered, but even on magnesium sulfate therapy, up to 10% may have two or more seizures (Pritchard et al., 1984).

There are a number of pathophysiological mechanisms invoked in the eclamptic process including immunological dysfunction, coagulation abnormalities, endothelial damage, endocrine, dietary, genetic and vasospastic factors (Friedman et al., 1991). The hypertension is believed to stem, in part, from the incomplete deactivation of autonomic innervation of uterine spiral arteries in the inner myometrial layer preventing their maturation into utero placental arteries, which release nitric oxide (Furchgott, 1996). A failure in nitric oxide production favours vasoconstriction and the increase in circulating serotonin and affecting the renin–angiotensin–aldosterone systems (Khong et al., 1986; Talledo et al., 1968).

Many aspects of cerebral pathology are attributable to the loss of cerebral autoregulation with increased cerebral

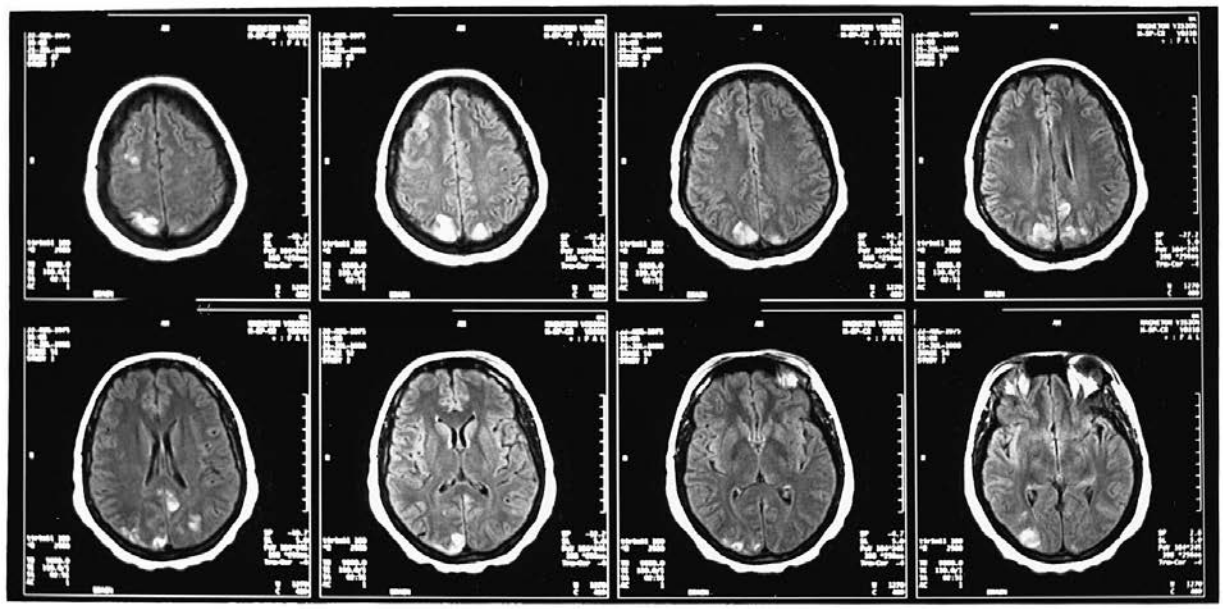

Fig. 121.1. Axial T_2-weighted MRI study shows peripheral edema in the frontal and parieto-occipital watershed zones. (From Kaplan, 1999, reproduced with permission from Masson Editeur.)

perfusion pressures. As hypertensive encephalopathy appears, there is associated vasospasm and areas of ischemia, as well as petechial and larger hemorrhages that can occur in most brain regions. The watershed zones, particularly posteriorly, are those most affected by ischemic changes (Fig. 121.1). The brain may be further adversely affected by platelet consumption and an active coagulopathy superimposed on a hypertensive and multifocally hemorrhagic brain (Anderson & Sibai, 1986; Gant et al., 1973).

Pre-eclampsia/eclampsia largely remains a clinical diagnosis, and where focal signs are seen, imaging for associated pathological problems such as cerebral venous thrombosis and intracranial hemorrhage should be performed. Recent MRI studies have shown a typical serpiginous or curvilinear, grey–white junction T_2-weighted signal increase, particularly in watershed zones (Digre et al., 1993).

Neurologists are usually consulted in the management of atypical cases of eclampsia, often complicated by intracranial hemorrhage, or coma. In addition to efforts aimed at rapid delivery of a viable baby, and decreasing maternal blood pressure to within the autoregulatory range, magnesium sulfate is widely advocated (Pritchard et al., 1984; Eclampsia Trial Collaborative Group, 1995). Although not an anticonvulsant, there is increasing evidence that it may have an effect on the vasospastic component of eclampsia which, in itself, may forestall further seizures and brain damage (Kaplan et al., 1988). Should seizures persist, intravenous phenytoin (Repke et al., 1992) or fosphenytoin are useful.

Multiple sclerosis (MS)

MS has no significant effect on conception, fertility, fetal viability or delivery, and some believe that pregnancy improves long-term prognosis. There is a very small increased risk for MS in the child.

Although previously pregnancy was considered to be contraindicated in MS patients, more recent studies fail to confirm a negative effect on MS. A recent study found that MS risk was higher in nulliparous women, with pregnancy appearing to confer a protective effect (Runmarker & Andersen, 1995). MS relapses decrease during gestation, particularly in the latter half, possibly via immune suppression with the changes in cytokines, prostaglandins, cell-mediated immunity, and enhancement of immunoglobulin responses (Abramsky, 1994; Gilmore et al., 1997).

Diagnosis and investigation

Most patients who are pregnant with MS will have had the diagnosis made before becoming pregnant. As noted, few

initially develop MS during pregnancy. Consequently, investigation with MRI, LP and evoked potentials are rarely warranted during pregnancy. Gadolinium contrast crosses the placenta but has no known teratogenic effects; nonetheless, it is not recommended in pregnancy. The slight concerns regarding unenhanced CT or MRI imaging during pregnancy are noted in the section on strokes, but regarding evoked potentials or lumbar puncture, there is no evidence that they pose a problem for mother or fetus.

Treatment

The newer maintenance immunotherapies used to prevent future demyelination such as glatiramer acetate (Copaxone®) and the interferon-betas, are contraindicated in pregnancy. Most studies indicate a postpartum rebound in relapses with a threefold increase, occurring 3 to 6 months postpartum (Coyle, 1998). Twenty to 40% of postpartum women with MS may have a clinical attack. A recent study suggests that postpartum immunotherapy may prevent such relapses (Achiron et al., 1996). Many medications used in the symptomatic treatment of MS enter breast milk, as do interferon-betas and glatiramer acetate, and cannot safely be used during breast feeding. There is no contraindication to vaginal delivery (nor to breast feeding), but spinal anesthesia is not recommended. Conversely, epidural anesthesia does not carry a particular risk for MS relapse and can be used for delivery. Steroid cover for the stress of delivery should be considered in women who have received 2 or 3 weeks of corticosteroid therapy in the prior year.

Peripheral nerve disease and muscle disease

Bell's palsy

Bell's palsy is 3.3 times higher in pregnancy, with 85% of cases occurring in the third trimester or first two weeks postpartum (Hilsinger et al., 1975; Mair Iain et al., 1973). Successful treatment has been obtained with steroids, or with symptomatic treatment only.

Carpal Tunnel Syndrome

By questionnaire, up to a quarter of women have had symptoms of carpal tunnel syndrome, particularly in the third trimester (Conwit & Good, 1998). It has been attributed to the increase in relaxin, a hormone that peaks in the third trimester, and that may cause relaxation of the transverse carpal ligament (Nicholas et al., 1971). Fluid retention and edema may cause local nerve compression. Surgery is rarely needed during pregnancy.

Neuralgia paresthetica

Neuralgia paresthetica (produced by compression of the lateral femoral cutaneous nerve of thigh as it goes under the lateral third of the inguinal ligament) increases with weight gain and abdominal girth, particularly after the 30th week of gestation. Most patients remit by 3 months.

Other neuropathies

Nutritional deficiency neuropathy is seen in developing countries, and the rare porphyric neuropathy may flare up in pregnant women with acute intermittent porphyria.

Compression neuropathies (Conwit & Good, 1998)

Compression neuropathies include sciatic nerve compression within the pelvis and lumbosacral plexopathies from compression by the descending fetal head, which most often affect the peroneal nerve, causing pain and foot drop. Femoral mononeuropathies may be produced by the lithotomy position used during vaginal deliveries, and mostly resolve within a few months. The iliohypogastric nerve may be stretched during pregnancy, presenting with pain in the pubic or periumbilical region, abdominal flank or back, but without weakness. The obturator nerve can be compressed by the fetal head against the lateral pelvic wall, producing pain in the groin and upper thigh with adductor weakness.

Myotonic dystrophy (Gilchrist, 1998)

Pregnancy rarely affects myotonic dystrophy, although the condition may first become symptomatic during pregnancy, particularly in the third trimester. Conversely, myotonic dystrophy may affect pregnancy, causing prolongation of the first and second stages of labor (because of poor uterine contractions), and increased postpartum hemorrhage from the failure of uterine contraction. There are risks with anesthesia and surgery because of the 'sensitivity' to depolarizing neuromuscular blockade with succinyl-choline. Non-depolarizing agents may be safely used. Thiopental may cause respiratory depression and local anesthesia is preferred.

Myasthenia gravis

In myasthenia gravis, studies have shown that 40% of pregnant women may worsen, 28% may improve, and the remainder remain unchanged (Plauche, 1991); however, long-term outcome is not changed (Batocchi et al., 1999). Exacerbations may be sudden, often with respiratory failure, and may change with subsequent pregnancies (Batocchi et al., 1999). Maternal mortality may reach 10% from cholinergic crisis, myasthenic crisis, or postpartum hemorrhage (Plauche, 1991).

The treatment of myasthenia is little affected by pregnancy, and anticholinergic agents, corticosteroids, and even plasmapheresis can be used. Pyridostigmine is not excreted in breast milk and does not cross the placenta.

One in eight babies of women with myasthenia have transient neonatal myasthenia with spontaneous remission in two to four weeks as the level of antiacetylcholine receptor antibody declines (Namba et al., 1970). There is increased perinatal infant death with neonatal myasthenia (Frenkel & Ehrlich, 1964).

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The brain and the cardiovascular system

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Normally, the brain and heart function in seamless harmony. The heart supplies the brain with nutrients and oxygen, while the brain regulates cardiac function. It is a long-standing fact that cardiovascular disease is a major source of neurological dysfunction. In addition, however, it has become recently apparent that besides playing a major role in basic cardiac homeostatis, the brain directly influences certain cardiovascular disease states. Among these influences are profound effects on the incidence of, and outcome from, coronary artery disease, congestive heart failure, and cardiac arrhythmias.

The influences of the heart on the brain

There is a strong association between heart disease and subsequent neurological dysfunction. Focal neurological syndromes due to cardiac diseases most often arise from emboli, typically associated with arrhythmias, valvular heart disease, myocardial infarction, as well as rarer situations, such as intracardiac tumours. Cardiac surgery, particularly coronary artery bypass grafting and valve replacements, may be associated with showers of athero-, air, and thromboemboli at the times of aortic manipulation.

In addition to embolic injury, other cardiac causes of neurological dysfunction include cardiac arrhythmias or cardiac arrest, which may result in anoxic injury to the brain. Finally, congestive heart failure may lead to a number of subtle neurological findings.

Cerebral embolic strokes of cardiac origin

The percentage of strokes that are cardioembolic is at least 20%, and may be as high as 50%. The major underlying cardiac conditions leading to cardioembolic strokes include atrial fibrillation, myocardial infarction, valvular heart disease, infectious endocarditis, and non-bacterial thrombotic endocarditis. Less common conditions which may be associated with cardioembolic strokes include patent foramen ovale, intracardiac tumours, and calcifications of the mitral or aortic valves/annulus.

Cardiac arrhythmias

Atrial fibrillation is a major risk factor for stroke, with a stroke rate of approximately 5%/year (Nademanee & Kosar, 1998). However, the risk varies greatly. For those under 65, without risk factors, the risk is about 1%/year. For others with increasing age, systemic arterial hypertension, diabetes, valvular heart disease, a dilated left atrium, thyrotoxic atrial fibrillation, mitral annular calcification, previous TIA/stroke, or poor ventricular function the risk can be as high as 10–12%/year (Nademanee & Kosar, 1998). The actual incidence of embolic infarction is undoubtedly higher than these percentages, as evidenced by the increased numbers of 'silent' brain infarctions on brain imaging studies in patients with arrhythmias (Ezekowitz et al., 1995).

There appear to be particular times in the evolution of atrial fibrillation that embolic complications are likely to occur: the onset of paroxysmal atrial fibrillation, and the first year after the transition from paroxsymal atrial fibrillation to chronic atrial fibrillation. In addition, as noted above, there exist certain high-risk clinical factors, which may identify those patients at risk for a cardiocerebral embolism. This emphasizes the need for attempts at maintenance of normal sinus rhythm, either by removing the 'fibrillogenic' stimulus (i.e. thyrotoxicosis), or by using antiarrhythmic agents to suppress the arrhythmia, or to prevent transition to chronic atrial fibrillation. Additionally, the role of anticoagulents for stroke prevention in atrial fibrillation of recent onset is crucially established (Petersen et al., 1989), as up to 7% of patients undergoing conversion of atrial fibrillation without therapeutic anticoagulation experience a significant cardiocerebral event (Munshauer et al.,

1997). This risk may be lowered to less than 1% with adequate anticoagulation therapy with oral warfarin sodium (Petersen et al., 1989; Koefoed & Petersen, 1999). In those at low risk there is less substantiated therapeutic benefit of aspirin, however data does exist to suggest that those patients with a structurally normal heart, with left atrial dimensions less than 45 mm (so-called 'lone' atrial fibrillation), may be safely managed with daily antiplatelet therapy (the SPA III Writing Committee, 1998; Hart et al., 1999). Finally, the stroke risk engendered by atrial fibrillation may persist for up to a month following restoration of electrical sinus rhythm, as mechanical atrial systole may not return for several weeks (Grimm et al., 1997). Anticoagulation is therefore mandatory during this period.

Electrical or pharmacological conversion of atrial fibrillation is a commonly used therapy for the acute conversion of this arrhythmia, typically with simultaneous oral anticoagulation. The use of transesophageal echocardiography (TEE) to evaluate for the presence of left atrial appendage thrombosis has been suggested to reduce the risk of stroke significantly, even in the absence of therapeutic anticoagulation, however the risk of stroke in contemporary TEE series is still measurable (Roijer et al., 2000).

The role of other atrial arrhythmias (especially atrial flutter) in the genesis of cardioembolic stroke remains hotly debated (Irani et al., 1997). As a small amount of atrial function persists during atrial flutter, it has been argued that the stroke risk is much lower than that of atrial fibrillation. Numerous studies do, in fact, support this contention, however the incidence of cardioembolic strokes due to atrial flutter still remains measurable (Grimm et al., 1997; Irani et al., 1997; Roijer et al., 2000), thus similar anticoagulation guidelines should be followed. Since a large percentage of patients with atrial flutter have concomitant atrial fibrillation, the true stroke risk of atrial flutter remains undefined.

Myocardial infarction

Most often, concomitant myocardial and cerebral infarction raises the possibility of a ventricular thrombus (usually in the setting of anterior/apical wall infarction), but less commonly one may see a similar picture from coronary/cerebral embolism from endocarditis. The multifocal nature of certain other causes of concomitant MI and cerebrovascular injury may mimic embolic events. Notable among these syndromes are coronary/cerebral arterial spasm in the setting of subarachnoid hemorrhage or migraine headaches. These are discussed later.

In the absence of appropriate anticoagulation therapy, embolism to the central nervous system following an acute myocardial infarction is not an infrequent event. The most common source of emboli is generally believed to be mural thrombi, which typically form at the site of infarcted, akinetic ventricular myocardium. In the setting of an anterior myocardial infarction, the risk of a cardiocerebral embolism may be as high as 40% among non-anticoagulated patients (Keren et al., 1990). This risk may be dramatically reduced with an appropriate anticoagulation regimen, including intravenous or subcutaneous heparins acutely, followed by chronic oral anticoagulation with warfarin sodium.

Although uncommon, concomitant coronary and cerebral events may be due to emboli arising from valvular lesions of endocarditis (see below). This should be suspected in any patient with a fever accompanying their event.

Valvular heart disease

Mitral stenosis is associated with embolic disease, particularly, as mentioned above, if there is coexisting atrial fibrillation (Munschauer et al., 1997). The annual incidence of embolic events in untreated patients is about 4%/year. For those with previous embolic events it is twice that. This emphasizes the fact that recurrent embolism is common, occurring in the majority of untreated patients. These reoccurrences occur in the first month in 40% and in the first year in 67% of patients (Munschauer et al., 1997). Fortunately, the long-term use of anticoagulents markedly reduces this risk of recurrent embolization, as much as 90% (Munschauer et al., 1997).

Mitral valve prolapse is a common disorder of the mitral valve, occurring in 1–3% (Freed et al., 1999) and defined by strict echocardiographic criteria (Levine et al., 1988, 1989). Clinically, mitral valve prolapse is most often due to myxomatous degeneration of the valve leaflets, resulting in redundancy, loss of competence, and consequent mitral regurgitation. Due to stress/strain effects on the mitral chordal apparatus, the chordae tendineae become elongated, and may ultimately snap, leading to chest pain, as well as worsening mitral incompetence. Mitral valve prolapse is a common source of either atrial or ventricular arrhythmias.

There is controversy regarding mitral valve prolapse as a source of emboli. Earlier studies suggested that in those under 45 years of age with transient ischemic attacks or strokes, mitral valve prolapse was found in 40% as compared to 7% in controls. However, in more recent studies (Marks et al., 1989; Freed et al., 1999; Gilon et al., 1999) mitral valve prolapse detected by either auscultation or transthoracic echocardiology was not associated with an increased number of strokes.

Infective endocarditis is commonly affected by neurological complications, including as a presenting sign of the disorder. Infective endocarditis should be actively sought in any patient presenting with concomitant neurological

symptoms and fever. Among these complications of endocarditis are focal neurological deficits (simulating a stroke), intracerebral or epidural abscess formation, mycotic aneurysms, seizures, as well as a diffuse meningoencephalitis (Tunkel & Kaye 1993; Roder et al., 1997; Heiro et al., 2000). Certain clinical factors predispose a patient with endocarditis to CNS complications. These include antecedent embolic events, large or bulky vegetations, those caused by *Staphylococcus* or *Streptococcus*, as well as fungal endocarditis (Sanfilippo et al., 1991). Although antibiotic therapy reduces the risk of CNS embolism in the setting of infective endocarditis, it does not eliminate the risk entirely, and some authors advocate valve replacement therapy if high-risk lesions are identified, or if a previous cardiocerebral embolism has occurred. This is because the risk of mortality is significantly increased in the setting of a neurological complication of endocarditis (Moon et al., 1997).

Non-bacterial thrombotic endocarditis (NBTE) is a lesser-recognized cause of cardiocerebral stroke. It is most often due to the development of sterile, thrombotic vegetations, which may be attached to one or more heart valves (Lopez et al., 1987). It may occur in association with advanced terminal illnesses, especially those resulting from neoplasia or acquired immunodeficiency syndrome (Johnson & Roodman, 1989; Kaul et al., 1991; Pinto, 1996). Furthermore, NBTE has been associated with certain acquired states of hypercoagulability, notably the anticardiolipin/lupus anticoagulent syndrome. Irrespective of the underlying cause NBTE is managed with anticoagulation therapy, reserving valve surgery for large/bulky vegetations, or recurrent embolic events.

Following valve replacement

Both mechanical and biologic prostheses are used for both mitral and aortic valve replacement and in addition to the risk of embolic events at the time of their implantation (see below), may be subsequently implicated in cardiocerebral embolism.

Given their synthetic nature, valve prostheses are a potential nidus for the development of thrombi and/or endocarditis. The risk of embolic disease varies with the type of valve used. Mechanical prosthetic valves require the use of long-term anticoagulation while biologic valves, those obtained from bovine, porcine or human sources, may not (Al-Ahmad et al., 2000; Braunwald, 2000). With the use of more modern 'low profile' mechanical prostheses and more aggressive anticoagulation protocols, the risk of thromboembolic events has been reduced substantially (Al-Ahmad et al., 2000).

Due to lower flow (as well as a higher incidence of concomitant/preoperative atrial arrhythmia), the risk is higher with mitral valve replacement, with the risk of thromboembolism with mechanical valves being about 3%/year even with anticoagulation, and about one-half that with porcine/bovine valves. Whether the growing use of human sources for aortic valve replacement (either pulmonary–aortic autografting or cadaveric homografting) will further lower this risk remains unclear (Kassai et al., 2000; Stahle, 2000).

The development of infective endocarditis on a prosthetic valve is a medical emergency, frequently accompanied by embolic events, and which almost always requires surgical intervention.

A recently recognized cause of embolic stroke following valve replacement or repair is thromboembolism originating from an incompletely ligated left atrial appendage (Katz et al., 2000). Katz and colleagues suggest that the small residual amount of flow entering the atrial appendage might allow for the formation of a thrombus, which could then potentially exit to the systemic circulation, and lead to cerebrovascular events.

Patent foramen ovale

Patent foramen ovale (PFO) is a common condition (up to 40% of the population), and may be associated with a higher than expected incidence of cerebral embolism (De Castro et al., 2000; Chant & McCollum, 2001; Sastry & McCollum, 2001). It consists of incomplete fusion of the septum primum and septum secundum, resulting in an interatrial connection, which is either continuously present or at least provokable with manoeuvres that raise the right atrial pressure (e.g. following Valsalva release), the so-called probe-patent PFO. In addition, patients with PFO not infrequently have abnormalities of the interatrial septum (e.g. hypermobility or redundancy), which are thought to further promote 'opening' of the foramen, with transient increases in shunt flow. It has been suggested that concomitant hypermobility with PFO of the interatrial septum increases the risk for cerebral embolism (Zhao et al., 1999; Marshall & Lock, 2000; Mattioli et al., 2001).

Like mitral valve prolapse, the association of PFO with embolic events is not clear. Several studies (Devuyst & Bogousslavsky, 1997; d'audiffret et al., 1999; De Castro et al., 2000; Chant & McCollum, 2001) suggest that the patent foramen ovale is a risk factor for recurrent embolism in young as patients, particularly those with right-to-left shunting as detected by transesophageal echocardiography (TEE). Whether long-term anticoagulation or prophylactic closure of the defect with either surgical or percutaneous techniques offers long-term protection against recurrent events is currently under investigation (Hung et al., 2000; Windecker et al., 2000; Hijazi et al., 2001).

Intracardiac tumours

The most common cardiac tumour implicated in cerebral embolism is a left atrial myxoma (Larsson et al., 1989; Majano-Lainez, 1997). These tumours may give rise to tumour emboli large enough to occlude cerebral arteries, which might be expected to lead to symptomatic neurological events (Reichmann et al., 1992; Vahedi & Amarenco, 2000). The cardiac symptoms of myxomas depend on numerous factors, especially how obstructive the mass is to the mitral orifice. Patients with atrial myxomata may present with a neurological event as their first sign of the syndrome (Bayir et al., 1999; Yuan et al., 1999), or may develop systemic symptoms, with an elevated erythrocyte sedimentation rate, arthralgias, fever of unknown origin (Andrews & Pollock, 1996; Boullanger et al., 1996), and changes in mental status (Saravay & Gupta 1998; Nhiwatiwa, 2000). It is believed that these unusual manifestations are due to production by the tumour of large amounts of inflammatory cytokines, such as interleukin-6 (Wiedermann et al, 1992). Furthermore, although rare, myxoma emboli may exhibit malignant potential, growing as cerebral tumours following embolism (Wada et al, 1993; Kanda et al., 1994). Embolism is particularly likely if the myxoma is of the villous variety (Shimono et al., 1995; Ha et al., 1999). Infective endocarditis of atrial myxoma ('myxocarditis') may be accompanied by an extremely high rate of embolism (Marshall & McDonald 1998; Revankar & Clark 1998). Urgent surgical extirpation is indicated whenever such a tumour is diagnosed.

Another cardiac tumour notably associated with a risk of cerebral embolism is the valvular papillary fibroelastoma (Brown et al, 1995; Yee et al., 1997). These uncommon tumours have a characteristic frond-like appearance, may be up to 3–4 mm in size, are occasionally multiple, and may occur on any valve structure, but in adults are most often found on the mitral or aortic valves (Giannesini et al., 1999; Golbasi et al., 2000; Grandmougin et al., 2000; Sastre-Garriga et al., 2000). Papillary fibroelastomas are thought to arise from focal injury to the valve structures, and thus may share a common pathogenesis with Lambl's excrescences, common irregularities found on heart valves, most often at the site of antecedent damage (Loire et al., 1998; Speights et al., 1998; Watchell et al., 2000). Both fibroelastomas and Lambl's excrescences may be diagnosed with cardiac ultrasound (Hicks et al., 1996; Yee et al., 1997). The treatment for symptomatic embolism in the setting of a papillary fibroelastoma is generally agreed to be valve replacement. The role of valve replacement for embolism in association with Lambl's excrescences is totally undefined.

Miscellaneous causes of cardioembolism

Calcification of the mitral annulus is diagnosed in a high percentage of patients with cryptogenic embolic strokes (Benjamin et al., 1992; Madias, 1992; Roijer et al., 1996; Vahedi & Amarenco, 2000). It is not entirely clear whether mitral annular calcification is the source of these emboli, however, on gross inspection, annular calcification may demonstrate fresh overlying thrombus, possibly explaining the higher risk of stroke noted among these patients. The risk of embolism has been clearly demonstrated in patients with mitral annular calcification and atrial fibrillation. Calcification of either the aortic or mitral valve leaflets themselves is occasionally implicated as a source of emboli, and may be the first sign of valve pathology in some patients (Oliveira-Filho et al., 2000).

A poorly defined entity known as 'valve stranding' has been documented among patients with cryptogenic embolic strokes (Tice et al., 1996; Nighoghossian et al., 1998; Palazzuoli et al., 2000; Vahedi & Amarenco, 2000). Most commonly noted on the mitral valve, it is thought that these strands represent fibrin, which coalesced under low flow conditions. The true stroke risk associated with fibrin valve stranding has not been defined.

Cardiac surgery and the brain

Coronary artery bypass surgery

Over 500 000 persons in the United States and 800 000 worldwide undergo coronary bypass grafting (CABG) each year for the treatment of coronary artery disease. There is little question that the surgery is very effective in reducing angina, and in stabilizing ventricular function in the majority of patients. For example, 5 years after CABG for severe, unstable angina, 86% of patients were free of angina, and of those with angina, only 3% had the severe, unstable form; 94% of patients remained free of angina without additional surgery (Bypass Angioplasty Revascularization Investigation, 1997). Those at higher risk have improved survival with CABG than with medical therapy (Solomon & Gersh, 1998; Yusuf et al., 1994).

With advances in anesthetic and surgical techniques, the population eligible for this coronary artery bypass grafting (CABG) is not only older, but also more likely to have associated health problems such as hypertension or diabetes. In addition, an increasing number of patients have had a previous angioplasty procedure, delaying the age of initial CABG. There is increasing recognition, however, that although CABG may be successful for the heart, it may have an adverse effect on the brain. Four neurological and

cognitive complications have been observed after CABG: stroke, postoperative delirium, short-term cognitive change and possible long-term cognitive change (Selnes, 1999a).

Stroke

Stroke is a well-recognized complication of CABG. The reported incidence ranges from 0.8% to 3.2% in retrospective series (Martin & Hashimoto, 1982; Coffey et al., 1983) and from 1.5% to 5.2% in prospective studies (Breuer et al., 1983; Roach et al., 1996). Stroke after CABG is reported to be more common than is stroke after other surgical procedures (Limburg et al., 1998). Moreover, the mortality among patients with strokes is 20%, whereas overall mortality for CABG patients is reported as 2 to 4% (McKhann et al., 1997). In addition to patient suffering, the economic impact of stroke is considerable: length of stay both in the intensive care unit and in the hospital are significantly prolonged, and hospital costs are doubled (Roach et al., 1996) (Table 122.1).

Table 122.1. Clinical evidence of stroke after cardiac surgery procedures

Procedure	Total cases	Stroke incidence
CABG	3974	3.2%
Valve	828	2.8%
CABG/Valve	463	6.7%
CABG/CEA	52	17.3%
CABG/Other	76	9.2%
Aortic procedures	310	4.2%
Heart transplant	94	1.1%
Other	174	1.1%
Total	5971	3.6%

Notes:
CABG = coronary artery bypass grafting; CEA = carotid endarterectomy; Other = other cardiac procedures requiring cardiopulmonary bypass (e.g. repair of atrial septal defect or left ventricular aneurysm)
Source: Adapted from McKhann et al. (1997).

A number of studies have developed models to identify patients at higher risk for stroke (McKhann et al., 1997; Newman et al., 1996; Herlitz et al., 1998) (Fig. 122.1, see colour plate section). In general, these predictive models are dominated by factors associated with cardiovascular disease such as hypertension, diabetes, peripheral vascular disease, evidence of cerebrovascular disease, and age. It is the combination of these factors that more strongly predicts outcome. Single factors alone, even age or diabetes, are less predictive. Thus, a 75-year-old man without a history of hypertension, diabetes, or a previous stroke, is at low risk for a stroke after CABG. In contrast, a 65-year-old man with a history of hypertension, a previous stroke, and diabetes is at high risk for stroke. The ability to identify patients at high risk for stroke has important implications. All of these risk factors can be assessed by a general physician in his/her office, before surgery. Thus, this information can assist informed decision making by patients and their families and physicians. For example, some patients may be better candidates for continued medical management or percutaneous transluminal coronary angioplasty (PTCA). For others, modification of the surgical procedure can be considered, such as changes in the placement of the aortic cannula from the cardiopulmonary pump, and different methods of clamping the aorta. Decisions at the time of surgery can be aided by evaluating the degree of arteriosclerosis of the ascending aorta. Recent studies have indicated that epiaortic ultrasound or transesophageal echocardiography are effective methods for detecting both the presence and severity of aortic arteriosclerosis (Davila-Roman et al., 1996). Identification of the location of arteriosclerotic plaques and subsequent modification of the surgical procedure can decrease the rate of stroke (Wareing et al., 1993).

Finally, although not proven, it would be expected that the increasing use of 'off pump' surgery (which minimizes the need to manipulate the aorta) would be accompanied by a lower incidence of embolic stroke.

Postoperative delirium

The symptoms of postoperative delirium are well known to the medical personnel involved with the care of elderly patients after major surgery. In one of the few prospective studies of this problem, Marcantonio and colleagues found that postoperative delerium occurred in 9% (117 of 1341) patients undergoing non-cardiac surgery (Marcantonio et al., 1994). The reported incidence after CABG has varied. In older studies it was as high as 10% to 28% (Breuer et al., 1983; Kornfeld et al., 1978), but recent experience suggests that the incidence may be decreasing (Van Der Mast & Roest, 1996). The mechanism of the encephalopathy postoperatively is not clear. However, the use of DWI imaging suggests that many of these patients have multiple small embolic infarctions (Wityk, 2000).

These patients are similar to stroke patients in length of hospital stay and consequent hospital costs (McKhann et al., 1997). The cognitive outcome in patients with postoperative delirium has not been systematically investigated. It is not known whether these are the patients who have subsequent cognitive deficits, particularly in the long term.

Cognitive changes

As a result of significant advances in anesthesiological and surgical techniques over the past several years, it is widely assumed that the incidence of postsurgical cognitive decline has been reduced. The benefits of such technological advances, however, may have been offset by inclusion of older patients with more comorbid disease. The extent to which postoperative cognitive dysfunction is detected will depend on measurement techniques, timing of the assessment, and statistical methods. Some of these methodological issues have been addressed by international consensus conferences in 1994 and 1997 (Murkin et al., 1995, 1997). One concerns the selection of neuropsychological tests. Because the cognitive changes may arise from more than one etiological mechanism, a test procedure that assesses all major cognitive domains is preferable. This is particularly relevant when interpreting studies with 'null' findings. If the test battery did not include assessment of, for example, frontal lobe functions such as planning and abstraction, or parietal lobe functions such as spatial and constructional abilities, abnormalities in these areas are missed. Because of limited time available for neurobehavioural testing preoperatively, few studies have included tests covering all major cognitive domains.

A second, but until now, relatively unexplored issue concerns presurgical baseline performance. There is considerable variability in neuropsychological performance at baseline, with some patients performing at expected age- and education-adjusted levels and others performing significantly below expected levels. It has been assumed that this variability might arise from high levels of presurgical emotional distress in some patients. More recent studies, however, have suggested that a subset of candidates for CABG may actually be cognitively impaired prior to surgery (Vingerhoets et al., 1977). These findings have several implications for interpretation of cognitive outcome studies. First, decline secondary to CABG in patients who are already impaired at baseline might be underestimated. A second, and more unexpected implication is the possibility that chronic cardiovascular disease may be associated with mild neurobehavioural impairment, which may actually improve as a result of CABG.

Several methods have been used to measure post-CABG cognitive change. The first, and most common strategy has been to assess the frequency of any cognitive change. The outcome measure is typically defined as decline in performance by, for example, 1 standard deviation on two or more tests. This approach is useful for estimating the incidence of cognitive change, particularly in intervention studies, such as reducing the number of microemboli (Stump et al., 1996). The second approach is to evaluate the frequency of change by specific cognitive domains, thus addressing the question of what proportion of patients show change in memory, language, and other areas. This approach is useful when addressing questions of pathophysiology of the cognitive changes after CABG. For example if, as has been suggested, some regions of the brain are more susceptible to the effects of emboli, changes might occur in certain cognitive domains but not in others. This domain-specific approach also has the advantage that the pattern of cognitive changes may be differentiated from expected changes with normal aging, Alzheimer's disease, or other causes of cognitive decline in the elderly.

Short-term changes

In the first few weeks after surgery the most common complaints relate to memory functions. The recognition of such cognitive changes by patients, their families and their physicians, led to series of studies in which different areas of cognitive performance were tested before, and at varying intervals after CABG. Many of these tests were administered at short times after surgery: while patients were still in hospital, or days and weeks after surgery. Estimating the relevance of short-term outcomes is complicated by the wide range of reported incidence of cognitive decline (from 33 to 83%) (Savageau et al., 1982; Shaw et al., 1987). Some of the discrepancies can be attributed to use of different tests and to evaluating diverse populations (for example, in general, European studies involved younger patients (Newman et al., 1987) and some studies excluded patients with comorbid disorders (O'Brien et al., 1992). More importantly, the majority of studies of outcomes after CABG reported in the literature are limited by lack of appropriate control groups. Thus although cognitive changes are well documented, it has been difficult to determine whether they are specifically related to the procedure itself or whether other surgical procedures would produce similar postoperative cognitive changes.

In a study comparing 1218 postoperative (non-cardiac) patients with non-operated controls, cognitive dysfunction was reported in about 26% of patients 1 week after surgery and about 10% of patients 3 months after surgery, compared with 3.4 and 2.8% of non-operated controls after 1 week and 3 months, respectively (Moller et al., 1998). Williams-Russo et al. (1995) compared outcomes in patients after CABG with outcomes in patients after total knee or hip replacements, and found a similar incidence of cognitive decline in both groups 1 week and 6 months after surgery. The cognitive domain with the highest frequency of decline was memory, with nearly 30% of patients showing clinically significant decline at 6 months. Vingerhoets and colleagues (Vingerhoets et al., 1997) and

Murkin et al. (1995) also found similar frequencies of cognitive decline after surgery for patients undergoing major vascular or thoracic surgery and those undergoing CABG. These findings suggest that some of the short-term cognitive changes after CABG may not be specific to this procedure, but may also accompany other surgical procedures.

Long-term changes

The longer-term cognitive complaints of patients are more difficult to characterize. They involve more subtle deficits, such as problems in following directions, especially in new locations, in planning complex acts, such as playing chess, and in performing calculations. Such changes are sometimes described by the non-specific complaint 'I'm just not quite right.' Although only a few studies have followed patients beyond 6 months, there have been reports of persisting cognitive symptoms, and in some cases, delayed cognitive decline (Aberg et al., 1983; Sotaniemi et al., 1986; Klonoff et al., 1989).

By extending the follow-up period to 1 year and beyond, we have found that some cognitive deficits persist and some, such as constructional praxis (the ability to copy a complex figure) may even progress from 1 month to 1 year. In the analysis at 5 years, the performance on cognitive testing had a two-stage course. From baseline to 5 years patients did well in most domains, actually improving in some. However between 1 year and 5 years after surgery, there was decline in almost all domains. Newman et al. (2001) have found a similar 'late decline' 5 years after surgery, but in a much higher proportion of patients. Interpretation of both of these studies is hampered by the lack of comparison with a non-operated group with similar risk factors for cardiovascular and cerebrovascular disease. This comparison is important because both hypertension and diabetes are association with cognitive decline, even in a middle-aged population (Knopman, 2001). Thus it is not clear that this late decline is specific to the surgery or would occur in a similar 'at risk' population over time.

A possible delayed effect of CABG may reflect damage, and possible continuing damage to an area of the posterior parietal cortex where the three vascular territories come together. This area, designated a so-called 'watershed area', is particularly vulnerable to effects of hypoperfusion (Howard et al., 1987). Although some of these changes may be subclinical in nature, they may nonetheless be markers of underlying brain changes.

One of the few studies that have compared cognitive outcomes after CABG and angioplasty at later time intervals such as 5 years concluded that long-term cognitive function did not differ between the two groups (Hlatky et al., 1997). However, this study did not include any measures to assess visuoconstruction or visual memory, domains that others have found to be particularly susceptible to longer-term change (Aberg et al., 1983; Sotaniemi et al., 1986; Klonoff et al., 1989).

Predictive factors for cognitive outcome

Several studies have attempted to identify pre- or intraoperative predictors of cognitive change after CABG. It appears that short-term studies have consistently identified a set of predictors different from those in long-term studies. For example, in shorter-term evaluations (1 week to 1 month), increasing age, low education and increased numbers of emboli as determined by carotid ultrasound, are all associated with a higher incidence of cognitive change (Pugsley et al., 1994). In longer-term assessment, age and education were not associated with worse outcomes, but diabetes and severity of arteriosclerotic disease of the aorta were associated with declines in specific cognitive domains (Newman et al., 1995). This provides additional support to the interpretation that some of the immediate postoperative changes may be due to non-specific effects of surgery or anaesthesia, whereas the persistent or late cognitive changes may be more directly attributable to the effects of CABG (Selnes, 1999). It is not clear at present whether short-term decline predicts late decline. However, the studies of Newman (Newman, 2000) suggest this may be the case.

Depression and cardiac surgery

Depression is commonly reported after most cardiac surgery procedures, with a frequency of up to 25% (Langeluddecke et al., 1989). Most of the reports, however, do not take into account the preoperative mood of the patient in relation to the incidence of postoperative depression. Recent studies indicate that newly acquired depression after CABG is relatively uncommon and that preoperative depression is the best predictor of postoperative depression (McKhann et al., 1997; Timberlake et al., 1997). A common perception among physicians is that depression accounts for the cognitive changes, particularly deficits in memory, that occur after CABG. However, these same studies found no association between depressed mood and change in cognitive performance. As with outcome after myocardial infarction, discussed below, depression either before or in the postoperative period influences the response to CABG. Those with depression at these time points are significantly more likely to have the return of angina at 1 year or 5 years after surgery, as compared to those without depression.

Mechanisms of neurological injury following cardiac surgery

There has been considerable interest in the possible mechanisms of brain injury. Two major mechanisms have been proposed: intraoperative hypotension and multiple emboli. A degree of genetic susceptibility may also play a role.

Intraoperative hypotension

Many patients (60%) who undergo CABG have a history of hypertension. Since the mean arterial pressure during cardiopulmonary bypass is often quite low, less than 50 mm Hg, these previously hypertensive patients are subjected to temporary or fluctuating hypotension. Nevertheless, on the basis of an automated anesthesia record, Newman and colleagues (Newman et al., 1995) did not find a correlation between mean arterial pressure and cognitive outcome, except in the visual memory in older patients, suggesting that hypotension and hypoperfusion may be more important in older patients, but in younger patients a different mechanism may be involved. Another possibility is that longer-term follow-up is required to detect the neurobehavioural effects of hypoperfusion.

The role of emboli

Pathological examination of the brain after CABG by Moody and colleagues (Moody et al., 1990) revealed the presence of thousands of emboli lodged in brain microvessels. Small capillary/arteriolar dilatations (SCADS), as they were named by these authors, were first thought to be the response to air emboli. It is now thought that SCADS are lipid-containing emboli and that they also contain silicon and aluminium, which may be derived from the cardiopulmonary circuit and its tubing. Other studies indicate that the degree of arteriosclerotic disease of the aorta and the number of emboli detected by transcranial Doppler ultrasound are correlated with changes in cognitive function, adding support to the hypothesis that the cognitive changes are related to multiple cerebral emboli (Stump et al., 1996). The distribution of these emboli in the brain might account for the selective changes in specific cognitive domains that we and others have observed. Showers of these small emboli most likely scatter to distant branches of vessels.

It is possible that both hypoperfusion and embolic factors, as well as the effects of anesthesia, are involved in neurobehavioural changes: short-term abnormalities might be related to the combined, and perhaps additive effects of embolic damage and anesthesia. In contrast, longer-term changes may be more specifically associated with the CABG procedure with the concurrent use of cardiopulmonary bypass, hypothermia, and the manipulation of a diseased aorta (Brown et al., 1997).

The role of genetic factors

Tardiff and colleagues (Tardiff et al., 1997) examined the role of apolipoprotein E-e4 (APO E-4), a known genetic marker for late onset Alzheimer's disease. APO E-4 was associated with a decline in cognitive function at hospital discharge and 6 weeks postoperatively in four out of nine cognitive measures. The authors suggest that some individuals have decline in cognitive function because of genetically determined deficits in maintenance and repair of neuronal functions, but further study is required to confirm this possibility.

Cardiac arrest

The term 'cardiac arrest' refers to people who have the sudden onset of ineffective cardiac function. About half of these people have ventricular fibrillation or tachycardia with the remainder having asystole or pulseless electrical activity. Most cardiac arrests occur outside hospitals, and overall survival of this group is poor, despite prompt response of emergency personnel. For example, in New York City, the overall survival varied from 2% to 12% depending on the presence of emergency medical services (Westfal, 1996). In smaller cities, perhaps with better-organized emergency services, survivals are better: 14% are discharged from the hospital alive and 12% are alive 1 year later (Bottiger, 1999). The best survivals are in those with ventricular fibrillation/tachycardia, the worst in those in asystole or pulseless electrical activity. Favourable circumstances are younger persons with ventricular fibrillation, a witnessed cardiac arrest, early CPR by bystanders, and arrival of trained medical personnel within a very short time (four or less minutes) (Grubb, 2001).

Not surprisingly, the outcome after an in-hospital cardiac arrest is significantly better than when the event occurs outside the hospital. In addition, the increasing use of more novel antiarrhythmic agents (such as intravenous Amiodarone) to suppress further arrhythmia, together with higher-dose epinephrine or vasopressin (to promote a 'head-heart' circulation) may improve the initial procedural success.

Following successful resuscitation, the immediate survival in those with restored circulation is more dependent on cardiac than neurological factors, involving the prevention of further arrhythmias, maintenance of blood pressure, management of cardiac ischemia. Given the generally poor neurological outcome of cardiopulmonary arrest,

long-term improvements in cardiac outcome do not often translate to sustained benefits, however the combination of intravenous antiarrhythmic agents together with aggressive efforts towards revascularization may reduce the long-term mortality of such patients. Whether this translates to lower morbidity rates remains unproven.

Neurological outcomes after cardiac arrest

The increasing availability of emergency medical services and a more general use of CPR by the public has resulted in more people with cardiac arrest having restored circulation but with severe brain damage that is either irreversible or incapacitating. Thus it becomes increasing important to be able to make predictions about possible outcomes. If a person has a very low probability of surviving to discharge from the hospital then persistent acute management, such as continuing CPR, use of antibiotics and life saving interventions may be not be indicated. Further, if the long-range prognosis for functional brain recovery is slight, the family should be informed and discussion of approaches to therapy initiated (Grubb, 2001).

Outcomes predictions have been based primarily on clinical criteria, but have been augmented by neurophysiologic, laboratory and neuroimaging evidence. It is important to be clear about what time points after the arrest are being used in making predictions. In addition, the outcomes being judged should be defined, and may include: survival, motor function and/or cognitive ability.

Clinical criteria for outcomes after cardiac arrest

Immediately, and during the first few days after a cardiac arrest, the focus has been on the persistence and depth of coma and the lack of brainstem reflexes. Lack of pupillary light responses, corneal responses to touch and eye movements in response to head movements or cold caloric stimulation all indicate severe brainstem damage, with the possible exception of those exposed to suppressive medications. The use of the responses to predict outcome has been exemplified by the work of Levy, Caronna and coworkers who evaluated over 200 comatose patients, 150 of whom had had cardiac arrest. Patients were examined at 1, 3, 7 and 14 days after arrest and functional state was then categorized at 1, 3, 6 and 12 months into five grades: (i) no recovery (i.e. coma until death), (ii) persistent vegetative state (i.e. wakefulness awareness), (iii) severe disability (i.e. conscious but dependent on others for aspects of daily living), (iv) moderate disability (i.e. independent but with residual neurological deficits), (v) good recovery (i.e. able to resume prior level of function) (Levy, 1985).

Certain early signs were associated with relatively good chances of recovery. At the initial examination, the most favourable sign was incomprehensive speech (moaning), but this was rare. At 1 day, the following signs were each associated with at least a 50% chance of regaining independent function: confused or inappropriate speech, orientation of spontaneous eye movements, normal oculocephalic or oculovestibular responses, obedience to commands, and normal skeleton muscle tone. Although the pattern of motor responses eventually correlated with recovery, neither the initial absence of motor responses nor the presence of extensor of flexor posturing ruled out recovery. After 3 days, however, absent or posturing motor responses were incompatible with future independent living.

The absence of certain brain stem reflexes at the initial examination identified patients with little or no likelihood of meaningful recovery. Most patients destined to recovery wakened within a short time. By 3 days, 25 patients had regained consciousness; 19 of them went on to regain independent function. By 2 weeks, the number of conscious patients had risen to only 28, with 21 of them recovering independence. The vegetative state also developed rapidly in many patients; 47 patients appeared vegetative within the first day, but only 11 subsequently became independent. Of the surviving 33 vegetative patients at 1 week, only 3 patients ever improved to an independent state. The number of comatose patients dropped rapidly after the insult, with 106 still comatose after 1 day but only 57 at 3 days and 17 at 1 week. Only one of the 17 comatose patients at 1 week subsequently regained consciousness. Improvement after 1 month was rare. None of the 15 patients who were vegetative at 1 month ever regained independent function, and only 3 of 16 patients who were severely disabled at 1 month did so.

The death rate associated with anoxic coma of 6 hours or more was extremely high: 4 patients (20%) died within the first 24 hours, 86 patients (41%) by the end of 3 days, and 134 patients (64%) by the end of the first week. Only 19 patients (10%) survived 1 year after cardiac arrest, the majority of whom succumbed to non-neurologic causes.

This study showed that mortality and morbidity are high among patients in coma after anoxia, but some patients still have the neurologic capacity to do well. The study also found that careful analysis of early clinical information distinguished between good-prognosis and poor-prognosis patients. Patients with the best chance of recovery had intact brain stem function at the time of the initial examination after the cardiac arrest (reactive pupils and motor responses), as well as spontaneous roving eye movements. At 1 day and beyond, evidence of intact cortical function (motor response withdrawal or better and orienting eye movement) indicated the patients who would recover.

Neurophysiological testing and cardiac arrest

The techniques of EEG and cerebral evoked potentials have been used as possible predictive measures. EEG patterns of alpha coma, burst suppression or isoelectric activity have all been associated with poor prognosis, but are not absolutely specific. To be sure, an isoelectric, flat EEG is incompatible with life. At the other extreme, an EEG with normal alpha rhythms suggests a good prognosis. The grades in between indicate severe brain abnormality at the time of recording, but may not accurately predict prognosis. The absence of central responses to somatosensory stimulation, usually elicited by repetitive stimulation to the median nerve, indicates a poor prognosis. Conversely, those with normal central responses may have good recoveries. These neurophysiological tests are used as adjuncts to the clinical examination. They may prove useful as outcome measures for pharmacological interventions that might promote recovery.

Laboratory tests and cardiac arrest

There has also been interest in laboratory tests that reflect structural damage to the brain such as protein S.100 and neuron-specific enolase (NSE) (Martens et al., 1998). Most studies of these compounds have been made in small numbers of comatose patients. In general they do correlate with severe brain damage and poor outcomes, but it is not clear that they have prognostic value for those destined to survive, but with significant brain damage.

Brain imaging and cardiac arrest

The sequence of responses of the brain, particularly the cerebral cortex, can be followed by diffusion-weighted magnetic resonance imaging (DWI). Normally in the brain, water molecules move in random fashion (Brownian motion), resulting in low signal intensity on high-strength DWI images. With global anoxia, cytytoxic edema occurs, which leads to restriction of Brownian motion and an enhanced signal intensity. Whereas more conventional imaging techniques, such as CT scanning and MRI may be normal or equivocal, particularly in the first few hours after a cardiac arrest, DWI can reveal specific changes (Arbelaez et al., 1999). Within 24 hours, a bright signal may be present in basal ganglia, cerebellum, and cerebral cortex. Between 1 and 13 days, bright signals are seen cortex and may also be in deeper structures like the basal ganglia or thalamus. Some of these changes are also seen on conventional MRI, but are better demonstrated by DWI. These changes on DWI imaging reflect the selective vulnerability of specific neuronal populations to anoxic damage. The reasons for this vulnerability are not known but a higher metabolic rate by neurons, abnormal blood flow, particularly in the border zones between the distribution of vascular territories, and the presence of receptors for excitatory amino acids, such as glutamate may all play a role. In later periods (21 days or more) following the insult, the changes in cortex may disappear, but new changes appear in the white matter. Some investigators have detected these white matter changes even earlier, suggesting a myelinotoxic effect of anoxic/ischemic insult (Chalela et al., 2001).

Imaging techniques that indicate the degree of brain perfusion, such as positron emission tomography (PET) or single photon emission computed tomography (SPECT) indicate hypoperfusion of frontal areas as well as areas of hypoperfusion in the border areas between vascular distributions (so-called 'watershed' areas), but the logistics of these techniques are difficult to accomplish with these severely ill patients.

At present, no prospective study of outcome after cardiac arrest, combining the clinical observations with promising imaging (DWI) and neurophysiological (evoked potentials) techniques has been performed. Such a study is badly needed, not only for the desirability of making more accurate predictions in clinical situations but also to determine outcomes for therapeutic attempts.

Treatments following cardiac arrest

A number of treatment measures have been tried, either singly or in combination. These include attempts to decrease brain metabolism (hypothermia, barbituates, or administration of glucose), to decrease brain edema (dexamethasone) or block movement of calcium into cells (Nimodipine). Few of these measures have been consistently shown to improve outcomes or have been evaluated in clinical trials. However, for most persons undergoing cardiac arrest the damage has already been done by the time medical intervention is possible. Thus, the focus is on preventing further damage to nerve cells. There are a number of agents that are being evaluated in experimental animals as neuroprotective agents such as antioxidants, NMDA receptor antagonists, calcium channel blockers or statins. Some of these agents will undoubtedly be tried in attempts to improve outcome after cardiac arrest.

Congestive heart failure

Patients with congestive heart failure may have encephalopathic symptoms, with varying levels of confusion, variability in neurological findings, and global decrease in intellectual functions (Caplan et al., 1999). Sometimes this

encephalopathy is secondary to poor perfusion or embolic damage to other organs such as the liver, kidneys or lungs. At other times the condition is related to the use of medications such as those to treat pain, anxiety or the congestive failure. Others may have an underlying disorder of blood volume or electrolyte balance. When these underlying conditions are ruled out or corrected, there remains a group of patients for whom the cause of the encephalopathy is not known. Caplan et al. have described two clinical syndromes: the first resembles the encephalopathy of other causes. The second they refer to as 'abulia', a condition characterized by a marked reduction in spontaneous behaviour. Such people are listless, may be non-responsive, or very slow in responding. The mechanism is not clear, but these authors suggest there is retention of CSF within the cranial cavity. Such patients may improve after removal of fluid by lumbar puncture.

The influence of the brain on the heart

Although suspected to be the case for many years, the influence of the central nervous system on several cardiovascular disease states is now undeniable (Januzzi et al., 2000). Several diseases have well-established associations with both acute and chronic heart disease. Among these are migraine headache, subarachnoid hemorrhage, cerebral infarction, head trauma, and seizure disorder. Each of these may result in marked electrocardiographic abnormalities, occasionally associated with arrhythmias, or even myocardial necrosis.

In the case of migraine headache, a clear association with coronary vasospasm has been established, which may explain the link to myocardial injury states that have been occasionally reported in migraneurs without CAD (Wayne, 1986; Lafitte et al., 1996). Typically, the patient with concomitant migraine and myocardial infarction, is female, and has a history of diffuse vasospastic tendency, including Raynaud's phenomenon. The role of agents used for the treatment of migraine (such as the ergot alkaloids) in coronary spasm has also been established (Koh et al., 1994; Dahlof & Mathew, 1998). In addition, even in the absence of clear signs of coronary spasm, these agents frequently lead to chest pain of an ischemic nature (Koh et al., 1994; Dahlof & Mathew, 1998), and may lead to elevations in markers of myocardial injury in the absence of clear electrocardiographic abnormalities (J.L. Januzzi: personal observation).

The association between blood in the subarachnoid space and myocardial necrosis has been recently clarified (Zaroff et al., 1999; Zaroff et al., 2000a,b). The myocardial injury associated with subarachnoid hemorrhage may be diffuse; however, an unusual predilection for both 'apex-sparing' and 'apex-only' left ventricular dysfunction has been described (Zaroff et al., 2000a,b). Similar to the phenomenon of combined cerebral/coronary spasm seen in migraine headache, coronary spasm might be operative in the setting of subarachnoid hemorrhage as well. In many cases, however, a single epicardial vascular occlusion cannot adequately explain the wall motion abnormalities produced. In an experimental model, the possible involvement of direct neurological-mediated injury to the myocardium in the setting of subarachnoid hemorrhage was proposed, as the wall motion abnormalities closely approximated the distribution of the sympathetic nerve terminals in the myocardium (Zaroff et al., 2000a,b).

The most common cardiac manifestation of cerebral hemorrhage, large cerebral infarctions, seizures or head trauma are the so-called 'cerebral' changes on the electrocardiogram (Salvati et al., 1992; Lindgren et al., 1994; Strauss & Samuels 1994). These changes typically consist of giant precordial T-wave inversions. In addition, marked QT interval prolongation has been described. Rarely, patients with this 'cerebral' QT interval prolongation may develop polymorphic ventricular arrhythmia (Torsades de Pointes). It is theorized that the cerebral ECG changes are due to an exaggerated imbalance in the balance between sympathetic and parasympathetic cardiac tone.

Among the most studied (but perhaps least well-known) paradigm for the association between the brain and heart is the role of acute and chronic disorders of mood and affect (including stress, anxiety, and depression) on cardiac illness. Similar to other brain–heart syndromes such as those seen with cerebral infarction, these 'psychosocial risk factors' are thought to exert their deleterious effects on the heart via abnormalities in autonomic nervous system balance, with direct effects on the heart. In contrast to the aforementioned syndromes, however, are the rather profound peripheral effects on platelet function and vascular tone as well as due to psychosocial risk factors. Taken together, these effects would be expected to result in an impressive impact on the development and the complications of coronary artery disease, cardiac arrhythmias, and sudden cardiac death. Recent work has confirmed this fact (Januzzi et al., 2000).

The brain and development of cardiac disease

The relationship between the brain and the development of cardiac disease (including arrhythmia and coronary disease) had previously been suggested by numerous studies documenting an elevated risk from stress, anxiety, or depression. In each study, these disorders were associated with significant increases in sudden death or myocardial infarction (Table 122.2).

Table 122.2. Selected modern studies of anxiety (and related syndromes), depression, and the development of heart disease

Authors	Risk factor	End-point(s)	RR (95% CI)
Corywell et al. (1986)	Panic disorder	Death	2.0 (NR)
Haines et al. (1987)	Phobic anxiety	Death	(1.6–8.6)
		MI	1.3 (0.6–2.5)
Kawachi et al. (1994a)	Phobic anxiety	Sudden death	4.5 (2.4–15.7)
		MI	0.9 (0.5–1.8)
Kawachi et al. (1994b)	Anxiety	Sudden death	4.5 (0.9–21.6)
		Fatal CHD	1.9 (0.7–5.4)
Kubzansky et al. (1997)	Worry	MI	2.4 (1.4–4.1)
Anda et al. (1993)	Depressive symptoms	MI	1.5 (1.0–2.3)
Aromaa et al. (1994)	Depressive symptoms	MI	3.5 (1.8–6.8)
Pratt et al. (1996)	Major depression	MI	4.6 (1.7–12.4)[a]
Barefoot & Schroll (1996)	Depressive symptoms	MI	1.7 (1.2–2.3)
Ford et al. (1998)	Depressive symptoms	MI	2.1 (1.2–4.1)

Notes:

[a] RR of 2.1 (95% CI = 1.2–3.7) for symptoms of dysphoria.

NR, not reported; MI, myocardial infarction; CHD, coronary heart disease.

The role of neurological factors in the development of CAD was initially suspected following the recognition that anxious or depressed patients had a higher incidence of angiographically proven CAD (Zyzanski et al., 1976), as well as a fourfold increase in the incidence of myocardial infarction (Pratt et al., 1996). This link has been well supported by the Johns Hopkins Precursor Study, which recently reported that depressed patients had a highly significant doubling in CAD risk over a 40-year follow-up period (Ford et al., 1998).

The association between extreme emotional states and a rather significant increase in sudden cardiac death (as high as sixfold in one study) raised the possibility that these deaths could be related to cardiac arrhythmia (Kawachi et al., 1994a,b). Patients with depression have been demonstrated to have a higher incidence of ventricular tachycardia on non-invasive monitoring (Carney et al., 1993). Furthermore, in studies of patients with extreme mental stress, impressive episodes of malignant ventricular arrhythmias have been demonstrated, even among patients with structurally normal hearts. In addition, an increased incidence of sudden deaths (presumably due to cardiac arrhythmia) has been demonstrated in the setting of major natural catastrophes, such as earthquakes (Rosenman, 1996; Kario & Ohashi 1997) as well as following missile strikes during the Gulf War (Kark et al., 1995).

The mechanism of this increased predisposition to cardiac arrhythmogenesis is probably related to abnormalities in autonomic nervous system (ANS) tone, with increased resting levels of catecholamines (Yehuda et al., 1998; Carney et al., 1999; Grossman & Potter, 1999). In addition, among patients with anxiety and/or depression, derangements in baroreflex sensitivity as well as heart rate variability have been noted. Both of these findings are related to abnormalities in ANS tone (possibly regulated by somatosensory thalamocortical neurons), and are each independently associated with an increased risk for sudden cardiac death. This combination of factors, including elevated levels of catecholamines, would be expected to lead to a propensity to ventricular arrhythmia. Imaging studies would suggest that interactions between these risk factors and the dominant insular cortex may play a role in the genesis of arrhythmias (Svigelj et al., 1994; Eckhardt et al., 1999; Tokgozoglu et al., 1999), but this association has not been confirmed.

In most studies examining the relationship of psychosocial risk factors and CAD, the risk appears to be independent of conventional cardiac risk factors such as tobacco use, and compliance to medical therapies. The biological link to premature or accelerated CAD may be perturbations in blood lipid levels and endothelial function, increased platelet aggregability as well as abnormalities in vascular tone, which have been noted among these patients.

Table 122.3. Selected studies regarding anxiety, depression, and established ischemic heart disease

Authors	Risk factor	End-point(s)	RR (95% CI)
Frasure-Smith (1995a,b)	Anxiety	Fatal/non-fatal MI, UAP	2.5 (1.6–5.6)
Moser & Dracup (1996)	Anxiety	Death, MI, VT/VF, UAP	4.9 (2.1–12.2)
Thomas et al. (1997)	Anxiety	Death	1.06 (NR)[a]
Denollet & Brutsaert (1998)	Anxiety	Death, MI, UAP	3.9 (1.2–9.6)
Herrmann et al. (1998)	Anxiety	Mortality	2.5 (1.4–4.4)
Carney et al. (1988)	Depression	Death, MI, PTCA, CABG	2.5 (NR)
Frasure-Smith et al. (1993)	Depression	Fatal/non-fatal MI, UAP	3.6 (1.3–10.1)[b]
Barefoot et al. (1996)	Depression	CD, ACM	$P = 0.002$ for CD $P = 0.001$ for TM
Denollet & Brutsaert (1998)	Depressive symptoms	CD, MI	4.3 (1.4–13.3)
Frasure-Smith et al. (1995a,b)	Depressive symptoms	CD	[c]3.3 (1.0–10.59) [d]3.05 (1.29–7.17)

Notes:

[a] $P = 0.0029$.

[b] RR = 7.8 (2.4–25.3) for depressive symptoms.

NR, not reported; MI, myocardial infarction; UAP, unstable angina pectoris; VT, ventricular tachycardia; VF, ventricular fibrillation; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; CD, cardiac death; ACM, all-cause mortality.

[c] Female patients.

[d] Male patients.

The brain and established heart disease

The link between the nervous system and established heart disease is widely accepted for several syndromes, including the long QT syndrome or those predisposed to neurocardiogenic (vasovagal) syncope. In both of these syndromes, extreme stress may provoke arrhythmic manifestations (ventricular tachycardia and severe bradycardia, respectively), which may be fatal. Until recently, however, the pervasively deleterious effects of the CNS on cardiac outcomes (especially among patients with CAD) were not recognized.

The effects of stress, anxiety, and depression on the outcomes of patients with established CAD is dramatic (Table 122.3). It has been repeatedly demonstrated that following an acute myocardial infarction (MI), the presence of any of these psychosocial risk factors may lead to as high as a fourfold increased risk of death (Frasure-Smith et al., 1995a), which may be due to either an increased incidence of recurrent MI, or malignant ventricular arrhythmias (Carney et al., 1988, 1993).

As among patients without known structural heart disease, the increased risk for CAD patients with stress, anxiety, or depression is probably mediated by the ANS, manifested as imbalances in sympathetic/vagal tone, increased levels of catecholamines, platelet hyperaggregability, high vascular tone, and abnormalities in hemostasis (Manuck et al., 1995; Markovitz et al., 1996, 2000; Markovitz, 1998).

Intense investigation into therapeutic intervention in this area is ongoing. At present, it is unclear whether management for psychosocial risk factors will rectify the increased risk for coronary events among these patients, however treatment with conventional serotonin reuptake inhibitor antidepressants has been shown to be safe in the coronary artery population (Roose et al., 1998; Shapiro et al., 1999). These drugs have been interestingly shown to possess effects on blood platelets, including an antiaggregatory effect (Markovitz et al., 2000). It is unclear whether this would be expected to result in a therapeutic benefit.

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Neurological complications of hepatic and gastrointestinal disease

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The liver plays a key role in the regulation of body metabolism, and its functions include the synthesis of essential substances and the degradation of toxins. Liver failure may be accompanied by system-wide disturbances. These are no better exemplified than by the striking cerebral syndromes that occur with hepatic dysfunction.

The brain depends on the gastrointestinal system as a source of nutrition. The neurological disturbances that occur as complications of gastrointestinal disease arise from a wide range of pathological processes and may be quite diverse in presentation.

This chapter focuses on the neurological syndromes that result from various types of liver failure. In addition, it describes the neurological complications of selected gastrointestinal disease.

Neurological complications due to liver disease

The relationship between the liver and the brain has been recognized since the time of Hippocrates. Since then, there have been many accounts of dramatic behavioural disturbances that may occur with liver dysfunction. These have been eloquently reported by Plum and Hindfelt (1976).

The spectrum of nervous system disturbances occurring with liver disease encompasses a wide range of neurological and behavioural disorders. The term 'hepatic encephalopathy' is commonly defined as a neuropsychiatric syndrome arising as a complication of liver dysfunction. Although the term 'encephalopathy' implies a disturbance of consciousness and behaviour only, the neurological syndromes occurring with liver disease encompass a much broader spectrum of neurological disorders. These diverse manifestations do not lend themselves easily to a single definition. Thus, hepatic encephalopathy cannot be regarded as a single clinical entity.

Furthermore, although hepatic encephalopathy has been defined as a reversible metabolic encephalopathy, and although this may often be true, chronic liver failure does sometimes result in progressive, irreversible neurologic dysfunction. The terminology is additionally confusing in that it is not uncommon to use the term 'portal systemic encephalopathy' interchangeably with 'hepatic encephalopathy' (Jones & Weissenborn, 1997) because pathological shunting of blood between the portal and systemic circulation frequently develops.

Liver failure may take several forms. Sometimes it develops rapidly, in a most dramatic fashion, but usually the onset is insidious and the evolution is slow, with permanent disturbances in liver system function occurring over time. Often, the course of chronic liver disease is punctuated by episodes of acute neurological deterioration. These episodes are usually reversible and are frequently related to a well-defined cause.

Syndromes

Thus, although the term 'hepatic encephalopathy' is frequently used to describe the neurological component of liver failure, the diverse neurological manifestations of liver disease do not lend themselves easily to a single definition. The neurological complications of liver disease may be considered as follows.

(i) Fulminant hepatic coma refers to neurological disorders developing as a consequence of acute hepatic failure (Bernstein & Tripodi, 1998).

(ii) Chronic hepatic encephalopathy (Jones & Weissenborn, 1997) has two subtypes: a slowly evolving syndrome and an intermittent disorder. The chronic subtype is gradual in onset, develops in the absence of a definable precipitating event, and becomes more severe over time. The intermittent subtype is character-

ized by sudden episodes of deterioration in neurological function, often precipitated by clearly definable causes such as protein overload or gastrointestinal hemorrhage. Both the chronic and the acute exacerbating syndromes are considered to be reversible.

(iii) Subclinical hepatic encephalopathy (Gitlin et al., 1986) refers to subtle disturbances in cognitive function that occur in association with chronic liver disease. The abnormalities are not clinically evident and are detected only by neuropsychometric testing.

(iv) Acquired hepatocerebral degeneration is a less common neurological complication of chronic liver disease characterized by progressive, non-reversible neurologic disturbances (Victor et al., 1965).

Fulminant hepatic coma

Fulminant hepatic coma occurs in the presence of acute, often fatal, liver dysfunction (Bernstein & Tripodi, 1998). The hepatic failure occurs without pre-existing liver disease, and the encephalopathy usually develops within several weeks of onset of the liver disease. Three subgroups of fulminant hepatic failure have been proposed (O'Grady et al., 1993): hyperacute, acute, and subacute. Causes of fulminant hepatic failure include viral disease, idiosyncratic drug reactions, toxins, metabolic disorders and cardiovascular disease (Shakil et al., 1999). The onset of the encephalopathy is usually abrupt and in some instances may precede the constitutional symptoms (Zacharski et al., 1970). Agitation, delusional behaviour and restlessness may dominate the clinical picture in the early phases, only to be followed by the rapid onset of coma. Restlessness may be an early feature; this often is accompanied by marked facial grimacing. Later, as the patient becomes lethargic and motor activities are reduced, tremors of the limbs may develop, but asterixis is uncommon. Myoclonus may be noted during this phase. Seizure has also been reported (Bernstein & Tripodi, 1998; Saunders et al., 1972). Hypoglycemia is a common complication of a fulminant hepatic failure, and this may be a factor in the causation of seizures (Samson et al., 1967).

The prognosis in fulminant hepatic failure was extremely poor before the introduction of liver transplantation (O'Grady et al., 1988). Now, survival ranges from 50% to 70% (Bismuth et al., 1987; Vickers et al., 1988). The principal reason for high mortality is the development of cerebral edema and resultant raised intracranial pressure (Ede & Williams, 1986).

The management of fulminant hepatic encephalopathy hinges on recognition and treatment of raised intracranial pressure (Ede & Williams, 1986). Intracranial pressure monitoring is required, and measures such as hyperventilation (Ede et al., 1986) or infusion of mannitol (Canalese et al., 1982) have been used to decrease intracranial pressure. Intravenous phenobarbital has a place in the treatment of this disorder (Forbes et al., 1989). Propofol, which is easy to titrate, is also coming into use in the management of fulminant hepatic encephalopathy.

Chronic hepatic encephalopathy

The clinical features of chronic hepatic encephalopathy vary considerably (Adams & Foley, 1953; Sherlock et al., 1954). Slow evolution is the rule. This is a complex syndrome and includes several components, namely neurobehavioural disorders, motor disturbances, and impaired consciousness (Adams & Foley, 1949; Sherlock et al., 1954).

Neurobehavioural disorders

Cognitive decline Cognitive decline may be an early manifestation of liver disease (Read et al., 1967), and the initial features may be subtle and evident only to friends and family members. Individuals become withdrawn and apathetic, lack interest and appear slow in response times. At this stage, bedside testing of cognitive function may reveal abnormalities such as an inability to reproduce simple geometric patterns, and handwriting may be altered. In some instances, verbal skills may be spared; patients are thus able to compensate and mask the true nature of the disturbance. Minor changes in intellectual function over time may give way to severe cognitive impairment, and eventually, severe confusion becomes apparent.

Personality changes Personality changes may become apparent early in the course of the development of this syndrome (Sherlock et al., 1954). The patients' behaviour may become inappropriate and somewhat childlike. These traits, however, are often quite subtle and are also apparent only to family and close friends. Patients also tend to be restless, wandering around aimlessly, often exhibiting irrational behaviour, but sometimes preoccupied by repetitive, seemingly aimless tasks. Inappropriate behaviour may become quite obvious. Patients fail to observe basic social graces and often appear dishevelled and pay little attention to their surroundings.

Disturbances of sleep Other early signs of chronic hepatic encephalopathy include hypersomnia and inverted sleep rhythm (Summerskill et al., 1956).

Motor disorders

Asterixis Asterixis, also known as flapping tremor, is a common feature in chronic liver failure (Adams & Foley, 1953; Read et al., 1967). The features of asterixis have been characterized by Leavitt and Tyler (1964). These authors describe a complex of movement disorders in which tremor is combined with typical asterixis, and the two conditions appear to be inter-related. Asterixis is best demonstrated by maintaining the arm in a static posture, outstretched and with the hand held in a position of fixed dorsiflexion. The involuntary movements develop after a latent period lasting from 2 to 30 seconds. Tremulousness develops first. There tends to be an initial involuntary movement of the fingers taking the form of flexion and extension excursions, with some rotation at the wrist. Fine, random motions of the fingers may also occur. As posture is maintained, tremulousness increases, and the random movements may become more rapid. Then follows the development of the asterixis, which takes the form of a sudden flexion movement of the fingers and hand. This downward movement varies in excursion. This 'flexion lapse' is followed by a rather rapid, sometimes violent, backward movement restoring the extremity to its former posture. Both upper limbs tend to be involved, although the asterixis may occur asynchronously. Often, the movements may occur in 'clusters' of two or three, followed by a quiet phase. The patient is unable to influence the movement. Whereas asterixis is commonly seen in liver disease, it may occur with other types of metabolic dysfunctions (Leavitt & Tyler, 1964; Tyler, 1968) and toxic states (Kobayashi et al., 1985). Electromyographic studies (Adams & Foley, 1953) reveal electrical silence at the moment of the onset of the postural lapse, suggesting inhibition of the anterior horn cell, perhaps secondary to a disturbance of supraspinal motor control.

Myoclonus Multifocal myoclonus may become apparent (Read et al., 1967). This complication is most often seen at times of waning consciousness.

Alterations in tone Liver disease may produce marked changes in muscle tone (Adams & Foley, 1953). This may be of pyramidal or extrapyramidal type. The latter is similar to the rigidity observed in Parkinson's disease.

Extrapyramidal disturbances Extrapyramidal disturbances may be a prominent component and include rigidity, bradykinesia, facial masking, speech disturbances, and tremor (Adams & Foley, 1953; Read et al., 1967; Victor et al., 1965).

Table 123.1. Grading of hepatic encephalopathy

Grade	Mental state
0	Normal function
1	Mild personality and cognitive disturbances
2	Lethargy, disorientation, inappropriate behaviour
3	Somnolence, arousable gross behavioural disturbances
4	Coma or unarousable

Pyramidal system abnormalities Signs of pyramidal tract dysfunction may emerge as hepatic failure progresses. Increased tone with hyperreflexia and clonus may be found (Adams & Foley, 1953; Read et al., 1967; Victor et al., 1965). Plantar responses may be initially flexor but later become extensor in nature. As coma supervenes, tendon responses diminish.

Impaired consciousness and coma

Coma may occur terminally but may also emerge as a component of an intermittent event (see below). Patients become lethargic over time, consciousness gradually dwindles, and patients may slip into profound coma. In some cases, however, the onset of coma may be abrupt (Adams & Foley, 1953). Motor reactions to painful stimuli persist until the late phase of coma. Decerebrate and decorticate posturing may be evident (Conomy & Swash, 1968; Juneja & Yovic, 1972). The pupillary light response and ocular motor reactions are often retained almost to the last (Plum & Hindfelt, 1976). Coma unrelated to a treatable precipitating cause has a poor prognosis (Bustamante et al., 1999), unless liver transplantation is performed.

Whereas disturbed awareness is perhaps the central feature of various forms of hepatic encephalopathy, the state of consciousness may vary considerably during any episode of hepatic dysfunction. Thus, it has become customary to grade hepatic encephalopathy into four stages, based on the level of consciousness. A commonly used scale is outlined in Table 123.1.

Seizures

Seizures may complicate the clinical picture. These may be of the partial or generalized type (Adams & Foley, 1953).

Disturbance of speech

Speech may become deliberate and slow; later dysarthria may become prominent (Adams & Foley, 1953). Paratonic rigidity and grasping and sucking reflexes may occur as coma develops (Adams & Foley, 1953; Sherlock et al., 1954).

Table 123.2. Conditions that may precipitate hepatic encephalopathy

Excessive protein intake
Diuresis
Gastrointestinal tract hemorrhage
Diarrhea and vomiting
Surgical procedures
Infection
Pharmacological agents
Constipation
Alcohol consumption

These signs may be seen in end-stage coma as well as in the episodic syndromes that complicate chronic hepatic disease.

Disorders of ocular motility

Disturbances in eye movements may become apparent as coma evolves: skew deviation and internuclear ophthalmoplegia have been described (Plum & Hindfelt, 1976). These abnormalities may be transient and resolve as metabolic function improves. Divergence of the eyes in the primary position and disturbed oculocephalic responses to caloric testing may also occur (Caplan & Scheiner, 1980; Cartlidge & Bates, 1978). Transient ocular bobbing has also been reported (Rai et al., 1976), as has reversible periodic alternating gaze (Averbuch-Heller & Meiner, 1995). Ocular motility disorders occurring with hepatic coma are reversible but closely resemble the ocular findings in structural brainstem disorders. Awareness of the similarities between eye movement disorders due to liver failure and those due to a structural brainstem process is important because the finding may divert attention from the true nature of the diagnosis (Caplan & Scheiner, 1980).

Intermittent hepatic encephalopathy

Intermittent hepatic encephalopathy is characteristic of chronic liver failure (Jones & Weissenborn, 1997; Plum & Hindfelt, 1976; Sherlock et al., 1954; Victor et al., 1965). The episodes are most often precipitated by well-defined events (Table 123.2) and may come abruptly. Alteration in consciousness occurs and motor disturbances may be prominent. The individuals become increasingly somnolent, and a state of deep coma may supervene. In some instances, however, restless behaviour and agitation may be the dominant manifestation. The patients may become disoriented, and signs of overt delirium emerge. Motor accompaniments include asterixis, involuntary facial movements, and tremulousness. These motor disturbances may abate as coma deepens.

Dramatic as the presentation may be, treatment of the precipitating factor will usually result in remission of the signs and symptoms.

Subclinical hepatic encephalopathy

The term 'subclinical hepatic encephalopathy' was introduced to describe a disorder in patients with chronic liver disease who have no overt signs of nervous system dysfunction, yet cognitive disturbances are evident on formal psychometric testing. This condition was first described by Zeegen et al. in 1970. Other studies have confirmed the presence of abnormality on psychometric testing in patients with chronic liver disease (Conn, 1994; Gitlin et al., 1986; Sarin & Nundy, 1985). Although the reported prevalence of subclinical hepatic encephalopathy varies widely (Groeneweg et al., 2000), there is a strong body of evidence to indicate that this entity does exist (Hartmann et al., 2000; Schomerus & Hamster, 1998; Tarter et al., 1989).

Acquired hepatocerebral degeneration

Acquired hepatocerebral degeneration, a chronic form of hepatic encephalopathy, was described in detail by Victor and colleagues (1965). This disorder usually occurs in patients with chronic liver disease complicated by extensive portal–systemic shunting (Victor et al., 1965). As with other neurological complications of liver disease, the clinical manifestations are diverse. The course is characterized by a steady decline in neurologic function. An episodic deterioration in neurologic status may be superimposed; these exacerbations are often related to defined precipitating factors. The condition progresses over time, and patients become increasingly disabled. There are two major components to this form of hepatic encephalopathy, namely cognitive dysfunction and motor disturbances (Jog & Lang, 1995).

Cognitive dysfunction

Acquired hepatocerebral degeneration evolves out of the more common reversible neurologic disturbances that complicate chronic liver disease. Thus, personality and intellectual changes are often apparent in the early course of the process. In time, cognitive disturbances become severe and persistent. Apathy and slowness in response times become apparent. There is a general lack of interest in the environment. As in other types of dementia, lack of attention to personal appearance and poor hygiene become apparent. However, signs suggestive of focal cortical dysfunction such as language disturbances and apraxia are rarely seen.

Motor disorders
Motor disorders may dominate the clinical picture, and various abnormalities are found.

Tremor Both resting and action tremors have been described. Resting tremor is common. This may resemble Parkinson disease, but a coarser, grosser type of tremor may also occur. The tremor may interfere with skilled tasks and at times may become severe enough to affect ability to perform simple daily tasks. Postural tremor is also common. This is most obvious when the limbs are held with the arms outstretched. The tremor is usually distal and has a large amplitude, with a frequency of 4 to 7 Hz (Jog & Lang, 1995). The upper limbs are more affected than the lower limbs, but such movements may also be seen in the head and trunk. In some instances, the tremors migrate from a distal to a proximal distribution and sometimes may be asymmetrical, involving one side of the body more than the other. The tremor can be disabling, making it impossible for the patient to write or lift a cup without spilling its contents (Read et al., 1967).

Chorea Choreiform movements may be generalized but in some instances may be most prominent in the tongue and face. These have been likened to the abnormal movements seen in Huntington chorea (Victor et al., 1965), but protrusion–retraction movements of the tongue with accompanying grimacing of the face suggest a similarity to tardive dyskinesia (Jog & Lang, 1995). The resulting distortion of facial expression can be quite marked. Repetitive lower limb movements, akathisia-like in nature, may also be present.

Parkinson-like syndrome A fine tremor of the fingers and hands, seen at rest and closely resembling that of Parkinson disease, has been described (Read et al., 1967). Other features suggesting Parkinson disease may also be seen, including mask-like facies, cogwheel rigidity, and severe bradykinesia. The last may involve all extremities. Extrapyramidal dysfunction may contribute to disturbances of speech and balance.

Asterixis Asterixis may be evident during the course of the disease. The clinical features are similar to those found in the reversible form of chronic hepatic encephalopathy as described above.

Disturbances of gait Gait disturbances may take the form of slowness of ambulation, poor postural control with a tendency to fall on turning, and a staggering gait (Victor et al., 1965). The abnormalities of gait may reflect involvement of numerous structures, and in addition to cerebellar disturbances, extrapyramidal and pyramidal impairment may contribute to the overall disruption of gait.

Cerebellar disturbances Cerebellar ataxia is a common feature of chronic hepatic dysfunction and has been described by many authors (Bernstein & Tripodi, 1998; Jog & Lang, 1995; Victor et al., 1965). Both truncal and limb ataxia may be prominent. Intention tremor may be evident in upper and lower limbs. Gait may be wide based and unsteady, with a tendency to lurch from side to side. The disturbance in ambulation may be prominent. Speech may be affected, and in some cases the dysarthria may be extremely prominent.

Myelopathy Myelopathy, although relatively uncommon, is a well-described complication of chronic hepatic failure. Myelopathy in association with chronic liver disease was first reported by Leigh and Card (1949). They described a largely motor syndrome characterized by ambulation difficulties and bladder dysfunction with sparing of sensation. This patient did indeed have features suggestive of hepatocerebral dysfunction, but he later developed Hodgkin disease and spinal cord compression requiring radiation therapy. However, there have since been several reports of hepatic myelopathy (Campellone et al., 1996; Liversedge & Rawson, 1966; Pant et al., 1968; Zieve et al., 1960a,b). The clinical picture is usually of an insidious progression of a spastic paraparesis. Bouts of hepatic encephalopathy may worsen the myelopathic features and the dysfunction appears to accumulate with each episode. Involvement is predominantly of the lower limbs, although some motor dysfunction may also occur in the arms. Sensation is largely spared but disturbance in bladder function does develop.

Pathogenesis of hepatic encephalopathy

Pathology

Histologically, chronic forms of hepatic encephalopathy are characterized by changes in the protoplasmic astrocytes (Bernstein & Tripodi, 1998; Finlayson & Superville, 1981; Victor et al., 1965). These cells proliferate and become hypertrophied, which results in morphological abnormalities termed 'Alzheimer type II astrocytosis'. The astrocytes appear swollen; the nucleus becomes pale. Other changes include prominent nucleolus and margination of the chromatin pattern (Butterworth et al., 1987; Norenberg, 1987). These morphological changes appear to be mirrored by disturbances in cell function, which include altered expression of the enzymes glutamine syn-

thetase (Lavoie et al., 1987) and monoamine oxidase (Rao et al., 1993). Alteration in peripheral-type benzodiazepine receptor density has also been described (Lavoie et al., 1990). These findings may have some implications for the pathogenesis of hepatic encephalopathy (Butterworth, 1998; Hazell & Butterworth, 1999).

Potential gut-derived toxins

The clinical features of hepatic encephalopathy appear to be best explained on the basis of altered brain chemistry induced by gut-derived toxins (Jones & Weissenborn, 1997). Distortion of hepatic cytoarchitecture is a characteristic of cirrhosis of the liver. This promotes the development of collateral venous channels (Gerber & Schomerus, 2000). These channels, which may be internal, namely within the liver itself, or external, result in shunting of blood from the portal to the systemic circulation, allowing blood to bypass the liver. Thus, substances derived from the gut may readily enter the systemic circulation without passing through the liver. As liver disease progresses, the metabolic capacity of the liver declines. This may compromise the ability of the liver to detoxify substances delivered by the portal vein, thus further increasing the systemic load of unaltered, gut-derived factors.

Ammonia

There are many potential toxins that may arise by way of the gastrointestinal tract (Jones & Weissenborn, 1997). Ammonia has received the most attention, and there is a strong body of evidence to indicate that this substance plays a major role in the genesis of hepatic encephalopathy. Ammonia is derived from several sources: intestinal tract, skeletal muscles, kidneys, and catabolism of proteins (Gerber & Schomerus, 2000). Ammonia originating in the gut is produced by the action of the intestinal flora on urea and food-derived protein substances as well as from the intestinal wall catabolism of glutamine. Ammonia is detoxified by two major pathways: (i) the Krebs–Henseleit cycle, resulting in the production of urea, and (ii) the synthesis of glutamine from glutamate by the action of glutamine synthetase.

Ammonia was one of the first toxins to be implicated in the genesis of hepatic encephalopathy, and this view still prevails (Gerber & Schomerus, 2000). Increased ammonia concentrations are often present in the blood of patients in hepatic coma (Gerber & Schomerus, 2000). Also, it has been shown that ammonia readily crosses the blood–brain barrier, and the cerebral metabolic rate for ammonia is increased in hepatic encephalopathy (Lockwood et al., 1991). Furthermore, there appears to be increased brain sensitivity to the adverse effects of ammonia in the presence of hepatic encephalopathy (Hazell & Butterworth, 1999).

Although it is clear that ammonia is toxic to the brain, the chemical basis for this action is complex and appears to involve a number of different processes. These may include alterations in neurotransmission, impairment of brain energy metabolism, increased expression of peripheral-type benzodiazepine receptors, excessive production of nitric oxide, and the inhibition of the ability of astrocytes to accumulate glutamate (Gerber & Schomerus, 2000; Hazell & Butterworth, 1999).

Ammonia appears to play a major role in the genesis of hepatic encephalopathy, but other mechanisms also appear to be involved.

Manganese

Manganese is neurotoxic and is excreted by the hepatobiliary system (Hazell & Butterworth, 1999). Blood manganese concentrations are increased in the presence of hepatocellular failure. Magnetic resonance imaging studies have revealed abnormal signals in the pallidum attributed to manganese deposition (Kulisevsky et al., 1992; Spahr et al., 1996). Histopathological studies have revealed Alzheimer type II astrocytosis in the pallidum of patients where magnetic resonance imaging studies had previously revealed abnormal signal indicative of manganese accumulation (Kulisevsky et al., 1992). Moreover, autopsy studies have confirmed the presence of high pallidal manganese concentrations in chronic liver disease (Krieger et al., 1995; Pomier-Layrargues et al., 1995). These findings suggest a role for manganese in the pathogenesis of certain components of hepatic encephalopathy.

Methionine derivatives

Increased levels of methionine derivatives, mainly mercaptans, have been described in hepatic encephalopathy, and earlier literature suggested they have a role in inducing hepatic encephalopathy (Chen et al., 1970; Phear et al., 1956). However, there are no indications that methionine derivatives increase ammonia concentrations, and they probably have no direct effect in inducing hepatic encephalopathy.

Synergism

Thus, many factors appear to contribute to the development of hepatic encephalopathy. Ammonia appears to play a central role in the genesis of the syndrome, but its actions are complex, affecting many aspects of cell function. Other substances, manganese in particular, appear to contribute to the pathologic disturbances in the central

nervous system, and may synergize with ammonia. Other processes may also be involved.

Neurological disorders after liver transplantation

Various neurological disturbances have been reported to occur after liver transplantation (see Chapter 129). The clinical features of some post-transplantation syndromes bear resemblance to the neurologic disturbances that occur with hepatic encephalopathy. These post-transplantation syndromes thus deserve further review.

Syndromes

Two clinical entities, in particular, are observed after liver transplantation, namely (i) impairment of consciousness and (ii) movement disorders.

Impairment of consciousness

Impairment of consciousness may be encountered in postliver transplantation patients. Well-defined conditions such as anoxic encephalopathy, central pontine myelinolysis, cerebrovascular events, and immunosuppressive agent-induced toxicity may account for the majority of such cases. In some, however, there is no immediate explanation for the patient's state of unresponsiveness.

Many features of such complications resemble the components of hepatic encephalopathy. Patients who fail to regain consciousness after liver transplantation may show decerebrate rigidity and abnormal movements, particularly in the form of facial grimacing, and the reflexes of release may be prominent accompanying features (Eidelman et al., 1991).

Akinetic states occurring after liver transplantation have been attributed to the toxic effect of immunosuppressive agents (Bird et al., 1990; Wijdicks et al., 1994, 1995), but a similar clinical picture may also be apparent in the coma associated with chronic liver disease.

Movement disorders

Severe movement disorders have been described in liver transplant recipients (Bird et al., 1990; de Groen et al., 1989; Eidelman et al., 1991). These have usually been attributed to the immunosuppressant agents tacrolimus and cyclosporine A. Such disturbances include severe postural tremor, myoclonus, bucco-facial-lingual dyskinesia, and Parkinson-like states as well as cerebellar tremor. These clinical disturbances in many instances bear striking resemblance to the movement disorders that may occur in the various forms of hepatic encephalopathy.

Causes of neurological disorders after liver transplantation

Immunosuppressive agents are neurotoxic, and immunosuppressive therapy has been implicated as a cause of postliver transplantation coma and neurologic complications, but this view has been challenged (Burkhalter et al., 1994). Not all postliver transplantation neurologic complications may be new, and the lingering effects of preexisting hepatic coma may contribute to neurological dysfunction after transplantation. Whereas postliver transplantation neurologic complications are likely to develop in patients who have severe, chronic, portal-systemic encephalopathy before transplantation (de Groen et al., 1989; Eidelman et al., 1991), severe neurological complications are less common in kidney and heart transplant recipients who receive similar immunosuppressant medication (Starzl et al., 1990). These findings lend credence to the hypothesis that pre-existing, severe hepatic encephalopathy may predispose to the development of post-transplantation neurological syndromes.

That the clinical syndromes seen after transplantation are extensions of pre-existing hepatic encephalopathy is not entirely unexpected. Even when the transplantation procedure results in the replacement of a functioning liver, the restoration of astrocyte function and reversal of other chemical changes due to the previous liver failure are not likely to occur immediately.

Furthermore, liver transplantation is an extremely complicated and often lengthy procedure and in itself is extremely stressful. Surgical procedures and exogenous factors are known to precipitate hepatic coma. The operation involves three stages: (i) the recipient hepatectomy, (ii) the hepatic phase, and (iii) the period of reperfusion (Carton et al., 1994). Marked hemodynamic fluctuations may occur during the course of the operation. Blood loss may be profound, often necessitating transfusion of large volumes of blood products. Blood pressure will often fluctuate, and profound hypotension may occur. Alterations in electrolyte concentrations may also occur, and at times there may be major fluxes in sodium and potassium concentration. Stress of this nature would be expected to have a negative effect. Thus, the transplantation procedure could itself result in acute neurological deterioration or exacerbate pre-existing hepatic encephalopathy.

Despite these negative effects, the advent of liver transplantation has improved survival of patients with fulminant hepatic encephalopathy (Bismuth et al., 1987) and of

those with more chronic forms of hepatic encephalopathy (Gordon et al., 1991; Jamieson et al., 1991). Post-transplantation improvement in neurological disturbances related to pre-existing hepatic encephalopathy has also been observed (Hockerstedt et al., 1992), demonstrating that recovery of neurological function does occur after transplantation. However, the process is likely to be slow. In one patient with advanced signs of chronic hepatocerebral degeneration, marked improvement in neurological status followed liver transplantation, but this process took 6 months or more (Powell et al., 1990).

Thus, although neurological disturbances occurring after liver transplantation may be due to the stress of the surgical procedures or to negative effects of immunosuppressive therapy, some may be due to previously existing hepatic encephalopathy. It appears possible for hepatic encephalopathy to resolve in the long term after liver transplantation.

Hepatic encephalopathy in the absence of cirrhosis

Portal–systemic encephalopathy

Excessive shunting of blood from the portal to the systemic circulation plays a critical role in the genesis of the neurologic complications observed in chronic liver disease. Abnormal portal–systemic shunting may also occur in the absence of liver dysfunction, resulting in similar neurological disturbances (Watanabe, 2000). The clinical entity of hepatic encephalopathy occurring in the absence of liver disease and associated with congenital intrahepatic shunting was first described by Raskin et al. in 1964. Portal–systemic shunts of various types have since been reported in patients without cirrhosis, and the subject has been extensively reviewed by Watanabe (2000).

The etiology of abnormal vascular channels is varied. Such channels may be of congenital origin and may be either intrinsic or extrinsic in nature. All allow large amounts of blood derived from the gut to bypass the liver, making it possible for gut-derived toxins to reach the brain and promoting the development of hepatic encephalopathy and its many neurological manifestations.

As in the cirrhotic form of hepatic encephalopathy, ammonia appears to play a key role in the development of the neurologic complications associated with this type of encephalopathy. In this entity, however, the clinical and biochemical features of liver disease are absent. Symptoms may be precipitated by protein loading as well as by exogenous factors in common with hepatic encephalopathy. Abnormal portal–systemic shunting, although rare, may be a cause of such neurological presentations as unexplained coma or episodic confusional states.

Increased ammonia concentrations in the absence of other chemical abnormalities indicative of liver disease suggest the diagnosis and should prompt further testing directed at detection of abnormal portal–systemic vascular channels. The diagnosis depends on elevated ammonia levels, absence of clinical and biochemical evidence of hepatic dysfunction, and the demonstration of abnormal vascular channels between the portal and systemic circulation.

Surgical occlusion of the portal–systemic channels may in some cases provide effective treatment. However, liver transplantation may be required if the vascular malformations are diffuse and not amenable to occlusion by surgical or other techniques.

Hyperammonemia

In most cases, increased ammonia concentrations occur as a result of liver-related disorders. Hyperammonemia, however, may occur in other circumstances, including certain bacterial infections, hemodialysis, drug-induced hyperammonemia, and inherited hyperammonemia.

Bacterial infections

Hyperammonemia with accompanying hepatic encephalopathy has been described in association with *Helicobacter pylori* infections (Ito et al., 1995) as well as with high urease-producing bacteria of the proteus type (Kuntze et al., 1985).

Hemodialysis

Ammonia concentrations may increase during the course of hemodialysis with the circle absorptions method together with a dialysis regenerating system (Canzanello et al., 1983).

Medication-induced hyperammonemia

Sodium valproate may induce hyperammonemia by impairing the urea cycle enzymes (Batshaw, 1984).

Inherited hyperammonemic syndromes

Hyperammonemic disorders unrelated to liver disease occur largely as a result of hereditary disorders of metabolism arising out of enzyme deficiencies of the urea cycle (Breningstall, 1986). These conditions are largely autosomal recessive and manifest primarily in the neonatal period or in childhood.

However, two of these disorders present in adulthood, namely ornithine transcarbamylase deficiency (Rowe et al., 1986) and argininosuccinic urea (Walser, 1983). Ornithine transcarbamylase deficiency may be characterized by episodic ataxia, periodic confusion, alterations in tone, bizarre behaviour, seizures, and coma. The episodes may be of short duration, sometimes lasting for only a few hours. They are often precipitated by protein ingestion, although they may occur after anesthesia and surgery. Ammonia and bilirubin concentrations may be increased during attacks. Seizures and intermittent cerebellar ataxia may occur with argininosuccinic acid urea. Excessive dryness and brittleness of the hair may complicate this condition.

An increased ammonia concentration in the absence of other features suggestive of liver disease signals the possibility of an inherited hyperammonemia. The diagnosis, however, rests on specific enzyme assays. Liver tissue is required for this and is usually obtained by biopsy.

Wilson disease

Wilson disease is an inherited disorder of copper metabolism and is transmitted in an autosomal recessive manner (Frydman, 1990). The disease is characterized by impaired hepatic excretion of copper, which accumulates to excess in tissues such as the brain, cornea and liver. Accumulation of copper in the liver eventually results in hepatocellular necrosis with the development of liver failure. Deposition of copper within the cornea produces the development of Kayser–Fleischer rings. Excessive copper within the brain results in degeneration of the basal ganglia and other structures, ultimately leading to nervous system failure (Pfeil & Lynn, 1999).

Pathophysiology

Copper is derived from the diet and is an essential component of some enzymes, including superoxide dismutase as well as dopamine beta-hydroxylase. Copper is normally transported to the liver, where it undergoes metabolic transformation. In one pathway it is incorporated with apoceruloplasmin to form ceruloplasmin. It is also excreted into the bile by an adenosine triphosphate-dependent carrier protein. In Wilson disease, both defective incorporation into ceruloplasmin and impaired biliary excretion occur.

Serum concentrations of ceruloplasmin are usually decreased in Wilson disease, but ceruloplasmin deficiency probably does not play a causative role in the manifestation of the disease, and the low concentrations may be an epiphenomenon (Pfeil & Lynn, 1999).

As copper accumulates, the hepatocytes are damaged. Copper is released into the circulation and deposited in other organs, including the brain and kidneys. Excess copper is toxic, acting as a pro-oxidant to promote the formation of free radicals and resulting in the harmful oxidation of lipids and proteins.

Genetics

The gene for Wilson disease was localized to chromosome 13 by Frydman et al. (1985). The gene has since been cloned (Bull et al., 1993; Tanzi et al., 1993). It codes for a P-type adenosine triphosphatase that functions as a copper transporter. The gene defects include small deletions, insertions, or missense mutations. If the gene defect is present, copper transportation is impaired, with a resultant decrease in biliary copper excretion and accumulation of hepatic copper.

Hepatic dysfunction

Hepatic dysfunction is the initial manifestation in more than 50% of patients with Wilson disease. This may take the form of chronic active hepatitis, cirrhosis, and fulminant hepatic failure.

Neurological manifestations

Nervous system manifestations of Wilson disease usually develop in the second or third decade of life (Strickland & Leu, 1975). Presentation before adolescence or after the age of 40 is unusual. Tremor is the most common initial symptom. This is quite variable, and it may be largely of the resting variety, although a strong postural or kinetic component may also be present. The tremor is often asymmetrical and may vary in amplitude. The head may be involved, and in some instances there may be a marked tremor of the 'wing beating-type' in the proximal upper extremity (Walshe, 1986). Drooling is a frequent early symptom, and this may be accompanied by dysarthria. Dystonia of the bulbar musculature may supervene, impairing movement of the lips, tongue, pharynx and jaw. The resulting speech disturbance may be severe enough to cause a state of mutism. The jaw may hang open and lip retraction may be prominent, resulting in a characteristic facial appearance. Impairment of gait may develop, and patients may eventually become bedridden as a result. Psychiatric features include emotional lability, impulsiveness, disinhibition, and affective symptoms.

Ocular findings

The Kayser–Fleischer ring is a characteristic ocular abnormality in Wilson disease. This is a brownish–green discolouration of the Descemet membrane in the limbic area of the cornea. It may be detected by the naked eye, but a slit lamp is often required to facilitate identification. Sunflower cataracts, night blindness, xerophthalmia and strabismus have also been reported. Kayser–Fleischer rings are present in nearly all patients with Wilson disease complicated by nervous system involvement, but may be evident in only 55% to 70% of patients with isolated hepatic disease (Ferenci, 1999).

Diagnosis

The diagnosis of Wilson disease rests on clinical findings and biochemical tests. There is no single laboratory test that is sensitive enough to specifically detect Wilson disease, but diagnosis rests on the measurements of serum ceruloplasmin, urinary copper excretion, the detection of Kayser–Fleischer rings, and slit-lamp examination. Wilson disease is suggested by the presence of at least two of the following conditions: (i) typical neuropsychiatric abnormalities, (ii) serum ceruloplasmin concentration $<$20 mg/dl; and (iii) demonstration of Kayser–Fleischer ring.

Low serum concentrations of ceruloplasmin are found in most patients with Wilson disease, but 15% of patients have values within the normal range (Steindl et al., 1997; Stremmel et al., 1991). Other conditions such as protein deficiency states may also result in low concentrations of ceruloplasmin. Twenty-four-hour monitoring of urine copper excretion has also been used to diagnose Wilson disease, although in some patients who are not yet symptomatic, copper excretion may not be excessive. High urinary copper concentrations may also occur in cholestatic liver disease, in which copper may be released from hepatocytes. Determination of total serum copper concentration is of little diagnostic value because the low serum ceruloplasmin fraction often contributes to a low total serum copper concentration.

The concentration of free serum copper is usually elevated in Wilson disease, and this may be potentially more useful as a diagnostic test. Although it has been stated that Kayser–Fleischer rings are invariably present once neuropsychiatric signs of Wilson disease have emerged, there are reports indicating that a small percentage of patients with this form of Wilson disease have no detectable Kayser–Fleischer rings (Ross et al., 1985; Willeit & Kiechl, 1991). Thus, if Kayser–Fleischer rings are absent and there is a strong suspicion of Wilson disease, further testing, including liver biopsy, may be required to determine hepatic copper content. This is regarded as a reliable diagnostic test.

Magnetic resonance imaging has increasingly been used to diagnose Wilson disease. A variety of abnormal findings have been detected (Hitoshi et al., 1991; Mochizuki et al., 1997).

Treatment

Treatment of Wilson disease consists of exclusion of copper-containing foods from the diet and use of chelating agents such as penicillamine and trientine. These may be combined with zinc acetate, which binds dietary zinc and copper. Ammonium tetrathiomolybdate, an experimental agent that forms complexes with albumin and copper in the bloodstream and decreases copper availability for cellular uptake, gives promise of being an effective treatment.

Liver transplantation has largely been reserved for treatment of patients with fulminant or end-stage liver disease. However, this mode of therapy has also been used with promising results, primarily for the treatment of neurologic manifestations. Neurological status improved in most patients (Chen et al., 1997; Schumacher et al., 1997).

Selected gastrointestinal disorders

Inflammatory bowel disease

The inflammatory bowel diseases include Crohn disease (regional enteritis) and ulcerative colitis. These conditions differ from each other in many aspects (Pfeiffer, 1996). Ulcerative colitis appears to be an autoimmune disorder, whereas the etiology of Crohn disease is less clear. Ulcerative colitis is largely confined to the colon and rectum. Crohn disease can involve all segments of the gastrointestinal tract. The pathology and clinical features also differ (Pfeiffer, 1996). However, extraintestinal manifestations occur with both conditions, and the neurological complications are similar. Thus, these diseases can be considered together.

General considerations

Nervous system manifestations of gastrointestinal tract disease may take several forms. Complications may arise from nutritional deficiency and from the side effects of the various medications used for treatment of the inflammatory bowel disorder. The majority of neurological complications,

however, appear to be mediated by the same pathophysiological mechanism responsible for the development of the primary intestinal disorder.

The development of the nervous system manifestations may precede the clinical onset of the gastrointestinal tract disease and does not always parallel the severity of the primary organ involvement. Intestinal manifestations may appear to be mild, but the accompanying neurological developments may be extremely severe and disabling. Neurological disturbances may be apparent during exacerbations of gastrointestinal tract disease, and they also occur during phases of remission. The nervous system manifestations of inflammatory bowel disease can be classified as follows.

1 Peripheral nervous system complications
   (a) Peripheral neuropathy
   (b) Myopathy
2 Central nervous system manifestations
3 Complications arising from vascular pathology
   (a) Arterial occlusions
   (b) Venous occlusions
   (c) Vasculitis
4 Complications arising from therapeutic measures
5 Complications of direct spread of infection

Peripheral nervous system

The peripheral nervous system is most commonly affected. Various types of neuropathy may occur, including acute inflammatory demyelinating polyneuropathy, mononeuritis multiplex, and brachial plexopathy. More chronic axonal or demyelinating peripheral neuropathy may also occur (Lossos et al., 1995). Abnormalities of the autonomic nervous system have also been reported (Straub et al., 1997).

Cranial nerves may also be involved, and there are reports of disturbances of the eighth nerve (Hollanders, 1986) and peripheral facial disturbances. The peripheral facial disturbances are a complication of an orofacial, granulomatous process, described as a complication of Crohn disease (Cleary & Batsakis, 1996). The features of the eighth nerve disturbance bear a strong resemblance to the Melkersson–Rosenthal syndrome, which is characterized by facial swelling, peripheral facial nerve palsy, and plication of the tongue. The facial nerve palsy may be recurrent in nature. There is indeed literature to support the contention that the Melkersson–Rosenthal syndrome is a component of Crohn disease (Ilnyckyj et al., 1999).

Inflammatory myopathy as well as dermatomyositis may occur as a complication of both ulcerative colitis and Crohn disease (Kulkarni et al., 1997; Lossos et al., 1995). Orbital myositis manifesting with orbital pain, swelling, and proptosis has also been reported (Durno et al., 1997).

Central nervous system involvement

Brain magnetic resonance imaging studies have demonstrated an increased incidence of focal white matter lesions in inflammatory bowel disease (Geissler et al., 1995). Such lesions are usually asymptomatic and may be of ischemic origin. Multiple sclerosis has also been described in association with ulcerative colitis. The concurrence of these diseases appears to be greater than expected, raising the possibility of similar pathogenesis (Kimura et al., 2000).

Myelopathy may also occur, usually of the chronic, progressive type. A rapidly evolving form of myelopathy occurring as a component of encephalomyeloneuritis has also been described (Kraus et al., 1996).

Neurological complications relating to vascular pathology

Inflammatory bowel disease appears to be associated with an increased risk of thrombosis, although the mechanisms have not been fully elucidated. Cerebrovascular complications have been reported, and these may arise from either arterial or venous thrombosis (Lossos et al., 1995). Venous thrombosis, including both venous sinus and cortical vein occlusion, appears to be more common (Das et al., 1996; Derdeyn & Powers, 1998).

The lupus anticoagulant has been implicated as a risk factor for the development of venous thrombosis in inflammatory bowel disease (Papi et al., 1995).

Central nervous system vasculitis, a complication of inflammatory bowel disease, has been implicated in the genesis of the central nervous system white matter lesions reported in ulcerative colitis (Dejaco et al., 1996).

Complications arising from therapeutic measures

Corticosteroids are used frequently in the treatment of inflammatory bowel disease. Benign intracranial hypertension (pseudotumour cerebri) has been described as a complication of corticosteroid use, both during maintenance therapy (Newton & Cooper, 1994) and during tapering of corticosteroid treatment (Liu et al., 1994).

Acute encephalopathy has been described as a component of sulfasalazine-induced hypersensitivity vasculitis (Schoonjans et al., 1993).

Complications of direct extension of disease

Meningitis and spinal epidural abscess may arise as a result of contiguous spread of infection from the bowel

into adjacent vertebral structures (Wallace & Luchi, 1995). The lumbosacral plexus may be involved in a similar manner (Demarquay et al., 1998).

Whipple disease

Whipple disease was first reported in 1907 (Whipple, 1907) and was then described as a primary gastrointestinal tract disorder. Whipple also identified rod-shaped bacteria, implicating an infectious etiology. It has since become apparent that this disease has wider ramifications and should be regarded as a multisystem disturbance. The diagnosis has traditionally relied on duodenal biopsy and the demonstration of macrophages that stain prominently with periodic acid-Schiff (PAS) (Pfeiffer, 1996). The organism can now be identified by polymerase chain reaction (PCR)-based assay (Relman et al., 1992). There is also evidence to suggest that the organism can under some circumstances be propagated in cell culture (Schoeden et al., 1997). The gastrointestinal manifestations include fever, weight loss, abdominal pain, and chronic diarrhea (Fleming et al., 1988). Extraintestinal features may be prominent, with involvement of the skin, joints, and lymph nodes. In some instances, this involvement may precede the onset of the intestinal symptoms. Neurological involvement, although rare, may result in profound disability. The central and peripheral nervous systems may be affected, and the presentation is quite varied.

Central nervous system manifestations

The neurological features of Whipple disease may include behavioral disturbances, progressive dementia, ataxia, hypothalamic dysfunction, seizures, myoclonus, and meningitis (Adams et al., 1987; Comer et al., 1983; Fleming et al., 1988; Pallis & Lewis, 1980; Pollock et al., 1981). Disturbances of eye movement may be prominent. Nystagmus and disturbances of conjugate gaze may occur (Finelli et al., 1977). An unusual combination of pendular ocular movements and associated syndromes with contraction of facial, masticatory, and limb muscles, termed 'oculomasticatory myorhythmia', is regarded as pathognomonic for cerebral Whipple disease (Adler & Galetta, 1990; Schwartz et al., 1985). The ocular component takes the form of convergent–divergent pendular nystagmus, although rhythmic vertical eye movements have also been described (Knox et al., 1976). The accompanying extraocular movements may include syndromes with contraction of the facial–masticating muscles as well as the limb muscles (Rajput & McHattie, 1997). Both the spinal cord (Clarke et al., 1998) and the peripheral nervous system may be involved.

Diagnosis

The diagnosis of Whipple disease depends on the detection of PAS-positive macrophages and the identification of rod-shaped bacilli within these cells on electron microscopy.

Traditionally, such studies have been carried out on duodenal biopsy specimens, but similar findings have also been reported in brain biopsy specimens (Mendel et al., 1999). PCR as described earlier in this section may be of value in detecting the organism.

Treatment

Treatment of Whipple disease requires the use of antibiotics that cross the blood-brain barrier. Response to antibiotic treatment is variable, but the neurologic manifestations may not remit and may recur after treatment is discontinued (Schnider et al., 1996).

Neurological complications of total parenteral nutrition

The small intestine is the primary site for absorption of food and other substances necessary to maintain adequate nutritional status. The mucosal surface of the small intestine may be compromised by disease processes that affect the absorption capacity of this organ. Trauma, bowel ischemia, and conditions (such as volvulus) that compromise circulation may result in gangrene with loss of a considerable portion of the small bowel, resulting in decreased capacity to absorb nutrition. Adaptive mechanisms may come into play. Depending on the length of surviving bowel, these may be adequate to maintain enteral nutrition. In some instances, however, a state of chronic malabsorption ensues, necessitating parenteral nutrition. This is termed 'short-bowel syndrome'. Permanent total parenteral nutrition (TPN) may be required to sustain life. Small bowel transplantation is a treatment option and may eliminate the need for TPN. However, this procedure is only offered in a few centres, and TPN is the most widely used method for maintaining nutrition in the presence of short-bowel syndrome.

TPN may be complicated by the development of several neurologic disorders. These may arise directly from disturbances occurring at the site of catheter placement but may also be more generalized, often developing as a result of metabolic disturbances (Wolfe et al., 1986).

Local vascular complications

TPN requires the placement of a large catheter in a proximal vein. The presence of such catheters, particularly in the long term, promotes the development of venous thrombosis. This may involve the internal jugular vein, with the secondary development of pseudotumour cerebri (Saxena et al., 1976).

Metabolic complications

Various metabolic disturbances have been described in TPN-supported patients (Wolfe et al., 1986). Hypophosphatemia is one of the more frequently reported occurrences, and this may be complicated by peripheral neuropathy with prominent sensory and motor features (Furlan et al., 1975; Siddiqui & Bertorini, 1998; Silvis et al., 1980). In some instances, hypophosphatemia may evolve rapidly, in a manner suggesting Guillain-Barré syndrome (Furlan et al., 1975; Siddiqui & Bertorini, 1998).

Wernicke encephalopathy has also been reported as a complication of TPN (Vortmeyer et al., 1992). This condition is promoted by inadequate (or lack of) thiamine supplementation. The clinical course has been shown to evolve at a rapid rate. Pathological abnormalities are extensive, and the findings are atypical, both in distribution of pathology and in the histologic abnormalities. This is possibly because of the rapid development of the deficiency state.

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Renal disease and electrolyte disturbances

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Renal disease can affect neurological function either directly, through the effects of retained uremic toxins, or indirectly through complications of renal failure or its treatment (Fraser & Arieff, 1994). With the exception of urological and ultimately nephrological complications of spinal disease or autonomic neuropathy, nervous system disorders rarely affect the kidney. Some systemic disorders may affect both the kidneys and the brain. These are discussed under the headings uremic encephalopathy (acute and chronic), uremic neuropathies and myopathy, complications of therapy for uremia and systemic disorders.

Uremic encephalopathy

Uremia is a clinical syndrome related to profound loss of renal function. Uremic encephalopathy is divided into acute (ARF) or chronic (CRF) varieties. These differ more than in acuity, as a number of metabolic and endocrine disturbances and compensatory adjustments take time to fully evolve in CRF. Some may ameliorate and others contribute to adverse effects of kidney failure on the CNS.

Acute uremic encephalopathy

Acute renal failure (ARF) can be divided into prerenal (circulatory failure), post renal (obstructions to outflow) and specific renal causes (Conger & Schrier, 1975). At least 40% of ARF cases occur in an acute medical setting (Hou, 1983).

Clinical features

There are few specific features that differentiate uremic encephalopathy from other metabolic encephalopathies. However, the following combination suggests uremia, after the exclusion of exogenous agents: (i) an encephalopathy with hyperventilation from a metabolic acidosis; (ii) excitability, including prominent myoclonus or seizures.

As with other metabolic encephalopathies, early changes include lethargy, irritability, problems with concentration and attention, disorientation, omissions in speech and sleep disturbances (Locke et al., 1961). Patients are usually subdued, but delirium, or an agitated confusional state, may be found. There may be periods of profanity, euphoria, depression or catatonic stupor (Wilson, 1940). Coma from acute uremia is found when the patient is *in extremis* (Gowers, 1888).

Cranial nerves are usually intact, although fundi may reflect arterial hypertension. Seizures, usually in the form of generalized convulsions and often multiple, occur in the oliguric phase (Locke et al., 1961). Focal seizures are not usually consistently from the same site, unless they relate to an associated structural lesion. Patients may feel weak and demonstrate multifocal myoclonus that is so prominent that the muscles appear to be fasiculating (Plum & Posner, 1980). Action myoclonus has been described (Chadwick & French, 1979). Tetany may also be found. Focal signs such as hemiparesis are not rare, but subside with dialysis and may switch sides with recurrent episodes.

Investigations

Blood tests confirm renal impairment and may show the alterations in electrolyte balance, acid–base balance and anemia that commonly accompany uremia. The electroencephalogram (EEG) reflects the level of consciousness: slowing of frequencies occurs in parallel with the severity of the encephalopathy (Cadilhac & Ribstein, 1961). Triphasic waves are commonly encountered in the obtunded patient (Fig. 124.1). Generalized epileptiform discharges occur in about 25% of children with acute uremia, but these are rare in adults (Chaptal et al., 1954).

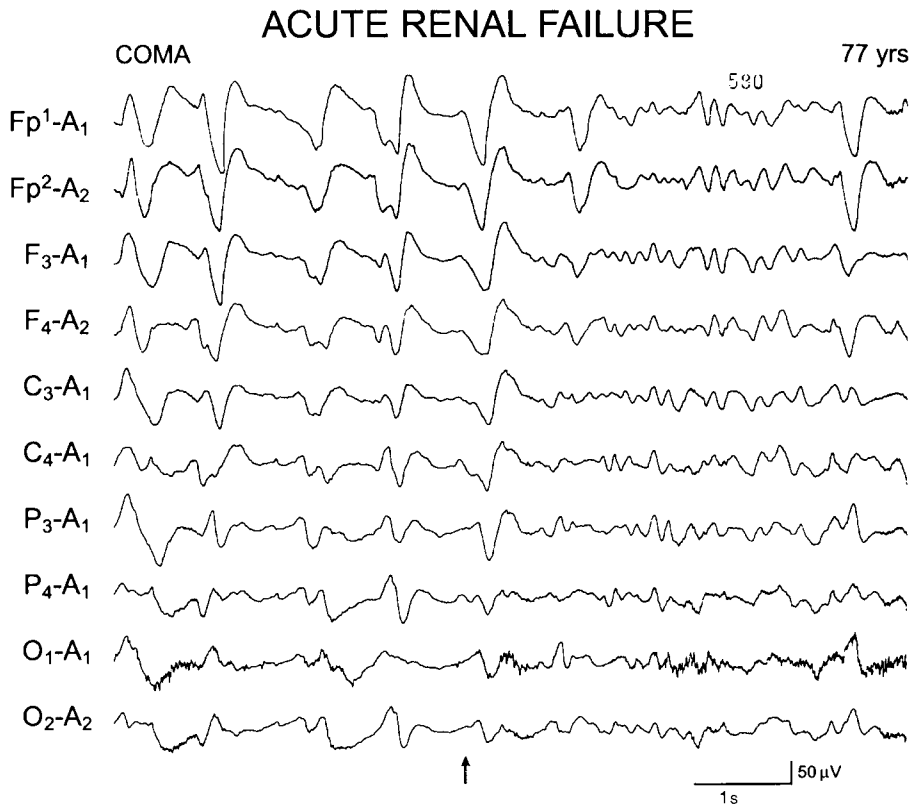

Fig. 124.1. Triphasic waves are seen in this EEG recording in a 77-year-old woman with acute renal failure that occurred with septic shock. The triphasic waves are attenuated and faster frequencies appear after the nail bed was squeezed (at arrow). There is a small amount of muscle artefact (very short duration, high frequency potentials) appearing intermittently in the second last channel.

Differential diagnosis

The main differential diagnosis is accelerated hypertension with hypertensive encephalopathy. The latter is usually associated with papilledema, which is rare and unexpected in uremic encephalopathy. Elevated CSF protein is more characteristic of hypertensive than uremic encephalopathy.

Other conditions that may cause both encephalopathy and systemic acidosis include exogenous toxins such as methanol, ethylene glycol, salicylates and paraldehyde. Diabetic ketoacidosis, anoxia, sepsis with circulatory failure and lactic acidosis should not pose diagnostic difficulty. Penicillin intoxication (with huge doses) may cause an encephalopathy with seizures as well as acute renal failure. In children, lead intoxication enters the differential diagnosis (Needleman, 1994). Papilledema and other evidence of raised intracranial pressure are commonly present in childhood lead intoxication with impaired consciousness. There may be a 'lead line' in the gingivae and radiological bony abnormalities (Needleman, 1994).

Management

The first step is to determine the category and specific cause of ARF, especially reversible causes. Pre- and post-renal causes, precipitants (myoglobin, hemoglobin, urate crystals) and nephrotoxic drugs should be sought first. These require specific management steps contained in general medical texts.

Fluid intake needs to be adjusted with respect to the cause of ARF, but usually needs to be restricted depending on urinary output. Steps should be taken to reduce catabolism by increasing carbohydrate intake. Serum potassium needs to be closely monitored, as life-threatening hyperkalemia is a constant risk. Congestive heart failure, acute hypertension, fluid and electrolyte imbalance and infections need to be looked for, prevented and managed promptly when they occur.

Not all patients require dialysis, but can be managed conservatively with correction of the underlying cause and expectant observation. Absolute indications for dialysis include: development of CNS complications, resistant

hypertension, fluid overload, severe acidosis and uremic pericarditis.

Other management, including antiepileptic drug therapy, is discussed under CRF.

Chronic renal failure

The specific neurotoxin of uremia has not been identified, but it is unlikely that a single retained chemical species will account for uremic encephalopathy for all patients (Massry, 1985; Bolton & Young, 1990; Moe & Sprague, 1994). Uremic neurotoxins could alter: neurotransmitter and synaptic function; enzymes; the sodium–potassium pump mechanism; transcription from DNA to messenger RNA, phosphodiesterase and phosphoinositide functions; or phosphate transfer in various enzymes and microtubular function.

Clinical features

In CRF, signs and symptoms are less florid or fulminant than in ARF; they are also considerably ameliorated by treatment, such as dialysis. Lethargy and fatiguability, problems concentrating, slowness in thinking and impaired memory function are common with CRF whether or not patients are on regular dialysis programmes (Tyler, 1970; Heilman et al., 1975). More detailed neuropsychological studies have shown impairment in complex cognitive functions, including spatial synthesis and other visual perceptual tasks, logical–grammatical and mathematical operations (Bosach & Schlebusch, 1991; Brancaccio et al., 1981). Headaches, sleep disturbances, dysarthric speech and abnormal hormonal, including sexual, functions occur *parri passu* with these issues.

The following motor phenomena are common manifestations of uremic encephalopathy: tremor, myoclonus, asterixis, paratonic rigidity, primitive reflexes (rooting, grasp and snout). A coarse, irregular postural action tremor is best seen on supporting the limbs against gravity or on reaching for something. Myoclonus may be multifocal or synchronous in uremia (Stark, 1981). Asterixis represents centrally mediated brief muscular relaxation in a part of the body that is being actively supported against gravity. Paratonic rigidity is the resistance to passive movement of a limb and tends to disappear when the limb is moved slowly. Seizures, usually generalized convulsions, may occur as a near terminal event, preceded by coma, in very advanced, untreated uremia (Glaser, 1974). They are uncommon in hemodialysed patients, unless they occur near the start of therapy (dialysis dysequilibrium) or if a complication arises, e.g. stroke or metabolic upset, such as a sudden change in acid–base or electrolyte composition or hypocalcemia (Tyler, 1968). Focal seizures are not often repeated in a stereotypic fashion unless there is an underlying structural lesion.

Uremic meningitis may complicate chronic uremic encephalopathy. Consciousness is not seriously compromised, but patients exhibit nuchal rigidity and a positive Kernig's sign (Madonick et al., 1950).

Investigations

Routine EEG may be normal with mild encephalopathy, but often shows intermittent bursts of low voltage theta (>4, <8 Hz rhythmic waves). With more severe encephalopathy the EEG shows slowing of frequencies and an increase in amplitude. The occipital rhythm may show progressive slowing in serial EEGs. Bursts of rhythmic delta (<4 Hz waves) are common, especially on arousal from sleep (Jacob et al., 1965). Triphasic waves (Fig. 124.1) may be superimposed on background slowing. A photomyogenic response (muscle twitches of the face coincident with light flashes) or photoparoxysmal (generalized epileptiform discharges in response to photic stimulation) may be found. Bursts of irregular generalized spike and wave may also occur spontaneously during the recording.

Frequency changes can be detected more readily with quantitative methods using the strategies developed by Teschan, Bourne and colleagues (Teschan, 1975; Bourne & Teschan, 1983). This can be a sensitive method for determining the optimal effectiveness of dialysis strategies. Event-related potentials, especially middle latency auditory evoked responses, can be used in a similar fashion to show improvement with dialysis.

Neuroimaging is usually unhelpful. Cerebral atrophy may accompany dehydration; magnetic resonance imaging (MRI) may show reversible changes (low signal intensity T_1-weighted and high signal on T_2-weighted) in the periventricular white matter, basal ganglia and internal capsule. These disappear or vary with dialysis (Okada et al., 1991).

In patients with CRF and meningismus, the cerebrospinal fluid may show up to 250 lymphocytes/mm^3 and up to 1.0 g/l (100 mg/dl) protein concentration.

Management

Every effort should be made to correct reversible causes of renal failure and to maximize the function of the kidneys with conservative means. Dietary restrictions of fluid, potassium, sodium, phosphate and ultimately protein are usually necessary.

When CNS symptoms persist or develop after correction of reversible factors and institution of conservative therapy, dialysis is necessary. Peritoneal dialysis and

hemodialysis reverse many of the neurological and systemic complications of uremia, but many are incompletely corrected. Patients on dialysis often feel chronically ill, with reduced stamina, problems concentrating or maintaining attention and have memory problems and sleep disorders. Some may continue to have seizures. Peripheral neuropathy may persist. In addition, a host of systemic problems including chronic anemia, secondary hyperparathyroidism, osteopenia, malnutrition, hypertension, immunological deficiency, bleeding diatheses and pruritis may persist.

Many of these are completely reversed by successful renal transplantation (Teschan et al., 1977).

Uremic neuropathies

Uremic polyneuropathy

The nature of the polyneuropathy induced by the toxic effects of renal failure is determined largely by the severity of the renal failure and the effects of various forms of treatment. Thus, it is absent or mild during the acute or the early stages of renal failure, although Brismar and Tegnèr (1984) have shown evidence of neuropathy in ARF in an animal model. By the time end-stage renal disease is reached, however, 50% of patients have polyneuropathy. It tends to stabilize during treatment by chronic hemodialysis or peritoneal hemodialysis, and then regularly improves with successful renal transplantation (Bolton & Young, 1990).

Clinical features

The earliest and most prevalent symptoms are restless leg syndrome, muscle cramping, and distal paresthesias, not always resulting from the neuropathy but at times from transient metabolic disturbances. The burning foot syndrome, caused by a deficiency of the water-soluble B vitamins that are washed out during the hemodialysis procedure, is now rarely seen because of proper vitamin supplementation. In more severe neuropathies, distal weakness (most marked in the legs), a stocking–glove loss of sensation to all modalities, and an unsteady gait occur.

The earliest signs of uremic polyneuropathy are loss of vibration sense in toes and reduction of deep tendon reflexes, beginning with ankle jerks (Jennekens et al., 1971). Severe cases of polyneuropathy causing quadriplegia are now rarely seen because of early institution of hemodialysis or peritoneal dialysis. When such cases do occur, one should be suspicious that intercurrent infection may be the important factor; it is now known that sepsis itself can induce a polyneuropathy called critical illness polyneuropathy (Zochodne et al., 1987).

The cerebrospinal fluid protein level in uremia may be normal or elevated, and the degree of elevation bears some relationship to the severity of the polyneuropathy (Jennekens et al., 1971). The cell counts are normal.

Overt clinical signs of autonomic dysfunction are probably uncommon, but more careful testing reveals abnormalities in a high percentage of patients. This appears to affect both the sympathetic and the parasympathetic nervous systems (Solders et al., 1985). The normal variation in the cardiac RR interval tends to decrease (Fig. 124.2); the more severe the renal failure, the more marked is the decrease. Sympathetic system abnormalities may be demonstrated by the Valsalva test, the tilt test, the forced handgrip test, the cold pressor test, the mental stress test, and the sweat test. Autonomic system neuropathy in uremia can be stabilized by chronic hemodialysis, and it regularly improves after successful renal transplantation.

Neurophysiological studies

Standard motor and sensory nerve conduction studies remain the best method of documenting the incidence and severity of polyneuropathy. Conduction velocity decreases in parallel with renal function, as measured by the creatinine clearance test (Nielsen, 1973b) (Fig. 124.3). Compound muscle and sensory nerve action potential amplitudes decrease because of dispersion from secondary demyelination or fallout of larger myelinated axons from a primary axonal degeneration (Bolton, 1976; Nielsen, 1973a). Needle electromyography may be distinctive. Fibrillation potentials and positive sharp waves may be relatively absent in human uremic muscle, possibly due to the inhibition of extrajunctional acetylcholine receptors. This may also explain failure of collateral reinnervation of muscle, which is dependent on the presence of these receptors (Bolton et al., 1997b). Thus, there may be little spontaneous activity, and motor unit potentials may be decreased in number, small in size, but polyphasic, suggesting a myopathy (as noted below).

Computer analysis (Hanson & Ballantyne, 1978) has shown the number of motor unit potentials as reduced to one-third of the normal value. Single-fibre electromyographic studies (Konishi et al., 1982; Thiele & Stålberg, 1975) indicate that the density of muscle fibres within a unit is normal; this suggests a failure of collateral reinnervation. The variation in the interval between the firing of single muscle fibre potentials, so-called jitter, is likely related to peripheral demyelination. Somatosensory evoked potential studies reveal that conduction is slowed along both the peripheral and the central segments of

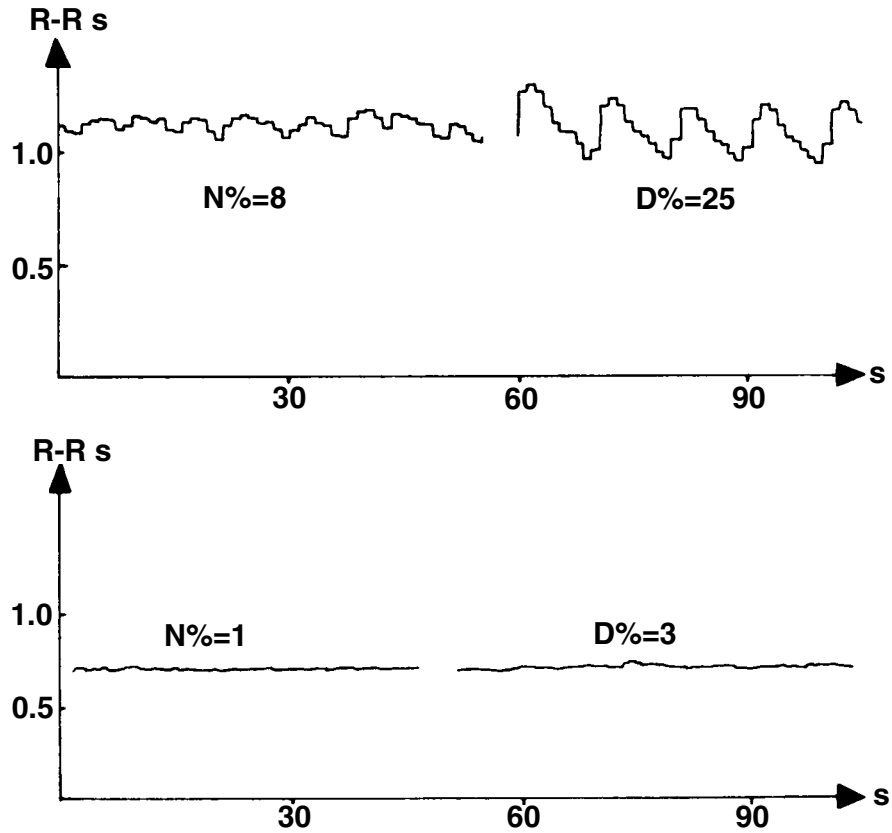

Fig. 124.2. Abnormality in the cholinergic autonomic nervous system in chronic renal failure. (Top) Electrocardiographic RR variation in a patient in advanced renal failure. At this time the RR variation was normal in the resting state and after deep breathing (N% and D% refer to the percentage variation with normal breathing and with deep breathing). (Bottom) The same patient developed more marked renal insufficiency, which required intermittent hemodialysis. The RR interval is now abnormal, with little variation either at rest or with deep breathing, indicating cholinergic autonomic insufficiency. (Reprinted with permission from Solders et al., 1985; Mnksgaard International Publishers Ltc., Copenhagen, Denmark).

primary sensory neurons, including transcallosal conduction (Serra et al., 1979; Vaziri et al., 1981). H reflex and F wave studies, which measure conduction on motor fibres both proximally and distally, have shown some prolongation of latencies in up to 85% of patients in end-stage renal failure, particularly those undergoing chronic hemodialysis (Panayiotopoulous & Laxos, 1980).

Because disordered sensation is the earliest symptom in uremic polyneuropathy, tests to measure it quantitatively would be quite valuable. Studies by Nielsen (1975) and Tegnèr and Lindholm (1985), with the use of hand-held vibrators, have shown elevated thresholds in 83% of patients in end-stage renal failure. Quantitative sensory testing shows abnormalities in 39% of patients with uremic neuropathy, and an unusual perception of heat in response to low temperature stimuli in 42%; it was an early sign of neuropathy (Yosipovitch et al., 1995).

Pathophysiology

The etiology and mechanisms or uremic neuropathy are still not understood (Bolton & Young, 1990). Conduction velocity is slowed in motor and sensory fibres, both large and small, along proximal and distal segments. There is clearly an underlying demyelination because conduction velocity is slowed more than would be expected from pure axonal degeneration. Moreover, there is a relative preservation of compound muscle action potential amplitudes that are often dispersed on more proximal stimulation. However, conduction block has not been seen. There is also elevation of excitation thresholds, a prolonged refractory period, abnormal responses to changes in limb temperature and ischemia, and evidence from voltage-clamp studies that there is a decrease in excitability and in the specific sodium permeability F-nodal membrane. Nielsen (1973a, 1974, 1978) theorized that uremic toxin inhibits the

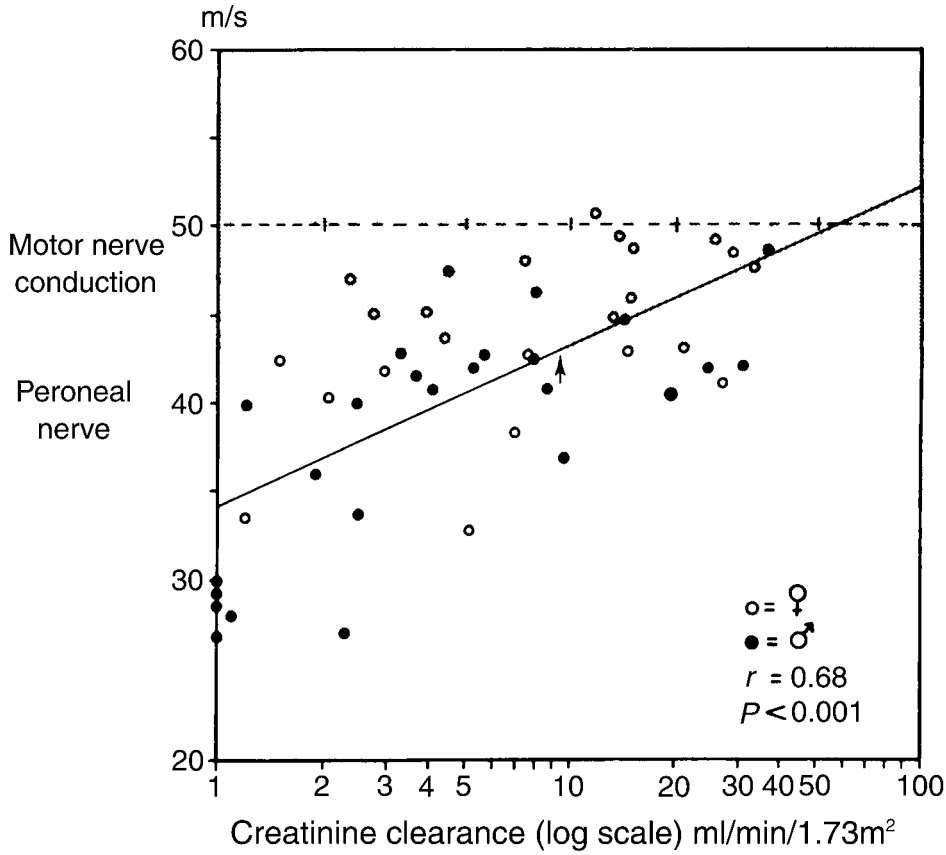

Fig. 124.3. Fall in nerve conduction as kidney function declined in 56 patients before the institution of hemodialysis. The arrow indicates when 50% of patients showed abnormal values. The conduction velocities tended to be lower in males than females ($P<0.01$). (Reprinted, with permission, from Neilsen, V.K., 1973b)

ouabain-sensitive Na^+, K^+-ATPase, resulting in a reduced flux, and increased intracellular sodium concentration, with a resulting decrease in transmembrane potential difference. Several investigations in animals tend to support this theory.

Morphologic studies of peripheral nerve in humans (Asbury et al., 1963; Dyck et al., 1980; Thomas et al., 1971) indicate a primary axonal degeneration of motor and sensory fibres with secondary segmental demyelination. Small and unmyelinated fibres are also involved. However, there is nothing in the pathology that appears to be peculiar to uremic neuropathy.

A wide variety of specific etiological factors have been considered. There appears to be no definite evidence for any of the following: deficiency of B vitamins, deficiency of biotin, accelerated breakdown of muscle protein, or accumulation of certain 'toxins' such as myoinositol, urea and creatinine (see earlier discussion of biochemical pathogenesis). More plausible has been the theory that proteins in the middle molecular mass range (500–500 000 daltons) may accumulate and be toxic to peripheral nerve. The toxicity of the b4–2 or C7 fraction may be even more specific.

Finally, although no vascular changes have been clearly seen in nerve, a microangiopathy has been demonstrated in skin that, in serial studies, did not improve during dialysis but did so after successful renal transplantation (Gilchrest et al., 1980).

Treatment and prevention

During the early stages of renal failure, all methods utilized to treat the underlying cause of the kidney disease and the various systemic effects of renal failure benefit the neuropathy, because it has been shown that conduction velocity falls in parallel with a decrease in renal function, as measured by the creatinine clearance. Such conservative measures include attention to nutrition (Rudman & Williams, 1985).

When end-stage renal disease has been reached, the patient is placed on either chronic hemodialysis or perito-

neal dialysis. It has been shown that both of these methods of treatment halt the progress of uremic polyneuropathy, and a few patients demonstrate either mild improvement or mild deterioration (Bolton & Young, 1990). It is important to start such treatment early enough; if there is some preservation of renal function beforehand, the degree of uremic neuropathy is less. There is no good evidence, however, that specifically manipulating the various hemodialysis schedules necessarily alters the course of uremic polyneuropathy. For example, utilizing hemodialysis techniques that clear middle molecular mass fractions does not necessarily improve uremic polyneuropathy, although it is still an important area of research.

Patients undergoing peritoneal dialysis seem to have the same incidence and severity of uremic polyneuropathy as those receiving hemodialysis (Bolton & Young, 1990). Because diabetic patients achieve better control of blood sugar with peritoneal dialysis than with hemodialysis, the former method is now most frequently used for those patients. The neuropathy, however, does not improve with this treatment, although it does stabilize (Amair et al., 1982).

Kidney transplantation has been shown to produce a much better quality of life than dialysis, and the procedure is much more cost effective (Eggers, 1988). Renal function becomes relatively normal within a month of transplantation, and 1-year survival rate of the transplanted kidney is 68% (Bolton & Young, 1990). The first symptoms of uremic neuropathy improve within a few days or weeks (Nielsen, 1974). The lessening of the distal numbness and tingling coincides with improvement in nerve conduction velocity, as well as in vibratory perception. This improvement is much more protracted when the uremic neuropathy is more severe and residual clinical signs and symptoms may remain (Bolton et al., 1971). Should the transplanted kidney undergo rejection, improved peripheral nerve function can be achieved with a successful second renal transplantation. Mononeuropathies (of a compressive nature) of the ulnar nerve at the elbow or peroneal nerve at the fibular head also improve after successful renal transplantation. Symptoms of autonomic insufficiency, including impotence and infertility, return to normal (Bolton et al., 1971).

The electrophysiological studies improve in parallel with the clinical signs and symptoms. The conduction velocities and distal latencies rise toward normal. The compound muscle (Fig. 124.4) and sensory nerve action potential amplitudes also rise but not to the same extent in more severe neuropathies. Needle electromyographic abnormalities eventually disappear. Autonomic function, as assessed by heart rate variability measurements, also improves (Yildiz et al., 1998).

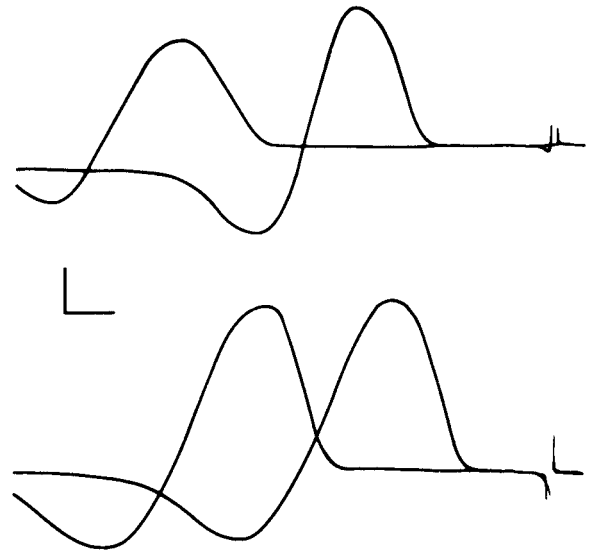

Fig. 124.4. Return of nerve conduction to normal after successful renal transplantation. (Upper trace) Three months before transplantation when the patient had a severe uremic polyneuropathy. (Lower trace) Twenty-seven months after transplanation when almost complete recovery had occurred. The median nerve was stimulated at the wrist, and elbow and the recording was made from the thenar muscle. Conduction velocity rose from 39 to 55 m/s, and the previously dispersed compound action potential became normal, consistent with segmental remyelination. Calibration: vertical, 2 mV; horizontal 2 ms. (Reproduced, with permission, from Bolton & Young, 1990, p. 99.)

The only exception to this improvement in neuropathy occurs in patients who are also diabetic. Here, it has been shown that neuropathy shows only marginal improvement (Kennedy et al., 1990) suggesting that the underlying cause of the neuropathy is mainly diabetes mellitus.

Combined diabetic and uremic polyneuropathy

With the increasing number of diabetic patients receiving chronic dialysis and transplantation, the problem of combined diabetic and uremic polyneuropathy is more prevalent. Both neuropathies manifest a symmetrical motor and sensory polyneuropathy with reduced deep tendon reflexes and varying degrees of ataxia, the distal parts of the limbs being particularly involved. However, diabetic neuropathy is more likely to induce the compressive palsies of ulnar neuropathy at the elbow, carpal tunnel syndrome, and common peroneal nerve palsy; autonomic disturbances and a tendency to multifocal involvement of peripheral nerves are more characteristic. There are also electrophysiological differences: conduction velocities

tend to be lower in chronic renal failure patients who have diabetes mellitus *(*Hansen & Ballentyne, 1978*)*, and in uremia, attempts at reinnervation of muscle (i.e. the re-establishment of nerve supply) are not as successful as they are in diabetic neuropathy (Mitz et al, 1984*)*.

A distinctive variant is subacute uremic and diabetic polyneuropathy (Bolton et al., 1997a). Weakness develops over 2–4 months, and clinical and electrophysiological features suggest a myopathy (with the usual feature of sparse fibrillation potentials and positive sharp waves, as noted previously). Creatine phosphokinase is only mildly elevated and muscle biopsy indicates denervation. Accumulation of advanced glycosylated end products may be a mechanism of this neuropathy, a process reversed by high-flux hemodialysis or renal transplantation, both of which may help these patients. This neuropathy may be similar to the one described by Ropper, except that Ropper's patients had a more acute onset (Ropper, 1993).

Uremic mononeuropathies

The dysfunction of peripheral nerves that occurs in a generalized fashion in chronic renal failure renders these nerves susceptible to local compression (Bolton & Young, 1990). Thus, with the cachexia associated with chronic renal failure, the ulnar nerves at the elbow or the common peroneal nerves at the fibular head are likely to be traumatized. At the time of transplant surgery, compression may occur by operating room equipment. The brachial plexus and radial nerves are particularly susceptible if the arm is kept in an abducted position during anesthesia and surgery. After successful renal transplantation, a patient with simple compressive neuropathies is likely to occur if the treatment of the renal failure is chronic hemodialysis.

Nerves may also be compressed as part of the compartment syndrome; for example, bleeding into the iliopsoas muscle causes acute swelling with compression of the femoral nerves. The process is demonstrated most effectively by computed tomographic (CT) scanning; electrophysiological studies are of little value in the acute stage. This is an emergency situation that requires surgical decompression.

The most common mononeuropathy is carpal tunnel syndrome. As in the non-renal patient, it may be due to narrowing of the carpal tunnel from old age, rheumatism, or other factors. In the renal patient, however, it is particularly likely to occur distal to a Cimino–Brescia forearm arteriovenous shunt used for access during hemodialysis. Here, there is a combination of venous congestion and arterial ischemia.

The signs and symptoms of carpal tunnel syndrome are remarkably similar to those in otherwise healthy persons, except that in uremic patients the symptoms are more pronounced during each hemodialysis procedure. Electrophysiological studies aid greatly in diagnosis by showing prolonged conduction in both motor and sensory fibres through the carpal tunnel region.

Decompressive surgery, with sectioning of the flexor retinaculum, has been found to be an effective method of treatment, particularly if the carpal tunnel syndrome occurs in the arm not containing a Cimino–Brescia forearm fistula. In the case of such a fistula, carpal tunnel surgery, in itself, may not be effective, and consideration may have to be given to either discontinuing or altering the degree of forearm shunting.

It has been previously believed that these were the only mechanisms of carpal tunnel syndrome, but it is known that patients who have received hemodialysis with a Cuprophan membrane for more than 10 years are susceptible to amyloidosis (Gejyo et al., 1986). The amyloid deposit is composed of ß2-microglobulin, which is normally present in small amounts in the serum and other body fluids in healthy persons. It is normally catabolized by the kidneys and, consequently, it rises progressively during renal failure. Such a rise may not occur if dialysis is performed with a newer AN-69-polyacrylonitrile membrane. Levels of α2-microglobulin may be just as high in patients receiving chronic ambulatory peritoneal dialysis; as yet, carpal tunnel syndrome has not yet been reported in this condition, perhaps because the patients have not used this form of dialysis for a sufficient period. Methods of hemodialysis are now being altered to prevent this serious complication, which may cause amyloid deposition not only in the carpal tunnel area but also in the bones and joints, particularly of the upper limbs (Bardin et al., 1986). This more widespread distribution causes a severe arthropathy and intractable pain. Moreover, decompressive carpal tunnel surgery may not relieve the situation; if there is relief, it may be only transient, with a tendency of the syndrome recur later (Fig. 124.5).

Mononeuropathies of a more diffuse nature may occur in the median and ulnar nerves as a result of Cimino–Brescia arteriovenous forearm fistulas. Although they are usually mild and subclinical and are demonstrated only by careful electrophysiological techniques, some dysfunction may occur in up to three-fourths of patients (Knezevic & Mastaglia, 1984). However, shunts located more proximally in the arms, between the brachial artery and antecubital vein, may sometimes produce acute, quite severe, and painful neuropathies involving median, ulnar and radial nerves (Bolton et al., 1979). This is an emergency situation in which electrophysiological studies are not of much value and clinical examination must be relied on. Consideration should be given to taking

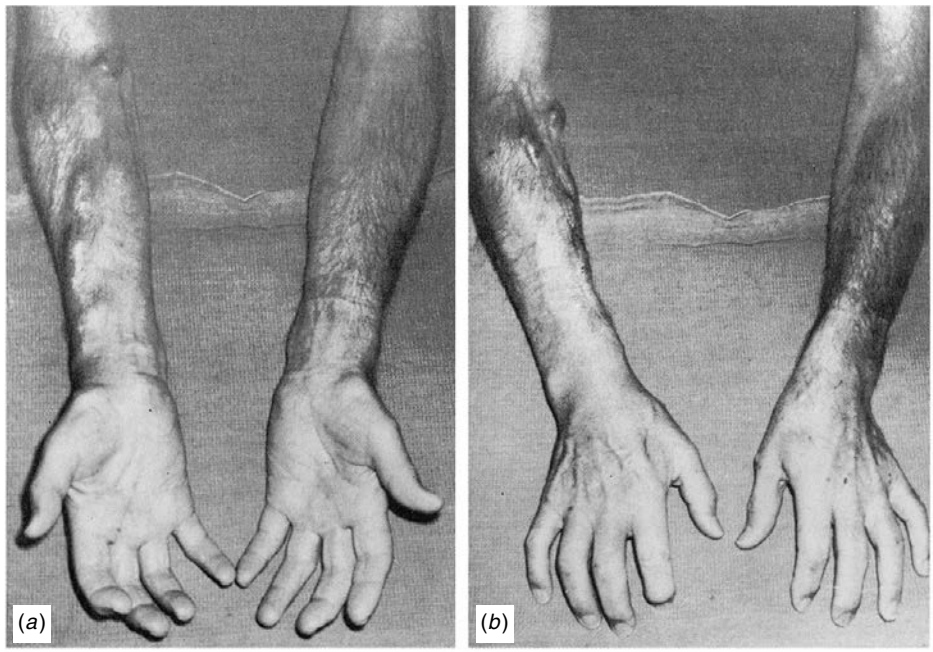

Fig. 124.5. The upper limbs of a patient who had a ß$_2$-microglobulin amyloidosis. It caused (*a*) bilateral carpal tunnel syndrome (note proximal thenar wasting) and (*b*) a right ulnar neuropathy (note the wasting of the interosseous muscles). Tissue biopsied at the time of the carpal tunnel surgery revealed infiltration of blood vessels with amyloid. The pain may have been due to an arthropathy (note thickening and flexion contraction of interphalangeal joints) and periodic nerve ischemia. Repeated surgery for carpal tunnel syndrome provided only transient relief. (The Cimino-Brescia forearm fistula caused the dilated veins in the right forearm.) Reproduced, with permission from Bolton & Young, 1990, p. 110.

down the shunt on an emergency basis, or a severe and possible permanent neuropathy may result. The clinical and electrophysiological studies of these neuropathies are typical of acute nerve ischemia, with a resulting primary axonal degeneration of motor and sensory fibres.

Cochlear and vestibular dysfunction may occur in chronic renal failure as a result of treatment by antibiotics, notably erythromycin and aminoglycosides, and also by diuretic drugs. Uremic toxicity, itself, however, is probably also a factor. Eighth cranial nerve dysfunction may improve during chronic hemodialysis and is most likely to improve after successful renal transplantation.

Myopathy in uremia

A defect in neuromuscular transmission does not occur as a direct manifestation of uremic toxicity, but it may occur as a complication of aminoglycoside antibiotics. Repetitive nerve stimulation studies show an incrementing response typical of the presynaptic defect in this complication. Discontinuance of the drug results in improvement.

Myoglobinuria (Penn, 1986) is an important cause of acute renal failure and may have a variety of etiologies. The clinical picture is mainly determined by the underlying disease. The urine is red, and special tests reveal myoglobin in the urine. The muscles themselves have been traditionally described as weak, swollen and painful, but they may be surprisingly normal on examination. The creatine kinase level is invariably elevated. The muscle disease and the kidney disease are both potentially reversible. Dialysis, or possibly plasmapheresis, may be effective.

Other relatively acute forms of myopathy associated with renal failure are those caused by water and electrolyte disturbances. If muscle weakness occurs in acute attacks, periodic paralysis associated with potassium disturbance should be considered. Hypocalcemia may occur and be manifested as tetany, but this is rare because of the often associated acidosis in renal failure.

A more chronic myopathy may be induced as a complication of steroid therapy.

The chief conditions to be considered in chronic myopathies are, first, the non-specific cachexia associated

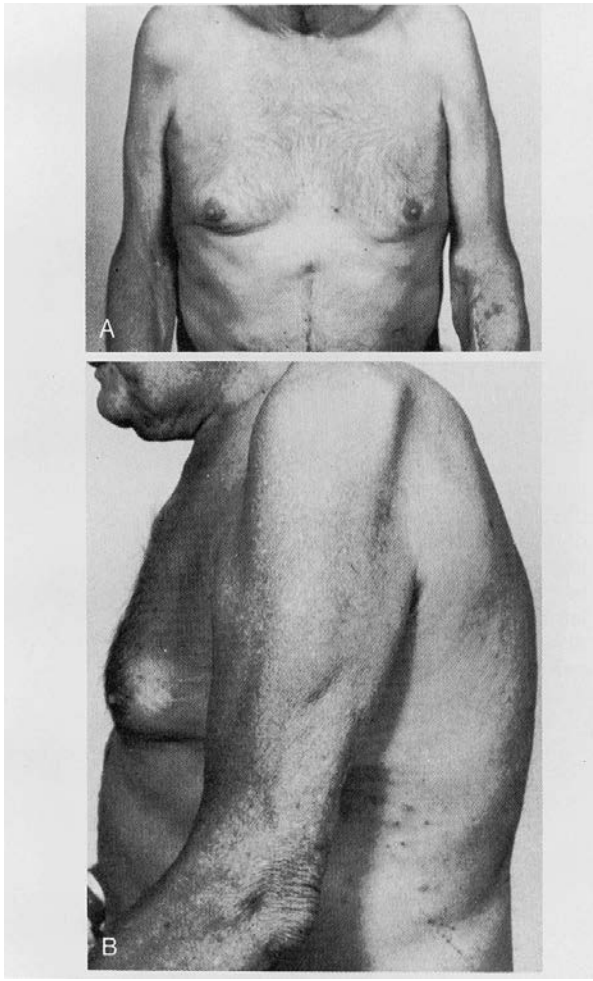

Fig. 124.6. (*a*) and (*b*) Severe muscle wasting in a 67-year-old man who had received chronic hemodialysis for 7 years. It was associated with underlying pain secondary to progressive bone disease. He also had a progressive dementia, but aluminium intoxication was never proved. Although he had a mild uremic polyneuropathy, needle electromyography of shoulder girdle muscles revealed only an increased proportion of polyphasic units, consistent with a primary myopathy. (Reproduced, with permission from Bolton & Young, 1990, p. 158.)

with CRF, and second, perhaps more frequently, the type of myopathy that may be associated with a remarkable proximal wasting of muscle in the limbs (Bolton & Young, 1990) (Fig. 124.6). It is associated with underlying bone disease that is due to either secondary hyperparathyroidism or aluminium accumulation. In both types of cachexia, needle electromyography reveals no clear-cut abnormalities, the creatine kinase levels are usually normal, and biopsy reveals some atrophy of type 2 muscle fibres.

Complications of dialysis therapy

Adverse effects from dialysis, especially hemodialysis, occur in every renal unit. These include: dialysis dementia, dysequilibrium syndrome, subdural hematoma and vitamin deficiencies. These are discussed in turn.

Dialysis dementia

This clinical syndrome was initially described in clusters of patients on chronic hemodialysis, although a similar syndrome may occur in patients on peritoneal dialysis (Alfrey et al., 1972). The condition is related to an accumulation of aluminium in the brain (Wing et al., 1980; Fraser, 1992; Roskams & Connor, 1990). Elimination of aluminium from the dialysate essentially eliminated epidemics of this syndrome; sporadic cases since then relate to the absorption of aluminium from the gastrointestinal tract, usually from the use of aluminium-containing phosphate binders (Sideman & Manor, 1982). Dialysis dementia is progressive and fatal unless recognized early and treated vigorously.

The essential components of the syndrome are an initial non-fluent speech disturbance (aphasia plus dysarthria), involuntary motor phenomena (especially myoclonus and seizures), gait disturbance (apraxia or ataxia) and mental changes (Bolton & Young, 1990). The latter consist initially of apathy and behavioural changes, combined with speech and writing errors. The mental changes can blend with the features described above as part of the uremic syndrome, but a striking behavioural change in a patient with CRF should raise the possibility of dialysis dementia, especially in the face of adequate (e.g. thrice weekly) dialysis. Confusional states appearing transiently shortly after dialysis are a typical early feature. These last longer with further dialysis treatments until they persist. Memory failure, poor attention, disorientation, psychotic behaviour, apraxia and dyscalculia have been described. Eventually the patient becomes bedridden, incontinent and stuporous. The condition is often associated with a fracturing osteodystrophy and a severe, refractory, microcytic anemia.

The EEG can be helpful diagnostically and in following therapy. Typically, patients have frequent 'projected' bursts of rhythmic delta activity, triphasic waves or irregular generalized epileptiform discharges, despite an adequate, e.g. thrice weekly, dialysis programme. (Figs. 124.7 and 124.8). Serum aluminium levels are helpful, but often not definitive. Although serum aluminium levels of <50 ng/l are unlikely to be associated with dialysis dementia, occasional cases may have low levels. Bone aluminium measurements and the desferoxamine infusion test are further refinements (Bolton & Young, 1990).

A high index of suspicion and vigilance for dialysis dementia in the uremic population is vital. With first symp-

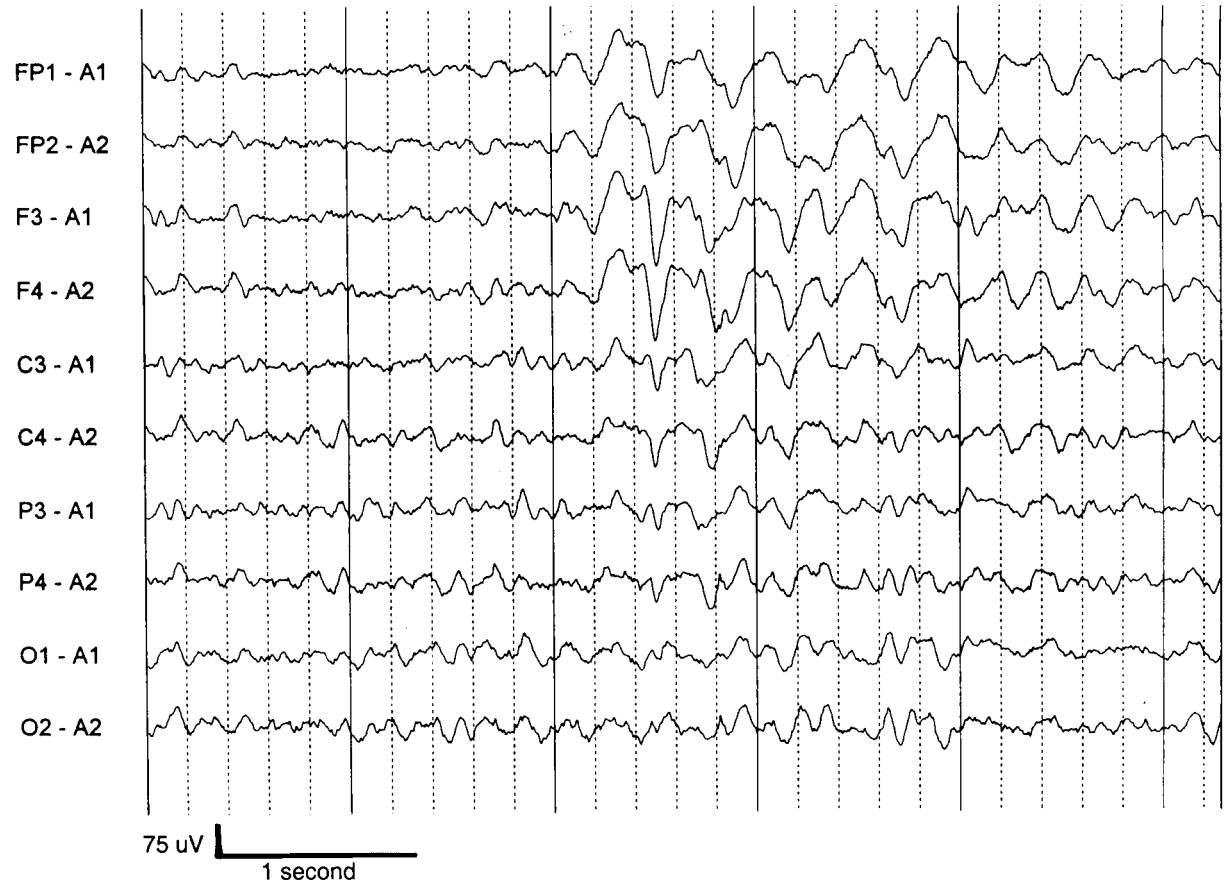

Fig. 124.7. This EEG shows a burst of triphasic waves and rhythmic, frontally predominant delta activity. The patient had secondary hyperparathyroidism and required an aluminium-based, phosphate binder. He had intermittent speech problems and ataxia; serum aluminium was over 800 ng/ml.

toms of the condition, the patient should be withdrawn from all sources of aluminium (especially in dialysate, aluminium-containing antacids). Desferoxamine, a chelating agent for aluminium, can be given safely on an intermittent or long term basis (Bolton & Young, 1990). This can help in arresting progression of the disorder and may reverse many of the features, although sometimes not completely (Bolton & Young, 1990).

Symptomatic therapy with antiepileptic drugs such as phenytoin or valproate may be necessary. Although benzodiazepines may have a transiently beneficial effect on the clinical features, their long-term usefulness has not been demonstrated.

Dialysis dysequilibrium

Dialysis dysequilibrium, a syndrome with close temporal relation to hemodialysis treatment, occurs mainly during, or after, the initial dialysis treatment in patients with CRF. The very young and very old may be more susceptible (Port et al., 1973). Although usually reversible, death or permanent damage from seizures occur in severe cases (Peterson & Swanson, 1964; Wakim, 1969).

Dialysis dysequilibrium syndrome is thought to be related to an osmotic mismatch between the plasma and brain, with relatively lower osmolality in the blood than in the brain during dialysis (Peterson & Swanson, 1964; LaGreca et al., 1982; Pappius et al., 1996). Arieff has shown an intracellular acidosis occurs in the brain, in association with dialysis dysequilibrium (Arieff et al., 1973). The relative roles of osmotic and pH changes are unclear.

Mild cases show headache, nausea, vomiting, restlessness or drowsiness and muscle cramps, variably accompanied by disorientation and tremors. Moderate features include disorientation, somnolence, asterixis and myoclonus. Severely affected patients develop an acute organic psychosis, coma or generalized convulsions. Features begin either during or immediately following the dialysis treatment.

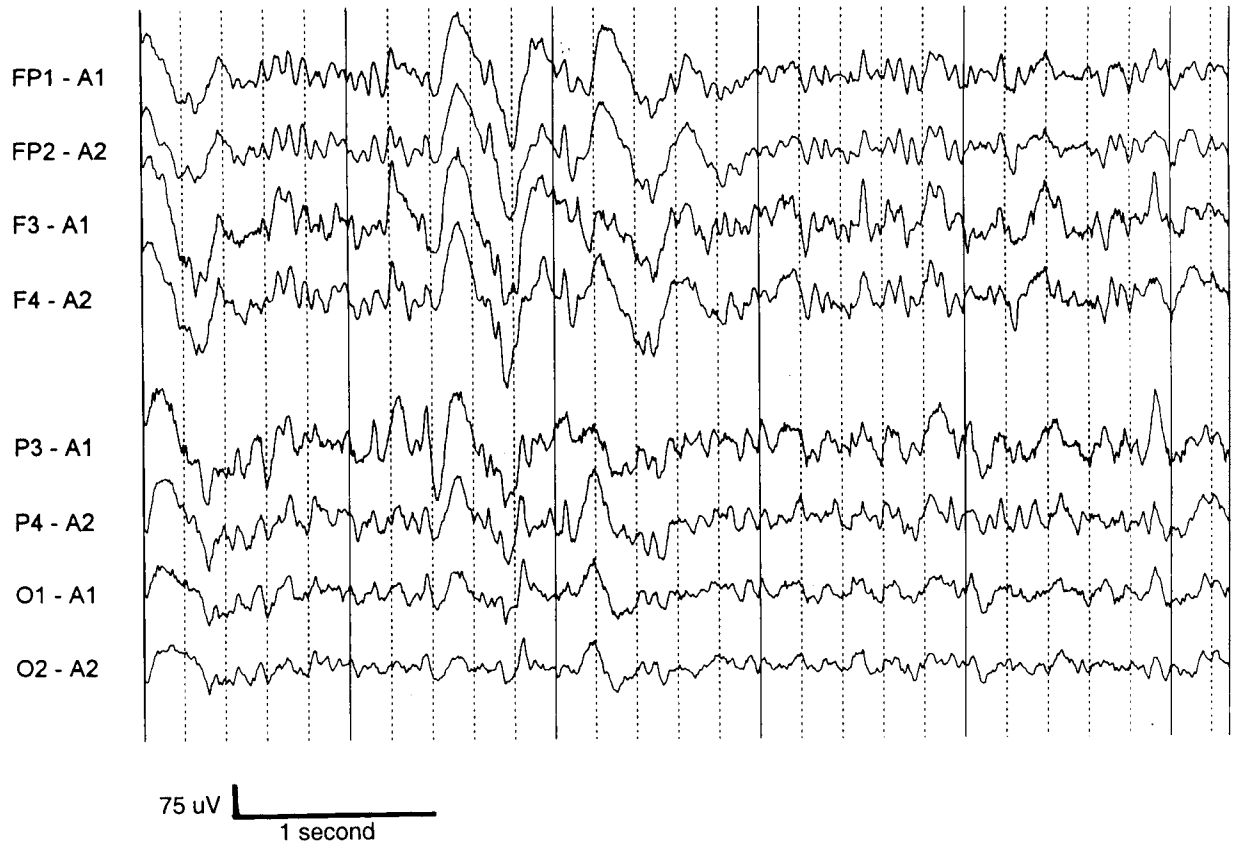

Fig. 124.8. Same patient as in Fig. 124.7; EEG done four months later. The EEG now shows bursts of irregular spike-waves. The occipital rhythm is poorly maintained, while the faster frequencies are from diazepam given for a recent seizure. Despite desferroxamine therapy, the patient worsened clinically and was mute with intermittent myoclonus and seizures at the time of the EEG. The patient subsequently became septic and died. He was thought to have had 'dialysis dementia' from aluminium intoxication.

EEGs show bursts of slow frequency waves, higher voltage and slower with increasing severity of the encephalopathy (Kennedy et al., 1963). These bursts occur against an abnormal, mildly slowed or markedly dysrhythmic background. Generalized epileptiform activity may be found in those with seizures. The EEG returns to normal with resolution of the encephalopathy. Quantitative methods may be more sensitive in detecting early changes during dialysis, but it is difficult to control for normal drowsiness (Arieff et al., 1978). The cerebrospinal fluid becomes acidotic during attacks (Arieff, 1994).

Dialysis dysequilibrium can be prevented by using slower blood flow rates in dialysis, by increasing the osmolality of the dialysate by the addition of urea, sodium, mannitol or glycerol or with the use of hemofiltration followed by dialysis or peritoneal dialysis. (Port et al, 1973; Arieff et al., 1978; Gilliland and Hegstrom, 1963). Glycerol prevents the intracellular acidosis noted by Arieff and colleagues (Arieff et al., 1978). The substitute of bicarbonate for acetate in the dialysate has also been recommended.

Subdural hematoma

Subdural hematomas, found in 1–3% of patients on hemodialysis sometimes associated with anticoagulant therapy, can occur at any age in uremia (Talalla et al., 1970; Leonard & Shapiro, 1975; Rotter & Roettger, 1973). The hematomas are large in about 10% of cases; most show fresh bleeding with evidence of older hemorrhage. Iatrogenic and intrinsic uremic coagulopathies likely both contribute.

Patients usually present with headache and tenderness of the head to percussion. The patient often show decreased alertness and cognition and may seem depressed. These are common features in uremia, so subdurals can easily be overlooked. Focal signs predominate in some patients. Hemiparesis or a language disturbance

may occur, but could be misinterpreted. Gait apraxia in older patients with subdurals is common (McLachlan et al., 1981).

Diagnosis is easily made with CT (beware of the isodense subdural, however) or MRI scans.

Because subdural hematomas are common, life threatening and treatable, they should be considered in any uremic patient who develops a change in CNS function. They can present in a variety of ways and may be insidious; hence a high degree of suspicion and vigilance is necessary.

Treatment is usually surgical drainage. Occasional patients can be managed conservatively, but require close follow-up.

Wernicke's encephalopathy

Wernicke's encephalopathy occurs in those dialysed patients who are too ill to eat or who repeatedly vomit and are placed on intravenous solutions that do not contain thiamine (Lopez & Collins, 1968; Jagadha et al., 1987). Uremics with hyperkalemia may be most at risk, as glucose boluses are often given to reduce the serum potassium concentration. It should be remembered that, in some patients, the classical features of ophthalmoplegia, nystagmus, encephalopathy and ataxia may not all be present. Without the ocular findings, there is great difficulty in differential diagnosis, unless Wernicke's encephalopathy is considered.

Complications of renal transplantation

(Note: Complications of immunosuppressive drugs are discussed in Chapter 129.)

Rejection encephalopathy

Rejection encephalopathy affects mainly patients between 10 and 38 years of age, usually within the first few months of renal transplantation. Symptoms include headache, confusion or convulsions along with systemic features of graft rejection. The release of cytokines may be of pathogenetic importance. The condition is treated symptomatically, mainly with antiepileptic drugs, and increased immunosuppression to combat the graft rejection response. The prognosis is usually favourable.

Infections

Infections of the central nervous system can be divided into viral, fungal and bacterial. Predisposing factors, besides the immunosuppression, include diabetes, intravascular lines, uremia and urinary catheters.

Viral infections peak between 1 and 6 months following transplantation and include cytomegalovirus (can cause retinitis, blindness and an encephalitis) and Epstein–Barr virus. Opportunistic fungi are mainly *Aspergillis fumigatus* and *Nocardia asteroides*. The main bacterial infection is *Listeria monocytogenes*. The same organisms and *Cryptococcus neoformans* may cause infection later, as may the JC virus, causing progressive multifocal leukoencephalopathy, and *Mycobacterium tuberculosis*. Initial symptoms and signs of CNS infection may be dampened by the anti-inflammatory effects of the immunosuppressive therapy, so a high index of suspicion needs to be maintained, with prompt neuroimaging and CSF analysis. Special tests, such as PCR on the CSF, e.g. for the JC virus and *Mycobacterium tuberculosis*, special stains and cultures, are sometimes helpful. Recruitment of expert microbiological expertise is recommended.

Indirectly, the CNS may be affected by hepatic failure in rapidly progressive hepatitis in patients with hepatitis C virus infection. In such patients a decrease or withdrawal of immunosuppressive therapy may improve the early hepatic failure without adverse effects on the graft (Ok et al., 1998).

Post-transplant lymphoproliferative disorder

This includes the proliferation of B-lymphocytes with disorders ranging from monoclonal gammopathy to B-cell lymphomas of the CNS (Patchell, 1994). The latter tend to be periventricular and multiple, with uniform contrast enhancement and indistinct or fuzzy margins. Brain biopsy is usually necessary. The condition may respond initially to radiation and chemotherapy but the overall prognosis is usually poor.

Systemic disorders affecting the nervous system and kidneys

Genetic disorders

Genetic disorders include von Hippel–Lindau disease (VHLD), polycystic kidney disease and Wilson's disease. In VHLD, an autosomal dominant disorder, the CNS is the site of hemangioblastomas, most commonly in the cerebellum (50–70%) and the retina (60%). Renal carcinoma occurs in both Types I and II VHLD. Renal cysts occur in about 85% of cases of VHLD. The VHLD tumour suppressor gene has been located on chromosome 3p25–p26; genetic testing is available (Latif et al., 1993).

Polycystic kidney disease (PKD) exists in both autosomal dominant and recessive forms; the dominant form has

Table 124.1. Systemic disorders affecting the kidney and nervous system

Disease	Renal condition	Neurological complication
Polyarteritis nodosa	renal failure, hypertension, proteinuria, granular casts	peripheral neuropathy, less commonly encephalopathy, strokes, SAH, cranial neuropathies, seizures
Wegener's granulomatosis	proteinuria, hematuria, RBC casts, renal failure	cranial neuropathies, multiple mononeuropathies, polyneuropathies, strokes
Infections: hepatitis B, esp. with polyarteritis nodosa	proteinuria, granular casts, renal failure	encephalopathy, strokes, mononeuropathies
Toxins, esp. with illicit drug use	proteinuria, granular casts, renal failure	encephalopathy, strokes, mononeuropathies
Lymphoid malignancy	proteinuria, granular casts, renal failure	encephalopathy, strokes, mononeuropathies
Systemic lupus erythematosus	hematuria, proteinuria, nephrotic syndrome, renal failure	encephalopathy, seizures, strokes, chorea, cranial and peripheral neuropathies
Rheumatoid arthritis	glomerulonephritis, amyloid kidney disease	polyneuropathies, mononeuropathies, cervical myelopathy (mechanical)
Sjögren's syndrome	tubular dysfunction	neuropathies, ganglionopathy, cranial neuropathies
Plasma cell dyscrasias (POEMS, myeloma, MGUS, Waldenström's, cryoglobulinemia)	proteiuria, nephrotic syndrome, renal failure	root and spinal cord compression/neuropathies, cerebral/cranial n. compression; IIH

Notes:
Legend: IIH = idiopathic intracranial hypertension; MGUS = monoclonal gammopathies of unknown significance; SAH = subarachnoid hemorrhage; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes, in association with plasma cell dyscrasia (osteosclerotic myeloma).
Source: Modified from Burn and Bates (1998), Table 3.

been linked to two different genetic loci (still incomplete evidence), the recessive to one locus (Zerres et al., 1994; Ong, 1997; San Millan et al., 1995). Polycystic kidney disease is associated with a risk of intracranial berry (saccular) aneurysms that may rupture and cause subarachnoid or intraparenchymal brain hemorrhage. (It should be noted, however, that there are more cases of hypertensive intracranial hemorrhage than of ruptured berry aneurysm in PKD patients (Ryu, 1990). Other conditions with a less strong association with PKD include arachnoid cysts, eosinophilic granuloma, moyamoya disease, familial amyloidosis, mitral and aortic valve incompetence and mitral valve prolapse (Ruggeri et al., 1994; Pracyk & Massey, 1989; Scelsi et al., 1989).

Wilson's disease is a disorder of copper metabolism and is discussed elsewhere. It should be mentioned that Wilson's disease can sometimes cause renal dysfunction, primarily at the proximal convoluted tubule region. This can result in a Fanconi syndrome, with generalized aminoaciduria, hypophosphatemia (see below) and systemic metabolic acidosis (Hoogrngraad, 1996).

Acquired disorders

Although various systemic disorders and their neurological complications are discussed elsewhere in this book, Table 124.1 summarizes the neurological and nephrological aspects of these disorders. Most of these either cause vascular lesions (either vasculitic or perfusion deficiencies), have a direct immunological effect on nervous tissue, have tissue infiltration by cells or proteins, predispose to chronic infections or a combination of these pathogenetic mechanisms.

Electrolyte disturbances

Hyperosmolality and hypernatremia

Hypernatremia, a rise in serum sodium concentration above 145 mmol/l, relates to a deficit of water relative to sodium and indicates a general hypertonicity of body fluids. Although hypernatremia can be acute or chronic, only the acute variety has established primary effects on the central nervous system. It is difficult to separate

Table 124.2. Causes of hypernatremia

Water loss	Water loss with sodium loss	Water loss with sodium gain
Extrarenal		
Skin: insensible perspiration	Skin: sweat	
Lungs		
Renal	Osmotic diuresis	Excessive sodium administration
Diabetes insipidus (CNS or nephrogenic)		Adrenal hyperfunction (hyperaldosteronism, Cushing's syndrome)
Hypothalamic dysfunction		

Source: Modified from Levinsky, N.G.: Fluids and electrolytes. In Braumwald et al. (1988).

chronic hypernatremia from its associated diseases; the latter are usually more likely than the hypernatremia to affect neurological function.

Pathophysiology of hypernatremia

Hypernatremia can develop with either excessive loss of water, decreased water intake with immobility or impaired consciousness that impair satisfying the strong thirst drive. With an increase in serum osmolality, water shifts from the intracellular to the extracellular compartment. Therefore, net rises in serum sodium or osmolality reflect large losses of body water.

Table 124.2 lists the main causes of hypernatremia. Hypernatremia from antidiuretic hormone (ADH) deficiency or excessive mineralocorticoid activity produces only modest elevation of serum sodium. The former may cause significant hypernatremia only if the patient cannot satisfy thirst needs. Insensible losses of water from skin and lungs may reach several litres per day in cases of extreme heat, fever, burns and hyperventilation. The sudden development of hypernatremia may be an indication of acute pituitary failure, i.e. pituitary apoplexy. Patients who suffer hypothalamic damage and coma are at risk for hypernatremia. Exceptionally, hypernatremia results from excessive sodium administration. This has happened inadvertently in the preparation of infant formulae or hemodialysis solutions, or the excessive administration of hypertonic saline solutions to comatose patients, e.g. correction of metabolic acidosis with the administration of sodium bicarbonate (Snyder & Arieff, 1992).

Central nervous system complications of hypernatremia

Acute/subacute hypernatremia with neurological manifestations occurs predominantly in very young infants and the elderly. It may occur in patients of intermediate ages, especially in the presence of a net loss of water, iatrogenic or self-induced salt loading and obtundation or inability to express needs or to satisfy thirst.

Neurological signs and symptoms relate to loss of volume of cells in the CNS, as brain cell membranes are highly permeable to water, allowing shifts to follow osmotic gradients. To prevent cell shrinkage, there are potent homeostatic mechanisms in the brain that allow neuronal and glial 'regulatory volume increases' in the face of acute hyperosmolality (Pesantes-Morales, 1996). Within minutes, there is an increase in sodium, potassium and chloride ion influx into cells due to activation of a neuronal and glial cotransporter (Pesantes-Morales, 1996). This is followed in about 10 hours by an increase in organic osmolites, especially myoinositol, glutamate, glutamine, and taurine (Pesantes-Morales, 1996). Myoinositol makes up much of the compensatory increase in osmolality; this occurs through increased production of a sodium-dependent cotransporter messenger RNA (Pesantes-Morales, 1996). The increase in organic compounds offsets some of the electrolyte imbalance that can alter neuronal functioning, e.g. seizures (Pesantes-Morales, 1996).

Because the brain adjusts its idiogenic osmoles to maintain cellular volume, only acute hypernatremia causes an acute loss of brain volume. If the rate of water loss outstrips the speed of homeostatic mechanisms, patients may develop lethargy, delirium, stupor or coma (Swanson, 1976). There is typically an increased muscular tone, probably paratonic rigidity. Brain shrinkage may be accompanied by tearing of bridging veins running from the cerebral cortex to the superior sagittal sinus, creating subdural hematomas (Finberg, 1963). Capillary and venous congestion and bleeding with multiple microscopic hemorrhages, macroscopic subcortical intracerebral and subarachnoid

hemorrhages have been described (Luttrell & Finberg, 1959). Furthermore, venous thrombosis, including the superior sagittal sinus, has been described in the context of acute hypernatremia (Luttrell & Finberg, 1959). Seizures can occur related to these vascular complications (Bruck et al., 1968; Finberg, 1963).

Rarely, central pontine myelinolysis can occur with the acute development of hypernatremia, in the context of severe systemic illness (McKee-Winelman et al., 1988).

Seizures mainly occur during the rehydration phase of patients with chronic hyponatremia, presumably due to acute osmotic swelling of cells following the administration of fluids that are lower in osmolality than the patient's sera and brain (Kahn et al., 1979). Patients with elevated serum urea, and acidosis are especially at risk for seizures during rehydration (Khan et al, 1979).

Diagnosis of hypernatremia

Serum electrolyte determination establishes the presence of hypernatremia. The cause should be apparent from the clinical setting.

EEG changes are non-specific, consisting of diffuse slowing that reverses after uncomplicated correction. Epileptiform discharges are not seen in acute or chronic hyponatremia in the absence of vascular complications (Dodge et al., 1962).

Management

Calculations of water deficit should be based on total body water that equals about 60% of body weight in non-obese patients. If there is an associated volume deficit, i.e. combined water and sodium loss, replacement should begin with normal or 0.9% saline solution. Volume deficits must be replaced first (Snyder & Arieff, 1992). Only profound acidosis, with pH less than 7.15, should be treated with sodium bicarbonate (Graf & Arieff, 1986). If the neurological syndrome of acute hypertonicity predominates, replacement should start with half-normal or 0.45% saline. It is best to avoid increases of plasma osmolality of greater than 2 mOsm/l/hour (Snyder & Arieff, 1992). Pure glucose solutions should be avoided, as the brain will not have time to adjust to the resultant shift of water into the intracellular compartment. This will probably result in coma, convulsions and acute brain swelling from cytogenic edema. Such complications are much more likely if the hypernatremia has been established for some time (e.g. days to weeks). Serum electrolytes should be monitored every 2 to 4 hours during acute therapy.

With the above, the underlying disease process should be sought and treated. It is vital to give corticosteroids promptly to patients with pituitary apoplexy. Excessive losses of water should be corrected. This may involve changes of medication and treatment of hyperthermia.

Hyponatremia

Hyponatremia, defined as a serum sodium of less than 135 mmol/l, has an incidence of about 1% and a prevalence of about 3% in inpatients in general hospitals (Anderson et al., 1985). Hyponatremia constitutes the most common electrolyte disturbance and is associated with a number of diseases.

Classification

Hyponatremia reflects water balance, which determines the osmolality of the plasma, and is classified as: isovolemic, hypovolemic, hypervolemic and iso-osmolar. See Table 124.3.

Most cases of hyponatremia are associated with hyposmolality of the blood or a relative excess of solvent to solute. This is associated with the kidney not excreting a dilute urine that can relate to: (i) inappropriate secretion of antidiuretic hormone (ADH) associated with a number of disorders; (ii) increased renal excretion of sodium due to enhanced secretion of naturetic factor or to defective sodium transport in the diluting parts of the nephron; (iii) insufficient glomerular filtrate reaching distal parts of the nephron, either due to decreased glomerular filtration rate or to increased proximal tubular reabsorption of fluid.

Hypo-osmolar hyponatremia can be divided according to volume status. Hypovolemic hyponatremia may be caused by loss of fluid or blood through the gastrointestinal tract, urinary tract (often with secretion of atrial natriuretic factor or loss of aldosterone effect), skin, blood loss from various sites or from third space sequestration (e.g. ascites with hypoproteinemia may be associated with a contraction of the vascular volume). This stimulates the secretion of ADH as volume replacement has precedence over osmolality. Normo- or hypervolemic hyponatremia is usually related to inappropriate secretion of antidiuretic hormone or drugs that cause this effect. As a corollary, the finding of normal volume or central venous pressure helps to separate SIADH from salt wasting and other conditions associated with contraction of blood volume. In some hospitals measurement of ADH (arginine vasopressin) can be performed.

Artifactual hyponatremia is associated with normal osmolality. It may be caused by hyperlipidemia, hyperglycemia or certain intoxications. In hyperlipidemia lipids occupy volume in the plasma as if they formed a compartment. If this compartment is excluded, the osmolality or serum sodium of the remaining component is normal.

Table 124.3. Hypovolemic hyponatremia (combined sodium and water deficiency)

Extrarenal losses: gastrointestinal, skin, third space sequestration (e.g. ascites), skin (sweating, burns)
Renal losses
Renal disease: CRF, salt-wasting tubular disease
Diuretic excess
Osmotic diuresis: diabetes mellitus, iatrogenic (e.g. mannitol)
Mineralocorticoid deficiency: Addison's disease, hypoadrenalism
Isovolemic hyponatremia
(no significant expansion of extracellular compartment)
Nausea, pain, emotion: temporary impairment of water diuresis
Psychogenic polydipsia
Endocrine (glucocorticoid deficiency, hypothyroidism)
SIADH
Drugs
Drugs that potentiate ADH action: clofibrate, NSAIDS, ADH analogues, cyclophosphamide
Drugs that stimulate ADH release: vincristine, Carbamazepine, narcotics, barbiturates
Drugs that potentiate ADH action and stimulate release: Thiazide diuretics, chlorpromazine, ADH analogues
Essential: 'sick cell syndrome'
Hypervolemic hyponatremia
(Expansion of extracellular compartment: edema)
Hepatic failure
Cardiac failure
Nephrotic syndrome
Without plasma hypo-osmolality
Osmotic: hyperglycemia, mannitol
Artifactual: hyperlipidemia, hyperproteinemia

Clinical features

Hyponatremia itself, if symptomatic, causes a metabolic encephalopathy consisting of inappropriate behaviour, confusion, headache, speech problems, lethargy, vomiting, tremor, weakness, malaise and seizures (Price & Mesulam, 1987). The latter are usually generalized convulsions. Muscle twitches and cramps may occur. The patient is much more likely to be symptomatic if the hyponatremia develops acutely or subacutely and if the serum sodium is less than 125 mmol/l. In some chronic cases, the mental changes may be due to the underlying condition, e.g. hypothyroidism, rather than the hyponatremia. Occasionally severe hyponatremia may develop acutely, e.g. in patients who become acutely volume depleted from prolonged outdoor exercise and replace the volume with excessive water. This can lead to life-threatening cerebral edema with coma and signs of herniation (Garigan & Ristedt, 1999).

Risk factors for development of symptomatic hyponatremia include: age over 75 years (and the use of certain drugs, e.g. thiazide diuretics in this age group), female sex, below average body weight, the rate and extent of fall of serum sodium concentration and the presence of underlying serious illnesses (Arieff et al., 1976; Ashraf et al., 1981).

Pathophysiology

A decrease in the osmolality of the plasma creates an osmotic gradient between the blood compartment and the cells of the body, including the brain. Unless the brain decreases its osmolality, there will be a shift of water across the cell membranes, causing the cells to swell. The brain can adjust to hyponatremia, thereby maintaining intracellular volume, by reducing its osmolality (Arieff et al., 1976). If hyponatremia develops quickly, the brain does not have time to adjust by reducing its idiogenic osmoles. With brain swelling, compensation for the increased volume can be accommodated only up to about 50 ml. After this, the swelling causes an increase in intracranial pressure (Ayus et al., 1992).

In addition, the ionic composition of the brain is altered and changes in neurotransmitter function follow. Acute hyponatremia with hypo-osmolality would be expected to cause partial depolarization of nerve cells, related to the extrusion of potassium, which makes them hyper irritable: reduced threshold for firing action potentials and increased tendency for seizures.

Management

The management of hyponatremia depends on the underlying cause and the neurological complications exhibited by the patient. The patient's hyponatremia should be classified into a broad category of hypovolemic, normovolemic, hypervolemic or normo-osmolar. Then the specific underlying disorder determined using clinical and laboratory means described in standard medical texts.

Correction of the underlying disorder usually corrects the hyponatremia. Asymptomatic patients with hypotonic hyponatremia who are hypervolemic or normovolemic are treated with volume restriction to 1.0 l per day and will correct at a maximum rate of 1.5 mmol/l per day (Ayus & Arieff, 1993). This can be supplemented with normal saline at amounts to create a rise in serum sodium of less than 12 mmol/day.

The management of acutely symptomatic patients is controversial. However, those with seizures and cerebral edema require more active treatment than water restriction alone (Ayus et al., 1987; Arieff, 1986). In these extreme and rare circumstances, prompt therapy with mannitol or hypertonic saline with a loop diuretic should be administered

such that the correction is no faster than 0.5–1.0 mmol/l per hour or 20 mmol/l in the first day. Electrolytes need to be checked hourly with prompt reporting facilities.

If possible, it is best not to correct the serum sodium too quickly or to normal values. It is important to give just enough to get the serum sodium concentration in the range of 130 mmol/l and not to strive for prompt normalization of serum electrolytes. This may put the patient at greater risk for CNS demyelination than the rapidity of sodium elevation (Ayus et al., 1987). In both chronically and acutely ill humans rapid correction can result in pontine and extrapontine myelinolysis. There is considerable variation in susceptibility to central myelinolysis, however (Karp & Laureno, 1995). Retrospective studies have led to the recommendation that myelinolysis can be avoided by limiting the rate of rise to less than 12 mmol in the first 24 hours or 25 mmol/l in the first 48 hours (Sterns et al., 1986). However, even with these guidelines, some patients develop CPM (Karp & Laureno, 1995). Karp & Laureno (1995) suggest striving for less than 10 meq/l for the first 24 hours and less than 21 meq/l over the first 48 hours. Studies on acutely hyponatremic animals showed that an increase of more than 12 mmol/l/day may produce CPM if this rate is continued for 2–3 days (Sterns, 1987).

The matter is still shrouded with some controversy. Water restriction, if too vigorous, may be associated with complications. In an experimental study, Ayus and colleagues (1985) found that, if the sodium rose to normonatremic values within 24 hours with water restriction, there were scattered brain lesions, including neuronal necrosis and myelin damage, but not the typical features of CPM. Treatment of hypovolemic shock may be necessary and may force a more rapid rise in osmolality than planned. The use of half normal saline might be considered in this circumstance.

Hypercalcemia

An increase in serum calcium concentration sufficient to cause alteration of central nervous function is not uncommon in certain populations, e.g. 5% of patients with cancer. Hypercalcemia has a prevalence of 0.5% of hospitalized patients (Fisken et al., 1984).

Pathogenesis

Table 124.4 gives a list of causes of hypercalcemia. Severe hypercalcemia is most commonly due to malignancy or hyperparathyroidism, followed by sarcoidosis, milk-alkali syndrome and adrenal insufficiency. In malignancies the main mechanisms are the production of parathyroid related peptide by the tumour and malignant bone destruction itself (Waxman, 1990).

Table 124.4. Causes of hypercalcemia

Disruption of normal bone–extracellular fluid equilibrium
Metastatic tumour
Multiple myeloma
Lymphoma
Hyperthyroidism
Immobilization in a young individual or those with underlying disease, e.g., Paget's disease
Excessive parathyroid hormone
Primary hyperparathyroidism
Non parathyroid-tumour producing parathormone-like substance, e.g. lung, breast, kidney, etc.
Lithium therapy
Familial hypocalciuric hypercalcemia
Excess vitamin D
Hypervitaminosis D
Sarcoidosis (increased formation of 1, 25-dihydrocholecalciferol)
Idiopathic hypercalcemia of childhood.
Other
Adrenal insufficiency
Thiazide administration
Milk-alkali syndrome
Hypervitaminosis A

Calcium plays a vital role in neurotransmitter release and in the activation of intracellular processes that result from neuronal excitation as well as in electrical stabilization of neuronal membranes. A high extracellular concentration of calcium decreases membrane permeability and reduces its excitability.

The early generalized weakness and fatiguability relate to reduced neuromuscular excitability.

Clinical features

The severity of neurological features depends on the serum concentration, the acuity of the hypercalcemia and the associated medical conditions. Mental status abnormalities commonly occur with serum calcium concentrations above 14 mg/dl (3.2 mmol/l) and consist of behavioural changes (ranging from personality changes to severe organic psychosis), confusion, progressing to lethargy, stupor and coma with clinical features of a diffuse or bihemispheric encephalopathy (Wang & Guyton, 1979). Convulsions occasionally occur. Severe hypercalcemia with impaired consciousness is more common with cancer than in hyperparathyroidism.

Ocular palsies, including internuclear ophthalmoplegia, and muscular wasting, weakness and areflexia have been associated with hyperparathyroidism (Patten & Pages, 1984). The association is not necessarily cause and effect, but one patient with this constellation improved with removal of the parathyroid adenoma and the other showed hemorrhagic lesions in the anterior horns of the spinal cord, as has been described with experimental animals with iatrogenic hyperparathyroidism (Patten & Pages, 1984).

Commonly associated problems include marked dehydration, abdominal pains, renal calculi and metabolic bone disease. Renal insufficiency (either prerenal, renal or obstructive uropathy) may add to the acute picture.

Laboratory features

Ionized calcium is the physiologically active component of extravascular calcium. Calcium is largely protein bound, but the ionized unbound portion's concentration is 1.16–1.32 mmol/l. in hypoproteinemia, it is important to correct for serum albumin concentration or to obtain an ionized calcium concentration.

Management

Severe, life-threatening hypercalcemia should be diagnosed from a combination of the clinical and laboratory features. It is important to sort out the underlying cause and to treat it, if possible (Nussbaum, 1993). The decision to treat should be based on the patient's anticipated quality of life and personal preferences, the diagnosis and prognosis of the underlying cause (often cancer). Hypercalcemia secondary to parathyroid adenoma, however, is cured with surgery.

Once a decision to treat has been made, it is usually best not to rapidly correct the hypercalcemia. The first step is to correct dehydration or volume replacement with intravenous saline. Potassium supplements are also usually needed. Subsequent specific treatment involves the correction of hypercalcemia over the next 24–48 hours.

A loop diuretic and further infusion of saline, after intravascular volume is adequate, enhance renal clearance of calcium. An intravenous biphosphonate drug (e.g. pamidronate or clodronate) is currently considered the drug of choice (Heath, 1989). Plicamycin (mithramycin), which inhibits bone resorption, is often effective but has significant dose and dose–duration toxic effects on the liver, bone marrow, coagulation system and kidneys. Gallium nitrate can be used as an alternative to plicamycin. Corticosteroids and calcitonin usually have modest, or transient effect at best, in controlling the hypercalcemia of malignancy (Thalassinos & Joplin, 1970; Hosking & Gilson, 1984). Calcitonin can help acutely while waiting for the effects of the biphosphonate. Corticosteroids may be effective in myeloma, lymphoma, sarcoidosis and vitamin D intoxication. Peritoneal or hemodialysis has been used to treat hypercalcemia from secondary hyperparathyroidism in patients with CRF (Cardella et al., 1979).

To prevent recurrence of the hypercalcemia, the malignant process needs to be controlled. Acute primary hyperparathyroidism requires surgical removal of the offending gland. Oral phosphate is effective in many patients but tolerated by few.

Hypocalcemia

Calcium exists in the plasma in three forms: an ionized or unbound portion (normally 50% of total), a protein-bound fraction (40%) and a chelated component (10%). The ionized portion, normally about 50% of the total, is physiologically active and homeostatically regulated (Zaloga et al., 1985).

Hypocalcemia is defined as a serum calcium of $<$8.15 mg/dl (2.12 mmol/l). About 10% of patients in ICUs have hypocalcemia, after correction for serum albumin levels and ionized calcium concentrations (Zaloga et al., 1985). A considerably smaller proportion is symptomatic.

Pathogenesis

The ionized portion can be altered by a change in pH; for example, with acidosis the protein binding is lessened and the percentage free fraction is increased. Conversely, in respiratory alkalosis the protein binding is increased and the free fraction is less, sometimes producing tetany.

Calcium homeostasis is regulated by secretion of parathyroid hormone (PTH). The parathyroid glands are sensitive to the plasma concentration of ionized calcium; secretion is prompt if the calcium concentration falls. PTH causes increased reabsorption of calcium from the kidney and gastrointestinal tract as well as increased mobilization of calcium from bone. A component of this is the PTH-mediated renal conversion of 25- to 1,25-hydroxyvitamin D. A deficiency of either PTH or Vitamin D can produce hypocalcemia. Parathyroid hormone secretion is inhibited by severe hypo- or hypermagnesemia. Table 124.5 gives a classification of the major causes, with emphasis on patients in the intensive care units.

Extracellular calcium ions have a stabilizing effect on the neuronal membrane. When reduced in concentration, the membrane is hyperexcitable, because of this membrane effect and the decrease in calcium-mediated potassium conductance.

Table 124.5. Causes of hypocalcemia

Category	Specific cause	Mechanism
Hypoparathyroidism	Postsurgical	Reduced PTH secretion
	Autoimmune disease	Reduced PTH secretion
	Infiltrative (e.g., cancer, hemochromatosis, sarcoid	Reduced PTH secretion
	Irradiation	Reduced PTH secretion
	Severe hypomagnesemia	Inhibits PTH secretion
Vitamin D deficiency	Inadequate intake, severe liver or kidney disease	Decreased formation of 25- or 1,25-hydroxyvitamin D
Acute complexing or sequestration of calcium	Acute pancreatitis	Sequestration of ionized calcium in an acute situation
	Rhabdomyolysis	(PTH secretion cannot compensate)
	Massive tumour lysis	
	Phosphate infusion	
	Toxic shock syndrome	
	Acute severe illness	
	Alkalosis	
Increased osteoblastic activity	Hungry bone disease	Postparathyroidectomy
	Osteoblastic metastases	Prostate or breast cancer
Drugs		
Anticalcemic agents	Biphosphonates	
	Plicamycin	
	Calcitonin	
	Gallium nitrate	
	Phosphate	
Antineoplastic agents	Asparaginase	
	Doxorubicin	
	Cytosine arabinoside	
	WR2721	
	Cisplatin	
Others	Ketoconazole	
	Pentamadine	
	Foscarnet	

Intracellularly, calcium is required for the activity of many enzymes and in the maintenance of the integrity of cells (Pappius, 1976). In hypoparathyroidism the concentration of intracellular calcium is reduced by 10% in the cerebral cortex, but by about 35% in the white matter (Pappius, 1976).

Clinical features

Although the threshold for neurological symptoms is not well defined, life-threatening complications frequently develop when the ionized portion falls to less than 2mg/dl (0.5 mmol/l).

Seizures, usually of the generalized convulsive type, are the main complication of acute, severe hypocalcemia (Eastell & Heath, 1992). They are more likely to occur in patients with pre-existing seizure disorders. Mental changes include depression, agitation, hallucinations, psychosis, but these are non-specific. Tetany with carpopedal spasm may occur, along with muscle spasms and cramps, paresthesiae and weakness.

The most important clinical signs are those of neuromuscular irritability: increased deep tendon reflexes and positive Chvostek's and Trousseau's signs. Pseudotumour cerebri with papilledema may complicate hypoparathyroidism.

Many of the classic clinical signs and symptoms of hypocalcemia may be absent or blunted in the ICU because of the use of drugs with paralysing, sedating and antiepileptic properties.

Laboratory features

Most hospital and private laboratories report the total serum calcium concentration; this comprises the protein

bound, free ionized and complexed forms. The normal total serum calcium concentration is 8.5–10.5 mg/dl (2.12–2.62 mmol/l). The concentration of calcium varies with serum albumin; as a rule of thumb, for each 1.0gm/l decrease in albumin, the serum calcium drops by 0.8 mg/dl (0.02 mmol/l). The normal ionized serum calcium is 4.1–5.1 mg/dl (1.02–1.27 mmol/l). One can estimate the ionized calcium under most conditions on regular wards. However, in many ICU situations, especially with rapid chelation by blood transfusions and rhabdomyolysis or pancreatitis, the extent of protein binding varies unpredictably; it is important to measure the ionized serum calcium.

Management

All patients with signs or symptoms of hypocalcemia should be treated. Patients with seizures and impaired consciousness require emergency treatment. Etiology-specific therapy is ideal.

Emergency management of hypocalcemia involves the prompt administration of calcium gluconate. Ten to 20 ml of 10% calcium gluconate, containing 93 mg of elemental calcium, is administered intravenously over 10 minutes. A more rapid infusion may cause cardiac irregularity. A continuous infusion can follow: an infusion of 15mg/kg will raise the serum calcium by 2–3 mg/dl; 11 ampoules are required for a 70 kg man to achieve this (Tohme & Bilezikian, 1993).

Chronic management requires correction of the underlying cause. In the case of hypoparathyroidism, lifetime supplementation is necessary. The mainstay of treatment is vitamin D. Orally administered, elemental calcium supplements, e.g. 1–1.5 g/day of elemental calcium in the form of calcium carbonate, citrate, lactate, gluconate or glubionate, are usually required as well. In malabsorption syndromes there may be malabsorption and deficiency of vitamin D itself. Large doses of vitamin D may be required, leading to a risk of vitamin D intoxication.

Hypocalcemia due to magnesium deficiency does not respond to calcium supplementation alone, but does recover following magnesium replacement. As a corollary, it is generally wise to measure the serum magnesium whenever hypocalcemia is found, and to correct any deficiency.

Hypermagnesemia

Normal serum magnesium ranges from 1.3 to 2.1 meq/l (0.8–1.3 mmol/l; 2–3 mg/dl); values over 2.1meq/l therefore constitute hypermagnesemia, although clinical symptoms begin at 4 meq/l. It is almost certainly under recognized. A survey in an Oklahoma VA hospital revealed elevated serum magnesium in 59 of 1033 samples (5.7%) (Whang & Ryder, 1990). Of these, physicians had requested serum magnesium determination in only 7 (13%).

Pathogenesis

Clinically significant hypermagnesemia mainly occurs in the context of renal failure and magnesium administration. The latter may be administered as a cathartic or as an antihypertensive, e.g. as treatment for pre-eclampsia or eclampsia (Smilkstein et al., 1988). Hypermagnesemia has been reported in cases of abuse of laxatives and/or antacids (Castelebaum et al., 1989).

Magnesium excess reduces the metabolic rate of glucose utilization in both the grey and white matter of the rat spinal cord (Szabo & Crosby, 1988).

Clinical features

Oral ingestion may cause gastrointestinal irritation and diarrhea. Hypotension may occur; this is usually mild, but can be marked if hypovolemia is also present (Zwerling, 1991).

Although hypermagnesemia causes central nervous system (CNS) depression, the loss of deep tendon reflexes usually precedes the mental status changes, and occurs at 5–6 mEq/l. At 8–10 meq/l, CNS depression develops. Neuromuscular paralysis may precede the clinical recognition of encephalopathy. Lethargy and confusion are, however, common early manifestations (Alfrey et al., 1970). High serum levels, e.g. more than 9 meq/l, may also cause parasympathetic paralysis, besides coma, neuromuscular paralysis (including cranial nerve innervated and respiratory muscles) and areflexia (Rizzo et al., 1993). At times, this may mimic a brainstem stroke.

One should be suspicious of hypermagnesemia in any patient with renal failure who develops encephalopathy with weakness and areflexia, with or without palsy of cranial nerve innervated muscles.

Laboratory features

Serum magnesium determination is essential. However, since magnesium is mainly intracellular, it gives only a rough estimate of the total body burden of magnesium.

EEG slowing is found with serum magnesium concentrations above 15 meq/l (Somjen et al., 1966). EMG may show a presynaptic defect in neuromuscular transmission: compound muscle action potential amplitudes are reduced; there is a decremental amplitude of response to muscle nerve stimulation at low rates and marked amplitude

increase following brief exercise or high stimulation rates (Swift, 1979).

Treatment

Since the effects of magnesium on the neuromuscular junction are the most life-threatening and since these are antagonized by calcium, treatment of Mg intoxication includes calcium gluconate administration. This is usually given as 10 ml of a 10% solution and can be repeated as necessary to overcome neuromuscular blockade. Hemodialysis may be necessary to lower the serum magnesium concentration in very symptomatic patients, especially in the presence of renal failure.

Supportive care, especially concerning ventilatory function in the ICU, may be necessary. Blood pressure support, especially with optimization of blood volume, may be necessary if the patient is hypotensive.

Hypomagnesemia

Hypomagnesemia is defined as a serum magnesium of less than 1.7 mg/dl (Al-Ghamdi et al., 1994). Neurological features are usually only present with a serum concentration of less than 0.8 meq/l. Since only 10% of magnesium is extracellular, the estimate of total body magnesium deficiency may be grossly inaccurate. A low serum concentration usually reflects a severe body deficit in magnesium, but the serum magnesium may be normal despite a general body deficiency. Magnesium concentrations are higher in the CSF than in the plasma, due to active secretion by the choroid plexus (Pappius, 1976).

Prevalence and significance

Since magnesium is present in abundance in most foods, its deficiency in normal individuals is rare. In hospitals, however, the estimated percentage of patients with low body amounts of magnesium ranges from 4 to 47% (Croker & Walmsley, 1986; Whang & Ryder, 1990; Rysen et al., 1985). The prevalence is highest in acute care, especially intensive care, settings.

Magnesium is absorbed from the small bowel. Most of the body's magnesium is intracellular and chelated to ATP, ADP, proteins, RNA, DNA and citrate. Only 5–10% of the intracellular magnesium is free or ionized. In the plasma 60% is free or unbound. The kidney is responsible for maintaining the serum concentration of Mg within a narrow range. Phosphate depletion can produce hypomagnesemia through an uncertain renal mechanism. Intracellular Mg is maintained at the expense of extracellular Mg and bone reservoirs (Quamme, 1993).

Etiology and pathogenesis

The most common causes are protein calorie malnutrition, malabsorption, diabetic ketoacidosis, sepsis, diuretic use, alcohol abuse, hyperaldosteronism, hypocalcemia (Olerich & Rude, 1994). In addition, certain drugs such as loop diuretics, aminoglycosides, cisplatin and cyclosporin may lower the body's magnesium stores. There may also be an inborn error of metabolism in some affected infants (Pappius, 1976). Some of these causes may act synergistically to create an acute deficiency syndrome: in alcoholics, pre-existing magnesium depletion, catecholamine-induced Mg redistribution and respiratory alkalosis (causing a shift of Mg intracellularly) may coincide to precipitate seizures and other features of the alcohol withdrawal syndrome (Al-Ghamdi et al., 1994).

The main effects of low magnesium are membrane effects. Low intracellular magnesium can modify current flow through calcium, potassium and chloride channels (Kelepouris et al., 1993). Magnesium ion also reversibly occludes the ion channels governed by the *N*-methyl-*D*-aspartate receptor, one of the main excitatory receptors in the brain. Thus, some ionic currents may be affected. Magnesium, however, probably plays a more important role in relation to receptor sites, because of its association with second messenger systems (Iyengar & Birnbaumer, 1982). Magnesium is involved in many enzyme systems: those for intermediary metabolism, biosynthesis of nucleic acids, proteins and lipids and most enzymes that require adenosine triphosphate (ATP) (Pappius, 1976).

Serum magnesium is maintained in a narrow range by the kidney and small intestine and concentrations in the CSF and brain are well regulated. It requires extremely severe malnutrition to significantly lower brain magnesium concentration to a concentration that would interfere with enzymatic function (Pappius, 1976).

Some of the manifestations of hypomagnesemia may be due to low extracellular concentrations of ionized calcium. This may explain the hyperexcitability found in some patients. In others, the features may be due to the membrane effects of hypomagnesemia itself (Wacker & Parisi, 1968).

Clinical features

Neurological manifestations are similar to those of hypocalcemia, including hyperexcitability, muscle cramps, tetany (with positive Chvostek's and Trousseau's signs), hyperreflexia and seizures. Other clinical features that have been described include vertigo, nystagmus, dysphagia, athetoid movements, focal signs such as hemiparesis and aphasia (Hamed & Linderman, 1978; Leicher et al.,

1991; Hall & Joffe, 1973). An acute organic brain syndrome with psychiatric manifestations may develop.

In children, problems are mainly in the neonate and early infancy: decreased intestinal absorption and impaired renal reabsorption, neonatal hepatitis and maternal conditions (vomiting, diabetes mellitus, diuretics and excessive lactation). Seizures, tetany, hyperirritability and impaired consciousness are the main features.

Serious cardiac complications including arrythmias and congestive heart failure, that are refractory to standard therapy, are due to magnesium deficiency (Whang et al., 1994).

Laboratory investigations

Besides the serum magnesium concentration, there are other methods of estimating the deficiency of magnesium. A simple physiological test is the measurement of magnesium excretion in a 24-hour urine collection (Sutton & Domrongkitchaiborn, 1993). If the value exceeds 24 mg in 24 hours, there is evidence of renal magnesium wasting. If 12 mg or less are excreted, magnesium deficiency is highly likely.

The measurement of magnesium in erythrocytes or leukocytes offers a more accurate assessment of the total body deficit in magnesium (Geven et al., 1993). This is not commonly available, however.

Treatment

Parenteral magnesium is needed when convulsions occur. In such symptomatic magnesium deficiency, the average body deficit is 12–24 mg/kg body weight (Sutton & Dirks, 1991). This should be replaced by magnesium sulfate as a 50% solution, given in divided doses either intravenously or intramuscularly. About 50% will be lost in the urine. It can be given intravenously or intramuscularly for a total dose of 8–12 g of magnesium sulfate or 0.8–1.2 g of elemental magnesium. Caution should be used in the presence of renal failure. In any case, the serum magnesium and deep tendon reflexes should be closely monitored. Calcium should be available as a treatment in the event of hypermagnesemia. Since hypocalcemia often accompanies hypomagnesemia, calcium supplementation is usually needed. Potassium supplements are also often needed in magnesium deficiency (Al-Ghambi et al., 1994).

Caution should be exercised in the presence of renal failure since magnesium toxicity may quickly develop.

Prophylaxis of adding 100–200 mg per day to parenteral nutrition helps to prevent hypomagnesemia in the intensive care setting. A diet rich in magnesium will allow more gradual replacement of magnesium stores. Correction of risk factors (alcoholism, hypophosphatemia, diabetic control) may prevent excessive urinary losses.

Table 124.6. Causes of severe hypophosphatemia

Chronic alcoholism and alcoholic withdrawal
Dietary deficiency and phosphate binding antacids
Severe thermal burns
Recovery from diabetic ketoacidosis
Hyperalimentation
Nutritional recovery syndrome
Marked respiratory alkalosis
Therapeutic hyperthermia
Neuroleptic malignant syndrome
Recovery from exhaustive exercise
Renal transplantation
Acute renal failure
Shock with replacement with high volumes of glucose solutions

Hypophosphatemia

Hypophosphatemia is defined as a serum phosphate of $<$2.5 mg/dl ($<$0.83 mmol/l). 'Severe hypophosphatemia' (Table 124.6), during which symptoms relevant to the serum phosphate concentration appear, is reserved for a serum phosphate of $<$1.5 mg/dl (0.5 mmol/l) (Knochel & Montanari, 1992).

Pathophysiology

Like magnesium and potassium, phosphate is mainly intracellular and a low serum phosphate may or may not reflect a total body deficiency. Most of bound phosphate is attached to calcium in bone. Phosphate is extremely important in cellular energy and enzymatic processes (Pappius, 1976). Intracellular phosphate exists mainly as organic phosphate compounds such as creatine phosphate, adenosine mono-, di- or tri-phosphate. In red blood cells phosphate is involved in 2, 3 diphosphoglycerate (2, 3 DPG) that is involved in the energy metabolism of the erythrocyte. In hypoxia, phosphate stimulates anaerobic metabolism by activating phosphofructokinase, an enzyme that controls the rate of glycolysis (Siesjo et al., 1971).

Hypophosphatemia may arise from loss of total body phosphate, e.g. in the urine in diabetic ketoacidosis, poor absorption or inadequate phosphate in feeds (oral hyperalimentation), shifts from serum into cells (treatment of diabetic ketoacidosis, administration of high volumes of glucose-containing fluids, hyperventilation) and in alcoholism with or without alcohol withdrawal (possibly due to

increased phosphaturia) (Knochel, 1977; Territo & Tanaka, 1973).

The nadir of serum phosphate concentration is within 24 hours in diabetic ketoacidosis, between 2 and 4 days in acutely hospitalized alcoholics and often after 10 days of hyperalimentation (Knochel, 1977).

All levels of the nervous system can be clinically affected in hypophosphatemia. The cause of central nervous system dysfunction in hypophosphatemia is uncertain. This may relate to inadequate oxygenation of tissues due to red blood cell 2, 3-DPG dysfunction. Associated hyperventilation, e.g. in hyperammonemia, hypoxemia, or decreased 2, 3-DPG may cause reduced cerebral blood flow and further compromise cerebral energy metabolism. Altered neurotransmitter function has been found in an animal model, but uncertainty exists as the animal may have been hypotensive (Knochel & Motanari, 1992; Bhaskaran et al., 1987).

In clinical practice, there are often coexisting disorders that may also cause an encephalopathy, e.g. alcoholism with infections, pancreatitis, hypomagnesemia, hepatic failure. It may be difficult to know which are the main factors causing the impaired consciousness. The fact that apparently isolated severe hypophosphatemia, especially if there is cellular depletion of phosphate, can cause encephalopathy is an argument for replacement therapy (Knochel, 1977).

Clinical features

Patients with hypophosphatemia may demonstrate an acute confusional state with irritability and apprehension, variable motor abnormalities including athetosis, ballismus, myoclonus, ataxia, asterixis, weakness or paralysis with areflexia (peripheral) or a Guillain–Barré-like syndrome. Lethargy, distal paresthesiae, dysarthria and abnormal respiratory patterns may be early features (Prins et al., 1973).

A syndrome of impaired eye movements, confusion and ataxia, closely resembling Wernicke's encephalopathy has been noted (Vanneste & Hage, 1986). This can be a diagnostic problem in treating alcoholics or the nutritionally deprived. Hypophosphatemia should be considered in patients with the clinical picture of Wernicke's encephalopathy who fail to respond to thiamine. Leigh's syndrome may also be mimicked in infants. Other cranial nerve palsies may resemble botulism.

Reversible coma can occur, with or without seizures. We have also seen hypophosphatemia mimic brain death in a trauma patient who received large amounts of glucose solutions (Young et al., 1982). The cranial nerve areflexia and paralysis of movements were reversed by phosphate administration.

Management

It is wise to consider hypophosphatemia (as well as hypomagnesemia) when patients at risk (patients with malnutrition who are being fed, patients on hyperalimentation, alcoholics in hospital) show altered consciousness or awareness with or without the other neurological complications mentioned above. Long-term infusions that do not contain phosphate, calcium or glucose may be especially problematic (Prins et al., 1973; Dudrick, 1972).

While replacing phosphate, it is best to temporarily stop the hyperalimentation program, or to reduce calorie supplementation, until the neurological symptoms clear. This is often essential for prompt recovery; phosphate supplementation alone may not affect the clinical condition for some time (Prins et al., 1973).

In most cases it is unclear whether hypophosphatemia reflects a total body deficiency of phosphorus. In previously healthy patients who become acutely ill, it is unlikely that there is a phosphate deficiency. In the nutritionally deprived, however, it is likely that there is such a deficit. In milder cases the need for phosphate supplementation can be determined by history, review of medications, nutrition and therapy, blood gases, urinary phosphorus and creatinine (calculation of fractional excretion of phosphate).

If supplements are needed and the patient is able to take fluids orally, it is safest to give milk, which contains 0.9 mg of phosphorus per ml. Other oral phosphate solutions are available. Parenteral administration of 9mmol of phosphorus in 77 mM NaCl solution over 12 hours to provide 4 mg/kg body weight over this time has been implemented (Vannatta et al., 1981). Magnesium supplementation should also be considered as magnesium deficiency will contribute to further excessive losses of phosphate in the urine (Knochel & Montanari, 1992).

Complications of phosphate administration include hyperphosphatemia, hypocalcemia, hyperkalemia (if potassium salts of phosphate are used), metabolic acidosis, and volume excess with intravenous solutions. Oral treatment may cause diarrhea. It is thus important to monitor the serum phosphate and other electrolytes and calcium during therapy.

Hyperkalemia

Hyperkalemia refers to a serum potassium concentration of over 5.5 meq/l (5.5 mmol/l).

Potassium homeostasis is largely dependent on renal function. Hence, clinically significant hyperkalemia is mainly seen in renal failure. These complications are discussed above. Hyperkalemia may also accompany adrenal

insufficiency, especially with lack of the mineralocorticoid hormone, aldosterone. Acidosis with, or without, insulin deficiency may also be associated with hyperkalemia

Clinical features

Usually cardiac complications of hyperkalemia eclipse any neurological complications. However, hyperkalemia is sometimes associated with diffuse muscle weakness and fatiguability, most strikingly in adrenal insufficiency. Rarely, hyperkalemia can produce a flaccid quadriparesis that mimics an acute motor polyneuropathy.

Hyperkalemia does not appear to have significant central nervous system complications. Patients commonly are lethargic or nervous, but these symptoms may relate to the associated underlying diseases rather than to the potassium concentration.

Hypokalemia

Hypokalemia, defined as a serum potassium concentration of less than 3.5 mEq/L (mmol/L), is the most common electrolyte disturbance. Causes include excessive losses through the gut or kidney (various disorders, some iatrogenic), diminished dietary intake or with shift of potassium into cells (as in hypokalemic periodic paralysis, insulin effect or systemic alkalosis).

Clinical features

The main neurological complication is muscular weakness (Raymond & Kunau, 1987). This begins at about 3.0 meq/l (mmol/l), but concentrations of 2.5 meq (mmol/l) or less are associated with significant proximal weakness. Cranial nerve innervated muscles are typically spared. Rhabdomyolysis may develop with concentrations below 2.0 meq/L (mmol/l). Exceptionally, an encephalopathy may develop; it is rare for this to progress to coma.

Management

The underlying cause should be determined and addressed. When mild, oral supplementation is usually sufficient, but with ongoing losses (e.g. diarrhea), or when hypokalemia is profound, parenteral administration is necessary.

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Disorders of intracranial pressure

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Intracranial pressure (ICP) is the pressure within the cranial vault relative to the atmospheric pressure. Quincke first measured cerebrospinal fluid (CSF) pressure in 1891 via a lumbar puncture (Quincke, 1891). In 1902, Cushing demonstrated hypertension, bradycardia and respiratory changes in an animal model with severe ICP elevation (Cushing, 1902). In 1951, Guillaume and Janny first described the use of continuous ICP monitoring using an intraventricular catheter (Guillaume & Janny, 1951). Nine years later, Lundberg described ICP wave patterns and their response to medical and physiological interventions (Lundberg, 1960).

ICP measurement has been an invaluable tool in research and clinical practice. It has contributed much to the understanding of intracranial pathologies, and assessment of therapeutic interventions. Intracranial hypertension is the elevation of the intracranial pressure to levels that may lead to neurological injury. ICP monitoring is used for patients with neurological disorders that have a high risk of further neurological injury from increased ICP or mass effect. In this chapter, we discuss the physiology related to ICP, the techniques in measuring ICP, interpretation of ICP recordings, common ICP disorders and their management (including intracranial hypotension), and outcome studies of ICP monitoring and management of intracranial hypertension.

Intracranial physiology and intracranial pressure

The pressure wave of the ICP is generated by the transmission of arterial pressure from the major cerebral arteries (Martins et al., 1972) and CSF production by choroid plexus (Cardoso et al., 1983) in the cranial vault. In normal conditions, the transmitted pressure is attenuated by displacement of CSF back and forth through the foramen magnum into the distensible spinal dural sac. This provides a compliance mechanism for the cranial vault (Martins et al., 1972). In adults, the range of normal resting ICP is 0 to 15 mm Hg (0 to 20 cm H_2O). Sustained ICP greater than 15 mm Hg is considered abnormal. The relation of ICP to brain injury depends on the cause, acuity, severity and duration of the ICP. Transient elevations of ICP occur with coughing, sneezing, or Valsalva manoeuvres and do not cause harm in most persons.

Cranial vault mechanics

Monro in 1783, and Kellie in 1823 (Monro, 1783; Kellie, 1824) described cranial vault mechanics in the light that: (i) the skull is a rigid container; (ii) the normal intracranial contents may be considered liquid or viscous gel, and are therefore incompressible; and (iii) any mass added to the cranial vault requires the displacement of one of the normal contents. The intracranial space opens via the foramen magnum to the spinal space. The normal adult intracranial volume is 87% brain, 9% CSF and 4% blood (Rasomoff, 1953). The blood compartment can be further divided into arterial (30%) and capillary/venous (70%) compartments. Intracranial CSF is divided equally between intraventricular and subarachnoid compartments, including the cisterns. Under normal physiological conditions, CSF production is nearly constant at about 20 ml/h or 500 ml per day (Cutler et al., 1968). However, CSF production declines with elevated ICP (Borgesen & Gjerris, 1987) or inadequate cerebral perfusion (CPP) (Weiss & Wertman, 1978).

Intracranial elastance

Elastance is the change in pressure as a function of a change in volume (Miller & Leech 1975). Elastance

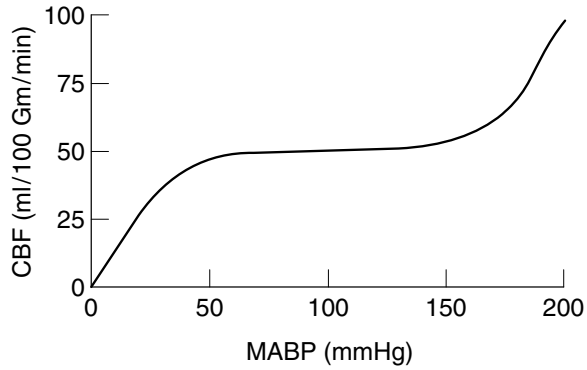

Fig. 125.1. The cerebrovascular autoregulatory curve.

describes the effect of a change in volume on ICP. Given the Monro–Kellie doctrine, displacement of intracranial CSF to the spinal CSF compartment initially accommodates the addition of volume by intracranial masses to the intracranial vault. This compensatory response allows for the maintenance of normal ICP in most cases. Further enlargement of an intracranial mass may not be accommodated, leading to a rise in ICP. After CSF is displaced from the cranial vault, then intravascular blood is displaced, reducing cerebral blood volume, and potentially reducing perfusion. As an intracranial mass further enlarges, brain tissue may be displaced, a process known as cerebral herniation. Depending on the nature of the mass and its rate of expansion, these physiologic and pathophysiologic responses may overlap. While CSF displacement may be asymptomatic, displacement of intravascular blood can lead to ischemia, causing either focal or global deficits. Herniation can cause secondary injury by compression of vascular and neural structures.

Cerebral autoregulation

Cerebral perfusion pressure (CPP) is a critical determinant of cerebral blood flow (CBF). CPP is defined as mean arterial blood pressure (MABP) minus the ICP (or jugular venous pressure (JVP) if it is higher than the ICP). The ability of the brain to maintain a near constant CBF over a wide range of CPP by adjusting cerebrovascular resistance is known as autoregulation. Between CPP of approximately 50 and 150 mm Hg, there is very little rise of CBF (Fig. 125.1). The constancy of CBF over this range is governed by changes in cerebrovascular diameter and resistance. Autoregulation depends on an intact vasculature and blood brain barrier (BBB). Changes in cerebrovascular diameter are associated with corresponding changes in cerebral blood volume, which may affect ICP. When CPP is outside the autoregulatory range, the relationship between CPP and CBF becomes linear. When CPP is too low, as is seen either with severe ICP elevation, or circulatory collapse, the risk of cerebral ischemia is high. When CPP is too high, as in hypertensive encephalopathy, the risk of cerebral microvascular disruption with hyperemia and cerebral edema is high.

Intracranial pressure measurement and monitoring

ICP can be measured continuously via an ICP monitoring system and transiently during lumbar puncture via a manometer attached to the spinal needle. ICP monitoring systems can be categorized by the coupling medium, the interface medium between the patient and the pressure transducer. The 2 types are fluid-coupled and solid-state systems.

Fluid-coupled ICP systems

Fluid-coupled systems with external transducers include intraventricular catheters (IVC), subarachnoid bolts (SA bolt) and lumbar catheters (LC). The IVC is considered the most precise and accurate method of measuring ICP (Anon., 1996b). The catheter is passed through a burr hole into the lateral ventricle for CSF access. The IVC is then coupled to an external transducer via fluid-filled tubing. Injury to brain parenchyma is an important consideration in IVC insertion, although the incidence is low. The most significant risk of IVC usage is infection (Mayhall et al., 1984) and the risk appears to be related to the duration of the IVC (>5 days) (Mayhall et al., 1984). The use of prophylactic antibiotics with IVCs varies among institutions, and its role in preventing infection has not been definitely established.

The subarachnoid (SA) bolt is a hollow, self-tapping bolt that is inserted into the skull via a burr hole, and the dura at the base of the bolt is perforated with a spinal needle to allow subarachnoid CSF to fill the bolt. Fluid-filled tubing establishes the fluid coupling to the transducer. The ICP waveform and pressure reading are reliable, but error may occur if the dural perforations become plugged (Mendelow et al., 1983). The infection risk for SA bolts is low (Winn et al., 1977) and injury to brain parenchyma is rare. The bolt does not require contact with the ventricle, so it can be used in patients with compressed ventricles (Vries et al., 1973).

Lumbar catheters can be used to monitor ICP via the lumbar subarachnoid space. The use of a lumbar catheter

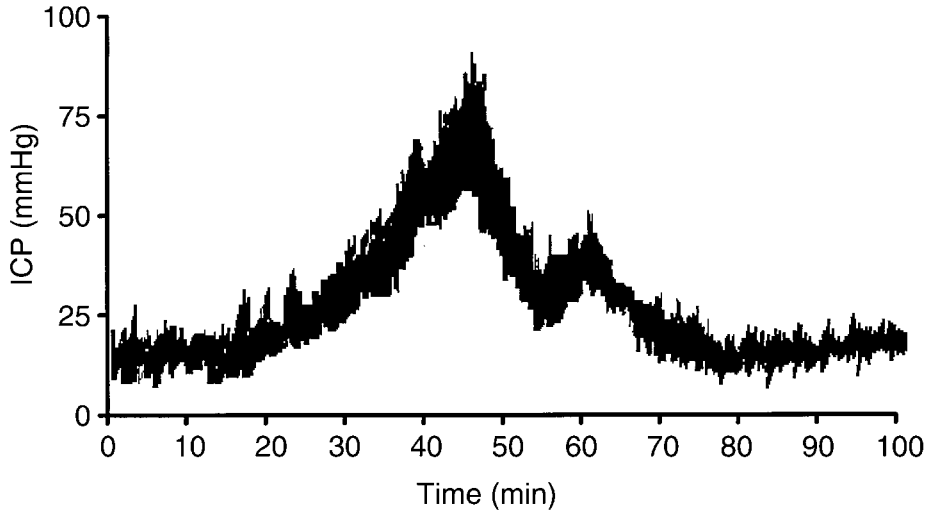

Fig. 125.2. Lundberg A or plateau wave.

is contraindicated with obstructive hydrocephalus or intracranial masses because of the risk of cerebral herniation, and effectively reflects ICP only when the spinal CSF pathways are patent.

Solid-state ICP systems

Solid-state ICP monitors use miniature transducers at the end of a wire, fibre-optic cable, or ventricular catheter that are coupled to an external instrument. These devices can be used for ICP monitoring alone, or incorporated into an IVC for simultaneous ICP monitoring and CSF drainage. Depending on their construction, solid-state devices can be inserted in the ventricles, the brain parenchyma, the subarachnoid space, or the epidural space.

Indications for ICP monitoring

The decision to begin ICP monitoring is often based on individual patients' risk of further neurological injury and deterioration. This is influenced by the primary pathology, coexisting systemic injuries, neuroimaging (head computerized tomography (CT) or magnetic resonance imaging (MRI)), and the availability of skilled physicians to insert the devices, interpret the ICP readings, and undertake therapeutic manoeuvres. The Brain Trauma Foundation (BTF) guidelines for ICP monitoring in severe traumatic head injury (Anonymous, 1996a) recommend ICP monitoring when: (i) GCS is 3–8 after CPR with an abnormal head CT (hematoma, contusion, edema and compressed basal cisterns; or (ii) a normal head CT scan with two or more of the following: age >40 years, unilateral or bilateral posturing, or systolic BP <90 mmHg. Other conditions that can cause secondary cerebral injury by intracranial hypertension may warrant ICP monitoring, including intracranial tumours, massive ischemic strokes, intracranial hemorrhages, cerebral edema, and hydrocephalus. There are no established guidelines for the placement of an ICP monitor in these clinical situations. If a monitor is inserted and the ICP is normal, and the clinical condition suggests no risk of ICP elevation after 24–48 hours of monitoring, the ICP monitor can be removed.

Interpretation of ICP and ICP waveforms

Proper interpretation of ICP requires assessment not only of the mean ICP (the value usually displayed on the ICU monitor), but also the pattern of ICP changes and the response to different stimuli. Lundberg performed systematic observation of ICP and its response to medical and physiological interventions, and described three patterns of pressure fluctuations: A-, B- and C-waves (Lundberg, 1960).

A-waves (plateau waves) are the most extreme form of ICP elevation, consisting of sudden, rapid elevation of ICP from a baseline of 20–30 mm Hg to 70–100 mm Hg and higher (Fig. 125.2). They are sustained for 5 to 20 minutes, and terminated by a rapid decline of ICP to levels at or below the baseline ICP. Plateau waves may represent near exhaustion of intracranial compliance mechanisms (Czosnyka et al., 1999) and often accompany cerebral herniation and cerebral circulatory arrest (Tsementzis et al.,

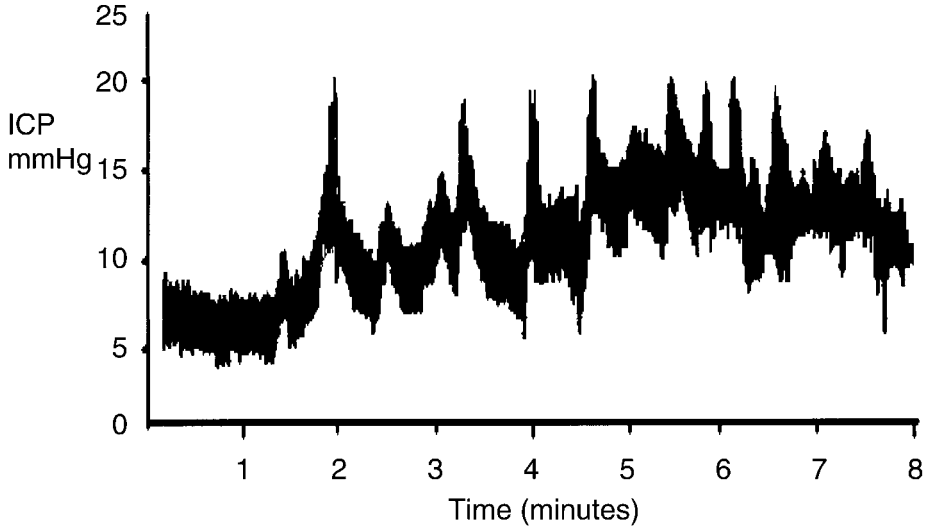

Fig. 125.3. Lundberg B waves.

1979). Emergent intervention with medical and neurosurgical decompression is usually needed.

B-waves are shorter and lesser ICP elevations that occur at a frequency of 0.5 to 2 cycles per minute (Fig. 125.3). B-waves are probably caused by fluctuations of CBV related to hypercapnea or hypoxia-induced cerebral vasodilation, and suggest reduced intracranial compliance, though not to the degree seen with plateau waves. C-waves are low amplitude oscillations with a frequency of 4 to 8 cycles per minute closely related to blood pressure variation (Traube–Hering–Mayer waves) (Kjallquist et al., 1964). The appearance of B-waves is an indication to initiate therapy to reduce ICP; the appearance of C-waves does not require intervention. These waveforms, which last for minutes, are difficult to identify with standard bedside ICU monitors that display only 4–5 seconds of activity.

Disorders of intracranial pressure

Clinical aspects of intracranial hypertension

With mass lesions in the cranial or spinal spaces, pressure gradients may occur. Local, compressive ICP effects are commonly seen with masses, and diffuse ICP effects are seen in hypoxic–ischemic injury, hydrocephalus or pseudotumour cerebri. Causes of disordered ICP include acute obstructive and communicating hydrocephalus; intracranial masses, such as tumour, edema, intracranial hemorrhage (parenchymal, epidural, subdural, subarachnoid and intraventricular); and pneumocephalus. The relation of ICP to secondary neurological injury depends on the etiology, acuity and severity of any ICP change or mass effect.

The signs and symptoms of intracranial hypertension are generally due to pressure effects on critical structures, and can manifest as headache, diplopia, ataxia, nausea, vomiting, drowsiness, stupor, respiratory arrest and coma. Compression of the midbrain is key in central and uncal (transtentorial) herniation syndromes. Central herniation is typically caused by bilateral or centrally placed supratentorial lesions that displace the midbrain caudally below the plane of the tentorial opening (Fig. 125.4). Patients become drowsy and lapse into coma rapidly. Respiration can be impaired, and airway and ventilatory support should be readily available. The pupils can be normal initially, but can rapidly dilate and become unreactive. Loss of extraocular eye movements, and oculovestibular reflexes also occurs. Uncal herniation is typically associated with unilateral lesions in the basal ganglia, thalamus, or the temporal and frontal lobes. The midbrain is generally distorted and compressed, and sometimes is displaced laterally into the tentorial edge, which can incise the cerebral peduncle (Kernohan's notch) (Kernohan & Woltman, 1929). The perimesencephalic cisterns are often effaced, and the posterior cerebral artery or oculomotor nerve can be compressed (Fig. 125.5). The level of consciousness will deteriorate, and a phase of restlessness and irritability is often seen. There can be ipsilateral pupillary change, from round to ovoid, and eventually to an unreactive and dilated pupil. Bilateral pupillary dysfunction may follow, as well as paresis, motor (extensor or flexor) posturing, irregular

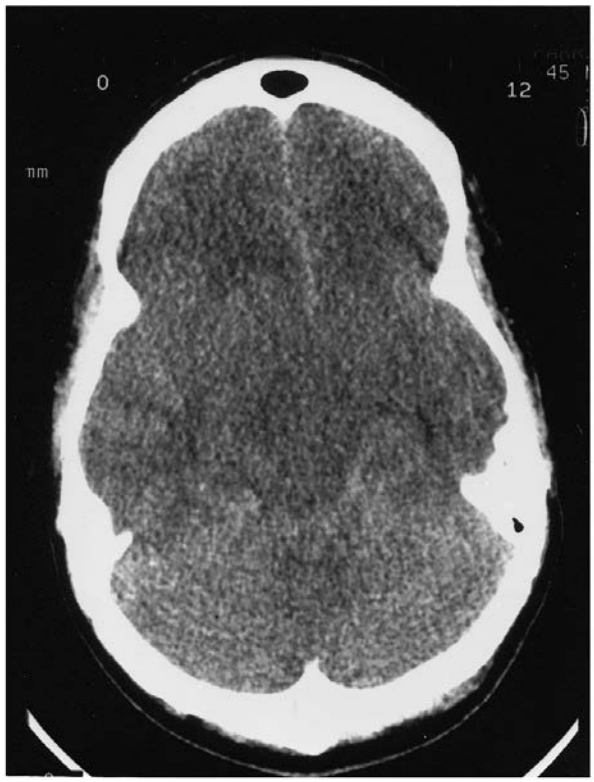

Fig. 125.4. A head CT scan of a comatose 45-year-old man with central herniation syndrome. He had bilateral fixed and dilated pupils, secondary massive cerebral edema and intractable intracranial hypertension. The CSF spaces, especially the perimesencephalic cisterns are effaced.

respiration and hemodynamic instability. The paresis is due to the compression of the cerebral peduncle. Medullary involvement can be manifested as the Cushing reflex: apnea, bradycardia and hypertension.

Management of acute intracranial hypertension

The goals of management are (i) reduction of intracranial pressure, (ii) maintenance of adequate cerebral perfusion pressure, and (iii) prevention of cerebral herniation. The Brain Trauma Foundation guidelines recommend treating ICP above 20–25 mm Hg in severe head injury (Anon., 1996a). ICP at 20 mm Hg or more is a strong predictor of neurological deterioration (Juul et al., 2000), while ICP below 20 mm Hg is associated with improved outcome after head injury (Eisenberg et al., 1988). The interaction of ICP and CPP should not be overlooked, and maintenance of adequate CPP also improves morbidity and mortality outcomes (Rosner et al., 1995).

Therapeutic strategies for ICP reduction can be directed at the different intracranial components: intravascular blood, CSF, brain and the mass lesion. We describe as follows the strategies for rapid ICP reduction, for maintenance or control of ICP, and for surgical intervention.

Medical management

Head positioning

Head elevation to 30 degrees above horizontal may help to optimize cerebral perfusion pressure (Durward et al., 1983; Moraine et al., 2000). The head should be in the midline, rather than turned to the side, in order to preserve jugular venous drainage. Circumferential binding or taping of the neck, as is sometimes done to secure endotracheal tubes, should be avoided.

Endotracheal intubation and hyperventilation

Hyperventilation (HV) is an effective and rapid therapeutic intervention that works by causing hypocapnea, and acute respiratory alkalosis, which leads to vasoconstriction in areas of the cerebrovascular bed that have not been injured. In patients who are not yet intubated, HV can be done manually with a facemask, followed by endotracheal intubation as quickly as is safe and feasible. Endotracheal intubation itself can increase ICP and potentially precipiate cerebral herniation, therefore adequate premedication with drugs such as thiopental, lidocaine or etomidate to blunt this effect is necessary.

The effect of HV is both rapid and short lived (Muizelaar et al., 1991), and excessive HV can potentially cause cerebral ischemia. Moderate hyperventilation (P_aCO_2 to 30 ± 2 mm Hg for 30 minutes) has been shown to be safe after traumatic brain injury with no impairment of global cerebral metabolism (Diringer et al., 2000). Neither prophylactic nor chronic hyperventilation benefits patients and should be avoided (Anon. 1996c). During acute intracranial hypertension, we maintain P_aCO_2 at 30 ± 2 mm Hg for 4 to 6 hours, and initiate other treatments for ICP. Once ICP is controlled, reduction of HV can be attempted gradually.

Treatment of brain edema with corticosteroids

Corticosterids are effective in reducing intracranial pressure associated with tumour-induced cerebral edema (French & Galicich, 1964). Intravenous dexamethasone reduces ICP and improves intracranial compliance leading to fewer and briefer plateau waves in patients with supratentorial tumours (Alberti et al., 1978). Corticosteroids are

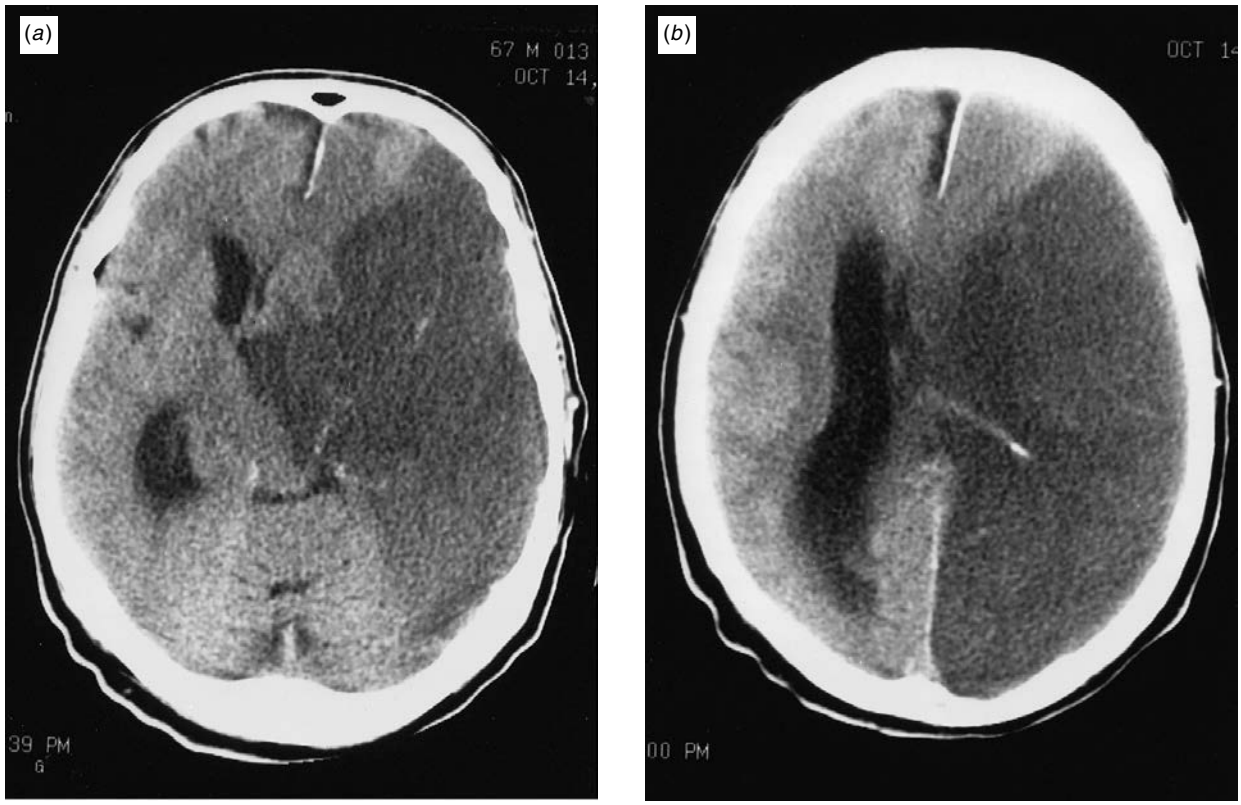

Fig. 125.5(*a*), (*b*). Head CT scan of an 80-year-old man with right MCA infarction and uncal herniation. He had unilateral pupillary dilatation. The herniation caused the infarct of the midbrain region (*a*) and the right occipital lobe. Both areas are perfused by the right PCA. The region supplied by the ACA is spared.

not effective in traumatic brain injury (Anon., 1996f), or in focal (Patten et al., 1972) or global cerebral ischemia (Jastremski et al., 1989). Corticosteroids can cause hyperglycemia, which should be monitored and controlled.

Hyperosmolar therapy: mannitol

Hyperosmolar therapy depends on establishing an osmotic gradient across an intact blood brain barrier that leads to the reduction of cerebral edema volume, leading to ICP reduction. Mannitol is the most commonly used osmotic agent in the United States, and is effective in head injury (Anon., 1996d). Mannitol has immediate and delayed actions in controlling ICP. The immediate action is believed to be caused by rheologic and plasma-expanding effects leading to reduction of hematocrit and blood viscosity. This increases cerebral oxygen delivery to the brain, which results in vasoconstriction believed to cause the ICP reduction (Muizelaar et al., 1983, 1984). The immediate effect occurs within minutes, and is best accomplished with bolus infusion in the range of 0.25–1.0 g/kg. The delayed effect is attributed to establishment of an osmotic gradient across the blood–brain barrier, which can decrease the water content of the brain by as much as 6% (Nath & Galbraith, 1986). ICP control may last for 90 minutes to 6 hours. Because mannitol is an osmotic agent with diuretic effect, it can cause hypovolemia and hypotension, which may cause cerebral ischemia. Attention to intravascular volume status after mannitol administration is important. Intermittent boluses of mannitol may be more effective than continuous infusion (Anon., 1996d).

Hyperosmolar therapy: hypertonic saline

Hypertonic saline solutions are re-emerging as a popular therapy for intracranial hypertension. NaCl is tightly regulated at the blood–brain barrier, and does not pass freely across it. Intravascular hypernatremia (i.e. increased serum Na concentration) reduces intracranial pressure, and avoids hypovolemia. Saline infusion (3% NaCl) to maintain serum Na at 145–155 meq/l reduces ICP. This therapy seems to work better in head trauma and postoperative brain edema, than in non-traumatic intracranial hemorrhage or cerebral ischemia (Qureshi et al., 1998).

Bolus administration of concentrated saline solutions (23.4% NaCl (4 meq/ml)) is effective in treating refractory ICP elevation, and this effect lasts about 6 hours (Suarez et al., 1998). The potential risks of hypertonic saline therapy include renal injury, injury to myelinated tissues (i.e. central pontine myelinolysis), intravascular fluid overload and hyperchloremic acidosis. Controlled studies comparing hypertonic saline to mannitol have not been performed, and hypertonic saline is not yet accepted as a standard therapy.

Metabolic suppression: barbiturate coma

The ultimate purpose of CBF is the delivery of oxygen (DO_2) to the brain. Impaired CPP and CBF cause a mismatch between DO_2 and cerebral metabolic demand ($CMRO_2$) which can cause cerebral ischemia or infarction. Barbiturates reduce $CMRO_2$, which is coupled to DO_2 and CBF in intact brain. CBF reduction is caused by vasoconstriction, which lowers CBV and ICP. Thus, barbiturate therapy can be used to correct this mismatch between DO_2 and $CMRO_2$ by reducing $CMRO_2$. The goal of this therapy is to reduce ICP while maintaining adequate CPP.

Barbiturate therapy entails the induction and maintenance of general anesthesia for a prolonged period of time (days to weeks), and thus carries significant risks along with the potential benefits. First, barbiturates obliterate neurological responsiveness, and much of the clinical examination cannot be used to monitor the patient's response to therapy. The pupillary light reflex is relatively preserved, though attenuated, and pupillary changes such as dilation secondary to herniation may still be observed. It is essential to monitor ICP because the goal of therapy is ICP and CPP control. Very high dose barbiturate administration can produce a clinical examination that mimics brain death, including bilaterally dilated and unreactive pupils. Therefore, screening tests of cerebral circulation (such as transcranial Doppler sonography or assessment of CPP) may be necessary to guide clinical suspicion of brain death, which would then require specific testing of cerebral circulation to confirm.

Barbiturates also suppress autonomic nervous system tone and myocardial contractility, and hypotension is commonly seen. The beneficial effects of barbiturates cannot compensate for hypotension so severe that it compromises CPP, and hemodynamic monitoring with a pulmonary artery catheter and aggressive hemodynamic support with fluids and vasopressors are often needed. Barbiturates cause ileus, and enteral feedings often cannot be continued, so that parenteral nutrition is often needed. Barbiturates also suppress ventilatory drive, as well as mucociliary function in the tracheobronchial tree, putting patients at high risk for atelectasis and pneumonia. Strict attention to pulmonary toilet is required. Fever may not manifest with the use of barbiturates, and infection surveillance should be pursued with a high index of suspicion. The risk for deep venous thrombosis and pulmonary embolism is higher because of immobility, and preventive therapies such as subcutaneous heparin should be used.

The Brain Trauma Foundation guidelines suggest use of high dose barbiturate therapy in hemodynamically stable and salvageable traumatic brain injury patients with medically and surgically refractory intracranial hypertension (Anon., 1996e). Pentobarbital is the most commonly used barbiturate. We use a loading dose of 10 to 40 mg/kg i.v. over approximately 2 hours, followed by a maintenance dose of 1–2 mg/kg/h, with the goals of ICP control, a pentobarbital serum concentration of 20–40 μg/ml, or burst–suppression pattern on EEG. After controlling the ICP for 48 to 72 hours, or if the mass effect is seen to diminish on neuroimaging studies, the pentobarbital infusion rate can be reduced gradually over 24–48 hours. If intracranial hypertension recurs, the pentobarbital can be restarted.

Surgical management

Reduction of cerebrospinal fluid volume

When hydrocephalus is the cause of ICP elevation, CSF should be removed. The method of removal depends on the cause of hydrocephalus and the presence of an intracranial mass, if any. An intraventricular catheter (IVC) is required for obstructive hydrocephalus (Figs. 125.6, 125.7(*a*) and (*b*)). Common concerns with IVC insertion and CSF drainage are worsening shift of intracranial contents when hemispheric lesions are present (Frank, 1995), and the possibility of 'upward herniation' when infratentorial lesions are present (Cuneo et al., 1979). After an IVC has been inserted, CSF is drained externally until adequate spontaneous CSF circulation and resorption is restored. Once this has occurred, the IVC can be safely removed. CSF resorption is roughly gauged by the CSF drainage rate. If resorption is intact, then there will be little external CSF drainage. If it is impaired, the CSF drainage volume will be high. No standards for abnormal CSF drainage volumes exist. In clinical practice, we consider CSF resorption to be adequate if 100 ml CSF or less drains per day with the drip chamber at 20 cm H_2O (15 mm Hg) above the head. CSF drainage is then stopped and ICP is monitored for 24–48 hours. If ICP stays in an acceptable range, the IVC can be

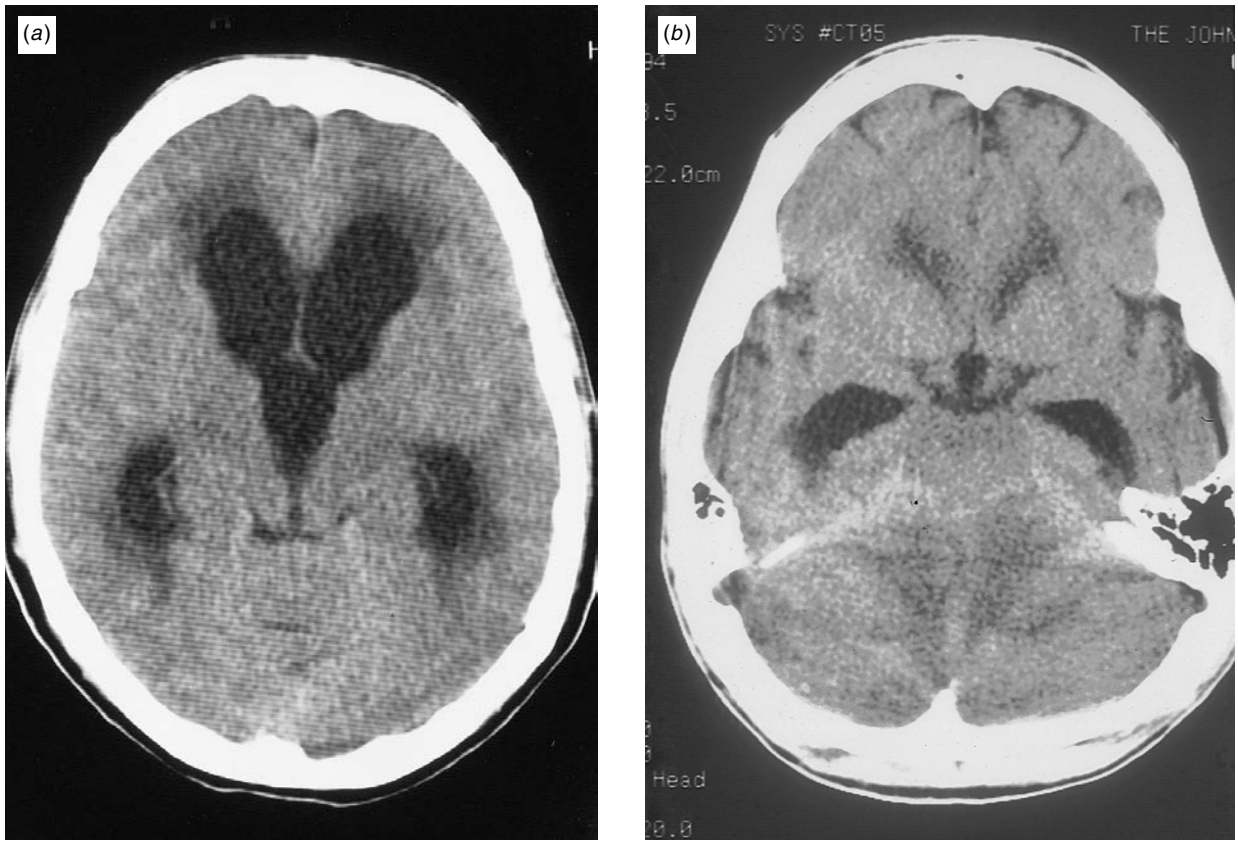

Fig. 125.6(*a*). Head CT scan of a 36-year-old woman with obstructive hydrocephalus. There is dilatation of the bilateral frontal and temporal ventricles. The third ventricle is also oval and dilated. Transependymal edema is noted in the frontal and temporal horns.
Fig. 125.6(*b*). Same patient. Lower cut. The perimesencephalic cisterns are effaced.

removed. If ICP rises, the IVC should be reopened for drainage.

Removal of intracranial masses

Depending on the nature of the lesion, surgical removal of masses causing ICP elevation can be an important ICP management strategy. Surgical removal is indicated for subdural and epidural hematomas, tumours, abscesses, and cerebellar infarction and hemorrhage. Surgical removal of hemisperhic intracerebral hemorrhage can be successful in individual cases, but cohort outcome studies do not show definite benefit (Batjer et al., 1990; Morgenstern et al., 1998).

Decompression of the cranial vault

There is a high incidence of cerebral herniation (Hacke et al., 1996) and death (Schwab et al., 1998) associated with massive cerebral infarctions. Neuronal death is associated with the breakdown of the Na-K ATPase pump leading to cellular swelling, or cytotoxic edema. As yet, there is no effective medical therapy for cytotoxic edema. The only promising therapeutic strategy is hemicraniectomy, which does not treat the edema directly, but rather makes room for the swollen brain by removing a large bone flap, incising the dura, and expanding it with a patch (Schwab et al., 1998). A recent study highlighting the importance of the hemicraniectomy size, reported that complication such as hemicraniectomy-associated bleeding occurred more often with smaller hemicraniectomies (Wagner et al., 2001). Early recognition of neurological deterioration and early surgical decompression (within 24 hours symptom onset) may result in better functional outcome (Schwab et al., 1998) with lower mortality (Rieke et al., 1995). If it is to be done for a large hemispheric infarction, we recommend that hemicraniectomy be performed prior to frank clinical herniation. Controlled clinical trials are still needed to definitely validate this therapy.

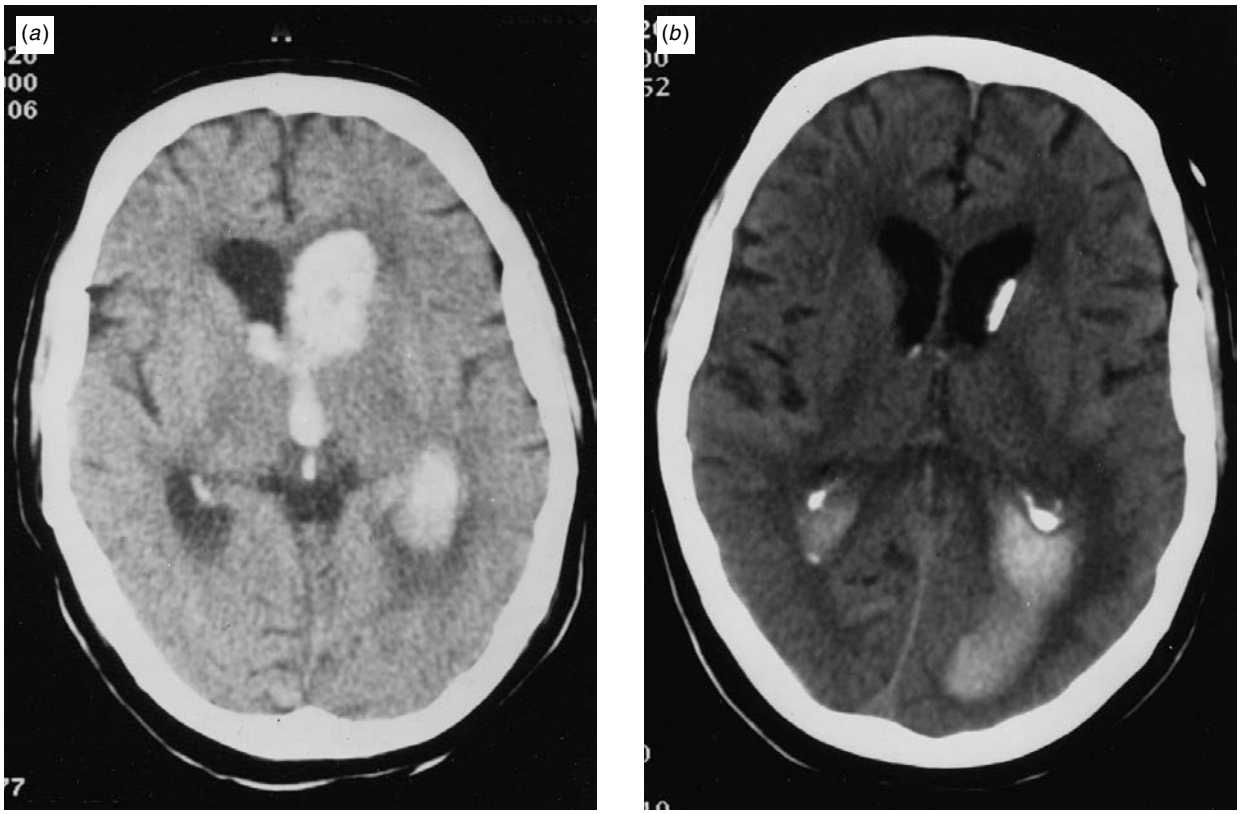

Fig. 125.7(*a*), (*b*). Head CT scan of an 81-year-old man with intraventricular hemorrhage. The blood clot has casted the left frontal, left temporal and third ventricles. Mild spillage of blood is seen in the right frontal horn. Blood in the ventricles led to the formation of an obstructive-type hydrocephalus. The insertion of a left intraventricular catheter (*b*) facilitated drainage of CSF and blood and the relief of the obstructive hydrocephalus.

General factors that may initiate or aggravate intracranial hypertension

Agitation and pain can elevate ICP, and agitation poses the risk of self-injury, including extubation, or removal of vascular catheters or IVCs. Thus, sedation and analgesia are important adjunctive therapies for ICP. The goals of sedation are to prevent ICP elevation and risk of self-injury, while preserving the ability of the ICU team to perform frequent neurological examinations. Short-acting drugs (propofol or midazolam) or drugs that can be readily reversed (i.e. fentanyl) are preferred. Sedation with propofol may control ICP better than morphine (Kelly et al., 1999). We do not routinely use neuromuscular blockade for ICP control because it masks the neurological examination, but in some instances paralysis is necessary. Neuromuscular blockade should not be used without analgesia or sedation.

Prolonged use of neuromuscular blockade in patients with severe head injury does not improve outcome and may lengthen ICU stay (Hsiang et al., 1994). Sedation, analgesia, and neuromuscular blockade pose the significant risk of suppression of airway reflexes, respiratory drive, or both, particularly in patients with coma or diminished level of consciousness, and these therapies are best reserved for patients with protected airways (i.e. intubation).

Brain temperature can mitigate or aggravate neurological injury. Rising brain temperature leads to increased $CMRO_2$ and CBF that can further increase ICP. Fever can be treated or prevented with antipyretics or cooling blankets, but care is necessary to avoid shivering. Seizures occur in as many as 20% of patients with head injury (Vespa et al., 1999). Seizures also can increase $CMRO_2$ and CBF, leading to a rise in ICP. Antiepileptic agents should be used to prevent seizures, especially if cortical injury is present.

Outcome studies and ICP control

The impact of ICP monitoring on patient outcomes is still unclear. The majority of studies show reduced mortality and improved functional outcome when ICP is monitored and treated in head-injured patients (Narayan et al., 1982; Saul & Ducker, 1982), although the Traumatic Coma Data Bank results suggest that ICP has no effect on neurobehavioural outcome one year after injury (Levin et al., 1990).

In subarachnoid hemorrhage (SAH), the presence of B-waves or maximum daily ICP over 30 mm Hg has been associated with poor outcomes (Takeuchi et al., 1989). Early aggressive monitoring of intracranial hypertension and hydrochephalus has been shown to benefit patients with severe SAH (Hunt–Hess Grade IV or V) (Bailes et al., 1990).

A relationship between ICP management and long-term outcome in spontaneous intracerebral hemorrhage has not been demonstrated nor seriously evaluated.

Up to 80% of patients with large hemispheric infarction die from cerebral herniation and brain death (Schwab et al., 1996). Yet, ICP monitoring in stroke has not demonstrated a group benefit (Woodcock et al., 1982) and may not be helpful in guiding long-term treatment of ICP elevation (Schwab et al., 1996). However, in cases of massive hemispheric strokes, we believe that the decision for aggressive management such as hemicraniectomy must be made before the measured ICP is elevated or before frank clinical herniation.

Cerebral venous or dural sinus thrombosis can lead to ICP elevation. ICP monitoring can improve outcome in dural sinus thrombosis when it is used to guide therapies that reduce cerebral blood volume simultaneously with treatments to restore normal venous drainage (Hanley et al., 1988).

Encephalitis is often accompanied by cerebral edema that can lead to cerebral herniation. Monitoring and treatment of ICP leads to better neurological outcomes (Schwab et al., 1997).

Cerebral edema and intracranial hypertension are well-recognized complications of fulminant hepatic failure (FHF) that contribute significantly to its morbidity and mortality. The presence of overt signs of intracranial hypertension at the time of hospitalization in patients with FHF complicating viral hepatitis is associated with poor outcome (Dhiman et al., 1998). The management of ICP in hepatic encephalopathy is complicated by the fact that insertion of ICP monitoring devices has a higher risk of hemorrhagic complication because of coagulation defects.

Drowning can cause global hypoxic/ischemic injury and resulting brain edema and ICP elevation. No clear improvement in outcome has been demonstrated by monitoring ICP in drowning (Bohn et al., 1986; Donovan et al., 1998). ICP elevation in drowning may merely be a marker of severe global hypoxic injury which is not amendable to ICP therapies.

Chronic disorders of intracranial pressure

Normal pressure hydrocephalus (NPH)

Normal pressure hydrocephalus (NPH) is an important, treatable syndrome of dementia, gait apraxia, and urinary incontinence that may be the underlying cause in 5% of demented patients (Vanneste & van Acker, 1990). The importance of making this distinction is the treatable nature of NPH, as opposed to the essentially untreatable nature of most dementias. NPH is treated by surgical cerebrospinal fluid (CSF) shunting, often with significant neurologic recovery, which results in improved functional outcome (Borgesen, 1984; Raftopoulos et al., 1994).

The selection criteria for identifying patients who will actually respond to shunt surgery are poor. The most common tests used to identify NPH have proven to be less accurate than desired; other more accurate tests exist but are in limited use because of their invasive nature. Adding to the diagnostic confusion is that NPH clinically overlaps with many conditions that can coexist in elderly patients, including vascular dementia, Alzheimer disease, vitamin B12 or folate deficiency, and disorders such as cervical spondylitic myelopathy, lumbar stenosis, and peripheral neuropathy. As a result, inaccurate treatment decisions can occur in two ways. First, many patients with the potential to respond to surgery are not identified and thus not shunted, resulting in unnecessary disability. Secondly, patients with no potential to respond to surgery are selected for surgery, resulting in unnecessary risk and potential for long-term complications. On average, only 50% of patients with suspected NPH have a good response to shunt surgery (Thomsen et al., 1986; Vanneste & van Acker, 1990).

Although a syndromic triad characterizes NPH, there are no signs, symptoms or symptom onset order that are specific to NPH (Raftopoulos et al., 1994). The most frequent presentation of gait disturbance in NPH appears to be imbalance (Adams et al., 1965; Hakim & Adams, 1965). Falling is a frequent, serious problem and most patients require the use of an assistive device for ambulation. With progression of the disease, the gait pattern is characterized by shorter, shuffling steps and difficulty with turns. Eventually standing, sitting, and even bed mobility are impaired.

The urinary incontinence of NPH typically presents as urinary urgency and frequency, and appears to be associated with a hyperreflexic bladder (Ahlberg et al., 1988). The reversibility of urinary incontinence in NPH distinguishes it from other cerebral lesions that cause voiding dysfunction (Gerstenberg et al., 1982). The urological symptoms are believed to be distinct from the gait disturbance or dementia components of NPH and have an independent course (Jonas & Brown, 1975). The pathophysiology is postulated to involve a loss of voluntary supraspinal control of micturition, probably from the effects of ventricular enlargement, but there has been virtually no systematic evaluation of the neurourological aspects of NPH.

The dementia syndrome of NPH is characterized by slowing of mental processes, memory impairment, visuoconstructional impairment, inattention and apathy (Benson, 1985). Mental status abnormalities vary according to disease severity, and cognitive testing has suggested a pattern of abnormalities common to the subcortical dementias (Thomsen et al., 1986), but no features of the subcortical dementia in NPH are thought to be specific. Attempts to predict the response to shunting by measuring change in cognitive performance after temporary CSF removal have had meagre results. One study found improvement in a subgroup of patients for some cognitive tests with temporary CSF removal. However there were a number of false negatives compared with the response to surgical shunting (Wikkelso et al., 1986).

Computed tomography (CT) and magnetic resonance imaging (MRI) studies are in widespread clinical use for diagnosing NPH. Common features associated with NPH include rounding of the temporal and frontal horns of the lateral ventricles, rounding of the third ventricle, and enlargement of the lateral and fourth ventricles. Characteristic MRI findings associated with NPH include periventricular white matter hyperintense signal, CSF flow void in the Sylvian aqueduct, and thinning of the corpus callosum (Jack et al., 1987). A common subjective criterion used to distinguish NPH from hydrocephalus *ex vacuo* is 'ventricular enlargement out of proportion to cortical atrophy', that is, widened cortical sulci. However, a direct comparison of ventricular size and sulcal width to CSF outflow resistance (see below) found that these CT criteria do not distinguish NPH from brain atrophy (Kosteljanetz & Ingstrup, 1985).

Radionuclide CSF imaging, or cisternography, has a physiologic basis relevant to NPH. It should demonstrate slowed CSF passage through the ventricles and subarachnoid space caused by the increased resistance to CSF flow. Diagnostic crtieria usually quoted for lumbar radionuclide injection are ventricular entry (i.e. retrograde CSF flow) and prolonged retention in the cranial vault (i.e. delayed conductance or resorption) (McCullough et al., 1970). The clinical experience with cisternography has not matched its physiologic potential (Black, 1980). The best studies of cisternography in NPH have a positive predictive value of 50% or less, and studies that directly compared cisternography to CSF conductance testing further confirm the poor diagnostic power of this test (Borgesen, 1984). Cisternography seems to have little utility in the diagnosis of NPH.

The relationship between disordered CSF circulation and NPH is well established, and tests to evaluate this have a high predictive value for outcome after shunt surgery. There are complex interactions between CSF pressure, resistance to CSF flow and resorption, cerebral venous pressure and the area of the ventricular surface that determines the development and maintenance of NPH. Implicit to the development of ventricular enlargement in hydrocephalus is the development of increased resistance to CSF flow or resorption that is necessary to raise CSF pressure. Whether the site of increased resistance is the subarachnoid space or the arachnoid villi, CSF pressure increases proximal to the site of resistance and the ventricles dilate. Diseases that are known to predispose to NPH (subarachnoid hemorrhage, head injury, tumour, meningitis and encephalitis) commonly cause inflammation and scarring of the arachnoid mater or the arachnoid villi that can increase resistance to CSF flow or resorption (Albeck et al., 1991).

Tests of CSF physiology used to diagnose NPH fall into three categories: (i) tests of CSF conductance, (ii) CSF pressure monitoring, and (iii) tests of response to CSF removal. CSF conductance is a quantitation of the ease with which CSF flows through the subarachnoid space to the arachnoid villi. Mathematically it is the inverse of CSF outflow resistance. CSF conductance determination usually consists of the infusion of artificial CSF into the lumbar subarachnoid space through a spinal needle while recording the CSF pressure response simultaneously at a second site (usually another spinal needle) (Borgesen & Gjerris, 1982). Objective, reproducible measurements of the CSF pressure–flow or pressure–volume relationships are obtained, and can be compared to normal values for CSF conductance, CSF production rate, and pressure–volume relationships (Albeck et al., 1991). There is strong evidence that these tests are highly predictive of shunt responsiveness in NPH, with a high likelihood of improvement seen with CSF conductance above 0.12 ml/min/mmHg (Borgesen & Gjerris, 1982) or CSF outflow resistance above 18 mm Hg/ml/min (Boon et al., 1997), although not all investigators have found such high diagnostic accuracy (Malm et al., 1995).

CSF pressure (Pcsf) monitoring was first advocated as a diagnostic test for NPH about 30 years ago (Nornes et al., 1973). Although it is a chronic disorder, NPH has the same abnormal Pcsf waveforms that were originally described in patients with brain tumour or acute injury (Borgesen & Gjerris, 1982). Some patients have Pcsf that is nearly always over 15 mm Hg (20 cm H_2O), but many others have normal baseline Pcsf that is punctuated by B-waves and A-waves, indicators of impaired intracranial compliance from impaired CSF resorption. The presence of unstable Pcsf wave forms (predominantly B-waves) in NPH is well documented (Borgesen & Gjerris, 1982; Williams et al., 1998) and the correlation of unstable Pcsf with NPH shunt responsiveness varies from 50% to 90% (Pickard et al., 1980; Borgesen & Gjerris, 1982; Williams et al., 1998). Most Pcsf monitoring in NPH has been done with ventricular catheters, subarachnoid bolts or other intracranial devices (Borgesen & Gjerris, 1982; Raftopoulos et al., 1994). As a result, the technique never gained favour as a diagnostic test for NPH because of fear of causing cerebral injury (Borgesen & Gjerris, 1982). Pcsf monitoring can be performed safely via lumbar catheter (Williams et al., 1998). Clinical response to CSF drainage via a lumbar catheter has been reported to correlate with response to shunting in NPH (Haan & Thomeer, 1988; Williams et al., 1998). The advantage over a single LP is that CSF can be drained continuously for several days, providing a more sustained and controllable normalization of ICP and intracranial volume/pressure relationships. Continuous CSF drainage can be considered as a trial of shunt-like conditions without shunt surgery.

Common characteristics to these three categories of CSF physiology tests are invasiveness, labour intensity, and a generally high predictive value for response to shunting. Unfortunately, the invasiveness and labour intensity have made these tests unpopular for the diagnosis of NPH. A revealing survey of neurologists and neurosurgeons from the Netherlands found that few used the more invasive techniques of CSF infusion tests or ICP monitoring despite the higher predictive value (Vanneste & van Acker, 1990).

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (IIH), also known as pseudotumour cerebri or benign intracranial hypertension, is a syndrome characterized by increased ICP in the absence of intracranial masses or hydrocephalus. Quincke first described the syndrome and its cardinal presentation of bilateral papilledema (Quincke, 1897). The term benign intracranial hypertension has been used, but because serious visual impairment may occur, many prefer the term idiopathic intracranial hypertension.

The incidence of IIH is 0.9 per 100 000 per year in the general population (Durcan et al., 1988; Radhakrishnan et al., 1993) and 3.5 per 100 000 per year in women between the ages of 15 and 44 years (Radhakrishnan et al., 1993). Obesity is a significant risk factor. The incidence is 19 per 100 000 for those 20% or more over ideal weight from age 20 to 44 years (Durcan et al., 1988). Recent weight gain is also associated with the diagnosis with IIH (Ireland et al., 1990).

The most common presenting symptom is headache, which may be associated with diplopia. Pulsatile tinnitus has also been described (Sismanis et al., 1990). The most common clinical finding is papilledema, usually bilateral, but sometimes unilateral (Chari & Rao, 1991). Sixth, and occasionally seventh nerve palsies can be appreciated (Krishna et al., 1998). Visual loss is the most serious complication of IIH (Corbett et al., 1982), and its prevention should be the focus of therapy (Brourman et al., 1988). Detailed ophthalmologic evaluation is critical for the diagnosis and monitoring of disease progress. A variant of IIH without papilledema has been described typically in young obese women with elevated intracranial pressure (Marcelis & Silberstein, 1991).

The diagnosis of IIH should be based on the signs and symptoms of intracranial hypertension, verification of ICP elevation by lumbar puncture, normal CSF composition, and the absence of intracranial masses or hydrocephalus on neuroimaging (Brazis & Lee, 1998). In addition to ruling out intracranial masses, thin-section CT of the orbits can also show enlarged optic nerve sheaths and empty sella (Gibby et al., 1993).

The pathophysiology of IIH is still unclear. Increased cerebral water (Gideon et al., 1995) and increased cerebral blood flow have been described in comparison to controls (Gross et al., 1990). Obesity and increased intra-abdominal pressure are also thought to contribute (Sugerman et al., 1997; Brazis & Lee, 1998). The list of differential diagnosis for IIH is provided in Table 125.1.

The mainstay of medical therapy for IIH is acetazolamide, a carbonic anhydrase inhibitor that reduces CSF production. Furosemide can also be used (Schoeman, 1994). Serum electrolytes should be monitored because of the risk of metabolic acidosis and hypokalemia. In obese patients, weight reduction has been associated with more rapid recovery of papilledema and visual field deficits compared to those who do not lose weight (Kupersmith et al., 1998). One study found that weight loss of about 6% was more effective in reducing papilledema than acetazolamide (Johnson et al., 1998). Surgical-induced weight loss was also effective (Sugerman et al., 1995). The headache is usually relieved once ICP is controlled, but symptomatic treatment with analgesics may be necessary.

Table 125.1. Differential diagnosis for IIH

Disorders of cerebral venous outflow
Cerebral venous sinus thrombosis
Jugular vein thrombosis
Intrathoracic disorders affecting cardiac venous return
Infections and autoimmune disorders
Syphilis
Lyme's disease
Infectious meningitis
CNS lupus
Antiphospholipid antibody syndrome
Sarcoidosis
Drugs associated with IIH
Corticosteroids
Minocycline
Erythromycin
Cyclosporine
Vitamin A intoxication
Growth hormones
Lithium carbonate
Medical or physiological conditions associated with IIH
Pregnancy
Hypothyroidism

The decision to proceed to surgical therapy depends on the response to medical therapy and the progression of visual loss (Corbett & Thompson, 1989). Optic nerve sheath fenestration can stabilize or improve vision in the majority of patients (Sergott et al., 1988; Kelman et al., 1992; Spoor & McHenry, 1993). Visual improvement with optic nerve fenestration may be related to improvement of retrobulbar circulation (Mittra et al., 1993). Shunting of CSF, usually with a lumboperitoneal shunt (LPS) is a satisfactory treatment for the majority of patients with IIH who require surgical therapy (Johnston et al., 1988). The vision of most patients improves or stabilizes (Miller & Leech, 1975), but CSF shunting is associated with high failure rate and side effects (Rosenberg et al., 1993). In a retrospective study of 27 patients treated with at least one LPS and followed for a mean of 77 months, 15 patients (56%) required surgical revision (Eggenberger et al., 1996).

Intracranial hypotension

The syndrome of intracranial hypotension (IH) is characterized by frontal or occipital headaches, worse when erect or straining, and ameliorated by lying down. This is commonly seen after a lumbar puncture and is attributed to reduced CSF pressure and volume likely caused by persistent dural leak. In some cases, there is also nausea, vomiting, photophobia, or tinnitus. Cranial nerve palsies (III and VI) have been also described (Ferrante et al., 1998). IH occurring in the absence of LP, or any procedure, or overt cause of CSF leak is known as spontaneous intracranial hypotension. The symptoms are similar to the post LP cases and may last for weeks. The mechanism is believed to be spontaneous CSF spinal leakage, most commonly occurring in the cervicothoracic or thoracic spine (Schievink et al., 1996). Other sites of CSF leakage are the cribriform plate and spinal dural diverticuli. The clinical presentation is very often suggestive of IH, with orthostatic headaches, but coma and bilateral subdural hematoma have also been reported (Nakajima et al., 1996).

The diagnostic work-up includes head CT scan, which may show subdural CSF collection or hematoma. MRI of the head typically shows diffuse pachymeningeal gadolinium enhancement, often with imaging evidence of sinking of the brain, subdural fluid collections, engorged cerebral venous sinuses, enlarged pituitary gland, or decreased size of the ventricles (Mokri, 2001). The dural venous sinuses may also appear engorged and diffuse venodilation is believed to cause the gadolinium enhancement on MRI (Bakshi et al., 1999). Other diagnostic tests include radionuclide cisternography and contrast myelography to show the site of the leak. The urinary excretion of radioisotope after spinal injection may reflect a dural deficit with the passage of the tracer from the subarachnoid space to the systemic circulation (Benamor et al., 1998). Performance of lumbar puncture in these patients may worsen the problem. The CSF pressure is low, as would be expected, and 'dry' tap may be encountered. High CSF pressure can occur, which may signify subdural CSF collection or hematoma formation.

Symptoms of IH are usually self-limited and supportive care includes hydration and analgesics. With careful anatomic location of the CSF leak, a blood patch (Mokri, 2001) can be used, and surgical repair of dural defect (diverticuli) is sometimes needed (Schievink et al., 1996).

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Neurological manifestations of endocrine disease

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Neurological signs and symptoms occur in virtually every known endocrine disturbance. This chapter focuses primarily on the neurological manifestations of diseases of the thyroid and the adrenal glands. The neurological complications of parathyroid disease largely reflect disordered calcium metabolism and are discussed in Chapter 124. The numerous neurological complications of diabetes mellitus, hypoglycemia, and pancreatic disorders are also dealt with elsewhere. Neurological manifestations of the hypothalamus and pituitary disease are reviewed in Chapter 57. The endocrine disturbances associated with anorexia nervosa are considered in Chapter 54.

Neurological complications of thyroid disease

Hyperthyroidism

Neuropsychiatric disorders, seizures, and headaches

Neuropsychiatric symptoms are common in hyperthyroidism. Many patients complain of feeling nervous, anxious and restless. They note difficulty in concentration and a shortened attention span. Friends or relatives describe them as irritable or capricious. Frank psychoses are uncommon, but agitated depression has been reported in severe thyrotoxicosis (Logothetis, 1961). In elderly patients, an apathetic state with lethargy, depression (Ettigi & Brown, 1978) or cognitive impairment may occur (Martin & Deam, 1996). Although the mechanism by which thyroid hormone produces these mental changes is unknown, symptoms usually resolve when thyroid function is restored to normal.

In patients with the life-threatening forms of hyperthyroidism known as thyroid storm, agitated delirium progresses to lethargy and coma (Newcomer et al. 1983). Patients may have signs of bulbar palsy (see below) and convulsions can occur. There are serious systemic complications, including hyperpyrexia, tachycardia and other cardiac arrythmias, and a variety of electrolyte abnormalities. Treatment includes hydration, cooling, antithyroid medication, iodine, and corticosteroids (Tiegens & Leinung, 1995). Plasmapheresis may be useful (Newcomer et al., 1983).

Patients with epilepsy may show increased frequency of their seizures with hyperthyroidism. In some cases, hyperthyroidism is associated with a seizure disorder that disappears after the patient becomes euthyroid (Smith & Looney, 1983). In one study, nearly 10% of hyperthyroid patients had convulsions as their initial symptom (Jabbari & Huott, 1980); however, this figure is unusually high. The electroencephalogram in hyperthyroid patients may be moderately abnormal and returns with restoration of the euthyroid state (Leubscher et al., 1988)

Headache is a common symptom with hyperthyroidism. It is usually symmetric, periorbital, and frontal in location. Many patients complain of paroxysms of fullness in the head or episodes of tinnitus. In some cases, headache may be related to vascular mechanisms or coexisting exophthalmos.

Movement disorders

A fine tremor that resembles an exaggerated physiological tremor is common. It appears to be mediated by peripheral ß-adrenergic receptors (Marsden et al., 1970; Young et al., 1975). The movements are most prominent in the small metacarpophalangeal joints of the fingers and in the tongue and eyelids. The tremor is regular, with a rate of 8–10 Hz and is of small amplitude. It is best seen when the patient attempts to maintain a posture against gravity, such as when holding the arms and fingers extended forward. The movements persist during action and are

present at rest. Electromyographic studies show simultaneous activity in agonist and antagonist muscles.

Chorea and athetosis are rare complications of hyperthyroidism (Nagaoka et al., 1998). The disorder has been attributed to enhanced striatal dopaminergic sensitivity (Delong, 1996). Paroxysmal choreoathetosis has also been reported (Fischbeck & Layzer, 1979; Drake, 1987).

Cranial nerve abnormalities

Many of the ophthalmic signs of hyperthyroidism (except for ophthalmoplegia) appear to be caused by increased tissue sensitivity to activity of the sympathetic nervous system. The palpebral fissures appear widened and the lids seem retracted (Dalrymple's sign). The patient seems to be staring and blinks infrequently (Stellwag's sign). When the patient looks down, the upper lids remain elevated, leaving a larger than normal portion of the sclera visible (von Graefe's sign). Patients seem to have convergence insufficiency (Möbius' sign) and often do not contract the frontalis muscle when looking up (Joffroy's sign).

Some cranial nerve abnormalities result from compression by an enlarged thyroid. Compression of the recurrent laryngeal nerve can produce vocal cord paralysis with dysphonia. In severe cases with bilateral laryngeal nerve compression, there may be respiratory stridor. Laryngeal nerve involvement may occur with benign thyroid disease (Fenton et al., 1994), but should always raise the suspicion of malignancy. Compression of the sympathetic chain can produce Horner's syndrome. Dysarthria or dysphagia may be seen with one of the coexisting neuromuscular problems associated with hyperthyroidism such as bulbar paralysis or myasthenia gravis.

Neuromuscular disorders

Spinal and peripheral nerve disorders

Hyperthyroid neuropathy is uncommon, although an association of hyperthyroidism and polyneuropathy with primarily proximal weakness (Basedow's paraplegia) has been recognized for many years. Signs of peripheral neuropathy with hyperthyroidism have been reported to resolve with treatment of the thyroid disease (Fisher et al., 1985). A carefully studied case of acute areflexic quadriparesis in association with thyroid storm revealed evidence of a mixed axonal and demyelinating sensorimotor neuropathy. Ultrastructure of the sural nerve showed abnormalities in mitochondria and cytoskeletal elements. Neuromuscular function improved with treatment of the hyperthyroid state (Pandit et al., 1998). Upper motor signs are rare, but well documented. In a few cases, they are accompanied by muscular wasting and fasciculations, producing a clinical picture resembling amyotrophic lateral sclerosis (Logothetis, 1961).

Subclinical motor axonopathy has been detected by electrodiagnostic studies in about half of patients with hyperthyroidism (McComas et al., 1974). Muscle twitching or fasciculations occur in some patients (Puvanendran et al., 1979) and, in a few cases, takes the form of generalized myokymia involving the face, tongue, limb and trunk. The electromyogram may show continuous, repetitive, grouped discharges, apparently arising from distal portions of the motor nerves (Harman & Richardson, 1954).

Thyroid ophthalmopathy

Thyroid ophthalmopathy is present in about 50% of patients with Graves disease (autoimmune hyperthyroidism). The disorder may also be seen in euthyroid or hypothyroid individuals, presumably due to a shared immunologic abnormality. Orbital tissue, predominantly the extraocular muscles, becomes inflamed and edematous, with infiltration of lymphocytes and histiocytes. The etiology of the syndrome remains uncertain with thyroid postulated to possess an antigen, possibly the TSH receptor, which cross-reacts with orbital tissue. Cellular and humoral immune responses initiate an inflammatory reaction that leads to a proliferation of connective tissue and swelling of orbital contents (Warwar, 1999). Clinically, eyelid retraction (Dalrymple's sign) is seen at presentation in 75% of patients and ocular pain may be the most common symptom (30%) (Bartley et al., 1996). The process is usually bilateral, but asymmetric, with erythema and swelling of the lids and conjunctiva, proptosis and restriction of eye movements. The abnormality in eye movement is mainly mechanical with forced duction tests showing resistance to passive movement. Rarely, in severe cases, compressive-ischemic optic neuropathy, papillitis, and papilledema may develop. Visual-evoked potentials may be useful in identifying those patients at risk for the developing optic nerve damage in thyroid ophthalmopathy (Salvi et al., 1997).

Thyroid ophthalmopathy can usually be distinguished from other causes of orbitopathy by imaging studies. Classic findings demonstrate exophthalmos, herniation of retrobulbar fat through the orbital septum, enlargement of extraocular muscles with normal tendons and enlargement of the lacrimal glands (Perros & Kendall-Taylor, 1992). Treatment may include immune suppression usually with corticosteroids (Wiersinga, 1992), radiotherapy, and surgical decompression of the orbit.

Myasthenia gravis

It has long been recognized that myasthenia gravis can occur in association with hyperthyroidism (Drachman,

1962; Engel, 1961). Myasthenia may accompany, follow, or precede the development of thyrotoxicosis. Treatment of the hyperthyroidism does not have a predictable effect on the myasthenia. In some cases, the myasthenia appears to worsen as the hyperthyroidism is controlled. Differentiation between the ophthalmoplegia associated with myasthenia gravis and thyroid ophthalmopathy should not be difficult. Unlike patients with thyroid eye disease, patients with ocular myasthenia gravis usually have ptosis, do not develop exophthalmos or conjunctival edema, and have no impairment of forced ductions. Antibodies to acetylcholine receptor are usually present in myasthenia and orbital imaging is abnormal in thyroid ophthalmopathy.

Myopathy

Muscle weakness is common in hyperthyroid patients and the majority of patients have clinical signs of myopathy (Ramsay, 1974). Painless weakness is most prominent in the muscles of the shoulder girdles and the upper arms and in the proximal lower limbs. A few patients experience significant respiratory muscle weakness. The deep tendon reflexes are brisk and fasciculations are occasionally noticeable. Serum creatine kinase levels are normal to mildly reduced (Graig & Smith, 1965), although elevated creatine kinase levels have been reported in association with treatment with antithyroid medications (Suzuki et al., 1997). The electromyogram shows myopathic abnormalities without fibrillations; fasciculations and myokymia may also be found. Muscle biopsy usually shows few abnormalities, although there may be scattered, non-selective atrophy of single muscle fibres (Carpenter & Karpati, 1984). Muscle weakness partially improves in thyrotoxic patients when treated with propanolol and improves further with restoration of the euthyroid state. This suggests that thyroid hormone and catecholamine in concert contribute to mediate the muscle dysfunction (Olson et al, 1991).

A few hyperthyroid patients experience bulbar muscle weakness that is not related to coexisting myasthenia gravis. Dysphagia, aspiration or regurgitation of liquids, nasal dysphonia, and hoarseness may occur, sometimes with weakness of the face, jaw, tongue or ocular muscles. Most of these patients have proximal limb weakness. This syndrome tends to have a fulminating course, sometimes associated with thyroid storm. The weakness may improve with beta-blocker therapy (Kammer & Hamilton, 1974; Weinstein et al., 1975) and, similar to other myopathic symptoms, resolves when the patients become euthyroid (Joasoo et al., 1970).

Periodic paralysis

Attacks of hypokalemic periodic paralysis, indistinguishable from the familial variety, may accompany endogenous or exogenous thyrotoxicosis (Layzer & Goldfield, 1974). The disorder is rare in non-Asian populations and in the United States, patients with thyrotoxic periodic paralysis reflect the ethnic make-up of the local population (Ober, 1992). Although thyrotoxicosis is much more common in women, 90% of patients with thyrotoxic periodic paralysis are male. Attacks of periodic paralysis may be the first symptom of thyrotoxicosis, which is the most common cause of non-hereditary periodic paralysis in adults.

As in the familial form, attacks of weakness come on during rest after exercise and especially during sleep. Attacks can be precipitated by insulin or a carbohydrate-rich meal. Weakness starts in the proximal lower extremities and spreads upward, usually sparing the bulbar, cardiac, and respiratory muscles. The serum potassium level is usually reduced during a major attack, because of a shift of extracellular potassium into muscle cells (Shizume et al., 1966). Two varieties of familial hypokalemic periodic paralysis have been identified as 'channelopathies' with genetic defects in calcium channels resulting in defective coupling of excitation-contraction in muscle (Greenberg, 1999). The genetics of thyroid periodic paralysis or the mechanism by which thyroid hormone may influence excitation–contraction in muscle is unknown (Layzer, 1982). Administration of potassium hastens recovery from an attack. Beta-blockers tend to prevent attacks (Conway et al., 1974; Yeung & Tse, 1974) and restoration of normal thyroid function abolishes the disorder.

Hypothyroidism (myxedema)

Cerebral symptoms

Cognitive and psychiatric symptoms are common in hypothyroidism. In their most mild form, these consist of headaches, difficulty in concentrating, poor memory, and generalized dulling of mental processes. The clinical picture may be easily mistaken for depression. Excessive sleepiness is probably a direct cerebral symptom of thyroid deficiency, but there is controversy as to whether hypothyroidism may contribute to the development of obstructive sleep apnea (Skjodt et al., 1999). Alveolar hypoventilation attributable to diaphragmatic weakness may also occur and possibly contribute somnolence (Martinez et al., 1989).

Frank psychiatric disorders or dementia may appear in more profoundly hypothyroid individuals. 'Myxedema madness' refers to a syndrome characterized by irritability, suspiciousness, hallucinations, delirium and psychosis (Asher, 1949; Pitts & Guze, 1961). Dementia is often associated with apathy, sleepiness, and slowing of speech and

thought processes (Jellinek, 1962). These symptoms may be only partially reversible with correction of thyroid deficiency (Dugbartey, 1995).

Untreated patients may develop hypothermia, hypotension, and respiratory failure. Hypoglycemia and hyponatremia occur and seizures or fatal myxedema coma will follow. Although the mortality of myxedema coma is significant, the advent of intensive respiratory care and use of intravenous thyroxine has resulted in improved survival, with mortality dropping from 60–70% to 15–20% (Jordan, 1995). Neuropathological studies of myxedema coma are few. There is generally evidence of cerebral edema and non-specific generalized neuronal damage. ^{31}P magnetic resonance spectroscopy of brain shows that the phosphocreatine/inorganic phosphate ratio increases with L-thyroxine treatment indicating reversible alterations in phosphate metabolism (Smith & Ain, 1995).

Seizures and electroencephalographic changes

There appears to be a higher than expected incidence of seizures among patients with hypothyroidism. Nearly 20% of these patients, in one series, had seizures or syncope (Millichap, 1974). In some patients, return to a euthyroid state facilitates seizure control. The electroencephalogram generally shows slow alpha rhythms and low-voltage activity. In extreme cases, the electroencephalogram may appear virtually flat.

Ataxia of gait

Some hypothyroid patients (5–10%) have a syndrome of cerebellar ataxia (myxedema staggers) (Cremer et al., 1969; Harayama et al., 1983). Many patients seem heavy, slow or stiff. In others, the gait ataxia seems typically cerebellar, but limb ataxia is uncommon. The truncal ataxia is presumed to be of cerebellar origin and cell loss has been detected in the anterior superior vermis (Barnard et al., 1971). The dysarthria of hypothyroidism is usually caused by enlargement of the tongue, rather than cerebellar disease. The gait ataxia usually resolves with thyroid replacement.

Cranial nerve abnormalities

Deafness and tinnitus are common symptoms. In one series, 85% of patients had hearing loss, usually bilateral with improvement noted after treatment (Van't Hoff and Stuart, 1979). However a more recent study of a group of hypothyroid patients showed no difference in hearing with an age- and sex-matched population. Thyroid hormone replacement did not improve hearing thresholds, speech reception thresholds, or speech discrimination (Parving, 1990). Taste disturbances have been reported (McConnell et al., 1975). Disturbed visual acuity with optic atrophy may occur. Visual evoked responses may be abnormal (Ladenson et al., 1984). Other cranial nerve involvement is quite rare and not well documented. The slow, muffled, gravely voice appears to be due to local changes in the tissues of the larynx, rather than neural factors.

Neuromuscular disorders

Myopathy

Neuromuscular disorders are common in hypothyroidism, but severe disturbances of function are unusual. Many patients have pain and stiffness, probably because of slow muscle contraction and relaxation. Muscle stiffness may increase during physical activity. Deep tendon reflexes, particularly the ankle jerks, will show a prolonged relaxation phase. The slow relaxation is probably due to a reduced uptake of calcium by the sarcoplasmic reticulum (Fanburg, 1968). Direct percussion of muscle may elicit a local contracture with transient mounding of muscle (myoedema). This electrically silent contracture is thought to result from mechanically induced local release of calcium from the sarcoplasmic reticulum (Mizusawa et al., 1983). Myoedema is not specific for hypothyroid muscle disease and may not be indicative of a neuromuscular disorder (Hornung & Nix, 1992). True muscle cramps are common in hypothyroidism and are thought to be of neural origin. Subclinical hypothyroidism is also associated with an increase in neuromuscular symptoms such as paresthesiae, cramps, weakness and fatigue. These symptoms correlate directly with TSH levels and inversely with calcium levels, although total calcium and ionized calcium are in the normal range (Monzani et al., 1999).

Muscle enlargement occurs in 20% of hypothyroid children (Najjar, 1974; Tashko et al., 1999) producing an unusual 'infant Hercules' appearance (Kocher–Debré–Semélaigné syndrome). Muscle enlargement with pain and stiffness occurs less commonly in adults with hypothyroidism (Hoffmann's syndrome) (Norris & Panner, 1966). The cause of muscle enlargement is unknown. Overactivity of muscle caused by slow relaxation may contribute to the muscle enlargement, however, histologic studies do not show hypertrophy of muscle fibres (Ono et al., 1987).

Exercise intolerance and fatigue, without overt weakness, are common in hypothyroid patients. In subclinical hypothyroidism, blood lactate is elevated with exercise and correlates with the duration of the disease (Monzani et al., 1997). In general, MR spectroscopy of muscle has shown impaired oxidative metabolism that is reversed by thyroid hormone. This suggests that hypothyroidism may cause secondary mitochondrial dysfunction in muscle (Argov & Arnold, 2000).

Circulating creatine kinase levels are elevated in hypothyroid myopathy (Graig & Smith, 1965). Creatine kinase levels may be increased due to diminished turnover or clearance in myxedema thus may not be indicative of muscle disease. EMG abnormalities consistent with myopathy are common with nearly 50% of patients having evidence of myopathy in one recent series (Cruz et al., 1996). Muscle biopsy is typically non-diagnostic. Type II fibres have been reported to be atrophic and decreased with increased numbers of central nuclei (McKeran et al., 1975), although Type II fibres were found to predominate over Type I fibres in other series (Ono et al., 1987). With thyroid hormone replacement, the myopathy usually resolves in a few months.

Myasthenia

Hypothyroidism occurs in up to 6% of patients with myasthenia gravis and at autopsy, 12–19% of myasthenic patients have Hashimoto's disease (Ramsay, 1974). Thyroid antibodies are also found more often in patients with myasthenia than in control subjects. A few hypothyroid patients have muscle weakness that appears to be caused by a defect of neuromuscular transmission that differs from that in myasthenia gravis.

Peripheral nerve disorders

Minor signs of a distal, mainly sensory polyneuropathy occur in about 10% of hypothyroid patients (Rao et al., 1980). Rarely a severe polyneuropathy occurs with diminished motor nerve conduction velocities and evidence of axonal degeneration on nerve biopsy (Pollard et al., 1982). Carpal tunnel syndrome occurs in 15–29% of hypothyroid patients, whereas hypothyroidism increases the risk of carpal tunnel syndrome by 70% (Solomon et al., 1999). Deposits of mucopolysaccharide in the soft tissue of the carpal tunnel have been suspected to cause the problem, although definitive evidence is lacking. Carpal tunnel caused by hypothyroidism rarely requires surgical intervention. Symptoms usually subside with hormone replacement therapy.

Cerebrospinal fluid and pseudotumour

The cerebrospinal fluid protein is often elevated in patients with myxedema. Levels between 100 and 340 mg/dl were found in 44% of reported cases (Fishman, 1980). The protein elevation reflects an increased permeability of the blood–cerebrospinal fluid barrier, and possibly impaired function of the arachnoid villi, as well (Fishman, 1980). In children, pseudotumour cerebri may occur after initiation of thyroid replacement for hypothyroidism (Van Dop et al., 1983). This may be related to increased cerebral blood flow (Sokoloff et al., 1953), which in turn may lead to increased intracranial pressure.

Cretinism

Cretinism results from thyroid deficiency in the prenatal period or during early postnatal development (LaFranchi, 1999). In the United States, cretinism is rare due to the vast majority of patients with neonatal thyroid deficiency being identified through newborn screening programmes. Sporadic cases of cretinism usually result from dysgenesis of the thyroid with the remainder due to genetic defects in thyroid hormone biosynthesis. Iodine deficiency remains the most important cause of cretinism worldwide, having been essentially eliminated from the United States due to iodine supplementation of food staples such as bread.

The clinical syndrome is one of striking grotesque physical abnormalities and severe mental deficiency. Children are generally dwarfed and have thick necks, short crooked limbs, a protuberant abdomen, thin dry hair, coarse baggy skin, and a virtually pathognomonic facial appearance. The forehead is low; the eyes are puffy; the nose is broad and flat; lips are thick and the tongue is large and protruding. Neurologically, there is mental retardation, with pyramidal and extrapyramidal signs in a proximal and truncal distribution. Squint, deafness and primitive reflexes are common (Halpern et al., 1991). MR imaging abnormalities in cretinism have been noted in the globus pallidus and substantia nigra (Ma et al., 1993). In many patients, thyroid hormone therapy administered within the first two months of life results in nearly complete restoration of normal physical and mental function. Treatment should begin during the first two weeks of life for optimal intellectual development (Bongers-Schokking et al., 2000). Thyroid function tests should be monitored frequently for several years. When therapy is delayed beyond 6 months, significant improvement is rare.

Pathological studies indicate that thyroid deficiency in utero results in diminished size and density of neurons and defective myelination (Rosman, 1976). However, MR studies in newborns with congenital hypothyroidism before treatment have been reported to show no abnormalities in myelination patterns and no morphological abnormalities (Siragusa et al., 1997).

Neurological complications of parathyroid disease

Many neurological manifestations of parathyroid disease result from associated hypercalcemia or hypocalcemia, as

discussed in Chapter 124. However, the myopathic features of hyperparathyroidism may not be related directly to disturbed calcium metabolism.

Hyperparathyroidism

Primary hyperparathyroidism most commonly accompanies hypersecretion of parathyroid hormone by a solitary parathyroid adenoma. Fatigue and subjective weakness are common symptoms. The ease of obtaining serum calcium levels has made the triad of nephrolithiasis, osteitis and peptic ulcer disease ('stones, bones, and abdominal groans'), which characterizes advanced primary hyperparathyroidism relatively uncommon (Heath, 1989).

Cerebral and spinal symptoms

Diverse neuropsychiatric symptoms have been described including irritability, anxiety, personality changes, cognitive impairment, and psychosis (Tonner & Schlechte, 1993). There have been reports of parkinsonism, which improved after parathyroidectomy (Kovacs et al., 1993). Myelopathy may develop when osteoclastic lytic lesions or 'brown tumours' involve the vertebrae and compress the spinal cord (Ganesh et al., 1981; Daras et al., 1990). Compressive myelopathy from brown tumour also has been described in secondary hyperparathyroidism in association with renal disease (Bohlman et al., 1986)

Neuromuscular disease

Neuromuscular symptoms include proximal weakness, myalgia, muscle stiffness, and paresthesiae. About 2–4% of patients with florid primary hyperparathyroidism develop proximal muscle weakness and atrophy with normal muscle enzymes, myopathic features without fibrillations on electromyogram (EMG), and type 2 fibre atrophy on muscle biopsy (Patten et al., 1974). This myopathic syndrome may be even less common with modern earlier diagnosis of primary hyperparathyroidism (Turken et al., 1989). Parathyroidectomy relieves neurological and systemic symptoms in both mild and severe disease (Silverberg et al, 1999; Toft, 2000). A similar myopathic syndrome develops in secondary hyperparathyroidism (Mallette et al., 1975).

Hypoparathyroidism

Seizures and tetany, reflecting central and peripheral neuronal irritability, are classic clinical features (Shulian et al., 1984). Other cerebral manifestations include cognitive impairment, psychosis, and extrapyramidal syndromes. CT may reveal calcification, usually asymptomatic, in basal ganglia, cortex, brainstem or cerebellum (Illum & Dupont, 1985). Less common neurologic syndromes include sensorineural hearing loss, myopathy, and idiopathic intracranial hypertension (Tonner & Schlechte, 1993; Mor & Wysenbeek, 1988). Neuropsychiatric manifestations may not completely reverse with correction of hypocalcemia.

Neurological complications of adrenal disease

Hyperadrenalism (Cushing's syndrome)

Excessive amounts of adrenocortical hormones cause Cushing's syndrome, with its familiar somatic manifestations. Hypercortisolism may be exogenous, from glucocorticoid administration, or endogenous, from excessive pituitary ACTH secretion (Cushing's Disease), adrenal steroid secretion or ectopic adrenocorticotropic hormone secretion.

Cerebral symptoms

Affective disturbances, delirium, and acute psychosis, are common in Cushing's syndrome, and may antedate somatic signs and symptoms (Cohen, 1980, Kelly et al., 1996). Memory impairment is also common (Mauri et al., 1993). These neuropsychiatric manifestations resolve completely after effective endocrine therapy. Idiopathic intracranial hypertension has been described in association with Cushing's syndrome, particularly with steroid withdrawal in exogenous cases or after resection of a pituitary adenoma in Cushing's disease (Neville & Wilson, 1970; Parfitt et al., 1994).

Cranial nerve abnormalities

Over 90% of ACTH-secreting pituitary tumours are microadenomas (less than 1 cm in size), because the distinctive systemic features usually lead to early detection of the tumour (Shimon and Melmed, 1998). Patients with macroadenomas may develop bitemporal hemianopic or superior quadrantic visual field deficits from chiasmal compression or central or junctional scotomata from optic nerve compromise (Melen, 1987). Large tumours may invade the cavernous sinus, causing dysfunction of cranial nerves 3, 4, or 6. Transphenoidal surgery and modern pharmacological management have decreased the necessity for bilateral adrenalectomy. This procedure was complicated, in up to 30% of cases, by rapid expansion of the pituitary tumour (Nelson's syndrome), due to loss of corticosteroid inhibition (Miller & Crapo, 1993).

Spinal cord disorders

Patients with hypercortisolism occasionally develop compressive myelopathy due to epidural lipomatosis (Sivakumar et al. 1995). Epidural lipomatosis may also cause compressive radiculopathy or cauda equina syndrome (Lipson et al., 1980).

Neuromuscular disorders

By far the most common neuromuscular complication of hypercortisolism is myopathy. Fatigue and subjective weakness are common complaints, accompanied in many patients by true proximal weakness, or steroid myopathy (Anagnos et al., 1997). On physical exam, there is proximal atrophy and weakness beginning in hip and thigh muscles, and later in neck flexors and proximal arms. Tendon reflexes are usually preserved, and muscle enzymes are normal. The severity of weakness does not necessarily correlate with the degree of hypercortisolism. The EMG shows myopathic changes, but may be normal in mild cases. Typically, there is no suggestion of muscle fibre irritability, although complex repetitive discharges and increased insertional activity have been described (Lacomis et al., 1993; Olafsson et al., 1994). Muscle biopsy shows type 2 fibre atrophy, but these changes may also be seen in steroid-treated patients without clinical myopathy. Exercise training may partially prevent weakness in patients taking steroid therapy (Horber et al., 1985). Weakness usually improves when the steroid dose is reduced and complete recovery occurs within a few months after steroid levels return to normal.

Hypoadrenalism (Addison's disease)

Cerebral symptoms

Patients with adrenal failure are frequently fatigued or apathetic and personality changes are common (Werbel & Ober, 1993). Insomnia is common. Frank psychosis and dementia occur rarely and there can be a general enfeeblement of all mental processes. The electroencephalogram often shows lowered voltages and generalized slowing, which resolve after steroid therapy.

In acute or severe adrenal failure, delirium or seizures may develop, usually due to associated hypoglycemia, hyponatremia, or both. It has been observed that patients with Addison's disease have signs and symptoms of hypoglycemia at higher glucose levels than normal individuals. Untreated, delirium or confusion can rapidly progress to coma.

Idiopathic intracranial hypertension has been described in association with Addison's disease (Leggio et al., 1995; Condulis et al., 1997), as well as with steroid withdrawal in hypercortisolism (see above). Headaches are common even in the absence of increased intracranial pressure.

Spinal cord disorders

Adrenal insufficiency accompanying spastic paraparesis, or occurring in a patient with a family history of either adrenal or spinal cord disease, suggests a diagnosis of adrenoleukodystrophy or adrenomyeloneuropathy. These are genetic X-linked disorders (Moser, 1997). Adrenal insufficiency may precede neurologic manifestations and thus the diagnosis should be considered in young men with Addison's disease (Carey, 1997).

Neuromuscular disease

Occasional reports of Addison's disease and Guillain–Barré syndrome have appeared, but the association is probably coincidental (Abbas et al., 1977). Patients may note areas of decreased sensation or paresthesiae over hyperpigmented skin areas. Neuralgic pains in lumbar and epigastric regions are common, as are joint pains.

Hyperkalemic periodic paralysis develops in occasional patients and resembles familial hyperkalemic paralysis (Anagnos et al., 1997). Ascending paralysis evolves over several hours, often associated with paresthesiae, distal sensory loss, and areflexia. Acute respiratory failure may result. The clinical picture suggests a neuropathic, rather than myopathic mechanism, but electrophysiological studies are lacking. Acute treatment to lower serum potassium, including intravenous hydrocortisone, glucose and insulin, is necessary due to the danger of cardiac arrest.

Muscle cramps and stiffness may occur with adrenal insufficiency, but overt proximal weakness is uncommon. The clinical picture can resemble stiff-person syndrome, with painful muscle stiffness and reflex muscle spasms, mainly affecting the abdomen and legs in patients with Addison's disease (George et al., 1984). Stiff-person syndrome is associated with a variety of autoimmune endocrinopathies, including adrenalitis (McEvoy, 1991).

Hyperaldosteronism

The neurologic features of primary and secondary hyperaldosteronism are related to potassium depletion, alkalosis, and hypertension. Hypertension and headaches are common presenting features. Vertigo may be caused by abrupt fluid and electrolyte shifts. Tetany, due to alkalosis, and hypokalemic periodic paralysis occurs in about 20% of cases (Conn, 1963). Potassium depletion may also cause a necrotizing, vacuolar myopathy (Atsumi et al., 1979).

Phaeochromocytoma

The neurological complications of these tumours derived from chromaffin cells appear to result from high circulating levels of epinephrine and norepinephrine (Young, 1997). Most phaeochromocytomas develop sporadically, but they also occur in association with type 1 neurofibromatosis, von Hippel–Lindau disease, tuberous sclerosis, and Sturge–Weber syndrome (Werbel & Ober, 1995). Hypertension, either sustained or paroxysmal, is a feature in nearly all cases. Hypertensive paroxysms may be accompanied by headache or subarachnoid or parenchymal intracerebral hemorrhage (Redman et al., 1983). Other acute manifestations include hypertensive encephalopathy and seizures. Elevated catecholamines can cause exaggerated physiologic tremor, which is typically distal, high frequency (7–12 Hz), and most prominent with posture or movement.

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* denotes key references

(Key references are designated with an asterisk.)

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Neurological manifestations of hematological diseases

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Anemia

General issues

Anemia is present when the concentration of hemoglobin in the peripheral blood is below the normal range for the patient's age and sex (i.e. 14 ± 2 gm/dl for women, 16 ± 2 gm/dl for men and 12 ± 2 gm/dl for children). When anemia is present, the red blood cell population is usually reduced. The normal red blood cell count is $4.8 \pm 0.6 \times 10^6/mm^3$ for women and $5.4 \pm 0.9 \times 10^6/mm^3$ for men. The hematocrit indicates the proportion of red blood cells in the blood. Greater than 40% for men and 37% for women is considered normal. The major red blood cell indices, which may be helpful in the differential diagnosis of anemia are: the mean corpuscular volume (MCV) which is the average red blood cell size (normal is $87 \pm 5u^3$); the mean corpuscular hemoglobin (MCH) which is the amount of hemoglobin per cell (normal is 29 ± 2 pg of hemoglobin/cell); and the mean corpuscular hemoglobin concentration (MCHC) which is the average concentration of hemoglobin per cell (normal is $34 \pm 2\%$).

These erythrocyte indices may be useful but it should be emphasized that they are averages and complete evaluation requires microscopic examination of the peripheral blood smear which will reveal evidence of red blood cell size (macrocytosis, microcytosis) and shape as well as evidence of the degree of maturity of the red blood cells (i.e. presence of reticulocytes or nucleated cells), the intensity of hemoglobin staining (hypochromia, normochromia or hyperchromia), or the presence of macrocytes, target cells, spherocytes, schistocytes or other abnormally shaped cells. In some situations, automated analysis of erythrocyte indices may reveal normal range results, but direct observation of the peripheral blood smear shows evidence of a dimorphic anemia (e.g. iron deficiency plus megaloblastic anemia) in which some cells are clearly microcytic and hypochromic and others are macrocytic, accounting for the normal indices which reflect an automated average of the two abnormalities. No analysis of anemia is complete without a direct observation of the peripheral blood smear by an experienced observer

Neurological aspects of the anemias

Non-specific neurologic effects of anemia

There are very few neurological effects of anemia *per se*. Headache and lightheadedness may occur in severe anemias but these symptoms usually require that the hemoglobin concentration be reduced by at least one-half. In slowly developing anemias, many patients may have little or no neurological symptoms with hemoglobin concentrations as low as one-tenth normal. The most easily examinable part of the nervous system which reflects the effect of anemia itself is the eye. The retina, optic nerve head and their vascular supply are easily observed with the ophthalmoscope and probably reflect similar changes in the rest of the brain. The reddish colour of the fundus is the result of the light from the ophthalmoscope reflected by the choroidal blood altered to a pink colour by the pigment content of the retinal epithelium. As the hemoglobin concentration falls, the reddish colour of the fundus pales. The optic disc also becomes paler with a reduction in the colour contrast normally seen between arteries and veins.

Aside from pallor of the optic fundus, the most common ocular lesion in anemia is retinal hemorrhage, which is usually small and spindle shaped and occasionally associated with a cotton wool exudate. The presence of hemorrhage correlates with the degree of anemia. It is very unusual to see a retinal hemorrhage when the hemoglobin concentration is greater than 50% of normal. It is believed

that blood escapes from the capillaries by diapedesis and that the exudates are composed of fibrin. Both the hemorrhages and the exudates seen in anemia are transient. In severe anemia (i.e. hemoglobin concentration below 6 gm/dl) a minor degree of edema of the optic disc and adjoining retina may be observed. This is not too surprising since the oxygenation of the optic nerve head depends not only on local blood flow but also upon oxygen carrying capacity of the blood. The retinal vessels appear to be of different calibre than normal in anemic patients. The arteries are widened and the usual width relationship between arteries and veins of 2: 3 approaches 1: 1.

There have been rare reports of patients with moderately severe chronic anemia (i.e. hemoglobin less then 10 gm/dl) due to blood loss who presented with focal cerebral symptoms, which resolved upon transfusion. Whether the symptoms reflected an unmasking of underlying previously asymptomatic occlusive vascular disease is not clear, but it is certain that focal cerebral symptomatology is a very rare manifestation of anemia *per se*. Aside from these few general features, anemia itself has little neurological expression. The following sections review the specific neurologic effects of particular anemias, namely: iron deficiency anemia, megaloblastic anemias (B_{12} and folate deficiency) and hemoglobinopathies (sickle cell anemia and thalassemia).

Iron deficiency anemia

Iron deficiency from chronic blood loss remains the most common form of anemia. Iron deficiency in the absence of anemia (sideropenia) may decrease the deformability of red blood cells leading to ischemia in the distribution of small cerebral vessels. This mechanism is particularly important in the context of polycythemia (either primary or secondary) in which there are increased numbers of red blood cells each one of which may be iron deficient. Both the polycythemia and the relative sideropenia lead to increased blood viscosity with associated neurological symptoms and signs (see the section on hyperviscosity below). Iron deficiency causes a microcytic, hypochronic anemia.

Iron deficiency (usually but not always with anemia) is associated with obsessive–compulsive behaviours which fall into two categories: compulsive eating (pica) and compulsive moving of the limbs, usually the legs (restless legs). Common pica behaviours include the eating of starch, paint chips, clay (terra sigillata), earth (geophagia) and ice (pagophagia). The relationship between the iron deficiency and pica is unknown. It is clear that it does not represent replacement of iron since ice eating, the most common pica behaviour, usually does nothing in this regard and many clays contain substances that actually chelate iron, thereby worsening the problem. It seems more likely that pica represents some form of compulsive behaviour akin to a tic.

The restless legs syndrome is a very common cause of insomnia. It consists of an unpleasant creeping sensation which occurs deep in the legs (and occasionally in the arms), when the person is at rest. The person feels compelled to move the legs to avoid the unpleasant feeling. Most sufferers are women, who pace the floors at night, and complain of insomnia. Polysomnographic studies often reveal nocturnal myoclonus (periodic movements of sleep). It is likely that restless legs, nocturnal myoclonus and akathisia represent various fragments of a single disorder, sometimes called the Ekbom syndrome (Ekbom, 1970). It is known that the basal ganglia are rich in iron and that this may predispose to oxidative stress injury in these locations. Many of the movement disorders associated with iron deficiency anemia are reminiscent of those associated with basal ganglia diseases, but the precise relationship between systemic iron deficiency and these movement disorders is cryptic. Many such patients are iron deficient, as judged by serum iron, total iron binding capacity as well as serum and spinal fluid ferritin levels. In this case the symptoms respond to iron replacement. The rest are treated, usually very successfully, with benzodiazepines, L-dopa, pramipexole, clonidine, or clomipramine. When iron deficiency anemia is diagnosed, a search for blood loss should be initiated; including several tests of stool for occult blood.

Megaloblastic anemias

General issues

The term megaloblastic anemia refers to a characteristic pattern of morphological abnormality in the blood and bone marrow which probably arises from impaired DNA synthesis. Clinically, this is usually the result of a deficiency of one of two factors, cobalamin (vitamin B_{12}) or folic acid, both of which are essential to the formation of the deoxyribosyl precursors of DNA. This deficiency results in abnormal development of erythroblasts in the marrow such that there is intramedullary hemolysis resulting in anemia. The peripheral blood contains macrocytic erythrocytes. The disordered DNA metabolism also affects the maturation of granulocytes resulting in hypersegmented polymorphonuclear leukocytes in the peripheral blood.

This disordered DNA metabolism is clearly not confined to the blood cells, since giant epithelial cells are found in many other organs including the mouth, stomach and skin. The neurologic effects of the megaloblastic anemias are probably due to a primary metabolic derangement in neural tissue and are clearly not directly related to the anemia *per se*. Since the blood-forming organs are particularly sensitive to the effects of cobalamin or folate deficiency, it is unusual to find the neurologic effects in patients in whom no disorders of the blood are found. Anemia is, however, only one and probably a relatively late sign of cobalamin or folate deficiency, so it is possible to find a clear example of the neurologic effects of cobalamin or folate deficiency without anemia. It is distinctly rare, however, to find no hematological signs of cobalamin or folate deficiency in a patient with proved neurological effects of these vitamin deficiencies. Some patients of this kind have been reported, but the degree of completeness of the hematological evaluation or the precise nature of the neurological lesions is often questioned in analysing these rare case reports. Some of these cases may represent other forms of degenerative spinal cord disease in which the lateral and posterior column lesions are unassociated with vitamin B_{12} deficiency. Such may be seen with cervical spondylosis or with multiple sclerosis.

Cobalamin (vitamin B_{12}) deficiency

This may be due to a number of causes summarized as follows:

1. Defective diet (low in animal or bacterial products)
2. Defective absorption
   (a) Deficiency of intrinsic factor
      (i) Pernicious anemia
      (ii) Gastrectomy
   (b) Intestinal disease
      (i) Malabsorption (sprue; resection, bypass or disease of terminal ileum)
      (ii) Blind loop syndrome
      (iii) Fish tapeworm infestation
3. Deranged metabolism or increased requirement (thyrotoxicosis, pregnancy, neoplasia).

Of these, the most prevalent form of cobalamin deficiency is pernicious anemia (or Addisonian anemia, Biermer's anemia, Primary anemia). It arises from failure of the gastric fundus to secrete adequate amounts of intrinsic factor to insure intestinal absorption of vitamin B_{12}. This failure of secretion of the mucoprotein intrinsic factor is due to atrophy of the fundic glandular mucosa, a process which is usually an immune-mediated gastritis, but may be familial or result from gastric neoplasia. Patients with autoimmune pernicious anemia often have anti-intrinsic factor and antiparietal cell antibodies as well as clinical and laboratory evidence of other conditions characterized by autoimmunity such as vitiligo and thyroiditis. Serum B_{12} levels have occasionally been measured to be erroneously normal in documented cases so it is now routine to assess intracellular function by directly measuring serum homocysteine and methylmalonic acid (Toh et al., 1997). Cobalamin (vitamin B_{12} or extrinsic factor) exists in two forms, methylcobalamin and adenosylcobalamin, each of which acts as an important cofactor in reactions vital to cellular function. The methylcobalamin system acts to transfer methyl groups from methyltetrahydrofolate to homocysteine, thereby creating tetrahydrofolate, which is required for DNA synthesis, and methionine. Failure of this system results in impaired DNA synthesis and accumulation of homocysteine. Nitrous oxide, an inhibitor of methyl transferase, causes the syndrome of subacute combined degeneration of the nervous system, a fact which argues that DNA synthesis failure can cause neurological disease even though neurons are postmitotic and therefore are themselves resistant to such a toxin. It is likely that this toxicity acts on oligodendrocytes, resulting in the demylinating lesion that is characteristic of subacute combined degeneration. Acute exposure to nitrous oxide in the form of general anesthesia may precipitate acute deterioration (anesthesia paresthetica) in patients with an otherwise mild or asymptomatic case of cobalamin deficiency (Kinsella & Green, 1995).

The adenosyl cobalamin system acts to metabolize propionic acid by converting methylmalonyl CoA to succinyl CoA which then enters the Krebs cycle. Failure of this system results in an accumulation of methylmalonic acid which is toxic to the nervous system by promoting the formation of long chain fatty acids with odd numbers of carbon atoms. Normal long chain fatty acids that contain even numbers of carbon atoms, are formed using malonic acid. Thus, when methylmalonic acid replaces malonic acid, an extra methyl group leads to odd numbers of carbon atoms and an unstable myelin.

Thus, serum homocysteine and methylmalonic acid levels are elevated when there is intracellular failure of the two cobalamin related chemical reactions, making measurement of these levels the most sensitive test for vitamin B_{12} deficiency.

Since vitamin B_{12} is stored in various tissue in large amounts, the appearance of cobalamin deficiency after the cessation of B_{12} absorption or intake is delayed by at least 3 years. Despite the fact that pernicious anemia is the most common cause of cobalamin deficiency, it seems clear that vitamin B_{12} deficiency of any of the above listed causes may

result in the identical clinical picture. The three neurologic manifestations of vitamin B_{12} deficiency are subacute combined degeneration of the spinal cord, mental changes and optic neuropathy.

Subacute combined degeneration of the spinal cord (or subacute combined sclerosis, posterolateral sclerosis)

This is the term used to designate the spinal cord disease due to cobalamin deficiency. The inaccurate term 'combined systems disease' should be avoided. The patients tend to complain of generalized weakness and paresthesias which usually begin distally in the arms. As these symptoms progress, stiffness and weakness in the limbs develops. Loss of vibration sense is the most profound sign often joined later in the course by joint position sense loss as well. The Romberg sign is positive and the gait is unsteady and awkward primarily because of propriceptive loss (pseudotabetic gait). Weakness and spasticity are usually worse in the legs than the arms and may progress to a spastic paraplegia if untreated. Babinski signs are present, but the deep tendon reflexes are variable. They may be grossly increased with clonus, absent, or show any intermediate degree of activity. If a sensory level is found on the trunk implicating the spinothalamic tracts, this should always be viewed with the greatest scepticism and lead one to exhaustively exclude other causes of spinal cord disease. All of the findings of pure vitamin B_{12} deficiency may be attributable to myelopathy alone and there is no convincing evidence that B_{12} deficiency itself causes a neuropathy. However, in practice, the frequent concomitant existence of folate and other vitamin deficiencies, makes it difficult to be sure of this point. Many patients with vitamin B_{12} deficiency have distal symmetrical impairment of cutaneous sensation, absent deep tendon reflexes and even slowed nerve conduction velocities suggesting a neuropathic component. This is probably due to concomitant folate deficiency, but the outside chance that vitamin B_{12} deficiency itself may cause a peripheral neuropathy cannot be rigorously excluded. Pathologically the lesion in the nervous system is a degeneration of white matter in the spinal cord and occasionally the brain. The myelin sheaths and axis cylinders are both involved, the former more profoundly than the latter. These changes begin in the posterior columns of the lower cervical and upper thoracic segments and spread from there up and down and also laterally in the cord to involve the lateral columns. This pathology can often be visualized using magnetic resonance imaging in which a bright lesion can be seen on T_2-weighted images. On microscopic study, early changes consist of swelling and destruction of myelin sheath with subsequent axonal destruction. Later, a cribriform appearance develops. Eventually, white matter is lost and is replaced by gliosis. The focal lesions have a rough but not absolute symmetry, and they extend caudally and rostrally so that ultimately the entire area of the dorsal columns is involved. In the meantime, the lesions have begun in the lateral columns and extend into the other long tracts. The grey matter is spared. Similar changes can be seen in the cerebral hemispheres and optic nerves. The myelin of peripheral nerves may also be involved but axons have not been shown to be unequivocally affected.

Mental changes

These are frequent in patients with vitamin B_{12} deficiency. In most cases these changes reflect abnormalities in level of consciousness with inattention, confusion, somnolence, apathy and delirium being the cardinal features. True dementia, defined as intellectual impairment in the absence of a disorder of level of consciousness, is certainly a relatively rare manifestation of pure vitamin B_{12} deficiency. Pure mental change as the only manifestation of vitamin B_{12} deficiency is exquisitely uncommon. Case reports of true dementia and pure mental change as manifestations of vitamin B_{12} deficiency are contaminated with concomitant causes of dementia and disordered mental status.

Optic neuropathy

This is the third and last major neurologic complication of vitamin B_{12} deficiency. It is characterized by bilateral involvement of the optic nerves resulting in loss of central visual acuity and depressed sensitivity greater for colour than for white in the centrocecal area of the field of vision. This is the rarest of the three neurologic manifestations of vitamin B_{12} deficiency, but may be the only or presenting manifestation of the syndrome. It may be subclinically present in many more cases than previously believed if one uses a very sensitive measurement of optic nerve function such as visual evoked responses. This syndrome is clinically similar to a number of other bilateral optic neuropathy syndromes including the so-called tobacco–alcohol amblyopia, diabetic optic neuritis, Leber's hereditary optic atrophy, and tropical ataxic neuropathy. Some feel that the etiology of all of these syndromes including vitamin B_{12} deficiency optic neuropathy is linked to an abnormality in cyanide metabolism due to a shortage of sulfur donating amino acids. In recent years there was an epidemic of optic neuropathy and myelopathy in Cuba, which was thought to be due to multiple B vitamin deficiency due to malnutrition combined with alcohol and cyanide from cigar smoking and cassava consumption. The epidemic was

terminated by vitamin supplementation (Roman, 1995.) The suspicion that people who became symptomatic in the face of severe vitamin malnutrition harboured an otherwise asymptomatic mutation in the mitochondrial genome akin to the one known to cause Leber's hereditary optic neuropathy is interesting but has not been demonstrated.

Folic acid (folate)

This deficiency accounts for nearly all of the cases of megaloblastic anemia not due to vitamin B_{12} deficiency. The causes of folate deficiency may be summarized as follows:

1. defective diet (low in vegetables and liver)
2. defective absorption
   (a) intestinal malabsorption (sprue; steatorrhea, massive diverticulosis, short circuits of gastrointestinal tract).
   (b) 'blind loop' syndrome
3. deranged metabolism
   (a) increased requirement (hemolytic anemia, pregnancy, neoplasia).
   (b) impaired utilization (liver disease, administration of folic acid antagonists or anticonvulsants).

Unlike vitamin B_{12}, the bodily stores of folic acid are quite limited. A folate deficiency syndrome may commence within several months of dietary deprivation, making it a much more common problem among the malnourished than is vitamin B_{12} deficiency. Folate, once absorbed through the entire small intestine, is reduced by specific liver enzymes to tetrahydrofolic acid, a compound that plays a major role in the metabolism of one-carbon fragments by its synthesis and transfer of methyl groups. Via this mechanism folate is vital for the conversion of deoxyuridate to thymidylate, a precursor needed for DNA synthesis. Thus, tetrahydrofolate derivations are closely linked to vitamin B_{12}-dependent reactions, and the hematologic alterations in vitamin B_{12} and folate deficiency are indistinguishable. Deficiencies of the two vitamins have very similar effects and a deficiency of one may lead to faulty utilization of the other. For example, patients with vitamin B_{12} deficiency may have an initially elevated serum folate, which will plummet rapidly when vitamin B_{12} is administered, thus requiring concomitant treatment with folate lest a folate deficiency state, previously masked by the vitamin B_{12} deficiency, should become clinically significant. Many patients with vitamin B_{12} deficiency have concomitant folate deficiency, but the vast majority of those with the overwhelmingly more common folate deficiency state will have no vitamin B_{12} deficiency. Folic acid deficiency is almost never pure. Since it accompanies malnutrition it is nearly always associated with multiple vitamin deficiencies. The most common neurological manifestation of this multivitamin deficiency state is a polyneuropathy.

The symptomatology of nutritional polyneuropathy includes distal paresthesias, burning and weakness. On examination, there is a distal loss of reflexes and sensation. The essential pathological change is an axonal degeneration with 'dying-back' of the axons according to length. Some minor degrees of segmental demyelination may also occur usually due to entrapment of metabolically weakened nerves. The common entrapment neuropathies (e.g. carpal tunnel syndrome; meralgia paresthetica; peroneal palsy; ulnar palsy) are all more frequent in patients with an underlying metabolic axonopathy such as that due to vitamin deficiency. In circumstances in which the major vitamin deficiency is likely to be folic acid (i.e. when folate antagonists have been given), a mild polyneuropathy of the type described above occurs but even in these patients, the concomitant existence of other vitamin deficiency and/or neurotoxic substances cannot be rigorously excluded. Folate is important to normal nervous system development in that folate deficiency during pregnancy heightens the risk of neural tube disorders in the fetus.

Hemoglobinopathies and thalassemia

General issues

In normal people, variations in the concentrations of the three normal varieties of hemoglobin (A, A_2 and F) are known to take place with maturation. Disorders in which the presence of a structurally abnormal hemoglobin is considered to play a primary pathological role are referred to as hemoglobinopathies. Disturbances involving alterations in the percentages of normal forms of hemoglobin are designated by individual terms, such as thalassemia. Hemoglobin consists of four coiled polypeptide chains. The four chains are of two varieties so that two of each type are present. There are four normal polypeptide sequences designated alpha, beta, gamma and delta. Hemoglobin A consists of two alpha and two beta chains designated $\alpha_2\beta_2$. HbA_2 consists of $\alpha_2\delta_2$ and HbF consists of $\alpha_2\gamma_2$. Several mechanisms that result in abnormal hemoglobin are known. Many examples of abnormal hemoglobins have been defined in which a single amino acid substitution has occurred in one of the two pairs of polypeptide chains. Other abnormal hemoglobins result from crossing over of the adjacent structural genes for the beta, gamma and delta polypeptides. Hemoglobins consisting of a single

variety of polypeptide rather than the normal two have been described, and abnormalities resulting in the switch from fetal to adult hemoglobin are known. Finally, abnormalities in the mechanism controlling the rate of release or synthesis of various polypeptide chains are thought to result in the thalassemia group of disorders. Most of the abnormal hemoglobins cause no hematologic difficulty. However, some diseases are directly attributable to changes in hemoglobin structure which lead to a variety of steric changes in the molecule. Sickle hemoglobin forms insoluble polymers when deoxygenated; the HbM variants lead to excessive levels of methemoglobin. HgM combines irreversibly with oxygen while other types such as HbQ are easily denatured and precipitate within the erythrocytes to form Heinz bodies.

A person homozygous for a structural mutation involving one of the polypeptide chains of HbA will produce only a single abnormal adult variety of hemoglobin. Three examples of such a disease are HbS, HbC, and HbE. Of these, the most important is HbS which causes sickle cell anemia. HbC and HbE diseases are generally mild and have no known neurologic complications.

Sickle cell anemia (HbS disease)

Most of the manifestations of sickle cell anemia are related to the characteristic property of HbS to crystalize under conditions of reduced oxygen tension. This leads to sickled erythrocytes becoming trapped in terminal arterioles and capillaries which results in more hypoxia, increased sickling, thrombosis and infarction. Tissues that normally contain blood at low oxygen tensions such as renal medulla and pulmonary arterioles are at greatest risk but sickling may occur in other organs including the relatively well oxygenated brain and spinal cord. The hemolysis results largely from the fact that the sickled erythrocytes are mechanically rigid, less flexible and more fragile than normal cells.

The neurological complications of sickle cell anemia may be divided into four categories: painful crises, vascular disease, infection and fat embolism.

Painful crises are among the most common clinical problems in the management of patients with sickle cell anemia. The abdominal and bone pain so common in this disease is probably ischemic pain related to the sickling phenomenon as described above. The treatment consists of hydration, bed rest and analgesia.

Vascular disease is the more serious neurological aspect of this disorder and probably contributes in a major way to the decreased life expectancy in patients with sickle cell anemia. The prevalence of overt strokes is about 20% among patients with sickle cell anemia, obviously a massive increase over other patients of similar age. Most of the strokes are due to small vessel occlusions, often resulting in seizures at the onset of the stroke. In some cases, progressive small vessel occlusions with recurrent development of collaterals can lead to a bizarre angiographic picture similar to that seen in moyamoya disease. Hemorrhages may occur due to rupture of these fragile collateral vessels leading to intracerebral, subarachnoid, spinal and retinal hemorrhagic strokes in patients with sickle cell disease. The progressive stenosis of the supraclinoid internal carotid artery that leads to the development of the moyamoya pattern may be detected non-invasively using transcranial Doppler ultrasound (Adams et al., 1997). Stroke risk is reduced dramatically using prophylactic transfusions in patients in whom transcranial Doppler examinations show the time-averaged mean blood velocity in the internal carotid or middle cerebral artery is 200cm per second or higher (Adams et al., 1998). Among children under the age of 15 years, sickle cell anemia is present in 7% of patients with strokes making it an important cause of stroke in childhood. Spinal cord infarction is also seen in patients with sickle cell anemia much more commonly than in the general population. Massive intracranial hemorrhage is a rare but devastating complication of sickle cell anemia. However, most of the literature comes from the pre-CT scan era and it is not clear whether the incidence of intracranial hemorrhage in patients with sickle cell anemia is higher than a matched control population. Large vessel occlusions have also been reported to occur in patients with sickle cell anemia. The supraclinoid carotid has been the site of predeliction. The mechanism for large vessel disease in this circumstance is unclear. Some believe that a hyperdynamic circulation leads to endothelial damage. Others hold that chronic stasis leads to diminished blood volume and thrombosis while others have postulated that sickled erythrocytes occlude the vasa vasorum of large vessels that causes ischemic damage to the vessel wall leading to thrombosis. The moyamoya phenomenon may be treated with extracranial – intracranial arterial bypass grafting or with temporal-pial synangiosis, hoping to reduce the likelihood of rupture of the fragile moyamoya vessels.

Sepsis is the most common cause of death in patients with sickle cell anemia and bacterial infection is the reason for as many as one-half of all hospitalizations in these patients. Of all the infections, meningitis is particularly important accounting for 20% of the deaths from sepsis. Some older children and adults with meningitis have been reported but most of the patients are under three years of age. *S. pneumonia* is an unusually common organism in these patients accounting for about three-quarters of the

cases of meningitis most of whom were patients under three years old, whereas, other children in this age group with meningitis tended to show *H. influenza* type B as the leading cause of infection. This group of patients have a peculiarly malignant course often leading to death within a few hours. Recurrent meningitis seems also to be unusually common in these patients. The unusual susceptibility of patients with sickle cell anemia to infection is not totally understood, but the factors which are believed to be most important include their functional asplenia and an opsonizing defect which causes leukocyte malfunction.

Fat embolism in sickle cell anemia patients occurs with higher than expected frequency and the brain is involved in greater than 80% of the patients in whom it is examined. Bone pain, fever and changes in mental status, are the major presenting features. Treatment is controversial but most advocate systemic anticoagulation and exchange transfusion.

Heterozygous hemoglobin states and complex hemoglobin combinations

Only the presence of some amount of HbS leads to the risk of a neurologic problem. Sickle cell trait is occasionally associated with neurologic complications especially when patients at risk are exposed to an extremely low oxygen tension (e.g. high altitude flying, anesthesia). The HbSC; HbSD; HbSF; and HbS-thalassemia syndromes are all situations in which there is a risk of neurological complications similar to those mentioned above for homozygous HbS disease. However, there are fewer neurological problems in these combined hemoglobin disorders than in the pure sickle cell disease.

Thalassemia

The genetic defect underlying thalassemia involves rates of synthesis of the individual polypeptide chains. Two major varieties of thalassemia exist: one involving defective alpha chain synthesis, the other involving beta chain synthesis. The more common beta-thalassemia may occur in the heterozygous or homozygous form to produce the syndromes of thalassemia trait or Cooley's anemia (thalassemia major) respectively. Heterozygosity for alpha thalassemia results in a very mild condition and may require an associated hemoglobin abnormality for clinical expression (thalassemia minor). Homozygous alpha thalassemia is thought to be incompatible with normal fetal development. The neurologic dysfunction seen in the thalassemias may be divided into three distinct categories: meningitis following splenectomy (discussed above under sickle cell anemia), spinal cord compression due to extramedullary hematopoiesis, and a mixed group of neuromuscular disorders.

The susceptibility to infection seen in thalassemia corresponds to that seen in sickle cell anemia, but is confined to those patients who have undergone splenectomy for control of their hemolysis.

About a third of patients with myelopathy due to extramedullary hematopoiesis have thalassemia as their underlying disease. When extramedullary hematopoiesis exists in the presence of a hemolytic anemia, it is believed to be produced as a compensatory mechanism by totipotential cells in various locations. The usual location for extramedullary hematopoiesis is various parts of the reticuloendothelial system, particularly the liver, spleen and lymph nodes. However, the spinal epidural space, and rarely the intracranial subdural space, may be involved with consequent compression of the spinal cord, and/or brain. Nearly all spinal cases have involved the thoracic spinal segments posteriorly, usually over multiple levels and treatment with surgical decompression and/or radiotherapy has lead to dramatic and sometimes prolonged remissions of myelopathic symptoms and signs.

In addition to the complications of infection and extramedullary hematopoiesis, a large number of other less well defined syndromes may exist in thalassemia. Logethetis and colleagues reported on 138 patients from their own experience with thalassemia major. Twenty per cent had transient episodes of dizziness, blurred vision and fainting, which improved following transfusion. Two strokes occurred. One had convulsions followed by an acute transient hemiparesis four days following splenectomy, and the other had headaches and visual blurring followed by a right hemiparesis two days after a transfusion. Major motor seizures were observed in 7%, and 49% had absent or diminished deep tendon reflexes. Muscular wasting was prominent in 23%, muscle cramps in 4% and muscle wasting in 32%. Nineteen per cent had a myopathic syndrome, eleven of which had a myopathic electrophysiologic study. The possible pathophysiological mechanism for this myopathic syndrome is totally unexplained.

Myeloproliferative disorders

The myeloproliferative disorders include polycythemia rubra vera, myelofibrosis with myeloid metaplasia, chronic myelogenous leukemia, and essential thrombocythemia. The proliferation in all of these diseases originates in the bone marrow or in the liver or spleen where extramedullary

blood formation may occur. The growth is self-perpetuating and involves all cell lines although in each syndrome one line may predominate. This proliferation may be confined to a single cell form or may involve several different strains of cells simultaneously or at separate times. Since overlap syndromes occur so frequently, precise diagnosis in a given patient is often difficult and perhaps fruitless.

The neurological manifestations of these conditions depend primarily on the tendency to thrombosis, hyperviscosity or the effects of extramedullary hematopoiesis.

Strokes are the most common neurologic complication seen in polycythemia vera occurring in 15–32% of the patients. As many as 15% of patients with polycythemia vera die of a stroke, five times that of an age-matched control population. Headache which occurs in nearly half the patients and dizziness and vertigo, which occurs in about a third of the patients, are the most frequent neurologic symptoms.

Several cases of sudden unilateral or bilateral chorea have been described. Pathogenesis is presumed to be vascular, but the precise location of the lesions has been variable in different case reports; most involve the subthalamic nuclei, cerebral cortex and corpus striatum bilaterally in various combinations.

Extramedullary hematopoiesis is a common manifestation of the myeloproliferative disorders but neurologic complications due to extramedullary hematopoiesis are rare. A few cases of intracranial dura matter involvement by extramedullary hematopoiesis have been recorded, but all were asymptomatic and only found incidentally at autopsy or by imaging techniques. About half of the cases of extramedullary hematopoiesis are associated with a myeloproliferative disorder; the rest secondary to various hemolytic anemias, the most frequent of which was thalassemia.

Polycythemia may rarely be due to an erythropoietin-secreting cerebellar hemangioblastoma.

Hemorrhagic diathesis

Hemophilia

This may be defined as an inherited hemorrhagic diathesis, characterized by impairment of the first stage of coagulation, the production of thromboplastin from the interaction of platelets and three or more plasma factors. Among the factors necessary for thromplastin formation are antihemophiliac globulin (AHG, or Factor VIII), plasma thromboplastin component (PTC or Factor IX or Christmas factor) and plasma thromboplastin antecedent (PTA or Factor XI). Factor VIII deficiency is responsible for 75–90%, Factor IX deficiency for 10–20% and Factor XI deficiency for 1–5% of hemophiliacs. Factor VIII and IX deficienty are X-linked recessive disorders and therefore are seen almost exclusively in males. Factor XI deficiency is inherited as an autosomal dominant trait and is thus seen equally in men and women, primarily of Ashkenazy Jewish descent. It is now possible to determine specifically the deficient factor in the patient's plasma and, with the exceptions of hemophiliacs who have circulating antibodies to specific factors, produce normal hemostasis by factor replacement. One may classify the hemorrhagic diathesis as mild (7–15% of normal factor levels), moderate 1–6%, and severe (<1%). Neurologic complications of hemophilia may be divided into those affecting the peripheral nervous system and those affecting the central nervous system.

Peripheral nervous system complications of hemophilia

The major problem with respect to the peripheral nervous system results from intramuscular hemorrhages which may expand muscle tissue or extend into fascial planes and compress peripheral nerves. This most commonly occurs with the femoral or ulnar nerves but cases involving the sciatic, peroneal, median and even facial nerves have been reported. Actual intraneural hemorrhages have been postulated but never proved. Most patients with peripheral nerve compressions may be managed with factor replacement alone, but some may require fasciotomy as well.

Central nervous system complications of hemophilia

Intracranial hemorrhage is becoming increasingly common in patients with hemophilia possibly because of the more active lives permitted by vigorous replacement therapy for intra-articular hemorrhages. Intracranial hemorrhage is an important cause of death in hemophiliacs, possibly the largest hemophilia-related mortality factor other than AIDS. Bleeding may be intracerebral, subarachnoid, subdural and epidural. Before 1970, the mortality rate from intracranial bleeding was 70%. It is now about 30%. In mild cases (7–15% of normal factor levels), intracranial bleeding only occurs after significant trauma. Patients with moderate cases (1–6%) require only minor trauma and severe cases (<1% normal levels) no trauma at all. The best method for accurate diagnosis of intracranial hemorrhage in this setting is the CT scan or MRI.

Subarachnoid hemorrhage may be treated successfully with factor replacement alone, although a ventricular catheter may be required to treat hydrocephalus.

Subdural, and epidural hemorrhages will usually not respond to factor replacement alone and ordinarily require surgical therapy. Surgical evacuation of the hematoma may be safely accomplished after factor replacement. Intracerebral hemorrhages are the most difficult to treat. Some patients have been successfully managed with medical therapy alone or with medical therapy plus a ventricular cannula for measurement and control of intracranial pressure. However, if the hematoma is accessible, surgical resection may lead to higher rates of recovery. General guidelines for the management of head trauma in hemophiliacs are as follows. In patients with mild head trauma and a normal neurologic examination, one would suggest factor infusion to a measured post-infusion level of 70% of normal. In patients with more severe head trauma and/or abnormal neurologic examination, an emergency CT scan should be obtained. If normal, then 48 hours of 30–70% factor levels should be maintained by factor infusion. If the CT scan shows a hemorrhage, then factor infusions should continue for 7–10 days after the bleeding has stopped or 14 days after the neurosurgical procedure, whichever is longer.

Thrombocytopenia and other purpuras

Thrombocytopenia is usually an acquired reduction in the number of platelets due to either diminished production or increased peripheral destruction. Thrombocytopenia due to diminished production is seen from drug effects on the bone marrow, myelophthisic phenomena and ineffective thrombopoiesis. Thrombocytopenia due to increased peripheral destruction of platelets may be due to mechanical factors such as a prosthetic device or vasculitis, disseminated intravascular coagulation, or thrombotic thrombocytopenic purpura. Thrombocytopenia not of mechanical origin but due to peripheral destruction of platelets has been called immune thrombocytopenic purpura. Immune thrombocytopenic purpura may be subdivided into the secondary forms due to drugs (e.g. heparin induced thrombocytopenia), virus, lymphoproliferative disorders and collagen vascular diseases and the primary or idiopathic thrombocytopenic purpura (ITP). Splenomegaly, while it does not shorten platelet lifespan, increases the size of the sequestered platelet pool and causes thrombocytopenia.

The neurologic complications of thrombocytopenia revolve around intracranial bleeding, the severity and frequency of which is dependent on the severity of the thrombocytopenia rather than the underlying diseases. There are a few exceptions to this rule in which the underlying disease affects the neurological picture apart from the thrombocytopenia itself. Those are: lupus erythematosus, thrombotic thrombocytopenic purpura (see succeeding section in this chapter) and leukemia, in which the leukemic infiltrates in the brain add to the tendency for intracranial hemorrhage.

The incidence of intracranial bleeding in thrombocytopenia is substantial ranging to as high as 26% in older work to figures around 1.5% in more recent surveys. This wide variation is partly due to improvement in treatment, but also reflects the definition of cases said to have intracranial hemorrhage. The more recent surveys generally refer only to true intracerebral hemorrhage and exclude cases in which hemorrhagic spinal fluid is found in the absence of signs of an intraparenchymal hemorrhage. The CT scan has now made this an easy differential point, since only large intracerebral hemorrhages would be seen by this technique whereas episodes of brain purpura (see below) with hemorrhagic spinal fluid would not likely yield a positive CT scan. Intracerebral hemorrhage is one of the most common causes of death directly attributable to thrombocytopenia.

Intracranial bleeding in thrombocytopenia can be in the form of multiple small punctate or petechial hemorrhages due to capillary bleeding. This ‘brain purpura’ consists of small ring-shaped hemorrhages in both the grey and white matter of the brain. The basic pathophysiology of cerebral hemorrhage in thrombocytopenia is probably capillary bleeding which may become confluent with continued bleeding in severe cases, leading to frank intracerebral hemorrhages. This intracerebral source of bleeding probably explains the sparsity of subdural, subarachnoid and epidural hematomas seen in the thrombocytopenias compared with the frequency of intracerebral hemorrhages. Peripheral nerve involvement with hemorrhage and spinal cord hemorrhage are both rare in the thrombocytopenias. The symptom complex associated with ‘brain purpura’ is not known. It is probable that most of these petechiae are asymptomatic.

Treatment depends on the etiology of the thrombocytopenia. Platelet transfusions are useful in situations in which decreased production is the difficulty. When increased platelet destruction or splenic sequestration is an important factor, therapy may require splenectomy, corticosteroids, intravenous immunoglobulin (IVIg) and platelet transfusions. In the presence of central nervous system bleeding, corticosteroids, IVIg and platelet transfusions may be administered. Emergency splenectomy has been advocated when intracerebral hemorrhage is suspected in a patient with immune thrombocytopenia even before a full evaluation of the intracerebral hemorrhage is carried out. This should be accompanied by corticosteroid

and platelet administration followed by neurosurgical evacuation of the hemorrhage if technically possible. The efficacy of IVIg, which can transiently raise the platelet count in patients with ITP, may alter this practice. When heparin-induced thrombocytopenia is recognized, the patient is switched to another drug, such as danaparoid or hirudin. In the case of the heparin-induced thrombocytopenia (HIT), there are antibodies (usually IgG) directed against a complex of heparin and platelet proteins (usually platelet factor 4) which activate platelets resulting in thrombocytopenia and thrombosis (Warkentin et al., 1998). Thus, the neurological consequences of HIT are thrombotic rather hemorrhagic. Low molecular weight heparin is usually ineffective.

Thrombotic thrombocytopenic purpura (Moschcowitz disease)

This is usually considered a triad of thrombocytopenic purpura, hemolytic anemia and neurological manifestations. Fever and evidence of renal disease are also almost invariably present. The diagnosis requires histological demonstration of the characteristic pathological lesion consisting of widespread hyaline occlusion of terminal arterioles and capillaries. This can be accomplished using many tissues, the most accessible of which are lymph node, bone marrow, skin and spleen. The blood smear often shows a microangiopathic hemolytic anemia. The most important pathological changes in the nervous system are a striking increase in the cellularity of the walls of arterioles and capillaries and platelet thrombi associated with multiple small foci of parenchymal necrosis and petechial hemorrhages. These changes are identical to those seen in other organs and thus are considered part of a systemic disease. Grey matter is affected to a greater extent than white matter. The neurologic manifestations of the disease reflect the widespread grey matter involvement. The most common are headache, mental change including altered states of consciousness, agitation, confusion, delirium, hemiparesis, aphasia, syncope, visual changes, dysarthria, seizures, coma, cranial nerve palsies, paresthesias and vertigo.

The pathogenesis of thrombotic thrombocytopenic purpura remains obscure. Multiple theories including toxins, drug sensitivity, bacterial infections, autoimmune reactions, collagen disease, abnormality of serum lipids, intravascular thrombosis and hemolysis as related to intravascular thrombosis all have been postulated. At present most arguments favour an immunologically mediated phenomenon. The disorder has occurred in association with an immune response (triggered by vaccination, medication or infection) often in the setting of certain autoimmune disease such as systemic lupus erythematosus. Subnormal levels of serum complement and immunoglobulins in the vascular lesions, elevated levels of platelet bound immunoglobulins and the presence in serum of antibodies directed against fragments of Von Willebrand factor have been reported. The hemolytic uremic syndrome, a childhood disorder similar in many respects to thrombotic thrombocytopenic purpura may be triggered by immune complexes. The same can be said for the HELLP (hemolytic anemia, elevated liver function tests, low platelets) syndrome seen in peripartum patients. Exchange transfusion has been reported to dramatically reverse the syndrome. It has also been noted that remission can be induced with fresh frozen plasma but not albumen. If there were an unusual class of immune complex active against vascular tissue and perhaps platelets which provoked thrombotic thrombocytopenic purpura, this would explain the effectiveness of exchange transfusions. Furthermore, normal plasma might promote clearing of these presumptive immune complexes if, fortuitously, it contained an antibody with high affinity for their antigenic component. These postulated immune complexes have, however, not yet been identified. Other treatments for thrombotic thrombocytopenic purpura have included heparin, antiplatelet agents, corticosteroids, dextran and splenectomy, all aimed at various parts of the syndrome. The prognosis is poor and mortality in most series is about 50% though better results have been reported in groups using exchange transfusions with whole blood or plasmapheresis.

Hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu disease)

This is an autosomal dominant disease involving several systems. The neurological manifestations may be produced by vascular malformations of the central nervous system or by complications of pulmonary arteriovenous malformations.

Pulmonary arteriovenous malformations are the most common large visceral vascular anomalies in hereditary hemorrhagic telangiectasia. Several mechanisms may cause the development of neurogenic symptoms: erythrocytosis may induce cerebral thrombosis; cerebral air embolism may follow hemoptysis; thrombosis may develop in the pulmonary malformation with subsequent cerebral embolism and the right to left extracardiac shunt, which allows bacteria and septic microemboli to bypass the pulmonary filter, predisposes to the development of brain abscess. Multiple and

solitary abscesses have been described as occurring anywhere in the brain.

In addition, the brain, spinal cord or meninges may be the site of telangiectasias or larger vascular malformation. Seizures, headaches, progressive neurologic deficits or spontaneous subarachnoid or intracerebral hemorrhage are the typical clinical presentations.

Henoch–Schonlein (allergic or anaphylactoid) purpura

This is characterized by serosanguinous effusions into the subcutaneous submucous and subserous tissues. The pathogenesis of the disorder is obscure but much indirect evidence suggests an allergic etiology. The disorder is most common in children and young adults. The skin lesions are variable in appearance but the purpura is usually associated with one of the manifestations of allergy such as erythema or urticaria. Effusions into joints or viscera may produce various localized symptoms such as joint pain or abdominal pain. Involvement of the nervous system is rare, but cerebral hemorrhages and peripheral nerve involvement have been reported. Treatment is largely symptomatic. Corticosteroids have been used but with questionable success.

Disseminated intravascular coagulation (DIC)

This is a relatively common acquired hemorrhagic thrombotic syndrome, which occurs as a result of the presence of thrombin in the systemic circulation. The syndrome follows other disease states such as viral infections, bacterial infections, obstetrical and surgical complications, neoplasms, fat embolism, diabetic ketoacidosis, head injury and others. DIC causes thrombosis and bleeding at multiple sites including the nervous system. The essential neuropathologic changes are multiple infarctions, petechial hemorrhages, and occasional small subdural and subarachnoid hemorrhages. Fibrin thrombi are found in the cerebral vessels. The clinical syndrome depends upon the particular pathology but may include seizures, mental changes and focal findings. Most patients with DIC show xanthochromic cerebrospinal fluid and angiographic abnormalities consistent with multiple small vessel occlusions. The treatment of subacute or chronic DIC with heparin has been effective, particularly in patients with thrombotic complications. However, no specific treatment apart from removal of the underlying cause (e.g. evacuation of the uterus in cases of abruptio placentae) is useful in acute DIC (also see section on hypercoagulable states related to underlying malignancy).

Anticoagulants

Hypoprothrombinemia is a common cause of clinical bleeding. The rare causes include congenital (vitamin K resistant) and idiopathic (vitamin K responsive) hypoprothrombinemia, hemorrhagic disease of the newborn as yet unable to provide its own vitamin K; diseases that interfere with vitamin K absorption (e.g. sprue, steatorrhea, surgical resection); disorders that interfere with bile access to the vitamin K in the gut (biliary obstruction); liver diseases which interfere with prothrombin production, and salicylate therapy. However, by far the most important and frequent cause of hypoprothrombinemia is anticoagulant drugs. The neurologic complications of anticoagulant drug usage are related to the presence of hypoprothrombinemia. Any other cause of hypoprothrombinemia as listed above can result in the same spectrum of disorders. In addition, the following discussion will include the neurologic complications of heparin therapy, a drug which inactivates thrombin, inhibits the conversion of prothrombin to thrombin and prevents the agglutination of platelets. Its complication spectrum is similar to that of the agents which lower the prothrombin content of the blood by acting as a metabolic antagonist to vitamin K (e.g. coumarin and related agents).

Nervous system hemorrhage in patients on anticoagulants may involve numerous locations including intracerebral, subarachnoid, subdural, cranial epidural, spinal epidural and spinal intramedullary. In addition, roots, plexus and peripheral nerves may also be compressed by bleeding of this type. Before the advent of CT scanning, lumbar punctures were used to diagnose nervous system bleeding of this type. However, lumbar puncture itself may be dangerous in the presence of a hemorrhagic diathesis and has led to epidural and cauda equina compression syndromes. When CT scanning is not available, every effort should be made to correct the coagulation defect before the lumbar puncture is performed, though this process should not be permitted to delay a lumar puncture too long if an infection is being considered. In general the incidence of serious neurological hemorrhage rises above the benefit of anticoagulation when the international normalized ratio (INR) exceeds 3.0. For neurological purposes, the target INR is 2.0–3.0 for all conditions except antiphopholipid antibody syndrome and mechanical heart valves.

Paraproteinemias

Paraparoteinemias may be seen in many conditions including connective tissue diseases, multiple types of

malignancy and even in the absence of any known underlying disease. The most important group of disorders associated with the production of abnormal proteins are the plasma cell dyscrasias.

Plasma cell dyscrasias

The plasma cell dyscrasias are a group of disorders characterized by the uncontrolled proliferation of cells normally involved in antibody synthesis. This is usually accompanied by the synthesis of a homogeneous immunoglobin or one of its constituent polypeptide chains. These disorders are often classified according to type of protein that is produced. Thus, they fall into three major categories: (i) multiple myeloma: IgG, A, D and E; (ii) macroglobulinemia: IgM; and (iii) heavy-chain diseases: gamma, alpha, and mu.

Multiple myeloma

This is the most common plasma cell dyscrasia and is characterized by infiltration of the bone marrow with neoplastic plasma cells. Characteristic 'punched-out' bony lesions, often involving the skull and associated with hypercalcemia, may be found but the disease may certainly be present without any bony lesions. The disease may be present in a subclinical form for many years prior to the development of symptomatology, the most characteristic components of which are: (i) frequent and recurrent bacterial infections due to impaired normal antibody synthesis; (ii) chronic renal dysfunction due to several factors including tubular damage secondary to the reabsorption of large amounts of Bence–Jones proteins (light chains) filtered by the glomeruli, secondary amyloid renal disease, hypercalcemic renal damage, recurrent pyelonephritis and hyperuricemia; and (iii) damage to other organs, such as the spinal cord and nerve roots by pathologically fractured vertebrae or local development of plasmacytomas. In about 5–10% of patients with multiple myeloma, symptoms are induced by the presence of the abnormal proteins, the characteristics of which are described below. The peripheral blood smear may show abnormal clumping of erythrocytes in stack of coin-like rows (rouleaux), due to the fact that the normal surface charges that cause red cells to repel each other are coated with the paraprotein.

Macroglobulinemia

This is defined by the presence of an excessive amount of IgM gammaglobin in the serum. It includes a spectrum of disorders ranging from an apparently benign monoclonal gammapathy to progressive malignant lymphoma. Clinically the disease is generally seen in the elderly and resembles a malignant lymphoma with weakness, weight loss, adenopathy and hepatosplenomegaly as the characteristic clinical picture. Bone lesions are rare. Like myeloma, anemia is occasionally seen as a complication. Neurological complications are primarily related to the viscosity of the large abnormal protein or the development of malignant lymphoma.

Heavy-chain diseases

These are defined by the finding of characteristic immunoglobin heavy-chain fragments in the serum or urine. Three of the five possible types of heavy-chain diseases have been recognized. Gamma heavy-chain disease resembles a lymphoma more than a myeloma. Alpha heavy-chain disease is the most common heavy-chain disease and is the almost invariable accompaniment of a malignant lymphoma of the intestine with malabsorption. Mu heavy-chain disease is the rarest of these disorders having been seen in association with chronic lymphocytic leukemia.

Neurological manifestations of the paraproteinemias may be divided into the following categories: hyperviscosity syndrome; cryoglobinemia; cold agglutinin disease; amyloidosis; hemorrhagic diathesis; polyneuropathy; mononeuropathy; paraneoplastic syndromes (e.g. progressive multifocal leukoencephalopathy; cerebellar degeneration); encephalopathy (Bing-Neel syndrome); and infections (fungus, bacteria).

The hyperviscosity syndrome

This refers to the symptom and sign complex of abnormal levels of consciousness (inattention, drowsiness, stupor, coma, delirium), fundoscopic changes characterized by venous engorgement ('sausage veins'), retinal hemorrhages and exudates, blurred vision and headache. The term 'coma paraproteinemia' refers to the encephalopathy of the hyperviscosity syndrome. The syndrome requires that the relative viscosity of the blood as measured by a viscosimeter be greater than 3.0 (normal is less than 2.0). This increase in viscosity may be due to an increased red blood cell mass (as in polycythemia) but more often is due to the presence of large amounts of an abnormal protein, usually a macroglobulin. When abnormal proteins are the cause, treatment consists of plasmapheresis, usually with dramatic relief of the symptoms and signs. When indicated, treatment must then be directed toward the underlying disease (e.g. plasma cell dyscrasia, polycythemia).

Cryoglobulinemia

This refers to the presence in the serum of proteins that precipitate in the cold and redissolve on warming. These

proteins are most often associated with hepatitis C infection, myeloma and macroglobulinemia, but may be seen as part of a connective tissue disease or as an isolated finding in the absence of any known underlying cause. About a third of the cryoglobulins are myeloma IgG proteins (Type I), a third are IgM macroglobulins (Type II) and a third a mixture of IgM and IgG molecules (Type III). Many cryoglobulins may actually be antibodies against gamma globulins. The mechanism of the cryoprecipitation is not known and there is not a direct relationship between the amount of cryoglobulin or the temperature at which precipitation occurs and the symptom complex. The neurological syndrome associated with cryoglobulinemia is most common in the Type III form which is the type most often related to an underlying connective tissue disease. These patients often show purpura and a progressive renal lesion which is suggestive of an antigen-antibody (immune) complex nephritis. The most frequent neurologic syndrome is a sensory motor polyneuropathy, the precise pathology of which is not understood. It may represent a form of mononeuropathy multiplex due to disease of the vasa nervorum or an axonal polyneuropathy. There is no clear explanation for the latter possibility. Central nervous system syndromes are poorly described but may represent episodes of brain purpura associated with the bleeding diathesis.

Cold agglutinins

These are an unusual group of macroglobulins which induce red cell agglutination and hemolysis on exposure to cold. Although the phenomenon may be seen transiently in certain infections such as mononucleosis, it rarely causes clinically relevant hemolysis in conditions other than lymphomas and macroglobulinemia. These proteins contain only kappa light chains and are generally directed against the I antigen of erythrocytes. These proteins may also interact with clotting factors or coat platelets thus interfering with the blood coagulation mechanism. This may lead to central nervous system bleeding and the retinal hemorrhages so commonly seen in the paraproteinemic states.

Polyneuropathies

These have been described in cases of paraproteinemias, particularly in myeloma and macroglobulinemia. Most often there is a sensory polyneuropathy manifested by cramps, parasthesias and acral sensory loss. Cranial nerve palsies and an acute demyelinating polyneuropathy (Guillain–Barré-like illness) have been encountered, however the number of such cases is so few that it is difficult to ascribe the polyneuropathy to any particular characteristic of the paraproteinemia state. Some may represent paraneoplastic syndromes while others may be due to more common concomitant causes of peripheral nerve dysfunction such as vitamin deficiency.

Paraneoplastic syndromes

Paraneoplastic syndromes of many types have been recorded in patients with various paraproteinemias including polymyositis, cerebellar degeneration, polyneuropathy and progressive multifocal leukoencephalopathy. The cause of the latter is known to be a viral infection. The etiologies of the other syndromes in this group remain cryptic though an immune-mediated mechanism is most likely.

The Bing–Neel syndrome

This is loosely defined as the central nervous system syndrome seen in macroglobulinemia and was actually described prior to Waldenstrom's naming of the disease in 1944. Central nervous system involvement occurs in about 5–15% of the patients with macroglobulinemia, however, it is clear that many of the manifestations of the syndrome are due to the effects of hyperviscosity. This aspect of the Bing–Neel syndrome is reviewed above in the section on the hyperviscosity syndrome. In addition, however, some patients show a multifocal disease with a rapid downhill course which is uniformly fatal and unresponsive to plasmapheresis. The spinal fluid in these patients is abnormal with some pleocytosis and elevated protein. The pathology consists of infiltration of lymphocytes and plasma cells particularly around veins. Sometimes the pathological appearance is that of a histiocytic lymphoma (formerly called reticulum cell sarcoma or microglioma) of the brain.

Infections

These are common in patients with paraproteinemias probably because of the paucity of normal immunoglobulins associated with the over-production of the abnormal proteins. Since the defect is mainly in the sphere of humoral immunity, the patients are most susceptible to bacterial and fungal infections which may affect the nervous system. The most important of these include fungal and tuberculous meningitis and bacterial meningitis.

POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes)

This is a multisystem syndrome seen in patients with osteosclerotic myeloma. The mechanism is unknown, but it is likely that it is an immune mediated paraneoplastic syndrome. The polyneuropathy is a subacute or chronic

painful polyneuropathy. There is usually hepatosplenomegaly, sexual impotence and various skin lesions. The M component in the serum is produced by an osteosclerotic myeloma, which when treated, results in improvement in all components of the syndrome.

The hypercoagulable states

General issues

Patients are considered to have hypercoagulable states if they have laboratory abnormalities or clinical conditions that are associated with an increased risk of thrombosis (prethrombotic states) or if they have recurrent thrombosis without recognizable predisposing factors (thrombosis prone). The hypercoagulable states are subdivided into two categories: those in which a clearly identified, specific abnormality in hemostasis can be found (primary hypercoagulable states), and those in which various diverse clinical conditions have been associated with an increased risk of thrombosis (secondary hypercoagulable states). In both circumstances, it is becoming increasingly clear that cerebral thrombosis (venous and arterial) and embolism are important manifestations.

The primary hypercoagulable states

The primary hypercoagulable states are due to failure of one of the three physiologic anticoagulant mechanisms (e.g. antithrombin III, protein C, and the fibrinolytic system) and include antithrombin III deficiency, protein C deficiency, protein C resistance due to factor V Leiden, protein S deficiency, fibrinolytic disorders, dysfibrinogenemia, factor XII deficiency, prekallikrein deficiency, the antiphospholipid antibody syndrome, and the prothrombin gene mutation.

Antithrombin III deficiency

This may be either inherited as an autosomal dominant trait or acquired as a result of urinary excretion of the protein in patients with the nephrotic syndrome or in patients with severe disease of the liver, where much of the protein is produced. Venous is more common than arterial thrombosis and treatment consists of intravenous heparin.

Protein C or S deficiency and protein C resistance

This is inherited as an autosomal dominant trait, and occasionally acquired in patients with severe liver disease or disseminated intravascular coagulation. Protein S acts as a cofactor for the anticoagulant effects of protein C and can be deficient due to autosomal dominant inheritance or in severe liver disease or to DIC. The treatment of people with protein C or protein S deficiency who suffer recurrent thrombosis is chronic warfarin therapy. The factor V Leiden mutation leads to protein C resistance and recurrent usually venous thrombosis which can affect cerebral veins and dural sinuses.

Various fibrinolytic abnormalities

This can lead to defective digestion of fibrin. Some patients with hypercoagulable states have been found to have defective release of plasminogen activator from endothelial cells in the vessel walls. There may also be circulating inhibitors of plasminogen activators. Neurologists and neusosurgeons have ceased using epsilon aminocaproic acid (Amicar) to prevent rebleeding in subarachnoid hemorrhage patients because of the hypercoagulable state that is produced by this drug's inhibition of circulating plasminogen activator. Genetically produced tissue plasminogen activator (tPA) may have a role in treating such patients but the risk of hemorrhage may outweigh the potential benefits.

Dysfibrinogenemia

In a few patients with hypercoagulable states there is formation of a functionally abnormal fibrinogen molecule which forms gels that are extremely rigid and resistant to removal by the fibrolytic system. These dysfibrinogenemias are probably very rare causes of the hypercoagulable state.

Factor XII and prekallikrein deficiency

Patients with autosomal recessively inherited deficiencies of factor XII (Hageman factor) or other factors involved in contact activation of the coagulation cascade (e.g. prekallikrein and high molecular-weight kininogen) have prolonged partial thromboplastin times but paradoxically have an increased tendency to thrombosis, probably because these factors promote blood fluidity by helping to activate the fibrinolytic system and generate vasodilator kinins.

The prothrombin gene mutation

This is a reasonably common cause of a hypercoagulable state usually involving veins more than arteries.

The antiphospholipid antibody syndrome

Two major antiphospholipid syndromes are known: the lupus anticoagulant and the anticardiolipin antibody. The so-called lupus anticoagulant is actually an antibody to phospholipids which interferes with the formation of the

prothrombin activator, a complex of calcium ions, factors Xa, V and a source of phospholipid, usually the platelet membrane in the coagulation cascade. This IgG or IgM antiphospholipid antibody often, but not always, causes prolongation of phospholipid-dependent coagulation tests, such as the activated partial thromboplastin time (aPTT). This antibody is present in about 25% of patients with systemic lupus erythematosus (SLE), and may cross-react with cardiolipin, the antigen commonly used in a blood screening test for syphilis, thus producing a biologic false positive. Despite the prolonged PTT, this antiphospholipid antibody is actually a procoagulant as a consequence of several mechanisms including increased platelet adhesiveness, interference with the production of the vasodilator and antiplatelet aggregator prostacyclin by the endothelial cell, and decreased production of plasminogen activator. The lupus anticoagulant can only be diagnosed using a three-step functional test: (i) screening test such as a PTT; (ii) mixing test to determine that the factor which prolongs the PTT is in the serum and, (iii) phospholipid loading test such as platelet addition or octagonal phase to determine that the plasma factor that prolongs the PTT is an antiphospholipid antibody). It cannot be readily quantified. The anticardiolipin antibody may be quantified using an enzyme linked immunosorbent assay (ELISA). In addition to patients with systemic lupus erythematosus, other people at risk for anticardiolipin antibody include patients on neuroleptic drugs, patients with neoplasms, other autoimmune disorders and some people with no apparent underlying disorders. Those without underlying disease are said to have the primary anticardiolipin antibody syndrome.

The primary antiphospholipid antibody syndrome (Sneddon syndrome) is characterized by recurrent episodes of venous and/or arterial thrombosis, recurrent mid-pregnancy spontaneous abortions and thrombocytopenia. Migraine, mitral valve prolapse and livedo reticularis are also over represented in these patients. Echocardiography frequently reveals the presence of vegetations on the mitral valve, presumably representing foci of Libman–Saks endocarditis. The nervous system is commonly affected with large and small vessel arterial occlusions, venous occlusions and emboli probably arising from non-bacterial thrombotic endocarditis (NBTE) which in turn results from the hypercoagulable state. Many of the neurologic syndromes seen in SLE patients can be conceptualized as being due to either thrombosis *in situ* or emboli from NBTE (known as Libman–Sacks endocarditis in SLE patients). Treatment of patients who have the antiphospholipid antibody and who suffer recurrent thrombosis is long-term, high intensity, warfarin therapy. The precise dose of warfarin is unknown, but it is likely that fairly intense anticoagulation is required (i.e. international normalized ratio of 3.0 – 3.5).

The secondary hypercoagulable states

The secondary hypercoagulable states may be divided into three major groups based on the presumed predominant pathophysiological mechanism: (i) abnormalities of coagulation and fibrinolysis, such as malignancy, pregnancy, use of oral contraceptives, infusion of prothrombin complex concentrates and nephrotic syndrome, (ii) abnormalities of platelets, such as myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, hyperlipidemia, diabetes mellitus, heparin-induced thrombocytopenia and (iii) abnormalities of blood vessels or rheology, such as conditions promoting venous stasis (e.g. immobilization, obesity, advanced age, post-operative state), artificial surfaces, vasculitis and chronic occlusive arterial disease, homocysteinemia, hyperviscosity (e.g. polycythemia, leukemia, sickle cell disease, leukoagglutination, increased serum viscosity) and thrombotic thrombocytopenia purpura.

Hypercoagulable states related to underlying malignancy

The relationship between increased tendency for thrombosis and malignancy has been known ever since Armand Trousseau described the syndrome that bears his name. Migratory phlebothrombosis, pulmonary emboli and transient or permanent focal neurological deficit is viewed as a paraneoplastic syndrome usually in patients with mucin secreting adenocarcinomas. Some of the neurologic deficits are due to thrombosis *in situ* of cerebral vessels while others are due to emboli arising from non-bacterial thrombotic endocarditis (NBTE), which itself is caused by the paraneoplastic hypercoagulable state. Most data support the concept that this hypercoagulable state is due to a general activation of the clotting system resulting in chronic DIC. This DIC may be initiated by the tumour's production of procoagulant such as a cysteine protease which has been found in malignant cells and is known to activate factor X.

Hypercoagulable states related to pregnancy

Pregnancy increases the risk of thrombosis probably as a consequence of a chronic low grade DIC, which develops normally in pregnancy, presumably in preparation for the hemostatic challenge of placental separation. Cerebral venous thrombosis is the major neurologic complication of this hypercoagulable state, seen primarily in the postpartum period. It takes two major clinical forms: venous sinus occlusion and cortical vein occlusion. Though these two clinical forms often fuse as the illness progresses, venous

sinus thrombosis usually presents with increased intracranial pressure, whereas cortical vein thrombosis usually begins with partial seizures, often very resistant to anticonvulsant therapy. As in any venous occlusions, the resultant infarctions, if any, are hemorrhagic and, as such, are usually easily visible by imaging techniques. The contrast-enhanced CT and MRI have proved particularly useful in demonstrating the characteristic triangular thrombosis (empty delta sign) in the superior saggital sinus even when hemorrhagic infarction is not present. Magnetic resonance venography is now the gold standard neurodiagnostic study when venous occlusive disease is suspected. The treatment for the hypercoagulable state of pregnancy is reserved for patients with demonstrated thrombosis and consists of heparin, since warfarin crosses the placenta and is possibly teratogenic.

Hypercoagulable states related to oral contraceptive use

Oral contraceptives significantly increase the risk of thrombosis in a way similar to that seen in late pregnancy, but unlike in pregnancy, the fibrinolytic response is inappropriately blunted. Epidemiologic studies have suggested that use of an oral contraceptive raises the risk of stroke in young women, particularly in people with a history of migraine. The risk appears to be dose related

Hypercoagulable states related to prothrombin complex infusions

Prothrombin complex concentrates contain the vitamin K-dependent clotting factors II, VII, IX, and X and are used to treat patients with deficiencies of these factors. Transfusion with these concentrates is associated with an increased risk of thrombosis and DIC including stroke, particularly in patients with underlying liver disease. The thrombogenicity of these concentrates may be due to small quantities of activated clotting factors which cannot be adequately cleared by the patient's diseased liver.

Hypercoagulable states related to nephrotic syndrome and other causes of factor loss.

In patients with the nephrotic syndrome, there is an increased risk of stroke probably related in large part to an acquired antithrombin III deficiency, caused by urinary loss of the protein. Factor deficiency also explains the hypercoagulable state seen with L-asparagine therapy for acute lymphocytic leukemia.

Hypercoagulable states related to abnormalities in platelets

Abnormalities in platelet function probably underlie in part the thrombotic tendency seen in patients with myeloproliferative disorders, thrombocytosis, paroxysmal nocturnal hemoglobinuria, hyperlipidemia and heparin-induced thrombocytopenia.

Hypercoagulable states related to abnormalities of blood vessels or rheology

Lastly, many abnormalities in blood vessels and rheology may promote coagulation and thus produce cerebral thrombosis. Of particular importance from a neurologic perspective are artificial surfaces, such as seen in patients placed on extracorporeal circulation, vasculitic conditions, such as giant cell arteritis of the brain and Behçet's disease, homocysteinemia and hyperviscosity of any cause.

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128

Neurocutaneous syndromes

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Congenital or hereditary conditions which feature lesions of both the skin and the nervous system have been traditionally considered together as neurocutaneous disorders. Selected neurocutaneous disorders are presented in detail, and several other examples are listed in Table 128.1. While each of these conditions has unique clinical manifestations and a distinct pathophysiology, the concept of neurocutaneous syndromes does serve to highlight a group of neurological disorders the identification of which depends predominantly on simple visual diagnosis.

Table 128.1. Selected neurocutaneous syndromes

Ataxia telangiectasia
Ehlers–Danlos syndrome
Epidermal nevus syndrome
Hereditary hemorrhagic telangiectasia
Hypomelanosis of Ito
Neurocutaneous melanosis
Neurofibromatosis type 1
Pseudoxanthoma elasticum
Progeria
Tuberous sclerosis complex
Sturge–Weber syndrome
von Hippel–Lindau disease

Neurofibromatosis

Neurofibromatosis (NF) is actually two separate conditions, each caused by a different gene: neurofibromatosis type 1 (NF1), or von Recklinghausen's disease, and neurofibromatosis type 2 (NF2), which is characterized by bilateral vestibular schwannomas and often leads to other brain or spinal cord tumours (Roach, 1992; Riccardi & Eichner, 1992). The clinical manifestations of both conditions are highly variable (Friedman & Birch, 1997; Martuza & Eldridge, 1988).

Neurofibromatosis type 1 is the most common of the neurocutaneous syndromes, occurring in approximately 1 of every 3000 people (Crowe et al., 1956; Riccardi & Eichner, 1992). About half of the individuals with NF1 result from a spontaneous mutation. In contrast, NF2 occurs in only one in 50 000 people (Listernick & Charrow, 1990).

Cutaneous lesions of NF1

Cutaneous lesions of neurofibromatosis type 1 include cafe-au-lait spots, subcutaneous neurofibromas, and plexiform neurofibromas. Cafe-au-lait spots (Fig. 128.1) are flat, light to medium brown areas which have various shapes and sizes. They are typically seen at birth, but increase in size and number during the first few years. Additional freckle-like lesions, 1 mm to 3 mm in diameter, often occur in the axillae or intertriginous regions.

Neurofibromas are benign tumours arising from peripheral nerves (Fig. 128.1). These tumours are composed predominantly of Schwann cells and fibroblasts, but contain endothelial, pericyte and mast cell components (Riccardi & Eichner, 1992). Neurofibromas can develop at any time, and both the size and number often increase after puberty.

Plexiform neurofibromas are common and often cause substantial deformity (Fig. 128.1). In one series, 68 of 405 (16.8%) patients with NF1 developed one or more plexiform neurofibromas (Waggoner et al., 2000). Another report of 121 patients with plexiform neurofibromas documented tumour progression in 46% of the patients. Patients with plexiform tumours of the head, face, or neck and those who presented before age 10 years were more likely to do poorly (Needle et al. 1997). Plexiform neurofibromas have a 3–5% lifetime risk of malignant degeneration (Gutmann, 1998;

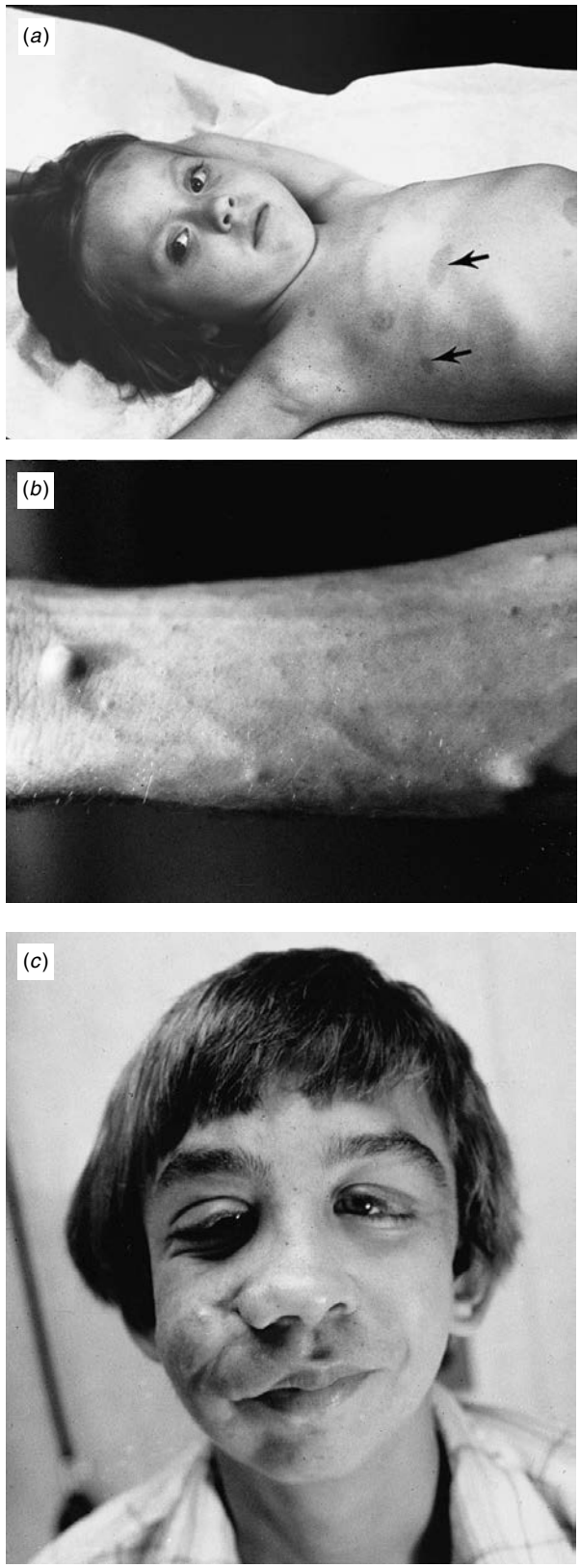

Fig. 128.1. Cutaneous lesions of neurofibromatosis type 1 include: (*a*). café-au-lait spots (arrows); (*b*) subcutaneous neurofibromas; and (*c*) plexiform neurofibromas. (Reprinted from Roach, 1988, with permission.)

Waggoner et al., 2000). Both rapid growth and non-traumatic pain should raise concerns about malignant transformation of a plexiform neurofibroma (Korf, 1999).

Ophthalmologic lesions of NF1

Lisch nodules are pigmented iris hamartomas (Fig. 128.2) which are asymptomatic but help to establish the diagnosis of NF1. Lisch nodules do not occur in all NF1 patients and may not be apparent during early childhood, so their absence does not exclude the diagnosis of NF1. Rare children with NF1 have retinal hamartomas, but these are also asymptomatic in most individuals.

Arterial lesions of NF1

Dysplasia of the renal or carotid arteries occurs in a small percentage of patients with NF1. Renal artery stenosis may lead to systemic hypertension. Another potential cause of hypertension is pheochromocytoma (Walther et al., 1999). Several forms of cerebral artery dysplasia occur, most commonly moyamoya syndrome, which promotes cerebral infarction in children and brain hemorrhage in adults (Rizzo & Lessell, 1994).

Neurologic lesions of NF1

Neurofibromatosis type 1 affects the nervous system in several ways, but the clinical features vary even among affected members of the same family. Tumours occur in the brain, spinal cord, and peripheral nerves, though not as frequently as with NF2 (Riccardi & Eichner, 1992; Thakker et al., 1999). Optic nerve glioma (Fig. 128.3) is the most common central nervous system tumour caused by NF1 (Listernick et al., 1999). About 15% of NF1 patients have either a unilateral or bilateral optic glioma (Gutmann, 1998; Listernick et al., 1999). The rate of growth varies, but optic gliomas tend to behave less aggressively in NF1 patients than in patients without NF1 (Listernick et al., 1995, 1999). Optic atrophy and progressive visual loss are more common than pain or proptosis. Precocious puberty is a common presenting sign of optic nerve tumours in NF1 patients, although occasional children with NF1 present with precocious puberty even in the absence of optic tumours (Listernick et al., 1995).

Ependymomas, meningiomas and astrocytomas of the central nervous system occur in patients with NF1, though less often than in patients with NF2. Neurofibromas and

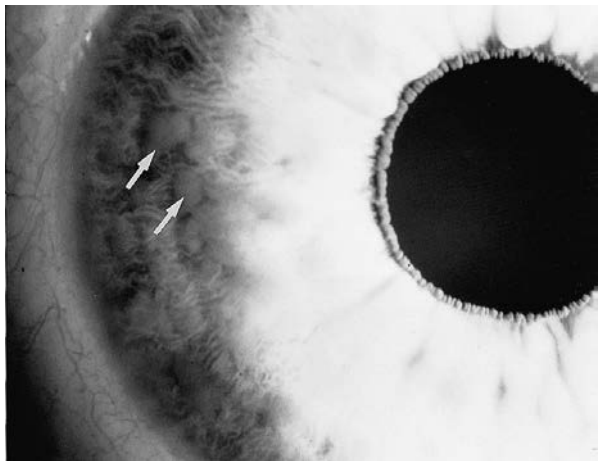

Fig. 128.2. Lisch nodules (arrows) of the iris in a patient with neurofibromatosis type 1. (Reprinted from Roach, 1992, with permission.)

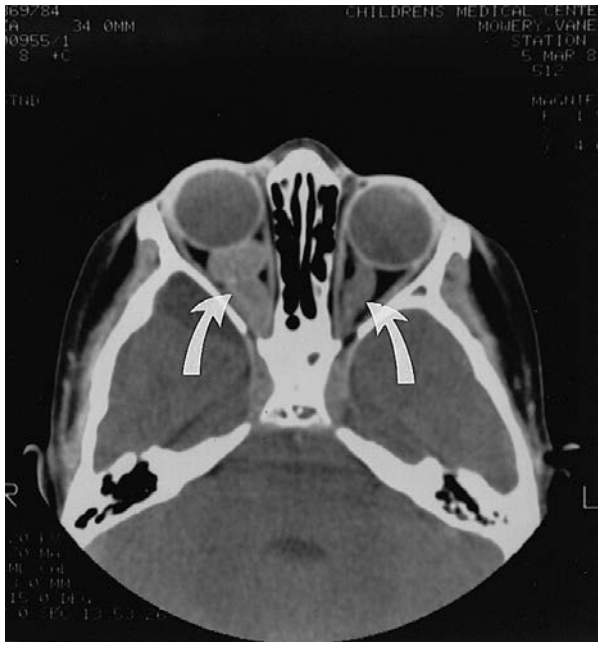

Fig. 128.3. Computed cranial tomography scan demonstrates bilateral optic nerve gliomas (arrows), larger on the right than the left, in a child with neurofibromatosis type 1. (Reprinted from Roach, 1992, with permission.)

Schwannomas are common but not always symptomatic; they can develop on either cranial nerves or spinal nerve roots. The symptoms from these tumours reflect their size, location and rate of growth.

Most patients with NF1 have high signal lesions of the basal ganglia, thalamus, brainstem, and cerebellum on T_2-weighted MRI sequences (Fig. 128.4), although these findings alone are not very specific (DeBella et al., 2000). Whether these MRI lesions correlate with the likelihood of cognitive impairment has been debated (Joy et al., 1995).

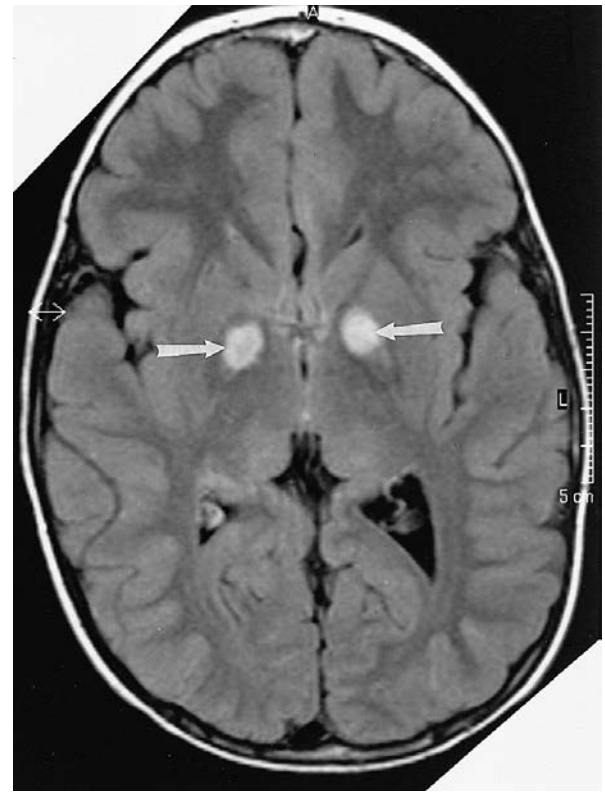

Fig. 128.4. Coronal T_1-weighted magnetic resonance scan shows bilateral high signal lesions in the basal ganglia (arrows), abnormalities typical of neurofibromatosis type 1.

Patients with NF1 often have non-specific cognitive defects such as reduced intelligence, behavioural difficulty, attentional problems and learning disability (Ozonoff, 1999). Intelligence quotient (IQ) scores are typically in the low normal range, and only 4% to 8% of individuals with NF1 are mentally retarded (North et al., 1995; Moore et al., 1994; Hofman et al., 1994). About 40% of NF1 patients have some type of learning disability or behavioural problem (Riccardi & Eichner, 1992).

Clinical features of neurofibromatosis Type 2

Patients with NF2 have few cutaneous lesions but often have multiple tumour types in the central nervous system (thus its occasional characterization as 'central neurofibromatosis'). The frequency of café-au-lait spots is not increased nor are Lisch nodules and subcutaneous neurofibromas typical of NF2. NF1 and NF2 do not occur in

Table 128.2. Diagnostic criteria for neurofibromatosis

Neurofibromatosis type 1 (any two or more)
Six or more cafe-au-lait lesions over 5 mm in diameter before puberty and over 15 mm in diameter afterward
Freckling in the axillary or inguinal areas
Optic glioma
Two or more neurofibromas or one plexiform neurofibroma
A first degree relative with NF1
Two or more Lisch nodules
A characteristic bony lesion (sphenoid dysplasia, thinning of the cortex of long bones, with or without pseudarthrosis)
Neurofibromatosis type 2
Bilateral VIII nerve tumour (shown by MRI, CCT, or histological confirmation)
A first-degree relative with NF2 and a unilateral eight-nerve tumour
A first-degree relative with NF2 and any two of the following lesions: neurofibroma, meningioma, schwannoma, glioma, or juvenile posterior subcapsular lenticular opacity

Source: Data from National Institutes of Health Consensus Development Conference (1988).

different members of the same family, which is not surprising considering that the two conditions are caused by different genes.

Most NF2 patients eventually develop bilateral vestibular schwannomas. In one series, 96% of the patients who met established diagnostic criteria for NF2 (Table 128.2) had vestibular schwannomas, and most of these were bilateral tumours (Mautner et al., 1996). Symptoms of NF2 typically develop in adolescence or early adulthood, although children can also be affected. Common complaints with larger acoustic tumours include hearing loss, tinnitus, vertigo, facial weakness and headache. Unilateral hearing loss is relatively common in the early stages.

Various other tumours of the central nervous system occur, although much less often than acoustic schwannomas (Mautner et al., 1996). The clinical features of these tumours depend primarily on the lesion's location within the brain and spinal cord. Schwannomas of other cranial nerves occur in some patients, and meningiomas, ependymomas and astrocytomas also occur with increased frequency. Patients with NF2 may develop multiple simultaneous tumour types.

Diagnostic criteria for neurofibromatosis

If several characteristics are present, the diagnosis of both NF1 and NF2 is obvious, especially when another family member is also affected. But when the clinical features are not classic and there is no family history, the diagnosis can be difficult. Very young children may have less apparent lesions and definitive diagnosis can be difficult in these children. Diagnostic criteria (Table 128.1) help to resolve some of these questionable cases, but the criteria should eventually be replaced by specific gene testing. Screening for the NF1 gene is technically difficult because of the gene's large size and the numerous different mutations that are known to affect the NF1 gene. This makes it difficult to efficiently exclude every possible mutation, and so the commercially available diagnostic analyses have a 30% false-negative rate.

Genetics of NF1 and NF2

Neurofibromatosis type 1 is caused by a mutation of the 60 exon NF1 gene on chromosome 17.q. The *NF1* gene product, neurofibromin, is partially homologous to GTPase-activating protein (GAP) (Upadhyaya et al., 1997). Multiple mutations of NF1 have been identified in various regions of the gene (Tonsgard et al., 1997; Upadhyaya et al., 1995, 1997).

Several patients have developed a somatic NF1 mutation affecting only a limited region of the body. With this 'segmental' neurofibromatosis, one extremity may have café-au-lait lesions, subcutaneous neurofibromas, and other signs of NF, but rest of the body is unaffected (McFadden et al., 1988; Hager et al., 1997). Similarly, patients with germline mosaicism have been described. These individuals have no outward manifestations of NF1, but can have multiple affected offspring (Lázaro et al., 1994).

Neurofibromatosis type 2 is caused by a mutation of the *NF2* gene on chromosome 22. The NF2 protein product is known as schwannomin. The *NF2* gene suppresses tumour function, and its dysfunction accounts for the common occurrence of central nervous system tumours with NF2 (Gutmann et al., 1998). As with NF1, multiple different mutations of the *NF2* gene have been described (De Klein et al., 1998; Gutmann et al., 1998; Ruttledge et al., 1996; MacCollin et al., 1996). The clinical severity may be related to the nature of the *NF2* mutation: missense mutations which allow some protein function tend to produce milder clinical manifestations, while frameshift and nonsense mutations often cause severe disease (Gutmann et al., 1998; Kluwe et al., 1996; MacCollin et al., 1996).

Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is a disorder of cellular differentiation and proliferation which affects the brain, skin, kidneys, heart and other organs (Sparagana & Roach,

Table 128.3. Diagnostic criteria for tuberous sclerosis complex

Major features	
1	Facial angiofibromas or forehead plaque
2	Non-traumatic ungual or periungual fibroma
3	Hypomelanotic macules (more than three)
4	Shagreen patch (connective tissue nevus)
5	Cortical tuber[a]
6	Subependymal nodule
7	Subependymal giant cell astrocytoma
8	Multiple retinal nodular hamartomas
9	Cardiac rhabdomyoma, single or multiple
10	Lymphangiomyomatosis[b]
11	Renal angiomyolipoma[b]
Minor features	
1	Multiple randomly distributed pits in dental enamel
2	Hamartomatous rectal polyps[c]
3	Bone cysts[d]
4	Cerebral white matter 'migration tracts'[a, d]
5	Gingival fibromas
6	Non-renal hamartoma[c]
7	Retinal achromic patch
8	'Confetti' skin lesions
9	Multiple renal cysts[c]

Notes:

[a] When cerebral cortical dysplasia and cerebral white matter migration tracts occur together, they should be counted as one rather than two features of tuberous sclerosis.

[b] When both lymphangiomyomatosis and renal angiomyolipomas are present, other features of tuberous sclerosis should be present before a definite diagnosis is assigned.

[c] Histological confirmation is suggested.

[d] Radiographical confirmation is sufficient.

Definite TSC: Either two major features or one major feature plus two minor features.

Probable TSC: One major plus one minor feature.

Suspect TSC: Either one major feature or two or more minor features.

Source: Reprinted with permission from Roach et al. (1998).

2000; Weiner et al., 1998; Gomez, 1988; Roach et al., 1998). Many of the clinical manifestations of TSC result from hamartomas; true neoplasms also occur, particularly in the kidney and brain. Abnormal neuronal migration plays a major additional role in neurologic dysfunction (Roach & Delgado, 1995). The clinical diagnostic criteria were recently revised (Table 128.3) and guidelines for ongoing diagnostic testing were proposed (Roach et al., 1998, 1999).

Population-based studies suggest a prevalence of 1 per 6000 to 9000 individuals (Osborne et al., 1991). However, because of its striking variability of clinical expression and severity, the diagnosis of TSC can be difficult in individuals with subtle findings (Roach et al., 1991b).

General features of tuberous sclerosis complex (TSC)

Skin lesions

The cutaneous lesions of TSC include hypomelanotic macules, the shagreen patch, ungual fibromas, and facial angiofibromas (Roach & Delgado, 1995). Hypomelanotic macules (ash leaf spots) are found in over 90% of patients (Fig. 128.5). The lesions are usually present at birth but may be difficult to see in the newborn without an ultraviolet light. Other pigmentary abnormalities include the 'confetti' lesions (an area with stippled hypopigmentation, typically on the extremities) and poliosis of the scalp hair or eyelids (Fig.128.5). Hypomelanotic macules are not specific for TSC: one or two of these lesions are common in normal individuals (Vanderhooft et al., 1996).

Facial angiofibromas (adenoma sebaceum) are made up of vascular and connective tissue elements. Although these lesions are considered specific for TSC, they are found in only about three-fourths of patients and often appear several years after the diagnosis has been established by other means. The lesions typically become apparent during the preschool years as a few small red papules on the malar region (Roach & Delgado, 1995); they gradually become larger and more numerous, sometimes extending down the nasolabial folds or onto the chin (Fig. 128.5).

The shagreen patch is most often found on the back or flank area; it is an irregularly shaped, slightly raised or textured skin lesion (Fig. 128.5). The lesion is found in less than a third of TSC patients, and even so may not be apparent in young children.

Ungual fibromas are nodular or fleshy lesions that arise adjacent to or from underneath the nails (Fig. 128.5). The lesion is usually considered specific for TSC, although a single lesion occasionally occurs after trauma. Ungual fibromas are seen in only 15–20% of unselected TSC patients, and are more likely to be found in adolescents or adults.

Retinal lesions

The frequency of retinal hamartomas in TSC has varied from almost negligible to 87% of patients, probably reflecting the expertise and technique of the examiner (Kiribuchi et al., 1986). Retinal lesions may be difficult to identify without pupillary dilatation and indirect ophthalmoscopy, particularly in uncooperative children. Retinal lesions vary

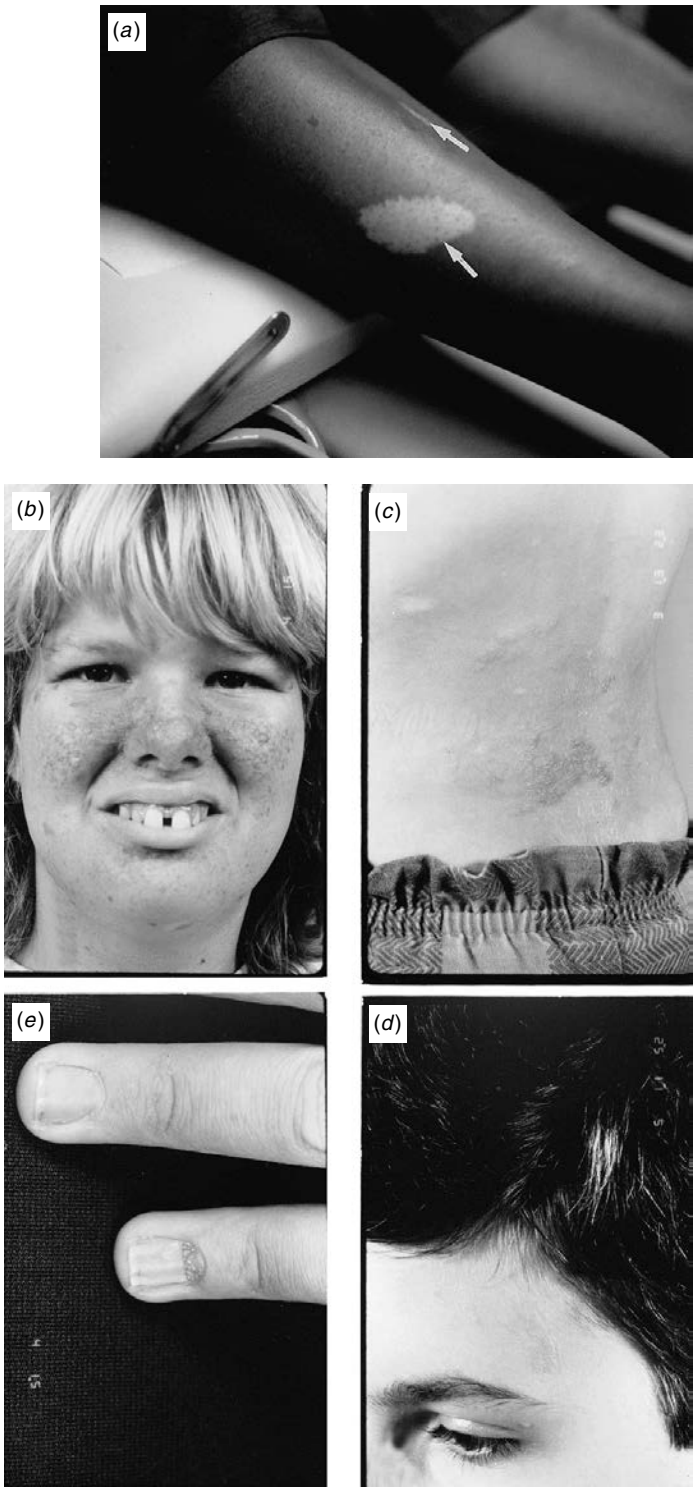

Fig. 128.5. Cutaneous features of tuberous sclerosis include: (*a*) hypomelanotic macule (arrows); (*b*) facial angiofibromas (adenoma sebaceum); (*c*) a shagreen patch; (*d*) poliosis; and (*e*) ungual fibromas. (Part (*a*) reprinted from Roach, 1988; parts (*b*)–(*e*) reprinted from Roach & Delgado, 1995, with permission.)

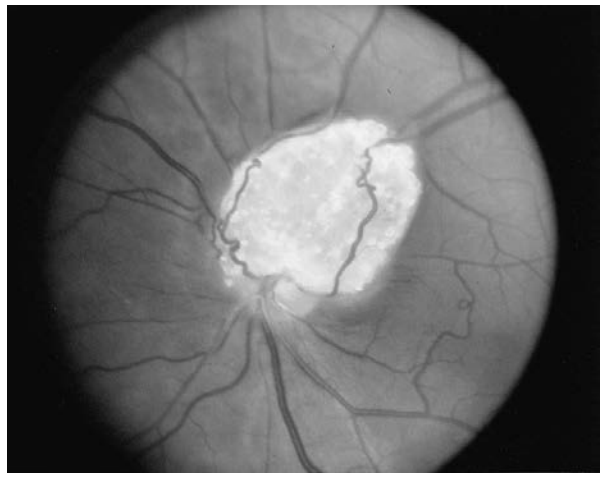

Fig. 128.6. A retinal astrocytoma ('mulberry lesion') adjacent to the optic nerve is typical of those found with tuberous sclerosis. (Reprinted from Roach, 1992, with permission.)

from the classic mulberry lesions adjacent to the optic disc (Fig. 128.6) to the plaque-like hamartoma or depigmented retinal lesions. Most retinal lesions are clinically insignificant, but occasional patients have visual impairment due to a large macular lesion, and rare patients have visual loss due to retinal detachment, vitreous hemorrhage, or hamartoma enlargement. Occasional patients have a pigmentary defect of the iris (Gutman et al., 1982).

Cardiac lesions

About two-thirds of TSC patients have one or more cardiac rhabdomyomas (DiMario et al., 1996), but few of these lesions are clinically important. Cardiac rhabdomyomas are hamartomas; they tend to be multiple, and there is evidence that their frequency diminishes with age (Smith et al., 1989; DiMario et al., 1996). These lesions are sometimes evident on prenatal ultrasound testing, and most of the patients with cardiac dysfunction present soon after birth with heart failure. A few children later develop cardiac arrhythmias or cerebral thromboembolism.

Renal lesions

Renal angiomyolipomas occur in 75–80% of TSC patients; most of these lesions are histologically benign tumours with varying amounts of vascular tissue, fat and smooth muscle. Bilateral tumours or multiple tumours per kidney are typical. The prevalence of renal tumours increases with age, and tumours larger than 4 cm are much more likely to become symptomatic than smaller tumours (Ewalt et al., 1998; Steiner et al., 1993). Renal cell carcinoma or other malignancies are less common (Al-Saleem et al., 1998; Bjornsson et al., 1996).

Pulmonary dysfunction

An estimated 1% of TSC patients develop lung disease. Pulmonary disease is five times more common in females than in males. Spontaneous pneumothorax, dyspnea, cough, and hemoptysis are typical symptoms of pulmonary TSC, although these do not often develop before the third or fourth decade (Scully et al., 1994).

Neurologic dysfunction from TSC

The predominant neurological manifestations of TSC are mental retardation, epileptic seizures, and behavioural abnormalities, although milder forms of the disease with little or no neurologic impairment are common (Roach & Delgado, 1995). Neurological lesions probably result from impaired cellular interaction resulting in disrupted neuronal migration along radial glial fibres and abnormal proliferation of glial elements. Neuropathological lesions of TSC include subependymal nodules, cortical hamartomas, areas of focal cortical hypoplasia and heterotopic grey matter.

Various types of seizures occur in up to 90% of patients. Most mentally retarded patients have epilepsy but there are exceptions. In contrast, many patients have seizures but not mental retardation. The number of subependymal lesions does not correlate with the clinical severity of TSC, but patients with numerous lesions of the cerebral cortex shown by MRI tend to have more cognitive impairment and more difficulty with seizure control (Jambaque et al., 1991; Roach et al., 1987; Goodman et al., 1997). Children with infantile spasms are more likely to exhibit long-term cognitive impairment (Jozwiak et al., 1998), but these patients, in turn, have more cortical lesions demonstrated by MRI (Shepherd et al., 1995).

The likelihood of mental retardation in patients with TSC is probably over estimated. Webb and colleagues, for example, found only ten mentally retarded patients among 26 TSC patients in a population survey (Webb et al., 1991). The severity of intellectual dysfunction ranges from borderline to profound mental retardation.

In addition to frank mental retardation, many children have serious behavioural disorders (Hunt & Dennis, 1987). Autism and various behavioural disturbances including hyperkinesis, aggressiveness and frank psychosis, are sometimes noted, either as isolated problems or in combination with epilepsy or intellectual deficit (Hunt & Shepherd, 1993; Curatolo, 1996; Shepherd & Stephenson, 1992). Prior immunization does not correlate with neurological outcome (Jozwiak et al., 1998).

The calcified subependymal nodules (Fig. 128.7) which characterize TSC are best demonstrated with CCT (Iwasaki et al., 1990). Superficial cerebral lesions can sometimes be seen with CCT but are far more obvious with T_2-weighted MRI (Fig. 128.8) (Roach et al., 1987). Cerebellar anomalies can be demonstrated in over one-fourth of TSC patients (Roach et al., 1987). Nodular subependymal lesions that have not yet calcified produce a high-signal lesion with T_2-weighted scans. Evidence of abnormal neuronal migration can be seen in some patients as a high signal linear lesions running perpendicular to the cortex on T_2-weighted scans (Roach et al., 1991a).

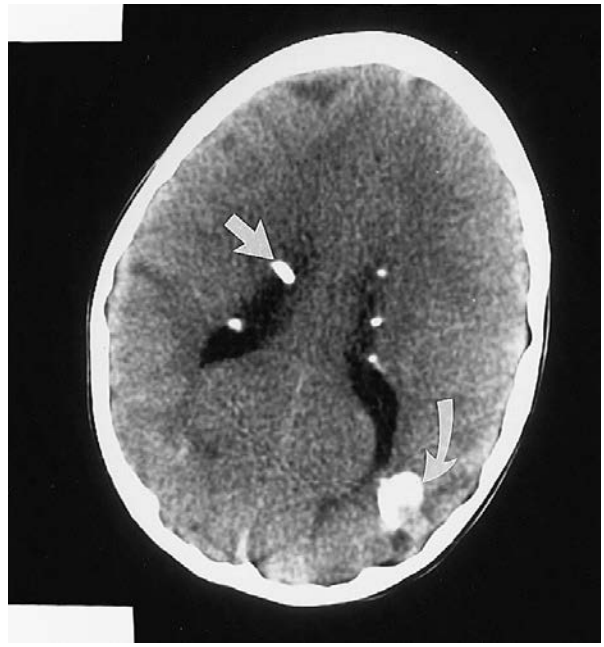

Fig. 128.7. Computed cranial tomography scan from a child with TSC demonstrates typical calcified subependymal nodules; a large calcified parenchymal lesion (curved arrow) and low-density cortical lesions (arrows) are seen as well. (Reprinted from Roach et al., 1991a, with permission.)

Subependymal giant cell astrocytomas (SEGA) develop in 6–14% of TSC patients (Shepherd et al., 1991). Unlike the more common cortical tubers, giant cell astrocytomas can enlarge and cause symptoms of increased intracranial pressure (Torres et al., 1998). Clinical manifestations include new focal neurologic deficits, increased intracranial pressure, unexplained behaviour change, or deterioration of seizure control (Torres et al., 1998). Acute or subacute onset of neurologic dysfunction may result from sudden obstruction of the ventricular system by an intraventricular SEGA. Rarely acute deterioration occurs because of hemorrhage into the tumour itself.

Giant cell tumours are usually benign but locally invasive, and surgery, performed early, can be curative (Torres et al., 1998). Identification of an enlarging SEGA before the onset of symptoms of increased intracranial pressure or

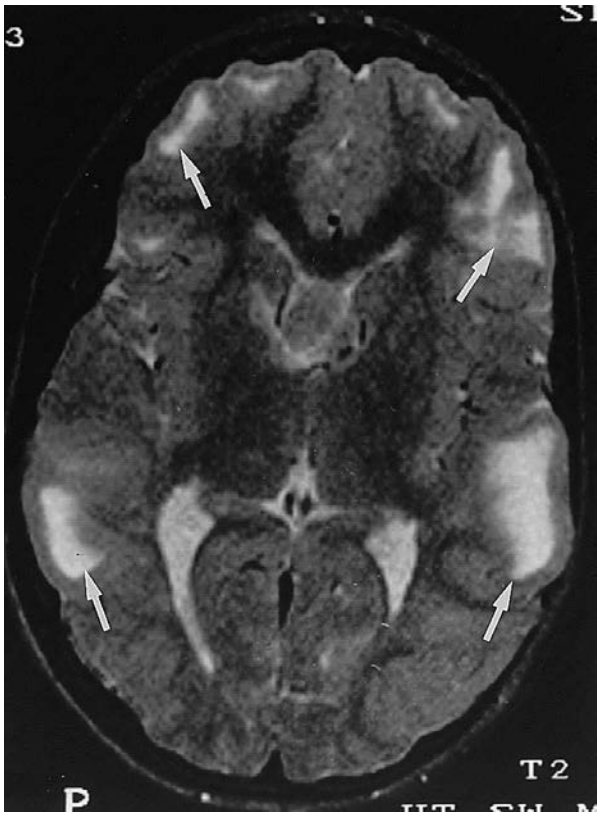

Fig. 128.8. Non-contrast T_2-weighted magnetic resonance scan from a child with tuberous sclerosis demonstrates extensive high-signal cortical lesions (arrows) typical of tuberous sclerosis. (Reprinted from Miller & Roach, 2000, with permission.)

new neurological deficits may improve surgical outcome (Roszkowski et al., 1995; Torres et al., 1998).

Genetics of tuberous sclerosis

Tuberous sclerosis is inherited as an autosomal dominant trait with variable penetrance (Weiner et al., 1998). The estimated spontaneous mutation rate for TSC varies from 66–86%, depending in part on the completeness of investigation of the extended family (Roach et al., 1991b). In addition, germline mosaicism accounts for an estimated 1% to 2% of the patients, making genetic counselling more difficult even when a specific mutation has been identified (Rose et al., 1999; Kwiatkowska et al., 1999; Verhoef et al., 1999; Yates et al., 1997).

Two genes are responsible for TSC. One gene (TSC2) was found adjacent to the gene for adult polycystic kidney disease at chromosome 16p13.3, and the other gene (TSC1) was recently located at chromosome 9q34 (European Chromosome 16 Tuberous Sclerosis Consortium, 1993; van Slegtnenhorst et al., 1997). Multiple mutations have been identified in each gene (Au et al., 1998). Tuberin, the gene product of *TSC2*, has a homologous area with the GTP-ase activating protein of rap1 (Wienecke et al., 1997). Tuberin colocalizes with hamartin, the gene product of *TSC1*, in the Golgi apparatus, suggesting that the two genes cause similar phenotypes because they interact in the same process (Wienecke et al., 1996; van Slegtenhorst et al., 1998).

Unlike neurofibromatosis types 1 and 2, there are no obvious phenotypic differences between *TSC1* and *TSC2*. Multiple mutations have been identified in different regions of both *TSC* genes (Au et al., 1998; Jones et al., 1999). The clinical manifestations cannot be reliably predicted by the specific gene or mutation site, but in general *TSC1* seems to be more likely to account for familial cases and on the whole causes less severe disease than *TSC2* (Jones et al., 1997, 1999).

Sturge–Weber syndrome

Sturge–Weber syndrome (SWS) is characterized by a facial cutaneous angioma (port-wine nevus) and an associated leptomeningeal and brain angioma, typically ipsilateral to the facial lesion. In addition to the facial nevus, classic findings include mental retardation, contralateral hemiparesis and hemiatrophy, and homonymous hemianopia (Roach, 1992; Roach et al., 1999). However, the clinical features are highly variable, and patients with the cutaneous lesion and seizures but with normal intelligence and no focal neurologic deficit are common. The syndrome occurs sporadically and in all races (Roach, 1992).

Cutaneous features of SWS

The nevus classically involves the forehead and upper eyelid, but it often affects both sides of the face and may extend onto the trunk and extremities (Fig. 128.9). Patients whose nevus involves only the trunk, or the maxillary or mandibular area but not the upper face, have little risk of an intracranial angioma (Uram & Zubillaga, 1982; Enjolras et al., 1985; Tallman et al., 1991). The facial angioma is usually obvious at birth, but occasional patients have the characteristic neurological and radiographical features of SWS yet have no skin lesion. More frequently, the typical cutaneous and ophthalmic findings are present without clinical or radiographic evidence of an intracranial lesion. Only 10–20% of children with a port-wine nevus of the forehead have a leptomeningeal angioma (Enjolras et al., 1985). The leptomeningeal angioma is typically ipsilateral to a unilateral facial nevus, but bilateral brain lesions occur

Fig. 128.9. A patient with the classic distribution of the port-wine nevus of Sturge–Weber syndrome on the upper face and eyelid. (Reprinted from Roach, 1989, with permission.)

in at least 15% of patients, including some with a unilateral cutaneous nevus.

Ophthalmologic features of SWS

Glaucoma is the main ophthalmologic problem of patients with SWS (Sullivan et al., 1992; Sujansky & Conradi, 1995a). In one study, 36 of 51 patients (71%) had glaucoma; 26 of these developed glaucoma by age 2 years (Sullivan et al., 1992). The risk of developing glaucoma is highest in the first decade, but young adults occasionally develop glaucoma. Buphthalmos and amblyopia are present in some newborns, evidently due to an anomalous anterior chamber angle (Wagner et al., 1988). In other individuals, glaucoma becomes symptomatic later and, if not treated, causes progressive blindness. Periodic measurement of the intraocular pressure is imperative, especially when the nevus is near the eye.

Neurologic features of SWS

Epileptic seizures, mental retardation, and focal neurological deficits are the principal neurological abnormalities of SWS. Seizures usually start acutely in conjunction with hemiparesis. The age when symptoms begin and the overall clinical severity vary, but onset of seizures prior to age two increases the probability of future mental retardation and refractory epilepsy. Patients with refractory seizures are more likely to be mentally retarded, while patients who have never had seizures are usually normal. Few patients who remain normal past age 3 are destined to have severe intellectual impairment.

Seizures eventually develop in up to 80% of SWS patients with unilateral lesions and in 93% of patients with bihemispheric involvement (Bebin & Gomez, 1988). Seizures can begin anytime from birth to adulthood, but 75% of those with seizures begin during the first year, 86% by age 2, and 95% prior to age 5 (Sujansky & Conradi, 1995a). Thus, the risk of a child developing seizures is highest in the first 2 years and thereafter tends to diminish.

Focal motor seizures or generalized tonic–clonic seizures are most typical of SWS initially, but infantile spasms, myoclonic seizures and atonic seizures occur (Chevrie et al., 1988). The first few seizures are often focal even in patients who later develop generalized tonic–clonic seizures. Older children and adults are more likely to have complex partial seizures or focal motor seizures. Some patients continue to have daily seizures after the initial deterioration in spite of various daily anticonvulsant medications, while others have long seizure-free intervals, sometimes even without medication, punctuated by clusters of seizures (Chevrie et al., 1988).

The neurological deficits due to Sturge–Weber syndrome depend on the location of the intracranial vascular lesion. Because the occipital region is so often involved, visual field deficits are common. Hemiparesis often develops acutely, in conjunction with the initial flurry of seizures. Although often attributed to post-ictal weakness, hemiparesis may be permanent or persist much longer than the few hours typical of a postictal deficit. Some children suddenly develop weakness without seizures, either as repeated episodes of weakness similar to transient ischemic attacks or as a single stroke-like episode with persistent deficit (Garcia et al., 1981). In patients with both hemiparesis and seizures, it is difficult to establish which came first. Not all patients have permanent focal neurological signs.

Early developmental milestones are typically normal, but mild to profound mental deficiency eventually develops in about half of SWS patients (Sujansky & Conradi, 1995b). Only 8% of the patients with bilateral brain involvement are intellectually normal (Bebin & Gomez,

1988). Behavioural abnormalities are often a problem even in patients who are not mentally retarded. The clinical condition eventually stabilizes, leaving a patient who has residual hemiparesis, hemianopia, retardation, and epilepsy but without further deterioration. Intracranial hemorrhage due to SWS is rare.

Resection of the brain containing the vascular abnormality sometimes improves seizure control and promotes intellectual development (Carson et al., 1996; Vining et al., 1997). Despite the general agreement that surgical resection is effective, there is debate about patient selection and about the timing of surgery. Almost one patient in five has bilateral cerebral lesions, limiting the surgical options unless one hemisphere is clearly causing most of the seizures, and there is also reluctance to resect a still functional portion of the brain and cause a new deficit (Arzimanoglou & Aicardi, 1992). Surgery is usually reserved for patients with severe seizures who do not respond to medication and who already have clinical dysfunction of the area to be removed (e.g. hemiparesis or hemianopia), an approach similar to that used in other children with refractory epilepsy (Roach et al., 1994).

Diagnostic studies in Sturge–Weber syndrome (SWS)

Most of the children with facial port-wine nevi do not have an intracranial angioma, and neuroimaging studies and other tests help to distinguish the children with Sturge–Weber syndrome from those with an isolated cutaneous lesion. Although gyral calcification is a classic feature of SWS, the 'trolley track' appearance first described on standard radiographs is uncommon especially in neonates, when the possibility of intracranial vascular anomaly typically arises. Intracranial calcification is best demonstrated with CCT (Fig. 128.10). Extensive cerebral atrophy is apparent even with computed tomography, but subtle atrophy is more readily demonstrated by magnetic resonance imaging (MRI) (Elster & Chen, 1990).

Magnetic resonance imaging with gadolinium contrast (Fig. 128.11) effectively demonstrates the abnormal intracranial vessels in Sturge–Weber patients (Elster & Chen, 1990), and gadolinium contrast MRI is currently the best test to determine intracranial involvement. Magnetic resonance angiography has recently been used to directly image the larger abnormal vessels (Vogl et al., 1993).

Functional imaging with positron emission tomography (PET) demonstrates reduced metabolism of the brain adjacent to the leptomeningeal lesion (Chugani et al., 1989). However, patients with recent onset seizures may have increased cerebral metabolism near the lesion. SPECT (single photon emission tomography) shows reduced perfusion of the affected brain (Chiron et al., 1989). Both PET and SPECT often reveal vascular changes extending well beyond the area of abnormality depicted by CCT (Chugani et al., 1989; Maria et al., 1999). While functional imaging may not be necessary for all patients, these tests may help to initially establish a diagnosis and may help localize the lesion prior to surgery.

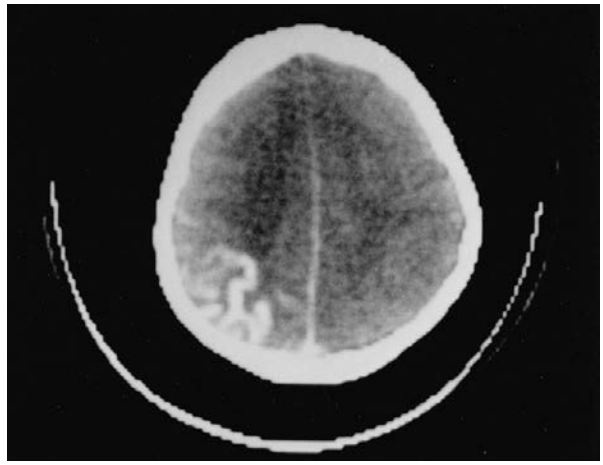

Fig. 128.10. Computed cranial tomography demonstrates an occipital gyriform calcification typical of Sturge–Weber syndrome (Reprinted from Garcia et al., 1981, with permission.)

Cerebral angiography is no longer needed in most patients with SWS, but it is sometimes useful in atypical patients or prior to surgery for epilepsy. The veins are more abnormal than the arteries (Probst, 1980). The subependymal and medullary veins are enlarged and tortuous, and the superficial cortical veins are sparse. Failure of the sagittal sinus to opacify after ipsilateral carotid injection may be secondary to obliteration of the superficial cortical veins by thrombosis (Bentson et al., 1971), and the abnormal deep venous channels probably have a similar origin as they form collateral conduits for nonfunctioning cortical veins (Probst, 1980; Bentson et al., 1971).

Pseudoxanthoma elasticum

Pseudoxanthoma elasticum (PXE) is a hereditary connective tissue disorder with skin, ophthalmic, and vascular manifestations (Carlborg et al., 1959; Viljoen, 1993). The clinical presentation and rate of progression varies considerably even among affected members of the same family (Altman et al., 1974). Both autosomal dominant and autosomal recessive forms of PXE exist (Pope, 1975).

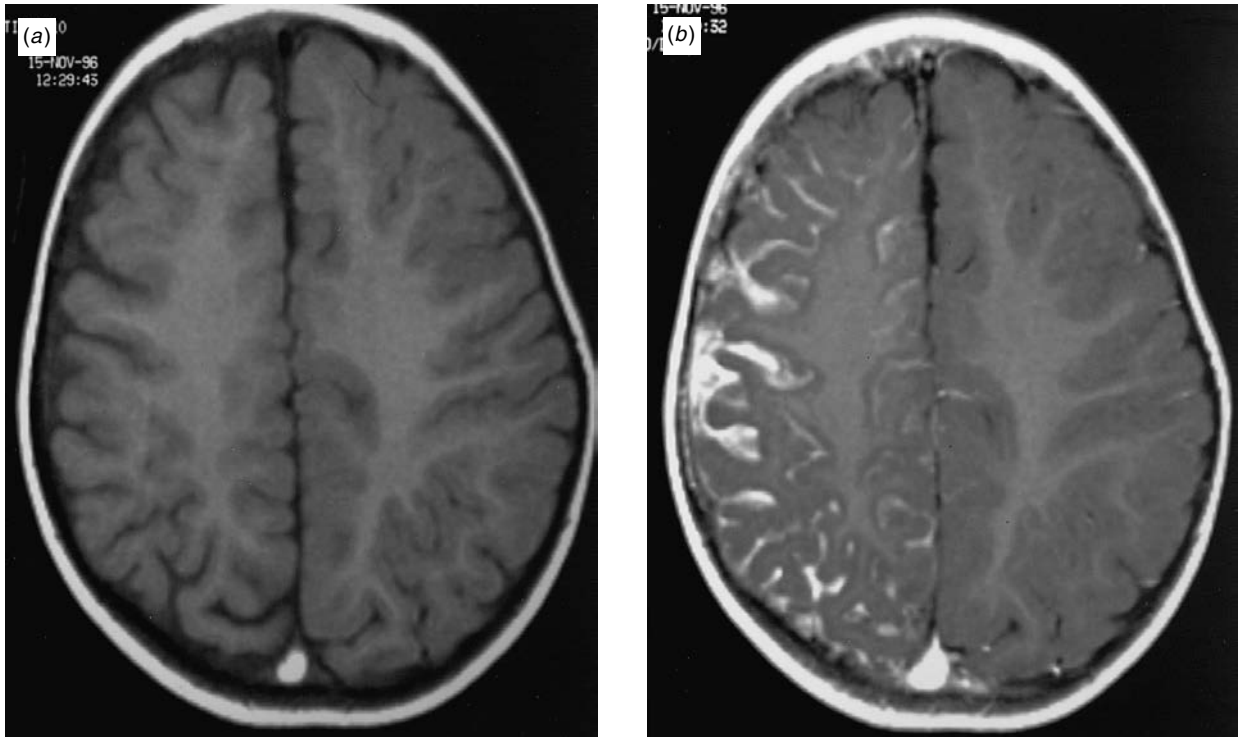

Fig. 128.11. (*a*) Normal T_1-weighted magnetic resonance scan without contrast infusion from a child with Sturge–Weber syndrome; (*b*) On the coronal view with gadolinium, his scan reveals a left frontal leptomeningeal and intraparenchymal angioma. (Reprinted from Roach & Bodensteiner, 1999, with permission.)

Cutaneous lesions of pseudoxanthoma elasticum

Cutaneous signs consist of yellowish plaques or papules of the neck, axilla, abdomen, or the inguinal, decubital or popliteal areas. Similar-looking lesions have been observed in the mucous membranes or intestinal mucosa. Older patients share a facial resemblance due to the lax redundant cutaneous changes of the face and neck. Pregnancy, puberty, and stressful emotional situations may increase the rate of progression of the cutaneous lesions (Reeve et al., 1979). Although the skin lesions of PXE become apparent before age 10 in about half of the patients, occlusive or hemorrhagic vascular complications occur primarily in adults.

Ophthalmic lesions of pseudoxanthoma elasticum

Angioid streaks of the ocular fundus, the result of ruptures of Bruch's membrane, are found in 85% of patients with PXE. These ocular lesions are grey or red irregular lines which radiate away from the optic disc (Secretan et al., 1998). Gradual visual loss may develop from macular degeneration, or visual loss can develop acutely from retinal hemorrhage (Carlborg et al., 1959).

Arterial lesions of pseudoxanthoma elasticum

Most of the systemic complications of PXE result from arterial degeneration and occlusion, but the exact clinical presentation depends largely on which organ system is affected. Progressive occlusion of the large arteries of the limbs may lead to intermittent claudication. Large arteries are sometimes palpably rigid, and radiographs of the extremities sometimes show arterial calcification. Coronary artery disease sometimes occurs in young patients with PXE. Gastrointestinal hemorrhage occurs in both adults and children. Epistaxis, hematuria, and hemoptysis occur but less often than gastrointestinal hemorrhage.

Neurological dysfunction with pseudoxanthoma elasticum

Neurological signs are secondary to vascular compromise. As in other parts of the body, brain dysfunction can result directly from arterial occlusion or rupture or indirectly from systemic hypertension or cardiovascular disease (Munyer & Margulis, 1981). Cerebrovascular lesions due to PXE do not usually manifest until adulthood, when

patients typically present with single or multiple cerebrovascular occlusions resulting from progressive narrowing and then occlusion of an artery (Rios-Montenegro et al., 1972). The angiographic pattern resembles that of severe atherosclerosis, but if the occlusion occurs gradually, sufficient collateral flow may develop to prevent acute neurologic signs (Rios-Montenegro et al., 1972).

Aneurysms of the intracranial carotid artery are common (Munyer & Margulis, 1981), but aneurysms of the other intracranial arteries also occur (Scheie & Hogan, 1957).

Genetics of pseudoxanthoma elasticum

Pseudoxanthoma elasticum results from a mutation of an ABC transporter gene at 16p13.1 (Le Saux et al., 1999, 2000; Bergen et al., 2000; Cai et al., 2000). Both the autosomal dominant and autosomal recessive forms of PXE have been linked to 16p13.1, suggesting that allelic heterogeneity of a single gene accounts for all of the cases (Struk et al., 1997; van Soest et al., 1997).

Ehlers–Danlos syndrome

Several subtypes of Ehlers–Danlos syndrome (EDS) can be defined by clinical manifestations, inheritance patterns, and specific molecular defects (Roach & Zimmerman, 1995; Beighton, 1993; Byers et al., 1979). Together these syndromes are characterized by fragile or hyperelastic skin (Fig. 128.12), hyperextensible joints, vascular lesions, easy bruising and excessive scarring after injuries (Beighton, 1993). About 80% of the patients with EDS have types I, II, or III, and the other subtypes are individually uncommon (Beighton, 1993). Vascular lesions such as aneurysm and arterial dissection are frequent problems in type IV EDS, and these complications often lead to premature death (Pepin et al., 2000). All of the familial Ehlers–Danlos patients with a documented abnormality of type III collagen have displayed autosomal dominant inheritance (Beighton, 1993).

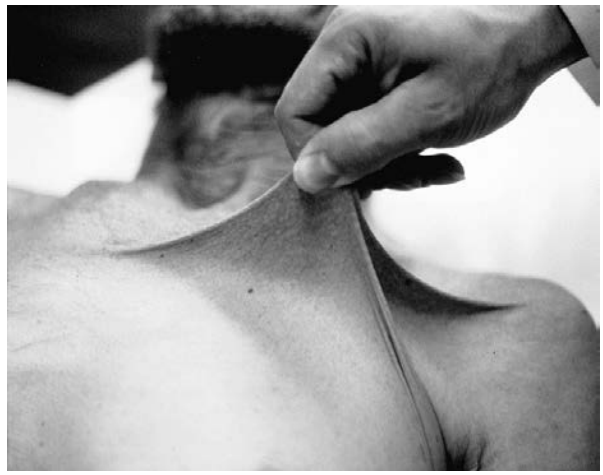

Fig. 128.12. Hyperelasticity of the skin in a patient with Ehlers–Danlos syndrome. (Reproduced from Roach, 1989, with permission.)

Intracranial aneurysm

Rubinstein and Cohen (1964) first reported an adult woman with EDS and aneurysms of both the internal carotid and vertebral arteries. Numerous other individuals with extracranial and intracranial aneurysms have been described, including several people with multiple intracranial aneurysms (Schievink et al., 1990). Most patients became symptomatic in early adulthood, but children and adolescents are occasionally affected.

The internal carotid artery is the most likely intracranial vessel to develop an aneurysm due to EDS type IV (Fig. 128.13). Typically, the aneurysm develops in the cavernous sinus or just as the carotid emerges from the sinus (Rubinstein & Cohen, 1964; Schievink et al., 1990), so aneurysmal rupture often creates a cavernous–carotid fistula. Aneurysms in other intracranial arteries are more likely to present with subarachnoid hemorrhage. In one family, members of three different generations suffered subarachnoid hemorrhage (Schievink et al., 1990).

Unsuspected mutations of the *COLA3A1* gene which causes EDS type IV were not found in a cohort of 58 patients with an intracranial aneurysms or cervical dissections but no other signs of EDS (Kuivaniemi et al., 1993).

Carotid–cavernous fistula

Carotid–cavernous fistula has been reported in several patients with EDS, in some after minor head trauma but most often spontaneously. Intracranial aneurysms and carotid–cavernous fistulae often occur together (Lach et al., 1987). Rupture of an internal carotid artery aneurysm within the cavernous sinus probably causes many of the fistulae (Fox et al., 1988), although spontaneous fistula formation without an aneurysm does occur (Schievink et al., 1991; Halbach et al., 1990). Fragmentation of the internal elastic membrane and fibrosis of portions of the carotid wall are typically found at autopsy (Schoolman & Kepes, 1967).

The vascular fragility of type IV EDS makes both standard angiography and intravascular occlusion of the fistula more difficult (Lach et al., 1987). Nevertheless, intravascular occlusion is sometimes successful (Kashiwagi et al., 1993; Kanner et al., 2000).

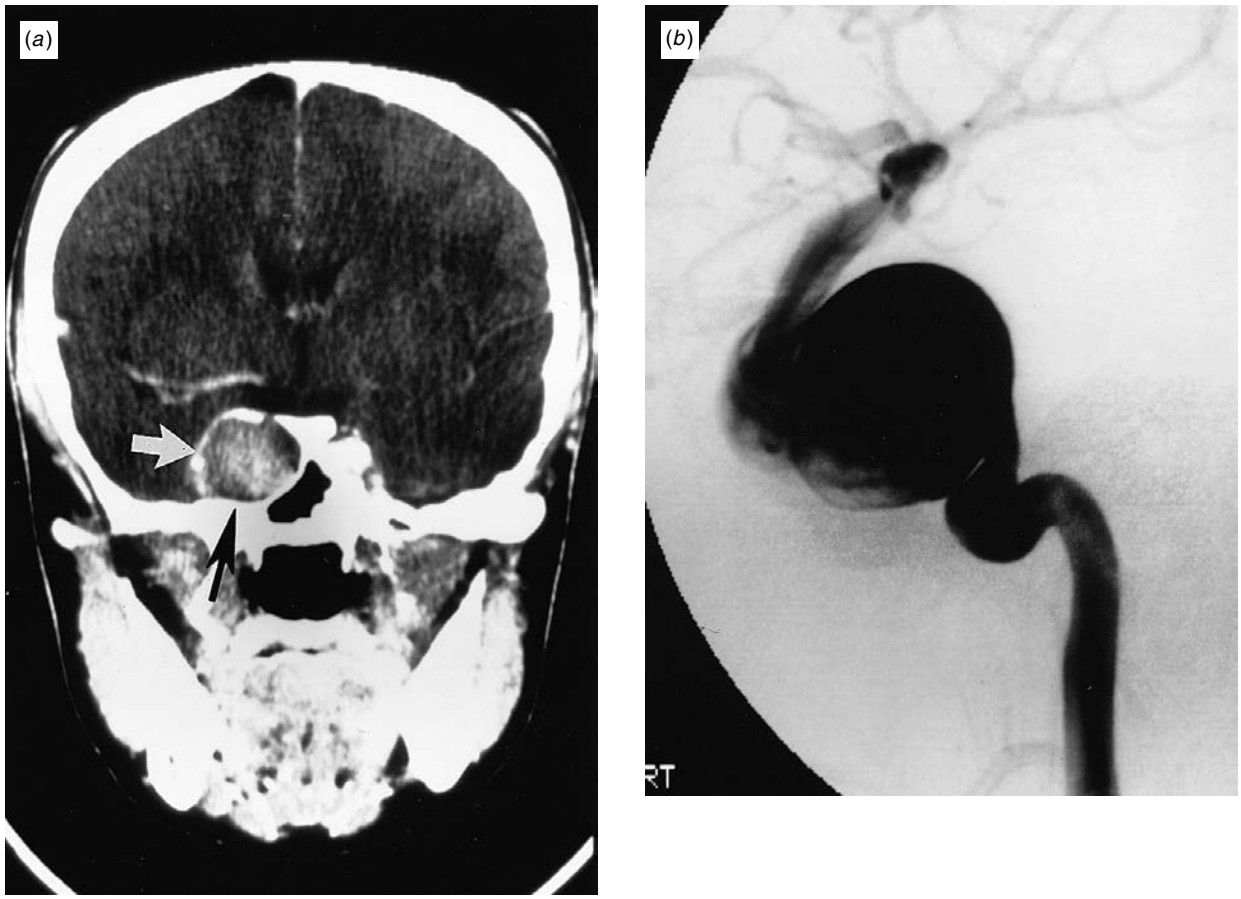

Fig. 128.13. (*a*) Coronal computed tomography with contrast (from an 18-year-old with headaches and a family history of Ehlers–Danlos type IV) reveals a large aneurysm (arrow) of the intracavernous carotid artery. (*b*) Internal carotid angiogram confirms the giant aneurysm of the intracavernous carotid artery. (Reproduced from Roach & Zimmerman, 1995, with permission.)

Arterial dissection

Arterial dissection has been documented in most of the intracranial and extracranial arteries, and the clinical presentation depends primarily on which artery is affected (Pope et al., 1991). One patient with a vertebral dissection developed a painful, pulsatile mass of the neck (Edwards & Taylor, 1969).

Surgery is difficult because the arteries are friable and difficult to suture (Edwards & Taylor, 1969). The arteries fail to hold sutures, and handling the tissue leads to tears of the artery or separation of the arterial layers (Sheiner et al., 1985).

Genetics of Ehlers–Danlos syndrome type IV

Ehlers–Danlos type IV is an autosomal dominant disorder with frequent spontaneous mutations. It results from a mutation of the *COLA3A1* gene on chromosome 2, a gene which codes for the alpha 1 chain of type III collagen, which is expressed in high levels in blood vessels (Gilchrist et al., 1999). Various *COLA3A1* mutations have been identified, but there is no consistent genotype–phenotype correlation (Gilchrist et al., 1999; Kontusaari et al., 1992; Sillence et al., 1991; Tsipouras et al., 1986; Richards et al., 1992; Schwartze et al., 1997).

Hereditary hemorrhagic telangiectasia (HHT)

Hereditary hemorrhagic telangiectasia (Osler–Weber-Rendu disease) is an autosomal dominant disorder which features telangiectasias of the skin, mucous membranes, and various internal organs (Garland & Anning, 1950; Reilly & Nostrant, 1984; Guillen et al., 1991; Shovin et al., 2000). Clinical diagnostic criteria have recently been published

Table 128.4. Diagnostic criteria for hereditary hemorrhagic telangiectasia

Criteria	Explanation
1 Epistaxis	Spontaneous nosebleeds
2 Telangiectases	Multiple lesions at typical sites (lips, mouth, nose, fingers)
3 Visceral lesions	Gastrointestinal telangiectasia (with or without bleeding) or AVMs of the lungs, liver, brain, or spinal cord
4 Family history of HHT	A first-degree relative with HHT by these criteria

Notes:
Definite: meets three criteria.
Possible/suspected: meets two criteria
Unlikely: fewer than two criteria.
Source: Modified from Shovlin et al. (2000), with permission.

(Shovlin et al., 2000; Table 128.4). However, both the clinical manifestations and the age of presentation are variable, and diagnosis may be difficult in younger patients who have not developed the full array of signs (Shovlin et al., 2000).

Cutaneous features of HHT

Cutaneous telangiectasias occur more often on the face, lips, and hands than on the trunk or legs (Bird et al., 1957; Reilly & Nostrant, 1984). Epistaxis due to telangiectasias of the nasal mucosa is often the first indication of HHT (Bean, 1958; Reilly & Nostrant, 1984; Plauchu et al., 1989). About a third of patients have conjunctival telangiectasias and 10% have retinal vascular malformations, although visual loss from these lesions is not common. Telangiectasias are not often prominent during the first decade, but thereafter they tend to enlarge and multiply (Plauchu et al., 1989).

Arterial lesions of HHT

In addition to the vascular lesions affecting the central nervous system, vascular malformations affect the lungs, gastrointestinal tract, or genitourinary system can lead to hemoptysis, hematemesis, melena, or hematuria (Bird et al., 1957; Reilly & Nostrant, 1984; Plauchu et al., 1989).

Neurologic features of HHT

Headache, dizziness, and seizures are common in individuals with HHT (Reagan & Bloom, 1971; Adams et al., 1977). Less common problems include paradoxical embolism with stroke, intraparenchymal or subarachnoid hemorrhage, and meningitis or cerebral abscess.

Paradoxical embolism through a pulmonary arteriovenous fistula leads to cerebral infarction in patients with HHT (Sisel et al., 1970), although rarely a clot may form within the fistula itself before migrating into the arterial circulation. Intermittent symptoms result from repeated small emboli with subsequent improvement. Transient deficits during hemoptysis could result from air embolism via a bleeding pulmonary arteriovenous fistula (Boczko, 1964).

About 1% of patients develop cerebral abscess or meningitis, probably because septic microemboli bypass the normal filtration of the pulmonary circulation via a pulmonary arteriovenous fistula.

Vascular anomalies may be found anywhere in the brain, spinal cord or meninges (Roman et al., 1978; Heffner & Solitare, 1969), and more than one type of lesion may be present in the same patient (Roman et al., 1978). Intracerebral vascular anomalies occur much more often than once suspected. One summary of 90 HHT patients from the literature listed 17 (19%) with arteriovenous malformations and 36 (40%) with telangiectasias or angiomas (Roman et al., 1978). Fulbright and colleagues identified 42 patients with various types of cerebral vascular anomalies among 184 consecutive HHT patients who underwent cranial MRI studies (Fulbright et al., 1998).

Many of these patients remained asymptomatic, and there is some evidence that the intracranial vascular lesions of HHT are less likely to bleed than sporadic arteriovenous malformations (Willemse et al., 2000). Hereditary hemorrhagic telangiectasia should be considered in patients with multiple cerebrovascular malformations (Aesch et al., 1991; Willinsky et al., 1990; Sobel & Norman, 1984; Willemse et al., 2000).

Intracranial aneurysms are much less common in HHT patients than arteriovenous malformations (Grollmus & Hoff, 1973; Roman et al., 1978; Fisher & Zito, 1983). The number of individuals with both HHT and intracranial aneurysm is small enough that the association could be coincidental. The same is true of spontaneous carotid–cavernous fistula.

Genetics of HHT

Hereditary hemorrhagic telangiectasia is an autosomal dominant disorder with variable expressivity and age-related penetrance. Its estimated incidence is 1 in 10 000 individuals (Pece-Barbara et al., 1999). About 30% of the time HHT develops via spontaneous mutation.

Genes on chromosomes 9 and 12 are responsible for HHT1 and HHT2 respectively. The *HHT1* gene at 9q33–34 codes for endoglin, an accessory membrane glycoprotein expressed at high levels in vascular endothelium (Pece-

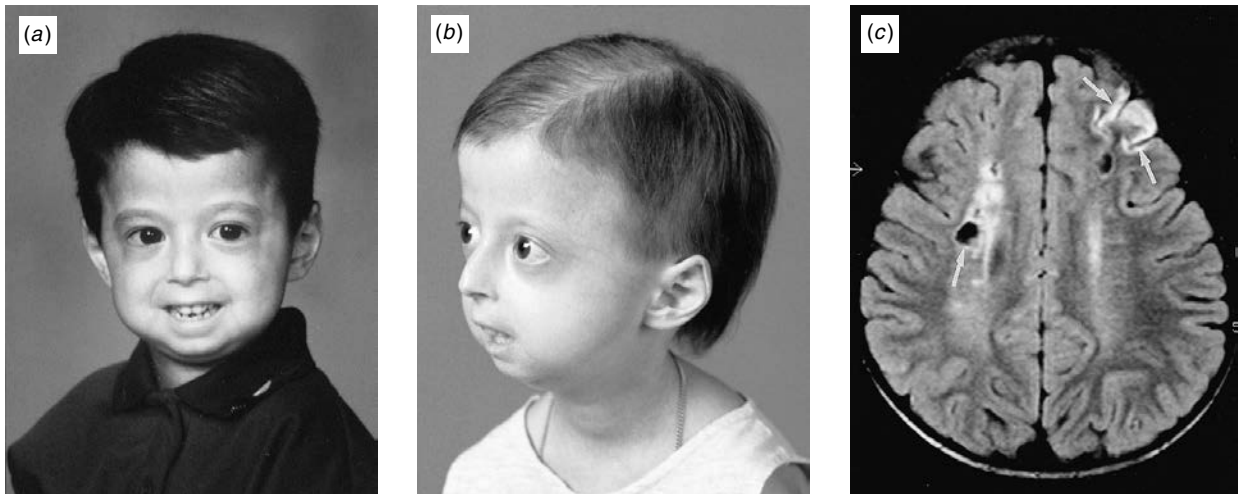

Fig. 128.14. Premature aging in a young boy with multiple ischemic infarctions. (*a*) School portrait prior to the onset of symptoms. (*b*) Later photograph reveals hair loss, stooped posture, and loss of subcutaneous fat. (*c*) Magnetic resonance image shows multiple ischemic infarctions of different ages (arrows). (Reprinted from Miller & Roach, 2000, with permission.)

Barbara et al., 1999). HHT2 results from mutation of the *ALK1* (activin receptor-like kinase-1) gene at 12q13. Like endoglin, ALK1 is expressed at high levels in endothelial cells (Abdalla et al., 2000). Individuals with HHT1 have a greater risk of pulmonary arterial malformations than those with HHT2, while those with HHT2 tend to have a milder phenotype and later onset of symptoms (Pece-Barbara et al., 1999).

Progeria

Hutchinson–Gilford syndrome or progeria (derived from *pro*, before, and *geras*, old age) is a rare condition characterized by premature aging (Fig. 128.14) and the early occurrence of age-related complications. DeBusk estimates that one person in eight million develops progeria (DeBusk, 1972).

Patients with progeria do not reproduce and most do not have affected family members. Some of the children with affected siblings have had atypical features (Viegas et al., 1974), leading to debate about the genetic nature of progeria. Both autosomal dominant and recessive traits have been proposed, but the clinical pattern is perhaps best explained by a dominant trait, usually arising via spontaneous mutation, with occasional instances of germline mosaicism in the families with affected siblings.

The pathogenesis of progeria is not well understood. In one study, cultured fibroblasts derived from a person with progeria reached senescence earlier than control cells, and patient fibroblasts had reduced levels of mRNA coding for the macromolecules of the extracellular matrix (Colige et al., 1991). It is tempting to speculate that progeria could result from an abnormality of telomerase, shown recently to determine the number of cell replications before cellular senescence.

Clinical features of progeria

The signs of progeria usually become apparent during the first 2 years of life. Some features may be subtle or absent initially, then worsen over time. Alopecia, for example, may not be present at first, but is almost universal by adolescence. The most common early features are short stature, decreased subcutaneous fat stores, joint restriction and alopecia (Gilkes et al., 1974; DeBusk, 1972). Skeletal changes include thinning of the bones, coxa valga, and small clavicles; some children have repeated poorly healing fractures. The characteristic physical appearance of progeria results from a combination of postural changes, decreased subcutaneous fat, alopecia, and facial hypoplasia and micrognathia. Children with progeria eventually develop premature atherosclerosis, leading to coronary artery disease or stroke (Fig. 128.14) (Dyck et al., 1987). Heart disease is the chief cause of death in patients with progeria (Dyck et al., 1987). Survival into middle age has been described, but death during the second decade is typical (Dyck et al., 1987).

Several other syndromes also cause signs of premature aging or carotid occlusion with stroke, and these disorders constitute the differential diagnosis of progeria. Werner's

syndrome is an autosomal recessive disorder characterized by cataracts, scleroderma with subcutaneous calcium deposition, a beak-like nose, and the premature appearance of disorders usually associated with aging, such as greying of the hair, senile macular degeneration, osteoporosis, diabetes, malignancies, and atherosclerosis (Gilkes et al., 1974; Epstein et al., 1966). Werner's syndrome has been described as adult progeria (Thannhauser, 1945). Affected individuals often live well into adulthood, and, even so, death from cardiac disease and stroke seem to be less common than in patients with progeria. Mandibuloacral dysplasia is another autosomal recessive disorder which features alopecia and short stature, along with clavicular and mandibular hypoplasia, stiff joints, and persistently open cranial sutures. Whether this is an entirely distinct condition is still in question.

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Neurological complications after organ transplantation

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The impressive progress of transplantation over the last 20 years has been made possible by surgical advances, the discovery of a superb immunosuppressive agent, cyclosporine, improved postoperative care, and infectious disease surveillance. These advances, however, were not devoid of neurological complications. The risk of such complications is after surgery when the graft may deteriorate in function from vascular complications. An entirely new field of neurological complications, unique to organ transplant recipients, has emerged, but only now are some of the basic mechanisms being unravelled. Neurologists have started to play an integral part in the postoperative evaluation and management of patients after transplantation and are able now to recognize the clinical presentations. We are beginning to understand how immunosuppressive agents can cause neurotoxicity, risks of infections of the central nervous system (CNS), management of seizures, and long-term effects, including demyelinating disorders (Wijdicks, 1995, 1999). This chapter targets the major neurological disorders seen after organ transplantation.

Epidemiology

Estimation of frequency of neurological complications after transplantation is fraught with difficulties. First, most studies have reported a retrospective analysis of surgical series that are probably skewed towards the more severe neurological complications. Neurologists would only be called on when a neurological complication appears to dominate the clinical picture or could invalidate the initial success of grafting. One can also expect that, with further categorization of neurological syndromes and consequently recognition by the transplant team, neurologists will be consulted less often and only when diagnosis and management become more complex or frustrating. Prospective studies may also not capture all of postoperative events, and to be accurate, they would need a neurologist participating in rounds with the transplant team. Neurological complications in organ-transplant recipients are more common after liver and heart transplants, because these surgeries are more prone to hemodynamic instability. Neurological complications in renal transplant recipients usually appear in the years after transplantation and may be due to comorbidity associated with end-stage renal failure and a result of long-term immunosuppression.

It is useful to categorize neurological complications into major complications, such as recurrent seizures, postoperative failure to awaken, neurotoxicity associated with immunosuppressive agents, and acute neuromuscular disorders, and minor manifestations, such as tremors, transient agitation, and confusional states.

The estimated frequency of major neurological manifestations is summarized in Table 129.1. Seizures are particularly common in liver and lung transplantation (Starzl & Demetris, 1990; Wong et al., 1999), and mononeuropathies appear more often in kidney transplantation. Ischemic and hemorrhagic stroke are uncommon occurrences in all transplantations, perhaps reflecting the low incidence of stroke in abdominal operations. Stroke is expected to occur more frequently relative to cardiac transplants, in which multiple vascular reattachments take place. The frequency of immunosuppressive agent neurotoxicity has decreased substantially, because transplant surgeons have become familiar with more appropriate titration of cyclosporine and FK506. Newer drugs, such as an oral microemulsion of cyclosporine (Neoral) and mycophenolate mofetil (Cellcept), which both have a much safer profile, may be responsible for this observation as well. Neurological complications after bone marrow transplantation are more difficult to estimate because of varied

Table 129.1. Estimated incidence of neurological complications

	Incidence (%)				
Type	Coma or stupor	Seizures	Immunosuppression neurotoxicity	Neuromuscular disorders	Stroke[a]
Heart	<1	Sporadic	Sporadic	Sporadic	1–5
Liver	5–10	2–40	10	5	<1
Kidney	<1	Sporadic	5	5–40	<1
Lung	10	20	NR	5	<1
Pancreas	<1	10	NR	NR	<1
Bone marrow	<1	10–15	5	5–20	1–3

Notes:

[a] Includes anoxic–ischemic encephalopathy in some series.

NR, not reported yet.

patient populations, the type of bone marrow transplant, and whether the patient received bone marrow from an alternative donor (patients who receive an allogenic graft from either a human leukocyte antigen [HLA]-matched unrelated donor or an HLA-mismatched related donor). Institutions with a major commitment to transplantation programmes should keep a prospective database to monitor trends over time. With these data we have been able to find a decreasing trend of neurologic complications except for stroke in heart transplantation (Jarquin-Valdivia et al., 1999) and decrease in major complications in patients using cyclosporine (Wijdicks et al., 1999).

Immunosuppression neurotoxicity

Traditional immunosuppressive regimens include cyclosporine or tacrolimus, azathioprine, and corticosteroids, but postoperative protocols are in flux. Novel agents include sirolimus, Neoral, and mycophenolate mofetil. Newer investigational agents are leflunomide (tyrosine kinase inhibitor), and monoclonal antibodies to CD4 on adhesion molecules. Polyclonal antithymocyte globulin or OKT3 is typically used in rejection therapy.

Cyclosporine remains the prime immunosuppressive agent in liver, kidney, and bone marrow transplantation. Cyclosporine is a cyclic oligopeptide composed of 11 amino acids, which are extracted from fungi. Its presumed mechanism of modulating T-cell function is linkage to an intracellular protein called 'cyclophilin', resulting in a complex that subsequently blocks calcineurin activity. Calcineurin regulates the interleukin-2 gene transcription and T-cell lymphocyte proliferation, and thus when blocked, would stop the immunological response to a new graft. T-cell activation, which after differentiation and clonal expansion induces cytokine synthesis, activates a complex cascade of interacting co-stimulatory molecules and will result in rejection. Cyclosporine also inhibits T-cell activation and thus prevents rejection. Nonetheless, it has been estimated that at least 50% of allograft recipients have at least one episode of acute rejection during the post-transplant period. Cyclosporine has a half-life of 8 hours and, like tacrolimus, is metabolized by the cytochrome P-450 microsomal enzyme system. Therefore, antifungal agents, calcium channel blockers, fluoroquinolones, macrolide antibiotics and metoclopramide, which may be used in the postoperative period, may cause cyclosporine toxicity as a result of inhibition of this metabolizing system.

Cyclosporine may cause hypomagnesemia, hyperkalemia, and hypertension, but neurotoxicity is most frequent. Cyclosporine neurotoxicity occurs in 1 of 10 patients with a transplanted liver, but is only found in 1 of 20 patients who receive renal or bone marrow transplants. The clinical spectrum of cyclosporine-associated neurotoxicity has changed dramatically over the years (Table 129.2). In the earlier days of transplantation, cyclosporine neurotoxicity was considered only after patients progressed to coma and status epilepticus. Early recognition and more careful intravenous titration of cyclosporine has reduced the severity of neurotoxicity. With the improved bioavailability of cyclosporine, severe neurotoxicity have become less common, and headache, tremors, and occasional seizures have remained as overwhelming side effects of cyclosporine microemulsion.

Although cyclosporine is highly hydrophobic, it does not permeate the intact blood–brain barrier, owing to tight

Table 129.2. Clinical features of immunosuppression neurotoxicity (increasing severity)

Insomnia
Vascular headache
Tremors
Acute psychosis
Visual hallucination
Stuttering speech, mutism
Cortical blindness
Dystonia, oculogyric crisis
Seizures
Coma

junctions and lack of lipoprotein transport (Begley et al., 1990). Therefore, a damaged blood–brain barrier is pivotal for cyclosporine penetration into the brain. Nonetheless, a recent study documented metabolites of cyclosporine in cerebrospinal fluid (CSF) in 4 of 17 liver transplant recipients. Only patients with high levels of blood urea nitrogen and bilirubin had these metabolites of cyclosporine in the CSF, and it appears that acute renal failure may have enhanced CSF penetration (Bronster et al., 1999).

Cyclosporine neurotoxicity is also associated with low plasma cholesterol. Cyclosporine penetrates the intercellular brain tissue through low-density lipoprotein receptors (de Groen et al., 1987). Hypocholesterolemia results in up-regulation of low-density lipoprotein receptors, which may facilitate transport. It has been documented that only a small percentage of cyclosporine exists in the free or unbound state, and changes in protein binding may result in a significant increase in the therapeutic and toxic effects of the drug. This mechanism cannot explain cyclosporine neurotoxicity in liver transplant patients with normal serum cholesterol levels and in other transplant recipients with cyclosporine neurotoxicity.

Another possibility for cyclosporine to exert its effect on the neuronal structures might be damage of the blood–brain barrier. It has been postulated that cyclosporine may directly damage the endothelium, leading to increased endothelin production and release of thromboxane, resulting in vasoconstriction and microvascular damage. It is possible that the blood–brain barrier may also have become damaged in patients who had an anoxic ischemic injury or in patients with prior hepatic encephalopathy, but none of these factors has consistently increased the risk in cohorts being evaluated for predictive factors for cyclosporine neurotoxicity. Disturbance of the blood–brain barrier may lead to vasogenic edema, and when exposure to the drug is prolonged, apoptosis may occur (Wijdicks, 2001). Other factors related to cyclosporine neurotoxicity are hypomagnesemia, corticosteroids, and hypertension, but whether these risk factors are simply covariants and therefore unrelated is not clear.

Cyclosporine neurotoxicity may produce a posterior leukoencephalopathy on magnetic resonance imaging similar to patterns seen in hypertensive encephalopathy. This suggests that hypertension from cyclosporine toxicity, another major management problem with its use, may be the main final common pathway. However, hypertension from cyclosporine typically occurs several weeks into the treatment. Hypertension is anticipated and aggressively treated by experienced transplant teams, resulting in controlled blood pressures in most patients with cyclosporine neurotoxicity (Wijdicks et al., 1995, 1999).

The clinical features of cyclosporine neurotoxicity typically occur during the intravenous administration phase. An acute psychotic period in a patient who also displays a fine hand tremor is characteristic. This psychotic period may involve bizarre delusions and visual hallucinations commonly with bright coloured lights and also paranoid behaviour, a panic state, or nihilism. Speech becomes rambling and nonsensical but may have other characteristics (Bronster et al., 1995), including mutism (Valldeoriola et al., 1996). Tongue tremors and an action myoclonus speech disorder may be seen in which a patient stutters during rapid speaking but has a normal voice when asked to slow down. Speech abnormalities may progress to mutism and orolingual apraxia, with the patient unable to open the jaw and lips and to move the tongue, often also associated with some degree of generalized hypokinesia (Bird et al., 1990).

Although seizures in transplant recipients can be caused by many triggers, cyclosporine and tacrolimus neurotoxicity are commonly present (Fig. 129.1). Other potential triggers for seizures such as an acute metabolic derangement, drug toxicity, hypoxic–ischemic injury, newly developed cerebral structural lesion, and particularly a rapidly evolving opportunistic infection should be strongly considered and excluded as well. Generalized tonic–clonic seizures may be the only presentation of cyclosporine neurotoxicity (Wijdicks et al., 1996a,b). Status epilepticus is exceptional, often because the earlier manifestation of tremors and confusion followed by a single seizure was recognized by the transplant team and prompted discontinuation of cyclosporine.

Visual manifestations of cyclosporine neurotoxicity may take the dramatic form of cortical blindness but are rare (Rubin & Kang, 1987). Posterior leukoencephalopathy is reversible, but a recent report described a 2-year-old child who, after bone marrow transplantation, developed oculogyric crisis with sustained upward and lateral eye deviation

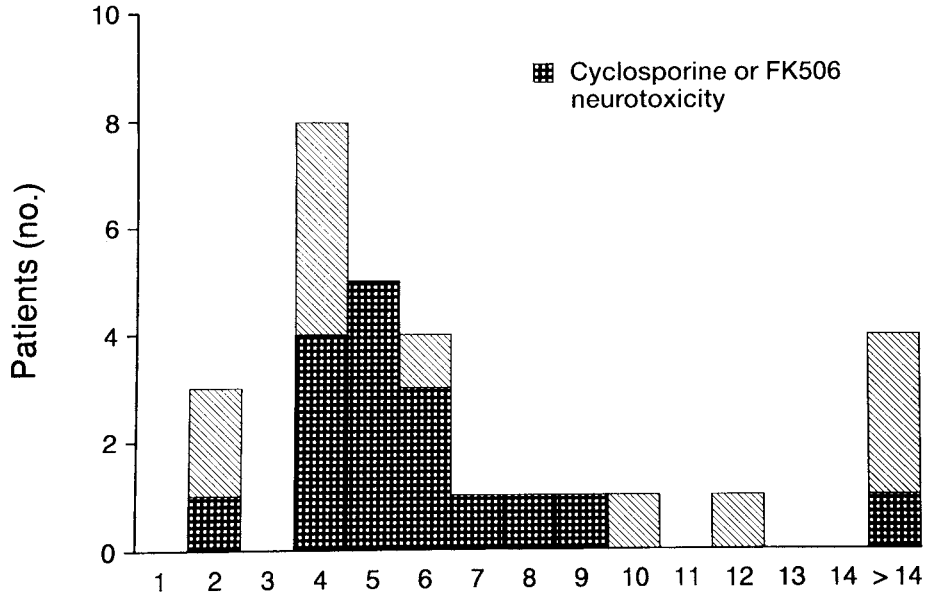

Fig. 129.1. Time of onset (in days) of new-onset seizures after liver transplantation indicates a large proportion of patients with cyclosporine or tacrolimus (formerly known as FK506) neurotoxicity. (From Wijdicks et al., 1996a,b, with permission from the American Academy of Neurology.)

and cortical blindness associated with bioccipital hemorrhagic infarcts (Antunes et al., 1999). Possibly a failure to recognize these dystonic eye movements led to prolonged exposure to cyclosporine neurotoxicity and permanent damage on MRI. More likely, permanent blindness, if it occurs in the setting of cyclosporine toxicity, is due to a retinal lesion (Esterl et al., 1996). In addition, cortical blindness in patients who underwent a heart or lung transplantation may not be related to cyclosporine neurotoxicity but due to hypotension or from cardiac emboli during removal of the diseased dilated myocardium.

Major management difficulties with cyclosporine are headache and insomnia. Headaches are often vascular-type headaches but may be unilateral and may have migraine features, such as nausea, vomiting and photophobia (Steiger et al., 1994; Rozen et al., 1996). We can now estimate that 10% to 20% of patients using cyclosporine in any formulation experience headaches. There is no relationship with the plasma cyclosporine levels, and headaches may persist or suddenly disappear after switching to another immunosuppressive agent, such as tacrolimus. Insomnia has emerged as a major nuisance leading to decreased productivity. Sleep studies are not available and dose adjustments are not always successful. It may be a reason for switching to tacrolimus as well.

Tacrolimus neurotoxicity has a virtually similar clinical profile to cyclosporine, and any of the above-mentioned features have been documented in tacrolimus (Eidelman, et al., 1991; Wijdicks et al., 1994; Small et al., 1996). Tremors, however, remain exceedingly more common, and speech abnormality associated with tacrolimus has more apraxic components characterized by a breathy phonation, imprecise articulation, vowel distortions, and the inability to perform non-speaking tasks, such as whistling and puckering of the lips. Many patients also complain of perioral tingling, hyperesthesias in the hands, and restless leg syndrome, but a polyneuropathy has not been documented clinically or defined electrophysiologically or pathologically in any of the patients.

The diagnosis of cyclosporine or tacrolimus neurotoxicity is based on clinical features alone and remains a tentative diagnosis until symptoms disappear after discontinuation of the drug. MRI scanning may document edema in the subcortical white matter of the occipital and parietal lobes (Fig. 129.2). These MRI changes are highly typical and can be seen in association with intracranial hemorrhage, predominantly subdural hematoma, acute cerebellar edema, and cortical hyperintensity. All of these changes disappear after a resolution of the symptoms. The sensitivity of magnetic resonance imaging in cyclosporine or tacrolimus neurotoxicity is low but increases with seizures and decrease in level of consciousness (Wijdicks, 1995; Wijdicks et al., 1996a,b). Extremely high blood levels of cyclosporine may confirm the clinical diagnosis, but a good clinical and laboratory correlation has not been found.

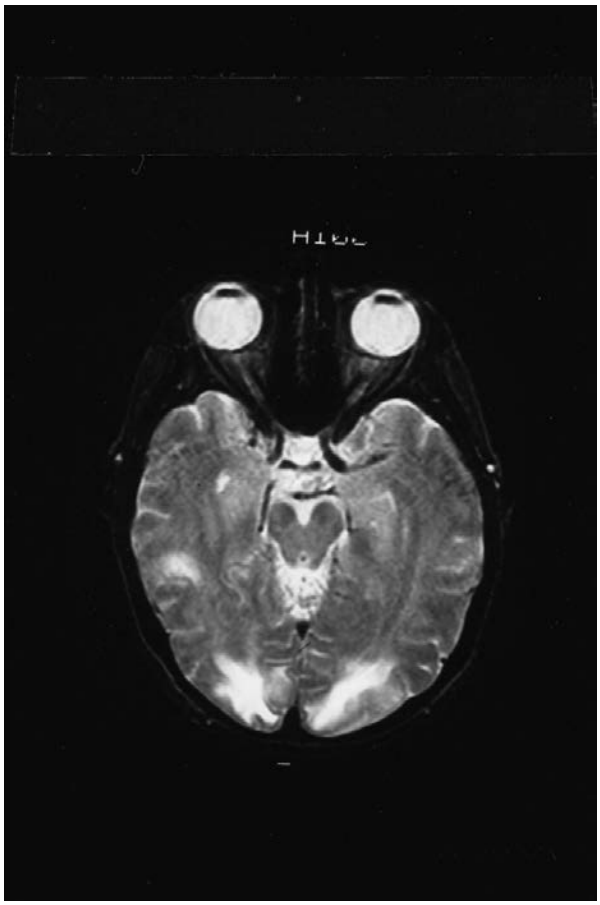

Fig. 129.2. Occipital lesions (posterior leukoencephalopathy) in cyclosporine neurotoxicity. (From Wijdicks, 1999, with permission from Mayo Foundation.)

Sirolimus is a novel immunosuppressive agent with a different target than tacrolimus (despite similarities in name). Neurotoxicity has not been reported yet except for mild headache and insomnia, thrombocytopenia and hyperlipidemia (Hong & Kahan, 2000; Kahan et al., 2000).

OKT3 has been used as a primary immunosuppressive agent in the initial phases in heart and lung transplantation. OKT3 has become part of many cardiac transplantation protocols, but neurotoxicity, after a few incidental reports, is rarely seen. OKT3 is combined with corticosteroids and azathioprine and after 2 weeks is replaced by an oral dose of cyclosporine. OKT3 is a monoclonal antibody targeting T cells and may block the T-cell receptor interaction with major histocompatibility antigens. In the first days of administration, a cytokine release syndrome may occur, leading to fever, headache, pulmonary edema, and deteriorating renal function, all potential contributors to a reduced level of consciousness. Profound headaches may indicate the development of aseptic meningitis and CSF examination documents lymphocytic pleocytosis, usually within the first 3 days after initiation of therapy. Mild headache may progress in exceedingly rare circumstances to brain swelling, bilateral papilledema, and vision loss as a presentation of a rarely seen OKT3 encephalopathy.

Management of immunosuppressive neurotoxicity is discontinuation of the immunosuppressive agent and after several days restarting with an alternative drug. Cyclosporine can be replaced by tacrolimus, surprisingly without much risk of recurrent toxicity, but many transplant teams now use mycophenolate mofetil. When neurotoxicity is associated with significant agitation, haloperidol (2–4 mg) given intravenously every 6 hours and lorazepam (2–4 mg) given intravenously every 4 to 6 hours can be suggested. When headache remains persistent, the dose should be reduced. High-dose aspirin (1 500 mg) is often effective. Drugs such as nicardipine, diltiazem, and verapamil are not advised, because they can significantly increase cyclosporine concentrations and thus have a paradoxical effect and perpetuate headaches.

Central nervous system infections

CNS infections are a lifetime risk after transplantation, and the United Network for Organ Sharing continues to list infections as a major cause of morbidity and mortality (Fishman & Rubin, 1998). These patients are at risk as a result of chronic immunosuppressive therapy, but environmental exposure is essential. An example is exposure to *Aspergillus* species within the hospital, which may be seen during construction and may seriously challenge transplantation wards and cause outbreaks (Massin et al, 1994; Brown et al., 1996). Most of the CNS infections occur 1 month after transplantation and after the perioperative period. Fulminant CNS infections in the early period, however, do occur and should be considered when seizures, fever and a rapid onset of coma are seen in a setting of a systemic infection. Many clinical presentations of CNS infections are attenuated unless the infection is advanced. Clinical symptoms may be vague, and similar symptoms can be due to drug toxicity or rejection. Patients who develop a *Listeria* meningitis may complain of only persistent headache and fever and may have normal results of neuroimaging study and spinal fluid examination until the CSF culture documents the offending organism.

CNS infections are divided into meningitis, cerebritis, and development of multiple cerebral abscesses. *Listeria monocytogenes*, *Cryptococcus neoformans*, and *Aspergillus fumigatus* are the major pathogens causing CNS infections

Table 129.3. Transplant-associated CNS infections

Organism	Time from Tx (mo)	Presentation	CT or MRI	CSF	Diagnosis	Therapy
Listeria monocytogenes	1–6	Headache, stupor (prior abdominal cramps and diarrhea)	Meningeal enhancement only	May be normal	CSF culture	i.v. ampicillin, 10–12 q/day; i.v. gentamicin, 1.0–1.5 mg/kg every 8 hours
Nocardia asteroides	1–6	Localizing findings: headache, stupor	Abscesses (may be solitary)	Pleocytosis	Biopsy, CSF blood culture	Trimethoprim-sulfamethoxazole, 2.5–10.0 mg/kg twice a day
Aspergillus	1–6	Rapidly developing coma, seizures (prior lung infection)	Ring lesion, hemorrhage scattered	Pleocytosis	Biopsy, blood culture	Amphotericin B, 1.0–1.5 mg/kg per day
Cryptococcus neoformans	>6	Unexplained headache, fever, cognitive changes, rarely focal signs	Thalamus, basal ganglia; widespread miliary; no edema	Pleocytosis; may be normal	CSF antigen	Amphotericin B, 1.0–1.5 mg/kg per day
Toxoplasma gondii	>6	Seizures, stupor, rarely focal signs	Multiple lesions, subcortical meninges spared	Pleocytosis; may be normal	Brain biopsy, SPECT	Trimethoprim-sulfamethoxazole, 2.5–10.0 mg/kg twice a day

Notes:
CSF, cerebrospinal fluid; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; SPECT, single photon emission computed tomography; Tx, transplantation.
Source: From Wijdicks 2002, with permission from Mayo Foundation.

in organ transplant recipients (Conti & Rubin, 1988; Hall et al., 1989). Details of these infections are found in other chapters of this book. Their clinical presentation, means of diagnosis, and laboratory tests are summarized in Table 129.3.

Transplant recipients are also at risk of Epstein–Barr virus-associated infections that may cause lymphoma or an Epstein–Barr virus-associated post-transplantation lymphoproliferative disease, which can cause seeding along the spinal cord as well as infiltration of the meninges.

Progressive multifocal leukoencephalopathy is caused by JC virus, which is reactivated in 20% of patients after transplantation but does not always lead to a clinical presentation (Worthmann et al., 1994; Coppo et al., 1999). Progressive multifocal leukoencephalopathy progresses fairly rapidly in most cases. Within months of diagnosis a patient may display cognitive decline, focal signs such as hemiparesis, ataxia, and sometimes a more specific frontal lobe dementia syndrome. Magnetic resonance images are fairly characteristic, with a focal white matter lesion that may be localized in any lobe. The JC virus cannot be cultured from spinal fluid examination, and a polymerase chain reaction needs to be performed (Aksamit, 1995). Seventy to ninety per cent of the patients with progressive multifocal leukoencephalopathy have a positive result of polymerase chain reaction, but biopsy is needed to document the enlarged inclusion-bearing oligodendrocytes, followed by in situ hybridization. No treatment for progressive multifocal leukoencephalopathy has been found, and most patients die within the first year after presentation.

Neuromuscular complications

Neuromuscular complications in transplant patients have been reported as mononeuropathy, myopathy, polyneuropathy and neuromuscular junction disorders (Junaid et al., 1993; al-Lozi, et al., 1994; Taylor et al., 1995; Lacomis et al., 1996; Wijdicks et al., 1996a,b). The recognition of these disorders is difficult and they may go undetected in

Table 129.4. Mononeuropathies after transplantation

Mononeuropathy	Proposed mechanisms	Transplants and incidence[a]
Phrenic nerve	Artificial cooling (ice), intraoperative injury	Lung, 3.2–29.0%; liver, up to 44%; (heart)
Brachial plexopathy	Stretch (shoulder hyperabduction), sternal retractors, trauma from cutdown for axillary vein cannulation	Liver, 0–5.8%; (heart, BM)
Ulnar	Compression (intraoperative, blood pressure cuff, or prolonged immobility), heterotopic ossification	Liver, 0.5–4.0%; kidney, up to 43%
Radial	Intraoperative compression	Liver, 0–0.4%
Peroneal	Compression (intraoperative or from prolonged immobility)	Liver, 0.4–1.3%; (heart, BM)
Femoral	Retractors, hematoma, lymphocele, vascular steal	Kidney, 4–11%; liver, 0–0.4%; (heart, BM)
Lumbosacral plexopathy	Hemorrhage	Liver, 0–0.2%; (BM)
Sympathetic nerve	Internal jugular vein cannulation, lower brachial plexus traction (usually from sternal retractors)	Liver, 0.2–2.0%; (heart)
Nerve root or ganglia	Herpes zoster virus reactivation from immunosuppression	BM, 4.5–19.0%; pancreas, 13%; liver, 0–0.3%

Notes:
[a] Incidence is given when reported. Transplant types in parentheses are case reports (see text for references). BM, bone marrow.
Source: From Campellone & Lacomis, 1999. With permission from Mayo Foundation.

the sickest patients. Mononeuropathies after transplantation are typically a result of trauma during surgery, immobilization and invasive procedures. Plexopathy may occur in a few patients after liver and heart transplantation, but almost always has its origin in sternal retractors or hyperabduction of the shoulder during procedures in liver transplantation. Although stretch and interoperative compression may be explanations for a plexopathy (Katirji, 1989; Wijdicks et al., 1996a,b), graft-vs.-host disease has been suggested as a possible mechanism of brachial plexopathy after bone marrow transplantation (Adams et al., 1995). Peroneal mononeuropathy is comparatively common in patients with liver transplants (Wijdicks et al., 1996a,b). It is caused by compression of the fibular head and is prone to occur in patients with end-stage liver disease due to major weight loss.

It has a good outcome and drop feet disappear within 3 months of transplantation (Table 129.4). Acute myopathy may occur after transplantation (Lacomis et al., 1996). A severe quadriplegia has been documented, typically sparing the extraocular musculature. Electrodiagnostic tests document decreased compound muscle action potential amplitudes and relative sparing of the sensory response on nerve conduction studies. An important recent study has shown that direct muscle stimulation decreases the compound muscle action potential, and this is helpful in discriminating between myopathy and neuropathy (Rich et al., 1997). Myopathy after transplantation is associated with corticosteroid use and with histopathological features of type 2 myofibre atrophy (al-Lozi et al., 1994). A causal relationship with cyclosporine seems improbable unless it is combined with lovastatin. Rhabdomyolysis, particularly when patients have survived a sepsis syndrome, should be considered and creatine phosphokinase values may be normalized. Outcome in our experience with a few patients has been good, with functional full recovery.

Acute polyneuropathy with progressive limb weakness over weeks has been described and may be inflammatory in nature. A Guillain–Barré-like syndrome has been reported associated with bone marrow transplantation (Wen et al., 1997) and with liver transplantation (Taylor et al., 1995) (Fig. 129.3). The triggers are not known and may include hepatitis B infection. Treatment with plasma exchange or intravenous immunoglobulin should be offered.

De novo tumours of the central nervous system

There is a three- to fourfold increased incidence of malignancies of all sorts in immunosuppressed organ transplant recipients (Penn & Porat, 1995). The vast majority of CNS tumours are non-Hodgkin lymphomas, followed by gliomas, with equal distribution of glioblastomas and astrocytomas (Table 129.5). CNS lymphomas are frequent with

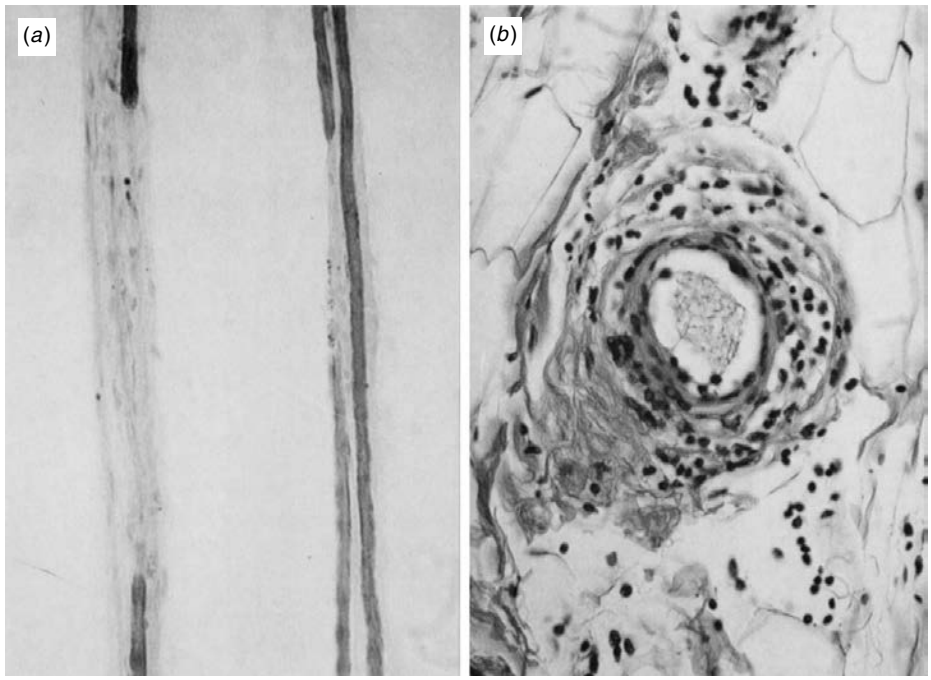

Fig. 129.3. Patient with chronic inflammatory demyelinating polyneuropathy 15 months after orthotopic liver transplantation. (*a*) Segmental demyelination in teased fibre preparation. (*b*) Perivascular lymphocytic infiltration around vasa vasorum. (From Taylor et al., 1995, with permission from the American Neurologic Association.)

Table 129.5. Types of neoplasms in the Cincinnati transplant tumour registry

Tumour	No.
Lymphoma	345
Glioma	44
Meningioma	4
Neuroectodermal	2
Miscellaneous	3

Source: From Penn (1999), with permission from Mayo Foundation.

renal transplantation because kidney transplantation is more commonly performed. Most CNS lymphomas occur within the first 12 months after the transplantation but may be seen as early as 3 weeks (Peterson & DeAngelis, 1997). In the Cincinnati registry, however, 18 of all 345 (5%) registered lymphomas occurred 10 years or more after transplantation. CNS lymphoma is largely located in the hemispheres or cerebellum (Fig. 129.4) but may coexist in the spinal cord or be in the spinal cord only. Non-Hodgkin lymphoma may appear as a focal mass, peripherally enhancing and centrally translucent (Fig. 129.4). Meningeal involvement may occur. Often the tumour has significant necrosis, which produces the central translucency (Johnson et al., 1997).

The diagnosis of CNS lymphoma is suspected with new-onset headache, papilledema, and seizures, and because of its common localization in the frontal lobe, personality changes are the first indicators. Evaluation should include stereotactic biopsy of the lesion. Therapy is limited but should include dexamethasone, 16 to 25 g/day, and local radiation therapy (DeAngelis, 1995). Stereotactic biopsy is necessary for the diagnosis, but the Mayo Clinic experience (Phan et al., 2000) involved increased incidence of intracranial hematoma after biopsy. These transplant-associated lymphomas probably are of a different nature than CNS lymphoma in a general population and more hemorrhagic. A complete remission may occur, although residual neurological deficit may persist. Approximately half of the patients with this lymphoma die as a direct result of the malignant disease despite treatment.

In conclusion, neurological complications have been identified since the early days of kidney transplantation. They may be an additional major cause of morbidity. The role of the neurologist in a transplantation programme has

Table 129.6. Neurologic complications after transplantation: classification by neurologic signs and symptoms and common diagnostic considerations

Sign or symptom	Consideration
Failure to awaken	Hypoxic–ischemic encephalopathy, central pontine myelinolysis, anesthetic agents, air embolism, acute uremia, acute graft failure, multiple intracranial abscesses
Loss of consciousness	ICH, fulminant meningitis, seizures, drug toxicity
Confusional state	Immunosuppressive toxicity, acute hypoglycemia, hyperglycemia, corticosteroids, fungal meningitis
Seizures	Cyclosporine or tacrolimus toxicity, ICH, lymphoma, meningitis, chemotherapeutic agents
Mute or stuttering	Cyclosporine or tacrolimus toxicity, cerebral infarct
Cortical blindness	Cardiac arrest, cyclosporine toxicity, cardiac catheterization, hypertensive encephalopathy
Hemiparesis	Brachial plexopathy, ischemic or hemorrhagic stroke, neoplasm, brain abscess
Tremors	Immunosuppressive drugs
Myoclonus	Hypoxic-ischemic encephalopathy, ketamine or penicillin intoxication
Asterixis	Acute liver, renal, or pulmonary disease
Rigidity	Haloperidol overdose, malignant hyperthermia
Muscle weakness	Acute critical illness polyneuropathy, polymyositis, corticosteroids, myopathy, neuromuscular junction blocking agents
Headaches	Fungal meningitis, OKT3 toxicity, cyclosporine or tacrolimus use, lymphoma, astrocytoma

Note: ICH, intracranial hemorrhage.
Source: From Wijdicks, 1999. With permission from Mayo Foundation.

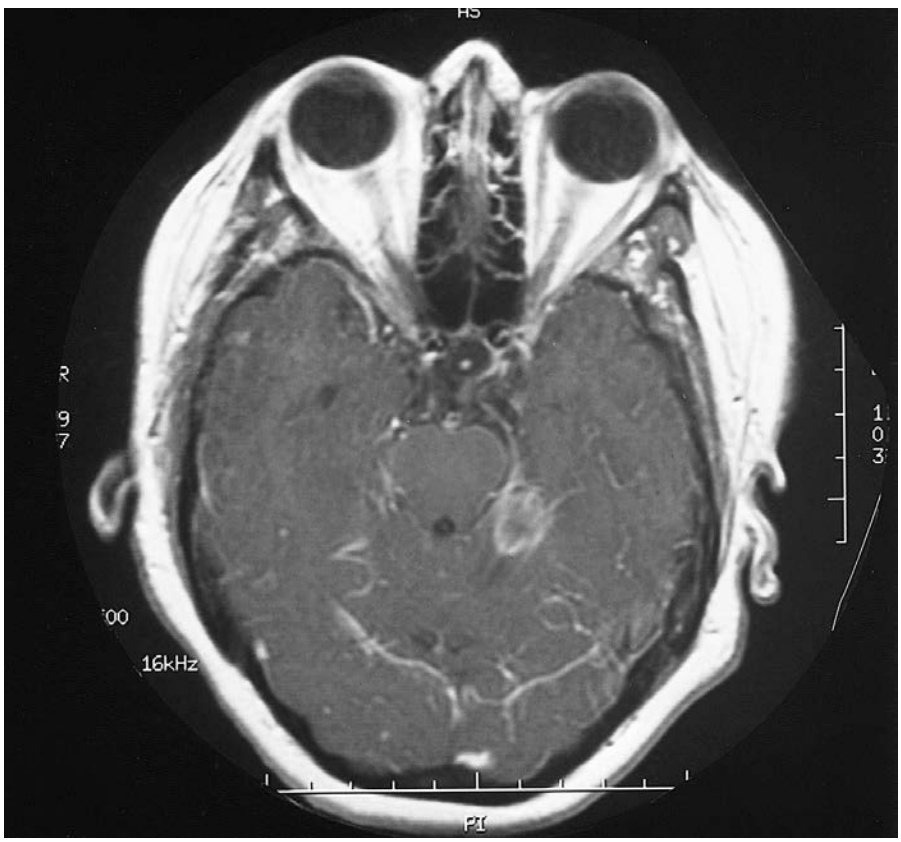

Fig. 129.4. Peripherally enhancing mass in superior cerebellum and peduncle confirmed as lymphoma by biopsy in renal transplant recipient.

been established. The spectrum of consultations seems to have narrowed down to a few major critical problems. For easy reference, the most common reasons for consultation with initial consideration for diagnosis are summarized in Table 129.6.

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Index

Note: this is a complete two-volume index

Note: page numbers in *italics* refer to figures and tables; 'Fig.' refers to illustrations in the plates section

Abbreviations of conditions used in subheadings (without explanation):
AD Alzheimer's disease
AIDS Acquired immune deficiency syndrome
ALS Amyotrophic lateral sclerosis
CJD Creutzfeldt–Jakob disease
FTD Frontotemporal dementia
HIV Human immunodeficiency virus
HD Huntington's disease
PD Parkinson's disease
SIADH syndrome of inappropriate secretion of antidiuretic hormone

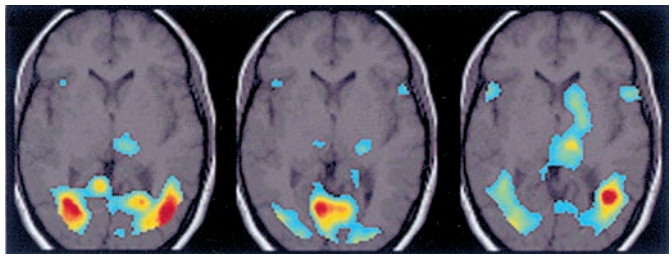
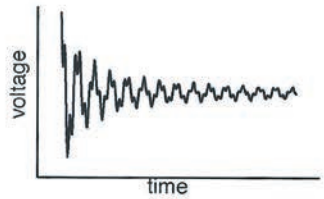


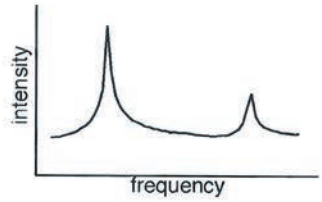
Fig. 1.1. Functional MRI signal changes during performance of a cognitive task. The above images are at the level of the thalamus for three normal controls showing that each of the participants exhibited signal changes in the thalamic hemispheres when they activated an object in memory (Kraut et al., 2001).

...and imaging

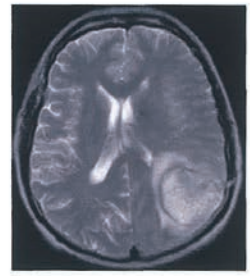
8 A coil in the spectrometer detects the vector in -X as an induced voltage, like this one showing 2 resonant frequencies:



9 Fourier transformation of such a signal into the frequency domain produces a spectrum with two frequency peaks:



10 Anatomical images can be made from large frequency peaks. A magnetic field gradient placed across the sample causes the peak's resonant frequency to assume a different value at each spatial point. If this is done in 2 or 3 dimensions, a computer can reconstruct a 2D or 3D image of the peak's intensity and relaxation properties, both of which vary due to differences in the local microchemical environment across the compartments of biological tissue. These variations provide the anatomical contrast in images like this one (from Fig. 4A), which is a standard T2-weighted MRI scan made from the water proton signal. A glioma and its surrounding edema are visible because they provide microchemical environments for water different from those of normal brain.



11 Several peaks from other compounds are sufficiently intense and well separated from each other to allow mapping of their anatomical distribution by a similar process. This example (Fig. 11.4D) shows the distribution of the signal from choline-containing compounds; signal intensity is color-coded, red high, blue low. The signal is strongest in the region of the glioma, a finding which is characteristic of many brain tumors and may reflect increased membrane synthesis. The map is coarser than the above MRI of the same brain, because the choline signal is several thousand times smaller than the one from water protons. Comparable maps can currently be made from the signals of N-acetyl aspartate, creatine, and lactate (see Figs. 11.4 and 11.5). Methods under development will extend the list to include glutamate, GABA, and other compounds of neurobiological interest.

Fig. 11.2. NMR principles continued.

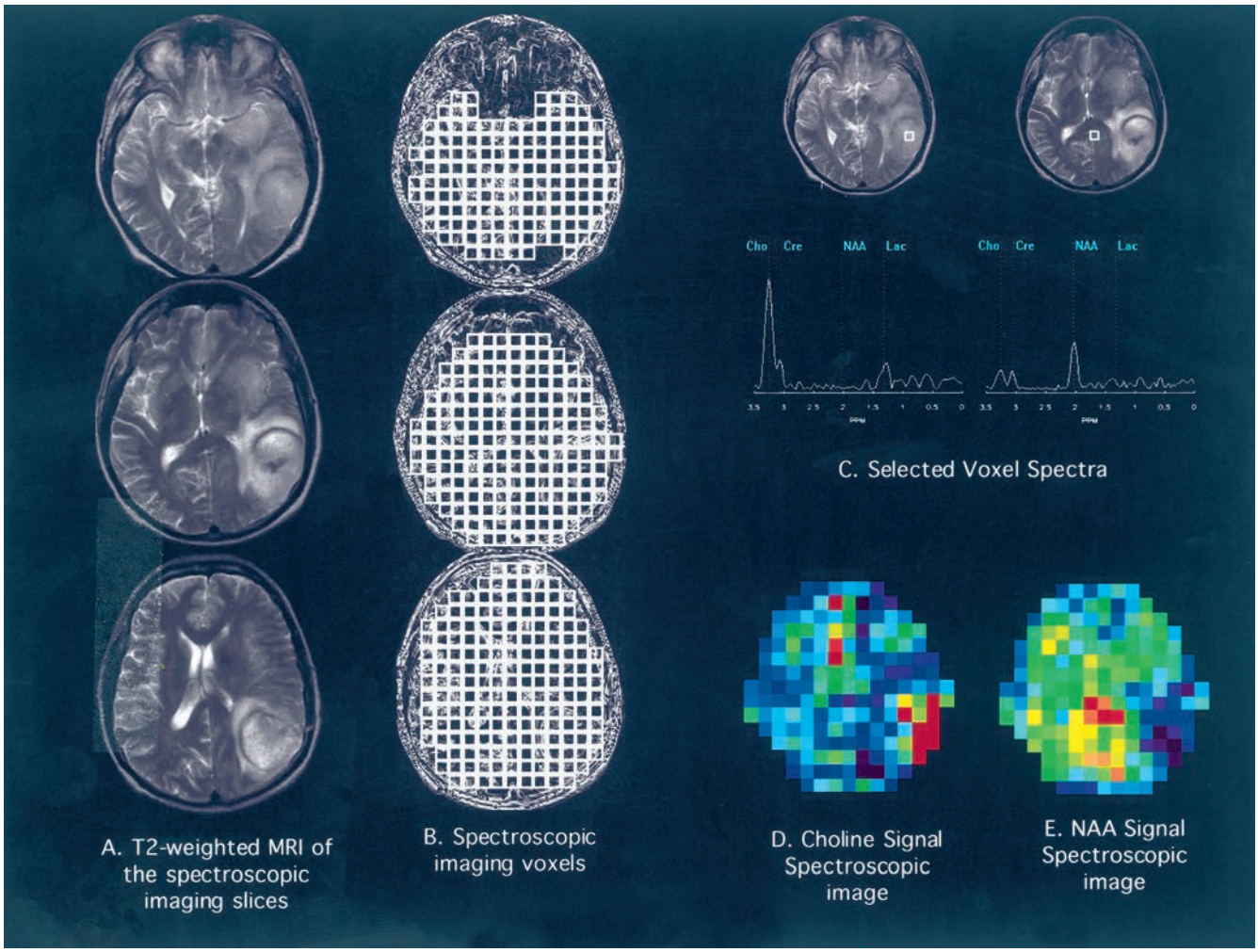


Fig. 11.4. MRI and MRS from a patient later found to have glioblastoma multiforme. (*a*) MRIs at three levels. (*b*) Locations of spectroscopic imaging voxels. (*c*) Images and spectra from voxels in tumour (left) and adjacent normal brain. (*d*), (*e*) Spectroscopic images made from the choline and NAA signals, showing the former elevated in the tumour and the latter depressed.

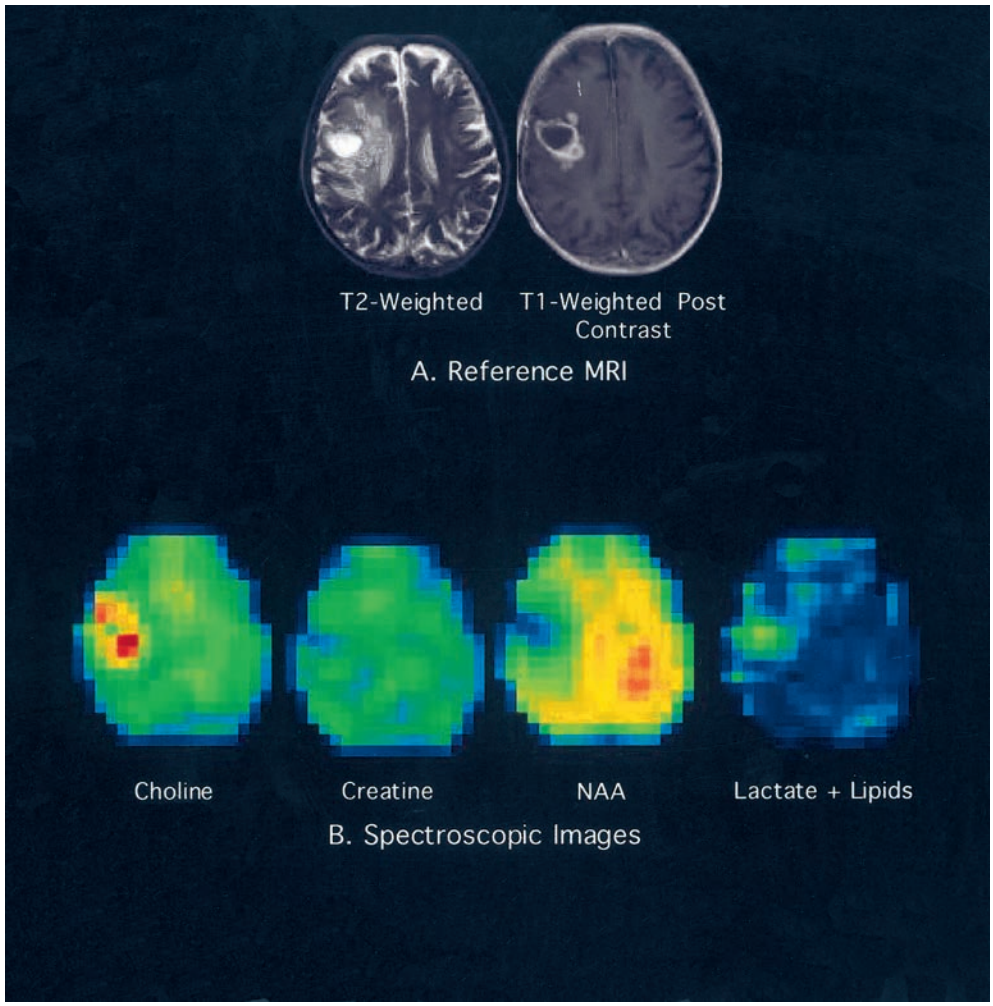


Fig. 11.5. MRI and MRS from a second patient later found to have glioblastoma multiforme. (*a*) MRIs showing the tumour. (*b*) Spectroscopic images showing elevated choline, lactate and lipid signals and depressed creatine and NAA signals associated with the tumour.

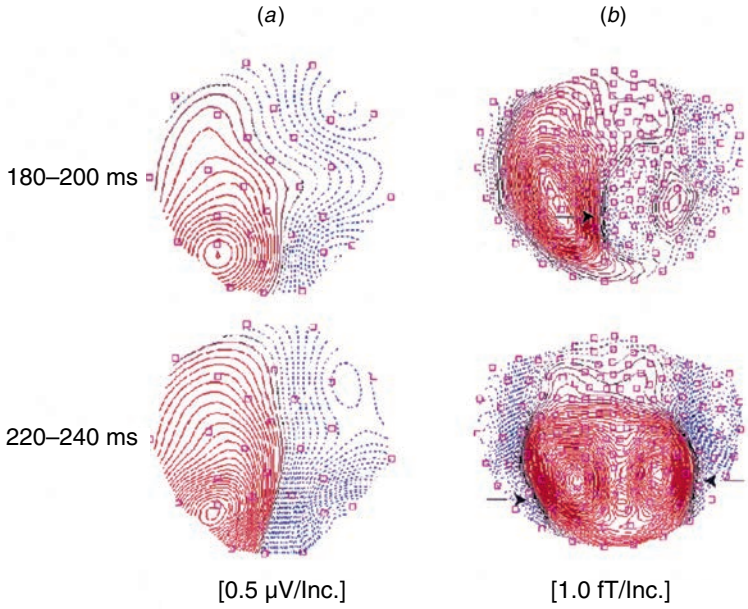


Fig. 12.1. ERP scalp distribution (*a*) and magnetic field distribution (*b*) of the N2pc component in two subsequent time windows (180–200 ms, 220–240 ms). Red lines indicate positive voltage of the potential distribution in (*a*) and magnetic flux leaving the cortex in (*b*). Note, polarities have relative character due to the direction of subtraction (LVF minus RVF targets) that was arbitrarily chosen. Arrows in (*b*) indicate locations of underlying current dipoles.

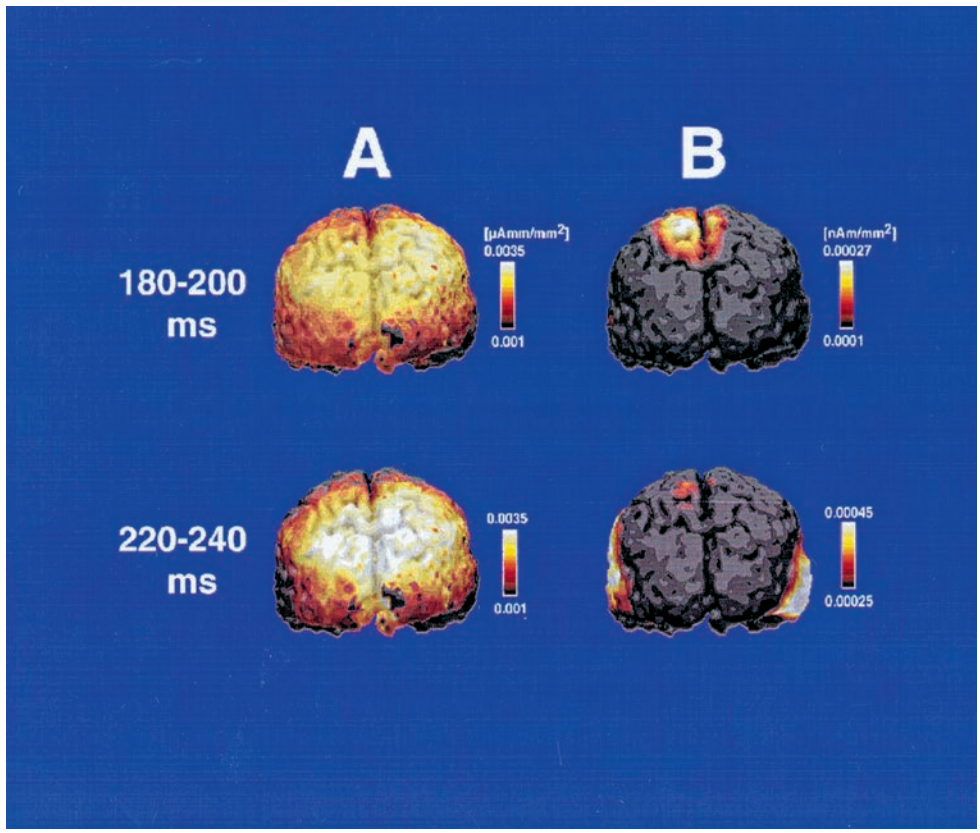


Fig. 12.2. Source density estimates (minimum norm least square) for the N2pc-component based on ERP difference waves (LVF minus RVF targets) (*a*) and MEG difference waves (*b*) in the early (180–200 ms) and late (220–240 ms) time window.

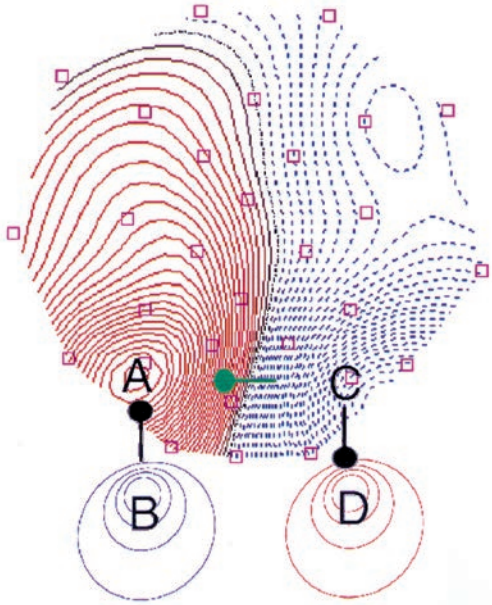


Fig. 12.3. An illustration of the erroneous link between ERP field components that gives rise to the discrepant source density estimates for ERP and MEG data as shown in Fig. 12.2. The measured ERP distribution between 220 and 240 ms is schematically completed by field components (*b*) and (*d*) that could not be picked up with the used electrode array, but are strongly implied by the magnetic field configuration. Specifically, linking field component (*a*) to (*b*) and (*c*) to (*d*) would give rise to source configurations as indicated by black dipoles. In contrast, the green dipole illustrates the potential mislocalization due to erroneous linkage of (*a*) and (*c*).

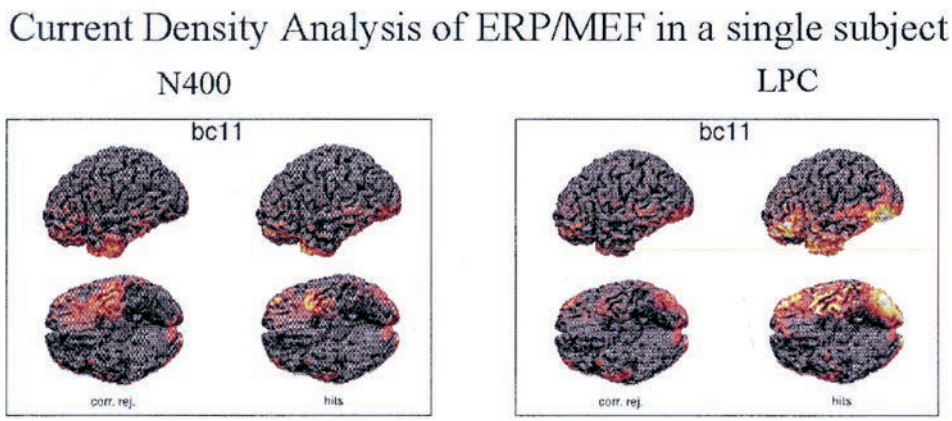


Fig. 12.4. *Upper part:* Single subject current density analysis for hits and correct rejections in the N400 time window and the LPC time window performed by taking into account the subjects 3D MRI. Red colours indicate areas of high current flows on the brain surface that account for the recorded electric and magnetic activity. It can be seen that in the N400 time window, correct rejections induce stronger current flows in the left anterior temporal lobe than hits. In contrast, hits induce stronger current flows in the posterior inferior temporal lobe than correct rejections.

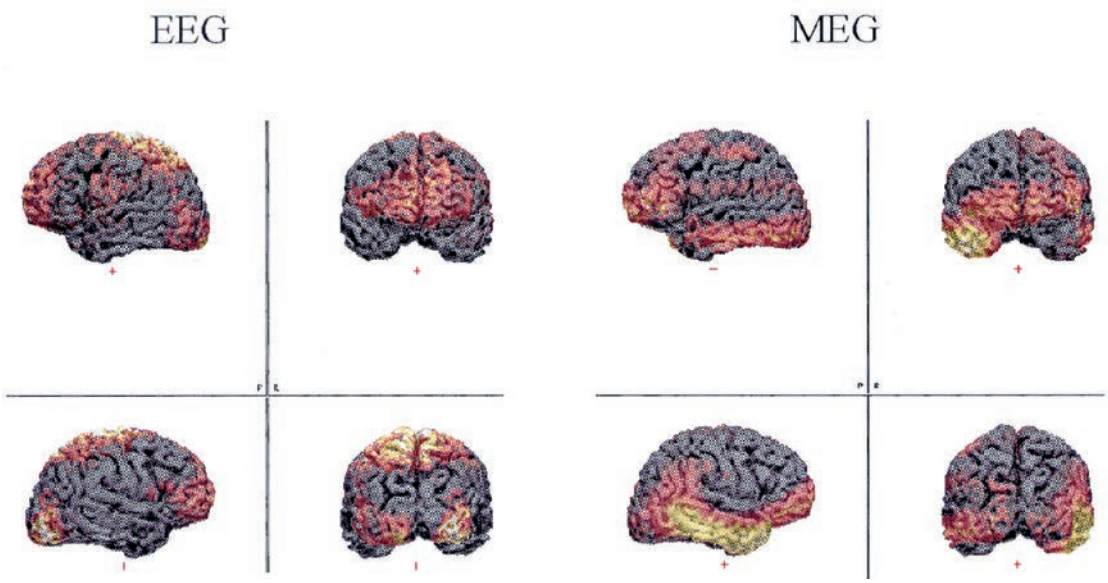


Fig. 12.7. Single subject current density analysis of EEG and MEG measured 200 ms prior to a motor response indicating the completion of a word fragment. While the MEG data reveal, in accord with a concurrent fMRI study, bilateral temporal activity, source analysis based on EEG data alone indicate a prominent parieto-central source.

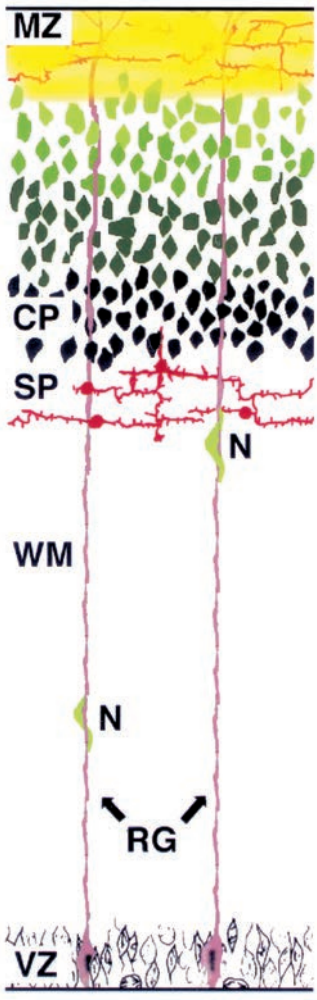


Fig. 13.1. A scheme of glia-guided migration. Postmitotic neurons (N), which are born in the ventricular zone (VZ), migrate along the radial glial fibres (RG) through the developing white matter (WM) and the subplate layer (SP) into the cortical plate (CP). They are added to the cortical plate in an 'inside-out' fashion, and stop immediately underneath the marginal zone (MZ). Reelin protein in the marginal zone (represented by yellow colour) serves as an apparent 'stop signal' for the neurons (see text).

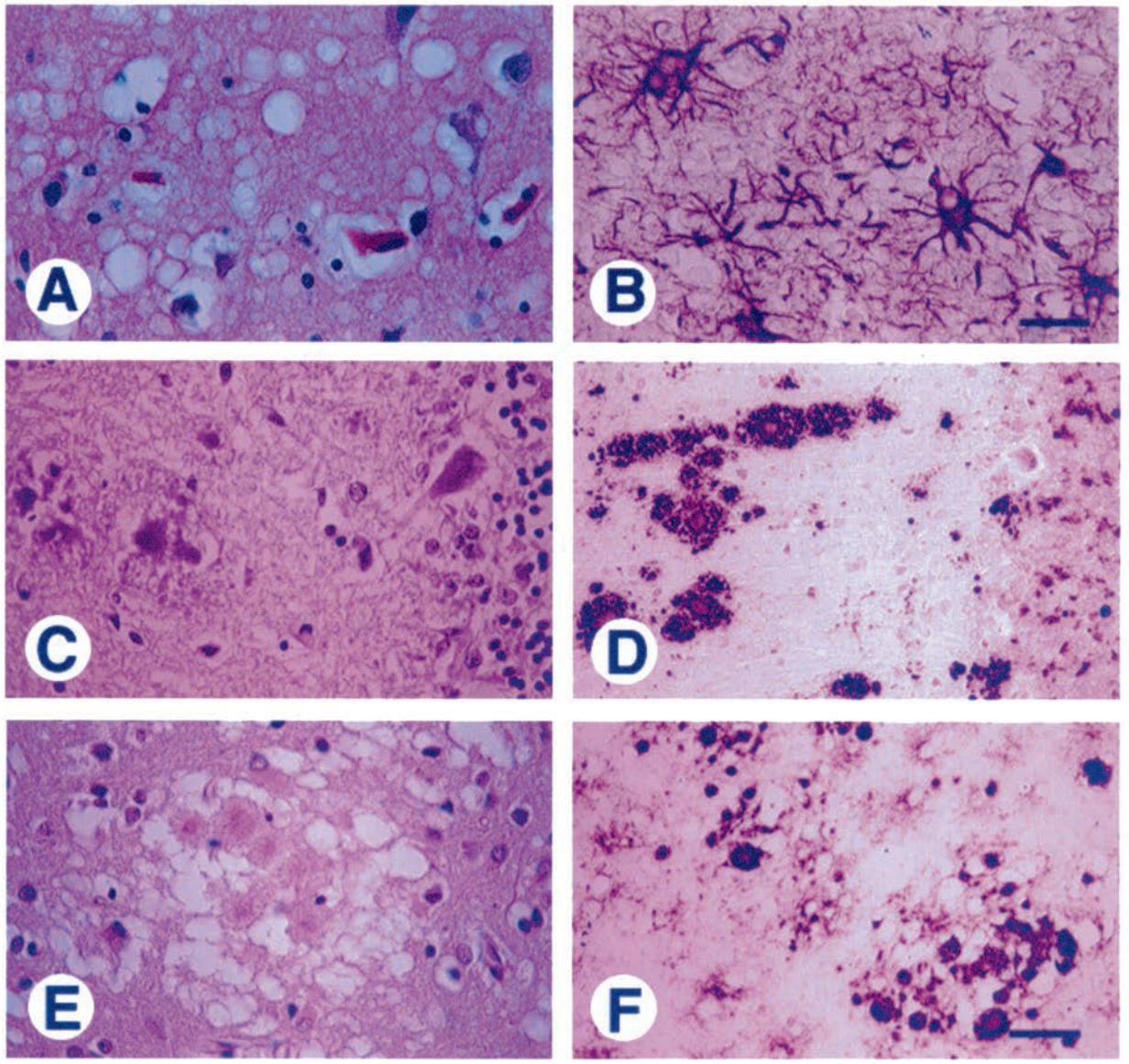


Fig. 15.4. Neuropathology of human prion diseases. Sporadic CJD is characterized by vacuolation of the neuropil of the grey matter, by exuberant reactive astrocytic gliosis, the intensity of which is proportional to the degree of nerve cell loss, and rarely by PrP amyloid plaque formation (not shown). The neuropathology of familial CJD is similar. GSS(P102L), as well as other inherited forms of GSS (not shown), is characterized by numerous deposits of PrP amyloid throughout the CNS. The neuropathological features of nvCJD are unique among CJD cases because of the abundance of PrP amyloid plaques that are often surrounded by a halo of intense vacuolation. (*a*) Sporadic CJD, cerebral cortex stained with hematoxylin and eosin showing widespread spongiform degeneration. (*b*) Sporadic CJD, cerebral cortex immunostained with anti-GFAP antibodies demonstrating the widespread reactive gliosis. (*c*) GSS, cerebellum with most of the GSS-plaques in the molecular layer (left 80% of micrograph), and many but not all are periodic acid Schiff (PAS) reaction positive. Granule cells and a single Purkinje cell are seen in the right 20% of the panel. (*d*) GSS, cerebellum at the same location as panel C with PrP immunohistochemistry after the hydrolytic autoclaving reveals more PrP plaques than seen with the PAS reaction. (*e*) New variant CJD, cerebral cortex stained with hematoxylin and eosin shows the plaque deposits uniquely located within vacuoles. With this histology, these amyloid deposits have been referred to as 'florid plaques'. (*f*) New variant CJD, cerebral cortex stained with PrP immunohistochemistry after hydrolytic autoclaving reveals numerous PrP plaques often occurring in clusters as well as minute PrP deposits surrounding many cortical neurons and their proximal processes. Bar in (*b*) = 50 mm and applies also to panels (*a*), (*c*) and (*e*). Bar in (*f*) is 100 mm and applies also to panel (*d*). Photomicrographs prepared by Stephen DeArmond. (New variant CJD specimens provided by James Ironside, Jeanne Bell, and Robert Will.)

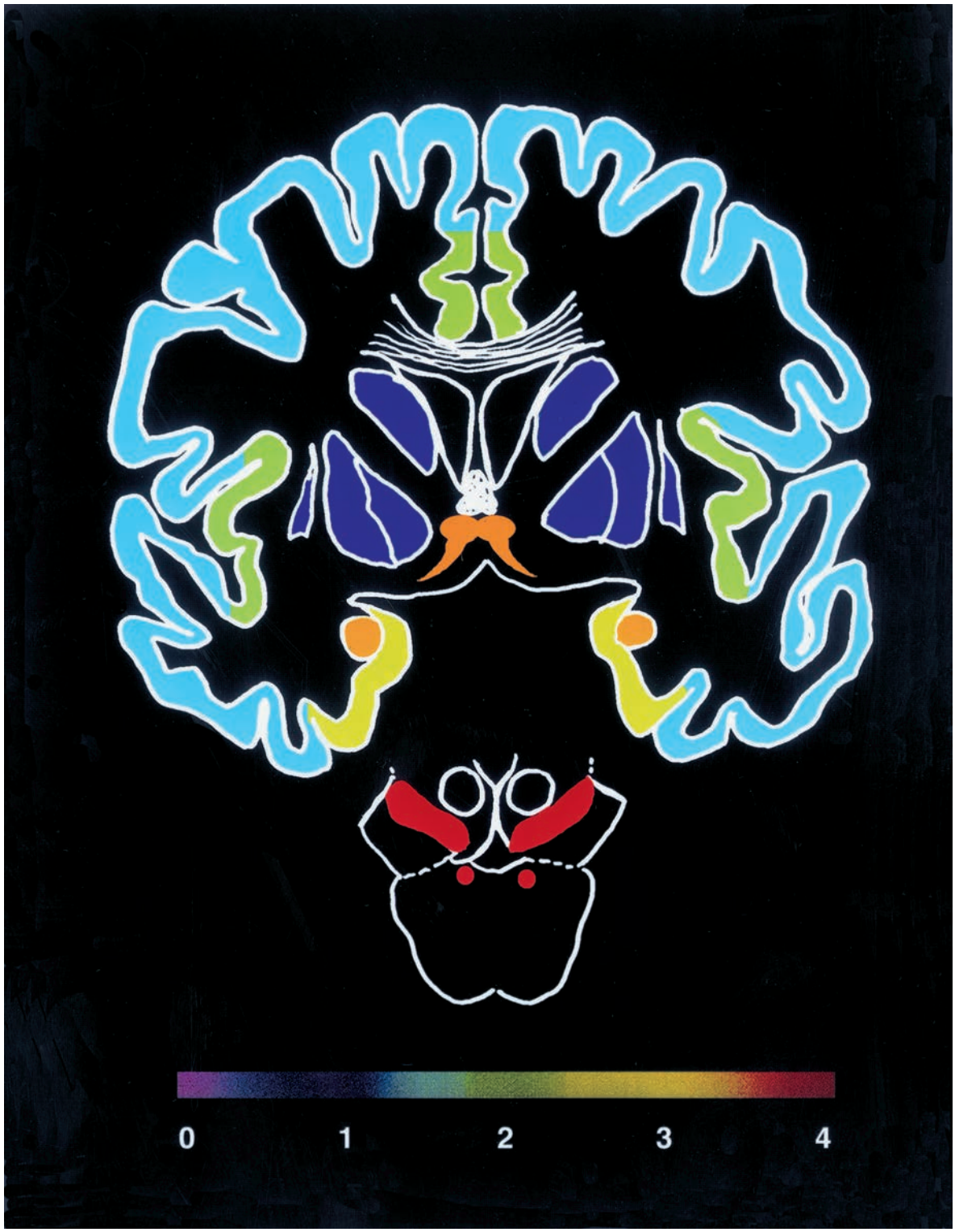


Fig. 18.2. A colour representation of the topography of Lewy bodies plotted onto a coronal human brain section at the level of the amygdala based on Lewy body density data from Gómez-Tortosa et al. (1999). The colour bar indicates red as the greatest quantity and blue as the least.

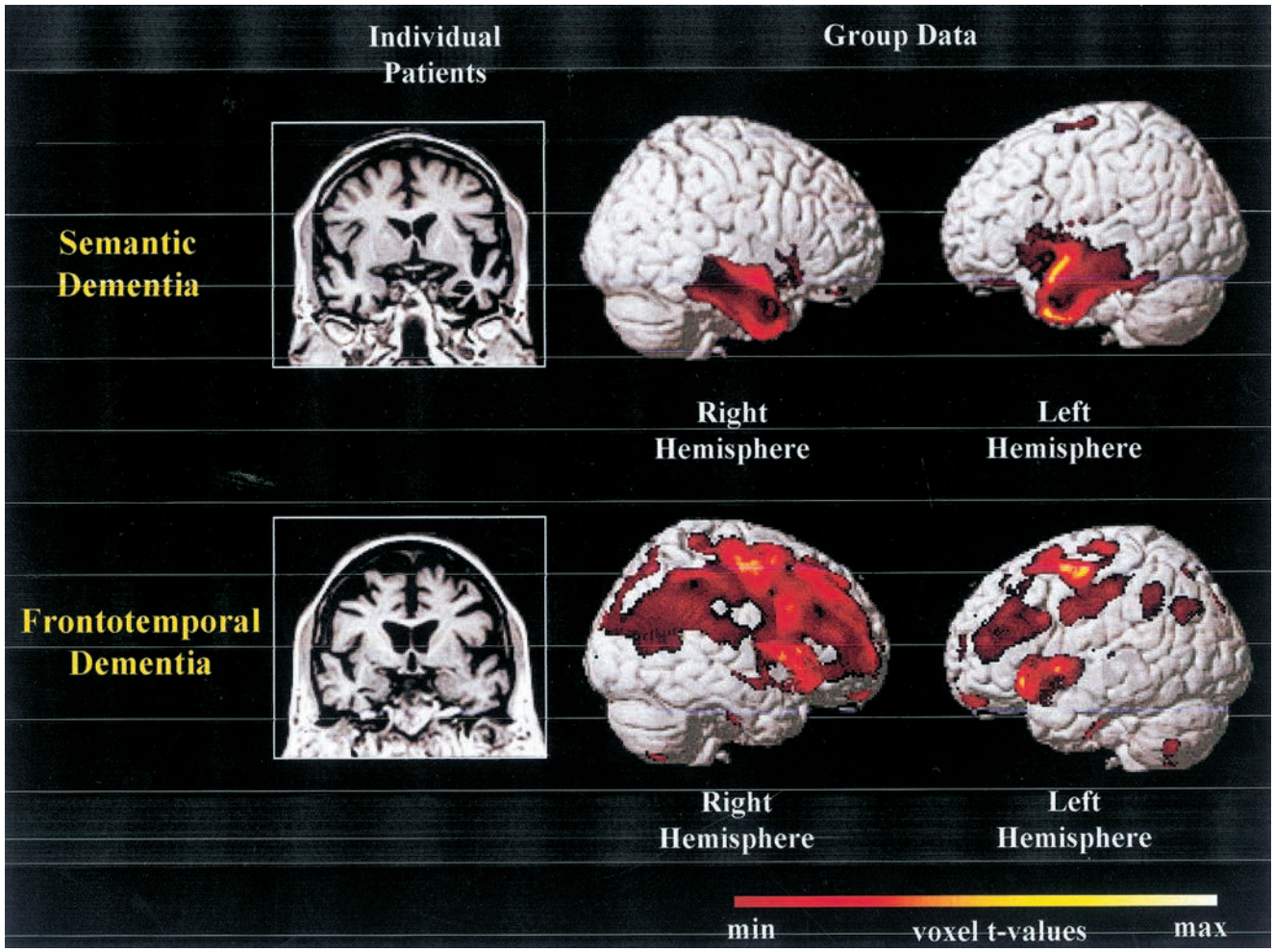


Fig. 19.1. Differing patterns of atrophy in patients with FTD are illustrated. On the left, coronal slices from T1-weighted MRI images in two individual patients are shown. The patient on top shows predominantly frontal atrophy, while the patient on the bottom shows predominantly temporal atrophy, more severe on the left. On the right, group data from a formal analysis of twenty patients with FTD are shown. Twenty patients with FTD were divided into two groups, those with ($N=12$, top) and without ($N=8$, bottom) semantic impairment, and compared with twenty age matched controls subjects. Anatomical analysis was performed using voxel-based morphometry, a technique that allows automated detection of regional atrophy (Ashburner & Friston, 2000). The *t*-values at the regions where atrophy was significant in each group ($P<0.001$) are superimposed on a normal brain. The group with semantic impairment shows atrophy predominantly in the anterior temporal regions, while the group without semantic impairment shows predominantly frontal atrophy. These data illustrate how specific clinical syndromes are associated with specific patterns of cerebral atrophy in FTD.

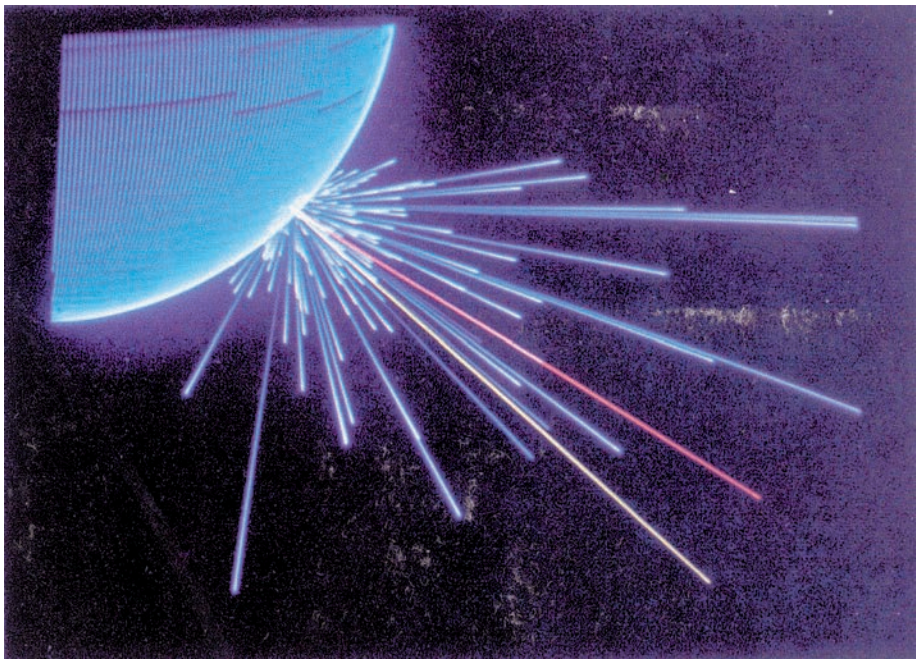


Fig. 31.5. An example of the population coding of movement direction. The blue lines represent the vectorial contribution of individual cells in the population ($N = 475$). The actual movement direction is in yellow and the direction of the population vector is in red. (From Georgopoulos et al., 1986, figure 1.)

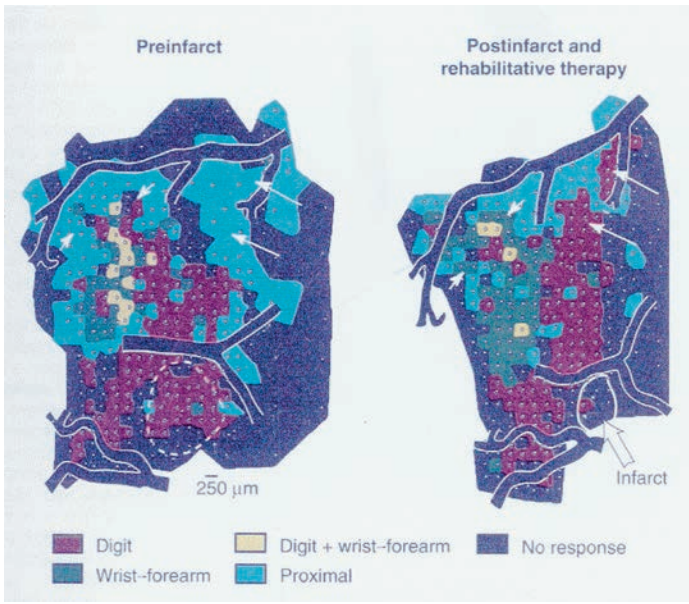


Fig. 31.8. Reorganization of hand representations in the primary motor cortex associated with rehabilitation following ischemic infarct. The volume circumscribed by a dashed line in the preinfarct map shows the area targeted for infarction, the solid line in the postinfarct map indicates the infarcted region. Digit representations all but disappear from the area of the infarct but after rehabilitation have invaded areas of cortex previously occupied by more proximal arm muscles (long thin arrows). In addition, the representation of the wrist–forearm expanded into areas previously occupied by shoulder (short thick arrows). (Adapted from Nudo et al., 1996, figure 3.)

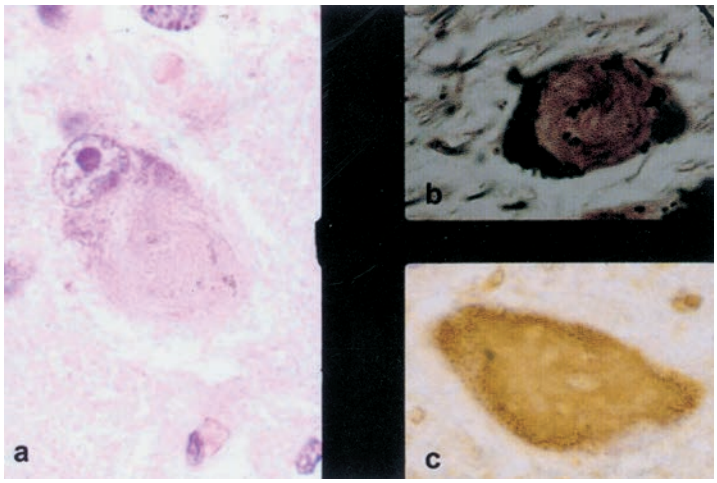


Fig. 34.1. Progressive supranuclear palsy ultrastructural pathology showing a typical globose neurofibrillary tangle in the substantia nigra stained with hematoxylin eosin (*a*); Bieschowsky's silver impregnation (*b*); tau immunohistochemistry (*c*). (Courtesy Dr Tamas Revesz, Dept of Neuropathology, Institute of Neurology, London.)

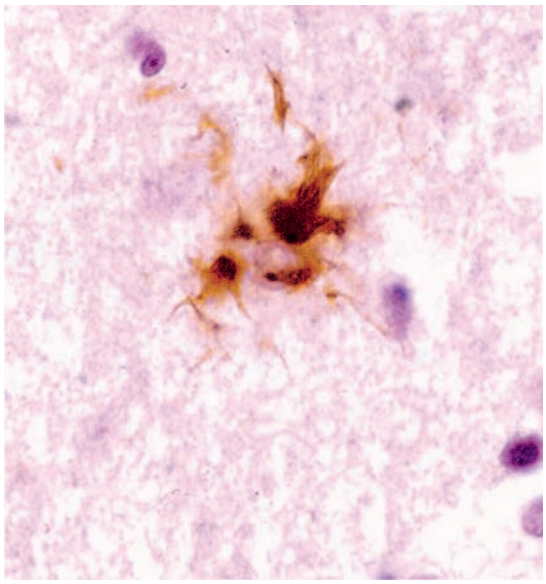


Fig. 34.2. Progressive supranuclear palsy ultrastructural pathology showing a typical tufted astrocyte in the motor cortex. Tau immunohistochemistry. (Courtesy Dr Tamas Revesz, Dept of Neuropathology, Institute of Neurology, London.)

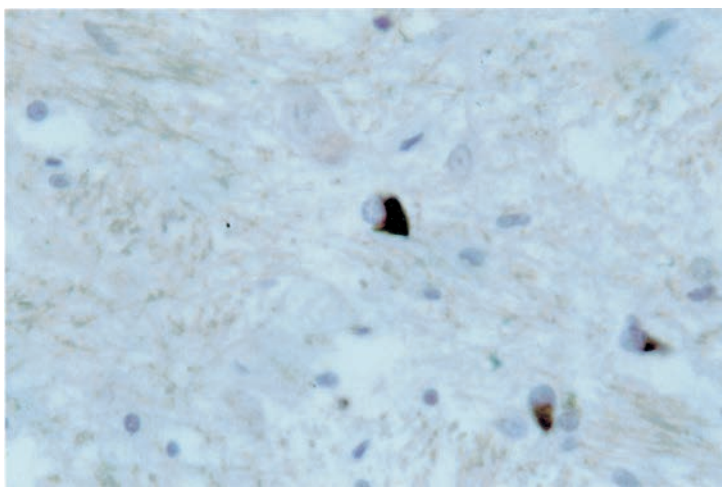
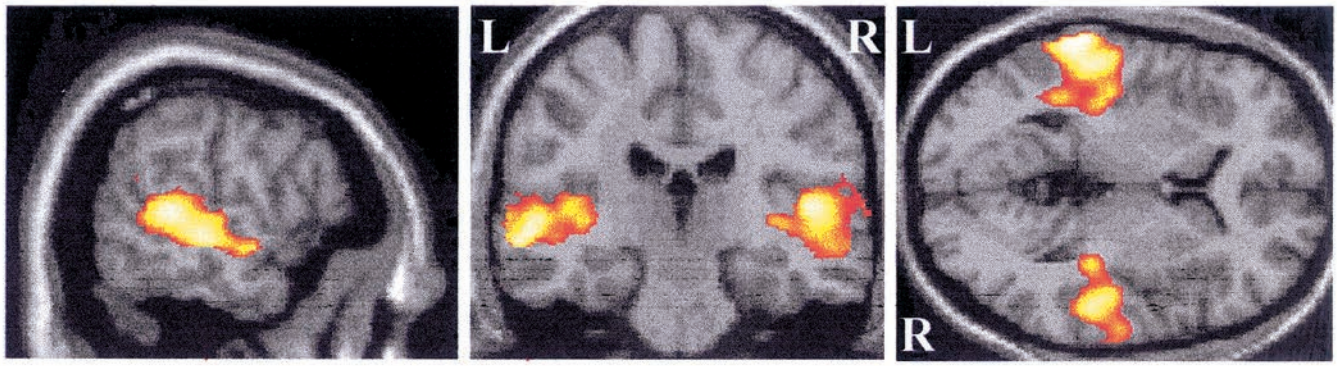


Fig. 34.5. Olgodendroglial inclusion seen in multiple system atrophy. (Gallyas stain). (Courtesy Prof. Francesco Scaravilli Institute of Neurology, London.)

(*a*)



(*b*)

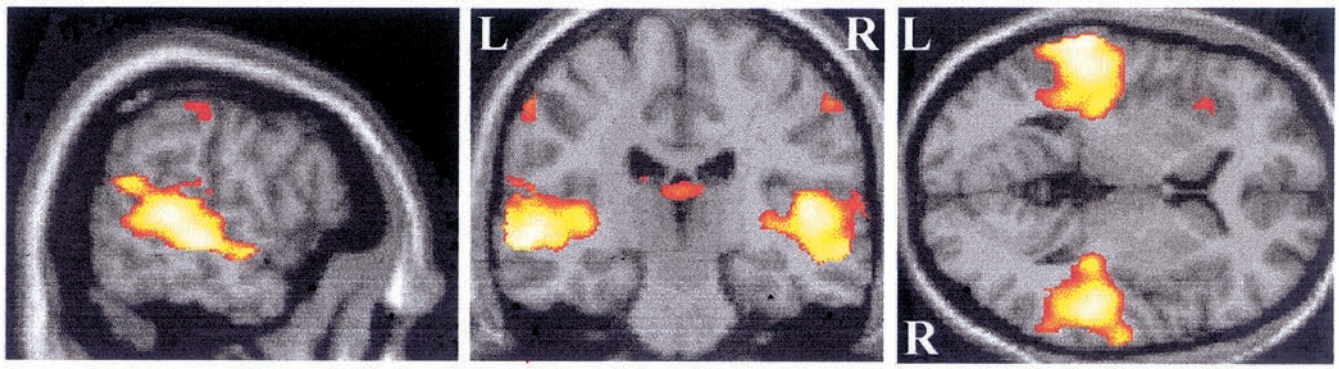


Fig. 45.11. Functional MRI: Activation of temporal cortex during (*a*) passive listening and (*b*) active listening to modulated tones projected into sagittal, coronal and axial planes; both A and B show that the volume of temporal activation is greater on the left side in both passive and active listening; only active listening produces activation in other areas (in this illustration, bilateral postcentral gyri and left insula cortex). (Hall et al., 2000.)

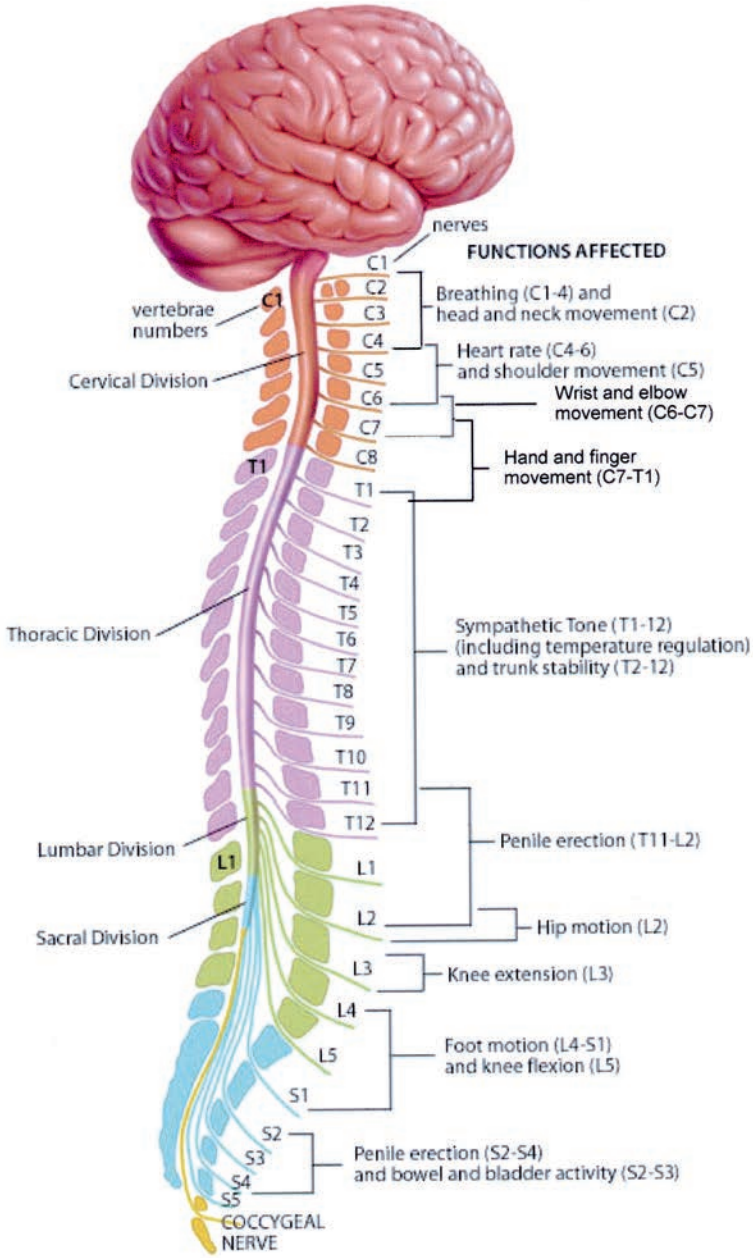


Fig. 47.2. Four divisions of the spinal cord and their associated nerves serve specific areas of the body. In general, the cervical nerves link to the neck, arms and respiratory apparatus; the thoracic nerves control posture and many internal organs; the lumbar nerves work the legs; and the sacral nerves regulate the bladder and bowel and play a role in sexual function.

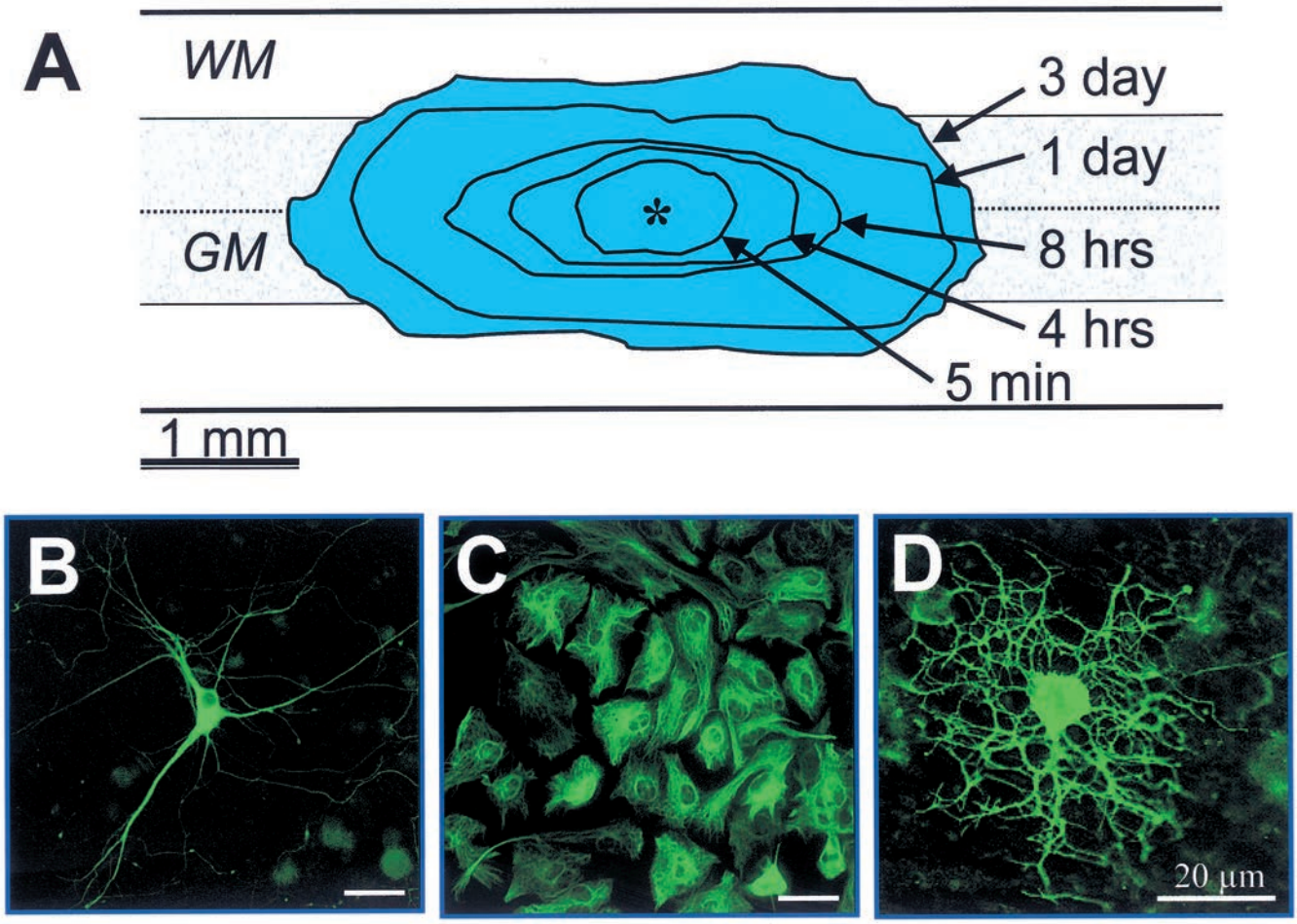


Fig. 47.3. (*a*) Schematic drawing illustrating lesion expansion over time in longitudinal sections through the central canal of rat spinal cords that sustained a moderate contusion injury. The cords were examined at 5 min, 4 and 8 h, and 1 and 3 days after the injury. *WM*, white matter; *GM*, grey matter. * Site of impact. (Adapted from Liu et al., 1997.) Panels (*b*)–(*d*) illustrate the three principal cell types of the central nervous system that are important for function and which are damaged following injury. The (*b*) neuron, (*c*) astrocyte, and (*d*) oligodendrocyte shown were derived from mouse embryonic stem cells, neurally induced with retinoic acid, and grown in culture for 9 days.

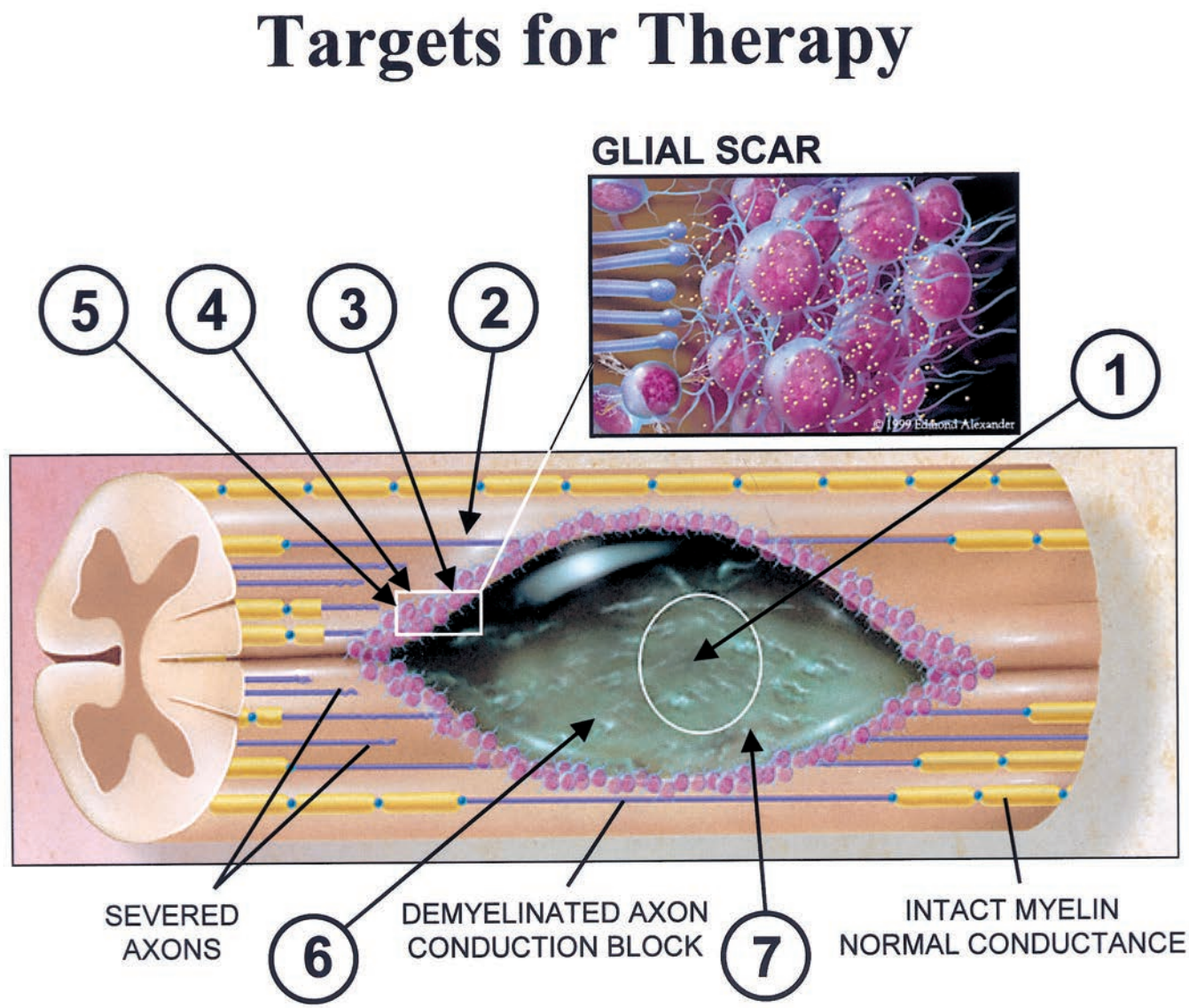


Fig. 47.5. Treatment of spinal cord injury will likely involve several interventions, delivered in an ordered sequence, each with incremental benefits. Illustrated are specific examples representing the different levels of intervention. 1. **Prevent progression of secondary injury**: Prevention of necrotic and apoptotic cell death using anti-excitotoxic drugs (glutamate-receptor blockers) and anti-apoptotic treatments (growth factors such as NT-3, BDNF, and ICE-protease inhibitors). 2. **Compensate for demyelination**: Supply chemicals that prevent action potentials from dissipating at demyelinated areas (prevent conduction block). Provide agents that encourage surviving oligodendrocytes to remyelinate axons. Replenish lost oligodendrocytes. 3. **Overcome inhibition**: Deliver agents that block the actions of natural inhibitors of regeneration (inhibitor neutralizing antibody, IN-1, masks an inhibitory protein) or drugs that down-regulate expression of inhibitory proteins. 4. **Promote axonal regeneration**: Delivery of growth factors that promote regeneration (sprouting) of new axons (e.g. NT-3, BDNF). 5. **Direct axons to proper targets**: Deliver targeting molecules or alter their expression in host cells to guide axons to appropriate targets. 6. **Create bridges**: Implant into the syrinx tissue that can serve as scaffolding for axons and that encourages them to grow (e.g. transplant peripheral nerves or cells competent to support axonal growth, such as ensheathing glia, into the empty syrinx). 7. **Replace lost cells**: Implant cells able to produce all the lost types (e.g. stem cells or ES cells). Deliver substances that can induce undifferentiated cells already in the cord to replace dead cells. In addition to replacing cells, transplanted cells can be used as cellular genetic vectors to deliver regenerative molecules on command (e.g. vectors producing NT-3, bFGF, or PDGF). (Figure reproduced with permission from *Scientific American* (McDonald et al., 1999).)

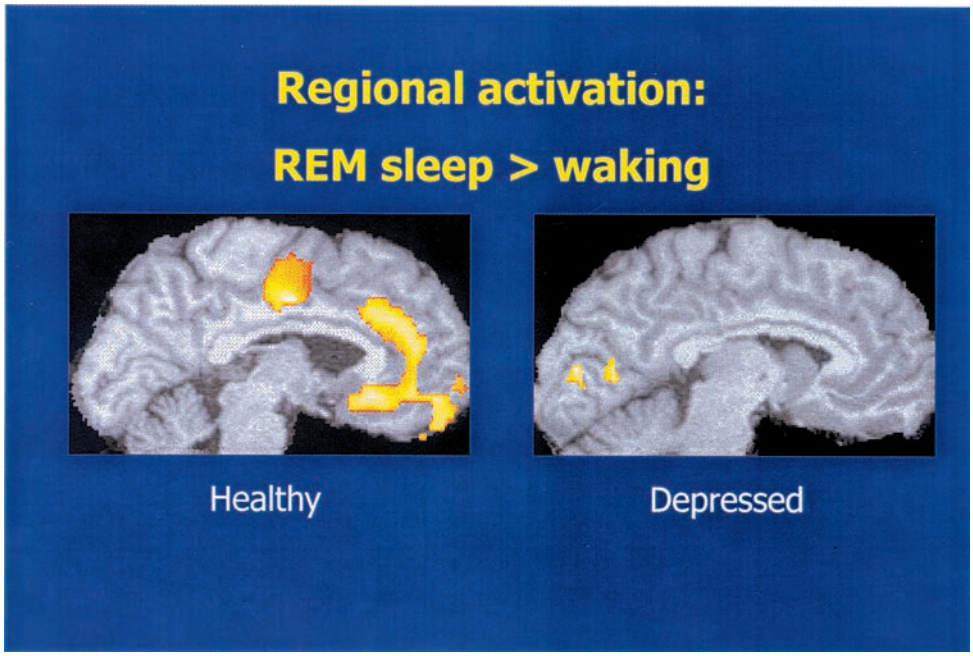


Fig. 55.4. PET studies of REM sleep. See text for description.

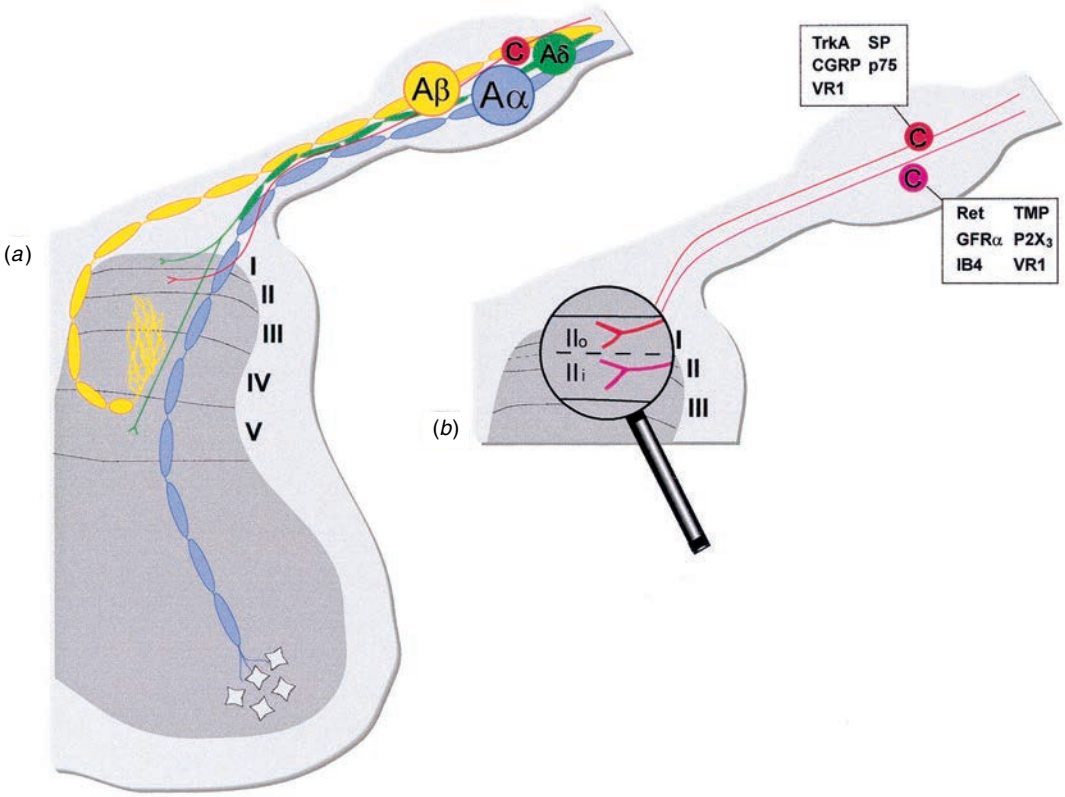


Fig. 58.2. (*a*) Subpopulations of primary sensory neurons synapse in a lamina-specific manner within the dorsal horn. (*b*) Within the C-fibre population of sensory neurons, different chemically defined cells synapse in different parts of lamina II.

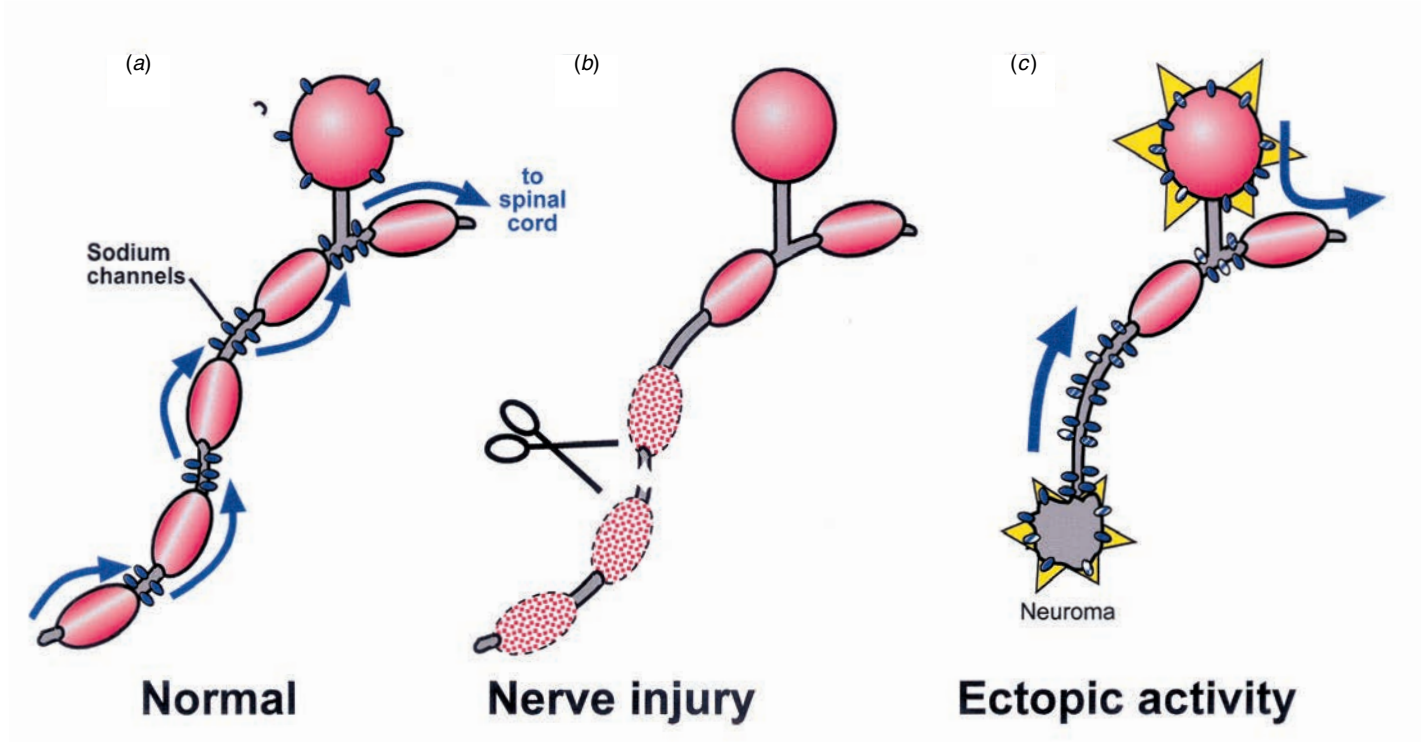


Fig. 58.5. (*a*) In sensory neurons with myelinated axons, fast saltatory conduction of action potentials occurs along the axon at speeds up to 100 metres/second, mediated in part by the expression and discrete localization of voltage gated sodium channels (VGSCs) at the Nodes of Ranvier. (*b*) Following nerve injury, the distal axon segment undergoes Wallerian degeneration, and the Schwann cells lining the end of the proximal axon dedifferentiate and stop producing myelin. (*c*) Injured sensory neurons then display ectopic discharge at the neuroma site, proximally on the axon and from the cell body as a consequence of altered ion channel expression, altered ion channel membrane organization and altered ion channel properties. Note that ectopic activity is also observed in adjacent uninjured fibres following nerve injury.

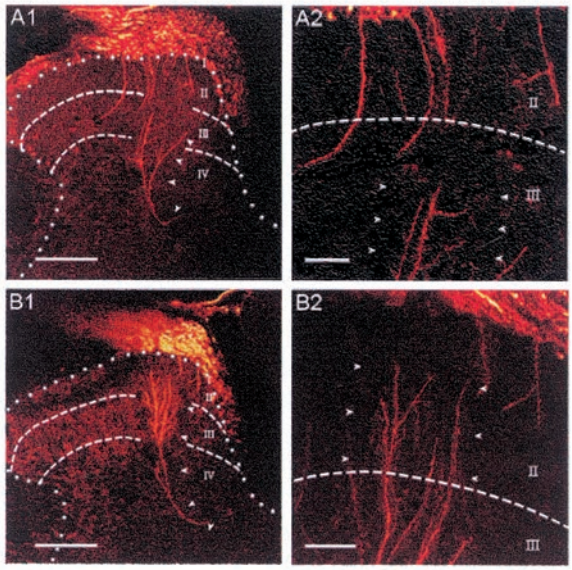


Fig. 58.12. (*a*) Normally, Aβ-fibre central terminals in the ipsilateral dorsal horn synapse within the deeper laminae (II and IV) and those innervating the skin have a characteristic flame shaped central arbour (arrow heads). (*b*) Two weeks after nerve injury in laboratory animals, Aβ-fibre central terminals sprout dorsally into laminae I and II, a region normally innervated only by C-fibres. (Printed with permission from Kohama et al., 2000.)

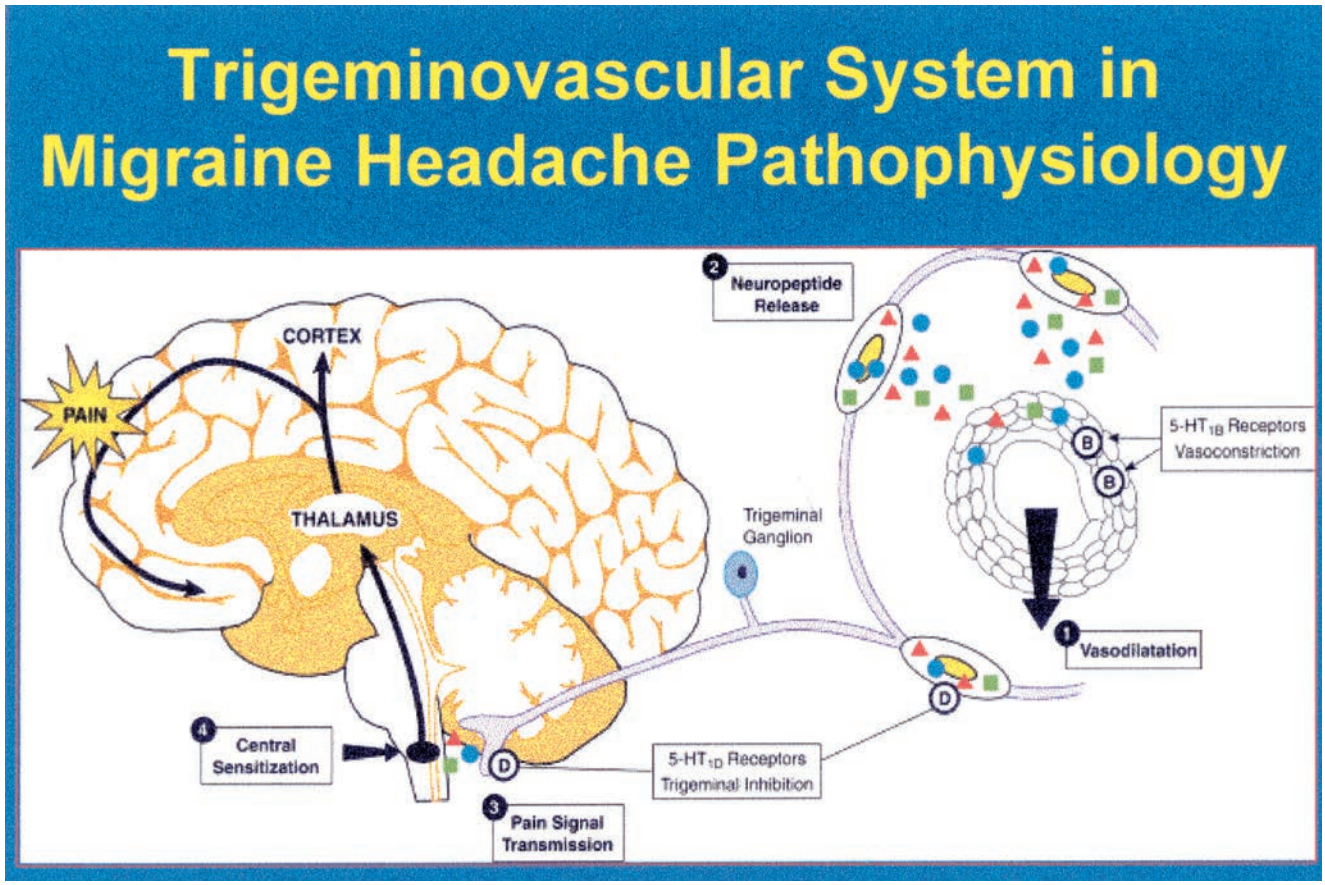


Fig. 61.1. Integrated hypothesis of the pathogenesis of the migraine headache and associated symptoms, and the role of the trigeminovascular system. For explanation, see the various sections in the text.

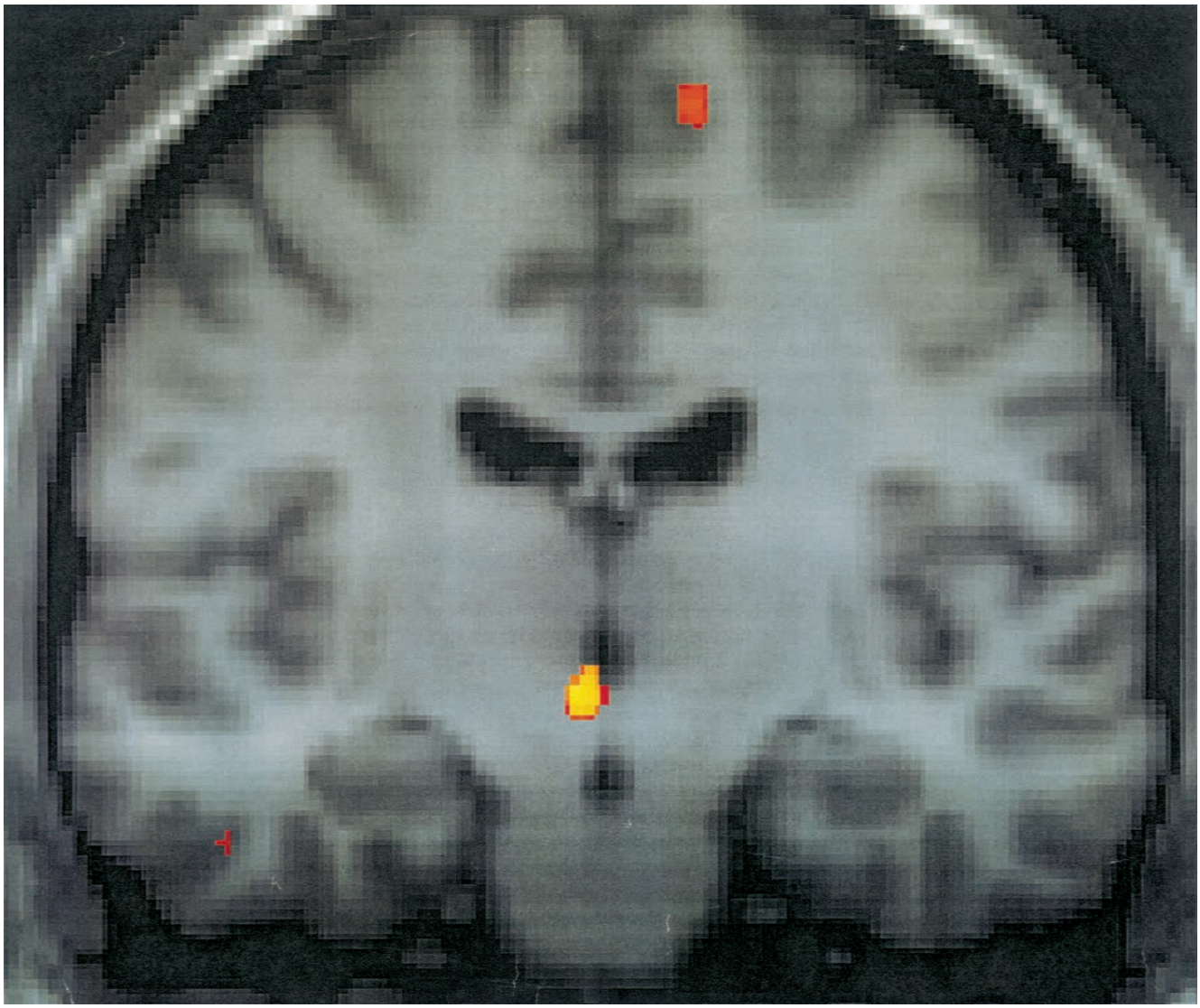


Fig. 62.1. Positron emission tomography (PET) in acute cluster headache illustrating activation in the posterior hypothalamic grey matter. This area is active only in acute cluster headache and not in migraine, nor experimental head pain. It is likely that the crucial neurons responsible for the fundamental pathophysiology of cluster headache are to be found in this region (May et al., 1998).

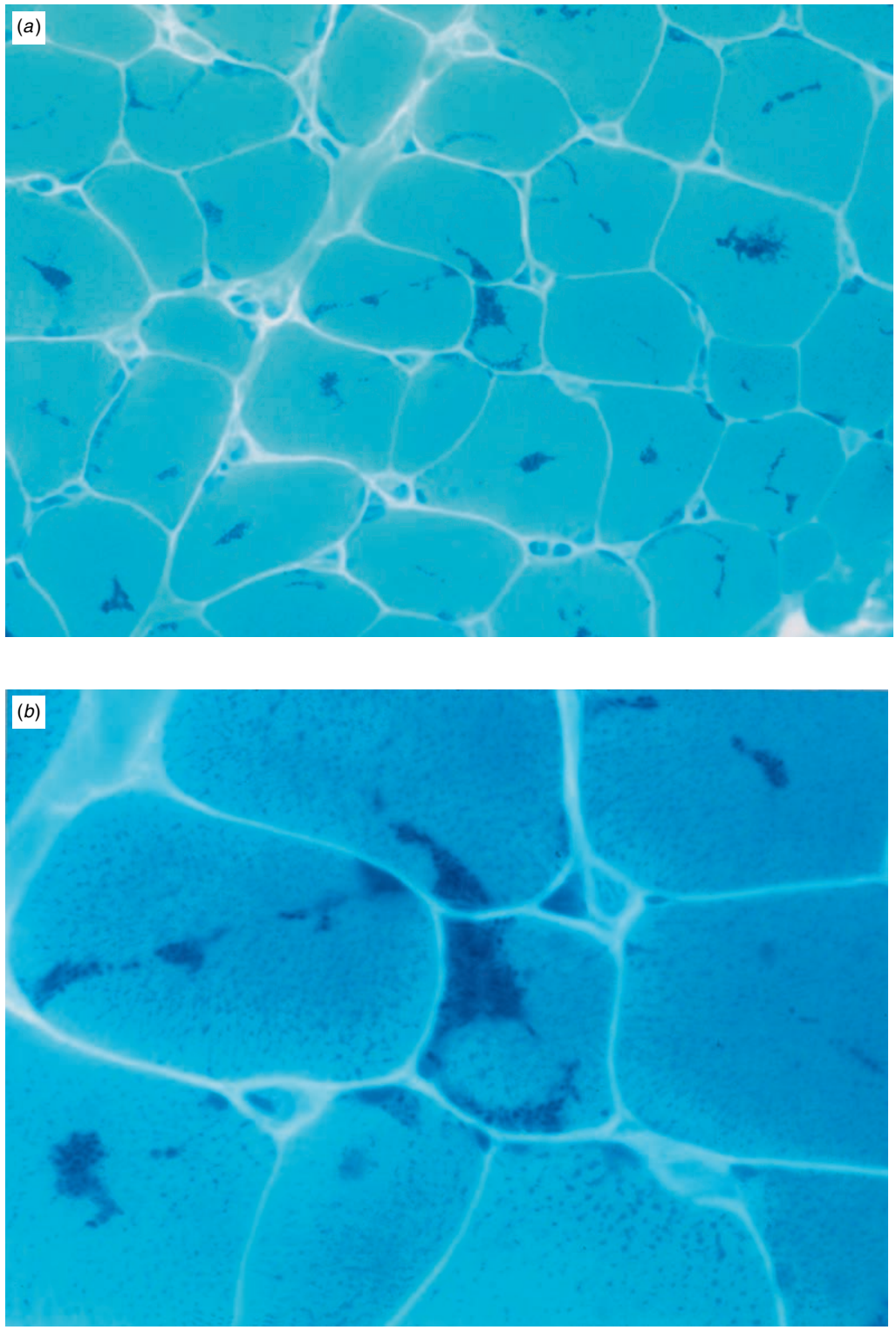


Fig. 70.8. (*a*) (*b*) Gomori trichrome stain of muscle biopsy showing nemaline bodies (rods).

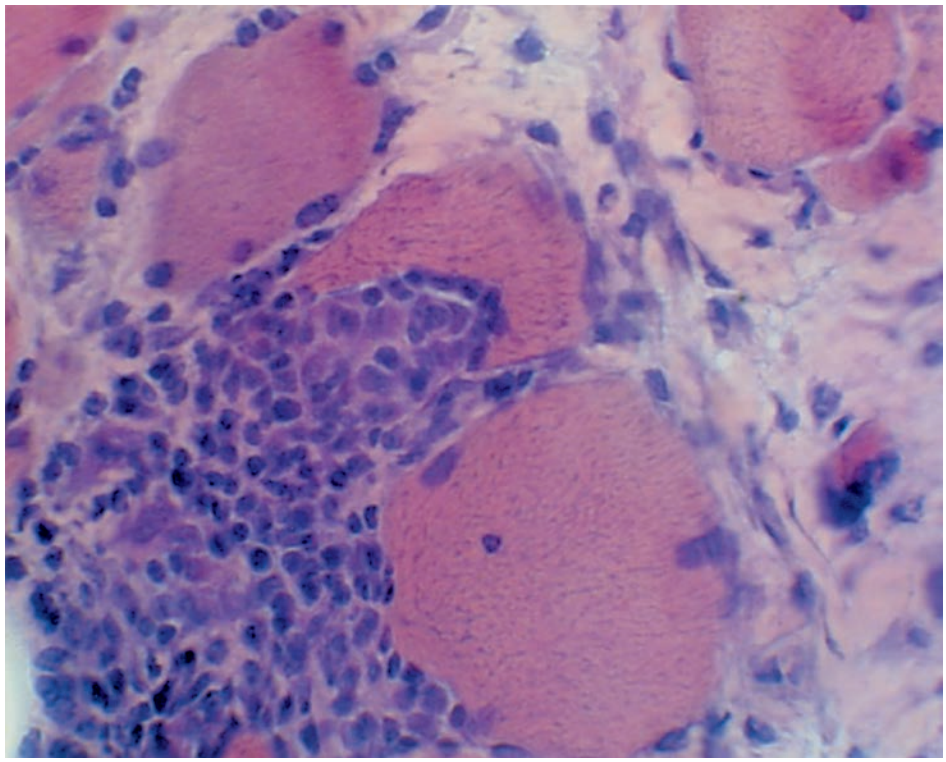


Fig. 70.9. Polymyositis. H and E stain of muscle biopsy showing inflammatory cells invading muscle fibre and in the interstitium.

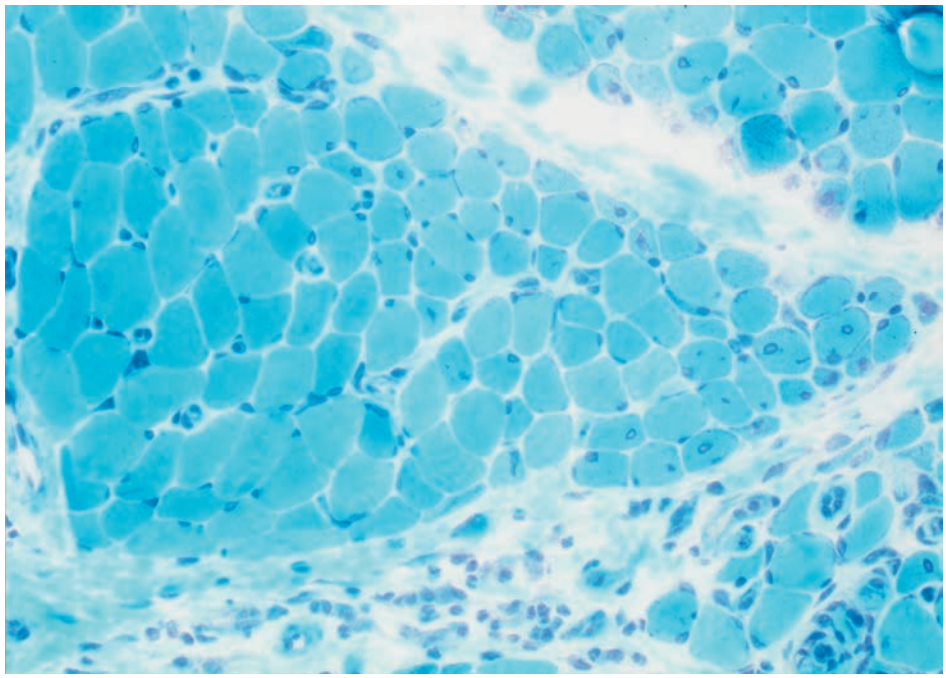


Fig. 70.10. Dermatomyositis muscle biopsy. (*a*) Gomori trichrome stain showing perifascicular atrophy. (*b*) See text.

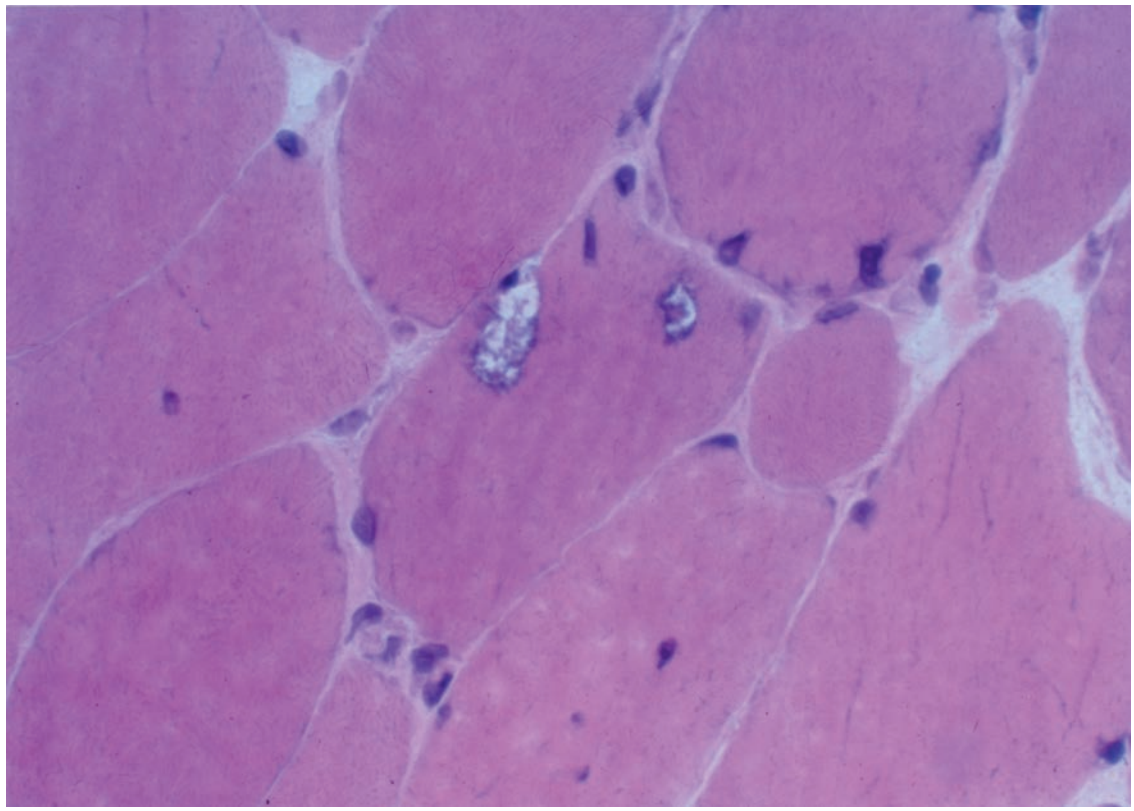


Fig. 70.11. Inclusion body myositis muscle biopsy. Gomori trichrome stain showing characteristic rimmed vacuole. Such vacuoles are not specific for IBM and occur in various other inclusion body myopathies.

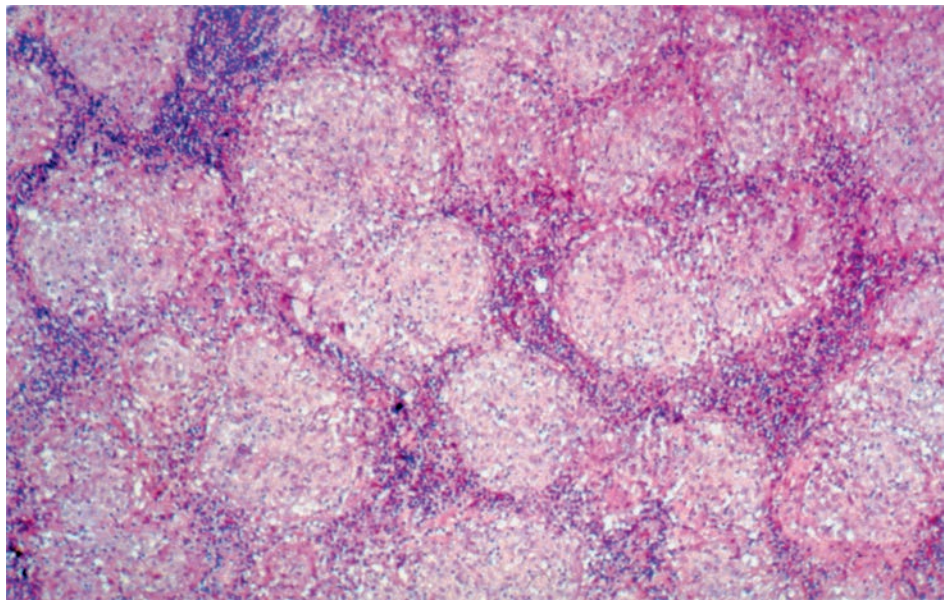


Fig. 95.3. Photomicrograph of mediastinal lymph node biopsy showing numerous non-caseating granulomata. (From Photographic Case Studies in Neurology: Cerenex Pharmaceuticals.)

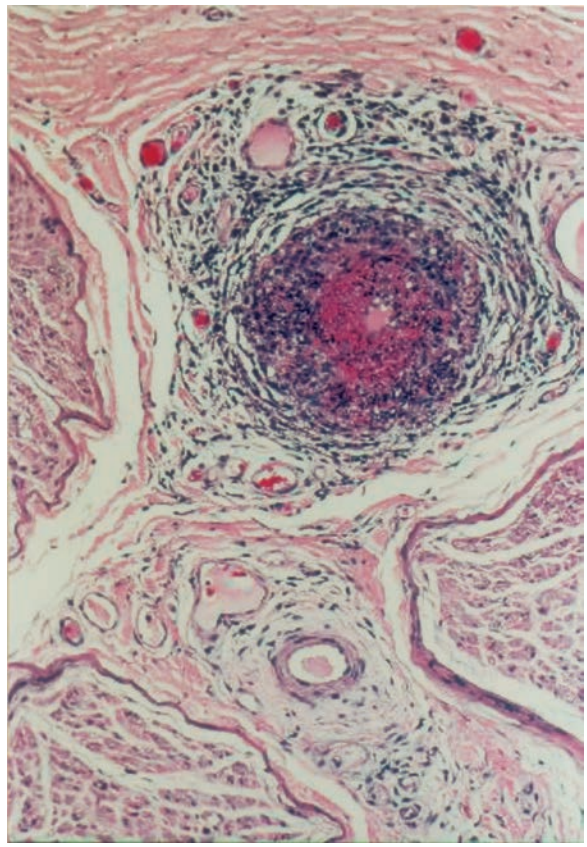


Fig. 96.3. Severe vasculitic neuropathy in polyarteritis nodosa. Inflammation extends through the wall of the blood vessel.

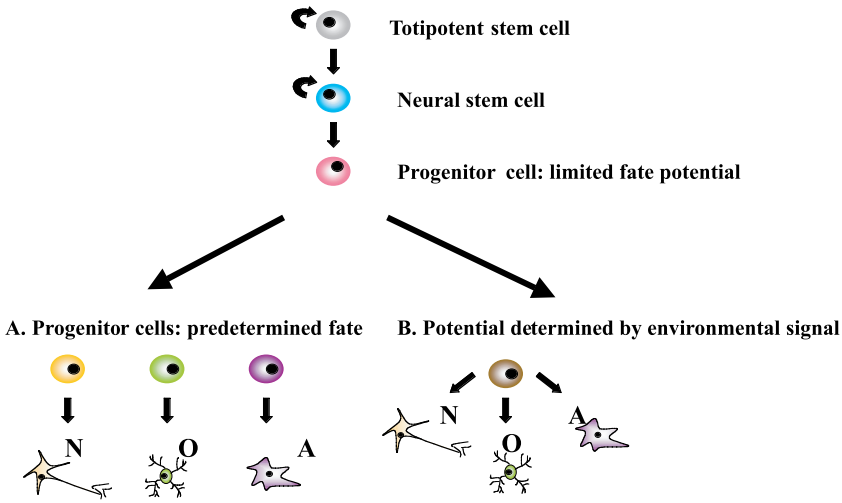


Fig. 97.1. Stem cells self-replicate and generate fate-committed progeny which differentiate into neurons, astrocytes and oligodendrocytes. (Kindly prepared by Dr Siddarthan Chandran.)

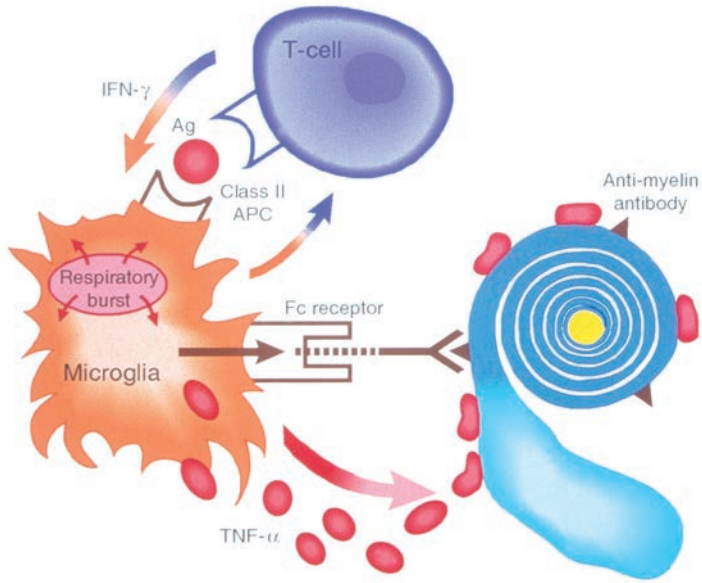


Fig. 97.4. Interaction between T-cells and microglia in the central nervous system. Microglia are activated by T-cell derived IFN-γ; they express class II MHC antigen and function as non-professional antigen-presenting cells, stimulating primed T-cells to secrete additional IFN-γ and recruit naive microglia. Activated microglia secrete proinflammatory cytokines, express Fc and other immune receptors, and damage opsonized oligodendrocytes by cell–cell contact and local production of TNFα. (Reproduced with permission from *McAlpine's Multiple Sclerosis*, 1998, Churchill Livingstone.)

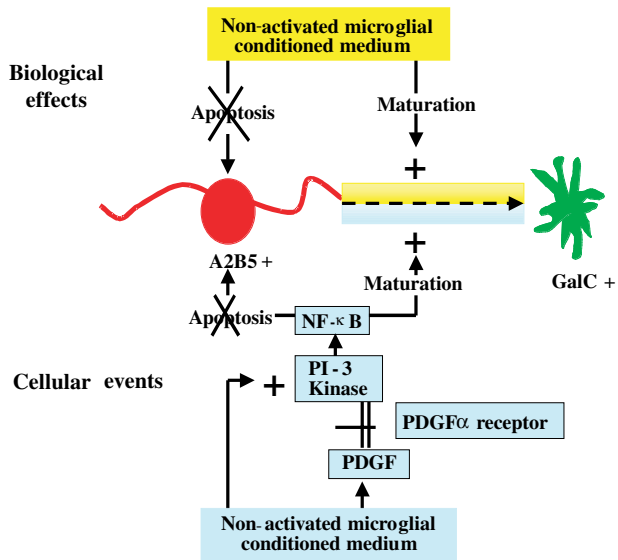


Fig. 97.5. Soluble factors released by non-activated microglia increase oligodendrocyte survival by inhibiting apoptosis and promoting differentiation of their precursors with signalling through the PDGFα receptor activating NF-kB. (Kindly prepared by Dr Richard Nicholas.)

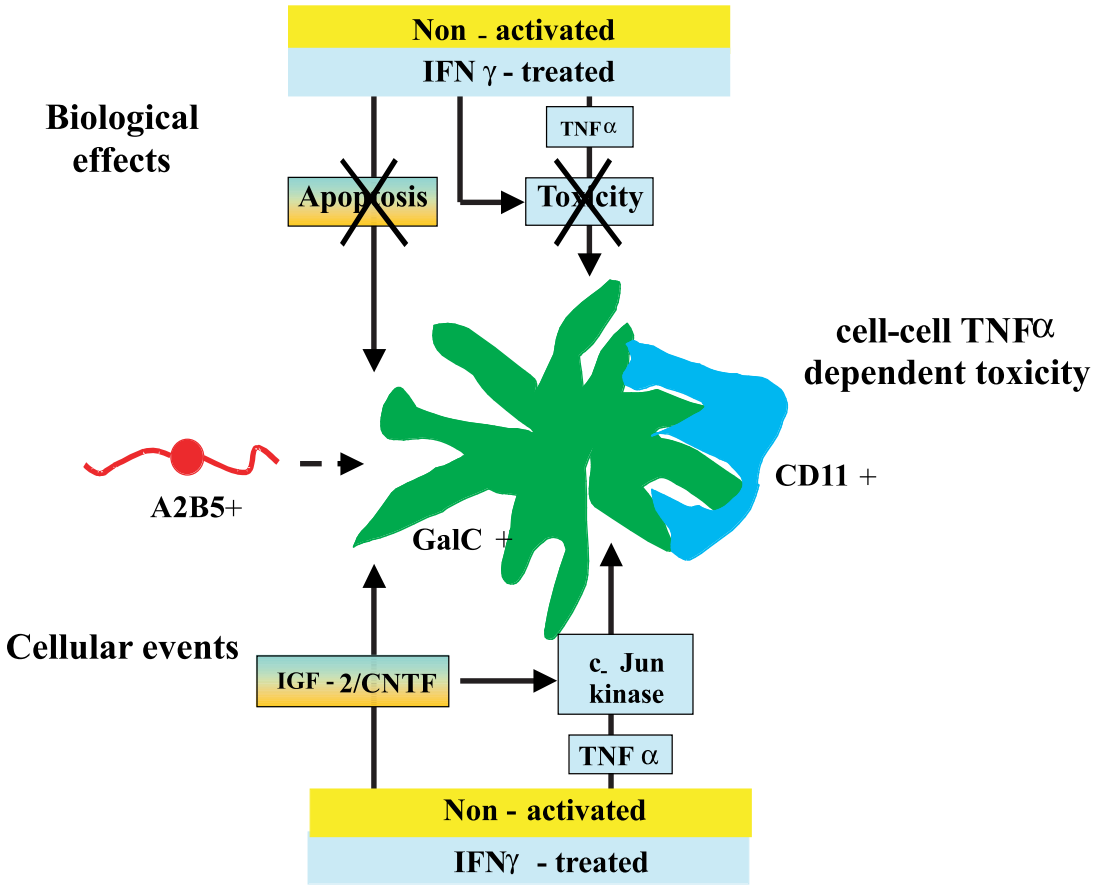


Fig. 97.6. Activated microglia kill opsonized oligodendrocytes by cell–cell contact and local release of TNFα. Oligodendrocytes are only susceptible to soluble TNFα in the absence of IGF-2 and CNTF. These growth factors are produced by microglia and so normally act to inhibit bystander damage of healthy oligodendrocytes. (Kindly prepared by Dr Richard Nicholas.)

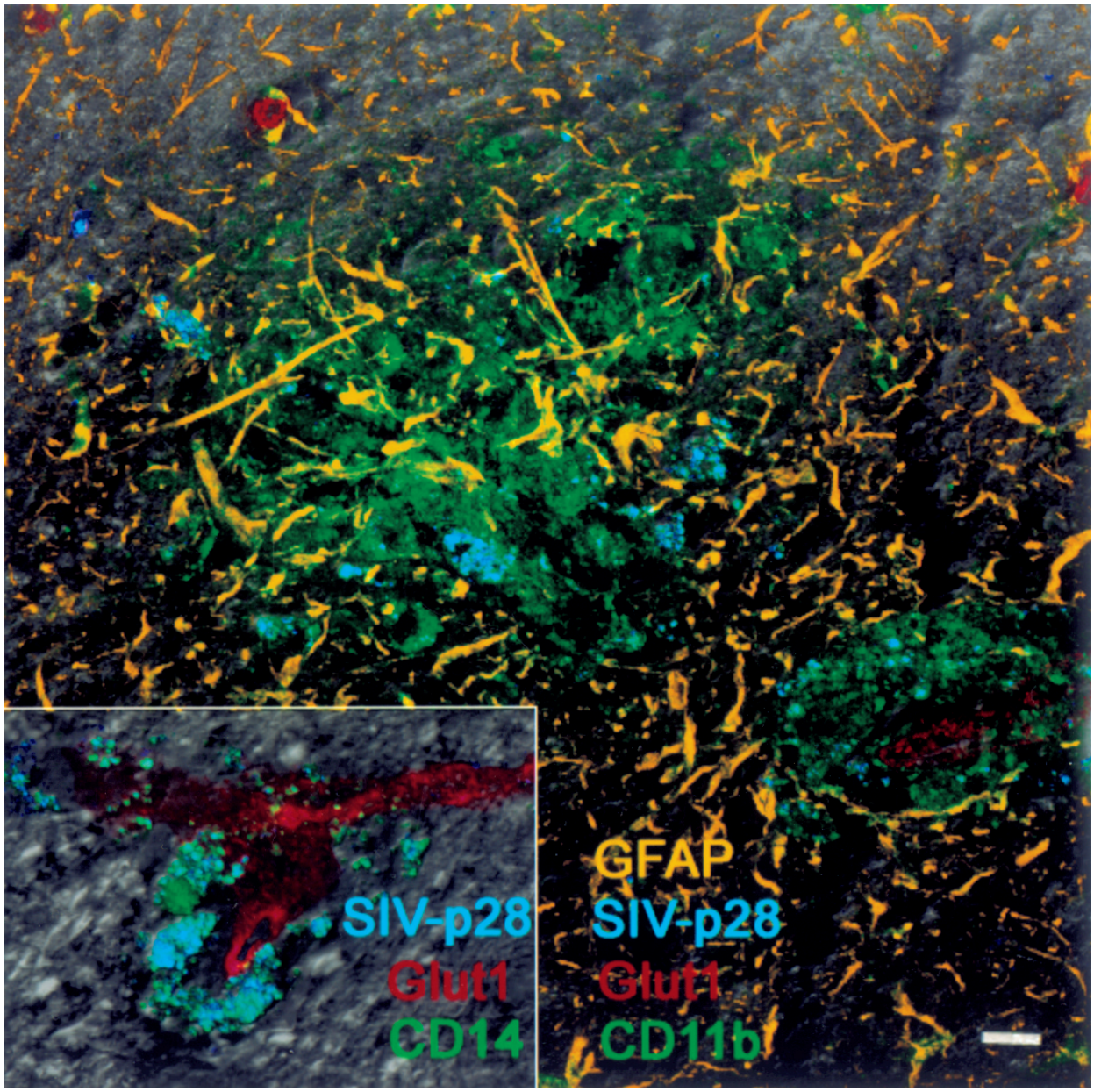


Fig. 103.10. SIV confocal: multilabel confocal microscopy demonstrating perivascular macrophages within the CNS showing that perivascular macrophages are the major cell type infected by SIV. Multilabel confocal microscopy demonstrating astrocytes (GFAP – yellow), SIV viral protein (SIV – blue), endothelial cells (Glut-1 – red), and brain macrophages including microglia and perivascular cells (CD11b – green). There is an accumulation of CD11b macrophages, some of which are SIV-infected as demonstrated by the production of viral proteins. Inset (lower left corner): demonstrates perivascular macrophages (CD14 – green) surrounding CNS endothelial cells (Glut-1 – red), that are productively infected (SIV-p28 – blue). These images demonstrate that CD14+ perivascular macrophages, and not parenchymal microglia, are the major target of SIV, and probably HIV infection. (Courtesy of Dr K. Williams: *Glia*, in press.)

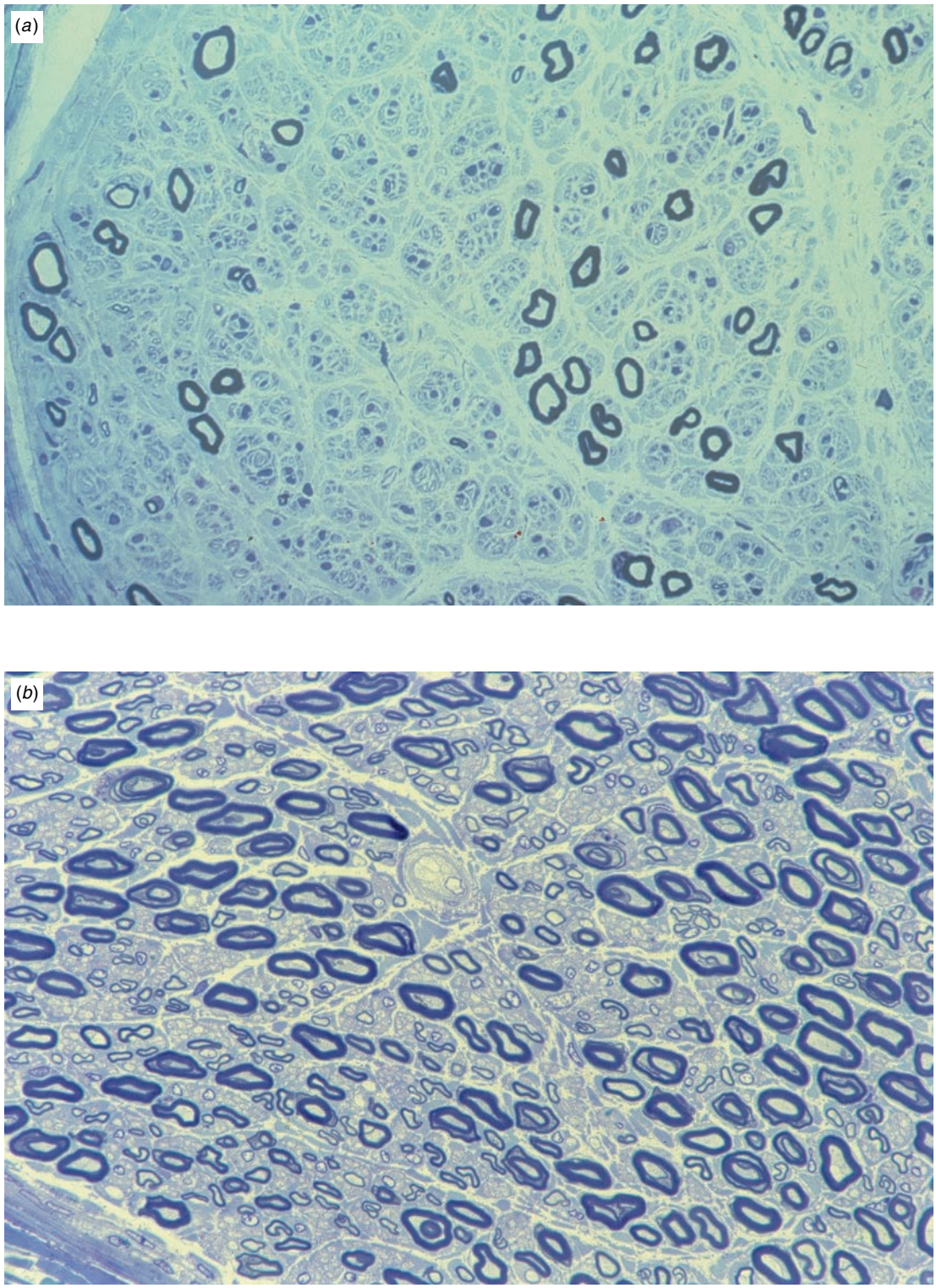


Fig. 103.13. HIV-SN: photomicrograph of sural nerve showing severe myelinated fibre loss in HIV-associated distal sensory polyneuropathy (*a*), compared to control (*b*).

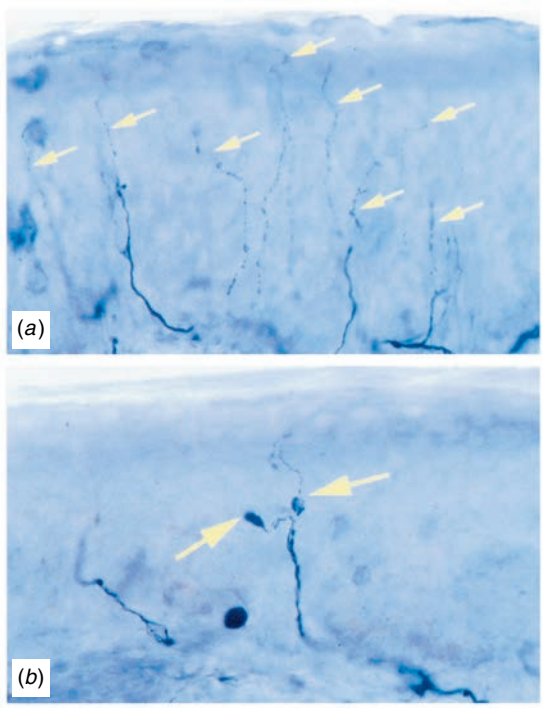


Fig. 103.14. HIV-SN2: Punch skin biopsies immunostained with the pan-axonal marker PGP9.5 to indicate epidermal nerve fibres. In normal region, taken from the thigh (*a*), there is a high density of unmyelinated nerve fibres (arrows). At the ankle, however, the density of fibres is very low, and nerve fibre swelling indicative of degeneration is seen (arrows) (*b*).

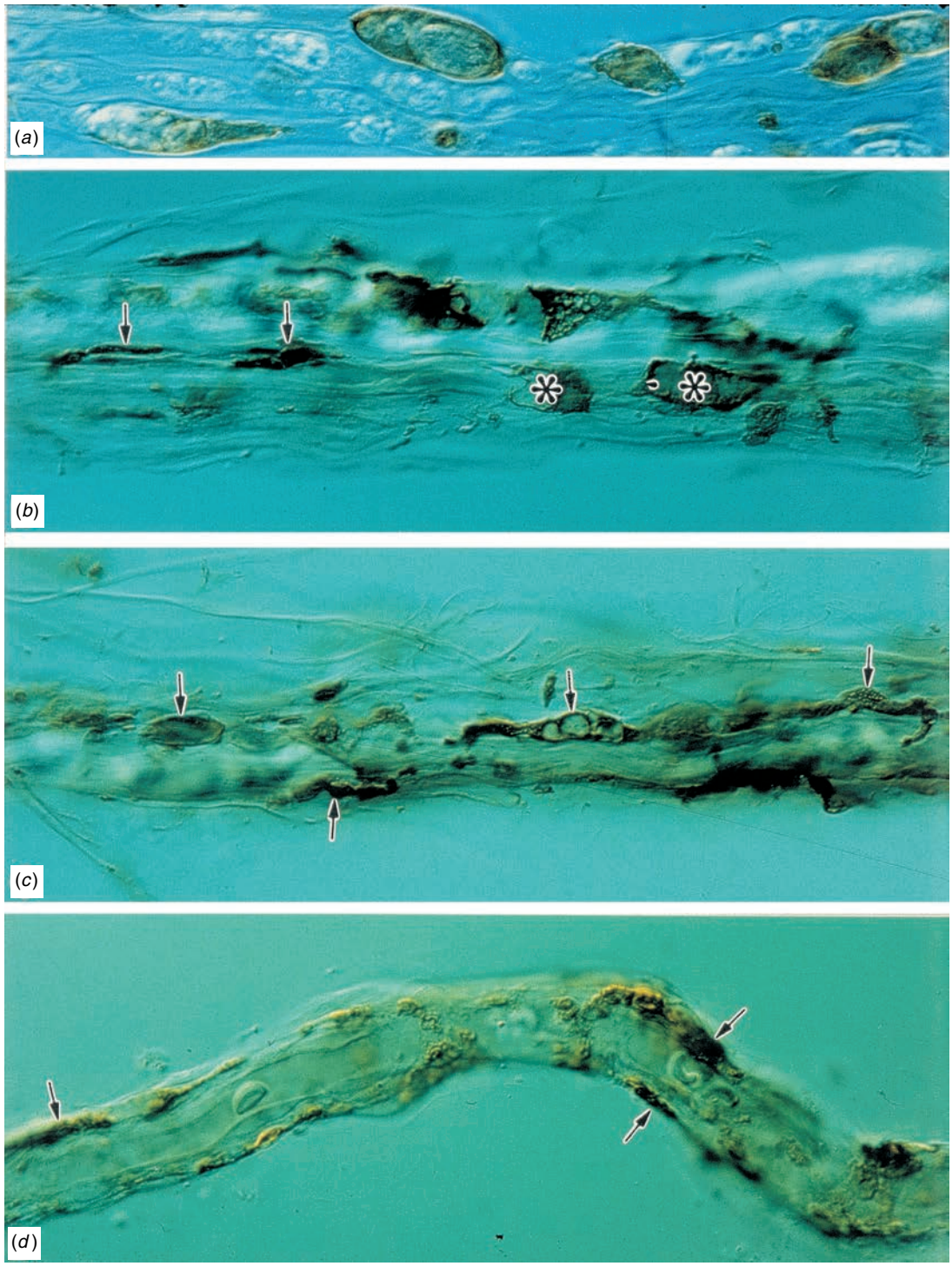
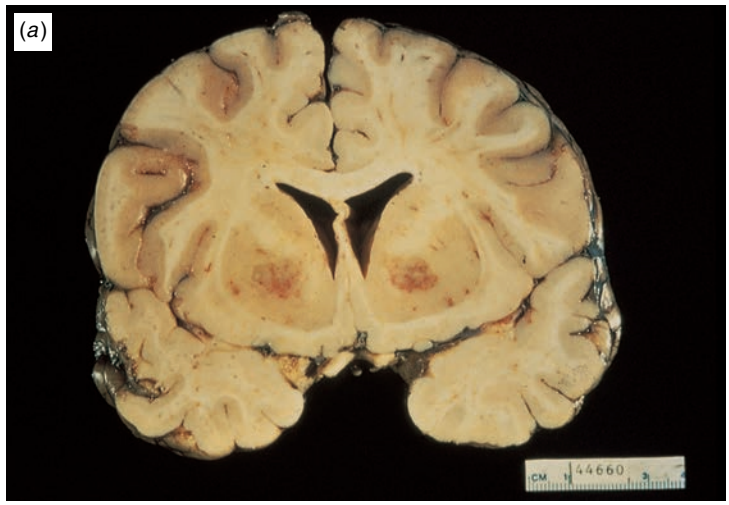
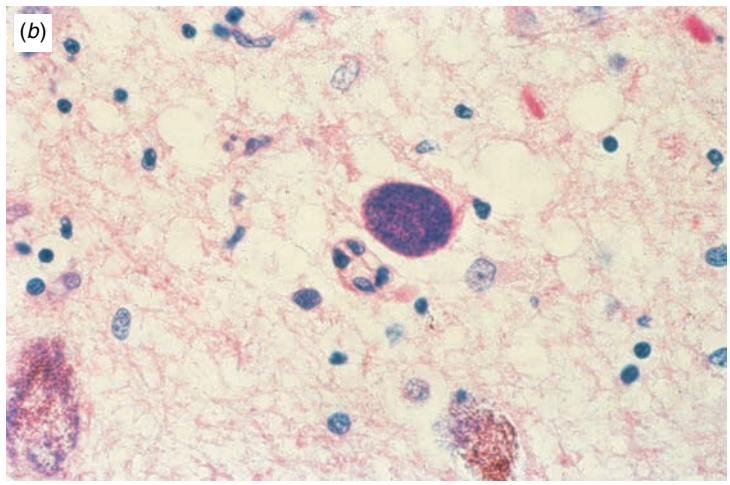


Fig. 103.15. Teased nerve fibres immunostained for various proinflammatory cytokines. In (*a*), macrophages are identifiable arrayed along the nerve fibre, and in (*b*), IL-1, (*c*) TNF-alpha, and (*d*) IL-6 products (arrows) and macrophages (asterisks) are visible with immunocytochemistry. (Courtesy of Dr JW Griffin.)





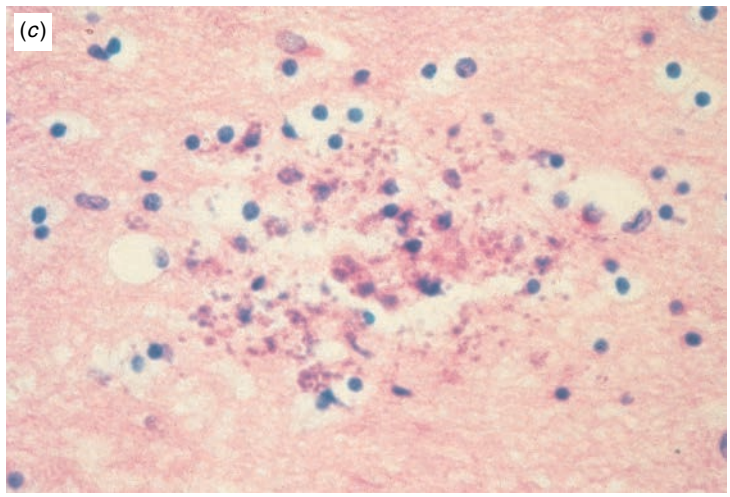


Fig. 103.16. (*a*) Gross specimen cerebral toxoplasmosis with paired basal ganglion abscesses. (*b*) Photomicrograph of bradyzoite. (*c*) Photomicrograph of tachyzoites.

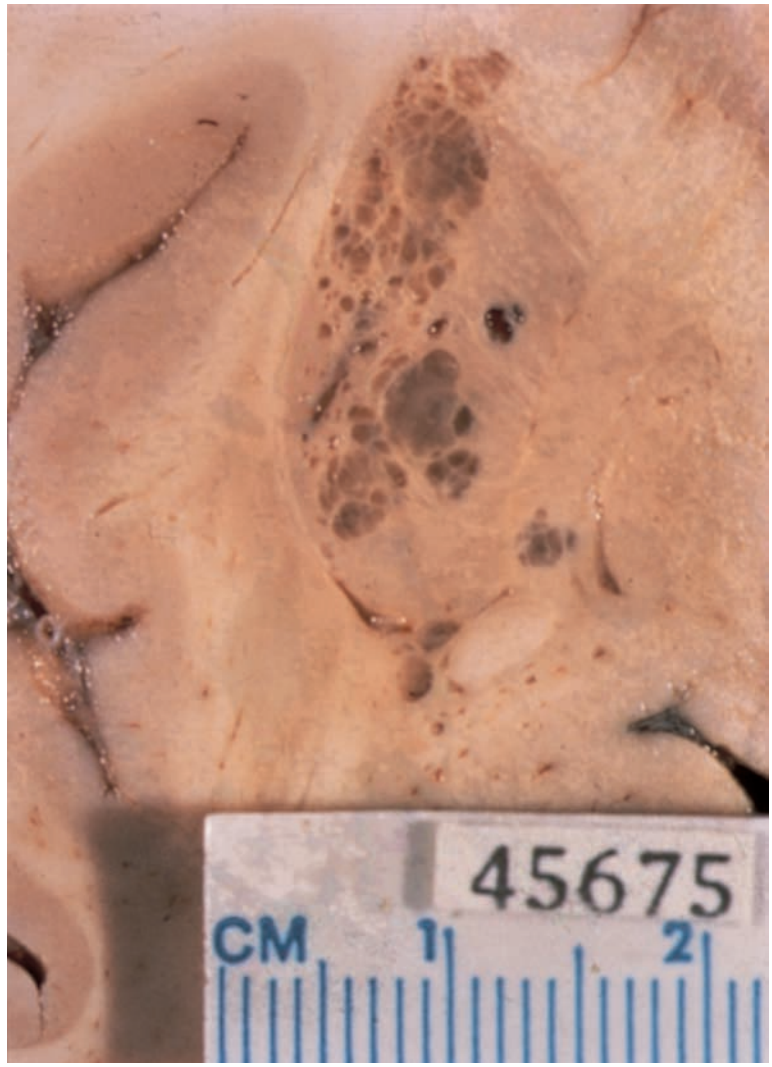


Fig. 103.18. Cryptococcal meningitis: cryptococcomas in fulminant cryptococcal meningitis in basal ganglia.

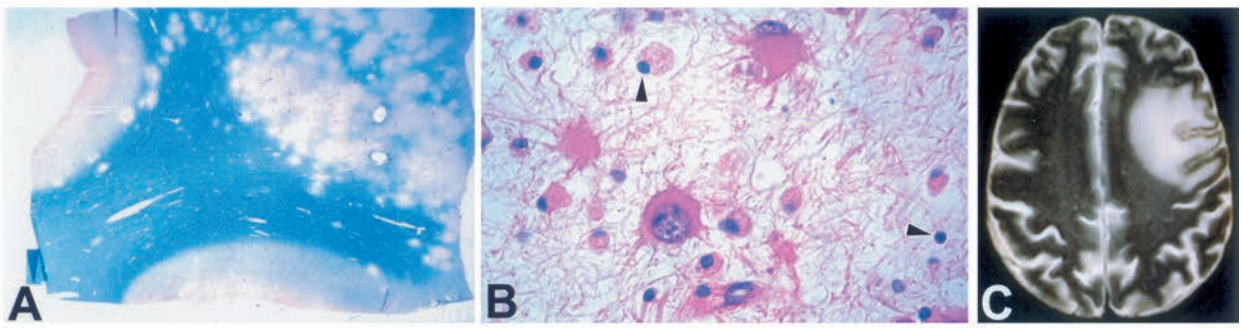


Fig. 103.19. Composite figure to illustrate demyelinating foci in progressive multifocal leukoencephalopathy (PML). (*a*) Multiple foci of demyelination, both discrete and coalescent, within the subcortical white matter. (*b*) Microscopic pathology, with bizarre astrocytes and inclusion-bearing oligodendrocytes (arrows). MRI, with typical subcortical white matter hyperintensities (*c*).

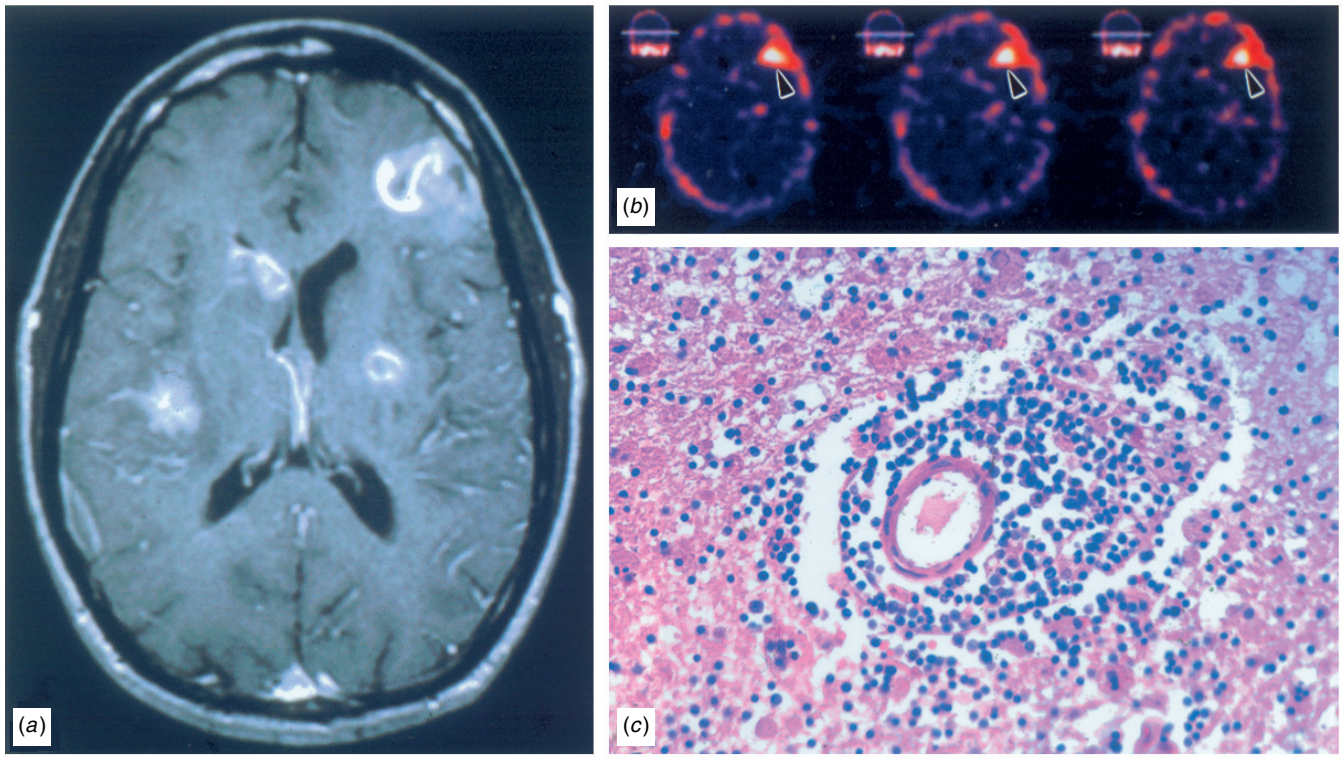


Fig. 103.20. Primary CNS lymphoma. Composite to illustrate (*a*) the heterogenous enhancement within multiple tumour foci on MRI scan, and (*b*) the focal uptake of thallium-201 into a frontal lesion (arrow heads), and (*c*) perivascular collection of lymphomatous cells.

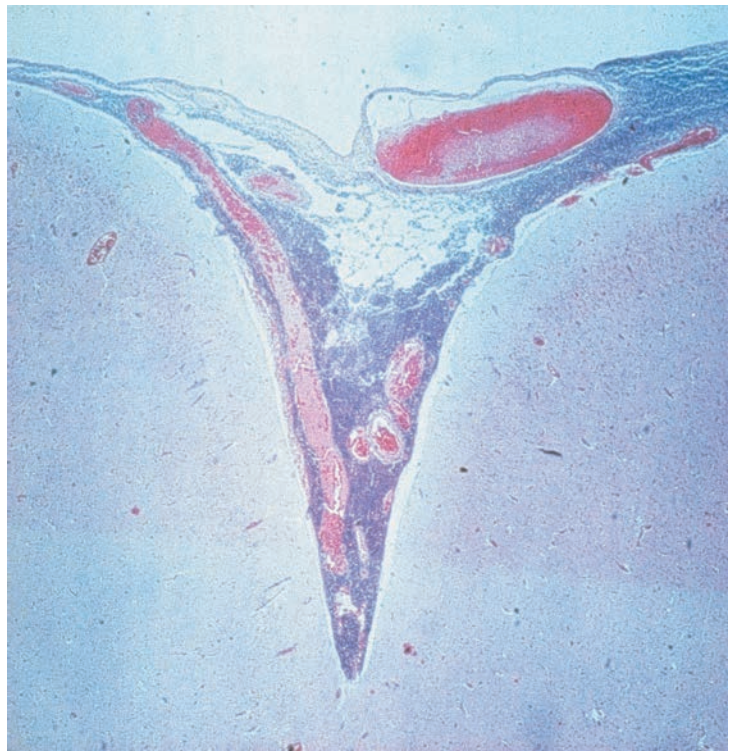


Fig. 106.2. Bacterial meningitis: photomicrograph of meninges in acute bacterial meningitis showing intense inflammatory response.

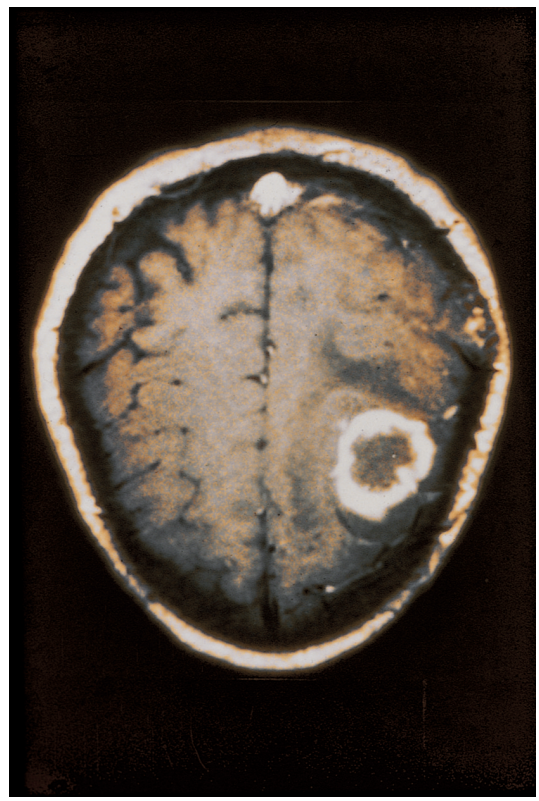


Fig. 106.3. Bacterial brain abscess: T_1-weighted contrast cranial MRI scan illustrating large contrast-enhancing lesion, with surrounding edema.

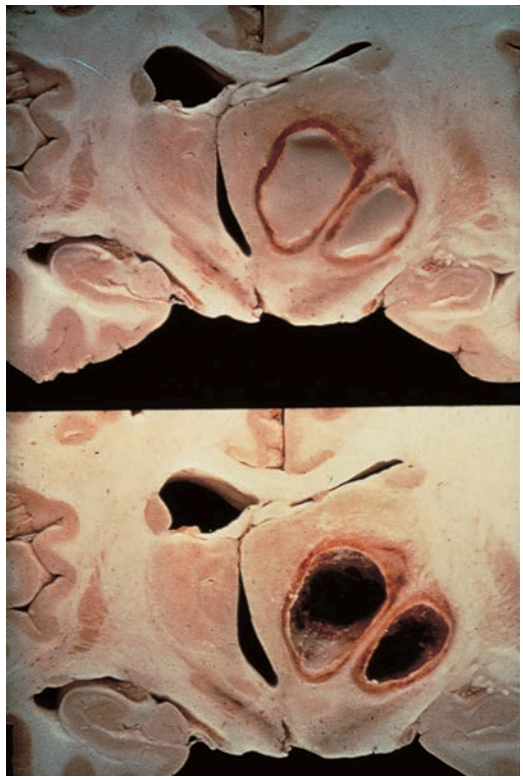


Fig. 106.4. Bacterial brain abscess: gross specimen.

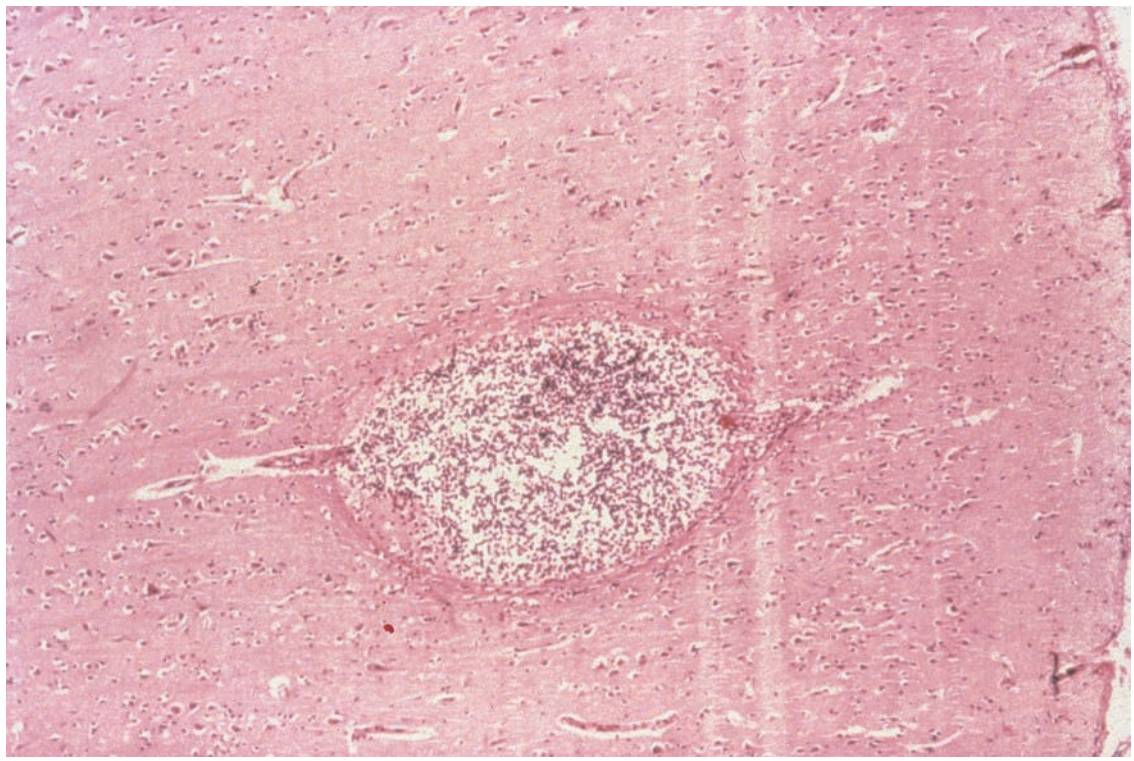


Fig. 106.5. (*a*) Septic embolization in bacterial endocarditis. Photomicrograph illustrates small vessel occluded by septic embolus. (*b*) See text. (Figure courtesy of Dr Justin C. McArthur.)

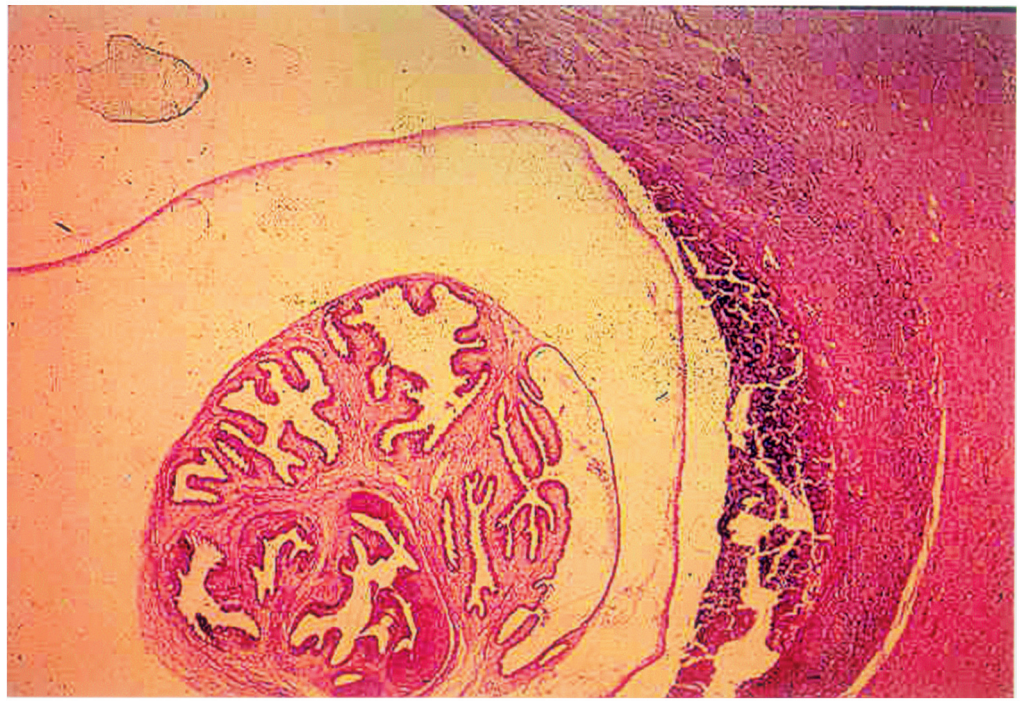


Fig. 107.1. Microscopic appearance of a cysticercus in brain parenchyma showing the cystic membrane and the scolex, discrete inflammatory response around the parasite is observed.

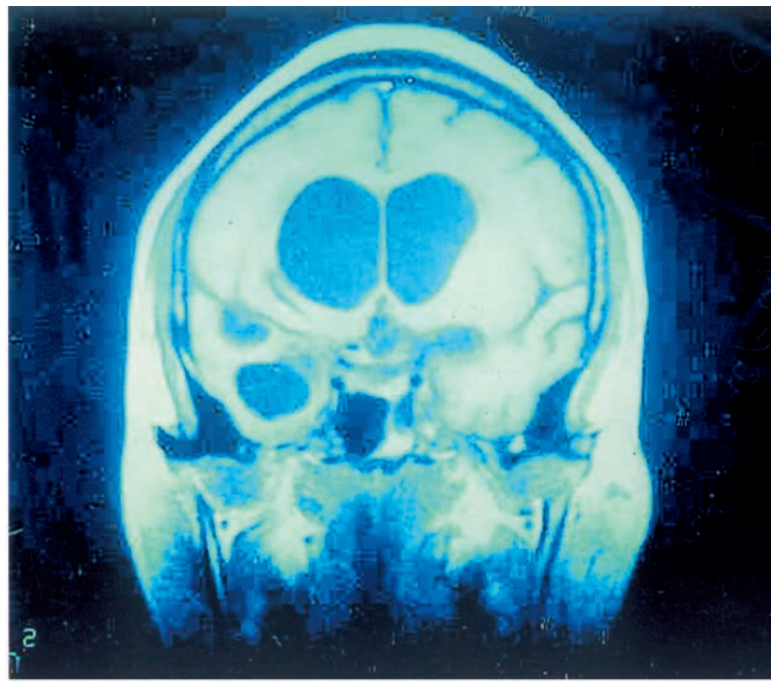


Fig. 107.2. Magnetic resonance from a patient with a mixed form of neurocysticercosis; hydrocephalus and a cyst in left temporal lobe.

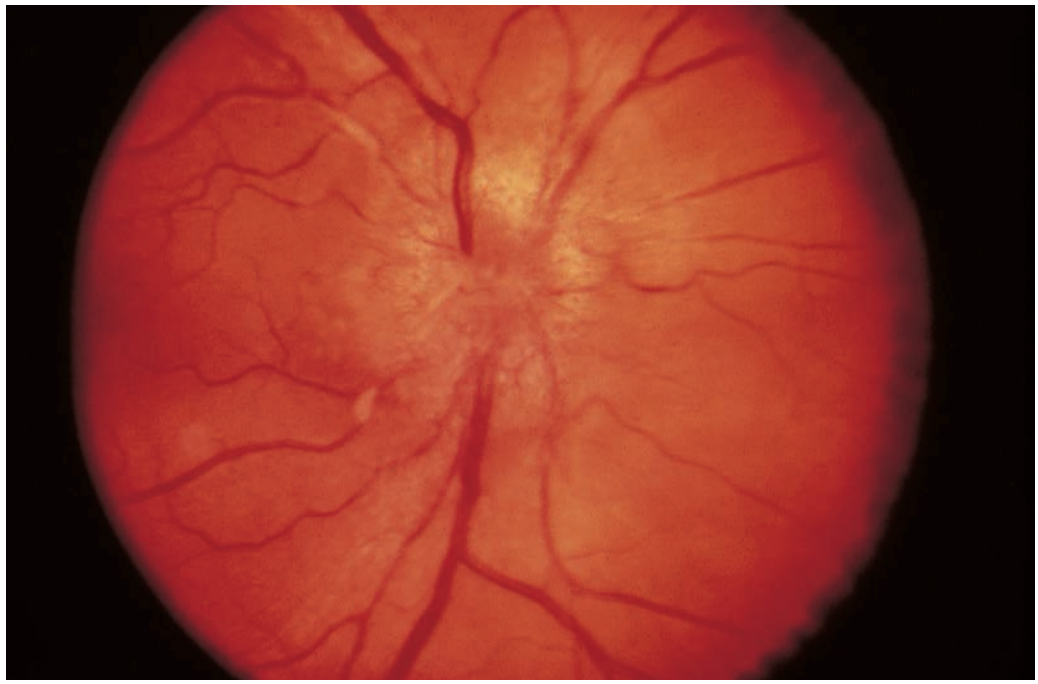


Fig. 109.2. Syphilitic papillitis.

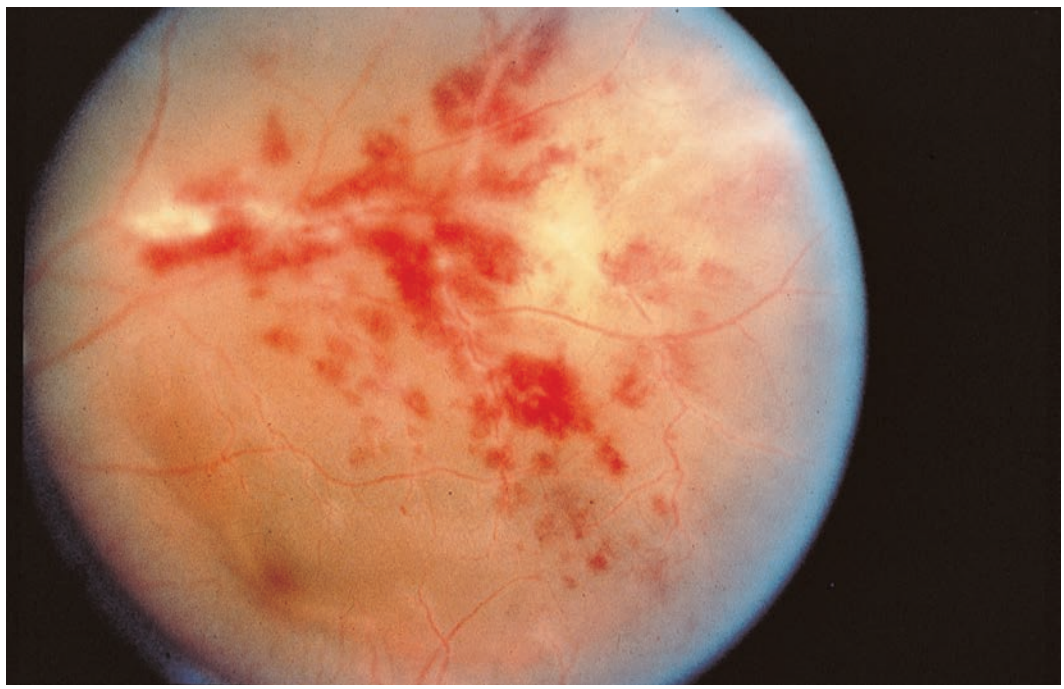


Fig. 109.3. Syphilic chorioretinitis.

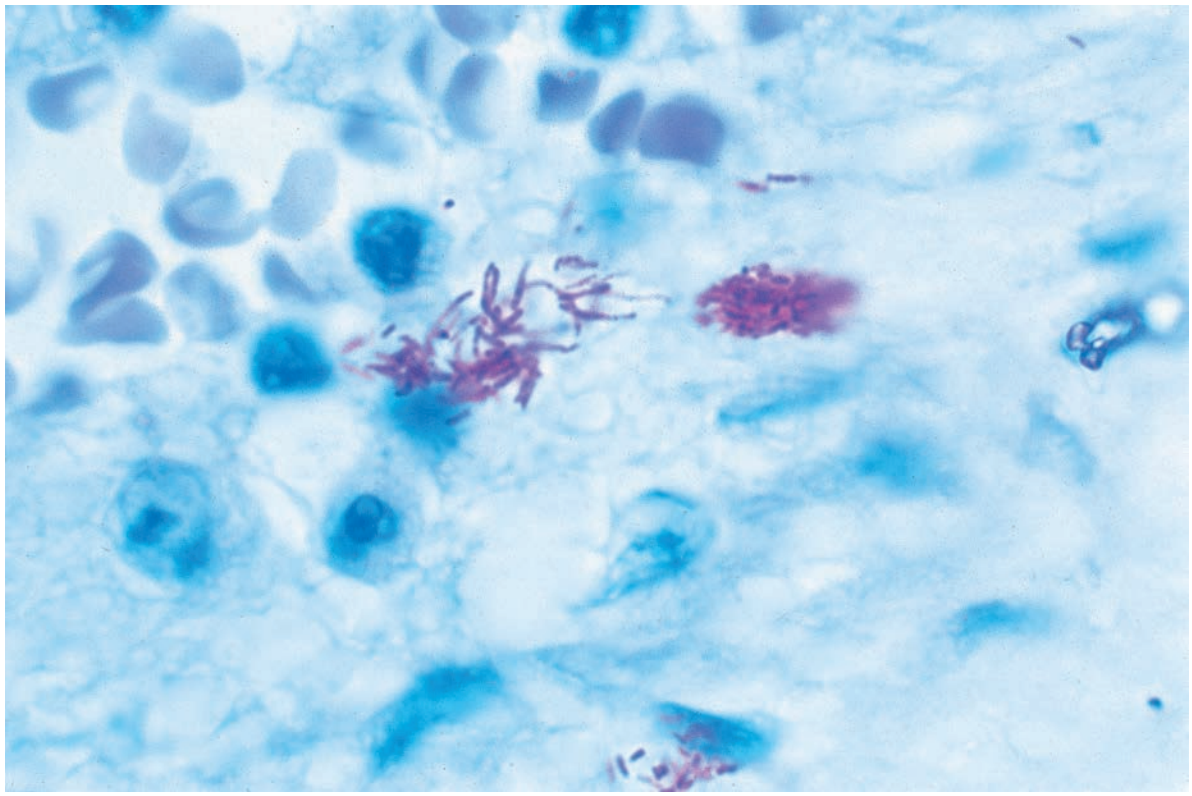


Fig. 110.1. Photomicrograph of blood vessel in TB meningitis: AFB stain for *Mycobacterium tuberculosis* demonstrates numerous red acid-fast bacilli. (Courtesy of Dr J.C. McArthur.)

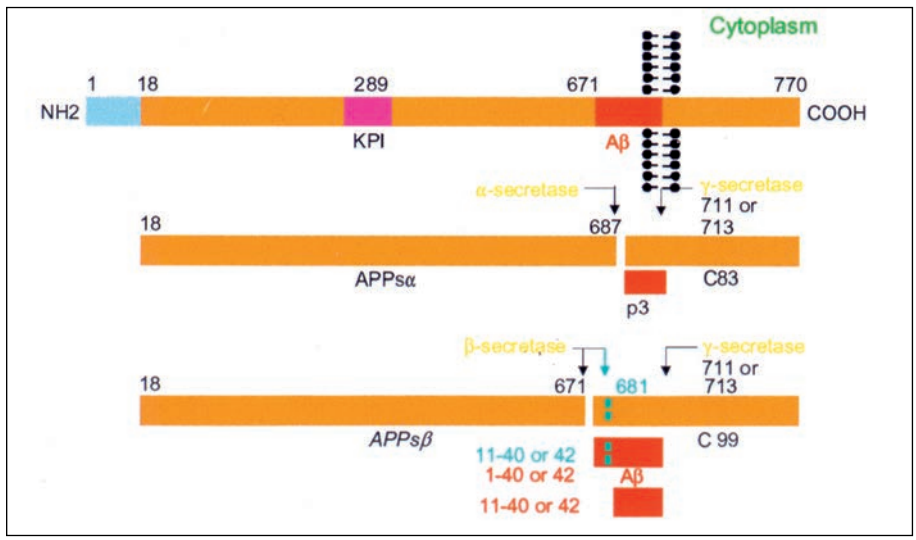


Fig. 115.2. Schematic of APP, a single pass transmembrane protein with a short cytoplasmic C-terminal domain and a large ectodomain. The Aβ peptide is situated partially within the membrane and partially outside the membrane. α-secretase, or tace cleavage, cuts Aβ between residue 16 and 17 and, following δ secretase cleavages, p3 fragments are generated. This cleavage is anti-amyloidogenic. In contrast, BACE1 cleavages at the $+1$ and $+11$ site are followed by γ-secretase cleavages which generate the Aβ peptides that are implicated in the human illness.

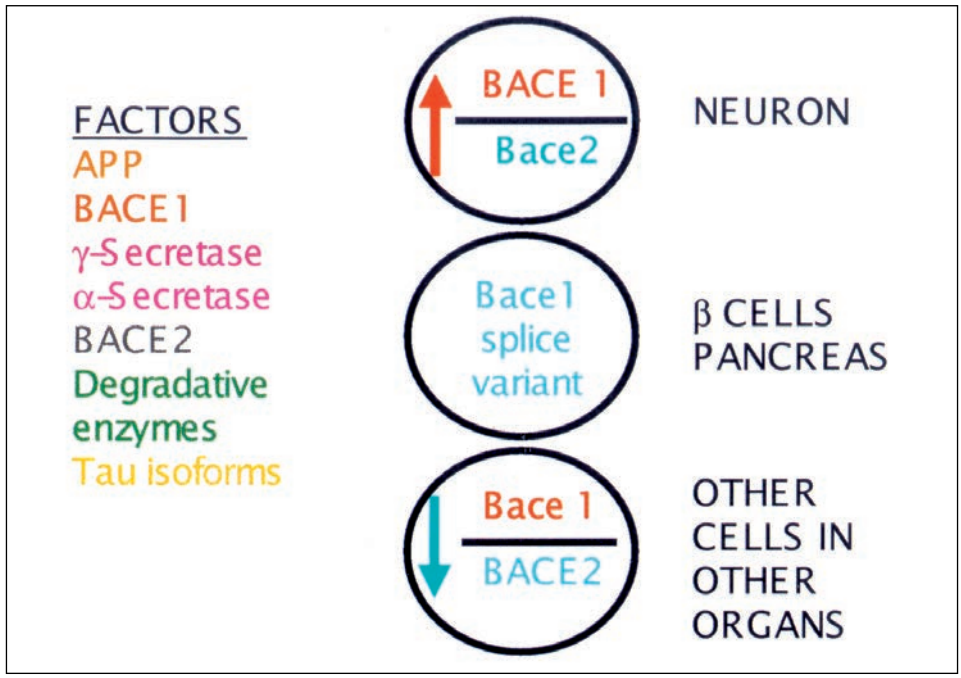


Fig. 115.3. Factors that are important in amyloidogenesis are listed. We have postulated that neurons are vulnerable in Alzheimer's disease because they have relatively high levels of APP and BACE1 and sufficient δ-secretase to generate Aβ. In contrast to other cells, neurons are not protected by α-secretase and BACE2 activities. Other cells have variable levels of APP, but because they have low levels of BACE1 and reasonable levels of BACE2, they are not predisposed to form amyloid. Although a subset of pancreatic cells have relatively high levels of BACE1 MRNA, the MRNAs are alternatively spliced to generate BACE1 isoform that is incapable of cutting APP.

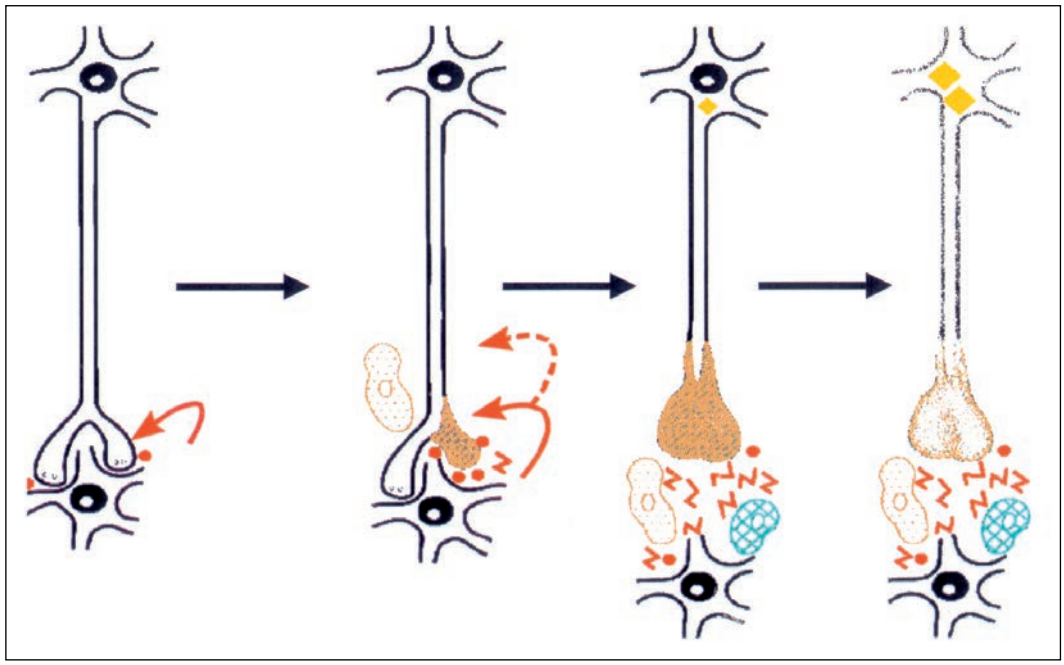


Fig. 115.4. In this model, APP is made in neurons and transported to axon terminals. BACE1 is also present at these sites and cleaves APP to generate C-terminal fragments, which in turn are cleaved by γ-secretase activity to generate small amounts of Aβ. In the presence of mutations, Aβ is generated at higher levels at axon terminals where it appears to be synaptotoxic, probably in the form of Aβ toxic oligomers, to damage synapses which retract from target cells; glial responses begin at this time. In the third image, the parent cell is disconnected from the target. There is a large APP-filled neurite decorated by amyloid deposits (red dots and Zs), astrocytes and microglial cells. Phosphorylated cytoskeletal elements appear in the cell body. It is hypothesized that phosphorylated isoforms of human tau could then begin to form tangles.

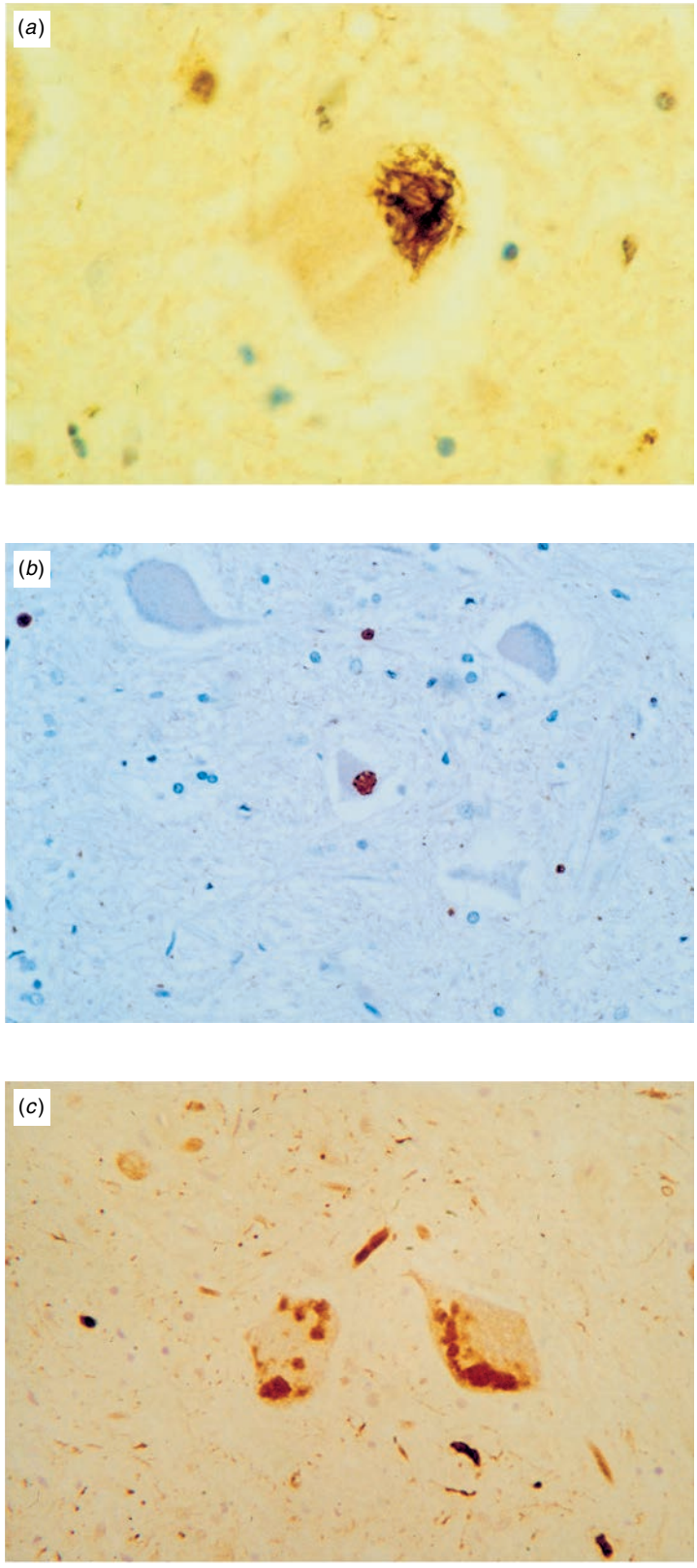


Fig. 116.5. Inclusion bodies in surviving spinal cord motor neurones in ALS patients. (*a*) skein-like ubiquitinated inclusion; (*b*) hyaline ubiquitinated inclusion; (*c*) hyaline conglomerate inclusion showing strong neurofilament immunoreactivity in a patient with SOD1-related familial ALS.

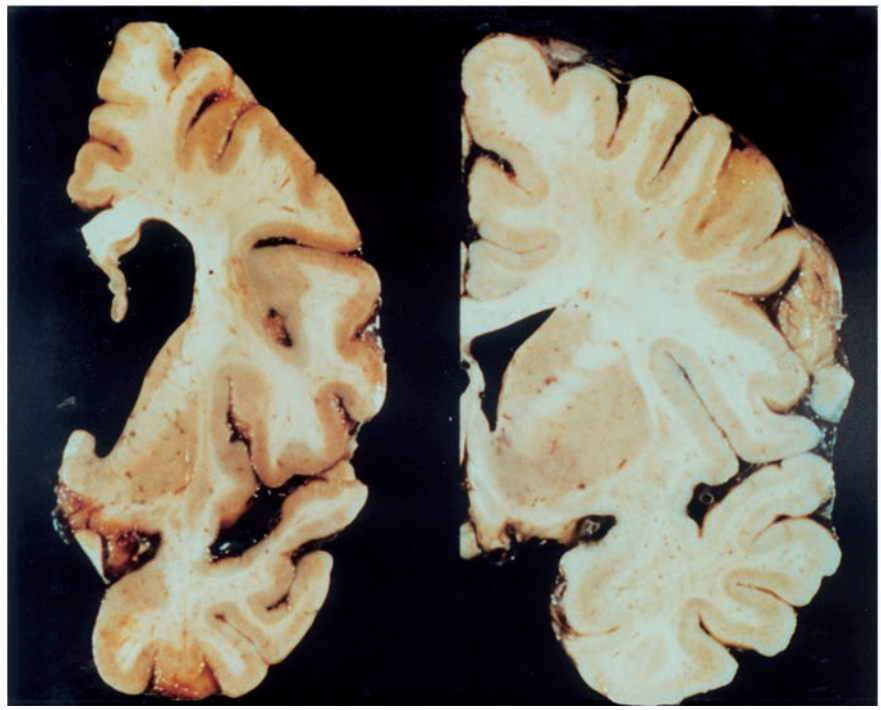


Fig. 118.2. HD gross pathology. Coronal hemisections of brain from HD patient (left) and normal individual (right). Note prominent atrophy of striatum and cerebral cortex, with ventricular enlargement.

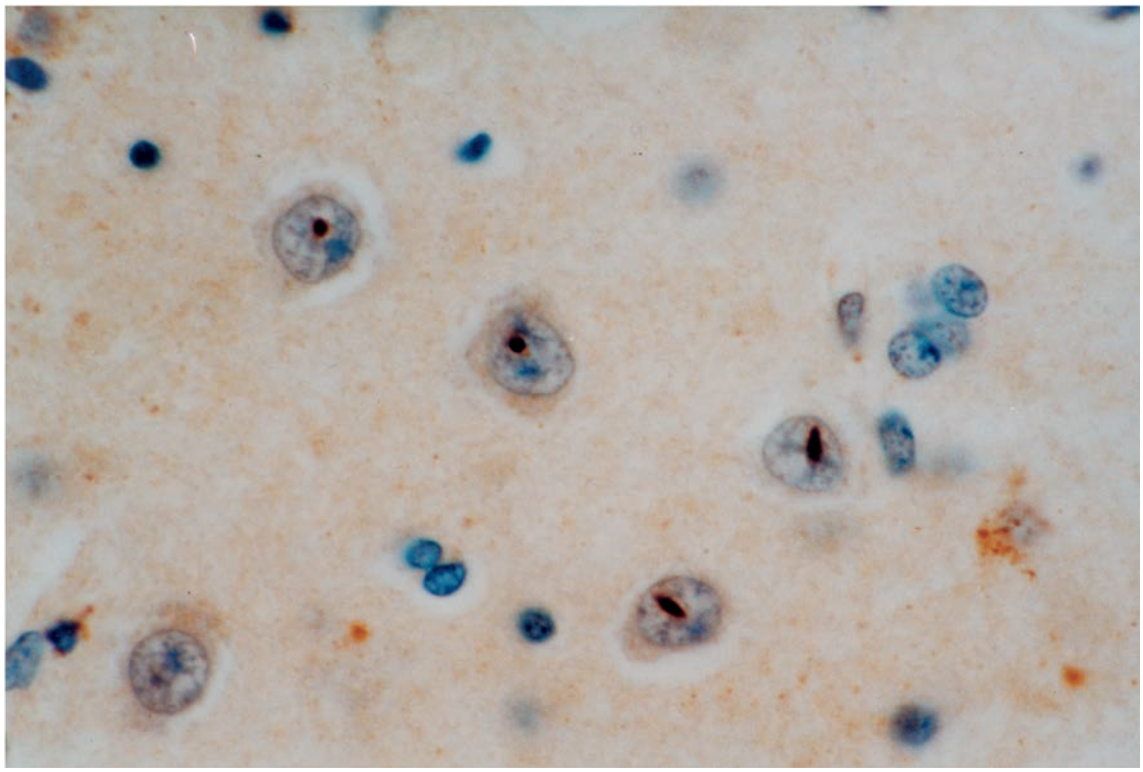
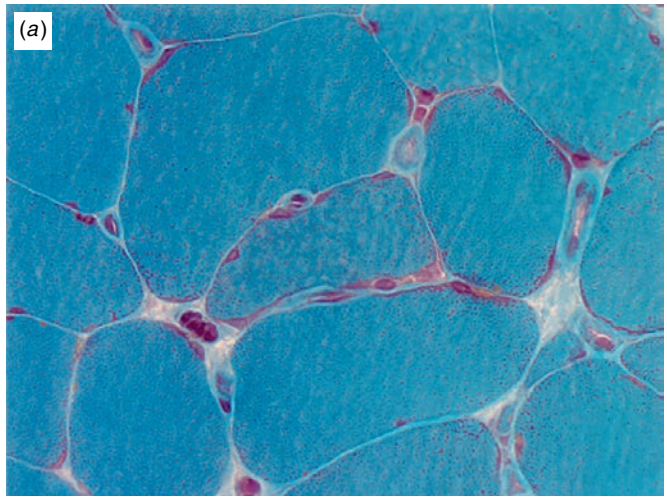
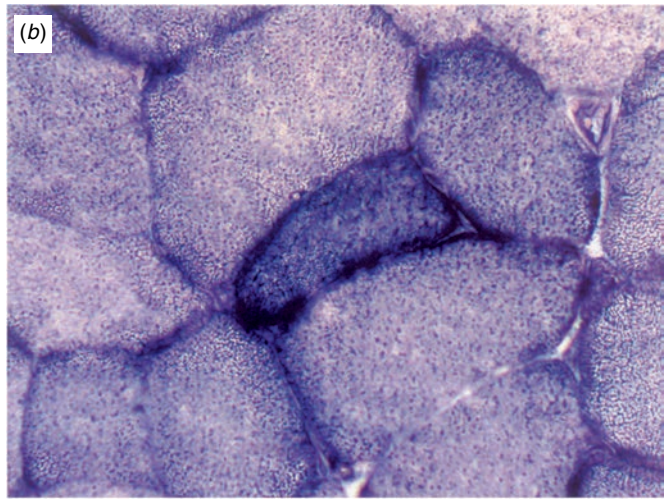


Fig. 118.3. Intranuclear inclusions. Cerebral cortex section from HD-affected brain, immunocytochemically labelled with antiubiquitin antiserum to reveal intranuclear inclusions (orange–brown). Note that the inclusions are limited to neuronal nuclei, and are distinct from the nucleolus.





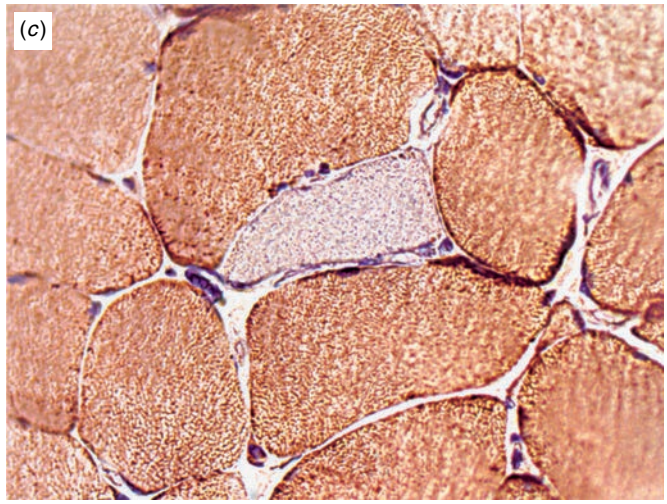
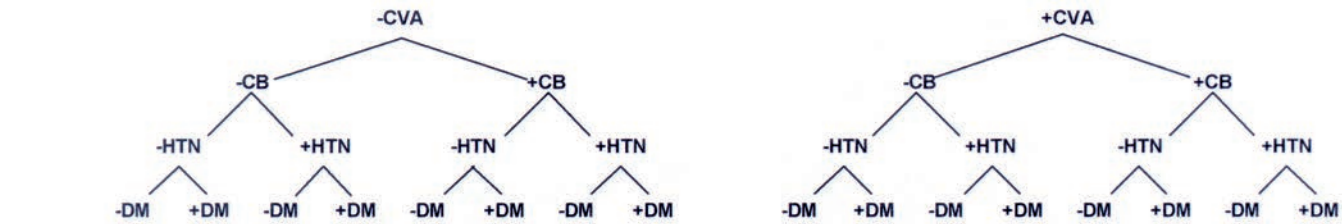


Fig. 120.3. (*a*) Modified Gomori trichrome stain of the muscle biopsy from a patient with CPEO and mitochondrial myopathy. The central fibre is atrophic but in staining shows only very mild and subtle abnormalities and could easily be passed as normal. (*b*) Succinate dehydrogenase staining of a serial section to (*a*). The central, dark staining fibre is now clearly abnormal and confirms the increased sensitivity of this stain in detecting 'ragged red' fibres. (*c*) A further serial section to (*b*) using the cytochrome oxidase (COX) stain. The succinate dehydrogenase positive fibre is COX negative.



AGE groups																
<65	.00	.00	.01	.03	.01	.01	.03	.08	.01	.03	.06	.16	.03	.08	.17	.35
≥65-<75	.01	.02	.05	.13	.02	.06	.14	.30	.05	.12	.24	.46	.13	.29	.48	.72
≥75	.01	.03	.06	.14	.03	.07	.15	.32	.05	.13	.26	.49	.14	.31	.51	.74

Fig. 122.1. Calculating probability of stroke using factors known preoperatively. To find the probability of stroke for any patient, respond yes (+) or no (−) to the following questions: Has the patient had a previous stroke (CVA)? If no, move to the left side of the figure. Does the patient have a carotid bruit (CB)? Does the patient have a history of hypertension (HTN)? Does the patient have diabetes mellitus (DM)? Match this column with the patient's age group (on admission), and you will identify the patient's estimate of stroke risk. Low stroke risks are shown in black, medium stroke risks in blue, and high stroke risks in red.