Foreword

It is entirely appropriate that a volume of the *Handbook of Clinical Neurology* should be devoted to disorders of consciousness, and the present volume is an outstanding compendium that will be of interest to all practicing neurologists as well as to others concerned with the care of patients with an altered level of consciousness. Neurologists frequently evaluate patients with these disorders and are often consulted by specialists in other fields to guide management and prognostication in individual cases. There are many causes for a disturbance of consciousness, and – regardless of their area of subspecialty interest – all neurologists should have some expertise in their approach to comatose or encephalopathic patients. Reversible disorders must be distinguished from irreversible ones, lesions requiring neurosurgical management distinguished from those that are managed medically, and patients requiring immediate intervention distinguished from those in whom any intervention is less urgent. In the past this depended on the acumen and skill of the clinician. Although these are still important, the technological advances that have occurred in neuroimaging have changed the approach to patients with an altered level of consciousness. Indeed, recent developments in functional brain imaging may eventually affect our understanding of the neurological substrate of consciousness. Furthermore, with the advances that have occurred in the management of patients in the intensive care unit, ethical issues and the provision of palliative care have also become important considerations.

In this context, we were delighted that Professors Bryan Young and Eelco Wijdicks agreed to serve as editors of this volume, as they have had enormous experience and have written extensively on disorders of consciousness, and we are grateful to them for all their efforts in seeing the book through to fruition. They assembled an outstanding group of coauthors, to whom we are also grateful for their contributions to the volume. As series editors, we looked over drafts of each of the chapters in the book, transmitting our comments to the volume editors so that they could be taken into account as the volume evolved. We greatly appreciated the tolerance and forbearance of the authors to our editorial suggestions. We are also greatly indebted to the editorial and production staff at Elsevier for their help at all stages during the development and production of this book.

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Chapter 1

Consciousness: concepts, neurobiology, terminology of impairments, theoretical models and philosophical background

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1.1. Concepts

1.1.1. Consciousness in context

There has been an extraordinary flowering of interest in the subject of consciousness since the topic was addressed in broad terms in this Handbook by J. A. M. Frederiks in 1969 (Frederiks, 1969). This flourishing is attested by a steady stream of publications, both technical and popular (Jasper et al., 1998; Damasio, 2000; Zeman, 2002; Dehaene and Naccache, 2003; Koch, 2004; Laureys, 2005), the emergence of an association dedicated to the study of the topic (Association for the Scientific Study of Consciousness), and a busy schedule of related scientific meetings (e.g., the annual meetings of the ASSC, the two-yearly Tucson meetings, Towards a Science of Consciousness).

It is worth asking why the subject has prospered so mightily in recent years. Several interrelated developments have contributed. First, experimental and clinical advances, in cognitive neuroscience and neuropsychology, are revealing ever more exquisite correlations between features of experience and events in the brain. The advent of functional imaging, in particular, is enabling us to *see* something of what happens in the human brain during experience – and in its absence, for example during coma. Second, the realization that unconscious neural processes are ubiquitous in the brain, and often affect our behavior, has helped to throw the topic of *conscious* processes into relief. Third, the design of increasingly sophisticated forms of artificial intelligence raises the possibility that we may become able to create conscious systems: what once was science fiction may soon be science fact. The fourth reason for the current fascination with the topic of consciousness is the most profound: the cartesian separation of brain and mind is untenable, both intellectually and in clinical practice. But what is the true nature of the opaque relationship between mind and matter? How does the brain give rise to consciousness?

This central 'problem of consciousness', the mind–brain question in its modern disguise, is ancient and persistent. The dichotomy between mind and brain is reflected in the apparent disconnection between work in the two great intellectual domains of relevance to the study of consciousness – the Humanities, focusing on the experiences of subjects, and the Sciences, highlighting processes in systems. Within medicine, this intellectual divide is mirrored in the historical separation of psychiatry and neurology. The hope of contemporary students of consciousness is that progress in solving the central problem of how the brain gives rise to consciousness will build a trustworthy bridge between mind and brain, explaining how experience can be at once real, functional and rooted in our physical existence (Zeman, 2001). Beyond question, the scientific world view will be incomplete until it incorporates a clearer understanding of our subjectivity.

Like the mind–body problem itself, the notion that the brain *is* the source of consciousness is very ancient,

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as revealed by this famous and prescient passage from Hippocrates' essay 'On the Sacred Disease' (Jones, 1923):

> *Men ought to know that from the brain, and from the brain only, arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, griefs and tears. Through it ... we think, see, hear, and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant ... sleeplessness, inopportune mistakes, aimless anxieties, absent-mindedness, and acts that are contrary to habit. These things that we suffer all come from the brain.*

Yet arguably progress in understanding exactly how experience 'arises' from the brain has been disappointingly slow. Writing 2500 years after Hippocrates, E.O. Wilson identifies the problem as a central issue for contemporary science (Wilson, 1998): 'the master unsolved problem of biology: how the hundred billion nerve cells of the brain work together to create consciousness'.

Granted that science has in fact made great strides in revealing the physical basis of consciousness over the past century, as outlined in the following sections, and yet the 'master problem' appears to be 'unsolved', one has to wonder whether part of the problem here may be conceptual rather than empirical. The philosopher Leibniz voiced an idea of this kind in his *Monadology*, in a passage that invites us to imagine walking into the midst of an artificial brain (Leibniz, 1714):

> *Perception and that which depend on it are inexplicable by mechanical causes, that is by figures and motions. And supposing there were a machine so constructed as to think, feel and have perception, we could conceive of it as enlarged and yet preserving the same proportions, so that we might enter into it as into a mill. And this granted, we should only find on visiting it, pieces which push against one another, but never anything by which to explain perception.*

Leibniz is suggesting here that no mechanistic theory can ever, in principle, provide a really satisfying explanation of consciousness. Many people have this intuition. What is its source?

For better or worse, the concept of consciousness has been shaped by our cultural, religious and philosophical history. Certainly 'consciousness', as it is generally understood, is far from being a simple scientific variable. Surveys suggest that the predominant notion of consciousness in our culture is of a private, invisible, immaterial process, inaccessible to the standard observational methods of science. On such an assumption it is indeed hard to see how science could truly fathom the relationship between consciousness and the brain.

However, it may well be that scientific advances, and philosophical analysis, will gradually modify both the scientific and the popular concepts of consciousness. There are strong reasons, discussed below, for doubting that our grasp of the contents and the nature of experience is as firm as we usually take it to be. When we look back from the terminus of the quest for consciousness we may see our point of departure in an entirely new light.

The aims of this introductory chapter are: 1) to outline the principal senses of consciousness, particularly those relevant to science and medicine; 2) to summarize current knowledge of the neurobiology of consciousness in its two key senses of wakefulness and awareness; 3) to relate this to the principal pathologies of wakefulness and awareness; 4) to sketch the currently prevailing, overarching, models and theories of consciousness; and 5) finally to return to the philosophical issues just touched on, with a succinct survey of contemporary philosophical views of the relationship between mind and brain.

1.1.2. Senses of consciousness and self-consciousness

Part of the problem of consciousness is semantic: it is an ambiguous term, with several strands of meaning. This is all the more true of 'self-consciousness'. I shall briefly discuss the etymology and principal senses of these words.

1.1.2.1. The etymology of 'consciousness' and 'conscience'

The word 'consciousness' has its Latin root in *conscio*, formed by the coalescence of *cum*, meaning 'with', and *scio*, meaning 'know' (Lewis, 1960). In its original Latin sense, to be conscious of something was to share knowledge of it with someone else or, metaphorically, to share it with oneself. The knowledge in question was often of something secret or shameful, the source of a bad *conscientia*, a bad conscience. This meaning of *conscientia*, implying knowledge shared, has been referred to as its strong or narrow sense. A weakened, or broad, sense coexisted with it in which *conscientia* meant, simply, knowledge. All three senses – of knowledge shared with another, knowledge shared with oneself and, simply, knowledge – entered the English language with 'conscience',

the first English derivative of *conscientia*. The words 'conscious' and 'consciousness' first appear early in the 17th century, followed by 'self-conscious' and 'self-consciousness'.

1.1.2.2. What is meant by 'conscious'?

The Oxford English Dictionary distinguishes 12 senses of 'conscious' and eight of 'consciousness'. Consciousness has two key senses in colloquial English that are of relevance to clinical practice, *wakefulness* and *awareness*.

Consciousness as the waking state: in everyday neurological practice consciousness is generally equated with the waking state and the abilities to perceive, interact, and communicate with the environment and with others in the well-integrated manner that wakefulness normally implies. But while 'consciousness' is often equated with wakefulness, it can also be used more broadly to refer to the family of 'states' that collectively describes our overall patterns of behavior. In this sense wakefulness is just one of several possible 'states of consciousness', distinguished from others such as sleep, coma, and anesthesia. Each of these states admits of degrees or levels: we can be wide or half-awake, lightly or deeply anesthetized. We are normally reasonably confident of our ability to assess and track an individual's state and level of consciousness, in this first sense, with the help of objective criteria, like those of the Glasgow Coma Scale (Teasdale and Jennett, 1974). Thus we speak of consciousness dwindling, waning, lapsing, and recovering; it may be lost, depressed, and regained. To be conscious in this first sense is essentially to be awake, aroused, alert, or vigilant.

Consciousness as awareness: while we are conscious in the first sense, we are as a rule conscious *of* something: our consciousness has content, we enjoy experience and there is 'something it feels like' to exist, whereas there is nothing it feels like to be a stone or lost in dreamless sleep. This second sense is often referred to as 'awareness', to underline the distinction between the behavioral features of wakefulness and the experiences that usually but not always accompany them. Objective criteria remain helpful in ascertaining the presence of consciousness in this second sense – anyone who can obey your instructions and tell you the date is presumably aware – but it has a much stronger connotation of subjectivity than the first sense: it is notoriously difficult to be sure of what is passing through another person's mind on the basis of his behavior. This second sense is much more problematic philosophically than the first: the technical term 'qualia', which has been used by philosophers to refer to the subjective texture of experience, is particularly controversial (Dennett, 1988).

Several authors, following William James, have tried to characterize the general properties of awareness (James, 1890; Shallice, 1988; Searle, 1992; Crick, 1994; Chalmers, 1996; Greenfield, 1998; Tononi and Edelman, 1998a). There is a consensus about the following: the contents of consciousness are relatively stable for short periods of a few hundred milliseconds, but characteristically changeful over longer ones; they have a narrow focus at a given moment, but over time our awareness can range across the spectrum of our psychological capacities, allowing us to be aware of sensations, percepts, thoughts, memories, emotions, desires, and intentions (our experience at a given moment often combines elements from several of these psychological domains); awareness is personal, allowing us a distinctive, limited perspective on the world; it is fundamental to the value we place on our lives: keeping people alive once their capacity for awareness has been permanently extinguished is regarded by many as a wasted effort (Jennett, 2004).

The relationships between wakefulness, awareness, and their behavioral indices are more involved than they appear at first sight. As a rule, while we are awake we are aware. But the phenomena of wakefulness and awareness do not always run in parallel. The vegetative state, which results from profound damage to the cerebral hemispheres and thalami, with relative preservation of the brainstem, is often characterized as a state of 'wakefulness without awareness'. Conversely, when we dream, we are asleep yet aware. Nor can we always rely on behavioral criteria to diagnose consciousness: patients paralyzed for surgery may be fully aware – if the anesthetic drug has failed to reach them – but completely unable to manifest their awareness; patients 'locked in' by a brainstem stroke may appear unconscious until their ability to communicate by movements of their eyes or eyelids is detected.

1.1.2.3. What is meant by 'self-conscious'?

The term 'self-consciousness' is sometimes used in medical contexts as if its meaning were self-evident. This seems doubtful: self-consciousness is a peculiarly complex idea, combining two others – 'self' and 'conscious' – each of which is multifaceted (Berrios and Markova, 2003). I shall try to tease apart its principal strands.

The distinction between 'self' and 'other' is biologically crucial: there are many activities that we need to direct towards other objects in the world – like eating them – which it would be disastrous if we directed towards ourselves. We should expect to find strategies

for drawing this distinction in the simplest organisms. But 'self-consciousness' of a sophisticated kind implies more than an ability to behave differently towards self and other: it requires a representation of self and other. A variety of different kinds of representation fall out of the senses I shall discuss.

Self-consciousness as proneness to embarrassment: this colloquial sense of self-consciousness implies that an individual is aware that the awareness of others is directed on him. It is therefore psychologically sophisticated, anticipating the penultimate sense discussed below.

Self-consciousness as self-perception: this rather minimalistic sense refers to a family of forms of self-consciousness that are probably present in many animals, enabling the organism to perceive stimuli or states that are close at hand or self-generated. These include awareness of stimuli that directly impinge on the body (the ant walking up your arm); of proprioceptive information about bodily position, which contributes substantially to our body image; of information about actions that we are performing, giving rise to a sense of agency; of information about bodily state (hunger, thirst, etc.); and of emotions, such as fear or affection, that signal the state of our relationship to objects and to people around us.

Self-consciousness as self-monitoring – this form of self-awareness involves the ability to monitor our past and predict our future behavior, extending self-perception in time into the past and future, and in range, to encompass more plainly cognitive abilities. It includes the ability to recall the actions we have recently performed (Beninger et al., 1974), and the ability to predict our chances of success in tasks that challenge memory (Hampton, 2001) or perception (Smith et al., 2003): we undoubtedly possess these metacognitive abilities, and ingenious experiments in comparative psychology (Beninger et al., 1974; Hampton, 2001; Smith et al., 2003) suggest that many other animals have them too. The remaining senses lie closer to what we normally have in mind when we speak of self-awareness.

Self-consciousness as self-recognition – this alludes to our ability to recognize our own bodies as our own, for example in mirrors (i.e., mirror self-recognition). Gallup showed in the 1970s that if apes are given experience with a mirror they will soon realize that they are looking at themselves, while their monkey cousins apparently fail to grasp this fact despite extensive exposure (Gallup, 1970). Recent evidence suggests that dolphins can also recognize themselves in mirrors (Reiss and Marino, 2001). Human children develop this ability at around 18 months (Parker et al., 1994).

Self-consciousness as awareness of awareness: between the ages of 18 months and around 5, human children take a further major intellectual stride. They come to appreciate that, as well as being objects that can be inspected in mirrors, they are also subjects, of experience – they possess, in other words, not only bodies but also minds (Parker et al., 1994). The awareness of ourselves as subjects of experience opens up a world of new possibilities for understanding our own behavior and the behavior of others in terms of desires and beliefs, and for implanting and manipulating these (Baron-Cohen, 1995; Frith and Frith, 1999). It has been described as the acquisition of a 'theory of mind'. Once we realize that others, like ourselves, have a limited, personal perspective on the world we can choose to inform, misinform and influence them, creating all the Machiavellian complexities of human behavior. The degree to which animals other than humans possess this awareness is debated.

Self-consciousness as self-knowledge: finally, we use 'self-consciousness' to refer to our self-knowledge in its broadest sense – one's knowledge of oneself as the hero, or villain, of a personal narrative, conditioned by one's personal circumstances and cultural background. This capacity to relive our past in a form of 'mental time-travel' constitutes the 'autonoetic awareness' that Endel Tulving has identified as one of the most distinctively human intellectual capacities (Tulving, 1985). Self-depiction is a central focus of art, another distinctively human activity.

1.2. The neurobiology of conscious states and contents

1.2.1. States of consciousness

1.2.1.1. The electrical correlates of conscious states

Nineteenth-century physiologists working across Europe had noted the occurrence of spontaneous electrical activity while recording from the brains of experimental animals, but it was not until 1929 that Hans Berger, a psychiatrist working in Jena, Germany, published his landmark observations in 'On the Electroencephalogram of Man' (Berger, 1929). His foremost achievement was to demonstrate that spontaneous electrical activity could be recorded from the human brain with extracranial electrodes, but his underlying purpose was to elucidate the physical basis of consciousness. His first paper closed with a series of questions that were to launch a fertile, continuing program of research: how is the EEG affected by sensory stimulation, by sleep, by drugs that alter mental states and by intellectual activity?

Recording from the scalp, Berger distinguished two contrasting rhythms of electrical activity occurring during wakefulness: 'alpha' at 8–13 Hz, which characterizes the 'passive EEG', typically recorded from occipital electrodes in wakeful subjects with their eyes closed; and 'beta' rhythm, occurring at frequencies >13 Hz, the 'active EEG' which accompanies mental effort and eye opening. It was soon appreciated that slower rhythms ('theta' waves at 4–7 Hz and 'delta' at <3.5 Hz) occurring at higher amplitudes characterize states of reduced arousal in adults. Their cyclical involvement in sleep became apparent in the 1950s, particularly from the work of Kleitman and his collaborators.

In 1955 Aserinsky and Kleitman reported the repeated occurrence of periods of 'rapid eye movement sleep' in the course of the night: sleepers woken at these times were likely to report concurrent dreams (Aserinsky and Kleitman, 1955). Two years later Dement and Kleitman demonstrated the cyclical structure of sleep on the basis of observations of eye movements, body movements, and EEG appearances in normal sleepers (Dement and Kleitman, 1957). This work established the distinction between 'slow wave sleep' (SWS), associated with a high proportion of delta activity in the EEG (20–50% in stage 3 sleep, >50% in stage 4), and 'rapid eye movement' (REM) or 'paradoxical' sleep, during which the features of the EEG resemble those in the waking state, although subjects are paradoxically difficult to arouse. Predictable cycles of descent through light sleep (stages 1 and 2) into SWS, followed by gradual reascent into REM sleep, recur four or five times each night, with decreasing proportions of SWS and increasing proportions of REM sleep as the night proceeds (Fig. 1.1). These observations have helped to define three principal states of consciousness in health: wakefulness, REM sleep, and non-REM/SWS, each of which has a characteristic psychological, metabolic, physiological, and pharmacological profile (Table 1.1). The Upanishads, dating from around 2000 BC, recognized the same three basic states (Jones, 1998a).

While massive synchronization of brain activity has classically been associated with states of reduced consciousness, such as deep sleep and coma, in contrast to the 'desynchronized EEG' of wakefulness and REM sleep, there is some evidence that very rapid activity in the gamma range (35–45 Hz), widely synchronized across the brain, occurs in the waking state and REM sleep but not in SWS (Llinas and Ribary, 1993) (Fig. 1.2). More generally, the very existence of the EEG suggests a tendency to widespread synchronization of brain activity whose functional significance has yet to be fully unraveled.

1.2.1.2. The control of conscious states

1.2.1.2.1. Anatomy: the reticular activating system

Clinicopathological studies made at the time of the epidemic of encephalitis lethargica that occurred during and after the First World War suggested to the Viennese pathologist Constantin Von Economo that structures in the upper brainstem and posterior hypothalamus play a key role in arousal (Von Economo, 1931). Frederic Bremer later confirmed this suggestion experimentally by showing that transection of the cat's brain at the cervicomedullary junction had no effect on arousal or on the sleep–wake cycle, while transection through the midbrain brought about a state resembling deep sleep (Bremer, 1929).

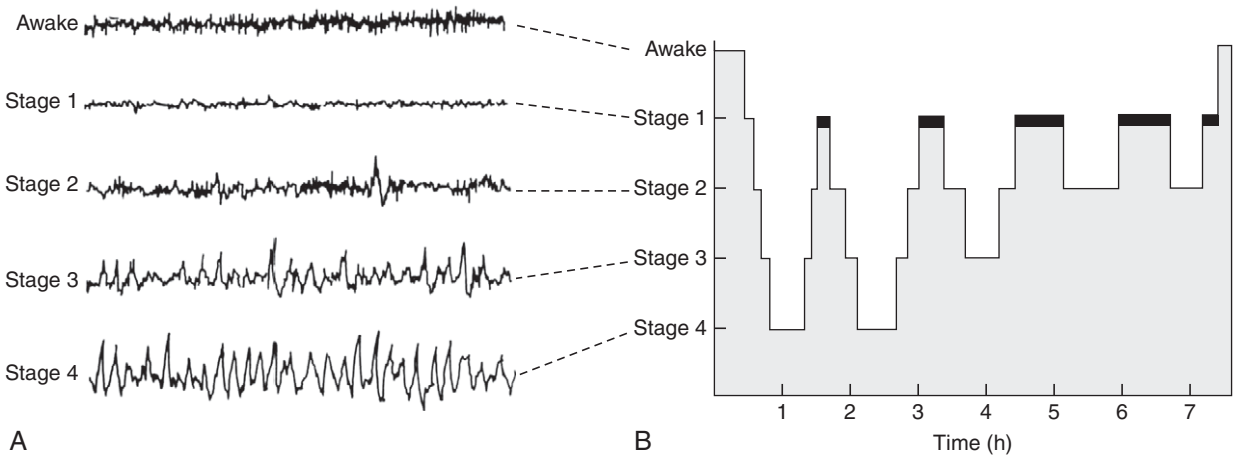

Fig. 1.1. The architecture of sleep. An example of sleep staging over the course of a single night. The sleeper passes from wakefulness to deep sleep and then ascends to REM sleep. Five similar cycles occur in the course of the night. The EEG tracings to the left show the EEG appearances associated with the stages of sleep; the EEG in REM resembles the 'awake' trace.

Table 1.1

Features of three principal states of consciousness in health

	Wakefulness	NREM sleep	REM sleep
Psychological functioning			
Orientation	Intact	Reduced	Delusional
Memory	Intact	Reduced	Dream recall; imp after delay
Thought	Logical, progressive	Reduced, persev	Illogical
Insight	Intact	Reduced	Impaired
Perception	External, vivid	Dull or absent	Internal, vivid
Emotion	Reactive	Dull or absent	Strong, basic
Cerebral metabolism			
Global	≈7 mg gluc/100 g/min	Up to 40% reduced	≈ wakefulness
Regional	Varies with task. See Gusnard, 2001 for hypothesis of 'functional resting state'	Most marked redn in upper brainstem, cbellum, thalami, b glia, b fbrain, PFC, ant cing, precuneus	Cf waking, redn in DLPF, inf par, precuneus; cf SWS activn of thalami, paralimbic rgns, temp-occ cortex
Physiology			
EEG	Alpha, beta dominate	I low voltage, mixed freq II sleep spindles, k complexes III, IV theta, delta dominate	~wakefulness
Eye mvts	Interactive	I rolling eye movements II, III, IV absent	REMs
Muscle tone	High, variable	Reduced	Atonic
Autonomic ftn	Reactive	Reduced c rate/output resp rate/ventilation, blood pressure	Aut arousal and lability, irreg breathing, reduced ventilation
Pharmacology	High but variable activity in ntr. systems modulating arousal (see text)	Globally red. activn	Cholinerg dom

activn = activation; ant cing = anterior cingulate; aut = autonomic; b fbrain = basal forebrain; b glia = basal ganglia; c = cardiac; cbellum = cerebellum; cholinerg = cholinergic; disorg = disorganized; DLPF = dorsolateral prefrontal cortex; dom = dominance; freq = frequency; ftn = function; gluc = glucose; imp = impaired; inf par = inferior parietal cortex; irreg = irregular; ntr = neurotransmitter; persev = perseverative; PFC = prefrontal cortex; red = reduced; redn = reduction; rgns = regions; temp-occ = temporo-occipital

For estimate of basal glucose metabolism (see Laureys et al., 2001); for hypothesis of functional resting state (see Gusnard et al., 2001).

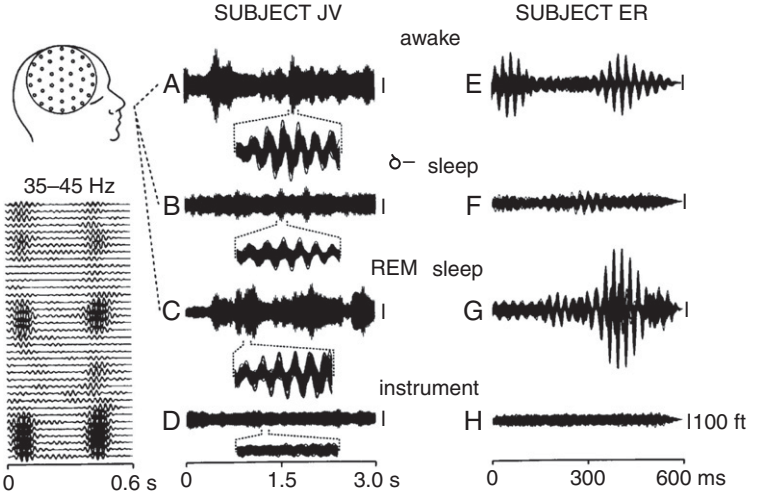

Fig. 1.2. Recordings of rapid (gamma) oscillations in wakefulness, delta, or slow wave, sleep, and rapid eye movement (REM) sleep made using magnetoencephalography (Llinas and Ribary, 1993). The diagram at top left indicates distribution of sensors over the head; recordings from these sensors, filtered to pass signals at 35–45 Hz, are shown below. The figures at right show superimpositions of these oscillations in two subjects during wakefulness, slow wave sleep, and REM sleep. Note the differing time bases of the two recordings. The amplitude of synchronized gamma oscillations is markedly diminished in slow wave sleep in comparison to wakefulness and REM sleep.

Bremer hypothesized that this impairment of arousal resulted from interruption of ascending sensory pathways in the midbrain. His student Giuseppe Moruzzi, working with Horace Magoun, later showed that the critical areas were not, in fact, in the sensory pathways but lay rather in the reticular core of the upper brainstem and their thalamic targets (Moruzzi and Magoun, 1949). This region is, at least in part, diffusely organized and polysynaptic, with widespread afferent and efferent connections, well suited to provide the substrate of a nonspecific 'alerting system'. Electrical stimulation of the region in a drowsy animal 'activates' the EEG and alerts the animal. These observations gave rise to the concept of the 'ascending reticular activating system' (ARAS). While the central insight, that structures in the brainstem regulate our states of consciousness, still holds true, a much more complex picture has emerged since the pioneering work of Moruzzi and Magoun. The ARAS is no longer regarded as a monolithic unit, nor as a system restricted to the classically defined reticular regions of the brainstem. Indeed activating structures are not confined to the brainstem at all, and their influence descends to the spinal cord as well as ascending to the cerebral hemispheres.

Rather than revealing any single 'place where consciousness dwells', the exploration of these structures has identified a series of somewhat specialized nodes in a complex network controlling aspects of arousal (see Figs. 1.4 and 1.5, below). It would be surprising if functions as fundamental as the maintenance of wakefulness or the control of the sleep–wake cycle depended exclusively and unalterably on any single region of the brain. Experimental work in animals and clinical observations in humans suggest that the following structures play key roles in the maintenance and modulation of wakefulness: cholinergic nuclei in the upper brainstem and basal forebrain; noradrenergic nuclei, in particular the locus ceruleus in the upper brainstem; histaminergic and hypocretinergic projections from the hypothalamus; and probably dopaminergic and serotonergic projections arising from the brainstem (Robbins and Everitt, 1995; Hobson and Pace-Schott, 2002; Pace-Schott and Hobson, 2002). Part of the influence exerted by these pathways is mediated by the thalamus, especially its intralaminar nuclei (Jones, 1998b), which makes a major contribution to the maintenance of cerebral arousal as well as providing a critical synaptic relay in sensory, motor and corticocortical pathways. The roles of the brain regions involved in arousal are not, of course, confined to the maintenance of wakefulness or vigilance: they are of profound importance to a range of interrelated functions including mood, motivation, attention, learning, memory, movement and autonomic function.

Some specific contributions made by these regions and related structures to the regulation of conscious states have been defined. For example, the suprachiasmatic nucleus of the hypothalamus is the main timekeeper of consciousness. It normally entrains the sleep–wake cycle to the alternation of night and day under the influence of the direct retinohypothalamic projection (Kilduff and Kushida, 1999). The molecular mechanisms of the circadian rhythm, controlled by a series of 'clock genes', have been elucidated recently (Pace-Schott and Hobson, 2002). Transection experiments by Jouvet and subsequent work have established the key importance of cholinergic nuclei at the pontomesencephalic junction, the laterodorsal tegmental, and pedunculopontine nuclei, in orchestrating the phenomena of REM sleep (McCarley, 1999). During SWS, there is a marked reduction in the activity of the cholinergic, noradrenergic, and histaminergic nuclei that maintain wakefulness, coordinated at least in part by activation of the ventrolateral preoptic nucleus of the anterior hypothalamus (Shneerson, 2005): mutually inhibitory interactions between the histaminergic tuberomamillary nucleus and ventrolateral preoptic nucleus are thought to play a particularly important role in controlling oscillations between wakefulness and sleep.

1.2.1.2.2. Physiology: patterns of neuronal discharge and brain metabolism

It should in principle be possible to explain the features of the three major states of consciousness in terms of the characteristics of relevant neuronal types and the networks into which they are organized. Progress in this direction is well illustrated by the contrast between the patterns of neuronal discharge during sleep and wakefulness within the thalamus.

In the waking state thalamocortical projection neurons are tonically depolarized by cholinergic, noradrenergic, and histaminergic inputs from the brainstem and hypothalamus, which block a hyperpolarizing potassium conductance (Steriade et al., 1993; McCarley, 1999; Steriade, 1999). This induces a 'spike' mode of response in thalamocortical cells, permitting faithful onward transmission of afferent signals to the thalamus. The reduction of this depolarizing input in sleep induces a contrasting 'burst' mode of response, dependent upon a low threshold calcium conductance, which predisposes these cells to repetitive discharge while hyperpolarized (Fig. 1.3). The simultaneous disinhibition of the reticular nucleus of the thalamus in early sleep, following reduction of inhibitory cholinergic input from the brainstem, allows it to exert a synchronized GABAergic inhibition of thalamocortical cells that ultimately gives rise to the distinctive spindles abounding in

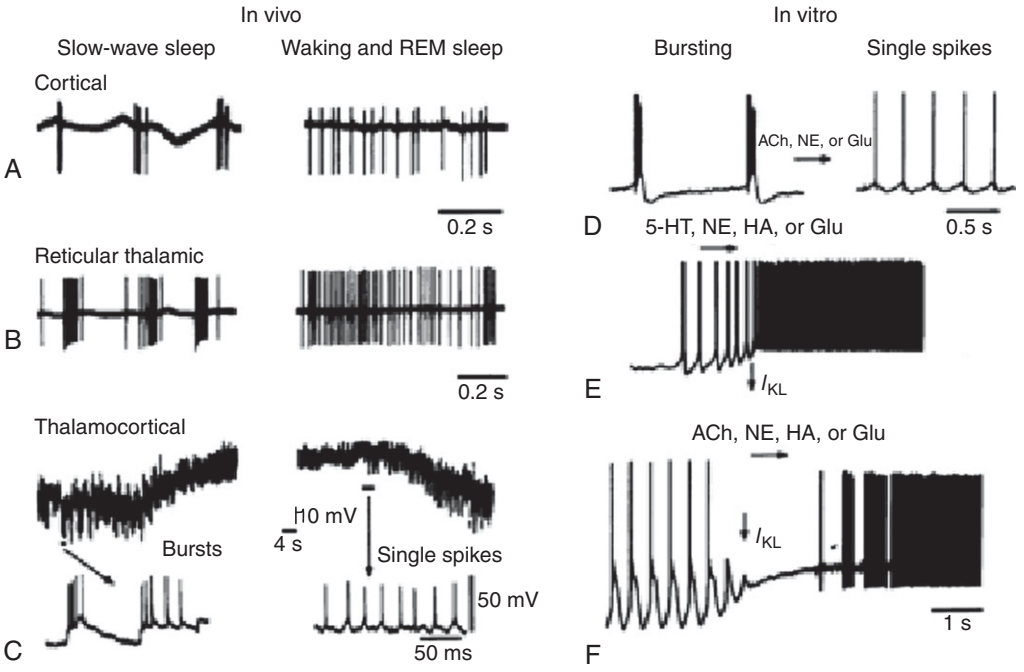

Fig. 1.3. State-dependent activity in thalamic and cortical neurones. Neurones from the cerebral cortex of chronically implanted, behaving cats, in the cerebral cortex **(A)**, reticular thalamic nucleus **(B)** and thalamic relay nuclei **(C)**, change their activity from rhythmic spike bursts during natural slow-wave sleep to firing of single spikes during waking and rapid eye movement sleep. Similar changes can be demonstrated in vitro in response to neurotransmitters involved in modulating sleep and wakefulness. **(D)** Cortical cell; **(E)** reticular thalamic nucleus cell; **(F)** thalamic relay cell. Depolarization results from the reduction of specialized conductances including I_{KL}, a potassium conductance. ACh = acetylcholine; Glu = glutamate; HA = histamine; 5-HT = serotonin; NE = noradrenaline (norepinephrine). (With permission from Steriade et al., 1993; © Copyright 1993 The American Association for the Advancement of Science, USA.)

the EEG of stage 2 sleep. Further hyperpolarization of thalamocortical cells, as sleep deepens, allows them to participate in slow wave oscillations, to which the individual and network properties of thalamocortical cells, corticothalamic cells, and neurons of the reticular nucleus all contribute. Reduction of direct nonspecific excitatory inputs to the cortex, as well as effects occurring primarily at the level of the thalamus, are conducive to the generation of these rhythms. Thus the distinction at an electrophysiological level between spike and burst modes of response in thalamocortical neurons corresponds with the behavioral distinction between the responsiveness of the waking state and the inaccessibility of sleep and underlies the global shift between the high-frequency EEG of wakefulness and the low-frequency EEG of sleep.

Functional imaging studies have made it possible to explore the anatomy and physiology of sleep and arousal in the healthy human brain. Global cerebral glucose metabolism falls in SWS by circa 20%, rising back to, or even above, waking levels in REM (Heiss et al., 1985; Buchsbaum et al., 1989). During SWS regional blood flow declines, in proportion to the amount of slow wave activity in the EEG, in the rostral brainstem, thalamus, prefrontal, and cingulate cortex (Hofle et al., 1997; Macquet et al., 1997). In REM sleep regional blood flow increases in the rostral brainstem, thalamus, and limbic regions, in keeping with the electrical and subjective features of dreaming sleep, but declines in prefrontal and posterior cingulate cortex and in some regions of parietal cortex (Macquet et al., 1996, 2005).

Variations in the level of arousal during wakefulness also appear to correlate with levels of activity in the structures of midbrain and thalamus that regulate conscious states. Kinomura et al. (1996) reported activation of the midbrain tegmentum and intralaminar nuclei of the thalamus by the transition from a resting state to the performance of visual and somatosensory reaction time tasks. Paus et al. (1997) described a decrease in midbrain and thalamic activation during a tedious 1 hour auditory detection task associated with declining performance and increasing slow wave activity on EEG. Finally, as discussed further below, there is evidence that the loss of consciousness induced by some anesthetics is associated with selective depression of thalamic function, linking the mechanisms of anesthesia and sleep (Fiset et al., 1999; Alkire, 2000).

1.2.1.2.3. Pharmacology: modulation of sleep and wakefulness

As we have seen, the pharmacological dissection of the 'reticular activating system' has revealed the presence of several chemically distinct but interactive subsystems: cholinergic, noradrenergic, dopaminergic, serotonergic, histaminergic, and, recently, hypocretinergic. The actions of each of these transmitters are complex, depending on the site of release and the nature of the receptor targeted. Nonetheless it is clear that the firing of cells in the nuclei synthesizing these transmitters is often state-dependent, varying with conscious state (Sutcliffe and de Lecea, 2002) (Fig. 1.4).

Evidence that REM sleep is dependent upon activity in cholinergic nuclei, while noradrenergic and serotonergic nuclei are least active in this phase of sleep, has given rise to a 'reciprocal interaction' model of sleep architecture (Pace-Schott and Hobson, 2002). This proposes that the regular interaction of SWS and REM sleep over the course of the night is regulated by the waxing and waning of mutually inhibitory activity in these nuclei.

The pharmacological basis of 'sleep debt', the increasing pressure to sleep as the period of wakefulness extends, remains a confusing area. A number of potential 'hypnogens', sleep-promoting substances, including peptidergic and other neurotransmitters, have been identified (Zoltoski et al., 1999; Shneerson, 2005). A gradual increase in extracellular adenosine levels during wakefulness appears to be one critical factor, leading to inhibition of activating cholinergic nuclei in the upper brainstem and basal forebrain (McCarley, 1999).

Further work on the pharmacology of wakefulness is likely to demonstrate distinctive roles for the neurotransmitters of the 'activating system' in modulating different aspects of arousal. 'Wakefulness', after all, is shorthand for a set of associated neural, behavioral and psychological functions that are, to some extent, independently controlled, as evidenced by a number of the disorders of consciousness discussed below. In work exploring the idea that the neurotransmitters linked with arousal make distinctive contributions, Robbins and Everitt (1995) have found, using a consistent set of behavioral tests, that selective damage

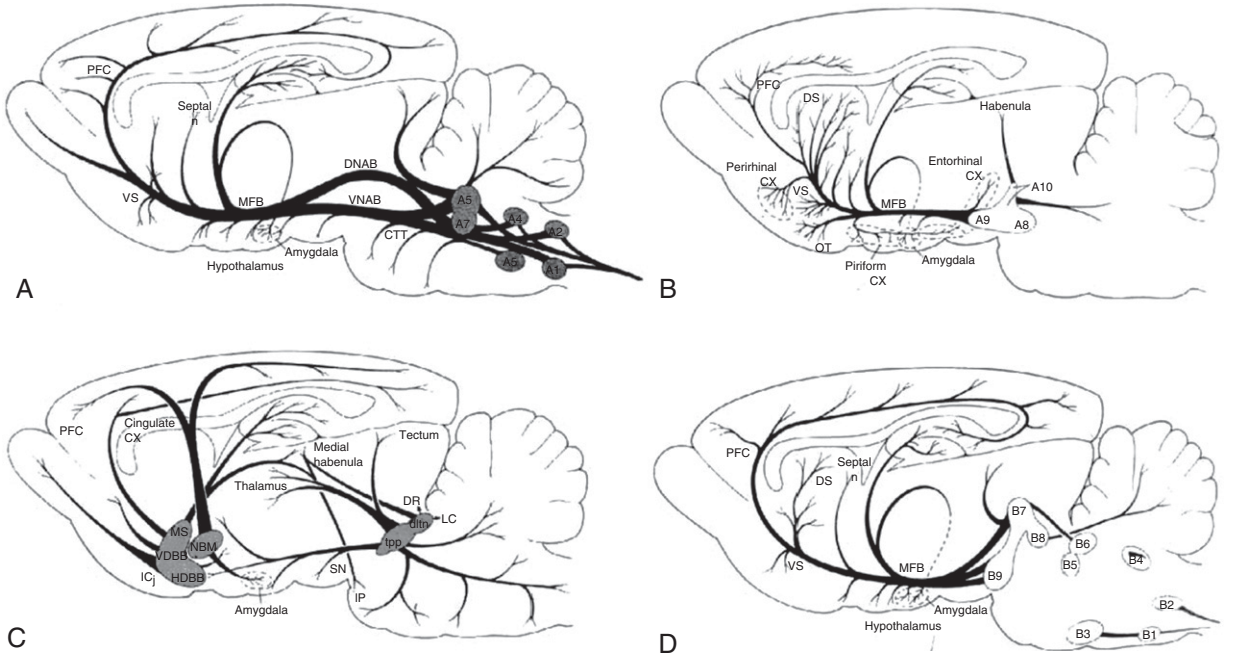

Fig. 1.4. The pharmacology of the brainstem activating systems. **(A)** shows the origin and distribution of the central noradrenergic pathways in the rat brain; **(B)** the dopaminergic pathways; **(C)** the cholinergic pathways; **(D)** the serotonergic pathways. CTT = central tegmental tract; dltn = dorsolateral tegmental nucleus; DNAB = dorsal noradrenergic ascending bundle; DR = dorsal raphe; DS = dorsal striatum; HDBB = horizontal limb nucleus of the diagonal band of Broca; ICj = islands of Calleja; IP = interpeduncular nucleus; LC = locus ceruleus; MFB = medial forebrain bundle; MS = medial septum; NBM = nucleus basalis magnocellularis (Meynert in primates); OT = olfactory tubercle; PFC = prefrontal cortex; SN = substantia nigra; tpp = tegmental pedunculopontine nucleus; VDBB = vertical limb nucleus of the diagonal band of Broca; VNAB = ventral noradrenergic ascending bundle; VS = ventral striatum. (With permission from Robbins and Everitt, 1995.)

to the noradrenergic system impairs selective attention, damage to the cholinergic system impairs baseline accuracy, damage to the dopaminergic system lengthens response latency and reduces probability of response and damage to the serotonergic system leads to impulsive responding.

1.2.2. Awareness: the 'contents of consciousness'

1.2.2.1. Do we know what we experience?

Many questions remain to be answered about the neurobiology of sleep and wakefulness but the phenomena under study are relatively unambiguous, objective, and quantifiable. The same cannot be said of awareness, experience, or the 'contents of consciousness', three terms often used interchangeably for the second principal sense of consciousness picked out in section 1.1. There is major controversy about both the ultimate nature and the detailed content of awareness. The question of its ultimate nature is discussed further in section 1.5. This is an appropriate moment to flag up the somewhat more empirical debate about its content.

We all tend to consider ourselves experts on the features of our experience: after all, how could we be mistaken about them? However, there is plenty of evidence that we are sometimes misled by introspection and that our experience is not always as we take it to be. How so? This may be a realm in which observation is more than usually 'theory-laden'. As we have seen our intuitive theories of consciousness owe as much to religion and philosophy as science: theoretical expectations about the features of our experience may distort our informal observations. For example, systematic research requiring subjects to give instantaneous reports of their current experience, at the moment that a random buzzer sounds, reveals a surprising preponderance of 'inner thought' (Hurlburt, 2000; Hurlburt and Heavey, 2001); research on change in our visual surroundings indicates that we fail to notice many large-scale alterations in a scene that most of us would expect to recognize readily, a phenomenon described as 'change blindness' (O'Regan and Noe, 2001); related work on visual attention reveals that salient stimuli go unnoticed when visual attention is highly focused, to the subsequent astonishment of the experimental subject, the phenomenon of 'inattentional blindness' (Mack and Rock, 2000).

Work along these lines suggests that our knowledge of our own experience is not incorrigible: on the contrary, it is often mistaken. This prompts the thought that other beliefs about experience that are often strongly held – for example that it is essentially private and somehow ineffable – are also open to question or redefinition (Kevin et al., 2005; O'Regan et al., 2005). These beliefs are relevant to science, as the questions we frame for neuroscience about awareness will of course depend on what we take our experience to be. Despite these reservations, there is a measure of agreement about at least some of the features of our experience and there has been spectacular progress in the definition of their correlates in the brain.

1.2.2.2. Exquisite correlations

1.2.2.2.1. Visual awareness

Although it has not, as a rule, been explicitly directed at the question of consciousness, the pathbreaking work of the past century on the neurology of perception, language, memory, emotion, and action has transformed our understanding of the neural basis of awareness. The study of vision has attracted particularly intense attention as a test case for students of consciousness. I shall briefly summarize the key findings.

These landmark discoveries include the definition of the retinotopic map in striate cortex (Holmes and Lister, 1916); the discovery of orientation-specific cell columns in visual cortex by Hubel and Wiesel (1977); the realization that 30–40 functionally and anatomically distinct visual areas surround area V1 (Cowey, 1994); the evidence that 'parallel' though interconnected streams of visual information flow through these areas, subserving the perception of form, color, depth, and motion (Livingstone and Hubel, 1988); the broad distinction between an occipitotemporal stream concerned with object identification and an occipitoparietal stream concerned with visually guided action (Milner and Goodale, 1995); the discovery of material-specific visual association areas such as the region of fusiform cortex that is highly responsive to faces (fusiform face area, FFA) and the region of parahippocampal cortex that is highly responsive to the visual appearance of locations (parahippocampal place area, PPA) (Kanwisher, 2001). The demonstrations of illusory and implied movement in stationary visual stimuli that activates area V5, the visual area most selective for moving stimuli, are elegant extensions of this broad line of work, elucidating the neural basis of visual experience (Zeki et al., 1993).

1.2.2.2.2. Changing experience without altering stimuli

Inferences about the generation of visual awareness, drawn from work of this kind, are open to the potential objection that the mere activation of a cortical visual area by an appropriate stimulus does not show that it mediates the conscious experience of vision. Correlation does not imply cause and, after all, much of the work on cortical visual responses in animals has been performed under anesthesia. Several authors have

argued, for example, that area V1 does not contribute directly to visual awareness (Crick and Koch, 1995; Rees et al., 2000). This objection can be met, at least in part, by using paradigms in which visual awareness changes while external stimulation is held constant. Changes in neuronal activity detected under these circumstances are likely, although not guaranteed, to be linked closely to visual awareness itself. Several lines of research have adopted this strategy, examining the neural basis of imagery, hallucinations, attentional shifts, and binocular rivalry.

We can summon up images 'in the mind's eye' and interrogate them much as we do a real visual scene. Psychological studies indicating that mental images are processed in similar ways to percepts of items in the real world (Shepard, 1978; Kosslyn and Shin, 1994) have recently been complemented by a series of functional imaging studies, showing that the neural correlates of mental imagery overlap substantially with the correlates of perception (Kosslyn et al., 1995; Cohen et al., 1996; Ishai et al., 2000; Kanwisher, 2000). Like mental images, visual hallucinations are visual percepts that occur in the absence of a corresponding external stimulus but, unlike images, hallucinations are perceived as if they occurred in the external world. Functional imaging studies in both visual and auditory domains reveal that hallucinations are accompanied by activity in cortical areas associated with the normal perceptual processing of the hallucinated items (Ffytche et al., 1998; Griffiths, 2000).

Attention is the sentry at the gate of consciousness: 'my experience is what I agree to attend to' (James, 1890). The essence of attention is selection: whether we are displaying 'preparatory attention' as we await an anticipated event, switching our attention between the senses or between several targets presented to a single sense or sustaining our attention on a task, we are excluding a range of rival stimuli from the focus of our interest. Changes in the neural representation of items as they move in and out of the focus of attention should shed light on the neural accompaniments of consciousness. These changes have been termed the 'neural expression' of attention (LaBerge, 1995).

Single cell recordings from monkeys trained to shift visual attention without moving their eyes indicates that firing rates are increased in cells responding to attended stimuli and reduced in cells responding to unattended stimuli in extrastriate visual areas, for example areas V4 and V5 (Moran and Desimone, 1985; Treue and Maunsell, 1996). Recent functional imaging studies suggest that the neural expression of attention in humans also involves focal enhancement and inhibition of neural activity; for example switches of attention between faces and places presented simultaneously are associated with detectable modulations of activity in the fusiform and parahippocampal regions mentioned above (Kanwisher, 2000).

Multistable or ambiguous visual stimuli, like the Necker cube, which appears to reverse in depth repeatedly during protracted viewing, are open to alternative visual readings. Similarly, if different visual stimuli are presented to the two eyes, most viewers see each of the two images alternately rather than experiencing a fusion of the two. This paradigm, binocular rivalry, has been applied both to animals and humans in studies of the neural correlates of the alternating percept. Logothetis, working with monkeys, reported that, while many neurons in visual areas respond to both stimuli throughout their presentation regardless of the current conscious percept, a subset of extrastriate neurons recorded in V4 and V5 raise or lower their firing rate markedly as the stimulus to which they respond gains or loses perceptual predominance (Logothetis and Schall, 1989; Leopold and Logothetis, 1996). Work by Engel and colleagues suggests that cells responding to the currently perceived member of a pair of rivalrous stimuli synchronize their discharges during the period of perceptual dominance to a greater degree than during periods of suppression (Engel et al., 2000).

Further down the processing stream, in experiments with human subjects, the modulation of neuronal activity in the FFA and PPA, as simultaneously presented faces and places alternate in awareness, is of similar size to the modulation seen when faces and places are alternately presented (Kanwisher, 2000). Thus, by this stage of processing in the human brain, activity correlates with the contents of awareness rather than with the raw features of the impinging stimuli. Using magnetoencephalography, Tononi and colleagues have reported that, as conscious perception shifts between two gratings of different orientation, flickering at different frequencies, so the power of electromagnetic activity at the corresponding frequency waxes and wanes by 30–60% over wide regions of cortex (Tononi and Edelman, 1998a). Lumer and colleagues have found that the moments of transition between multistable percepts are associated with right frontoparietal activation, suggesting that the neural control of these transitions shares common ground with the direction of spatial attention (Lumer et al., 1998).

These experiments, investigating imagery, hallucinations, attention, and binocular rivalry, are beginning to capture the neural correlates of visual experience. The precise definition of the 'neural correlate of consciousness' in humans remains a goal for the future and will probably require more sophisticated methods than those currently available, allowing the detailed measurement of disparate neuronal activity over short

time scales in the human brain. Nevertheless, these results help to bolster the neuroscientist's long-held article of faith: that distinctions drawn in experience will be reflected in distinctive patterns of neural activity.

1.2.2.3. Unconscious processes

1.2.2.3.1. The concept of unconscious processes

The idea that much of the activity occurring in the brain never gives rise to awareness is supported by a host of observations made in both health and disease, including the study of habitual and automatic behavior, procedural memory and unconscious perception (for a wide-ranging survey of concepts of the unconscious see Claxton, 2005). The existence of unconscious neural processes provides an opportunity to approach the neurology of consciousness by a process of contrast or subtraction, focusing on the differences between processes that are and that are not linked to consciousness.

The major methodological problem for students of unconscious processes is how to determine the presence or absence of awareness. Much of the neuropsychological work in this area relies on verbal report (Barbur et al., 1993) or the use of a 'commentary key' (Weiskrantz, 1997) to indicate the degree of awareness. But verbal reports and presses on commentary keys may not provide exhaustive measures of the information available to consciousness. Indeed, there are no conclusive reasons for holding that consciousness should always be reportable, even in principle (Zeman, 2000). On the other hand if every successful discrimination is taken to provide evidence of conscious perception, the possibility of unconscious perception is ruled out by definition (Kihlstrom et al., 1992). The lack of any 'exhaustive measure that exclusively indexes relevant conscious perceptual experiences' is therefore a significant problem, though not necessarily an insuperable one (Merikle and Reingold, 1992). Psychologists have suggested a range of solutions to the dilemma (Jacoby et al., 1992; Merikle and Reingold, 1992).

The terminology of unconscious processes is confusing. Besides the variety of cognate options – subconscious, preconscious, non-conscious – a number of technical terms have been used in related senses. 'Implicit' – or 'subliminal' – neural or cognitive processes are those occurring in the absence of any conscious experience of the information concerned, by contrast to 'explicit' – or 'suprathreshold' – processes. 'Direct' tasks are those that involve instructions referring directly to the dimension of interest to the experimenter: a direct test of memory might ask for the contents of a word list, whereas an 'indirect' task might examine whether prior exposure to the list increased the ease with which they are later identified on a brief presentation. Note that a direct task may tap an implicit process – if for example we are asked to guess at the location of a stimulus that we have not consciously perceived – and an indirect task may tap an explicit process, if I recognize the items from the word list on their brief presentation.

1.2.2.3.2. Changing behavior without altering experience

It is no surprise that stimuli impinging on the nervous system can have neural effects in the absence of any discernible effect on our awareness or behavior. There is greater theoretical interest in events that 'influence our experience, thought, and behavior even though they are not consciously perceived' (Kihlstrom et al., 1992). Examples include the effects of 'unperceived' stimuli on judgements made by normal subjects in direct and indirect tasks (unperceived because, for example, they are too weak, too brief, or 'masked' by preceding or succeeding stimuli); their effects in normal controls subjected to procedures like anesthesia or hypnosis; and their effects in subjects with neuropsychological syndromes such as blindsight, neglect, and, possibly, hysteria.

A 19th-century experiment by Pierce and Jastrow illustrates the effect of stimuli too subtle to allow confident verbal report on judgment in a direct test. Subjects were required to judge or guess which of two similar pressures was the greater. At the same time they indicated their degree of confidence in their judgment. Even when the confidence rating had fallen to zero, their guesses proved correct significantly more often than chance would have allowed (Kihlstrom et al., 1992). In a modern reworking of the theme, a study of the functional imaging correlates of the perception of low concentration odors demonstrated above chance detection in the absence of reported awareness, associated with brain activation in the anterior medial thalamus and inferior frontal gyrus (Sobel et al., 1999). 'Mere exposure' effects illustrate the effects of unperceived stimuli in an indirect test (Zajonc, 1980). Abstract stimuli presented extremely briefly, for 1 ms, tend to be chosen in a subsequent task in which subjects are asked to state which of two stimuli they prefer, even though they are not recognized as familiar. In a study directed to the neural correlates of unperceived stimuli rather than to their behavioral effects, Dehaene et al. found that in a task requiring subjects to classify numbers as larger or smaller than 5 by pressing a button with the left or right hand, presentation of masked, unreported, numerical primes sets in train a stream of perceptual, cognitive, and motor processes in precisely

the areas that are also engaged by the perceived stimulus (Dehaene et al., 1998). The occurrence of implicit perception under anesthesia has been supported by a number of studies. Schwender and colleagues, for example, showed that, in the absence of any explicit recall of events during cardiac surgery, some patients associated key words with material that had been read aloud during the operation; these patients were distinguished by the relatively normal latencies of their mid-latency auditory evoked potentials under anesthesia (Schwender et al., 1994).

In neuropsychology, the most widely quoted example of unconscious perception is undoubtedly blindsight (Stoerig and Cowey, 1997; Weiskrantz, 1998). This paradoxical term, coined in 1974 by Sanders et al., describes a range of visually based abilities that can be demonstrated in the absence of visual awareness following damage to striate cortex in some, but not all, subjects. The possibility that abilities of this kind might exist was suspected on the basis of the relatively good recovery of visual function in monkeys after experimental ablation of striate cortex. An experiment by Poppel and colleagues, in which war veterans with scotomata due to gun shot wounds were encouraged to look in the direction of 'unseen' stimuli, suggested that similar abilities might be found in humans (Poppel et al., 1973). This was confirmed when D.B., a patient in whom the right calcarine cortex had been excised as part of the surgical treatment of an arteriovenous malformation, was 'urged to guess' the nature and location of stimuli in his blind field (Sanders et al., 1974). His guesses, to his great surprise and despite his insistence 'that he saw nothing except in his intact visual field', proved to be substantially correct. Subsequent work has shown that, besides mediating neuroendocrine and reflex responses, blindsight can subserve accurate performance on a range of direct and indirect tasks (Stoerig and Cowey, 1997). Indeed on some measures, blindsight allows accuracy well beyond the performance of normal subjects making judgements close to the threshold of awareness. Its capacities include localization of the 'unseen' target by hand or eye and simple judgements about orientation, shape, and presence or absence of motion. A range of skeptical interpretations of these results, in terms of covert eye movements, scatter of light into the intact visual field, the survival of islands of cortex and the persistence of degraded but nevertheless conscious visual awareness have been substantially rebutted (Weiskrantz, 1998), although blindsight continues to provoke lively debate (Zeki and Ffytche, 1998). This line of research, inspired by observation made in monkeys, has come full circle with ingenious experimental evidence that destriated monkeys, like destriated humans, may lack 'phenomenal vision' and rely on blindsight for their well preserved visuomotor skills (Cowey and Stoerig, 1995).

The study of neglect also illustrates the effects of unperceived stimuli on subsequent behavior, although the puzzle in such cases, superficially at least, lies as much in the subjects' initial failure to perceive the stimuli as in their subsequent effects (Robertson and Marshall, 1993). Following brain lesions, most commonly affecting the right inferior parietal lobe, subjects may fail to attend to stimuli in contralateral space. The failure can affect imagined scenes as well as real ones (Bisiach and Luzzatti, 1978). The syndrome has been fractionated into several subtypes: primarily perceptual or primarily motor (Tegner and Levander, 1991); primarily perceptual or primarily representational; spatially or object-based, and affecting near or far space (Halligan and Marshall, 1991). Yet despite the apparent failure of awareness of stimuli in the affected half-field among subjects with neglect, there is clear evidence for implicit processing of information about these stimuli. Thus subjects with left hemineglect, invited to express a preference for one of two line-drawings that differ only in the plume of smoke rising from a house fire on the far left, tend to choose the fire-free home (Marshall and Halligan, 1988). In a similar vein, unidentified words presented on the neglected left-hand side of space can influence the identification of words presented later on the attended side (Berti and Rizzolatti, 1992). Rees and colleagues have demonstrated activation of visual areas contralateral to the unreported stimulus in a patient with the related syndrome of extinction, suggesting that the failure of awareness in these disorders in neglect is due to disturbance of a relatively late stage of stimulus processing (Rees et al., 2000).

These examples of the influence of unperceived stimuli on behavior have parallels in the domains of memory and action (Table 1.2). 'Declarative' memories are those we can explicitly recall and articulate, including our memories for autobiographical episodes (Squire et al., 1990). 'Procedural' memories, which include those acquired through classical conditioning, priming, and during acquisition of motor skills, are implicit, capable of influencing behavior without any need for conscious recollection. Declarative memories are associated with a network of limbic and neocortical areas, somewhat distinct from the subcortical and motor cortical regions implicated in procedural memory (Berns et al., 1997; Buckner and Koutstaal, 1998; Clark and Squire, 1998). Studies of the gradual learning of rules, which can, initially, gain an influence over behavior in the absence of any conscious appreciation of the rule, offer related insights (Berns et al., 1997). In the context of action, much of what we do is automatic, requiring little or no supervision by

Table 1.2

Paradigms for studying the neural correlates of conscious (upper row) and unconscious (lower row) processes

	Vision	Memory	Action
Stimulus constant, experience changes	Shifts of attention Visual imagery Hallucinations 'Multi-stable' percepts	Declarative recall	Free choice Delusions of control
Experience constant, behavior changes	Visually guided behavior in: Blindsight Neglect Agnosia	Procedural memory	Automatic behavior, alien limb

From Zeman, 2002; adapted from Frith et al., 1999.

consciousness: once again, there are illuminating differences between the underlying functional neuroanatomy of effortful, willed, 'conscious' actions and that of habitual or automatic acts. For example, as skills are acquired, global brain activation decreases and there are shifts in regional brain activation, with decreasing involvement of prefrontal regions as the requirement for conscious supervision declines (Haier et al., 1992; Passingham, 1997; Petersen et al., 1998; Raichle, 1998).

In each case – perception, memory, action – exploration of the neural basis of unconscious processes provides a promising approach to understanding the neurology of awareness, complementing the direct pursuit of the neural correlates of experience, discussed above. Comparison of conscious and unconscious states, and of conscious and unconscious processes, exemplifies the 'contrastive analysis' that informs much contemporary discussion of the neurology of consciousness (Table 1.3). We will return to the broader implications of both approaches in section 1.4.

1.3. Concepts of impaired and altered consciousness

This book is devoted to the detailed discussion of the full range of pathologies of consciousness. This section will therefore merely outline a taxonomy of these disorders, drawing attention to links with points made in the previous sections and with the global theories of consciousness discussed below (in section 1.4). As before it is convenient to discuss pathologies of state and of content in turn.

1.3.1. Pathologies of conscious state

1.3.1.1. A taxonomy of impairments

Pathologies of conscious state can be classified with respect to duration (brief, as in syncope or epileptic seizure, or more protracted, as in coma), underlying cause (e.g., hypoxia/ischemia, trauma, epilepsy, drugs, metabolic disturbance, infection, and inflammation, structural brain disease, psychogenic inter alia), or clinical features (e.g., brainstem death vs coma vs vegetative state vs akinetic mutism vs minimally conscious state).

Table 1.4 is a recent, conventional, British taxonomy of the major persistent pathologies of conscious state (Working Party of the Royal College of Physicians, 2003), classified by clinical feature and including the locked-in syndrome, which is of course not a pathology of consciousness but is all too easily mistaken for one. Coma is a state of continuous 'eyes-closed' unconsciousness in the absence of a sleep–wake cycle. It varies in degree from moderate to profound unresponsiveness and is associated with a comparably variable reduction in cerebral metabolism. It results from diffuse hemispheric or focal brainstem/diencephalic dysfunction and is usually a transitional state, en route to recovery, brainstem death, or a state of chronically impaired awareness with recovery of the sleep–wake cycle. The risk of confusing the 'locked-in state' with coma is now well recognized by neurologists. In this syndrome, which follows brainstem lesions abolishing the descending control of voluntary movement, patients are only able to communicate using movements of the eyes or eyelids.

Brainstem death implies the irreversible loss of all brainstem functions. In the UK it renders legal the removal of organs for transplantation, provided that appropriate consent has been obtained. It is generally followed by cardiac death, within hours to weeks, although there are reported exceptions to this rule.

The vegetative state, first defined by Jennett and Plum in 1972, is, in a sense, the converse of brainstem death. In this condition, characterized by 'wakefulness without awareness', patients regain their sleep–wake cycle and may be aroused by painful or salient stimuli

Table 1.3

'Contrastive analysis': examples of studies comparing conscious and unconscious brain activity

Study (context)	Comparison	Results
Laureys, 2000 (vegetative state)	Vegetative state vs recovery	Increase in cortical metabolic rate and restoration of connectivity with recovery
John, 2001 (anesthesia)	Anesthesia vs awareness	Loss of gamma band activity and cross-cortical coherence under anesthesia
Sahraie, 1997 (blindsight)	Aware vs unaware mode of perception in blindsight patient GY	Aware mode associated with DLPF and PS activn, unaware with medial F and subcortical
Dehaene, 1998 (backward masking)	Perceived numbers vs backward masked but processed numbers	Unreported numbers underwent perceptual, semantic, and motor processing similar but less intense to reported numbers
Kanwisher, 2000 (binocular rivalry)	Attention to 'face' or 'place' when stimuli of both kind are simultaneously in view, or perception of face or place during binocular rivalry	Activity in FFA and PPA locked to presence or absence of *awareness* of face and place
Moutoussis, 2002 (invisible stimuli)	Perceived vs 'invisible' but processed faces/houses	Similar but less intense activation of FFA and PPA by invisible stimuli
Engel, 2000 (binocular rivalry)	Perception of one or other of a pair of rivalrous stimuli	Firing of cells processing currently perceived stimulus better synchronized than firing of cells processing suppressed stimulus
Tononi, 1998 (binocular rivalry)	Perception of high vs low frequency flicker during binocular rivalry	More widespread and intense activation by perceived stimulus
Petersen, 1998 (task automatization)	Effortful verb generation task vs performance after training	LPF, ant cing, and cerebellar activation shifts to left perisylvian activation with training

ant cing = anterior cingulate; DLPF = dorsolateral prefrontal cortex; FFA = fusiform face area; LPF = lateral prefrontal cortex; medial F = medial frontal cortex; PPA = parahippocampal place area; PS = prestriate.

but show no signs of discriminative perception or deliberate action, including attempts to communicate (Multi-Society Task Force on PVS, 1994a, 1994b; Zeman, 1997; Jennett, 2004). Recovery from a vegetative state often occurs: younger age and a traumatic rather than hypoxic–ischemic causation improve the outlook. After 1 month the condition is often termed 'persistent' and in patients in whom recovery appears highly unlikely it may be deemed 'permanent', although permanence cannot of course be predicted with certainty. The underlying pathology usually involves some combination of (1) diffuse cortical injury, typically cortical laminar necrosis; (2) diffuse white matter injury, typically diffuse axonal injury, or leukoencephalopathy; or (3) thalamic necrosis. The 'minimally conscious state' is 'a condition of severely altered consciousness in which minimal but definite behavioral evidence of self or environmental awareness is demonstrated' (Giacino, 2005). Akinetic mutism is a related state of profound apathy with some evidence of preserved awareness, characterized by attentive visual pursuit and an unfulfilled 'promise of speech'. It is often associated with damage to the medial frontal lobes.

These distinctions are useful and modera robust in clinical practice. They are not immune to practical and theoretical problems. At a practical level, there are apparent examples of long survival in 'brain-dead' patients (Shewmon, 1998), and there is evidence that the vegetative state has often been misdiagnosed in patients who are in fact aware (Childs et al., 1993; Andrews et al., 1996). At a theoretical level, it is conceivable that brainstem death might become a treatable disorder as neural prostheses are developed, and it is open to question whether patients in a vegetative state are wholly unaware (Zeman, 1997). These concepts are still in evolution.

The classic impairments of consciousness mentioned so far are relatively severe and well defined. In the hinterland of coma lie a range of more subtle impairments of consciousness that have attracted an inconsistent and confusing terminology, including such terms as delirium, confusional states, acute organic brain syndrome, stupor and catatonia.

Delirium, confusion, and acute organic brain syndrome are probably best considered as a single, highly heterogenous, nosological entity, characterized by the acute or subacute onset of a 'clouding of consciousness', accompanied by incoherence of thought, impairment of working memory and delayed recall, abnormalities of perception often including hallucinations, and

Table 1.4

The differential diagnosis of impaired awareness

Condition	Vegetative state	Minimally conscious state	Locked-in syndrome	Coma	Death confirmed by brainstem tests
Awareness	Absent	Present	Present	Absent	Absent
Sleep–wake cycle	Present	Present	Present	Absent	Absent
Response to pain	±	Present	Present (in eyes only)	±	Absent
Glasgow Coma Score	E4, M1–4, V1–2	E4, M1–5, V1–4	E4, M1, V1	E1, M1–4, V1–2	E1, M1–3, V1
Motor function	No purposeful movement	Some consistent or inconsistent verbal or purposeful motor behavior	Volitional vertical eye movements or eyeblink preserved	No purposeful movement	None or only reflex spinal movement
Respiratory function	Typically preserved	Typically preserved	Typically preserved	Variable	Absent
EEG activity	Typically slow wave activity	Insufficient data	Typically normal	Typically slow wave activity	Typically absent
Cerebral metabolism (PET)	Severely reduced	Insufficient data	Mildly reduced	Moderately–severely reduced	Severely reduced or absent
Prognosis	Variable: if permanent, continued vegetative state or death	Variable	Depends on cause but full recovery unlikely	Recovery, vegetative state or death within weeks	Already dead

PET = positron emission tomography.
Source: Working Party of the Royal College of Physicians, 2003.

disturbance of emotion and of behavior, which may become either hypo or hyperactive (Lipowski, 1990; Lindesay et al., 2002). These features are, in delirium, the result of diffuse brain dysfunction, commonly due to metabolic derangement, organ failure, infection or the effects of drugs or drug withdrawal. The 'clouding of consciousness' that is often considered characteristic of delirium can be dissected into a number of components. These include disturbance of the sleep–wake cycle associated with abnormalities of arousal or alertness; an inability to sustain attention that is the neuropsychological hallmark of 'confusional' states; and abnormalities of awareness that, in delirium, often include fleeting hallucinations and delusions. This complex of features indicates that the distinction I have drawn between 'wakefulness' and 'awareness' is not always respected by the brain and its disorders: 'attention', in particular, is a composite function, related to both arousal and awareness, functions jointly disrupted in delirium. Their joint disruption is partly the result of the widespread brain pathology that underlies delirium but also reflects the joint role of certain brain regions, especially the thalamus, in mediating both arousal and awareness.

Stupor is a related disturbance of consciousness 'whose central feature is a reduction in, or absence of, relational functions: that is action and speech' (Sims, 2003). Akinetic mutism, mentioned above, is a neurological cause of stupor. The distinction between neurological and psychiatric causes of stupor, such as affective disorder, psychosis, and dissociative disorder, can be extremely difficult, as the following case illustrates.

An elderly woman became progressively withdrawn over the course of several months following minor surgery. Depression was suspected by her general practitioner, and later by a psychiatrist, but she did not respond to antidepressant treatment. Although a computed tomography (CT) scan showed somewhat dilated ventricles, the cortical mantle appeared normal and the ventricular dilatation was not considered significant. The patient became stuporose, was admitted under the psychiatry service and treated with electroconvulsive therapy (ECT), with no improvement. Neurological assessment was difficult but revealed hypertonia and, possibly, extensor plantars. A lumbar puncture showed a cerebrospinal fluid (CSF) protein concentration of 1.8 g/l, and a magnetic resonance imaging (MRI) scan of the brain revealed a meningioma at the foramen magnum. The tumor was thought to be causing hydrocephalus by elevation of CSF protein and interference with CSF reabsorption. The meningioma was removed and after some months the patient returned to her normal, independent existence.

Catatonia is another 'disorder of consciousness' falling awkwardly between the disciplines of neurology and psychiatry (Fink and Taylor, 2003). It is characterized by motor features, varying from catalepsy or 'waxy flexibility' to motor stereotypies including 'echo' phenomena, accompanied by a markedly altered mental state involving alteration of both arousal and awareness. Its most common causes are psychiatric, including bipolar disease, depression, and schizophrenia, but it occurs in neurological disorders including, for example, the neuroleptic malignant syndrome and encephalitis lethargica. The value of a combined neuropsychiatric approach to these clinical phenomena should be self-evident.

There is, finally, a group of candidate disorders or alterations of 'conscious state' whose status is deeply unclear. These include dissociative or functional coma and stupor, and alteration of consciousness during hypnosis (Halligan et al., 2001; Vuilleumier, 2005). It is uncertain at present to what extent these phenomena are best understood as perturbations of conscious state and to what extent as modulations of social behavior. Elucidation of their neural correlates may help to clarify their nature.

The possibility that the various classic states of reduced or absent consciousness, among them slow wave sleep, the varieties of coma, including anesthetic coma, and the vegetative state, may have important underlying common neurobiological features has been raised by recent research (Baars et al., 2003) and will be discussed further below (section 1.4.1).

1.3.1.2. State boundary dissociation

The impairments of conscious state considered so far represent more or less protracted deviations from the normal, healthy alternation of sleep and wakefulness. The parasomnias are disorders of behavior, autonomic nervous system functioning, and experience occurring in relation to sleep (Table 1.5). The newly revised International Classification of Sleep Disorders (ICSD-2) recognizes that parasomnias can emerge during entry into sleep, within sleep, or during arousals from sleep (American Academy of Sleep Medicine, 2005). Parasomnias occur in all NREM sleep and REM sleep stages (see Fig. 1.5 for the neuropharmacology of these sleep stages). They have been described illuminatingly as the result of 'state boundary dissociation', the breakdown of the boundaries that normally separate the principal conscious states described above, allowing elements of these states to commingle (Mahowald and Schenck, 1992).

Thus sleep paralysis, caused by the persistence of the atonia of REM sleep into wakefulness, results from a partial breakdown of the normal separation between

Table 1.5

Classification of the common parasomnias and related conditions, by sleep stage

Sleep–wake transition disorders	NREM arousal disorders	REM sleep parasomnias	Others
Sleep starts	Confusional arousals	Nightmares	Sleep bruxism
Exploding head syndrome	Sleep terrors	Sleep paralysis	Sleep enuresis
Rhythmic movement disorders	Sleep walking	REM sleep behavior disorder	Sleep related panic attacks
Restless leg syndrome			Sleep related hallucinations
			Periodic leg movements in sleep
			Sleep related choking episodes
			Sleep related groaning
			Sleep related eating disorder
			Sleep related dissociative disorders

these two states. In REM sleep behavior disorder, the muscle tone of wakefulness intrudes into REM sleep, allowing the release of dream-enacting behaviors. Hypnagogic hallucinations, intrusions of dream mentation into wakefulness, are expressions of a similar overlap. Sleepwalking occurs as a result of incomplete arousal from SWS, with motor activity appropriate to wakefulness occurring in conjunction with mentation of a kind that normally occurs in SWS (Bassetti et al., 2000).

1.3.2. Pathologies of awareness

If 'awareness' is taken to refer to the contents of experience, several of the pathologies referred to in the previous section profoundly affect it. The vegetative state

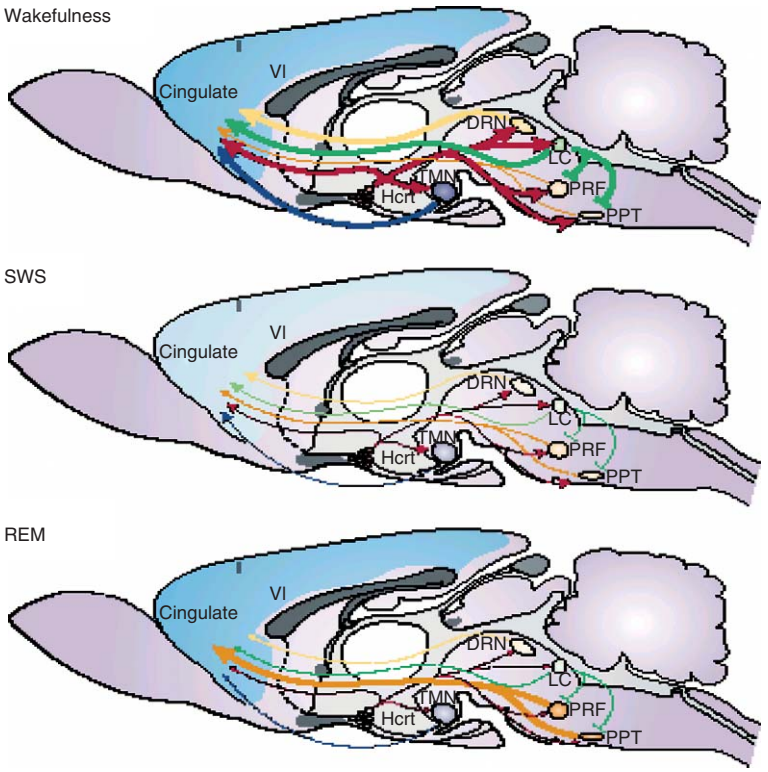

Fig. 1.5. State-dependent changes in the activating system. During wakefulness, hypocretin (Hcrt) activity excites noradrenergic (green), histaminergic (deep blue), and serotonergic (yellow) neurons, which give rise to enhanced cortical activity and arousal. Slow-wave sleep (SWS) is characterized by synchronous intrinsic cortical activity and most subcortical afferents show reduced activity. During rapid eye movement (REM) sleep, low hypocretin activity results in the disinhibition of REM on cholinergic neurons (orange). DRN = dorsal raphe nucleus; LC = locus ceruleus; PPT = pedunculopontine tegmental nucleus; PRF = pontine reticular formation; TMN = tuberomammillary nucleus. (With permission from Sutcliffe and de Lecea, 2002.)

has already been characterized as a condition of 'wakefulness without awareness'. In the 'minimally conscious state' the capacity for experience has recovered to some degree but remains severely limited.

Many of the focal deficits described in neuropsychology can also be regarded as 'pathologies of awareness', as these typically affect the contents of experience. Thus, for example, central achromatopsia (Zeki, 1990), akinetopsia (Zeki, 1991), prosopagnosia, the impairment of fear processing by damage to the amygdala (Young et al., 1995), the selective loss of the capacity for visual imagery (Farah, 1984), and the amnesic syndrome (Kopelman, 2002) are discrete disorders of cognition with distinctive effects on awareness. Much of neuropsychology and cognitive neuroscience therefore has a bearing on the 'science of awareness'. Many psychiatric disorders, especially those involving psychotic experience, profoundly affect the contents of consciousness and are in this sense 'pathologies of awareness' (Frith, 2004).

1.3.3. Pathologies of self-awareness

These are as at least as various as the senses of 'self-consciousness' discussed above. The senses distinguished there should provide a helpful approach to understanding the diversity of disorders of self-awareness.

Thus, the selective loss of proprioception, whether due to a disorder of the central or the peripheral nervous system, impairs self-awareness in the sense of self-perception. The experience of phantom limbs, and perhaps the alteration of self-perception that occurs in 'depersonalization', are disorders of self-awareness in a similar sense of the term.

Anosognosia, failure to appreciate the presence of disease, is a disorder of self-monitoring, the third sense of self-consciousness distinguished earlier (Adair et al., 2003). It occurs, for example, for memory deficit in Alzheimer's disease and for limb weakness in association with the phenomena of hemineglect and extinction.

Selective loss of mirror self-recognition, the fourth sense of self-consciousness, is a rare occurrence but has been described in dementia. Impairments of the 'awareness of awareness', or 'theory of mind', are more common and have been a focus of recent research. It is suggested that the core cognitive deficit in autism is failure to acquire the appreciation of the mental states of others that most of us acquire without effort as small children (Baron-Cohen, 1995; Frith and Frith, 1999). Similar deficits occur in the course of some degenerative disorders, notably frontotemporal dementia (Gregory et al., 2002). It has been suggested that a distributed network of brain regions in the parietal lobe, paralimbic regions and frontal lobes subserve this socially crucial form of self-awareness (Abu-Akel, 2003).

Finally, 'self-knowledge', the last sense of self-consciousness distinguished above, can be affected by a variety of neurological disorders, for example those affecting autobiographical memory (Evans et al., 1996, 2003; Manes et al., 2001; Kopelman MD, 2004). Unawareness of personality change in frontotemporal dementia (Rankin et al., 2005) might be regarded as another example of impaired self-knowledge in this final sense.

1.4. Contemporary models and theories of consciousness

The renaissance of empirical research on consciousness has stimulated several rather general accounts of its mechanisms. A common denominator of these theories is their ambition to do justice to the subjective features of experience, showing how these might plausibly emerge from the candidate mechanisms; most of the theories also incorporate an account of the functions of consciousness in the control of behavior. Some aim to specify anatomical foundations and physiological mechanisms; others have focused on the computational tasks that conscious processes might perform; a third group of theories has addressed the possible social origins and roles of consciousness. These approaches are not mutually exclusive: visual experience has subjective qualities, a neural basis, a computational role in controlling behavior and a social context. I shall review a selection of the more prominent proposals in each of these groups, leaving the fundamental question of whether any such theory is capable, in principle, of giving a complete account of consciousness until the final section (section 1.5).

1.4.1. Anatomy and physiology: the 'where' and 'how' of consciousness?

The majority of theories take it for granted that structures in the upper brainstem, thalamus, and basal forebrain play a critical role in arousal, while thalamic and cortical activity substantially determine the content of consciousness. Most assume that the neural correlate of consciousness will prove to be some variety of 'neuronal cell-assembly', defined by the Canadian psychologist Donald Hebb as a 'diffuse structure comprising cells in the cortex and diencephalon ... capable of acting briefly as a closed system, delivering facilitation to other such systems' (Hebb, 1949). Most theories, also, assume that the loosely linked but temporarily coherent network of neurons subserving

consciousness at a given time will be widely distributed in the brain and will engage a range of cognitive capacities. But agreement on the role of neuronal assemblies in the genesis of consciousness leaves scope for disagreement about many important details: Must the assembly be of a certain minimum size and undergo a particular duration, intensity, or pattern of activity to give rise to consciousness? Need it incorporate particular neuronal types, cortical layers, or cortical regions? Must there be a particular set of interregional connections? Must a certain set of psychological functions be engaged?

Edelman and Tononi (Tononi and Edelman, 1998b) have developed a model that envisages the emergence of 'primary consciousness', the construction of our multimodal perceptual world from a 'dynamic core of strongly interacting elements', cortical modules that are at once internally complex, potentially independent, and yet highly interconnected; these interactions depend on a process of 're-entry', via reciprocal links between regions of the thalamocortical system; this permits the integration of current sensory processing with previously acquired affect-laden memories. Tononi argues that this model of a constantly shifting 'dynamic core' of neural elements subserving consciousness accounts for many of its properties – its continuity and changefulness, its coherence and its pace of change, the existence of a focus of attention and a more diffuse surround, and the wide access of its contents to a range of psychological operations.

Crick and Koch have proposed a theory along broadly similar lines with some differences of emphasis (Crick, 1994; Koch, 1998). They argue that, in the case of visual awareness, the neural correlate of consciousness must be an 'explicit, multi-level, symbolic interpretation of part of the visual scene'. 'Explicitness' implies that the NCC must reference those features of the visual scene of which we are currently aware, for example by a synchronized elevation of the firing rate of the cells that reference the features; the NCC for vision will be 'multi-level' in the sense that several levels of processing in the hierarchy of cortical visual areas are involved; it is 'symbolic' in the sense that the NCC represents the relevant features of the visual scene. Crick and Koch anticipate that the NCC at any given time will involve a sparse but spatially distributed network of neurons and that its activity will stand out against the background of neuronal firing for at least 100–200 ms. They suggest that the neurons involved in the NCC may have 'some unique combination of molecular, pharmacologic, biophysical, and anatomic properties': for example Crick has speculated that 'bursty' pyramidal cells in layer 5 of the cortical visual areas may play a critical role in the NCC. With the aim of honing the definition of the NCC for vision, Crick and Koch have made the controversial proposal that neurons within Area V1, primary visual cortex, do not directly participate in the NCC for visual awareness, despite supplying much of the information that is processed in visual areas downstream (Crick and Koch, 1995). The idea has two main sources: the empirical observation that several characteristics of our visual experience correlate more closely with the activity of neurons in higher visual areas, such as V4, than in V1; and the theoretical view that only cortical regions that can directly influence action, via interconnections with the frontal lobes, can directly contribute to consciousness.

A number of other proposals offer variations on the themes of these two theories, some emphasizing the importance of particular brain regions, others the importance of particular processes, generally defined in broad psychological terms. Thus, arguing on the basis of evidence from experimental and clinical neuropsychology, David Milner has proposed that the 'dorsal' stream of visual processing is dedicated to the 'on-line' control of visually-guided behavior while the 'ventral' stream is responsible for the creation of our conscious visual world (Milner, 1995). Three other distinguished contributors to the field have suggested versions of the principle, mooted by both Edelman and Crick, that consciousness is conferred on otherwise unconscious neural processes by virtue of some further interactive process – of 'commentary', 'comparison', or 'remapping'. Larry Weiskrantz has argued that what is missing in both blindsight and in the amnesic syndrome is 'the ability to render a parallel acknowledged commentary' on activities – sensorimotor control, procedural memory – that the subject can in fact still perform (Weiskrantz, 1997). Weiskrantz helpfully draws a distinction between two views of the 'commentary stage': that it merely enables the acknowledgment of consciousness that is itself somehow achieved by other means, and that making the commentary actually endows us with consciousness: 'it is what is meant by being aware and what gives rise to it'. Weiskrantz favors the second, more radical view and draws attention to the parallel between this proposal and the ideas of the philosopher David Rosenthal, the originator of 'higher order thought' theories of consciousness (Rosenthal, 1986). Jeffrey Gray makes the analogous suggestion that awareness arises from a 'second pass' in which the unconscious data provided by sensory processes are compared with expectations generated by past experience and current intentions (Jasper et al., 1998). In a similar vein, Antonio Damasio proposes that awareness occurs when the brain represents the effects of sensory events on the organism by a

process of 'second order mapping' (Damasio, 2000). In other words, mere sensation is insufficient for awareness: it must first be transformed by a process that makes explicit the impact of the knowledge on the knower. Weiskrantz implicates 'fronto-limbic areas' in the commentary stage, Jeffrey Gray locates the critical 'comparison' in his theory to limbic regions of the temporal lobes and the basal ganglia while Damasio locates the neural representation of the self in the upper brainstem, thalamus, deep forebrain nuclei, and somatosensory cortex.

Among somewhat similar lines, Baars, Laureys and others (Baars et al., 2003) have recently drawn together the threads from studies of the conscious resting state, sleep, coma, anesthesia, and the vegetative state to identify a network of frontoparietal regions with an especially close relationship to consciousness: activity in these regions is tonically high in the resting conscious state and selectively depressed in all four states of unconsciousness. These authors propose that these brain regions subserve 'self systems' in the brain: when they are damaged or deactivated the 'observing subject' is no longer available to respond to the 'objects of consciousness' within the brain.

The theories discussed so far emphasize the anatomical organization of the brain networks and the nature of the psychological processes involved in consciousness. The notion that a certain 'kind' of distributed neuronal activity may also be crucial has also been raised. The most popular current candidate for a key role in the physiology of consciousness is neural activity synchronized in the gamma frequency range of 35–45 Hz. There is evidence to suggest a role for coherent gamma band activity in arousal, sensory segmentation, selective attention, working memory, and in aspects of 'higher order consciousness', motivation, action planning, and symbolic processing (Engel et al., 2000).

These theories are already diverse, although united by many common themes and principles. It would be misleading to fail to mention that the field has its share of intriguing outliers. For example, while most theories emphasize the importance of interaction between brain regions and psychological processes in the genesis of consciousness, Semir Zeki has proposed that individual visual areas may be associated with individual 'microconsciousnesses' (Zeki and Bartels, 1998). While most of these theories work within the boundaries of standard neuroscience, Roy John has suggested that mechanisms akin to those discussed throughout this section give rise to a 'resonating electrotonic field' that is the proximal physical substrate for awareness (John, 2005). Finally, quantum theorists of consciousness have argued that we need to appeal to the basic physical features of the subatomic constituents of the brain to understand how it gives rise to awareness (Penrose, 1994). These theories provide a reminder that the current scientific 'consensus' on the mechanisms of consciousness is far from universal: it remains possible that its explanation will require novel departures in scientific theory.

1.4.2. Cognitive/information processing approaches

What is consciousness for? Almost all theories assume that consciousness plays a role in the control of behavior, specifically in circumstances that involve novel challenges or unpredictable events to which we need to devote a substantial part of our psychological resources. In such circumstances instinctual or automatic behaviors may be inadequate: the capacities to select and acquire appropriate responses from a wide and adaptable repertoire, often on the basis of fine perceptual distinctions, will be advantageous. Functional theories propose that consciousness is bound up with these capacities, linking the evolution of awareness to the emergence of flexible patterns of learned behavior from more rigid instinctive patterns of response as the 'synaptic bridge' that links sensation to action gradually lengthened in the course of cerebral evolution. These are, broadly, 'integrative' theories of consciousness.

The most widely endorsed suggestion, made in Bernard Baars's and Stanislas Dehaene's closely related 'global workspace' theories (Baars, 2002; Dehaene and Naccache, 2003), is that consciousness is the expression of a mode of brain processing that allows information of crucial current importance to be broadcast widely through the brain, harnessing the activities of a wide range of potentially independent processors to the task in hand. Thus when we are conscious of information we are in a position to report on it by a variety of means, to use it to guide action of other kinds, and to memorize it. In switching from an unconscious to a conscious mode of processing we trade automaticity, speed, and high-capacity parallel processing for flexibility of response under relatively slow, serial control. Theories of this kind follow the lead of William James in associating consciousness with selective attention and 'primary' or 'working' memory: attention controls admission to the global workspace where information, once admitted, commands working memory and gains access to resources distributed throughout the brain. Whether a clear distinction can really be drawn between the two modes of information processing in the brain envisaged by these theories will be a key question for consciousness research over the coming years.

1.4.3. Social theories

The theories outlined so far have focused on brain anatomy and physiology, psychological processes within the individual brain, and computational algorithms. But there are several reasons for suggesting that consciousness has an important social dimension. First, we have seen that the Latin root of 'consciousness' referred, originally, to knowledge shared with another. Second, the sharing of knowledge with oneself, in awareness, and the sharing of knowledge with others, in social exchanges, may be interconnected: there is a theoretical argument and empirical evidence that awareness of self and awareness of others are acquired in parallel (Strawson, 1974; Parker et al., 1994). Third, language is a vital contributor to human awareness and language, clearly, is a social phenomenon. Proponents of social theories sometimes claim that the social dimension of consciousness explains the bafflement we tend to feel when we try to explain how the brain can generate experience: on these views experience is as much a social construction as a biological and psychological phenomenon (Rose, 1998; Singer, 1998).

Humphrey provided a lucid example of theories which propose a social function for awareness (Humphrey, 1978). He suggested that the purpose of consciousness is to allow social animals to model each other's behavior on the basis of their insight into its psychological motivation. In other words, our knowledge of our own mental states supplies us with insight into the mental states underlying the actions of others; the ability to predict these actions is a major determinant of our biological success. More recently, such knowledge has been described in terms of the possession of theory of mind: some social theories broadly associate this with consciousness.

There is no doubt that a comprehensive theory of consciousness needs to take account of its social dimension. But most commentators agree that this is the wrong level of explanation for the simpler forms of consciousness, providing an avenue by which to understand varieties of self-awareness or 'higher-order consciousness' rather than addressing the more basic phenomena of perceptual awareness.

1.4.4. A theory of theories?

The reader may be wearying, by this stage, of the variety of proposals on offer, and eager for a satisfying synthesis. Unfortunately, it is early days in the science of consciousness and there is no clear consensus view. It may be worth trying to encapsulate the common ground between the majority of models I have mentioned in a few lines. Admittedly vague, such a summary would run somewhat as follows: awareness, as defined at the start of this chapter, requires an appropriate background of brain activation by the nonspecific brainstem and diencephalic activating system that set the 'state' of consciousness. This must be linked to moderately prolonged, moderately high-intensity, locally differentiated yet well synchronized and widely integrated activity in a transient neocortical cell assembly interconnecting sensory, limbic, and executive regions in the parietal, temporal, and frontal lobes. Activity within the widespread resulting cortical-subcortical cell assembly facilitates the flexible selection (and acquisition) of appropriate responses, from a varied and adaptable repertoire, sometimes on the basis of fine perceptual distinctions. These responses include the various forms of self-report. Through these processes 'knowledge that is *in* the network' becomes 'knowledge *for* the network' (Cleeremans, 2005). To be undergoing brain activity of these kinds, potentially enabling these highly flexible forms of interaction with the environment, is, most contemporary theories suggest, to be conscious.

1.5. The philosophy of consciousness

Anyone reviewing the discoveries of the past century that bear on the brain mechanisms of wakefulness and awareness would surely conclude that we have learnt a great deal about consciousness. But many observers are left with the sense that there remains an 'explanatory gap' between the findings of brain science and the phenomena of consciousness. Why should these wonderfully elaborate, yet entirely physical, neural processes give rise to the qualities of experience at all? Why should particular subsets of brain activity give rise to particular experiences, such as those of seeing, hearing, and touching? Brain science, David Chalmers has argued, is poised to answer the 'easy', mechanistic, problems of consciousness, but the philosophically 'hard' problem remains (Chalmers, 1996). Even once we have achieved a comprehensive understanding of the inner workings and outward behavior of an organism, it seems that we can always ask these further questions: is it conscious and, if so, what is its experience like? A solution to the 'hard problem' must render transparent the opaque relationship between observable events and felt experiences.

In this final section I shall introduce the standard philosophical approaches to understanding the relationship between mind and brain in terms of three strong, widely shared, intuitions about consciousness. I shall close by suggesting, as others have done, that to solve the problem of consciousness we may need to refashion our concept of awareness and to broaden the boundaries of explanation.

1.5.1. Three intuitions about consciousness

Three central intuitions recur repeatedly in philosophical discussions of consciousness (Zeman, 2001, 2002). Philosophical accounts of consciousness can be helpfully judged against them.

The first intuition is that consciousness, in the sense of awareness or experience, is a robust phenomenon, rich and real, that deserves to be explained by science and not 'explained away'. Sensory experiences, for example, like those of color, sound, or pain, the simplest and most vivid instances of awareness, are phenomena that any full description of the universe must take seriously. Indeed experiences of this kind are arguably our point of departure in gaining knowledge of the world. Consciousness, in this sense, is 'the sea in which we swim' (Velmans, 2000). Almost everyone interested in the science and philosophy of consciousness would agree on these points in principle; but, of course, there is scope for plentiful disagreement about what is meant by the 'reality' of awareness.

The second intuition is that consciousness is bound up with our physical being. Everyone knows that fatigue, alcohol, knocks on the head, and countless other physical events can modify the state and contents of consciousness. The survey of the neurobiology of consciousness given above reinforces this prescientific view: consciousness is firmly rooted in the brain and the structure of experience appears to be mirrored by the structure of neural processes. It has become reasonable to suppose that every distinction drawn in experience will be reflected in a distinctive pattern of neural activity.

The third intuition is that consciousness makes a difference to our behavior. It seems self-evident that much of our behavior is explained by mental events. If we could not see or hear or touch, if we could not experience pain or pleasure, if we lacked conscious desires and intentions, we would not and could not behave as we do. If this is true, it is natural to suppose that consciousness is a biological capacity that evolved in the service of action.

The fact that these three intuitions are 'natural' and widely shared does not guarantee that they are true. But they help to identify the main points of disagreement between the contending theories of consciousness in the philosophy of mind – and to explain our reactions to them. I shall focus on three of these approaches: the view that conscious and neural events are closely correlated but fundamentally distinct classes of phenomena; the view that underlying neural events are identical with the corresponding conscious experiences; and the view that experiences are best understood in terms of the functions served by neural events.

1.5.2. Philosophical approaches

1.5.2.1. Dualism

Dualism, the view that there are separate classes of mental and physical entities, processes, or properties, is deeply entrenched in our vocabulary, our thinking, and our institutions. In medicine, for example, we often find ourselves sorting disorders into 'organic' and 'psychogenic' categories, a distinction that assumes, against all the evidence, that the 'psyche' is inorganic. We then use the results to divide medical labor between those who care for bodies – physicians – and those who care for minds – psychiatrists. The dichotomy between mind and brain is reinforced by the traditional physical separation of these two medical specialisms.

René Descartes is usually identified as the chief historical representative of philosophical dualism (Descartes, 1976). In the *Discourse on method*, published in 1637, he argued that, while it was possible to be mistaken about all other beliefs, it was not possible for him to be mistaken in his belief that he was a 'thinking thing'. This inference seems reasonably secure. He went on to conclude, much more questionably, that 'I [am] a substance of which the whole essence and nature consists in thinking, and which, in order to exist, needs no place and depends on no material thing'. Thus Descartes drew a radical distinction between immaterial 'thinking things', minds, and 'extended things', physical objects.

Contemporary dualists have replaced Descartes's 'supernatural substance dualism' with the naturalistic view that mental attributes are a special, but natural, class of properties of physical things, namely organisms. In David Chalmers's version, for example, conscious events are distinct from but closely related to neural events, to which they are yoked by fundamental 'psychophysical laws' (Chalmers, 1996). In Chalmers's vocabulary, a sophisticated computer, capable of reporting and acting on information sensed in its surroundings, would be 'aware*', that is to say in a physical state analogous to the state of the human brain during conscious experience, but not necessarily 'aware' in the crucial, experiential sense: this latter, subjective, form of awareness would only follow if additional psychophysical laws linked the computer's physical state to experiences like ours. The philosopher Ned Block has developed a distinction similar to Chalmers's distinction between 'awareness*' and 'awareness' using the terms 'access consciousness' and 'phenomenal consciousness' (Young and Block, 1996).

Theories like these certainly respect our first intuition, taking consciousness seriously. Chalmers's theory also does justice to the second intuition, by granting that mental events are causally dependent on

their neural substrate. But they fall foul of the third intuition, as there seems to be no scope for the non-physical properties of conscious events to make a difference to the physical trajectory of behavior.

1.5.2.2. Mind–brain identity theory

The suggestion that conscious events are identical with corresponding neural events offers a reductionist, physicalistic solution to the mind–body problem. It was proposed by Lucretius in the ancient world and Thomas Hobbes in the 17th century. Other recent examples of reductive explanations have reinvigorated materialistic theories of the mind. Often-cited instances include the reduction of heat to the kinetic energy of atoms, the explanation of light in terms of electromagnetic radiation and, perhaps of deeper relevance to consciousness, the analysis of 'life' as the property possessed by complex, highly integrated, physical systems that are able to utilize energy from their surroundings to sustain and reproduce themselves. Why should consciousness be an exception to the stream of successful reductions of phenomena once considered, like life, to be beyond the reach of science?

Some well known philosophical thought experiments suggest that it might indeed be an exception. Current physical theory teaches that light, as a physical entity, is nothing more than a certain type of radiation. To know everything about such radiation would be to know everything about light. But it is not clear that if we knew everything about the physicochemical properties of an organism we would thereby know everything about its experience. For example, how far can science take us towards an appreciation of the subjective experience of an animal equipped with a sense we lack, like the echolocatory sense of bats and dolphins (Nagel, 1979)? Or, to come closer to home, could a blind student of the visual system ever gain the knowledge, which the sighted naturally possess, of 'what it is like to see' (Jackson, 1982)? Some philosophers have taken these examples to show that conscious experience has subjective properties that are not fully specified by and cannot be reduced to the neural structures and processes on which they depend.

In terms of our three intuitions, mind–brain identity theories, with their claim that conscious events 'simply are' brain events, do justice to the physical basis of experience and allow for its functional role. But they fail to satisfy the first intuition, that the properties of experience are robust phenomena in need of explanation. In John Searle's uncompromising words, 'the deeper objection [to physicalism] can be put quite simply: the theory has left out the mind' (Searle, 1992).

1.5.2.3. Functionalism

Dualism is rooted in the intuition that awareness is 'rich and real', a phenomenon that goes beyond its physical substrate. Identity theory is rooted in the intuition that awareness is intimately bound up with events in the brain. Functionalism is most closely related to our third intuition: that consciousness makes a difference to our lives. Indeed this theory might be caricatured as the view that consciousness does not just make a difference to our lives: it *is* that difference. In other words the essence of awareness lies in the functions that it serves, the transformations of input into output with which it is associated.

This approach owes much to the developing science of artificial intelligence. Daniel Dennett has emphasized the analogy between the activity of the brain, and the awareness associated with it, and the implementation of a software package in a computer, to create a 'virtual machine': 'human consciousness ... can best be understood as the operation of a ... virtual machine ... in the parallel architecture of a brain' (Dennett, 1991). Taking vision as an example, functionalism suggests that visual experience consists in the countless acts of discrimination and classification that sight permits, and in their consequences for the rest of our mental life: functionalism reinterprets our experience in terms of a series of acts of judgment.

This approach has many attractions. Like identity theory, it finds a place for consciousness in the natural world. It accounts for, indeed it originates with, our conviction that consciousness has effects. It escapes the superficiality of its intellectual predecessor, behaviorism, by taking seriously what goes on within our heads. It allows for the occurrence of consciousness in other organisms or machines that perform the same cognitive computations as we do.

But, at least at first sight, functionalism appears to be vulnerable to the same fundamental objection as identity theory: that it fails to account for the qualitative properties of consciousness. We seem to be able to ask of a virtual machine, just as we can of a neural assembly, why should it be conscious at all and, if it is conscious, why should its consciousness be like this?

The debate between proponents of these three broad theories – identity theory, dualism, functionalism – continues. For the time being there is no alternative but to continue to use all three vocabularies of experience, biology, and behavior in our efforts to understand the mind.

1.5.3. Broadening the explanatory horizon

Describing the process by which mechanistic models replaced animistic ones to become the standard

approach to biological explanation, the historian of medicine, Charles Singer, wrote: 'The course of physiological advance may be described, briefly, as the expulsion of the mental element from process after process associated with vital activity' (Singer, 1928). This advance was of course highly successful. But as our mental lives are a crucial aspect of our biology, the process of expulsion eventually had to stop. The current fascination with consciousness reflects the mounting intellectual pressure to explain how 'vital activity' in the brain generates a mental element with rich subjective content.

This explanation may require a rethinking of what we mean by 'the mental', i.e., of what we are seeking to explain, as well as a reassessment of the role played by the brain. The traditional quest has been for a brain mechanism, or set of mechanisms, that will account for the occurrence of experience much as Descartes conceived it – an essentially private, invisible, and immaterial process. Both this conceptualization of experience and the exclusive emphasis on the brain have been called into question.

With regard to the brain, while its activity clearly plays a key role in the genesis of experience, it is only part of the story. The mind is typically 'embodied, embedded, and extended': that is to say, typical episodes of experience involve interactions between brain and the body that contains it; depend upon a long history of individual development, conditioned powerfully, in the case of human consciousness, by cultural inheritance; and are played out in a physical environment, through a process that is extended in both time and space. The brain is highly relevant to the study of consciousness but we probably need to look beyond it if we are to give a full explanation of awareness.

On the second count, we should not assume that the target of our explanation is the kind of immaterial function envisaged by René Descartes. After all, we determine whether others are conscious by interacting with them, or simply watching them: 10 seconds spent scrutinizing an expert mountaineer ascend a cliff would leave little doubt about his consciousness. Instead of regarding consciousness as a mysterious emanation from the brain, perhaps we should think of it as the exercise of a capacity for sophisticated forms of interaction with the world, enabled by the brain. This is broadly the approach taken by O'Regan, Noe, and others who have argued that sensation is not 'generated' by the neural processes but consists in the real or virtual exercise of exploratory skills (O'Regan and Noe, 2001; Noe A, 2004).

Whether this challenging approach will succeed in bridging or dispelling the 'explanatory gap' between the mind and brain remains to be seen. It is certain, however, that the study of consciousness, one of the major challenges for human understanding, has entered an immensely exciting phase.

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Chapter 2

Consciousness: its neurological relevance

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We live in an exciting time for understanding consciousness and its disorders. Both basic science and clinical neurology provide insights into the understanding of how alertness and awareness arise in the brain.

A recurring theme is that, although the functional anatomy of the brain is organized in a modular manner, for meaningful brain function there is a high degree of interaction among various regions. This includes feedback to sensory inputs that govern perception and the focusing and selectivity of attentional processes (Cudeiro and Sillito, 2006; Maunsell and Treue, 2006). The interaction of various seemingly distinct functional areas, e.g., visual and auditory systems, allows for integrated attention and also for learning through plasticity (rewiring, new synapses, and strengthened circuits and connections) changes in the thalamus and cerebral cortex (Cudeiro and Sillito, 2006). The key role of the hippocampus in acquiring new information is becoming better understood (Delgado-Garcia and Gruart, 2006). Just how conscious awareness arises from this integrated brain activity is still unclear but the processes that are involved are better understood. Powerful new neurobiological technologies in basic neuroscience hold promise for the detailed neurophysiology of various components of consciousness, especially processing of and combining of information and the initiation of responses. Dr Zeman provides a masterly discussion of consciousness from a neurological perspective in Chapter 1.

Clinical insights based on the jacksonian approach of studying excitatory and destructive phenomena in the brain (as discussed in Chs. 10 and 13) also provide us with similar insights and respect for the brain's functional organization and the fundamental importance of integration of various regions. Just as improved technological approaches have shed light in basic neuroscience, functional neuroimaging and electrophysiology will give us more answers on a more macroscopic level for clinical neurology and related fields, e.g., neuropsychology (Vallar et al., 2003).

The assessment of the unresponsive patient involves examination, history-taking, and tailored investigative tests (Fig. 2.1). The objectives are to classify and anatomically localize the site of abnormality, to grade its severity, and to determine the etiology. Management, including investigations, general supportive care, and specific therapy is given in Chapter 20. Although the approach to children shares many of these aspects, their special aspects are covered in Chapter 19.

The differential diagnosis of the unresponsive state includes psychogenic unresponsiveness and the locked-in syndrome. Psychogenic unresponsiveness is discussed in Chapter 18. In the locked-in syndrome the patient is awake and aware but cannot move the limbs, the lower bulbar musculature, or lower facial muscles. The orbicularis oculi and vertical and convergent eye movements are preserved. This constellation of clinical features is due to a lesion in the basis pontis, either due to ischemia in the basilar artery territory or another structural lesion, such as central pontine myelinolysis. It can be determined that the patient is conscious by having the patient visually track a target moving in the vertical plane or open and close the eyes to command. A more complete locked-in syndrome may be caused by generalized neuromuscular paralysis that may sometimes occur with a severe polyneuropathy or by sustained action of neuromuscu-

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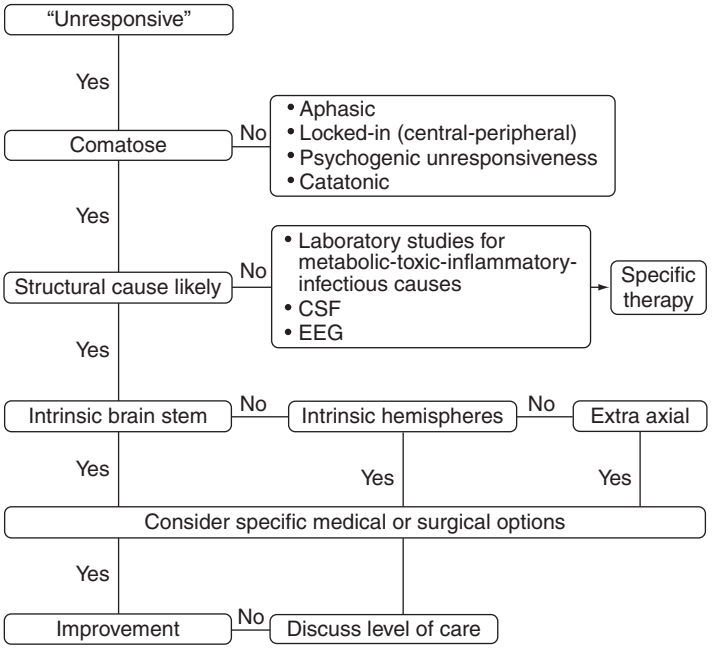

Fig. 2.1. Assessment of the unresponsive patient.

lar blocking agents. Proof of consciousness, especially with Guillain–Barré syndrome, can be obtained through an EEG recording, which should show normal awake rhythms, e.g., the alpha rhythm that blocks with passive eye opening and reappears with eye closure.

Impairment of alertness implies dysfunction of the ascending reticular activating system (ARAS): cerebral hemispheres (cerebral cortex, thalamus, or intervening white matter) and rostral brainstem. Acute dysfunction of the dominant hemisphere alone can sometimes produce a transient impairment of alertness (Salazar et al., 1986).

Awareness, the 'content of consciousness', requires integrated function of the cerebral cortex and thalamus. Impairments in various aspects of awareness (including perception, apperception, declarative memory, working memory, cognition, and planned activity) result from structural or metabolic disturbances of these regions.

2.1. Classification

Impairment of consciousness can be classified into a number of syndromes:

1. *Neglect syndromes* are best characterized as unilateral loss of awareness of contralateral extrapersonal space or personal body space, and constitute a restricted or focal type of diminished consciousness. Neglect syndromes can occur dissociated from any problems with sensory pathways or primary sensory areas. The main sites of abnormality are in the heteromodal cortices of the parietal (especially in the right or nondominant hemisphere) or frontal lobes. They thus represent a defect in higher order processing and are commonly accompanied by extinction (the loss of awareness of one of two simultaneously competing stimuli) and perseverative activity (Çiçek et al., 2007).
2. *Delirium* (Ch. 3) consists of impairment in the ability to maintain attention, along with various associated features, e.g., disturbance in the sleep–wake cycle, changes in psychomotor activity (increased or decreased), disorientation, and altered perceptions. Delirium, or confusion, reflects a generalized disturbance in integrated brain function, but regions that have been incriminated either singly or with other regions include the anterior cingulate region, the prefrontal cortex, and parietal regions as well as subcortical nuclei in the thalamus and rostral midbrain tegmentum.
3. The *vegetative state* (Ch. 6) refers to wakefulness without the capacity for awareness. Anatomically, the sites of involvement are either the cerebral cor-

tex bilaterally, the thalamus, or the intervening white matter that interconnects various cortical areas or the cortex to the thalamus.

4. The *minimally conscious state* (Ch. 6) consists of some interaction with the environment, such as tracking with the eyes (akinetic mutism) or limited responses, but the patient's integrated brain function is grossly impaired. The patient is dependent and does not initiate anything other than basic homeostatic activity.
5. *Stupor and coma* (Ch. 4). *Stupor* is a state of impaired alertness in which the patient can briefly be aroused to eye opening and some responsiveness. The patient goes back to an eyes-closed, non-interactive state when the stimulation ceases. *Coma* is unarousable unconsciousness and implies dysfunction of the ARAS.
6. *Brain death* is the total and irreversible loss of brain function. Clinical 'brain death criteria' for most countries are met if the entire extent of the brainstem and the hypothalamus are irreversibly destroyed. Ancillary testing, however, must show loss of total brain function, as revealed by tests revealing absence of blood flow to the entire brain.

2.2. Etiology

After defining the category and thus the approximate site of impairment of consciousness (above), clues as to the etiology should be sought.

2.2.1. History

This usually has to be obtained from family members, friends, or other witnesses who have been with the patient or who have witnessed a collapse. The time course is helpful. A sudden collapse favors a catastrophic cause such as an intracranial hemorrhage or loss of general circulation. A fluctuation in impairment suggests a metabolic or toxic cause (see Chs. 7–9 and 11), or occasionally an extra-axial lesion, e.g., a subdural hematoma or raised intracranial pressure. Intermittent discrete attacks occur in seizure disorders, syncope, recurrent hypoglycemia or, uncommonly, focal ischemia or ventricular obstruction. A gradual impairment in consciousness after preceding neurological symptoms could indicate a progressively increasing mass lesion with ultimate herniation (see Ch. 5). A history of depression, anxiety, or substance abuse raises other possibilities, including self-intoxication.

A history of underlying chronic or preceding illnesses or symptoms may be helpful. A recent fever suggests an infectious process, e.g., an encephalitis or meningitis or neurological complications of systemic infection (see Ch. 11). Previous valvular heart disease raises the possibility of endocarditis or multiple cerebral emboli. A background of cancer could indicate metastases, side effects of drugs, or 'remote effects' on the nervous system (see Ch. 15). Medications should be listed and a search should be undertaken for any personal information, such as a Medical Alert bracelet or a suicide note.

2.2.2. The neurological examination

The chief value of the neurological examination is to assess the level of consciousness (see above), assessment of cranial nerve functions, motor responses, and respirations. Funduscopy should form a part of the assessment routine. The presence of papilledema indicates raised intracranial pressure. A subhyaloid (preretinal) hemorrhage is almost always associated with an acute intracerebral hemorrhage, especially a ruptured berry aneurysm. Among cranial nerve reflexes, pupillary, corneal, vestibulo-ocular, pharyngeal, and cough reflexes are routinely examined. Most metabolic disorders spare the pupillary light reflex, although some drugs may affect pupillary size and/or reactions symmetrically. For example, opiates and organic phosphates cause small, reactive pupils, while intact pupillary reflexes indicate the optic nerves and the rostral brain stem are functioning and are unlikely to be involved in a structural cause for coma. The vestibular–ocular reflex (VOR) can be used to assess eye movements in the horizontal and vertical planes. Caloric (usually ice-water) testing is more potent than oculocephalic reflex testing, by moving the head, and is safer in the face of possible neck injury or instability of the cervical spine. A large part of the brainstem tegmentum (from medulla to midbrain) as well as the IIIrd and VIth cranial nerves are assessed with this testing. It should be remembered that the VOR can be selectively affected without impairment of the pupillary light reflex in Wernicke's encephalopathy and in sedative drug intoxication (unpublished observations). Spontaneous eye movements are also worth noting. Nystagmus retractorius and convergence nystagmus are due to diffuse excitation of the IIIrd nerve complex in the midbrain and often indicate a structural lesion in this region or an underlying seizure discharge (we have observed this in association with hyperglycemic coma and seizures). Ocular bobbing is a rapid downward movement of both eyes together followed by their slow return to the horizontal plane. It often indicates a lesion or dysfunction in the caudal pons. Its obverse, ocular dipping (slow downward followed by rapid

upward conjugate eye movements) also indicates pontine dysfunction but is most common in anoxic–ischemic encephalopathy. Palatal and pharyngeal reflexes involve brainstem regions caudal to those key structures responsible for consciousness and are useful for localization purposes and in the clinical assessment of brain death.

2.2.3. The general examination

Vital signs can provide key clues. Markedly elevated blood pressure could indicate hypertensive encephalopathy (almost always associated with papilledema) or the posterior reversible leukoencephalopathy syndrome (PRES). Otherwise hypertension may be secondary to the intracranial process, e.g., stroke, raised intracranial pressure. Severe hypotension (shock), of course, suggests global hypoperfusion but also indicates a serious underlying condition, e.g., sepsis, hemorrhage, etc. Hypothermia could be symptomatic of hypothyroidism, environmental cold exposure, intoxication, hypothalamic dysfunction (as in Wernicke's encephalopathy), or even severe systemic infection. Hyperthermia usually suggests central nervous system or systemic infection but acute adrenal failure, cocaine intoxication, brainstem stroke, malignant hyperthermia, or neuroleptic malignant syndrome are other possibilities.

Trauma is suggested by bruising (especially if linear) or lacerations but specific signs of head injury, especially basal skull fracture, include unilateral or bilateral periorbital ecchymoses (raccoon eyes) with extension to but not beyond the orbital ridges with orbital roof fractures, Battle's sign (bruising over the mastoid), or hemotympanium – both suggestive of a fracture through the petrous temporal bone. A bitten tongue or posterior fracture-dislocation of the humerus is suggestive of an earlier convulsive seizure.

Examination of the skin can reveal helpful information. Hepatic coma is suggested by jaundice or other stigmata of liver disease. Cherry red discoloration of the lips, mucous membranes, or skin implies carbon monoxide intoxication. Petechiae or purpura raise the possibility of meningococcemia, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, or Rocky Mountain spotted fever. Bullous skin lesions, 'coma blisters', are seen in massive barbiturate intoxication. Needle tracks suggest drug abuse or complications thereof. Hyperpigmentation of the skin or mucous membranes suggest Addison's disease. Myxedema coma is suggested by periorbital edema, a large tongue and pale, doughy, cool skin.

The breath can suggest alcohol or cyanide intoxication, liver or renal failure, or diabetic ketoacidosis.

Cardiac murmurs raise the possibility of cardiac embolism. The abdominal examination may reveal signs of liver disease or large kidneys in polycystic kidney disease (and subarachnoid hemorrhage from a ruptured berry aneurysm).

Signs of meningeal irritation, as found in meningitis or subarachnoid hemorrhage, may be absent in coma but are helpful when found and include: 1) resistance to neck flexion; 2) pain on straight leg raising (Kernig's sign) or flexion of the contralateral lower limb when one hip is flexed (Brudzinki's sign).

This volume should help us think in an anatomical and physiological manner as we attempt to understand the effects of various disorders affecting the brain at different times of life. While neurologists are clinical scientists, they are also doctors who are aware of their patients and families as fellow humans. These individual and collective aspects, along with the various ethical and legal implications of their work, are factored management decisions involving patients with the life-threatening illnesses discussed in this book (see Ch. 21).

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Chapter 3

Delirium in the critically ill patient

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The subject of delirium is generally looked upon by the practical physician as one of the most obscure in the chain of morbid phenomena he has to deal with; whilst the frequency of its occurrence under various conditions of the system renders the affection not a little familiar to his eye.

Gallway, 1838

3.1. Historical perspectives on delirium terminology

Delirium is an acute and transient brain dysfunction that is characterized by disturbances in consciousness and cognition. Though delirium is often recognized in older hospitalized patients and is associated with prolonged hospital stays and an increased likelihood of death in these patients, the occurrence of delirium in critically ill patients has been overlooked and misunderstood. In fact, delirium in the intensive care unit (ICU) was often viewed as an expected, inconsequential outcome of intensive care. However, recent studies have documented that delirium is both common and deleterious in critically ill patients. The adverse outcomes associated with delirium in previous studies of medical and surgical inpatients have now been identified in the ICU, an environment in which delirium occurs in up to 80% of the sickest patients.

The word 'delirium' is derived from the Latin word *deliro*, which means 'to be crazy, deranged, or silly'. With its root being the agricultural term *liro* ('to plow in a straight line'), *deliro* conjured up images of a madman plowing a field with no discernible plan. Patients with symptoms consistent with delirium are described throughout ancient medical writings. Hippocrates described patients with 'phrenitis', a syndrome marked by confusion and restlessness that fluctuated unpredictably and was associated with physical illness, often a febrile illness (Chadwick and Mann, 1950). Celsus and other Roman writers used 'delirium' interchangeably with 'phrenitis' to designate a temporary change in mental status associated with a physical illness characterized by restlessness and excitement. Alternatively, 'lethargus' was used to describe illness-associated confusion characterized by sleepiness and inertia (Lipowski, 1990).

Over the centuries, numerous terms have been used to refer to delirium and misunderstanding has arisen from the vague use of such terms. Even in recent medical literature more than 30 terms for delirium have been used interchangeably (Liston, 1982). For example, 'encephalopathy' often refers to delirium associated with a decreased level of arousal and muted psychomotor activity. Alternatively, 'ICU psychosis' and 'ICU syndrome' have been used to refer to delirium in ICU patients, but these labels are misnomers that should be discouraged. They imply that delirium is an expected, inconsequential outcome of intensive care (McGuire et al., 2000).

As stated by Dr. Zeman in Chapter 1, delirium is part of a spectrum of disorders of consciousness; it lies in the 'hinterland of coma' where it cannot and should not be arbitrarily distinguished from confusion, organic brain syndrome, and clouding of consciousness. In fact, the American Psychiatric Association's Diagnostic and *Statistical Manual of Mental Disorders,*

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3rd edition (DSM-III) identified 'delirium' as the recommended term in their nosology of organic mental disorders, noting that 'delirium is intended to include the broad spectrum of clinical states having in common the essential features described [in Table 1]' (American Psychiatric Association, 1980). Although the phrase 'organic mental disorders' appropriately suggested that delirium (and other disorders in this category) was due to brain dysfunction attributable to physiological abnormalities, the phrase was abandoned with the publication of the DSM-IV in order to avoid the implication that '"nonorganic" mental disorders do not have a biological basis' (American Psychiatric Association, 2000).

3.2. Definition and clinical features

Delirium is formally defined as a disturbance of consciousness and cognition that develops and fluctuates over a short period of time (Table 3.1) (American Psychiatric Association, 2000). Associated features that are not required for the diagnosis of delirium include an abnormal sleep–wake cycle, increased or decreased psychomotor behavior, and emotional disturbances. With each revision of the DSM, changes were made in the nomenclature of the diagnostic criteria of delirium, but the concepts have remained unaltered (see section 3.6).

3.2.1. Disturbance of consciousness

A defining feature of delirium is the inability to focus, sustain, or shift attention (American Psychiatric Association, 2000). Originally labeled 'clouding of consciousness', this ambiguous terminology was abandoned and the currently used 'disturbance of consciousness' refers to the patient's impaired awareness of the environment as manifested by inattention. The patient may be easily distracted and need questions repeated multiple times. While such a disturbance is obvious in many patients resulting in the inability to maintain or even initiate a conversation, more minor degrees of impairment may occur. Frequently used tests of attention include serial 7s (the patient counts backwards from 100 in increments of 7) and spelling the word 'world' backwards. Several tests have been validated to measure attention in nonverbal (e.g., mechanically ventilated) patients, including the 'A' random letter test, during which a patient listens as the examiner recites a series of 10 letters and squeezes the examiner's hand each time the letter 'A' is heard (Strub and Black, 2000; Ely et al., 2001b, 2001c) (see section 3.7).

While delirium reduces the clarity of a patient's awareness of the environment, their level of alertness may be increased or decreased. Both manifestations of delirium interfere with the patient's ability to maintain attention. In critically ill patients, decreased

Table 3.1

Diagnostic criteria of delirium

Diagnostic criteria
A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention
B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia
C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day
For delirium due to a general medical condition:
D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition
For substance intoxication delirium:
D. There is evidence from the history, physical examination, or laboratory findings of either (1) the symptoms in Criteria A and B developed during substance intoxication, or (2) medication use is etiologically related to the disturbance
For substance withdrawal delirium:
D. There is evidence from the history, physical examination, or laboratory findings that the symptoms in Criteria A and B developed during, or shortly after, a withdrawal syndrome
For delirium due to multiple etiologies:
D. There is evidence from the history, physical examination, or laboratory findings that the delirium has more than one etiology (e.g., more than one etiological general medical condition, a general medical condition plus substance intoxication or medication side effect).
All four criteria (A–D) are required to diagnose delirium.

From the DSM-IV-TR (American Psychiatric Association, 2000).

alertness, i.e., somnolence and lethargy, may be a manifestation of delirium, the underlying disease process, or treatment with sedatives and/or analgesics. Therefore, care must be taken to evaluate for the other characteristics of delirium when assessing a patient with decreased alertness.

3.2.2. Disturbance of cognition

Delirium invariably results in transient cognitive impairment. To some degree, all of the major aspects of cognition – thought, memory, and perception – are disturbed in the delirious patient (Lipowski, 1990). Initially, only judgment and abstract thinking are impaired but, with progression of the delirious state, thinking becomes disorganized and simple questions become difficult to answer (e.g., 'Does 1 pound weigh more than 2 pounds?'). This is compounded by increased distractibility, with the thought process being frequently interrupted by external stimuli. The flow of thinking may be either slowed or accelerated and thought content may likewise be depleted or unusually rich.

Disorganized thinking contributes to the formation of delusional thoughts, often of a persecutory nature. The use of physical restraints, bedrails, mechanical ventilators, and catheters, as well as invasive and noninvasive methods of monitoring in the ICU, may contribute to the common delusion that the patient is being imprisoned (Rotondi et al., 2002). While delusions are not universal in delirium, they are reported to occur frequently, in at least 40% of patients (Lipowski, 1990).

Memory is universally impaired in delirium. Disturbances in immediate and short-term memory are typical and intimately related to impairment in attention. Immediate memory is also necessary for orientation to time and place, and delirious patients exhibit disorientation. In mild cases, a patient may demonstrate only disorientation to time (American Psychiatric Association, 2000). Many patients confabulate during episodes of delirium, and directed questions must be used to determine that memory is impaired. These patients will usually fail to remember several unrelated objects (e.g., brown, shirt, and honesty) after a few minutes of distraction. A picture recognition tool can be used to test memory in nonverbal critically ill patients; the patient is shown several pictures of recognizable objects and asked to point out these same pictures when shown a series of pictures again several minutes later (Hart et al., 1996).

Perception, particularly discrimination and integration of new percepts with past ones, is always disturbed to some extent in delirium (Lipowski, 1990). This leads the delirious patient to misinterpret stimuli from the environment (illusions). Delirious ICU patients may misinterpret actions by health-care workers as intended for harm. In some cases, misinterpretation may result in hallucination, although this is not an invariable characteristic of delirium. Hallucinations occur in 40–75% of cases (Lipowski, 1990) and patients younger than 60 years of age may be more likely to report hallucinations than older patients (Robinson, 1956). Visual hallucinations are more common than auditory – a feature contrasting delirium with schizophrenia – and Lilliputian hallucinations are characteristic (Burns et al., 2004). Delirium associated with particular etiologies may lead to hallucinations of a stereotypical nature; for instance, patients in alcohol withdrawal delirium hallucinate small animals and insects, such as spiders, cockroaches, rats, and snakes.

3.2.3. Acute onset with fluctuating course

Delirium develops over a short period of time, most often measured in hours rather than days. Symptoms are often first manifest at night (Lipowski, 1990) and some patients appear normal during daytime hours. As the impairments due to delirium progress, the symptoms may be noted throughout the day and night. However, a defining characteristic of delirium is its fluctuating course, and this is a typical feature of even the most delirious patient's course. Lucid intervals occur unpredictably and are of varying durations.

The ICU is an environment in which the onset of delirium may occur inconspicuously. While the frequent use of sedatives and narcotic analgesics puts critically ill patients at higher risk for the development of delirium (Francis et al., 1990; Schor et al., 1992; Marcantonio et al., 1994b; Pandharipande et al., 2006), a decreased level of arousal is expected in patients treated with these drugs and clinicians may easily overlook symptoms of delirium in this circumstance. It is not uncommon for delirium in a mechanically ventilated and sedated patient to go unrecognized until the weaning period when sedatives are discontinued.

3.2.4. Disturbed sleep–wake cycle

The delirious patient is often sleepy during the day and awake and/or agitated at night. This reversal of the sleep–wake cycle may be partial or complete, although not every patient demonstrates this disturbance and it is not required for the diagnosis of delirium. In some patients the symptoms of delirium are only present at night ('sundowning'). The sleep–wake cycle is often disrupted in the ICU, where environmental cues of night and day are lacking (e.g., diurnal variation of light and noise).

3.2.5. Abnormal psychomotor behavior and autonomic phenomena

The cognitive disturbances of delirium are often accompanied by abnormalities of psychomotor behavior. Patients may demonstrate hyperactive or hypoactive activity. While many critically ill patients are sedated, increased psychomotor activity is not uncommon and may include nonpurposeful movements such as groping and picking or more purposeful activity such as attempting to get out of bed. Alcohol withdrawal delirium, i.e., delirium tremens, is classically associated with hyperactive behavior, but delirium associated with other medical illnesses may be hyperactive as well.

Signs of sympathetic hyperactivity are frequently associated with delirium due to withdrawal from drugs or alcohol and may include psychomotor agitation. Other autonomic phenomena that occur in such patients include tachycardia, hypertension, fever, tremulousness, and diaphoresis.

Psychomotor behavior has become the framework for a commonly used schema for subtyping delirium. Lipowski defines hypoactive and hyperactive subtypes of delirium and notes that a mixed subtype occurs as well (Lipowski, 1987). Patients with hyperactive delirium demonstrate psychomotor agitation, semipurposeful activity, and emotional lability. Tremor, asterixis, and other involuntary movements may be observed. In contrast, patients with hypoactive delirium demonstrate decreased responsiveness and lethargy. Rarely, a patient may be mute or catatonic. While hyperactive and hypoactive delirium appear to occur with equal frequency among non-critically-ill patients (Liptzin and Levkoff, 1992), Peterson et al. found that purely hyperactive delirium was rare (<5% of patients) among 307 medical ICU patients assessed over 2029 patient-days (Peterson et al., 2006). Hypoactive delirium was less frequently observed among mechanically ventilated patients than among nonventilated patients (51% vs 67%, $p = 0.02$), while mixed subtype delirium was more common among ventilated patients (47% vs 29%, $p = 0.008$). Of note, among the patients demonstrating mixed subtype delirium, the behavior observed during the majority of ICU days was hypoactive.

While the significance of the psychomotor subtypes of delirium in critically ill patients remains the subject of ongoing research, clinicians must be aware of the high rate of hypoactive and mixed subtype delirium. The misunderstanding that hyperactivity is a hallmark of delirium will lead to missing the diagnosis of delirium and failing to take measures to prevent possible complications.

3.2.6. Emotional disturbances

The delirious patient may exhibit a variety of emotional disturbances, ranging from euphoria to despair to anger. While not a diagnostic feature of delirium, dysphoria is typical, while other common emotions include fear, anxiety, and depression–apathy (Lipowski, 1990). Just as the cognitive impairment of delirium fluctuates frequently, the emotional state of the delirious patient may rapidly shift. In critically ill patients, the only clue to such shifts may be increased sympathetic activity, e.g., diaphoresis, flushing, and dilated pupils.

3.3. Epidemiology

The reported prevalence rates of delirium in an ICU are highly dependent upon the method(s) of assessment utilized and the population studied. Table 3.2 highlights 21 studies reporting that delirium occurs in 7–87% of ICU patients. When reviewing these studies it is essential to keep in mind the distinction between incident and prevalent delirium. Incident describes any newly occurring case of delirium; incident delirium is not present upon admission to the ICU but occurs at some point during the ICU stay. Prevalent delirium, alternatively, describes those cases of delirium that are present at the first assessment of the patient; it cannot be determined when the delirium began, i.e., with admission to the ICU, admission to the hospital or when the acute illness began prior to admission. As many as 50% of the patients who experience ICU delirium are delirious at admission (McNicoll et al., 2003), and premorbid evaluations are rarely possible, because critical illness is acute and ‘nonelective’. Therefore, the majority of studies have focused on prevalent delirium, and cases of incident and prevalent delirium are combined in Table 3.2 to give an overview of the percentage of all ICU patients who experience delirium.

Early investigations of ICU delirium were limited due to the lack of standardized diagnostic criteria (Hackett et al., 1968; Katz et al., 1972; Wilson, 1972; Holland et al., 1973). In the largest of these early studies, Wilson reviewed the charts of 100 postoperative ICU patients – 50 treated in an ICU with windows and 50 treated in an ICU without windows – and defined delirium as ‘an acute brain syndrome characterized by impairment of orientation, memory, intellectual function, and judgment with lability of affect’ (Wilson, 1972). Delirium was identified in 29% of the cohort (40% in the windowless ICU vs 18% in the ICU with windows, $p < 0.05$). Because of the retrospective design utilized in this study, we

Table 3.2

Reported prevalence of delirium in ICU cohorts

Study	*n*	Population	Delirium measure	Prevalence (%)[†]
Hackett et al., 1968	50	Coronary care	No formal measure	10
Katz et al., 1972	35	Mixed	'Confused', abbreviated MSE	31
Wilson, 1972	100	Surgical	Chart review	29
Holland et al., 1973	32	Medical	Psychiatric interview	13
Kishi et al., 1995	238	Mixed	DSM-III-R	16
Aldemir et al., 2001	818	Surgical	DSM-III-R	11
Bergeron et al., 2001	93	Mixed	Consulting psychiatrist, DSC	16
Dubois et al., 2001	216	Mixed	Psychiatric assessment	19
Ely et al., 2001a	38	Medical	DSM-IV, CAM-ICU	87
Ely et al., 2001b	48	Medical	DSM-IV	60
Ely et al., 2001c	96[‡]	Medical, mechanically ventilated	DSM-IV, CAM-ICU	83
Rincon et al., 2001	96	Mixed	CAM	7
McNicoll et al., 2003	118	Medical, >65 years old	CAM-ICU	62
Ely et al., 2004a	224[‡]	Medical, mechanically ventilated	CAM-ICU	82
Lin et al., 2004	102	Medical, mechanically ventilated	DSM-IV, CAM-ICU	22
Roberts, 2004	73	Mixed, in the ICU >72 h	No formal measure	40
Skrobik et al., 2004	1009	Mixed	DSC, DSM-IV	21
McNicoll et al., 2005	22	Medical, >65 years old	CAM	68
Micek et al., 2005	66[‡]	Medical	CAM-ICU	67
Pandharipande et al., 2005	100	Surgical and trauma	CAM-ICU	69
Thomason et al., 2005	261	Medical, nonventilated	CAM-ICU	48

Studies of postcardiotomy delirium are not displayed.
[†]Overall rate of delirium during the ICU stay (includes incident and prevalent cases).
[‡]Patients with persistent coma excluded.
CAM, Confusion Assessment Method; CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; DSC, Delirium Screening Checklist; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICU, intensive care unit; MSE, mental status examination.

cannot conclude that the lack of windows was responsible for the higher incidence of delirium.

Even with the use of standardized criteria (i.e., DSM criteria), a broad range of ICU delirium prevalence rates has been reported in the past 10 years. Much of this variation can be explained by the different patient populations studied. Specifically, those investigations focusing on the evaluation of medical ICU patients have reported a high rate of delirium, ranging from 22% to 87% (Ely et al., 2001a, 2001b, 2001c; McNicoll et al., 2003; Ely et al., 2004a; Lin et al., 2004; McNicoll et al., 2005; Micek et al., 2005; Thomason et al., 2005). Alternatively, cohorts including patients from surgical or mixed (surgical and medical) ICUs have reported that delirium occurs in 7–69% of patients (Kishi et al., 1995; Aldemir et al., 2001; Bergeron et al., 2001; Dubois et al., 2001; Rincon et al., 2001; Roberts, 2004; Skrobik et al., 2004; Pandharipande et al., 2005). A higher severity of illness amongst medical ICU patients, as compared to surgical ICU patients, may explain the higher delirium rates seen in these ICUs. Notably, only two of the eight studies that included surgical ICU patients reported a delirium rate over 20%; one of these excluded patients whose ICU length of stay was less than 72 hours, namely those patients with uncomplicated postoperative courses (Roberts, 2004), while the other had a mean APACHE II score of 23.6, indicating a high severity of illness (Pandharipande et al., 2005). Delirium occurred in 40% and 69% of the patients in these two cohort studies, respectively, while the remaining six cohorts that included surgical and mixed ICU patients reported that delirium occurred in 7–19% of patients.

3.4. Risk factors

Numerous factors have been identified that increase the risk of delirium in hospitalized patients. Although most of the research evaluating risk factors for delirium was performed using non-ICU cohorts (Table 3.3) (Francis et al., 1990; Schor et al., 1992; Inouye et al., 1993; Marcantonio et al., 1994b), several studies of ICU patients have reported results similar to studies of non-ICU patients (Table 3.4) (Wilson, 1972; Aldemir et al., 2001; Dubois et al., 2001; McNicoll et al.,

Table 3.3

Risk factors for delirium identified in non-ICU cohorts

Baseline characteristics	Features of acute illness	Iatrogenic factors
Hearing or vision impairment		Immobilization (e.g., catheters, restraints)
Alcohol abuse		
Depression		

Factors identified in both non-ICU cohorts and ICU cohorts are listed in Table 3.4.

Table 3.4

Risk factors for delirium identified in ICU cohorts

Baseline characteristics	Features of acute illness	Iatrogenic factors
Increasing age	Severity of illness	Medications (e.g., narcotics, benzodiazepines)
Cognitive impairment	Infection	
Hypertension	Respiratory disease	
Smoking	Metabolic disturbances (e.g., Na, Ca, BUN, bilirubin)	
	Acidosis	
	Anemia	
	Fever	
	Hypotension	

BUN, blood urea nitrogen; Ca, calcium; Na, sodium.

2003) and it is generally accepted that factors that increase a patient's risk for delirium in the non-ICU setting will do so in the ICU as well.

While one taxonomy divides delirium risk factors into predisposing/vulnerability factors and precipitating/facilitating factors (Inouye and Charpentier, 1996), we classify them further into baseline (host) characteristics, features of acute illness, and iatrogenic (or environmental) factors (Tables 3.3 and 3.4). This scheme allows the clinician to quickly identify those factors that are most amenable to modification, namely the iatrogenic/environmental factors (and some of the features of acute disease).

The ICU is an environment in which a high percentage of delirium risk factors coincide. When hospitalized patients are stratified into risk groups depending on the number of delirium risk factors present, those with three or more risk factors have at least a 60% risk of developing delirium (Francis et al., 1990; Inouye and Charpentier, 1996). Remarkably, nearly all critically ill patients have at least three risk factors for delirium. In a study of 53 consecutive medical ICU patients, Ely et al. found that the mean number ($\pm$ standard deviation) of delirium risk factors identified per patient was 11 $\pm$ 4 (range, 3–17) (Ely et al., 2001a).

One risk factor almost universally experienced during critical illness is exposure to psychoactive medications, typically in the form of sedatives and analgesics. In their cohort, Ely et al. identified exposure to benzodiazepines or narcotics in 98% of patients (Ely et al., 2001a). In a study of 198 mechanically ventilated patients, Pandharipande et al. found that lorazepam was an independent risk factor for daily transition to delirium (odds ratio (OR), 1.2 per mg; 95% confidence interval (CI), 1.0–1.4; $p = 0.003$) after adjusting for 11 covariates (Pandharipande et al., 2006). Additionally, Dubois et al. analyzed risk factors for delirium in 198 surgical ICU patients and found that morphine was the strongest predictor of delirium in a multivariate model (OR between 6 and 9.2 depending on dose) (Dubois et al., 2001). The association between psychoactive medications and delirium demonstrated in these studies of critically ill patients has been extensively studied in non-ICU cohorts. Francis et al. studied 229 older hospitalized patients and found that the use of psychoactive medications (defined as narcotics, sedative–hypnotics, and minor tranquilizers) independently predicted the development of delirium (adjusted OR, 3.9; 95% CI, 1.4–10.8) (Francis et al., 1990). In a similar study of 325 older hospitalized patients, Schor et al. divided psychoactive medications into neuroleptics, narcotics, benzodiazepines, and anticholinergics. On multivariate analyses, neuroleptic use (OR, 4.48; 95% CI, 1.82–10.45) and narcotic use (OR, 2.54; 95% CI, 1.24–5.18) were independently associated with delirium (Schor et al., 1992). Finally, in postoperative patients, Marcantonio et al. reported that delirium was significantly associated with exposure to meperidine (OR, 2.7; 95% CI, 1.3–5.5) and to benzodiazepines (OR, 3.0; 95% CI, 1.3–6.8) (Marcantonio et al., 1994b).

Numerous other medications have been reported to cause delirium (Table 3.5). Many of these are frequently utilized in the ICU, but no systematic study of ICU patients has evaluated the association of most of these medications with delirium. It is important to note, however, that delirium may occur as an idiosyncratic reaction to medication and health-care workers should not quickly dismiss the possibility that a medication is responsible, in part, for the development of delirium in a critically ill patient simply because of

Table 3.5

Medications reported to cause delirium

Medications frequently used in the ICU	Other medications
Benzodiazepines (e.g., lorazepam)	H_1 blockers (e.g., diphenhydramine)
Narcotics (e.g., morphine)	Antiparkinsonian agents (e.g., levodopa)
Antipsychotics (e.g., haloperidol)	Tricyclic antidepressants (e.g., amitriptyline)
H_2 blockers (e.g., ranitidine)	Warfarin
Nonsteroidal anti-inflammatory drugs (e.g., ibuprofen)	Digoxin
Promethazine	Theophylline
Antibiotics (e.g., ceftriaxone)	Nifedipine
Phenytoin	Oxybutynin
Corticosteroids (e.g., methylprednisolone)	Isosorbide dinitrate
Furosemide	Captopril

the lack of a strong association in studies evaluating delirium risk factors.

With patients older than 65 years of age incurring nearly 60% of all ICU days (Angus et al., 2000), the relationship between age and delirium is of vital importance to critical care practitioners. Several large studies in non-ICU cohorts have demonstrated that increasing age is an independent risk factor for delirium (Schor et al., 1992; Marcantonio et al., 1994a) as did one recent study of ICU patients (Pandharipande et al., 2006). This relationship however, has not been demonstrated in the several other studies that have evaluated delirium risk factors in ICU patients. There are several possible explanations for this. In the only study of risk factors for delirium in SICU patients, Aldemir et al. reported a significant difference in age between patients with delirium and those without (48.9 ± 18.1 vs 38.5 ± 13.8 years, $p = 0.000$), but this association was not significant upon multivariable analysis (Aldemir et al., 2001). The mean age in this study was significantly lower than that seen in the general population of critically ill patients, and inclusion of older patients may have revealed the independent association between age and delirium seen in non-ICU studies. Dubois et al. similarly reported that age was not associated with delirium in a study of general ICU patients, but the incidence of delirium in their study was low (11%) and the study may have been underpowered to assess for this association (Dubois et al., 2001). As age is a significant risk factor for delirium in multiple non-ICU cohort studies, it is likely that large prospective studies of ICU patients will confirm the findings of the single ICU study that showed age to be an important risk factor for delirium in critically ill patients.

Multiple studies of both ICU and non-ICU patients have demonstrated that a variety of metabolic derangements are associated with the development of delirium (Francis et al., 1990; Inouye et al., 1993; Marcantonio et al., 1994a; Aldemir et al., 2001; Dubois et al., 2001). While hyponatremia and azotemia are most commonly cited, hyperbilirubinemia, hypocalcemia, hyper- and hypoglycemia, and metabolic acidosis have all been reported as risk factors for delirium. Each of these factors is likely in critically ill patients, with abnormalities of sodium and glucose occurring in up to 50% of ICU patients (Ely et al., 2001a).

Immobilization resulting from the use of restraints, catheters, and mechanical ventilation is an almost universal aspect of the critical care experience. Although studies of ICU patients have not evaluated the relationship of this factor of ICU care to the development of delirium, an association has been noted in non-ICU cohorts (Inouye and Charpentier, 1996) and interventions resulting in the immobilization of critically ill patients should be limited to those of absolute necessity.

Infection was the most common etiology associated with delirium in a study of 229 hospitalized older patients (Francis et al., 1990), and the association between infection and delirium has been confirmed in multiple studies including one of ICU patients (Aldemir et al., 2001). This relationship should not simply be attributed to the hypotension that complicates the course of many critically ill septic patients; multivariable models of delirium risk factors demonstrate that infection and shock are independent risk factors in both ICU and non-ICU patients.

Other factors that may play a role in the development of delirium in ICU patients include dementia, hearing or vision impairment, alcohol abuse, and depression. McNicoll and colleagues studied 180 consecutive ICU patients aged 65 and older and documented that patients with dementia were 40% more likely to develop delirium than those without dementia, even after controlling for comorbidity, baseline functional status, severity of illness, and invasive procedures (RR, 1.4; 95% CI, 1.1–1.7) (McNicoll et al., 2003). While no study of ICU patients has evaluated the association between hearing or vision impairment and delirium, Wilson et al. reported that patients in an ICU without windows were significantly more likely to develop delirium than those in an ICU with windows (Wilson, 1972). Additional studies are needed to fully elucidate the effect of various factors on the development of delirium.

3.5. Pathophysiology

The pathophysiology of delirium remains poorly understood and the complex role that critical illness plays in the pathogenesis of delirium has not been studied. Several hypotheses have been outlined in detail, with most attempting to explain delirium as a behavioral manifestation of a 'widespread reduction of cerebral oxidative metabolism and imbalance of neurotransmission' (Lipowski, 1990).

Based on a series of investigations in which they evaluated delirious patients using electroencephalography (EEG), Engel and Romano postulated that delirium is a state of 'cerebral insufficiency', i.e., a global failure of cerebral oxidative metabolism (Engel and Romano, 1959). Their work showed that delirium is associated with diffuse slowing on EEG, a finding felt to represent a reduction in brain metabolism. This was supported by studies showing that hypoxia and hypoglycemia, both of which frequently occur in critical illness, produce slowing of the EEG (Engel and Romano, 1959). Such EEG changes are very nonspecific and can be produced by numerous toxic and metabolic disorders, including sepsis, many of which are known causes of delirium (Young, 2000).

The tendency of belladonna alkaloids to cause delirium has been recognized for centuries (Forbes, 1977) and this association led to the hypothesis that cholinergic blockade plays a role in the pathogenesis of delirium. Numerous studies in the 1960s showing that various anticholinergic agents induce delirium when administered to healthy volunteers supported this hypothesis. Atropine, scopolamine, and ditran (a congener of the piperidyl benzilates) all induce delirium associated with typical EEG findings in normal volunteers (Ketchum et al., 1973). Blass and colleagues provided a possible link between the state of cerebral insufficiency proposed by Engel and Romano and the hypothesis of cholinergic blockade by suggesting that impaired oxidative metabolism in the brain results in a cholinergic deficiency (Blass et al., 1981). The finding that hypoxia impairs acetylcholine synthesis supports this hypothesis (Gibson et al., 1981) and possibly explains the increased susceptibility of many critically ill patients to delirium.

The development of a functional competitive binding assay for serum anticholinergic activity (SAA) by Tune and Coyle (1980) led to additional work supporting the role of cholinergic blockade in the pathophysiology of delirium. Using this assay, studies have shown an association between elevated SAA and delirium in older medical inpatients (Mach et al., 1995; Flacker et al., 1998), postoperative patients (Tune et al., 1981), and surgical ICU patients (Golinger et al., 1987). To date, however, no large prospective investigation has evaluated the association of SAA and delirium in critically ill patients, a population at high risk for exposure to numerous medications with anticholinergic properties.

It is likely that endogenous anticholinergic substances exist and play a pathogenic role in delirium. This would explain the inability of some epidemiological studies to show a significant association between anticholinergic medications and delirium in medical (Francis and Kapoor, 1992) and surgical patients (Marcantonio et al., 1994b), despite the association of SAA and delirium found consistently. Flacker et al. evaluated 10 older medical inpatients who were carefully screened for evidence of exposure to anticholinergic medications. Despite the lack of such exposure, eight of the patients had significantly elevated SAA (Flacker and Wei, 2001), suggesting that cholinergic blockade was occurring as the result of an endogenous substance. Six of the eight patients with elevated SAA levels were acutely ill with infectious diseases, and another study showed that SAA levels decline with the resolution of an acute febrile illness (Flacker and Lipsitz, 1999), suggesting that the inflammatory state induced by an acute infection may play a role in cholinergic blockade.

Additional evidence supporting the role of inflammation in the pathogenesis of delirium comes from multiple studies documenting the occurrence of delirium in cancer patients treated with high doses of interleukin (IL)-2 (Rosenberg et al., 1989). This proinflammatory cytokine causes delirium in up to 50% of patients (Denicoff et al., 1987), and it induces increased latency and decreased amplitude on event-related evoked potentials (Caraceni et al., 1993), findings felt to indicate cholinergic blockade (Hammond et al., 1987). The effects of systemic inflammatory cytokines such as IL-2 on the brain are probably mediated by activation of vascular endothelial cells and perivascular cells in the brain itself (Uchikado et al., 2004).

Although significant attention has been directed toward the relationship between cholinergic blockade and delirium, it is unlikely that a single neurochemical aberration accounts for all cases of ICU delirium, a syndrome that is associated with numerous, varying risk factors. In fact, derangements of several other neurotransmitters have been implicated in delirium, including dopamine, glutamate, gamma-aminobutyric acid (GABA), and serotonin (Trzepacz, 1999). Dopamine may act in a way that is reciprocal to the actions of acetylcholine, with an increase in dopamine contributing to delirium (Trzepacz, 1996). For example, opiate analgesics, risk factors for delirium that

are frequently used in ICUs, increase dopamine activity while decreasing acetylcholine activity; hypoxia, in addition to reducing acetylcholine synthesis, increases dopamine release (Broderick and Gibson, 1989). While it has been shown that dopamine agonists cause EEG slowing and behavioral arousal in rats (Ongini et al., 1985), few studies have directly evaluated the relationship between dopamine and ICU delirium.

Glutamate, an excitatory amino acid neurotransmitter, is elevated in patients with sepsis-associated encephalopathy, a common type of ICU delirium, and this increase is felt to play a central role in the pathogenesis of brain dysfunction in patients with sepsis (Wilson and Young, 2003). In such patients, glutamate may be elevated in response to numerous stimuli, including lipopolysaccharide, interferon-γ, hypoxia, and hypoglycemia. Elevated glutamate concentrations, in turn, lead to neuronal injury via activation of *N*-methyl D-aspartate (NMDA)-type glutamatergic receptors (Wilson and Young, 2003).

It has been suggested that cortisol and beta-endorphins may play a role, but only preliminary evidence exists (McIntosh et al., 1985). In fact, there remain many unexplored hypotheses, and the high prevalence and marked severity of delirium in critically ill patients makes the ICU an ideal setting for future investigations regarding its pathogenesis. Future studies must face the challenge presented by the likelihood that multiple mechanisms play a role in the pathogenesis of delirium in the diverse population of critically ill patients. For instance, the pathophysiology underlying sepsis-associated encephalopathy is probably different from that underlying sedative-induced delirium or hepatic encephalopathy. Numerous risk factors lead to the development of delirium in critically ill patients and numerous mechanisms are probably initiated or exacerbated by these factors. Future research is needed to understand these complex interactions.

3.6. Diagnosis and diagnostic instruments

Despite occurring frequently in critically ill patients, delirium often goes unrecognized. This omission has been documented in emergency rooms (Kakuma et al., 2003) and inpatient wards (Inouye et al., 2001), and 80% of 912 ICU practitioners surveyed acknowledged underdiagnosis of delirium in the ICU despite their agreement that ICU delirium is a significant problem (Ely et al., 2004b). Although the effect of this oversight has not been studied in critically ill patients, Kakuma et al. reported that nondetection of delirium in patients discharged from the emergency room was independently associated with a sevenfold increase in the risk of 6-month mortality (HR, 7.24; 95% CI, 1.62–32.35) (Kakuma et al., 2003).

As stated above (see section 3.2), the diagnostic criteria for delirium are detailed in the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2000), and these criteria remain the gold standard for the diagnosis of delirium. However, familiarity with these criteria and experience in their application is often not within the armamentarium of the critical care practitioner, and a formal psychiatric consultation and evaluation may not be immediately available. Additionally, because of the fluctuating course of delirium, such an evaluation at a single point in time during the patient's ICU stay may result in failure to diagnose delirium despite its occurrence. Therefore, critical care nurses and physicians should use brief, reliable, validated instruments that can be repeated over time during a patient's ICU stay to evaluate for delirium. Several such instruments have been developed to allow nonpsychiatrists to make a formal diagnosis of delirium (American Psychiatric Association, 1999). Among the many validated delirium assessment instruments available, only the Cognitive Test for Delirium (Hart et al., 1996, 1997), the Intensive Care Delirium Screening Checklist (Bergeron et al., 2001) and the Confusion Assessment Method for the ICU (Ely et al., 2001b, 2001c) were designed specifically for the evaluation of intubated ICU patients, an essential feature for use in the ICU where up to 80% of patients are nonverbal because of endotracheal intubation (Bergeron et al., 2001).

The Cognitive Test for Delirium (CTD) was evaluated in a study of 22 nonconsecutive medical ICU patients diagnosed with delirium according to the DSM-III-R criteria (Hart et al., 1996). Because the CTD takes 10–15 minutes to administer, Hart and colleagues developed an abbreviated CTD and evaluated it in 19 delirious patients (15 were ICU patients) (Hart et al., 1997). The abbreviated CTD takes only a few minutes to administer and was shown to discriminate between delirium, dementia, schizophrenia, and depression ($p < 0.0001$). However, the CTD has not been evaluated in a study of consecutive ICU patients to determine its validity in a cohort including delirious and nondelirious ICU patients.

The Intensive Care Delirium Screening Checklist was studied in 93 consecutively admitted ICU patients who were also evaluated by a consulting psychiatrist who served as the reference standard rater (Bergeron et al., 2001). The Checklist consists of eight items (either present or absent) so that each assessment results in a score from 0–8 (Table 3.6). Of the patients studied, 15 (16%) were diagnosed with delirium by the reference standard

Table 3.6

The Intensive Care Delirium Screening Checklist

Altered level of consciousness
Inattention
Disorientation
Hallucination – delusion – psychosis
Psychomotor agitation or retardation
Inappropriate speech or mood
Sleep/wake cycle disturbance
Symptom fluctuation

Each feature is given a score of 0 (absent) or 1 (present) and the points are added for a total score.
Source: data from Bergeron et al., 2001.

rater, and a cutoff score of 4 was estimated to have a sensitivity of 99% and specificity of 64%. The authors concluded that the instrument was most appropriately used as a screening tool due to the high sensitivity for delirium.

The Confusion Assessment Method for the ICU (CAM-ICU) is the only delirium assessment tool designed for use in intubated ICU patients that has been validated against a reference standard rater in three separate cohorts of mechanically ventilated ICU patients (Ely et al., 2001b, 2001c; Lin et al., 2004). The instrument was modified from the Confusion Assessment Method (Inouye et al., 1990) and consists of four key features derived from the *Diagnostic and Statistical Manual of Mental Disorders*, including 1) change in mental status from baseline or a fluctuating course of mental status, 2) inattention, 3) disorganized thinking, and 4) an altered level of consciousness (Table 3.7). Delirium is diagnosed (i.e., the patient is 'CAM-ICU-positive') when features 1 and 2 are present along with either feature 3 or 4. The CAM-ICU was evaluated by Ely et al. in 2 cohorts of 38 and 111 consecutively admitted medical ICU patients and was shown to have high sensitivity (93–100%), specificity (89–100%), and inter-rater reliability (κ, 0.96; 95% CI, 0.92–0.99) (Ely et al., 2001b, 2001c). The CAM-ICU has been translated into numerous languages (e.g., Spanish, Portuguese, French, Dutch, Swedish, Greek, Italian, and Chinese) and Lin et al. confirmed its high reliability and validity in another language and region of the world (Lin et al., 2004).

The Confusion Assessment Method (CAM) (Inouye et al., 1990), a sensitive (94–100%), specific (90–100%), and reliable instrument intended for use in the clinical evaluation of hospitalized, elderly medical and surgical patients, is the most widely used delirium assessment instrument and it may be useful in the evaluation of verbal ICU patients. McNicoll and colleagues compared the CAM to the CAM-ICU in a study of 22 alert, nonintubated ICU patients (McNicoll et al., 2005). The two instruments agreed 82% of the time, with the CAM identifying delirium in four patients that the CAM-ICU did not. The applicability of this study to the care of ICU patients is limited, however, by the lack of a reference standard in this study, i.e., no formal psychiatric assessments based on DSM-IV-TR criteria were made. Additionally, the frequent use of sedation, analgesia, and mechanical ventilation in ICU patients calls into question the widespread applicability of this study, which excluded patients who were stuporous (McNicoll et al., 2005).

Other instruments that have been validated in non-ICU cohorts have been reviewed elsewhere (Breitbart et al., 1997; Rapp et al., 2000). These include the Delirium Rating Scale (Trzepacz et al., 1988), Delirium Symptom Interview (Albert et al., 1992), Memorial Delirium Assessment Scale (Breitbart et al., 1997), NEECHAM Confusion Scale (Neelon et al., 1996), Confusional State Evaluation (Robertsson et al., 1997), and Delirium Inventory (McCusker et al., 1998).

As a high percentage of critically ill patients experience delirium and are exposed to numerous delirium risk factors, it is often difficult or impossible to attribute the development of ICU delirium to one specific etiology. However, careful attention must be directed to every ICU patient with delirium and a focused evaluation may be warranted when the history, examination and/or routine labs and imaging suggest that a specific etiology is responsible for delirium. Examples include drug screens prompted by signs or symptoms of intoxication or withdrawal, blood cultures prompted by new fever, lumbar puncture prompted by signs or symptoms of meningitis, ammonia prompted by a history of cirrhosis, and EEG prompted by a history of seizures. An exhaustive list of the tests indicated by a given clinical scenario is beyond the scope of this chapter, but knowledge of these tests and their indications should be part of the armamentarium of every critical care practitioner.

3.7. Course and prognosis

Lipowski outlined five possible outcomes following an episode of delirium: 1) full recovery, 2) progression to stupor and coma, or death, 3) a transitional cognitive, affective, behavioral, or mixed abnormality and gradual full recovery, 4) progression to an irreversible mental syndrome, and 5) post-traumatic stress syndrome (Lipowski, 1990). In ICU patients as well as non-ICU patients, full recovery is the most common outcome. This fact has led many critical care clinicians to mistakenly assume that delirium in the ICU is inconsequential – i.e., that the 'ICU syndrome' is an

Table 3.7

The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) Worksheet

Feature 1: Acute Onset or Fluctuating Course	**Positive**	**Negative**
Positive if you answer 'yes' to either 1A or 1B.		
	Yes	**No**
1A: Is the pt different from his/her baseline mental status?		
or		
1B: Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (e.g., RASS), GCS, or previous delirium assessment?		
Feature 2: Inattention	**Positive**	**Negative**
Positive if score for either 2A or 2B is less than 8.		
Attempt the ASE Letters first. If the patient is able to perform this test and the score is clear, record this score and move to Feature 3. If the patient is unable to perform this test or the score is unclear, then perform the ASE Pictures. If you perform both tests, use the ASE Pictures results to score the Feature.		
2A: ASE Letters: record score (enter NT for not tested)	**Score (out of 10): ___**	
Directions: Say to the patient, *'I am going to read you a series of 10 letters. Whenever you hear the letter "A", indicate by squeezing my hand.'* Read letters from the following letter list in a normal tone.		
S A V E A H A A R T		
Scoring: Errors are counted when patient fails to squeeze on the letter 'A' and when the patient squeezes on any letter other than 'A'.		
2B: ASE Pictures: record score (enter NT for not tested)	**Score (out of 10): ___**	
Directions are included on the picture packets.		
Feature 3: Disorganized Thinking	**Positive**	**Negative**
Positive if the combined score is less than 4		
3A: Yes/No Questions	**Combined score (3A + 3B): ____ (out of 5)**	
(Use either Set A or Set B and alternate on consecutive days if necessary):		
Set A / **Set B**		
1. Will a stone float on water? / 1. Will a leaf float on water?		
2. Are there fish in the sea? / 2. Are there elephants in the sea?		
3. Does 1 pound weigh more than 2 pounds? / 3. Do 2 pounds weigh more than 1 pound?		
4. Can you use a hammer to pound a nail? / 4. Can you use a hammer to cut wood?		
Score ___ (Patient earns 1 point for each correct answer out of 4)		
3B: Command		
Say to the patient: 'Hold up this many fingers' (Examiner holds two fingers in front of patient). 'Now do the same thing with the other hand' (Not repeating the number of fingers). If pt is unable to move both arms, for the second part of the command say to the patient 'Add one more finger'.		
Score___ (Patient earns 1 point if able to successfully complete the entire command)		
Feature 4: Altered Level of Consciousness	**Positive**	**Negative**
Positive if the actual RASS score is anything other than '0' (zero)		
Overall CAM-ICU (Features 1 and 2 and either Feature 3 or 4):	**Positive**	**Negative**

ASE, Attention Screening Examination; GCS, Glasgow Coma Score; RASS, Richmond Agitation-Sedation Scale.
The ASE Pictures is used when the patient is unable to perform the ASE Letters and utilizes a series of pictures provided in the CAM-ICU training manual available at www.icudelirium.org.

expected consequence of the treatment of critically ill patients that is not independently associated with long-term adverse outcomes (McGuire et al., 2000). Recent studies have proved this line of thinking to be false.

In the acute setting, delirium is associated with multiple complications during the ICU stay. Confusion and a reduced level of consciousness put the delirious patient at increased risk of developing, or causing, complications of the complex monitoring and management strategies used in the ICU. Dubois et al. reported that 10% of delirious patients studied in a medical/surgical ICU self-extubated as compared to 2.3% of non-delirious patients ($p = 0.02$) (Dubois et al., 2001). Delirium was also associated with an increased rate of removal of catheters (20% vs 5.7% in nondelirious patients, $p = 0.003$) (Dubois et al., 2001). Although no study to date has specifically evaluated the association between delirium and failed extubation rates, it is likely that the altered mental status occurring in delirious ICU patients puts them at high risk for this complication. In fact, abnormal mental status was a significant predictor of failed extubation in studies of neurosurgical (Namen et al., 2001) and medical ICU patients (Salam et al., 2004). Namen et al. defined altered mental status according to Glasgow Coma Scale scores that independently predicted extubation failure ($p < 0.0001$) (Namen et al., 2001), while Salam et al. reported that inability to complete four simple tasks was independently associated with a 4.3 times higher risk of failed extubation as compared to the ability to do so (95% CI, 1.8–10.4) (Salam et al., 2004).

Several studies have shown that ICU delirium is independently associated with prolonged ICU and hospital stays. In a study of 238 ICU patients, Kishi et al. reported that the median ICU length of stay was statistically longer for delirious patients than for nondelirious patients (15 vs 5, respectively; $p = 0.0001$), despite the fact that the duration of delirium only represented a third of the time spent in the ICU (median duration of delirium, 5 days) (Kishi et al., 1995). Ely et al. studied 48 medical ICU patients and used multivariable analysis to determine the independent association of delirium with hospital length of stay (Ely et al., 2001a). After adjusting for severity of illness, age, gender, race, and days of benzodiazepine and narcotic drug administration, delirium was the strongest predictor of hospital length of stay ($p = 0.006$). These results were confirmed in two large follow-up studies. The first study evaluated 275 mechanically ventilated medical ICU patients and found that delirium was independently associated with longer hospital stays (adjusted hazard ratio (HR), 2.0; 95% CI, 1.4–3.0; $p < 0.001$) (Ely et al., 2004a). The second study evaluated 261 nonventilated medical ICU patients and showed that delirious patients were 41% more likely to stay in the hospital on any given day than nondelirious patients, again after adjusting for severity of illness, age, gender, race, coma, and comorbidities (HR, 1.41; 95% CI 1.05–1.89; $p = 0.023$) (Thomason et al., 2005).

As expected for a complication that increases length of stay, delirium in the ICU has been shown to increase costs. In a study of mechanically ventilated medical ICU patients, Milbrandt et al. found that patients who developed delirium at any time during their ICU stay incurred significantly higher ICU and hospital costs than those who never developed delirium (Milbrandt et al., 2004). The increase in median ICU costs in patients with delirium was more than $9000 per patient.

While studies of non-ICU hospitalized patients have demonstrated an increased risk for death in the 1- and 2-year period following hospital discharge (Francis and Kapoor, 1992; McCusker et al., 2002), several studies of delirium in ICU patients failed to show an association between delirium and in-hospital mortality (Kishi et al., 1995; Dubois et al., 2001; Micek et al., 2005). However, when survivors of critical illness were followed up to 6 months after hospital discharge, ICU delirium was independently associated with mortality. Ely et al. prospectively evaluated 275 mechanically ventilated medical ICU patients for the development of delirium and found that delirium was independently associated with a threefold increase in the risk of death at 6 months after adjusting for age, severity of illness, comorbid conditions, coma, and the use of sedatives and analgesics (adjusted HR, 3.2; 95% CI, 1.4–7.7; $p = 0.008$) (Fig. 3.1) (Ely et al., 2004a). Lin et al. confirmed these findings in a study of 102 mechanically

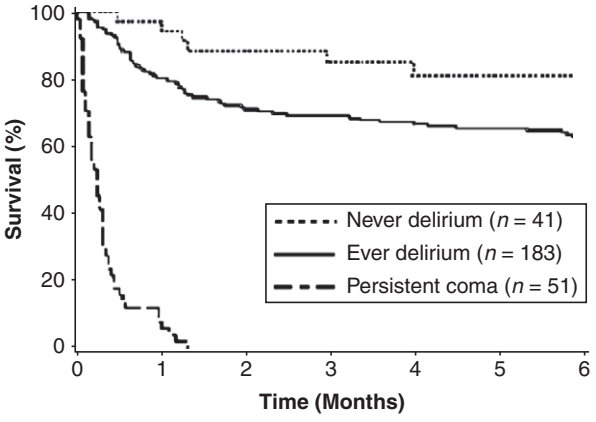

Fig. 3.1. Kaplan–Meier Analysis of Delirium in the Intensive Care Unit and 6-Month Survival. Adapted from Ely et al., 2004a. Copyright © 2004, American Medical Association. All rights reserved.

ventilated ICU patients (OR for delirium-associated mortality, 13.0; 95% CI, 2.69–62.91) (Lin et al., 2004).

Even for those patients who survive critical illness, delirium may increase the risk of long-term comorbidities. Specifically, studies of non-ICU patients have shown that delirium is an independent risk factor for the development of long-term cognitive impairment. Jackson et al. reviewed nine prospective studies evaluating a total of 1885 hospitalized medical and surgical patients and found that delirium was associated with the development of dementia over 1–3 years from the time of hospital discharge (Jackson et al., 2004). Although the only published study evaluating this relationship in survivors of critical illness did not show a statistically significant association, only 41 patients were evaluated and the study was not powered to detect an association between ICU delirium and long-term cognitive impairment (Jackson et al., 2003). Analogous to the high prevalence of delirium among ICU patients as compared to non-ICU hospitalized patients, several studies have documented a remarkably high incidence of cognitive impairment after critical illness, ranging from 25% to 78% depending on the population studied and the definition of impairment used (Hopkins and Brett, 2005). In light of these findings, large prospective cohort studies are ongoing in an attempt to identify risk factors for long-term cognitive impairment following critical illness with ICU delirium as the primary factor of interest.

3.8. Approaches to prevention and treatment of delirium

The intensive care unit arose out of the realization that specialized, multidisciplinary care can result in improved outcomes for patients with a high severity of illness attributable to disease processes affecting multiple organs. Delirium in such patients should prompt a multifaceted plan of prevention and treatment that includes eliminating modifiable risk factors, performing frequent delirium assessments and using pharmacologic therapies thought to treat delirium when it is identified.

3.8.1. Prevention and nonpharmacologic strategies

Although no study published to date has focused on the prevention of delirium in critically ill patients, numerous modifiable risk factors are common to patients in both the ICU and the general hospital ward. Therefore, several clinical trials that have evaluated multicomponent interventions designed to prevent delirium in hospitalized patients may have applicability to the critically ill population (Inouye et al., 1999; Marcantonio et al., 2001; Lundstrom et al., 2005).

In the largest of these studies, Inouye et al. studied 852 patients older than 70 years of age who were hospitalized with a variety of medical illnesses (Inouye et al., 1999). Patients were prospectively admitted to an intervention unit or usual-care units, and the intervention protocol included repeated reorientation with information boards and health-care worker communication, cognitively stimulating activities multiple times daily, a nonpharmacologic sleep protocol enhanced by a sleep-friendly environment, frequent ambulation and exercise, visual and hearing aids, and vigilant volume repletion to prevent dehydration. Those patients in the intervention group had a significantly lower incidence of delirium as compared to controls (9.9% vs 15%, $p = 0.02$) as well as a shorter duration of delirium (Inouye et al., 1999). Although there was no sustained benefit noted in clinical outcomes at 6 months following hospital discharge in the cohort as a whole, subgroup analysis revealed that high-risk patients in the intervention group had better self-rated health and functional status than high-risk patients in the control group (Bogardus et al., 2003).

As delirium complicates the course of a higher percentage of ICU patients than of non-critically-ill patients, and the average ICU patient is exposed to as many as 10 delirium risk factors (see section 3.4), it is likely that ICU patients will benefit from preventive strategies. Despite the lack of clinical trials evaluating primary prevention of delirium in critically ill patients, the approach to care used by Inouye et al. should form the basis of nonpharmacologic attempts to prevent delirium in ICU patients: frequent reorientation, restoration of the sleep–wake cycle, minimization of unnecessary stimuli, early mobilization and physical therapy, and judicious use of sedatives with frequent interruptions as tolerated.

3.8.2. Pharmacologic treatment

Despite these efforts, a significant percentage of ICU patients will develop delirium, and it is imperative that critical care clinicians recognize the significance of newly developed delirium. As this syndrome is often a sign of an acute change in a patient's clinical course, abrupt changes in mental status should alert the critical care team to evaluate the ICU patient for shock, hypoxia, hypercarbia, hypoglycemia, or other metabolic derangements. After the rapid evaluation and treatment of these life-threatening problems, attention can be turned toward the treatment of delirium.

Pharmacological management of delirium is frequently attempted in the ICU. Of 912 critical care practitioners surveyed, 717 (79%) reported that delirium requires active intervention (Ely et al., 2004b),

and two-thirds considered haloperidol to be the treatment of choice. This reflects the recommendations of both the Society of Critical Care Medicine (Jacobi et al., 2002) and the American Psychiatric Association (1999). There are no placebo-controlled trials to confirm the efficacy of haloperidol and there remain no drugs with an FDA approval for the treatment of delirium, so these recommendations were based on numerous case series, uncontrolled trials, and a small number of randomized trials comparing haloperidol to benzodiazepines or other neuroleptics.

The superiority of haloperidol over lorazepam for the treatment of delirium was demonstrated in a randomized, double-blind trial by Breitbart and colleagues (1996). They studied 244 hospitalized AIDS patients and randomized to treatment those who met DSM-III criteria for delirium as well as exceeded a threshold score on the Delirium Rating Scale (DRS) ($n = 30$). Treatment with haloperidol or chlorpromazine resulted in improvement of delirium symptoms as measured by the DRS, while lorazepam was ineffective ($p < 0.001$) (Breitbart et al., 1996). Additionally, the efficacy of haloperidol has been compared to risperidone, an atypical antipsychotic, in a double-blind trial in which 28 non-ICU patients diagnosed with delirium according to DSM-III-R criteria were randomized to treatment. Mean Memorial Delirium Assessment Scale scores decreased significantly in both treatment groups during the study period ($p < 0.05$), but no difference in scores was noted between the haloperidol group and the risperidone group ($p = 0.51$) (Han and Kim, 2004).

Only one clinical trial published to date has evaluated the efficacy of treatment with antipsychotics for delirium in critically ill patients (Skrobik et al., 2004). Skrobik et al. used an unblinded, pseudorandomized study design to evaluate the efficacy and safety of olanzapine compared with haloperidol (both in enteral form) in the treatment of 73 ICU patients diagnosed with delirium according to DSM-IV criteria. A statistically significant reduction in daily Delirium Index scores was seen in both treatment groups (ANOVA time effect, $p = 0.02$), but there was no difference between treatment groups (group effect, $p = 0.83$). Although the trial was not powered to detect a statistical difference in the rate of adverse effects, it is notable that none of the patients treated with olanzapine experienced an adverse effect, while 6 (13%) of those treated with haloperidol reported extrapyramidal symptoms. The generalizability of this trial to many ICU populations is limited because of a predominance of surgical patients and a relatively low severity of illness (mean APACHE II, 12.7).

Haloperidol and other neuroleptic agents are felt to stabilize cerebral function primarily by dopamine blockade as well as disinhibition of acetylcholine. Additionally, the anti-inflammatory properties of haloperidol – specifically, the inhibition of proinflammatory cytokine production (Moots et al., 1999; Song et al., 2000) – may be particularly important in the treatment of ICU delirium. These procognitive and anti-inflammatory effects may have resulted in the 15.6% absolute reduction in the risk of hospital mortality noted in a recently published retrospective cohort analysis of 989 mechanically ventilated, critically ill patients (Milbrandt et al., 2005). Several randomized, placebo-controlled clinical trials are currently under way that are designed to evaluate the efficacy and safety of haloperidol in the treatment of critically ill patients with delirium.

The optimal dose and formulation of haloperidol, as well as atypical antipsychotics, has not been defined in the ICU setting. Skrobik and colleagues used the enteral forms of haloperidol and olanzapine (0.5–1.0 mg and 2.5 mg initially, respectively) in their clinical trial of ICU patients due to the unavailability of the atypical agent in intravenous form (Skrobik et al., 2004). Haloperidol is most commonly administered in the intravenous form to agitated ICU patients, and an initial dose of 2–10 mg iv is commonly recommended (Tesar et al., 1985; Tesar and Stern, 1988; Jacobi et al., 2002). This dose is followed by higher doses (e.g., doubling the previous dose) every 20–30 minutes while agitation persists and 25% of the initial dose every 6 hours after agitation is controlled.

A number of adverse effects may occur in response to treatment with haloperidol, and ICU patients may be at increased risk because of multiple comorbidities as well as concurrent hepatic and/or renal impairment. A dose-dependent QT prolongation may occur with haloperidol administration increasing the risk of cardiac arrhythmias, including torsade de pointes (TdP) (Lawrence and Nasraway, 1997; Sharma et al., 1998; Perrault et al., 2000). Patients with preexisting cardiac disease are at highest risk (Lawrence and Nasraway, 1997). Doses of 20 mg have resulted in arrhythmias, and cumulative doses as low as 35 mg have resulted in significant QT prolongation (Sharma et al., 1998). The incidence of haloperidol-associated TdP has not been prospectively studied, but one retrospective review of 268 critically ill adult patients who received intravenous haloperidol at a tertiary care hospital reported an incidence of 3.6% ($n = 8$ cases; 45 patients were excluded because they had other risk factors for TdP) (Sharma et al., 1998).

Other adverse effects associated with haloperidol include extrapyramidal symptoms, including akathisia and oropharyngeal dysfunction (Bashford and Bradd, 1996); dystonia, e.g., laryngospasm and trismus (Ilchef, 1997); cognitive 'numbness' and dysphoria, occurring

in 40% according to some studies (King et al., 1995); and neuroleptic malignant syndrome (Adnet et al., 2000). Because they are associated with fewer side effects, especially extrapyramidal symptoms, atypical antipsychotics have been promoted in some reports as an alternative to haloperidol in hospitalized patients (Han and Kim, 2004) and ICU patients (Skrobik et al., 2004). However, adverse effects remain a concern with atypical antipsychotics. For example, these medications may result in QT prolongation such as that seen with haloperidol, and sudden cardiac death has been reported to occur in association with the use of atypical antipsychotics (Ravin and Levenson, 1997).

The majority of ICU patients require sedatives and analgesics, especially early in their ICU stay, and the careful use of these agents is as important as nonpharmacologic strategies aimed at the prevention of delirium. Although benzodiazepines are the drugs of choice for the treatment of alcohol withdrawal (as well as other drug withdrawal syndromes), this class of drugs is not recommended for the routine treatment of delirium because of the likelihood of promoting confusion, oversedation, and respiratory depression. As stated previously (see section 3.4), exposure to benzodiazepines and narcotics is a significant independent risk factor for the development of delirium and use of these drugs should be guided by goal-directed sedation protocols that promote intermittent bolus sedation and daily interruption of sedatives (Kollef et al., 1998; Brook et al., 1999; Kress et al., 2000).

3.9. Conclusions

Patients with critical illness are at high risk of morbidity and mortality. These risks only increase with the failure of multiple organ systems. Although delirium was previously often overlooked, practitioners are becoming increasingly aware of the crucial role that acute central nervous system dysfunction plays in the course of critical illness. Appropriate strategies for the prevention, diagnosis, and treatment of delirium in critically ill patients as outlined in this chapter are the subject of ongoing investigations and should be part of every ICU clinician's armamentarium in the care of patients with critical illness.

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Chapter 4

Coma and stupor

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Consciousness may be considered as a state of awareness of self and environment that gives significance to stimuli from the internal and external environment. It depends on two critical components – cognitive content and arousal. It is the cognitive content of mental functions that allows awareness and the expression of psychological functions of sensation, emotion, and thought. Zeman (2001) distinguishes three principal meanings of this content, defining consciousness in terms of: a waking state with abilities to perceive, interact, and communicate; a state of behaviors based on experiences; and a state of thought or a state of 'mind' including emotion, feelings, and intent. Impairment of arousal leads to obtundation, stupor, or coma, and a secondary impairment of cognitive content, which may be temporary or permanent depending on the etiology. The nature of consciousness has been considered in detail by a number of comprehensive and important reviews (Niedermeyer, 1994; Plum and Posner, 1995; Coslett, 1997; Zeman, 1997, 2001; Zeman et al., 1997; Young and Piggott, 1999; Ortinski and Meandor, 2004).

4.1. States of impaired consciousness

A number of terms have been applied to different varying states of altered consciousness.

1. *Clouding of consciousness* describes states of reduced wakefulness characterized by impaired attention and memory. Patients may be distractible, hyperexcitable, and irritable with slow thought processes.
2. *Acute confusional state* refers to a more severe impairment of consciousness in which stimuli are intermittently misinterpreted. Patients are drowsy, bewildered, disorientated in time, and have poor short-term memory and comprehension. They may have difficulty undertaking complex tasks and show day–night reversal.
3. *Delirium* is characterized by the rapid onset of a floridly abnormal mental state with disturbed consciousness, disorientation, severe motor restlessness, fear, irritability, consistent misperception of sensory stimuli and visual hallucinations. There may be lucid periods and the patient is often agitated, irritable, suspicious, and talkative.
4. *Obtundation* refers to a state of mental blunting with apathy and inactivity. The patient is drowsy, hypersomnolent, and there is reduced alertness with a lessened interest in the environment. Arousal may lead to responses to verbal or tactile stimulation but these are slow.
5. *Stupor* is a condition of unresponsiveness, similar to deep sleep, from which the patient can be aroused only by vigorous and repeated stimuli. Even when aroused communication is by monosyllabic sounds and simple behaviors and as soon as the stimulus ceases the stuporose subject lapses back into the unresponsive state.
6. *The locked-in syndrome* (see below) describes a deefferented state in which consciousness and cognition are preserved but the patient has lost motor function, making movement and speech impossible. The subject is usually able to communicate by opening and voluntarily moving his eye in the vertical plane but horizontal and other eye movements are lost.
7. *Akinetic mutism* is a rare state characterized by pathologically slowed or virtually absent bodily movements in the absence of paralysis or weakness.

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The patients are flaccid, do not respond to pain, and lie immobile, mute, and unresponsive to commands, questions, and greetings. There is no display of emotion but the patient appears awake and their eyes may follow movement of people around the bed or turn towards a sound in the environment. Wakefulness, alertness, sleep–wake cycles, and self-awareness are preserved although cognitive function is reduced; patients retain the ability to blink spontaneously and to visual threat. Primitive reflexes are common and there is bowel and bladder incontinence. The EEG shows reactive alpha and theta rhythms. The condition is described as being associated with bilateral impairment of the inferior frontal lobes but is also reported with extensive bilateral hemispheric disease and lesions of the paramedian mesencephalic reticular formation.

8. *Coma* may be defined as a state of unrousable unresponsiveness in which the subject lies with their eyes closed (Plum and Posner, 1995). There is no understandable response to external stimuli or inner need and the patient does not utter understandable responses nor accurately localize noxious stimuli. Thus there is a total absence of awareness of self and environment even when the subject is externally stimulated. There is no spontaneous eye opening, response to voice, localization to painful stimuli, or verbal output.

Coma and impaired consciousness are associated with either bilateral hemispheric damage or suppression, or a focal brainstem lesion or metabolic derangement that damages or suppresses the reticular activating system. In general, unilateral dysfunction of the cerebral hemispheres does not, by itself, cause stupor or coma although large dominant hemisphere lesions may cause drowsiness or obtundation in the absence of brainstem compression (Plum and Posner, 1995). Neuroanatomical studies of brainstem stroke confirm that the development of coma is associated with predominantly bilateral tegmental lesions of the upper pons and, to a lesser extent, the midbrain. These lesions particularly involve the rostral raphe complex, locus ceruleus, laterodorsal tegmental nucleus, nucleus pontis oralis, parabrachial nucleus, and the white matter in between these nuclei (Parvizi and Damasio, 2003).

4.2. Causes of coma

Coma may be due to a variety of neurological and general medical disorders. The causes may be classified according to several different schemes. None is entirely satisfactory as many of the underlying conditions are either multifactorial (e.g., mass lesions with secondary herniation) or may affect the brain at different levels (e.g., vasculitis, meningitis) (Bates, 1994; Wijdicks, 2003, 2004). Nonetheless the most important considerations in the initial assessment are the presence of lateralizing signs, the presence of meningism, and the pattern of brainstem reflexes (Table 4.1).

In most patients coma is due to a clear underlying medical cause: in patients admitted in coma (>6 hours) to a general accident and emergency department approximately 40% will be due to drug ingestion with or without alcohol, 25% to hypoxic–ischemic insult secondary to cardiac arrest, 20% to stroke and the remainder to trauma and general medical disorders. Primary neurological events causing coma include intracerebral hemorrhage, subarachnoid hemorrhage, pontine or cerebellar hemorrhage, and basilar artery thrombosis; however, infarction in the territory of the middle cerebral artery rarely leads to sudden onset of coma unless there is massive swelling causing brainstem shift and massive torsion.

4.3. Assessment of coma

4.3.1. Resuscitation and emergency treatment

While the underlying cause of coma must be treated as soon as possible, rapid and effective cardiopulmonary resuscitation is the priority if secondary cerebral damage is to be avoided (Table 4.2). A patent airway must be established by placing the patient in the left lateral position, introducing an oral airway, or performing endotracheal intubation. Similarly, hypotension will cause cerebral hypoperfusion and further cerebral ischemia and appropriate resuscitation with intravenous fluids and/or inotropic drugs must be undertaken as soon as possible. During resuscitation a glucose level should be undertaken immediately by Dextrostix and blood should be taken for estimation of electrolytes (especially sodium, glucose, and urea) and full blood count. Other tests including toxicology screen and anticonvulsant drug levels should be undertaken as appropriate. Having taken baseline blood samples, 25 ml of 50% glucose should be given intravenously as any potential harmful results in cerebral ischemia are far outweighed by the benefits of rapid treatment of hypoglycemia. Intravenous injection of 50–100 mg thiamine should be given to prevent the development of Wernicke's encephalopathy in alcoholic patients. If narcotic or benzodiazepine overdose is suspected, naloxone or flumazenil respectively should be administered (Doyon and Roberts, 1994; Gueye et al., 1996; Weinbroum et al., 1996). Further management of the unconscious patient will include adequate treatment of seizures (Shorvon, 1993),

Table 4.1

Causes of coma

1. Coma with intact brainstem function, no meningism, and no lateralizing motor signs	
Toxins	Carbon monoxide
	Methanol
	Lead
	Cyanide
	Thallium
Alcohol	
Drug toxicity	Sedatives
	Barbiturates
	Tranquilizers
	Opioids
	Psychotropics
	Amphetamines
	Others
Extrapyramidal	Status dystonicus
	Neuroleptic malignant syndrome
Seizures	Status epilepticus
	Postictal
	Postictal drug induced
	Functional
Psychiatric	Catatonia
	Conversion reaction
Infections	Transmissible spongiform encephalopathy
Anoxic–ischemic encephalopathy	
Respiratory	Hypoxia, hypercapnia
Electrolytes	Hyponatremia, hypernatremia, hypercalcemia, hypocalcemia, hypermagnesemia
Diabetic	Hypoglycemia
	Ketoacidosis
	Lactic acidosis
	Hyperosmolar nonketotic diabetic coma
Renal	Uremia
Hepatic	Hepatic encephalopathy
Endocrine	Hypopituitarism, hypothyroidism, hyperthyroidism
	Addison's disease
	Hashimoto's encephalopathy
Temperature	Hypothermia
	Hyperpyrexia
Nutritional	Wernicke's encephalopathy
Inborn errors of metabolism	Hyperammoniacal
	Aminoaciduria
	Organic aciduria
Others	Porphyria
	Reye's syndrome
	Idiopathic recurrent stupor
2. Coma with meningism (± intact brainstem function and lateralizing signs)	
Infection	Meningitis
	Encephalitis
Vascular	Subarachnoid hemorrhage

(Continued)

Table 4.1

(Continued)

3. Coma with intact brainstem function and lateralizing signs			
i) Asymmetrical lateralizing signs			
Vascular	Infarction	Ischemia	
		Embolic	Cardiac
			Large vessel
			Fat
		Hypoperfusion/hypotension	
	Hemorrhage	Extradural	
		Subdural	
		Subarachnoid	
		Intracerebral (primary or secondary)	
		Congophilic amyloid angiopathy	
		Angioimmunoblastic lymphoma	
	Vasculitis		
	Venous thrombosis		
	Mitochondrial disease		
	Hypertensive encephalopathy		
	Eclamptic toxemia		
	Endocarditis	Bacterial	
		Libman–Sacks	
		Marantic	
Infection	Abscess		
	Subdural empyema		
	Creutzfeldt–Jakob disease		
Tumor			
White matter	Multifocal leukoencephalopathy		
	Adrenoleukodystrophy		
	Multiple sclerosis		
	Leukoencephalopathy associated with chemotherapy/radiotherapy		
	Acute disseminated encephalomyelitis		
	Acute hemorrhagic leukoencephalitis		
ii) Symmetrical lateralizing signs			
Diffuse axonal brain injury			
Bilateral subdural hematoma/ empyema			
Vascular	Multiple infarcts due to	Fat emboli	
		Cholesterol emboli	
		Disseminated intravascular coagulation	
		Thrombotic thrombocytopenic purpura	
		Vasculitis	
4. Coma with signs of focal brainstem dysfunction			
Herniation syndrome			
Intrinsic brainstem disease			
Advanced metabolic/toxic encephalopathy			
Others	Central pontine myelinolysis		
Vascular	Vertebrobasilar occlusion		
	Vertebrobasilar dissection		
	Vertebrobasilar hemorrhage		
Tumor	Posterior fossa		

Table 4.2

Assessment of coma

1. Resuscitation and emergency treatment			
2. Medical assessment			
3. Establish level of consciousness	Eye opening		
	Motor response		
	Verbal output		
4. Identify brainstem activity	Brainstem reflexes	Pupils	
		Eye movements	Spontaneous
			Oculocephalic
			Oculovestibular
		Corneal reflex and facial movements	
		Bulbar	Cough
			Gag
		Respiratory pattern	
5. Motor function	Involuntary movements		
	Seizures		
	Muscle tone		
	Motor responses		
	Tendon reflexes		

correction of electrolyte and acid–base disturbances, and supportive treatment including adequate nutrition and physiotherapy (Berek et al., 1994; Wijdicks, 2003). Increasing evidence suggests that patients who remain in coma after resuscitation should be treated with controlled hypothermia (core temperature 32–34°C) for 12–24 hours (Bernard et al., 2002).

4.3.2. Medical assessment

4.3.2.1. History

It is essential to obtain as detailed and accurate a history as possible. This must include all available information concerning the previous history and circumstances of the acute event. Detailed history must be sought on admission from family members, witnesses, and the paramedical staff called to the scene. The patient's personal belongings may provide clues about pre-existing neurological or general medical disorder and any treatment. A search should be made for any evidence of alcohol or drug ingestion. It is important to contact family members or the GP by telephone to establish any history of a predisposing event, e.g., previous trauma, pyrexia, prodromal symptoms such as headache, neck stiffness, ataxia, epilepsy, or previous episodes of coma. Coma may present as failure to wake following general anesthesia or sedation on the intensive care unit. In this situation it is necessary to establish whether the coma has arisen as a result of a pre-existing neuromuscular disease (e.g., previous poliomyelitis, muscular dystrophy, or motor neuron disease), a neurological complication of general medical disorders (e.g., cardiogenic emboli or metabolic encephalopathy), or a primary neurological event (e.g., subarachnoid hemorrhage or meningitis).

4.3.2.2. Examination

An urgent and detailed general medical examination (Bates, 1994; Berger, 2004) must be undertaken immediately after resuscitation. The general appearance of the patient on discovery and admission may give important clues to the etiology of the coma. The breath may smell of ketones or alcohol, and renal or hepatic fetor may be present. The mucus membranes may show cyanosis, anemia, jaundice, or carbon monoxide intoxication. Orbital and basal skull fractures are suggested by bruising in the mastoid and orbital regions and blood in the external auditory meatus. There may be splinter hemorrhages suggesting endocarditis or needle tracks in the antecubital fossa indicating opiate intoxication. Relevant skin lesions include a purpuric–petechial rash suggesting meningococcal septicemia or other causes of sepsis including *Pseudomonas*, *Staphylococcus*, or endocarditis, maculopapular lesions indicating viral meningoencephalitis, endocarditis, or fungal infection, and a vesicular rash suggesting herpes simplex or varicella; barbiturate intoxication is associated with bullous lesions. Petechiae and ecchymosis indicate abnormal coagulation from a variety of causes including trauma, corticosteroid use, abnormal

coagulation from liver disease or anticoagulants, disseminated intravascular coagulation, and thrombotic thrombocytopenic purpura. Hyperpigmentation may suggest Addison's disease, porphyria, disseminated malignant melanoma, and chemotherapy. Human immunodeficiency virus (HIV) is suggested by Kaposi's sarcoma, anogenital herpetic lesions, oral candidiasis, or lymphadenopathy.

Pyrexia is usually due to systemic sepsis but its absence does not exclude infection, particularly in the elderly or immunosuppressed. Hyperpyrexia may be due to thyrotoxic crisis, heat stroke, drug toxicity, and malignant hyperpyrexia but is only rarely primarily neurological due to hypothalamic lesions or subarachnoid hemorrhage. Severe hypothermia may lead to coma due to environmental (accidental hypothermia) or metabolic causes, endocrine disorders (hypopituitarism, hypothyroidism), drugs (alcohol, barbiturate), and Wernicke's encephalopathy.

Hypertension occurs in response to primary cerebral causes such as subarachnoid hemorrhage and raised intracranial pressure but malignant hypertensive crisis may be associated with a disturbed level of consciousness. Hypotension may lead to reduced cerebral perfusion, coma, and irreversible cerebral injury. It is associated with hypovolemia due to hemorrhage, myocardial infarction, cardiac tamponade, septicemia, intoxication, diabetes mellitus, and Addison's disease. There may be abnormalities of the respiratory rhythm. Tachycardia may be due to a tachyarrhythmia, hypovolemia, pyrexia, toxins, and drug intoxication. Bradycardia may result from bradyarrhythmias, indicate raised intracranial pressure, or be due to drug intoxication.

Meningism suggests infective or carcinomatous meningitis, subarachnoid hemorrhage, and central or tonsillar herniation. However, the clinical assessment of meningism may be difficult in patients who have been intubated and, indeed, it has been suggested that meningism is unusual in deep coma whatever its cause (Fisher, 1969).

Examination of the fundi may reveal retinopathy due to diabetes or hypertension. Papilloedema suggests raised intracranial pressure, hypertensive retinopathy, or carbon dioxide retention and subhyaloid hemorrhage indicates subarachnoid hemorrhage. Otoscopic examination may show otorrhea or hemotympanum from a basal skull fracture. Rhinorrhea is suggested by the presence of glucose in the watery nasal discharge. Cardiac examination may indicate the presence of an arrhythmia, cardiac or valvular disease suggesting endocarditis, or a possible embolic source. Examination of the abdomen may show evidence of an ileus or increased bowel motility and there may be hepatomegaly due to cardiac failure, portal hypertension, or secondary carcinomatous deposits. Lymphadenopathy may indicate infection, neoplasia, collagen vascular disorders, or sarcoidosis.

4.3.3. Level of consciousness

The level of consciousness is expressed by the ability of the patient to respond to stimuli of varying intensity by speech, eye opening, and motor movements.

4.3.3.1. Level of responsiveness

The eyelids should be held open and the patient asked to move their eyes in a horizontal and vertical plane to exclude preservation of volitional control of these movements, as occurs in the locked-in syndrome. The patient should be tested using visual, auditory, and painful stimuli of increasing intensity (Wijdicks, 1996). Noxious stimuli should be presented bilaterally in cranial nerve and limb territories. The Glasgow Coma Score (GCS) is the most widely used scale to assess the level of consciousness (Teasdale and Jennett, 1974). It was introduced to assess the severity and follow the progression of traumatic brain injury but it has been increasingly applied to determining the level of coma regardless of etiology. The GCS is an extremely valuable and reproducible scale that can be easily applied by medical and nursing staff. However, there are many limitations: in particular it excludes assessment of many important neurological functions, it requires regular and consecutive observations to be effective, it is limited to the best response in a single limb and therefore cannot reflect asymmetry, and its reliability in inexperienced observers is poor as the level of maximal auditory, visual, and noxious stimuli varies between observers. Full assessment cannot be undertaken in patients intubated or with swollen eyes. Furthermore the scale represents the addition of ordinal values that are not equal and are not independent of each other. For these reasons a total GCS score makes little sense and is not a reliable predictor of outcome. The GCS should not replace detailed and careful neurological examination of the pattern of responsiveness. Nonetheless the GCS has provided an extremely valuable focus, which has emphasized the importance of intensive observation of the comatose patient, allowing rapid intervention with deterioration in consciousness level (Starmark et al., 1988; Rothstein, 1991; Bhatty and Kapoor, 1993; Moulton and Pennycook, 1994; Adnet and Baud, 1996).

Other scales have been introduced to improve the sensitivity and prognostic reliability of bedside assessment of coma. The Innsbruck Coma Scale (ICS) is similar to the GCS in being composed of ordinal measures aggregated together (Benzer et al., 1991). The criticisms of its validity are therefore similar but the scale

does extend the range of observations and can be used in intubated patients. As with other scales it is reliable in predicting poor outcome following trauma. More recently the Reaction Level Scale (RLS 85) has been advocated; it has the advantage of being ordinal without the need to aggregate the scores but it does depend entirely on limb motor responses (Johnstone et al., 1993; Diringer and Edwards, 1997).

4.3.4. Assessment of neurological function

4.3.4.1. Eyelids

In the comatose patient, opening of the eyelids by an examiner is followed by slow re-closure while in pseudocoma there is forced resistance to eyelid opening and active closure. Rarely the eyelids may be open in coma ('eyes-open coma') because of a failure of levator inhibition associated with lesions in the pontomesencephalic region. This condition may be difficult to distinguish from the vegetative state. Complete bilateral ptosis may occur in patients with massive infarction of the right cerebral hemisphere, possibly because of upper brainstem involvement (Blacker and Wijdicks, 2003).

4.3.4.2. Pupillary responses

In the assessment of pupillary responses it is important to ensure an adequate light source and, if necessary, to examine the pupils with a magnifying glass. Pre-existing ocular or neurological injury may lead to pupillary asymmetry or even a fixed dilated pupil. Topical and systemic medication may affect pupillary function. Fixed dilated pupils may be due to anticholinergic agents given during anesthesia or cardiopulmonary resuscitation and pupillary asymmetry may occur as the effects of these mydriatic agents wear off. Other agents that cause poorly reactive pupils include barbiturates, succinylcholine, and aminoglycoside antibiotics. Pupillary constriction with poor light reaction may be due to topical ophthalmological preparations containing acetylcholinesterase inhibitor (e.g., pilocarpine), used in the treatment of glaucoma, and narcotics (Gray et al., 1997). In the ciliospinal reflex, there is bilateral pupillary dilatation in response to a painful cutaneous stimulation in the cervical region. This reflex reflects the integrity of the sympathetic pathways in lightly comatose patients. It is absent in Horner's syndrome or IIIrd nerve palsy but the reflex persists in coma due to metabolic or toxic insults (Larson and Muhiudeen, 1995).

The presence of equal, light reactive pupils indicates that the afferent (II) and efferent (III) pathways and the midbrain tegmentum are all intact. Normal pupillary reaction to light in a comatose patient is strongly suggestive of a metabolic rather than structural cause of the coma. A unilateral small pupil with normal reactions to light may be due to an ipsilateral Horner's syndrome often associated with lesions involving the descending sympathetic pathways in the hypothalamus, midbrain, medulla (e.g., lateral medullary infarction), and ventrolateral cervical spine. There may be anhidrosis and enophthalmos but the normal responses may be difficult to observe because of the pupillary constriction. Similar pupillary changes occur in toxic or metabolic coma due to opiate overdose. Bilateral pinpoint pupils with preserved light reflexes also occur with pontine lesions in the tegmentum that interrupt the descending sympathetic pathways. The extent of constriction may make this difficult to observe and magnification may be required. Mid-position pupils that do not respond to light but in which the accommodation reflex is spared are associated with dorsal tectal, pretectal, or tegmental lesions. The pupils may spontaneously and rhythmically fluctuate in size (hippus) and dilate to ciliospinal reflex.

In progressive peripheral IIIrd nerve lesions the initial sign may be sluggish pupillary responses followed by the development of fixed pupillary dilatation (due to involvement of the parasympathetic with sparing of the sympathetic pathways) and extraocular motor abnormalities. A unilateral IIIrd nerve lesion may also cause an efferent pupillary defect in which a light stimulus elicits a consensual but not a direct response due to impairment of the ipsilateral efferent limb (IIIrd nerve) of the light reflex.

Widely dilated pupils may be due to anticholinergic agents (e.g., atropine) and do not reverse with pilocarpine. Irregular oval, unequal pupils follow brainstem transtentorial herniation that leads to midbrain infarction. Similar fixed and moderately dilated pupils may be seen in brain death because of the loss of both sympathetic and parasympathetic influences.

4.3.4.3. Ocular motor disorders

The position of the eyes at rest, the pattern of spontaneous eye movements and the presence of oculocephalic and oculovestibular reflexes indicates oculomotor function and the pattern of brainstem or higher cortical involvement. The preservation of normal ocular motility implies the integrity of the brainstem from the vestibular nuclei at the pontomedullary junction to the oculomotor nucleus in the midbrain and cerebellum (Leigh and Zee, 1991; Buettner, 1992). In the primary ocular position the eyes may be either dysconjugate, conjugate in the midline, or deviated in a conjugate manner. Dysconjugate deviation of the eyes is common in patients with impaired consciousness; this may reflect loss of voluntary fusional control or represent a pre-existing strabismus in which compensation has been impaired (Daroff and Troost, 1978).

A complete IIIrd nerve palsy will cause pupillary dilatation, ptosis, and deviation of the eye downward and laterally. Oculomotor nerve palsies occur as a consequence of midbrain lesions, due to direct trauma, or as a manifestation of transtentorial herniation. Internuclear ophthalmoplegia (INO), due to a lesion of the medial longitudinal fasciculus (MLF), is characterized by isolated failure of ipsilateral ocular adduction in the absence of pupillary changes but with normal vertical eye movements and ataxic nystagmus of the abducting eye. Dysconjugate vertical gaze may be due to IVth nerve palsy following trauma; a skew deviation associated with otolithic, cerebellar, or brainstem lesions, or with metabolic encephalopathy and drug intoxication. Inward deviation and failure of abduction indicates a VIth nerve palsy; this is a poor localizing sign which is common following trauma or due to raised intracranial pressure. Tonic horizontal conjugate ocular deviation is common in coma. The eyes usually deviate to the side of destructive hemispheric lesions and away from the hemiparesis (e.g., infarction, hemorrhage, or tumor). However, the eyes may deviate away from an irritative, epileptic focus and also from a thalamic lesion. In lesions below the pontomesencephalic junction the eyes deviate away from the lesion side and look towards the hemiparesis. In hemispheric lesions it is usually possible to drive the eyes across the midline with a vestibular stimulus but this is not the case for brainstem gaze palsies. The eyes may deviate to the side of the focus in postictal gaze palsy but intermittent aversive horizontal deviation is often due to seizure activity. Tonic downward deviation of the eyes is associated with tectal compression due to thalamic or dorsal midbrain lesions (usually hemorrhagic), although a similar deviation can be seen in metabolic coma and rarely in pseudocoma (Keane, 1985). Prolonged tonic upward deviation occurs as a consequence of extensive hypoxic–ischemic damage but may occur transiently in seizures or in oculogyric crises due to encephalitis lethargica or neuroleptic medication. Horizontal nystagmus occurring in comatose patients suggests an irritative or epileptogenic supratentorial focus. Nystagmus due to an aversive irritative focus is usually associated with other motor manifestations of seizures including movements of the eye, eyelid, face, jaw, or tongue. Unilateral nystagmoid jerks in a horizontal or rotatory fashion are associated with mid or lower pontine damage.

4.3.4.3.1. Spontaneous eye movements

Spontaneous roving eye movements are slow, random, lateral movements, which may be conjugate or dysconjugate. Their presence implies the ocular pathways are intact and coma is relatively light or associated with diffuse hemispheric involvement due to a metabolic or toxic cause. Periodic alternating gaze disturbance is characterized by a slow cycle of horizontal gaze deviation in which the eyes are deviated for several minutes before the eyes move to the opposite lateral gaze. This occurs in metabolic coma (particularly hepatic encephalopathy) and bilateral hemispheric infarction or diffuse anoxic injury. Ping-pong gaze consists of horizontal, conjugate deviations of the eyes that alternate every few seconds and are associated with severe diffuse involvement of the cerebral hemispheres or peduncles (Diesing and Wijdicks, 2004).

Conjugate vertical eye movements are separated into different types according to the relative velocities of the downward and upward phases (Table 4.3) (Ropper, 1981; Drake et al., 1982; Brusa et al., 1984; Keane, 1985, 1986a; Rosenberg, 1986). Repetitive rapid downbeat saccades followed by slow movement back to the midline (ocular bobbing) is associated with intrinsic pontine or cerebellar lesions and metabolic or toxic coma. The reverse situation, in which there is an initial slow downbeat phase followed by a rapidly correcting saccade (ocular dipping), has less localizing value but may be associated with hypoxic–ischemic injury. Rarely the eye movements may be upwards, in which the initial movement may be a rapid saccade followed by slow refixation (reverse ocular bobbing) or a slow initial upgaze phase followed by a corrective saccade (reverse ocular dipping). These movements are of little value in localization but may be associated with hypoxic–ischemic coma or toxic/metabolic encephalopathy. Upbeat nystagmus differs from ocular bobbing because there is no latency between the corrective saccade and the next slow deviation. Downward nystagmus (ocular myoclonus) may be rotatory or circular and may be associated with palatal myoclonus, which moves with the same frequency. It occurs after damage to the lower brainstem in the region of the inferior olive and is particularly associated with Arnold–Chiari malformation or other causes of low medullary compression. Optokinetic nystagmus (OKN) is only present when afferent visual pathways to the visual cortex and the connections to the brainstem oculomotor systems are intact. Its presence suggests either a light disturbance of consciousness or functional coma and it is lost in stupor and coma.

4.3.4.3.2. Vestibulo-ocular reflexes

The vestibulo-ocular reflexes (VORs) (Leigh et al., 1984; Buettner and Zee, 1989) are based in a three-neurone pathway. Horizontal VOR is associated with structures in or adjacent to the pons and vertical

Table 4.3

Rhythmic involuntary vertical eye movements in coma

Ocular bobbing	Acute pontine lesion Metabolic and toxic Extra-axial posterior fossa masses	Rapid downward jerks of both eyes followed by a slow return to the midposition Paralysis of both reflex and spontaneous horizontal eye movements
Monocular/paretic bobbing		Co-existing oculomotor palsy alters the appearance of typical bobbing
Atypical bobbing	Anoxia	Ocular bobbing when lateral eye movements are preserved.
Ocular dipping (inverse ocular bobbing)	Diffuse cerebral Anoxia Following status epilepticus	Spontaneous eye movements in which an initial slow downward phase is followed by a relatively rapid return reflex Horizontal eye movements are preserved
Reverse ocular bobbing	Nonlocalizing Metabolic Viral encephalitis Pontine hemorrhage	Slow initial downward phase, followed by a rapid return that carries the eyes past the midposition into full upward gaze. Then eyes slowly return to mid-position

VOR is determined by regions rostral to the oculomotor nucleus in the midbrain. VORs provide compensatory eye movements to stabilize the eye in space on the basis of neuronal activity arising in the semicircular canal and the otoliths. The VOR determines ocular movements after stimulation of the vestibular apparatus by mechanical rotation of the head (oculocephalic) and caloric irrigation (oculovestibular). Following rotation of the head, irrespective of the axis, if supranuclear influences are absent the eyes will normally remain fixed in space, i.e., continue to look forward. The reflex is tested by sudden passive rotation of the head in both directions laterally and flexion and extension of the neck while observing the motion of the eyes, but the VOR head turning maneuver should not be performed on any patient until the stability of the neck has been adequately assessed. During testing of VOR incomplete abduction suggests a VIth nerve palsy while impaired adduction suggests IIIrd nerve palsy or INO. Reduced or absent VORs indicate severe intrinsic brainstem impairment. The oculovestibular component is tested by the irrigation of cold water against the tympanic membrane. The maneuver is undertaken with the head tilted 30° up from the horizontal to allow maximum stimulation of the lateral semicircular canal, which is most responsive for reflex lateral eye movements. Iced water is slowly instilled after ensuring that the ear canal is patent and the tympanic membrane is free of defect. This is a more effective stimulus than the oculocephalic reflex in producing tonic deviation of the eyes towards the irrigated ear. In the awake subject irrigation of cold water causes a slow conjugate deviation of the eyes towards the stimulated ear followed by a corrective nystagmoid jerking of the eye back towards the midline. Warm water irrigation causes conjugate eye deviation with a slow phase away from the stimulated ear followed by a normal corrective phase towards the ear. Simultaneous bilateral cold water application results in slow downward deviation, whereas simultaneous warm water application causes a slow upward deviation. Impaired abduction suggests a VIth nerve palsy while impaired adduction is compatible with IIIrd nerve lesion or INO. Limited oculovestibular movements may be associated with metabolic/toxic coma or drug intoxication. Vertical movements are impaired by disorders of the midbrain particularly affecting regions responsible for maintaining consciousness, while pontine lesions lead to loss of horizontal saccadic movements.

4.3.4.4. Fifth cranial nerve

The eyes are usually closed in coma but, if both the afferent and the efferent limbs of the corneal reflex are intact and the eye is held open, a blink reflex can be elicited in response to stimuli or even spontaneously if the patient is in light coma. Stimulation may elicit a consensual blink because of the crossover of afferent fibers centrally. Spontaneous blinking in coma implies intact pontine reticular formation while reflex blinking (in response to bright light and sound) suggests intact visual, auditory afferent pathways, although a blink reflex induced by bright light may be mediated by the superior colliculus and remain even in the presence of occipital damage. Unilateral absence of blinking suggests a lesion affecting the

efferent pathway due to damage to the VIIth nerve and the stimulus may induce deviation of the jaw to the opposite side (corneopterygoid reflex). Stimulation of the corneal reflex causes the eyes to roll upward (Bell's phenomenon) if the pons and midbrain are intact. The blink reflex is lost with a lesion at the level of the pons, interrupting the afferent pathway along the Vth cranial nerve. The corneal reflex has a higher threshold in comatose patients but may be totally lost with deep sedation. In coma the jaw jerk may be brisk and the presence of clonus suggests involvement of the corticobulbar tract or metabolic encephalopathy but it is also seen in the vegetative state or during weaning from sedation.

4.3.4.5. Seventh cranial nerve

In coma the facial grimace to painful stimuli reflects VIIth nerve function. Involvement of the descending pathways of the VIIth nerve, the nucleus, or fascicle leads to ipsilateral weakness and a grossly asymmetrical grimace. Lesions in the pons may involve the facial nerve nuclei and produce ipsilateral complete facial weakness. UMN lesions produce contralateral facial weakness and tend to spare the forehead and orbicularis oculi muscles because of the bilateral cortical representation of these structures. Furthermore, failure of facial movements in response to stimuli in a deeply comatose patient may be due to depressed sensory function (Keane and Baloh, 1992).

4.3.4.6. Bulbar

The clinical assessment of bulbar function in patients with altered level of consciousness is unreliable. Airway protection may be impaired despite the presence of palatal movement and a pharyngeal and cough reflex. In an intubated patient the cough reflex may be tested by manipulating the endotracheal tube or by suction. An impaired reflex is manifest as a poor or absent cough response and absence of distress and lacrimation. Loss of the cough reflex implies a central medullary lesion although the response may also be depressed by metabolic encephalopathy, or by lesions of the afferent vagal pathway or efferent limb to the respiratory muscles. The pharyngeal reflex is also difficult to assess in comatose patients. Failure of stimulation of the palate or posterior pharyngeal wall failing to elicit palatal and uvula excursion also implies low brainstem impairment, but the reflex is suppressed by sedation.

4.3.4.7. Respiration

It has proved difficult, in humans, to attribute precise respiratory function to localized anatomical substrates because lesions are rarely localized and coexisting pulmonary, cardiovascular, or autonomic influences may complicate the clinical picture. Furthermore accurate diagnosis of incipient respiratory insufficiency has led to earlier therapeutic intervention with controlled ventilation. A number of characteristic patterns may be seen in patients in stupor or coma (Howard and Hirsch, 2000). Primary central neurogenic hyperventilation is a rare condition characterized by rapid, regular hyperventilation that persists in the face of alkalosis, elevated Po_2, low Pco_2, and in the absence of any pulmonary or airway disorder (Rodriguez et al., 1982; Pauzner et al., 1989). It is associated with structural mesencephalic lesions or brainstem tumors (particularly lymphoma). However, hyperventilation in coma is common and is usually due to intrinsic pulmonary involvement (Leigh and Shaw, 1974). In apneustic breathing there are sustained inspiratory cramps with a prolonged pause at full inspiration or alternating brief end-inspiratory and end-expiratory pauses. The pattern has been associated with bilateral tegmental infarcts in the pons. Ataxic respiration is characterized by a completely irregular respiratory cycle of variable frequency and tidal volume alternating with periods of apnea; it is particularly associated with medullary impairment due either to brainstem stroke or compression caused by rapidly expanding lesions and may be an important sign of impending respiratory arrest. Hiccups consist of brief bursts of intense inspiratory activity involving the diaphragm and inspiratory intercostal muscles. Glottic closure occurs almost immediately after the onset of diaphragmatic contraction, thus minimizing the ventilatory effect. Intractable hiccups may be the result of structural or functional disturbances of the medulla or its afferent or efferent connections with the respiratory muscles. The development of hiccups in this context is an ominous sign that may anticipate the development of irregularities of the respiratory rhythm culminating in respiratory arrest.

Voluntary control of breathing may be impaired by bilateral lesions affecting the descending corticospinal or corticobulbar tracts and is particularly seen in association with destructive vascular lesions of the basal pons or of the medullary pyramids and adjacent ventromedial portion, which may result in the 'locked-in' syndrome (Heywood et al., 1996). Selective interruption of the voluntary pathways in humans leads to a strikingly regular and unvarying respiratory pattern, with loss of the ability to take a deep breath, hold the breath, cough voluntarily, or initiate any kind of volitional respiratory movement. Cheyne–Stokes Respiration (CSR) is characterized by a smooth waxing and waning of breath volume and frequency separated by periods of apnea (Naughton, 1998); the

hyperpneic phase is longer than the apnea and the entire cycle typically lasts 1 minute or more. The respiratory oscillations are associated with phasic changes in cerebral blood flow, cerebrospinal fluid (CSF) pressure, arterial and alveolar O_2 and CO_2, level of alertness, and pupillary size; periodic heart block and ventricular arrhythmias are also common. CSR is associated with diffuse metabolic encephalopathy, vascular disease, and raised intracranial pressure and may occur with supratentorial or, less commonly, infratentorial lesions.

4.3.4.8. Motor responses

Examining the motor responses involves assessment of the resting posture of the limbs and head, involuntary movements, spontaneous movements (purposeful or nonpurposeful), and the response to external stimuli. The motor response to deep, painful stimuli is one of the most valuable signs in the diagnosis of coma.

The patient may lie in a fixed posture, which is exacerbated by stimulation. A decorticate posture refers to flexion at the elbows and wrists with shoulder adduction and internal rotation and extension of the lower extremities. This posture is common and poorly localizing as it may result from lesions of the contralateral hemisphere or thalamus with the structures below the diencephalon being intact. A decerebrate response describes bilateral extensor posture with extension of the lower extremities, adduction and internal rotation of the shoulders, and extension at the elbows and wrists. This carries a poor prognosis as it is usually due to brainstem lesions, particularly of the bilateral midbrain or pons. Occasionally it may be due to severe metabolic encephalopathy (e.g., hypoglycemia or liver failure) or bilateral supratentorial lesions involving the motor pathways. Decerebrate rigidity due to hypoxic–ischemic encephalopathy may be associated with extension and pronation of the upper extremities and forcible plantar flexion of the foot and intermittent opisthotonus induced by painful stimuli. Other patterns of spontaneous extension and internal rotation of the arms and weak flexion of the legs may occur with pontine or midbrain lesions but medullary lesions are associated with total flaccidity, although posturing may occur spontaneously or in response to variable stimuli such as the patient's own breathing (Greenberg and Simon, 1982; Brown, 1994; Plum and Posner, 1995).

4.3.4.9. Tone

The pattern and asymmetry of muscle tone may help in localizing focal structural lesions and in differentiating metabolic from structural coma. Acute structural damage above the brainstem or metabolic encephalopathy usually results in hypotonia and flaccidity, while spasticity implies established lesions. The presence of a unilateral grasp reflex indicates an ipsilateral frontal lobe disturbance. The finding of plucking or clutching movements of the limbs indicates that the coma is relatively light and that the corticospinal pathways are intact.

4.3.4.10. Involuntary movements

Tonic–clonic or other stereotyped movements infer the presence of generalized or focal seizures or epilepsia partialis continuans. Myoclonic jerking is characterized by nonrhythmic jerking movements in single or multiple muscle groups and may be seen in anoxic encephalopathy, metabolic comas (e.g., hepatic encephalopathy) or, occasionally, following pontine infarction. Touch, tracheal suction, or loud hand clapping can precipitate the jerks. Rhythmic myoclonus must be distinguished from epilepsia partialis continuans. Myoclonic seizures typically lack a tonic component and may involve facial muscles and other axial structures as a result of a focal hemisphere lesion. Myoclonic status should be distinguished from a single myoclonic jerk or other types of generalized seizure. Generalized myoclonic status is seen in approximately 40% of survivors from postanoxic coma immediately following resuscitation and is highly predictive of permanent vegetative state or death (Wijdicks et al., 1994; Wijdicks and Young, 1994). However, some patients who recover from postanoxic coma may develop late-onset multifocal stimulus-sensitive action myoclonus (Lance–Adams syndrome). This improves with time and is only rarely associated with persistent or severe additional neurological deficit (Morris et al., 1998). Cerebellar fits resulting from intermittent tonsillar herniation are characterized by a deterioration in the level of arousal, opisthotonus, respiratory rate slowing and irregularity, and pupillary dilatation.

4.4. Mechanisms of coma

4.4.1. Cerebral herniation

One important mechanism of coma and permanent neurological impairment is cerebral herniation (see also Ch. 5) in which raised intracranial pressure (e.g., cerebral edema) or supratentorial lesions with mass effect (e.g., hemispheric tumors, subdural or intracerebral hemorrhage, or massive infarcts) cause brain substance to be forced downward towards the tentorial opening leading to torsion or compression of the diencephalon and upper brainstem structures against the tentorium or bony structures (Fisher, 1995; Wijdicks and Miller, 1997). Two major syndromes of herniation are recognized.

4.4.1.1. Tentorial herniation of the uncus

This occurs as a result of asymmetrical mass effect causing the temporal lobe, uncus, and hippocampus to shift towards the midline and compress the midbrain against the tentorial edge. The initial manifestation is the involvement of the ipsilateral IIIrd nerve, initially causing a sluggish light reaction and pupillary dilatation. Deviation of the midbrain leads to compression against the contralateral rigid dura causing damage to the cerebral peduncles and thus a hemiparesis ipsilateral to the lesion in addition to a complete IIIrd nerve palsy. The rigid tentorium carves out a notch on the lateral aspect of the midbrain (Kernohan's notch phenomenon). Torsion, anteroposterior elongation and downward displacement of the midbrain cause tearing of the paramedian perforating vessels leading to consequent brainstem infarction and hemorrhage. Compression of the ipsilateral posterior cerebral artery against the tentorial edge leads to occlusion and hemorrhagic occipital lobe infarction. Eventually, the dilated pupil may become a little smaller as the sympathetic pathway is damaged, while the other pupil becomes midsized and unresponsive. Established oculomotor paresis appears, first in the eye originally involved and shortly afterwards in the other eye (Keane, 1986b).

Survivors of tentorial herniation may be left in a 'locked-in' or vegetative state and may demonstrate blindness, oculomotor nerve dysfunction, INO, vertical gaze paresis, pretectal signs, homonymous hemianopia, spastic leg weakness, or parkinsonism and other extrapyramidal syndromes.

4.4.1.2. Central herniation of the brainstem

This occurs as a result of diffuse, symmetrical raised intracranial pressure. Downward displacement of the hemispheres leads to compression and torsion of the diencephalon and midbrain, which may descend through the tentorial notch. Initially, compression of the midbrain leads to impairment of concentration and attention with progressive stupor and unconsciousness. The pupils remain reactive but constricted because of sympathetic involvement and roving eye movements are gradually lost with progressive compression. As supratentorial pressure increases there is a further downward shift leading to compression and torsion of the pons with rupture of the paramedian perforating arteries supplying the tegmentum of the midbrain and pons. The patient becomes deeply unconscious with abnormal patterns of respiration and temperature control. The pupils are unequal, unreactive, midsized, and irregular, VOR elicits restricted vertical gaze and a progressive ophthalmoplegia develops. There may be decerebrate posturing to painful stimuli. Eventually, apnea, hypotension, and irregularity of the pulse develop (Ropper, 1990).

Despite these classical clinical descriptions, the mechanisms of uncal and central herniation remain uncertain. Early depression of the level of alertness in a patient with an acute hemispheric mass lesion may be more clearly related to distortion of the brain by horizontal displacement than to transtentorial herniation with brainstem compression. Ropper has shown that, with raised intracranial pressure due to an extratemporal mass, horizontal displacement of the pineal body on coronal magnetic resonance imaging (MRI) scan of 0–3 mm from the midline was associated with alertness, 3–4 mm with drowsiness, 6.0–8.5 mm with stupor, and 8–13 mm with coma (Ropper, 1986, 1989). He found that, in the presence of an extratemporal mass, the perimesencephalic cistern was often widened, suggesting that the space was not necessarily filled by a herniated temporal lobe. Thus, uncal herniation may be due to a prominent horizontal shift and rotational torsion at or above the tentorium, even in the absence of significant brainstem descent.

4.4.1.3. Other forms of herniation

4.4.1.3.1. Subfalcine herniation

This occurs when the cingulate gyrus is displaced across the midline and under the falx. This may lead to compression of the ipsilateral anterior cerebral artery with secondary frontal infarction and edema. It is particularly associated with frontal tumors.

4.4.1.3.2. Upward transtentorial herniation

Upward transtentorial herniation of the brainstem may occur as a result of lesions that compress the upper brainstem, including tumor or hemorrhage in the pons, medulla, cerebellum, or region of the IVth ventricle. The tectum of the midbrain and the anterior cerebellar lobules are forced upwards through the tentorium leading to signs of midbrain dysfunction including small, asymmetrical, and fixed pupils, vertical ophthalmoplegia, abnormal respiratory pattern, and decerebrate posturing and coma. The process may be exacerbated by hydrocephalus secondary to aqueduct stenosis and compression of the vein of Galen leading to raised supratentorial venous pressure; compression of the superior cerebellar arteries will result in superior cerebellar infarction.

4.4.1.3.3. Tonsillar herniation

This occurs when there is downward displacement of the inferior medial part of cerebellar tonsils into the foramen magnum as a consequence of an Arnold–Chiari malformation or a posterior fossa mass lesion. This may lead to progressive medullary compression and ischemia characterized by cough, headache, downbeat

nystagmus, skew deviation of the eyes, respiratory irregularities, coma, and death.

4.4.2. Distinction of toxic and metabolic coma from structural coma

It is often possible to distinguish metabolic from structural causes of encephalopathy and coma on the basis of clinical examination. The preceding medical history may indicate the presence of a metabolic abnormality and the onset is more likely to be acute in the presence of a structural lesion. Metabolic or toxic lesions usually cause coma without lateralizing or brainstem signs while structural lesions may be indicated by asymmetrical motor signs. The presence of involuntary limb movements (tremor, myoclonus, and asterixis), abnormalities of the respiratory pattern (hypo- or hyperventilation), and acid–base disturbances suggest a metabolic etiology. The level of consciousness tends to fluctuate and be lighter in patients with metabolic disorders. However, these clinical features are merely indicators and structural lesions such as subarachnoid hemorrhage, cortical venous thrombosis, bilateral subdural hematoma, or multifocal central nervous system (CNS) disease may present with bilateral, symmetrical signs while metabolic disorders (e.g., complication of diabetes mellitus) may present with focal signs.

4.4.3. Psychogenic unresponsiveness

Patients with psychogenic unresponsiveness (pseudocoma) may be distinguished by history, examination and, if necessary, investigations. There may be atypical factors in the history and occasionally obvious psychiatric precipitating factors. In psychological unresponsiveness there are inconsistent volitional responses, particularly on eyelid opening; spontaneous roving eye movements are present and pupillary constriction occurs on eye opening. Occasionally the patient may appear to have no response to deep, painful stimuli but oculovestibular stimulation with cold stimulus will show preservation of the fast phase away from the stimulated side. Finally, the EEG will show responsive alpha rhythms.

4.5. Outcome from coma

Most patients who survive the initial insult only remain in coma for 2–4 weeks before they regain signs of responsiveness or enter a vegetative state. The extent of eventual recovery is highly variable.

It is not possible to assess the prognosis of a patient in coma with complete accuracy but a number of clinical factors help to guide the observer in predicting the likely outcome. For example, coma associated with drug and alcohol ingestion or metabolic disturbance generally carries a good prognosis for recovery providing there is no severe underlying disorder, the patient has received adequate systemic support while in coma and there has been no secondary hypoxic or hypoperfusion insult. The prognosis for a patient in traumatic coma is generally better than that for a patient at a similar level of coma from nontraumatic causes. These patients are usually younger and continued improvement may occur despite prolonged coma and severe disability. The most important predictive features for survival in patients in coma due to severe head injury for more than 6 hours are depth of coma (as defined by the Glasgow Coma Score, pupillary responses, eye movements, and motor responses) and patient age (Jennett and Bond, 1975; Jennett and Teasdale, 1977; Levy et al., 1985; Mueller-Jensen et al., 1987; Van de Kelft et al., 1994; Kane et al., 1995; Combes et al., 1996). The extent of injury and presence of skull fracture, hemispheric damage, or extracranial injury are less important in determining survival and residual disability. However, secondary insults such as raised intracranial pressure and low cerebral perfusion pressure are associated with an increase in severe disability (Hamel et al., 1995; Chen et al., 1996) and higher mortality.

The prognosis for patients in non-traumatic coma is poor and depends on several important factors (Bates et al., 1978; Levy et al., 1981; Bates, 1991; Berek et al., 1994):

1. *Etiology:* Patients in coma due to structural cerebral disease (e.g., cerebrovascular disease or subarachnoid hemorrhage) carry the poorest prognosis, with only 7% achieving moderate or good recovery. The outlook for hypoxic–ischemic insults is little better in published studies but it is increasingly apparent that patients who are resuscitated out of hospital following cardiac arrests but remain in coma from hypoxic insults carry a very poor prognosis. The best outlook is in patients with coma due to metabolic or toxic insults, of whom 35% achieve a moderate or good recovery (Costa, 1992).
2. *Depth of coma* as determined by GCS augmented by cranial nerve territory reflexes including vestibulo-ocular and corneal reflexes is a sensitive guide to outcome. At 24 hours if there is no eye opening, vocal response, or motor function the patient has a 6% chance of making a moderate or good recovery. In the presence of eye opening, grunting, and limb flexion to noxious stimuli, up to 20% will make a moderate or good recovery.

3. *Duration of coma:* Nontraumatic coma lasting for more than 1 week is said to carry only a 3% prospect of good recovery while a shorter duration (<6 hours) is associated with a 15% prospect of good recovery.

Following hypoxic–ischemic insult, the most sensitive predictors of a bad outcome are the absence of pupillary light reflexes, corneal reflexes, and motor responses (except extensor plantar responses) at 3 days. However, the absence of other brainstem reflexes, GCS <5, loss of cortical N20 response on short-latency somatosensory evoked potentials (SSEPs) at 1–3 days, elevated serum neuron-specific enolase level, and an EEG showing alpha coma, burst suppression, or an isoelectric trace provide strong supporting evidence for a poor prognosis and when these abnormalities are seen at 3 days they provide adequate prognostic information to allow discussion with relatives about the patient's wishes and likely outcome (Geocardin et al., 2006; Wijdicks et al., 2006). However, these indicators are not specific and so a poor outcome may also occur even if the initial signs suggest recovery (Levy et al., 1985; Bassetti et al., 1996; Zandbergen et al., 1998). CT scan findings may also be important in determining prognosis. The presence of anteroseptal shift, temporal lobe infarction, and hydrocephalus imply a worse outlook. Intracranial pressure is also important as a prognostic determinant, particularly in traumatic coma. Finally, it must be emphasized that many of these findings relate to studies that are more than 15 years old. It seems possible that with better techniques of intensive care, physiological measurement, and cerebral protection these data are no longer accurate and should be used as a general guide only (Garcia-Larrea et al., 1992; Krieger et al., 1993).

4.6. Brain function in coma

In a number of recent elegant studies using PET scanning and functional MRI it has been possible to measure cerebral metabolism and brain activation in response to sensory stimuli. These techniques have shown that regional cerebral gray matter metabolism is 50–70% of normal in patients with post-traumatic or hypoxic coma but cerebral metabolism has a variable correlation with clinical assessment. Even after recovery from postanoxic coma the metabolic rate for glucose is reduced to 75% of normal. Local impairment in cerebral metabolism has also been described in the thalamus, brainstem, and cerebellar cortex; a similar reduction is noted with deep anesthesia and during stage III and IV sleep.

4.7. Vegetative state

The diagnosis, prognosis, and management of the vegetative state have received considerable attention in Europe and the USA over the last few years. This has partly been because of legal rulings on highly publicized individual cases (Dyer, 1992; Angell, 1994; Jennett, 2002; Annas, 2005; Quill, 2005) but also because a series of professional bodies have attempted to establish guidelines on clinical and ethical aspects of management (BMA Medical Ethics Committee, 1992, 1994; American Neurological Association Committee on Ethical Affairs, 1993; Institute of Medical Ethics, 1993; Multi-Society Task Force on PVS, 1994a, b; Ashwal et al., 1995; Howard and Miller, 1995; Quality Standards Subcommittee of the American Academy of Neurology, 1995; Giacino, 1997; Zeman, 1997; Wade and Johnston, 1999; Royal College of Physicians, 2003). In a comprehensive and valuable review the American Multi-Society Task Force on PVS sought to clarify the situation by summarizing information on the available literature concerning prognosis to facilitate consensus management recommendations (Multi-Society Task Force on PVS, 1994a, b).

4.7.1. Clinical aspects

The vegetative state occurs following acute cerebral injuries, degenerative and metabolic disorders, or developmental malformations. The first is by far the largest and most important group and can be subdivided into traumatic (e.g., road traffic accidents or direct cerebral injury) and nontraumatic (e.g., hypoxic–ischemic encephalopathy, stroke, CNS infection, tumor, or toxic insult). It usually develops after a variable period of coma; it may be partially or totally reversible or may progress to a persistent or permanent vegetative state or death. The persistent vegetative state (PVS) is defined as a vegetative state that has continued for at least 1 month but this definition does not imply permanency or irreversibility.

Patients in a vegetative state (Jennett and Plum, 1972) appear to be awake with their eyes open but show no evidence of awareness of self or environment, are unable to interact with others and have no evidence of sustained, reproducible purposeful or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli. There is no evidence of language comprehension and expression. Patients are able to breathe spontaneously. Cycles of eye opening and closing that simulate sleep are present, as are the hypothalamic and brainstem autonomic responses that maintain respiration and circulation. There is bladder and bowel incontinence but cranial nerve (pupillary,

vestibulo-ocular, corneal, blinking, pharyngeal, cough, sucking, and swallowing), spinal and primitive reflexes are variably preserved. Inconsistent nonpurposive movements, facial grimacing, smiling and frowning, chewing, swallowing, bruxism, vocalization, grasping, and inconsistent auditory and oculomotor orientating reflexes to peripheral sounds or movement may occur. Painful stimuli may elicit a withdrawal response but no localization, there may be a brisk grasp reflex and patients may occasionally appear to laugh or weep inappropriately but these behaviors have no consistent relationship to appropriate stimuli. The diagnosis of vegetative state is not tenable if there is any degree of voluntary movement, sustained visual pursuit or tracking, consistent and reproducible visual fixation, or response to threatening gestures or to command. In occasional patients there may be isolated stereotypical episodes of complex behavior including uttering occasional words or appropriate responses to stimulation. These imply that isolated corticothalamic networks remain intact but do not imply awareness or consciousness.

The absence of SSEPs is a potent indicator of death or irreversible vegetative state (Fischer and Luaute, 2005; Guerit, 2005; Fischer et al., 2006). However, some patients, apparently in vegetative state, show some response to evoked potentials, suggesting the capability to process semantic stimuli, indicating some comprehension. Functional imaging shows that cortical metabolism of patients in the vegetative state is 40–50% of normal but there is a further reduction of 30–40% when the state is permanent. There appears to be selective impairment of frontotemporal parietal association cortices accounting for the loss of content (attention, language, and memory) but relative sparing in the brainstem, hypothalamus, and basal forebrain, explaining retained arousal and autonomic function (Laureys et al., 2004).

Brain activation studies have suggested that isolated activation of primary cortex may occur following visual, auditory, or painful stimuli but that there is little evidence for activity in the higher order associative cortices necessary for processing emotional and behavioral responses. Single or limited stereotyped responses including vocalization may be associated with residual activity in isolated functional areas such as the left-sided thalamocortical–basal ganglia loop supporting language (Menon et al., 1998). However, functional imaging is providing increasing evidence that patients thought to be in a vegetative state may retain cognitive abilities that have evaded detection using conventional clinical testing. Owen et al. (2006) described a 23-year-old woman who had been in vegetative state for 5 months after a traumatic brain injury following a road traffic accident; functional MRI showed appropriate speech activities bilaterally in the middle and superior temporal gyri equivalent to those seen in normal controls. The authors then went on to show responses to mental imagery tasks that were also indistinguishable from healthy conscious control subjects. Thus, although apparently in vegetative state, the subject retained the ability to understand spoken commands and to respond to them by appropriate brain activity, showing clear evidence of consciousness as manifest by awareness of herself and her surroundings.

4.7.2. Pathology

There is no single pathological pattern of brain damage that produces the vegetative state. Following hypoxic brain damage there may be generalized or focal loss of the neocortical ribbon, worse in parieto-occipital or border zone regions, with widespread laminar necrosis as seen in the brain of Terri Schiavo (see below) (described in Wijdicks and Cranford, 2005). There is also necrosis of the thalamus, cerebral white matter, caudate nucleus, hippocampus, and Purkinje cells of the cerebellum. Following trauma the lesions are more complex with diffuse axonal injury disconnecting the largely intact cerebral cortex and thalamus from other parts of the brain. In other patients there may be prominent cortical and thalamic involvement similar to that seen after hypoxic–ischemic damage. There is often a secondary progressive wallerian degeneration of subcortical white matter leading to progress atrophy. It is likely that the thalamic lesions in these patients ultimately interrupt afferent and efferent connections between any structurally intact cortical area and the brainstem (Kinney et al., 1994; Adams et al., 2000).

4.7.3. Diagnosis

Several authors have emphasized the difficulties in diagnosing the vegetative state and the rate of misdiagnosis may be up to 43% (Childs et al., 1993; Andrews et al., 1996). In the presence of profound disability (paralysis, spasticity and/or dysphasia), the patient may only be able to demonstrate awareness through specific motor acts (e.g., nonverbal gesture or specific movement). The diagnosis of vegetative state requires multiple observations, repeated for short periods over a considerable amount of time using standardized assessments and clear criteria for recording responses. It is important to ensure that the assessments are undertaken with the subjects in good general health, a good nutrition state, and with any sedating drugs withdrawn. The assessments should be undertaken in an optimal seating position and well rested.

4.7.4. Outcome

There are two dimensions of recovery from vegetative states: recovery of awareness and the recovery of voluntary motor function. Recovery of awareness may occur without functional recovery but functional recovery cannot occur without recovery of awareness. The Multi-Society Task Force emphasizes that the most important factors in determining the outcome of PVS include the patient's age and the etiology and duration of PVS. Overall the available data indicate that the mortality rate for adults in PVS after an acute brain injury is 70% at 3 years and 84% at 5 years. Death is associated with pulmonary or urinary tract infections, respiratory failure, and sudden death of unknown causes. The Multi-Society Task Force estimated the outcome probability at 12 months for patients who remained in PVS 3 and 6 months after the initial insult. In adults with PVS 3 months after traumatic injury approximately one-third will recover by 12 months with more than half being severely disabled. After 6 months in PVS, approximately 12% recover to severe disability and 4% to moderate disability or good recovery. The outcome is worse following nontraumatic insults: after 3 months in PVS approximately 7% will recover, usually with severe disability, and there were no cases of recovery after 6 months in PVS. In children the data are limited: while the outcome for traumatic PVS at 12 months seems to be better than adults there is little difference from adults for nontraumatic insults. On the basis of these data it was concluded that a persistent vegetative state can be judged to be permanent 12 months after a traumatic injury and 3 months after a nontraumatic insult in adults and children. Although occasionally a verified recovery has been reported after these times, such recovery is virtually always associated with severe disability (Andrews, 1993a; Childs and Mercer, 1996). Recent media reports suggesting that zolpidem may bring patients out of a vegetative state have not been supported by experience.

4.7.5. Management

What are the implications of these findings for the management of patients in coma or a vegetative state after acute brain injury? At the onset it is appropriate to provide aggressive medical treatment where the prognosis remains uncertain. This will include the provision of adequate hydration and nutrition (via nasogastric tube or gastrostomy), airway protection, and appropriate attention to posture, contractures, skin, bowel, and bladder care. It is important to ensure that stimulation and rehabilitation are available as soon as the patient is stabilized (Andrews, 1992, 1993b), although the role of coma arousal programs remains unproven.

Once the diagnosis of PVS is established continuing treatment is justified if, as the British Medical Association Ethics Committee states, 'it makes possible a decent life in which a patient can reasonably be thought to have a continued interest' (BMA Medical Ethics Committee, 1992, 1994; Jennett, 1992). The level of treatment will depend on clinical assessment by the physician and discussion with the patient's family or surrogate decision makers. The role of high-technology treatments (e.g., mechanical ventilation, dialysis, cardiopulmonary resuscitation) and routine medications (e.g., antibiotics) or other commonly ordered treatments (e.g., supplementary oxygen) can only be determined in the context of the individual case.

However, the debate concerning the management of the PVS remains volatile and the legal situation is unclear worldwide. Many cases have now passed through the courts leading to an important body of case law. The first important case in this area was that of Karen Ann Quinlan, a 21-year-old woman who had been found collapsed following an excess of alcohol and drugs. She sustained anoxic–ischemic brain damage and remained in a vegetative state, apparently dependent on ventilatory support. Her parents sought the assistance of the court in discontinuing the ventilatory support as the treating physicians refused to do so, believing that they could be held criminally liable for murder. The New Jersey Supreme Court ruled that competent persons have a right to refuse life-sustaining treatment and that this right should not be lost when a person becomes incompetent. They accepted that Quinlan would not have wished to continue living in such a state. They therefore formulated a mechanism to allow the treating physicians to remove her 'life-sustaining treatment' (ventilatory support) if there was no reasonable possibility of her returning to a 'cognitive, sapient state'. In the event Quinlan was weaned from a ventilator and lived for a further 10 years in a vegetative state. Following the Quinlan judgment, in the USA it became clear that, for mentally capable adults, the doctor is bound by the person's refusal of treatment. This clearly also extends to the case of the mentally incapable adult who has made an advanced refusal of treatment while mentally capable (Angell, 1994).

In 1983 Nancy Cruzan sustained a severe head injury and entered a permanently vegetative state. After 3 years her parents requested the 'right to die' on the grounds that she would not have wished to lived in a PVS. The physicians agreed to the removal of artificial nutrition and hydration (ANH) via a PEG tube. However, the State of Missouri objected, citing that

Cruzan had not completed a living will and stating that the family and friends had not provided clear and convincing evidence of her wishes not to be treated. The State concluded that it held an unqualified interest in the preservation of life and that this outweighed any consideration about the quality of that life or any constitutional or common law rights to have treatment withheld. The US Supreme Court upheld the state judgment, but eventually further evidence of Cruzan's wishes were submitted and withdrawal of ANH was undertaken, leading to her death. This case, and subsequent discussion, emphasized the need for clear advanced directives, particularly relating to the provision of life-supporting treatment for patients in PVS or with terminal illness. Although the Cruzan case did appear to undermine the family role in reflecting the patient's wishes, the ultimate result was to confirm the appropriateness of withdrawing ANH from patients in a permanent vegetative state.

In the UK the case of Anthony Bland established a similar legal precedent. Bland was a young man left in a PVS after being crushed in the Hillsborough football stadium disaster. The court supported the application by the Trust (hospital administration) to withdraw ANH. It recognized that the application was strongly supported by the family and this was regarded by the court as being of great significance. The case was accompanied by considerable publicity and public debate and established the following fundamental points in UK law (Dyer, 1992; Jennett, 2002):

1. Medical decisions for a mentally incapable patient should be made by the treating doctor in the best interests of the patient.
2. If a decision to withdraw or withhold life prolonging treatment is in the best interests of the patient then it is lawful.
3. There is no legal difference between the decision to withhold treatment and the decision to withdraw treatment.
4. Artificial nutrition and hydration constitute medical treatments and can be withdrawn if it is in the best interests of the patient to do so.

In reviewing the case the House of Lords concluded:

1. Life-prolonging treatments could lawfully be withdrawn from patients in PVS.
2. For such patients doctors should seek a declaration from the courts before stopping treatment.

The unfortunate case of Terri Schiavo has emphasized the difficulties in making appropriate decisions for these patients. This patient sustained a cardiac arrest leading to severe hypoxic–ischemic encephalopathy. Unlike the cases of Quinlan, Cruzan, and Bland there was a family dispute. The judge agreed with the independent medical opinion that there was clear and convincing evidence that Ms Schiavo was in a vegetative state but, in a legal hearing 12 years after the event, doctors hired by the patient's parents disagreed with the diagnosis and suggested that improvements might still occur. It was concluded that there was clear and convincing evidence that Ms Schiavo would have chosen not to receive life-prolonging treatment but the situation was complicated because of the denial of the diagnosis of vegetative state. Following a court ruling, the feeding tube was removed for the first time but a bill was passed by the State of Florida demanding re-insertion. Eventually, in 2005, the tube was removed again after a further appeal and despite an extended and acrimonious debate in the Senate (Annas, 2005; Quill, 2005).

For a fuller account of these cases the reader is referred to the comprehensive review by Jennett (2002) or to the original case material. In summary however, in the USA and UK, the rights of the competent patient to refuse unwanted medical treatment is a settled ethical and legal issue and thus there is now considerable pressure on the population to make advanced directives concerning their wishes. If a 'living will' has not been prepared there remains considerable debate about further management and courts have not always been clear in determining responsibility. However, both medical and legal authorities have advised that, in some circumstances, it may be legitimate and ethically acceptable to withdraw life-sustaining treatment, including tube feeding, when the patient's condition is irreversible. When the diagnosis of PVS has been established and it is accepted that further therapy will merely prolong an insentient life for the patient the decision should be communicated sensitively to the relatives, who must then be given time to consider the possibility of withdrawing artificial means of administering food and fluid. In the UK, at present, the courts require that the decision to withdraw nutrition and hydration, resulting in the inevitable death of the patient, should be referred to the court before any action is taken. The American Academy of Neurology and the American Medical Association guidelines allow physicians to withhold and withdraw ANH from permanently unconscious patients when it has been determined that the patients or their surrogates have expressed informed refusal of ANH (American Medical Association, 1990; American Academy of Neurology, 1993, 1995). However, individual state legislation may require clear and convincing evidence of intent to refuse ANH expressed prior to the onset of unconsciousness (Larrivier and Bonnie, 2006). The decision to withdraw other life-sustaining medication such as insulin for diabetes may also need to be referred to the courts because the legal situation is uncertain.

However, the decisions not to intervene with cardiopulmonary resuscitation or not to prescribe antibiotics or undertake dialysis remain clinical.

4.8. Minimally responsive state

Minimally responsive patients are no longer in coma or vegetative state but demonstrate low-level behavioral responses consistent with severe neurological impairment and disability (American Congress of Rehabilitation Medicine, 1995; Giacino et al., 2002). Patients who are minimally responsive are able to show consistent evidence of awareness of themselves or their environments by following simple commands, gestural or verbal yes/no responses, intelligible speech, or purposeful behavior in response to a stimulus (e.g., sustained visual fixation or tracking, appropriate smiling or crying to stimuli, appropriate verbal or gestural responses to questions, reaching for an object, or using it appropriately). They are not able to communicate consistently. These patients may remain in a minimally responsive state or become able to communicate or use objects functionally.

Using auditory evoked potentials preserved semantic processing can be observed in minimally responsive patients although the responses are delayed (Perrin et al., 2006). Functional imaging studies show that in the minimally responsive state cerebral metabolism is reduced to values comparable with the vegetative state. Studies suggest these patients show activity in the medial parietal and posterior cingulate gyrus. These are association areas thought to subserve awareness (Burke et al., 2002; Bekinchtein et al., 2004). The results of brain activation studies are uncertain but there may occasionally be preservation of large-scale association networks in some patients, suggesting that meaningful recovery is at least possible.

4.9. The locked-in syndrome

The locked-in syndrome is characterized by preservation of consciousness and awareness of the environment in the presence of horizontal gaze palsy, anarthria, and tetraplegia. There is dissociation between automatic and volitional control of lower cranial nerve and limb function. Volitional respiratory, facial, bulbar, and limb control is lost but there may be involuntary phenomena including ocular bobbing, facial grimacing, oral automatisms and trismus, palatal myoclonus, and emotional responses including laughing and crying (Patterson and Grabois, 1986; Munschauer et al., 1991; Heywood et al., 1996). Vertical eye movements are preserved with synergistic elevation of the upper eyelids when looking upwards. These vertical eye movements are slow and incomplete, but are the only way in which the patient can communicate. The patients are conscious and aware of the environment around them despite being severely restricted in motor function (Gutling et al., 1996). They are able to communicate using residual motor function. Because they are alert it is important to establish a consistent form of communication to be used with the patient (Smith and Delargy, 2005).

The most frequent cause of locked-in syndrome is occlusion of the vertebrobasilar artery, usually predominantly in the rostral or middle segments. Pontine hemorrhage or embolic disease may also cause the condition. Other causes of locked-in syndrome have been described in which the lesion was situated in the ventral pontine tegmentum, in the basis pontis or in the mesencephalic region at the level of the cerebral peduncles. Cases of locked-in syndrome due to bilateral internal carotid artery lesions have also been described. The etiologies of nonvascular cases have included central pontine myelinolysis, trauma, encephalitis, tumor, pontine abscess, multiple sclerosis, and heroin abuse. Peripheral lesions (i.e., severe neuropathy such as Guillain–Barré syndrome) may cause an apparent locked-in syndrome with severe limb, facial, and bulbar paresis, although respiration is frequently affected because of respiratory muscle paralysis (Vargas et al., 2000; Stojkovic et al., 2001).

Functional recovery is possible in both vascular and nonvascular groups and it is therefore necessary to introduce an aggressive rehabilitation program as early as possible to allow the patient to achieve the highest possible level of recovery as soon as possible. However, the prognosis for most patients in locked-in syndromes is poor with severe residual disability and the risk of aspiration being the usual outcome. The mortality rate is high, with most deaths occurring in the first 4 months, either from extension of the lesion or from respiratory complications (pneumonia, respiratory arrest, or pulmonary embolus).

There are several important and harrowing accounts of living in a locked-in state, which should be consulted by physicians charged with the care of these patients (Bauby, 1997; Chisolm and Gillet, 2005).

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Chapter 5

Herniation

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Observations on herniation, particularly its association with coma, have occupied the attention of neurologists and neurosurgeons for a century. Herniation, strictly speaking, is a translocation of brain tissue from one compartment of the cranium to another. In more recent times it has also taken on the status of a group of clinical syndromes. The unqualified term 'herniation' is applied most often to the displacement of tissue that normally resides in the anterior fossa of the skull; to an unnatural location beneath the plane of the tentorial membrane in to the posterior fossa, i.e., transtentorial herniation. In the material that follows, the emphasis is on this type of herniation because of its intimate relation to coma.

The driving force in most of the pathological and clinical changes that are called herniations is a localized mass that distorts adjacent brain tissue and leads indirectly to the squeezing of regions of the brain across openings in dural boundaries. For this reason, the clinical features that result from herniations, including coma, may be considered 'false localizing signs' or signs that arise at a distance from the inciting mass. An extensive listing of various false localizing signs that include cranial nerve dysfunction can be found in a series of 250 cases of intracranial meningiomas by Gessel (1961) and is discussed in greater detail further on.

A linkage between changes in brain conformation due to a mass and constellations of clinical signs has been a part of the literature from the earliest writings. Either implicitly or explicitly, certain herniations have been associated with particular patterns of signs. Despite a fair amount of anatomical information concerning intracranial masses and the distortions of brain tissue that they cause, the various schemes that connect certain clinical syndromes to these anatomical changes all have shortcomings.

Another basic detail has emerged from clinical experience and must be taken into account when discussing the effects of herniations. While brain tissue displacements may be the result of either an acutely expanding or a more chronically evolving mass, and the pathological configuration in these two circumstances is no different, the clinical signs depend to a large degree on the abruptness with which the brain tissue distortion occurs. Also complicating the interpretation of clinical signs in the herniations are a number of secondary phenomena such as hydrocephalus, vascular occlusions with ischemic infarction, and the effects of the mass itself on local brain tissue. These are commented upon below.

With the exception of the movement of inferior cerebellar tissue into the foramen magnum, all the herniations refer to shifts between compartments bounded by dural boundaries. Thus the names transtentorial, transfalcine (referable to the falx), upward cerebellar, and cerebellar–tonsillar (through the foramen magnum) are used. Herniation of tissue into a surgical or traumatic defect in the skull might be included as a special case among these. The term 'incisura' has been adopted from anatomical studies and was introduced in the early literature for the opening in the dural boundary (the tentorium itself is called in some papers by its proper anatomical name, tentorium cerebelli, thus the term transtentorial) through which the brainstem passes.

Before reviewing what each of the herniations of brain tissue encompasses, a brief review of the historical developments of the understanding of herniation is useful in framing the current state of affairs.

5.1. Historical aspects

As pointed out by Simonetti and colleagues (1997), Pierre Marie can perhaps be credited with the earliest

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descriptions of displacements of supratentorial tissue into the tentorial opening in 1899. He curiously emphasized secondary compression of the superior cerebellum, a feature not often discussed subsequently. He also pointed out that continued pressure of this nature would eventually force the cerebellar tonsils through the foramen magnum and that medullary compression could have contributed to a fatal outcome in the case he described.

In the early 20th century, neurosurgeons studying cerebral trauma and brain tumors were the first to draw attention to the distortions of brain observed at the autopsy table. In 1904, Collier attributed certain signs in 161 cases of large brain tumor to displacement of the brainstem and cerebellum and pointed out that the tentorial edge caused a crease in the medial temporal lobe under these circumstances. This linear impression on the medial aspect of the brain was to prove insightful since it later directed attention to the transtentorial herniations. Included in Collier's observations were two cases with third nerve palsies and 12 with sixth nerve palsies. At approximately the same time, and less ambiguously 5 years later, Cushing described his observations on the insinuation of the medial temporal lobe into the tentorial opening during operation and in experimental animals. His emphasis on the features that later came to be called the Cushing reflex (the result of a rapidly expanding mass) did not, however, focus on the clinical effects of the tissue shifts referable to the upper brainstem.

It was not until 1920, in a paper read before the 46th annual meeting of the American Neurological Association, that Adolph Meyer framed in explicit terms the notion of displacements of brain tissue in cases of postmortem material with brain tumor for which he coined the term 'herniation'. He was attracted to hemianopia and a vascular bruit as important reflections of herniation. Jefferson and later Van Gehuchten confirmed these findings in pathology material and were the first to attempt a systematic correlation between compression of the brainstem and clinical features (although few of their observations would be accepted as valid today). Spatz and Stroescu in 1934 published extensive illustrations of pathological specimens with transtentorial hernias but emphasized mostly the features of 'cruciate paralysis' that would be later attributed to Kernohan and Woltman. Horizontal translocation was emphasized by Kernohan and Woltman of the Mayo Clinic in 1929. They described a paradoxical hemiplegia that arose from an intracranial mass and made the astute clinicopathological correlation of this sign with compression of the contralateral cerebral peduncle against the tentorial edge. Their pathological observations included the demonstration of demyelination along the groove on the peduncle.

Important refinements of the pathological configuration were brought out by Hasenjäger and Spatz (1937), who are credited with emphasizing displacement of the midbrain and thalamus as consistent features of transtentorial herniation but who also alluded to horizontal translocation as a potentially important feature in producing clinical signs. However, their study was of pathological material and they made little attempt to infer what clinical signs would result from compression of deep structures.

A series of clinical misinterpretation punctuated many of the aforementioned papers and most of those published in the first half of the 20th century. For example, in an influential and often cited paper, Vincent and colleagues (1936) attributed nuchal rigidity, paresthesias, cardiac irregularities, headache, black vomitus, somnolence, cyanosis, ptosis, irregular respiration, pulmonary edema, and respiratory arrest to 'le cône de pression temporal'. Jefferson (1938) sought to bring some clarity to the situation in a review in which he cited a constellation of four clinical aspects of a mass lesion and herniation that he called 'vegetative storm': meningismus, decerebrate rigidity, and a dilated pupil. An additional notion, expressed repeatedly in articles of the time, typified by LeBeau's report (LeBeau and Houdart, 1947), was that the signs of transtentorial herniation presaged imminent death. In contrast, Jefferson was of the opinion that the main clinical signs were all the result of diencephalic pressure and that medullary failure occurred as a much later manifestation.

For many years, the work published in 1949 by Moruzzi and Magoun that established the central role of the brainstem reticular formation in alertness was not brought into relation with the concept of transtentorial herniation. One of Jefferson's later lectures edged toward making the connection but was not entirely specific, as it dealt mostly with the mechanism of concussion. Prominent workers during this period, such as Munro and Sisson (1952), concluded that herniation was not associated with any specific clinical signs except perhaps for a dilated pupil and autonomic instability. Nonetheless, what emerged from the cumulation of literature to this point was that *in fatal cases* a mass, usually a tumor, caused distortion of adjacent tissue that eventually could be seen at autopsy to be pressing the upper brainstem downward into the incisura and that these pathological changes were implicated in coma, pupillary enlargement, and eventually respiratory and vascular collapse.

The evolution of thinking regarding pupillary dilatation, a clinical staple of the terminal stages in cases of large cerebral masses, was somewhat less disordered. The first clear mention of pupillary enlargement with head trauma is attributed to Cock in 1842. This sign was later called the 'Hutchinson pupil' because of its mention in the latter author's monograph in a case with

cerebral abscess (Hutchinson, 1878). Pupillary enlargement was generally established as an accompaniment of severe head injury in many papers published during the early part of the last century. The work of Reid and Cone (1939), and later Sunderland (1958) and Sunderland and Bradley (1953), related it to compression of the third nerve by the advancing medial temporal lobe or to the descending posterior cerebral artery. An alternative view was offered by Fischer-Brügge (1951), who suggested that the third nerve was instead stretched on the clivus as a result of horizontal displacement of its origin at the upper midbrain. No cogent explanation has been offered for enlargement first of the pupil opposite a mass, but several theories have been put forward, as noted further on.

It was on this background that the careful investigative work of McNealy and Plum (1962) and Plum and Posner (1966) cohered and codified the relationships between herniations and clinical signs. Their publications marked a watershed in that, for the first time, a systematic aggregation of clinical signs was based on serial observation at the bedside. In contrast, all prior work had been derived from either clinical observation devoid of pathological confirmation, or pathological observation alone. By placing a pointed emphasis on coma in the clinical herniation syndromes, these authors anchored the understanding of transtentorial herniation from a mass lesion. At the same time, they made clear and understandable the previous disparate clinical aspects by eliminating many of the numerous signs incorrectly attributed directly to transtentorial herniation, e.g., the physiological changes of the Cushing reflex, stiff neck, vomiting, headache, etc. To suggest that this was the limit of the scope of McNealy and Plum's monograph is incorrect; they made a careful study of all aspects of coma. As alluded to above, a deficiency of most reports to that date was simply that a lengthy list of clinical features was given from a series of tumor or trauma cases observed operatively or on the autopsy table and no clinical consistency came with them. An example of the confusion preceding the McNealy and Plum report is an otherwise excellent paper by Schwarz and Rosner (1941) in which 16 of 43 patients with a hemispheral mass had stiff neck but only nine were observed to have pupillary changes on the side of the mass (another nine had pupillary enlargement on the other side!) with later observed transtentorial hippocampal herniation. Examples can be given from many other papers of the Plum and Posner era that gave tabular accumulations of disembodied clinical signs.

However, the work of McNealy and Plum that formed the basis for much of the central dictum of the Plum and Posner (1966) monograph did not include pathological studies of the patients under their observation. Mindful of previous works, the authors of the original article went to pains to emphasize that they did not endorse or imply a relationship between the postmortem appearance of the brain herniations and the like-named clinical syndromes. Nonetheless, by naming the constellations of clinical signs as 'uncal' and 'central' transtentorial syndromes, what emerged after years of broad exposure to Plum and Posner's monograph was the notion that a series of dynamically progressing brainstem signs could unambiguously be attributed to the pathological changes of the same name. The net result was an equivalence in the minds of most clinicians between clinical features, particularly coma, and the pathological configuration of transtentorial herniation. The elegance, simplicity, and plausibility of an orderly deterioration of neurological function from rostral to caudal brainstem structures as a result of compression by mass from above had such intellectual appeal and utilitarian value for teaching brainstem function to students that it has led to a tacit adoption of the so-called central and uncal herniation clinical syndromes.

Less well recognized from the same period but quite profitable for review are three monographs, one by Finney and Walker (1962), the same year as the publication of the paper by McNealy and Plum (1962); another in 1967 by Blinkov and Smirnov of the Burdenko Institute in Moscow (Blinkov and Smirnov, 1971), who carefully summarized virtually all the known data and their own observations on what they called 'dislocational syndromes', and the extraordinary paper by Fisher (1969) detailing the signs of coma and remarking on the prognostic value of these signs, including changes in respiration.

Other herniations were commented upon at intervals in the literature. Among these are the ones listed at the beginning of this chapter: foramen magnum–cerebellar herniation, upward cerebellar herniation, transfalcine herniation, and herniation of tissue through surgical skull defects. The clinical correlates of these brain dislocations are somewhat less certain than for the transtentorial ones, although it has been assumed that cerebellar–foraminal impaction is the proximate cause of respiratory arrest from medullary compression, as discussed below.

5.2. Intracranial pressure and herniation

Worth noting are the concurrent clinical phenomena with herniation. These changes in systemic physiology are broadly encompassed by the term 'Cushing reflex'; namely, hypertension, bradycardia, and changes in respiratory pattern. That some of these features occur in conditions of raised intracranial pressure but not

necessarily in the presence of a mass and tissue distortion suggests that transmission of pressure to sensitive areas in the fourth ventricle can occur by direct compression of the brainstem from a contiguous mass or indirectly through raised pressure within the ventricular system.

With the emergence in the 1960s and 1970s of extensive studies of intracranial pressure, somewhat less attention was given to the clinical syndromes relating to herniation. Ultimately, attempts to correlate pressure with either coma or pupillary changes were largely unsuccessful. It became recognized, as emphasized by Andrews and colleagues (1988), that the location, as well as the earlier mentioned rapidity of enlargement of the mass and its size, were the critical elements in the nature of tissue shift produced. Masses in the temporal lobe were, for example, more likely to produce early uncal herniation and pupillary changes. Restated, raised intracranial pressure per se does not cause herniation. However, as demonstrated by Weaver and coworkers (1982), there are substantial differential pressures between intracranial compartments in the presence of a mass and, in all likelihood, these gradients are the proximate causes of tissue shifts (my observations suggest that intracranial pressure sometimes drops suddenly in the supratentorial compartment just after the appearance of signs that indicate tissue shift). Elevated pressure and tissue shifts may therefore be conceived of as parallel reflections of the addition of a mass to the cranium.

5.3. Anatomy of the dural openings

The dural membrane that separates the supra- from the infratentorial compartment (or anterior from posterior fossa) is properly called the tentorium cerebelli, hence the common use of the term 'tentorium' for this structure. It is anchored anteriorly on the petrous ridges and the anterior clinoid process. It slopes downward in a slightly cantilevered form to attach laterally along the transverse venous sinuses. Posteriorly, it is attached to the internal occipital protuberance. A large, roughly oval opening in the center of the membrane allows passage of the brainstem from the upper to the lower compartment.

The size and configuration of the tentorial opening almost certainly figure into the manifestations of transtentorial herniations in a given individual. In most autopsy studies, the anteroposterior diameter of the opening ranges from 5–7 cm and the horizontal axis from 2.5–4 cm. Sunderland (1958) gave a measurement for the tentorial opening of 5.5 cm long by 3 cm wide. With the exception of one specimen he estimated the surface area of the opening to be between 10 and 18 cm^2. Careful studies by Corsellis (1958) and by Plaut (1963) gave similar ranges for the width of the incisura, between 2 and 4 cm. Corsellis's photographs of the tentorial opening and composite tracings indicated that there was a difference between the male and female tentorial configurations. His study also maintained the anachronism (popular at the time probably because of the teachings of Boas, the influential anthropologist) that separated white from black patient measurements and correlated the size of the tentorial opening with the bitemporal diameter of the skull. He also pointed out that aging-related atrophy may have played a role in changing the outline of the opening between specimens.

Measurements from a more modern paper by Ono and colleagues (1984; also referred to below) generally conform to earlier studies. The average width of the opening was 29.6 mm, range 26–35 mm; average length – dorsum sella to apex of the opening – 52 mm, range 46–67 mm; and, perhaps most importantly, the average width of the space of Bichat, from the edge of the midbrain to the tentorial margin was 0.7 mm with a range of 0–6.6 mm. It is the variability in these sizes and the usual location of the entire midbrain above the tentorial opening that are notable.

The plane of the dural tentorial membranes slopes downward at approximately 30° in most specimens but the incisural opening is in the axial plane of the brain (in some texts, it virtually defines the axial or horizontal plane). The shape of the tentorial opening simulates a U with considerable variability in its shape at the apex posteriorly, at times being closer to a V with a pointed posterior termination. The schematic drawings of Sunderland (1958) give one of the best demonstrations of the variability in shape, ranging from a small tentorial opening that barely accommodates the midbrain and allows only a small amount of anteriosuperior vermis to show through from above to a virtually oval and very accommodating opening.

The uncal gyrus in most cases slightly overhangs the edge of the tentorium by 3–4 mm and the immediately posterior parahippocampal gyrus can usually be seen from under the tentorial opening, particularly in its anterior portion. The groove produced normally by the tentorial edge on the uncus and parahippocampal gyri is discussed above.

Also of interest is the considerable variability in the location of the branches of the circle of Willis and exact course of the third nerves and their relationship to the tentorial edge. The third nerves exit from the ventral midbrain, consistently rostral to the tentorial plane (contrary to what is stated in many textbooks). They then proceed superolaterally to pass under the posterior cerebral artery and above the superior

cerebellar artery. Their location in the crotch formed by those two arteries is variable, at times allowing direct contact with one or the other vessel, most often the posterior cerebral. They then come into contact with, or close proximity to, the uncus at the lateral tentorial edge and then course over the petroclinoid ligament to enter the dura of the posterior cavernous sinus.

As mentioned, the vermis of the cerebellum fills the posterior part of the tentorial opening.

Several careful studies have been made, all pointing out that the relationship between the brainstem and the lateral edge of the tentorium in the vertical dimension may vary by as much as 2 cm and that the size of the subarachnoid space (of Bichat) between the free edge of the tentorium and the lateral edge of midbrain varies from less than 1 mm (essentially bringing the two structures into contiguity) to just over 6 mm, as already noted. Also quite variable is the position of the pontomesencephalic sulcus (marking the anterolateral border between the pons and midbrain and created by the transition from the cerebral peduncle to the basis pontis). In one of the most extensive studies of the anatomical relationships between the tentorial dura and surrounding structures, including striking color drawings, Ono and colleagues (1984) from Rhoton's neurosurgical group showed that in cadavers the pontomesencephalic junction lies, on average, only 0.2 mm below the incisural plane so that considerable damage can be done to the midbrain, diencephalon, and upper pons by advancing temporal lobe tissue without any displacement of tissue through the tentorial opening. In a way, this creates a semantic problem with regard to herniation – is the encroachment of tissue into the perimesencephalic cisterns and compression of the midbrain truly 'herniation' or simply tissue displacement that crushes the midbrain? Since this displacement occurs on average well above the plane of the tentorial opening, it is not per se a herniation.

The subfalcial opening is approximately 10 cm long and 5 cm vertically (i.e., 50 cm^2 in cross-sectional area). It merges posteriorly with the anterior tentorial opening. The size of the foramen magnum and the precise location of the inferior cerebellum and medulla also vary considerably and little is served by reviewing the details given in the literature.

Given these observations it is not surprising that the precise configuration of tissue displacement and herniation also vary greatly from case to case and that the clinical signs are not entirely predictable in any given instance. How cerebral atrophy plays a further role in altering these relationships has been commented on by several authors but has not been studied systematically.

5.4. Pathological changes of herniation

Most reports in the first half of the 20th century on the pathological appearance of transtentorial herniation parsed the different aspects of the tissue shifts that occurred around the tentorial opening into downward movement (Howell, 1961), insinuation into the tentorial notch of the medial temporal lobe, and rotational distortion of the midbrain (Sunderland, 1958) when, in fact, most cases embodied all three changes, at least at different stages of the evolution of the herniation. Blackwood and Corsellis in *Greenfield's Neuropathology* (1976) emphasized the pathological results of pressure changes in the following order:

1. injury to the third cranial nerves on the side of a space occupying lesion as it passed between the posterior cerebral artery and the superior cerebellar artery, suggesting that the nerve had been held tightly against one of the vessels or across the petroclinoid ligament;
2. temporal incisural herniation by which was meant movement of a portion of the uncus or hippocampal gyrus through the incisura, and secondary effects of which were thought to lead to obstructive hydrocephalus;
3. elongation of the midbrain in the anteroposterior plane, mainly also as a result of hippocampal herniation;
4. compression and damage to the cerebral peduncle opposite to a mass;
5. various secondary vascular lesions in the occipital and temporal lobes, usually in the nature of hemorrhagic infarction of the cortex, suggesting obstruction of the posterior cerebral artery or one of its branches at the tentorial edge;
6. vascular lesions in the rostral brainstem tegmental regions and elsewhere, possibly related to shearing of capillaries and arterioles from displacement of the brainstem in the vertical plane (see below);
7. infrequent hemorrhages and ischemic vascular lesions in the thalamus.

In the extreme, Howell (1961) described 'buckling' of the brainstem; he used the terms 'diencephalic drooping' and 'shortening of the tectum'. In relation to the tectum, which forms the roof of the aqueduct, he made measurements in midline sagittal brainstem sections of the distance between the superior medullary velum and the superior border of the tectum. In 100 patients with normal brains this dimension varied between 13 and 17 mm, with an average of about 15 mm; by contrast, in nine patients who displayed a clinical syndrome of upper brainstem compression in the last hours of life (not specifically defined) this dimension was shortened to between 10 and 13 mm.

Not typically acknowledged in discussions of these pathological changes is the fact that they represent very advanced stages of tissue displacement and are difficult to correlate with clinical signs during life. The only aperture through which enlarged and displaced supratentorial brain tissue can move is, of course, the tentorial opening. In evolved late cases, downward displacement of the brainstem may be so extreme that the entire midbrain and parts of the thalamus are pushed caudad and found to be displaced below the tentorial opening (Fig. 5.1). Similarly, large portions of the uncus, hippocampus, and parahippocampal gyrus on one side may be found squeezed into the space between the tentorial edge and the medial edge of the upper midbrain (Fig. 5.2).

5.4.1. Medial temporal grooving

To the abovementioned changes should be added the pathological feature perhaps most specifically associated with a mass and with raised intracranial pressure, namely grooving of the medial temporal lobe by the tentorial edge, particularly on the parahippocampal gyrus. Klintworth (1968) found such a visible groove on one or both sides in 88% of normal brains. In 1% of normal brains the impression was on the posterior portion of the parahippocampal gyrus. In pathological specimens this change may be grossly evident or detected only by a small degree of microscopic change in the brain tissue

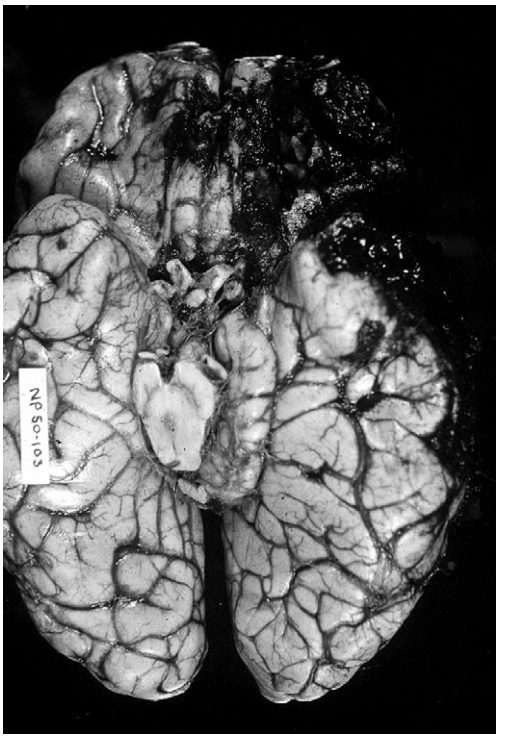

Fig. 5.2. Extreme downward and medial uncal and parahippocampal herniation from a traumatic lesion. The groove produced by the edge of the tentorium on the medial temporal lobe is clearly seen and the temporal lobe tissue is applied to, both displacing and distorting, the midbrain. (With permission from Ropper, 1992.)

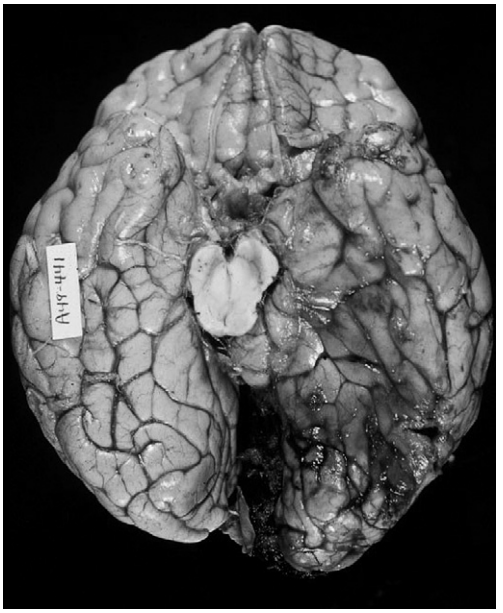

Fig. 5.1. Severe downward herniation of the upper brainstem through the tentorial aperture with ischemic changes in the midbrain. The source of the mass effect was traumatic contusion and swelling.

along the line of the tentorium. There has been considerable ambiguity in the literature regarding the necessity for actual herniation in the creation of this change. Since this groove has also been used as a marker of raised pressure during life, another problem that arises is the degree of grooving that should be considered pathological.

5.4.2. Secondary brainstem hemorrhages

A literature on the nature of secondary brainstem hemorrhages emerged in parallel with the descriptions of tissue distortions and herniations. These hemorrhages represent the most severe degree of brainstem compression and displacement and are typical of cases that were acutely fatal, usually with coma from the onset (Fig. 5.3). Varying opinions have been offered regarding the origin of these lesions but the bulk of evidence favors arterial rupture, as pointed out by Johnson and Yates (1956). Scheinker (1945) and Poppen et al. (1952) had previously suggested venous congestion as the cause. An often cited paper by Klintworth (1968) repeats this view, with little substantiation, and posits venous congestion from downward herniation, followed by restoration

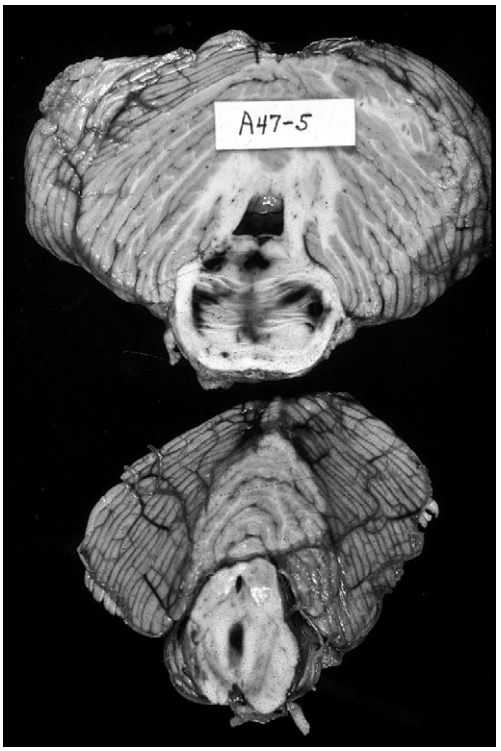

Fig. 5.3. 'Duret' hemorrhages in the midbrain (lower section) and pons (upper section). The likely mechanism is tearing of arteries as noted in the text. The pons does not appear to be distorted but it was displaced caudally. (With permission from Ropper, 1992.)

of circulation. Articles by Moore and Stern (1938) and others addressed this question and the predominant opinion was that small arteries were torn as a result of the downward movement of the brainstem and the relative fixity of the basilar artery. The pathology studies of Fisher (1972), and of Blackwood and colleagues (1949), provided evidence of rupture of small penetrating branches of the basilar artery in the end stages of downward brainstem displacement. It has become customary in the literature to use the term 'Duret hemorrhage' for all of the secondary brainstem hemorrhages created by tissue shifts. Duret's original description referred to medullary hemorrhages but the terminology is so embedded in clinical and pathological parlance that there is little point in attempting to change it. The residua of these brainstem lesions in surviving patients are discussed further on.

5.5. Physiological mechanism of brain dysfunction with tissue distortion

Whatever the connection between tissue displacements and clinical syndromes, the intervening mechanism has been presumed to be ischemic based on pressure from adjacent tissue. Experimental work documenting this mechanism has, however, been sparse. Wozney and colleagues (1985) had the opportunity to study an instructive head-injured patient by xenon cerebral blood flow technique. She was initially unresponsive, with one large fixed pupil and another sluggishly reactive pupil. After evacuation of subdural hematoma she remained unresponsive with decorticate posturing but the pupil became reactive. There was a residual right frontal hematoma. At a time when she became decerebrate and began to show intermittent dilatation of the pupil on the side of the hematoma, blood flow was reduced in the basal ganglia bilaterally. There was an implication that thalamic blood flow was likewise diminished but this was not clear from the data Wozney et al. presented. Evacuation of the frontal hematoma resulted in a restoration of blood flow in deep structures to normal levels. In a correlative study by Ritter and coworkers (1999) there was a rough association between reduced blood flow (xenon) in the midbrain and bilateral unreactive pupils.

The few related experimental studies that can be interpreted suggest that extreme degrees of tissue distortion and greatly raised intracranial pressure are required to produce ischemia of the brainstem. In anesthetized dogs, Schrader and colleagues (1985) expanded a supratentorial epidural balloon to the point of respiratory arrest. A microsphere method was used for cerebral blood flow. The focus of the study was the resultant Cushing response but extensive measurements were made of various areas in the thalamus and brainstem. The extreme nature of the experiment precluded any firm conclusions, but blood flow in the midbrain, pons, and medulla decreased dramatically from 40–60 ml/100 g/min to single-digit values once apnea occurred. This was despite a marked increase in systemic blood pressure. In unpublished experiments I performed 20 years ago with my colleague K. Swann we found that brainstem blood flow (measured by hydrogen polarographic electrodes implanted in the midbrain and pons) was initially low in anesthetized animals and dropped further as an epidural balloon was inflated. We could not dissociate the drop in blood flow in the brainstem from the same degree of reduction throughout the cerebrum as a result of a global increase in intracranial pressure.

An alternative mechanism for the dysfunction of neurons in compressed tissue is a reduction of neurophysiological activity simply from mechanical factors. Numerous studies have demonstrated a reduction in various components of the brainstem auditory evoked responses in relation to either coma or pupillary changes. However, it is notable that the wave most easily studied (V) arises in the colliculi, not in the brainstem

tegmentum, and none of the studies clarifies the issue of the proximate cause of brainstem dysfunction. In other words, it cannot be determined if the waves were lost because of a reduction in local blood flow or from the effects of tissue distortion.

As tissue shifts progress, hemorrhages in the brainstem arise as discussed in the section on pathological changes. Also found are areas of ischemia, particularly in the upper brainstem and diencephalon. Reversal of coma with relief of a mass would require that brainstem ischemia, if that is the mechanism, be entirely reversible. Therefore, factors such as the duration of compression and mechanical changes must come into play.

5.6. Clinical syndromes of herniation

In conformation with current practice, it is useful to delineate the clinical features that result secondarily from large intracranial masses according to the type of presumed displacement of brain tissue. As an idealized concept, transtentorial herniation is divided into a central syndrome and uncal syndrome and separated distinctly from transfalcine, upward cerebellar, and foramen magnum herniations. In many cases, these entities are found to occur together but to progress to different degrees and at different rates. Emphasis is placed here on transtentorial herniation and its putative clinical signs, since it is of most practical interest to the clinician. Fundamental to the transtentorial syndromes is the premise that pressure on the midbrain, particularly its rostral portion, results in a graduated reduction in the level of consciousness. While this tenet has been challenged, most recently by Parvizi and Damasio (2003), observations by neuroradiological techniques continue to support the notion that it is necessary and sufficient to compress these regions of the reticular activating system in order to produce drowsiness, stupor, and coma.

5.6.1. Uncal transtentorial herniation and pupillary enlargement

Signs of third nerve and midbrain compression from a medially displaced uncus are more common in our experiences than are other syndromes. Plum and Posner (1966) expressed the view that, with medial temporal lobe masses, the diencephalon is not the first structure compressed and that the initial state of alertness is therefore variable. Instead, pupillary signs are, in their opinion, the earlier feature in uncal herniation. In our own material the first indication of third nerve compression is usually a sluggish or absent light reaction on the side of the mass (Ropper and Shafran, 1984). This sign may persist for hours or longer before the pupil actually enlarges. Plum and Posner (1966) also commented on the rapidity with which subsequent signs may evolve, including deep stupor and then coma. It is the pupillary enlargement, of course, that is the signature feature of uncal herniation.

Fluctuations in pupillary size, corectopia (eccentric position of the pupil) and, as pointed out by Fisher (1980) and by Marshall and others (1983), an irregularly shaped oval, oblong or 'football'-shaped pupil may be a transitional sign before frank enlargement and also a transient feature during recovery of the light reaction. These shapes probably represent incomplete stages of compression of the pupilloconstrictor fibers in the third nerve. Marshall and colleagues (1983) attributed the oval-shaped pupil to raised intracranial pressure but the information contained in their paper demonstrates pressures ranging between 6 and 34 mmHg and midline shift ranging from none to 18 mm on computed tomography (CT). In most of the instances they reported, the pupil returned to normal shape after reduction of intracranial pressure. As has already been mentioned, the correlations between intracranial pressure and pupillary signs is indirect, both being parallel phenomena reflecting the presence of a mass.

The subsequent evolution in the uncal syndrome is of deepening coma and then dilation of the contralateral pupil. Plum and Posner (1966) also noted that the contralateral pupil may become fixed in mid-position and that later both pupils often assume a mid-position (5–6 mm) diameter. If pressure continues to be exerted on the structures of the posterior fossa, there is then a loss of eye movements, loss of corneal response, more prominent posturing, aberrant respiratory rhythms and, eventually, death from medullary compression. As already discussed, it is the orderliness of this rostral to caudal progression that makes the Plum and Posner (and McNealy) model so appealing by matching anatomical structures to the herniation syndromes.

Reversal of the pupillary changes upon treatments that reduce intracranial pressure or mass effect is a notable phenomenon. Often such reversals occur repeatedly before the patient is saved by operation, or as a transitional phase to further brainstem compression and death. Fisher has raised an objection to the attribution pupillary enlargement to uncal herniation by pointing out that it is unlikely that herniated tissue, once having molded itself to the space between the free edge of the tentorium and the lateral midbrain, would then be lifted out of this space (not to mention extracting itself repeatedly) simply by reducing intracranial pressure (Fisher, 1995).

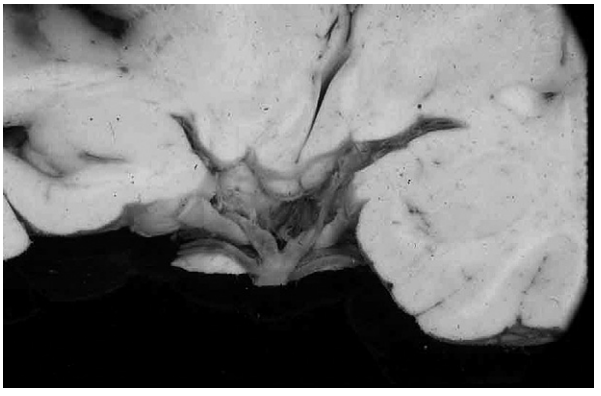

Fig. 5.4. Coronal section of brain at the level of the mamillary bodies showing the relationship between third nerves and posterior cerebral arteries emanating from the top of the basilar artery in a case of cerebral hemorrhage (the clot can be seen in the upper left). The posterior cerebral artery is draped over the third nerve and is pulling it caudally. This is one of the presumed mechanisms of pupillary enlargement (see text). (With permission from Ropper, 1992.)

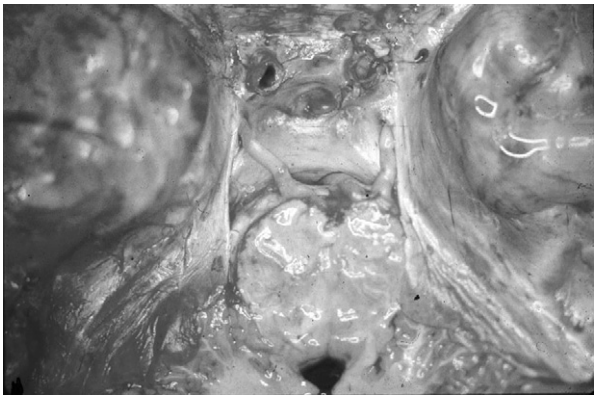

Fig. 5.5. Dissection in situ of the third nerve and adjacent structures from a patient with a cerebral hemorrhage who had an enlarged pupil on the side of the mass prior to death. The hemorrhage was on the reader's left; the third nerve on that side can be seen to be stretched over the clivus because of horizontal displacement of its origin but the contralateral third nerve is slackened. There was no uncal herniation. (With permission from Ropper et al., 1991.)

Plum and Posner (1966) in fact indicated that the mechanism of third nerve compression on the side of a mass is most likely the descent of the posterior cerebral artery and compression of the superior aspect of the nerve (Fig. 5.4). For the most part, the uncus is implicated, largely because it pushes this vessel caudally. This is in accord with the work of Sunderland (1958), Sunderland and Bradley (1953), and Weintraub (1960). However, I have observed, and others have posited, alternative mechanisms. Reid and Cone (1939), based on autopsy observations, suggested that the advancing edge of the uncus compresses the third nerve directly against the petroclinoid ligament or the free edge of the tentorium. Our dissections from patients with large cerebral masses, performed in situ by sectioning the diencephalon (Ropper et al., 1991), indicate that this mechanism of nerve stretching is valid. In this configuration, the laterally displaced midbrain pulls the origin of the third nerve away from the clivus and the entry of the third nerve into the posterior cavernous sinus (Fig. 5.5). The nerve is thereby angulated acutely over the clivus so that pressure and hemorrhagic changes can be found at that point. This mechanism was detailed in dissections performed by Fischer-Brügge (1951) and termed by him 'das Klivuskantensyndrom'. It was also described in specimens examined by Lazorthes and colleagues (1954) and by Blackwood et al. (1949). In an interesting case with magnetic resonance imaging (MRI) performed in which pupillary changes could be induced by placing a patient in the lateral decubitus position, Simonetti and colleagues (1993) found that the uncus barely touched the nerve but instead stretched it and thus caused this same angulation of the nerve against the posterior clinoid (Fig. 5.6). It is worth noting that most of the aforementioned authors inspected the brain after it had been taken out of the skull so that it no longer bore its in vivo relationships to the tentorial membranes. The key to observing this angulation over the clivus is performing the autopsy with retention of the in situ relationships between the midbrain, third nerves, dural folds, and clivus – it cannot be appreciated if the brain is removed from the skull, which is the usual method.

In all likelihood, different configurations are responsible for pupillary enlargement in different cases (stretching at the clivus, uncal herniation, compression

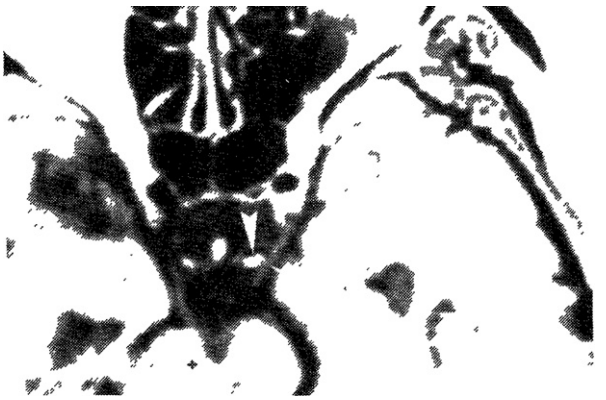

Fig. 5.6. MRI showing displacement of the third nerve (long arrowhead) and the juxtaposition of the nerve against the clivus (white arrow) in a patient with reversible pupillary enlargement when placed in the decubitus position. The uncus is barely in contact with the nerve. (Reproduced from the Lancet, in Simonetti et al., 1993, with permission from Elsevier.)

by descended posterior cerebral artery) but it is my impression that uncal compression is no more common than the others. Differences between individuals in the shape and size of the tentorial openings and in the course of the third nerves also plausibly change the relationships of the structures from one individual to another.

Two problems posed in the analysis of pupillary enlargement are 1) the cause of contralateral pupillary enlargement and light unreactivity as the syndrome progresses, and 2) that small proportion of cases in which the pupil opposite to the mass enlarges first. Clinical investigation into the first problem suggests that in late stages the upper midbrain is compressed and produces bilateral nuclear or fascicular third nerve palsies (Ropper, 1990). This conceptualization, however, is based on serial clinical observations of the second pupil to enlarge and can be considered only circumstantial.

How the opposite pupil dilates first is as much of a puzzle. Gessel (1961), Jefferson (1938), and Pevehouse and colleagues (1960) tackled the problem with no success. The phenomenon has been said to occur in up to 10% of subdural hematomas (Pevehouse et al., 1960) but the proportion has been far lower in my clinical experience. Uncal herniation on the opposite side would seem to be the obvious explanation but this is almost impossible once the midbrain has been shifted over and the perimesencephalic cisterns are closed off. One possible mechanism is that the posterior cerebral artery on the side of the mass in these cases is considerably higher than its opposite, or has a fetal origin from the internal carotid artery and therefore does not come into contact with the ipsilateral third nerve. This explanation is somewhat unappealing since contralateral pupillary enlargement may occur at an early stage of brainstem compression, at a time when there is only drowsiness or stupor. Another even less likely possibility is that horizontal translocation of deep structures pulls the contralateral third nerve up against its adjacent tentorial edge.

It is the case that the uncus and part of the third nerve lie entirely above the tentorial plane so that contact can be made without actual transtentorial herniation but again this is a semantic objection to the use of the term transtentorial herniation. Nonetheless, one might take issue with the entire notion of the advancing medial temporal lobe insinuating itself into the open space over the free edge of the tentorium as the proximate cause of third nerve compression. Such objections are based on the early enlargement of the perimesencephalic cisterns on the side of a mass, as opposed to the expected compression by an advancing edge of temporal lobe (see below). It is as likely that the uncus and parahippocampal gyrus are passively pulled along into this open space rather than being the wedge that opens it.

One practice that derived from the conceptualization of transtentorial herniation as presaging coma and imminent death was surgical removal of the herniated tissue in moribund patients. Scoville and Bettis (1979) reported on 27 such cases, in 15 of which they considered the operation to be lifesaving. The procedure involved cutting directly through the then inferior temporal lobe encompassing the lower two temporal gyri, down to the medial hippocampus that presumably at this time lay subtentorial, and resecting the entire wedge of herniated temporal lobe in one piece. LeBeau is quoted in Scoville's article (Scoville and Bettis, 1979) as using a subtentorial approach to remove the hernia. Mori and colleagues (1998) treated 13 patients with pupillary enlargement and ostensible transtentorial herniation by resecting the uncus and parahippocampal gyrus and reported survival in 11 of them. Others have suggested simply sectioning the tentorial dura on one or the other side.

5.6.2. Central herniation

The central diencephalic and upper midbrain structures can be seen to be squeezed through the tentorial aperture in a downward direction at autopsy in cases with drastic mass effect, as discussed. In the extreme, the type of buckling of the brainstem described by Howell (1961) may be seen. This ostensibly corresponds to the central syndrome, which was the more common type of clinical deterioration in McNealy and Plum's material (McNealy and Plum, 1962). The breathing pattern was affected early, often in the form of a Cheyne–Stokes cyclic pattern but also with sighs, yawning, and pauses in respiration. In distinction to the uncal syndrome, the pupils were initially small, presumably as a result of compression of hypothalamic structures that pertain to pupillary control. Alternatively, a type of 'functional decortication' of the pupils was proposed by the authors. Roving eye movements or easily elicitable oculocephalic movements then follow. As the syndrome evolved, posturing or hemiplegia ipsilateral to the cerebral lesion arise.

Plum and Posner (1966) attributed the initial clinical changes, confusion and agitation or drowsiness, to compression of diencephalic structures. (A parenthetical comment is made here that this implicitly forwarded the idea that confusion lies in the spectrum of diminished level of consciousness.) They were further of the opinion that horizontal shift across the midline was of less importance and more the result of contralateral hemispheral compression than of diencephalic compression horizontally. As the central syndrome progresses, cyclic respirations are said to give way to sustained tachypnea. The initially small pupils

enlarge to approximately 3–5 mm but do not dilate until the end stages. The eye movements become dysconjugate including at times the presence of internuclear ophthalmoplegia. There is then a presumed progression of ischemia to caudal parts of the brainstem until the terminal medullary stage. In these latter parts of brainstem deterioration, the uncal and central syndromes converge.

While numerous examples of squeezing of the central diencephalic and upper midbrain structures through the tentorial opening in the purely vertical direction can be found, including in our own material, this appearance represents a very advanced stage of tissue distortion and it is difficult to infer the configuration at the time that drowsiness and small pupils are present.

Among the most compelling data in support of a central syndrome are those few cases in which a low-pressure cerebrospinal fluid (CSF) situation has resulted in purely and symmetrically downward vertical displacement of the midbrain. The circumstances are not entirely comparable to downward pressure by a mass but this configuration does speak to the clinical effects of caudal displacement of midbrain structures; in essence they are being pulled down rather than pushed. In the cases reported by Pleasure and colleagues (1998), by Bloch and Regli (2003), by Roland et al. (1992), and by Binder and colleagues (2002), a decrease in the level of consciousness was attributed to overdrainage or leakage of lumbar CSF that causes symmetric downward displacement of the upper brainstem through the incisura. In some cases, the level of consciousness could be restored by the infusion of fluid into the lumbar space and a presumed elevation of the brainstem to its original position. If the ischemic theory of midbrain–diencephalic function applies, then there must be some type of buckling of the brainstem to alter microvascular flow; this seems unlikely from a tugging action exerted from below. On the other hand, Pannullo and coworkers (1993), using as a marker the top of the aqueduct of Sylvius (see below), found that a substantial degree of downward brainstem movement could occur in a low-pressure CSF syndrome without any change in the level of consciousness. Three of their seven patients also displayed cerebellar downward displacement below a line drawn from the inferior tip of the clivus to the base of the posterior foramen magnum (twining line).

Several attempts have been made to quantitate downward displacement of central structures from radiographic and magnetic resonance imaging (MRI) images. One telling observation by Fisher (1984) was that the pineal calcification remained in the same vertical plane as the choroid plexus on CT scan, despite the presence of a cerebral mass and diminished level of consciousness. In studying the vertical location of the pontomesencephalic junction in relation to the tentorial plane on sagittal MRI images, I found that vertical displacement was variable, and not an obligate feature in cases of diminished consciousness; indeed, some cases with stupor or coma showed a slight upward displacement of the midbrain (Ropper, 1989). Moreover, in many instances the displacement of centrally placed tissue was purely horizontal or even slightly upward. In the studies by Ross and colleagues (1989) and Andrews and coworkers (1988), vertical descent of brain structures was slight and did not correlate with the degree of depression in the level of consciousness. However, the most careful study of vertical displacement was by Reich and colleagues (1993), who ingeniously identified the opening of the aqueduct (the iter) as lying almost on a line drawn between the dorsum sella and the confluence of the deep venous sinuses. (Their assumption that the line reflects the position of the incisural opening is not in accord with all the earlier listed studies.) In this way, it became possible to measure downward vertical displacement of a structure close to the area of the reticular activating system. They found that in normal adults the iter of the aqueduct lay 0.2 ± 0.8 mm below the aforementioned line. With supratentorial masses, the iter was displaced 2–11 mm below the line and, in those who had recovered clinically, the iter was restored to its normal position (Fig. 5.7). While all cases with a mass, including those who remained awake, showed some descent of the iter, there was no quantitative relationship between the level of consciousness and the degree of vertical displacement. Their explanation that substantial degrees of downward displacement could occur without clinical manifestations relates to the slow progress of certain mass lesions and that such downward shifts often preceded clinical deterioration. In our own material, the iter has usually been displaced laterally and sometimes cannot be seen in mid-sagittal images. Also of interest is the similar study by Feldmann and colleagues (1988) in which the older contrivance of Twining's line (between the dorsum sella and the internal occipital protuberance) was used. These authors measured the distance from the line to the pontomesencephalic junction and to the apex of the midbrain aqueduct. Technical factors regarding magnification clouded the interpretation of their data but they were successful in demonstrating that downward movement does indeed occur and that it can be quantified. Their additional assessment was that lateral shifts often accompanied descending transtentorial herniation but to an unpredictable degree. Wijdicks and Miller (1997) reported on a case with serial MRI and demonstrated mainly downward displacement of the diencephalon and mesencephalon that paralleled clinical deterioration.

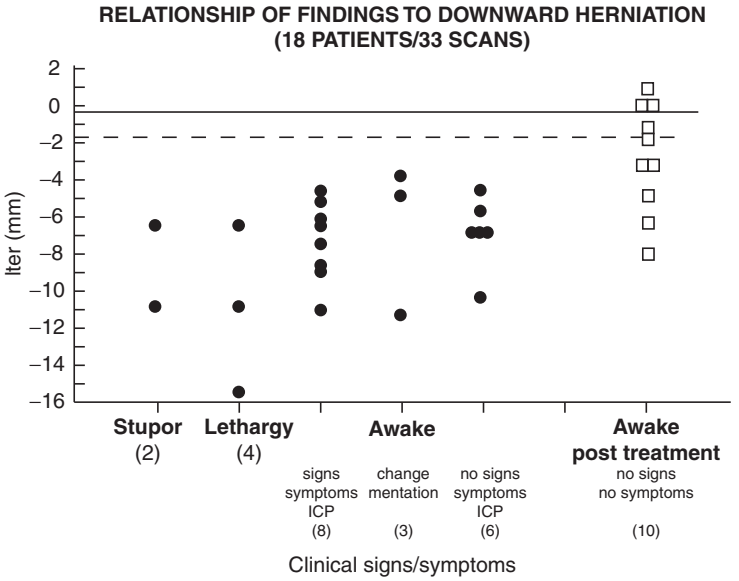

Fig. 5.7. Downward displacement of the iter of the aqueduct in patients with supratentorial masses and correction of the displacement after treatment of the mass. (With permission from Reich et al., 1993.)

Many reports and opinion pieces comment that it is often not possible to distinguish the clinical deterioration caused by the uncal and the central syndromes; i.e., they may in essence occur together. More specifically, unilateral or bilateral pupillary dilatation may appear at the same time as stupor. In observations in my critical care unit this is perhaps more the rule than the exception. This has been particularly true in cases of rapidly expanding deep intracerebral hematomas. Also unverified since the original publication is how often there is truly an orderly progression of brainstem signs from rostral to caudal as set forth by McNealy and Plum (1962).

5.6.3. Horizontal displacements

The horizontal shift of central structures ('midline shift') was the focus of radiologists who favored measurement of pineal displacement on skull X-rays for the detection of mass lesions. Curiously, no attempt was made to correlate the degree of displacement from the midline with the level of consciousness. Several authors, particularly Hasenjäger and Spatz (1937), were of the opinion that horizontal translocation occurred before downward herniation across the tentorial plane. In general, when one observes the onset of drowsiness or stupor, as in the patient with a cerebral hemorrhage whose MRI is shown in Figure 5.8, the degree of horizontal distortion tends to be more pronounced than the degree of downward movement. Moreover, the brainstem cisterns on the side of the mass are usually open and widened at this time, belying any compression of the midbrain by the medial temporal lobe.

However, the degrees of horizontal and vertical displacement are difficult to measure and, as is clear from cases such as that shown in Figure 5.8, the vector of tissue distortion includes both. My attempts to study this phenomenon with CT scans suggested that there was a more consistent and linear relationship in acute cases between horizontal displacement and the level of consciousness in cases of acute mass effect (Ropper, 1984, 1989). Almost without exception, patients remained awake if there was less than 4 mm of pineal shift, became drowsy with 4–6 mm shift, stuporous with 6–9 mm shift, and comatose with more than 9 mm of midline displacement (Fig. 5.9). This data corresponds fairly closely to several other studies including the one by Ross and colleagues (1989), which was largely meant to temper the importance of this measurement by showing that there was no relationship between the degree of initial shift and outcome after evacuation of a cerebral hematoma. Few studies have compared horizontal and vertical displacements in the same patients but our impression, based on an MRI investigation, is that the former is more consistently associated with the level of consciousness, unrelated to herniated tissue in the perimesencephalic cisterns (Ropper, 1989). It must be acknowledged, however, that it is difficult to determine which anatomical markers or structures should be used in such comparisons.

One further comment pertains to the use of the term 'midline shift'. In much of the neurosurgical literature this refers to displacement of the septum pellucidum rather than to the pineal or other midline structure. In my study of midline shift using CT measurements,

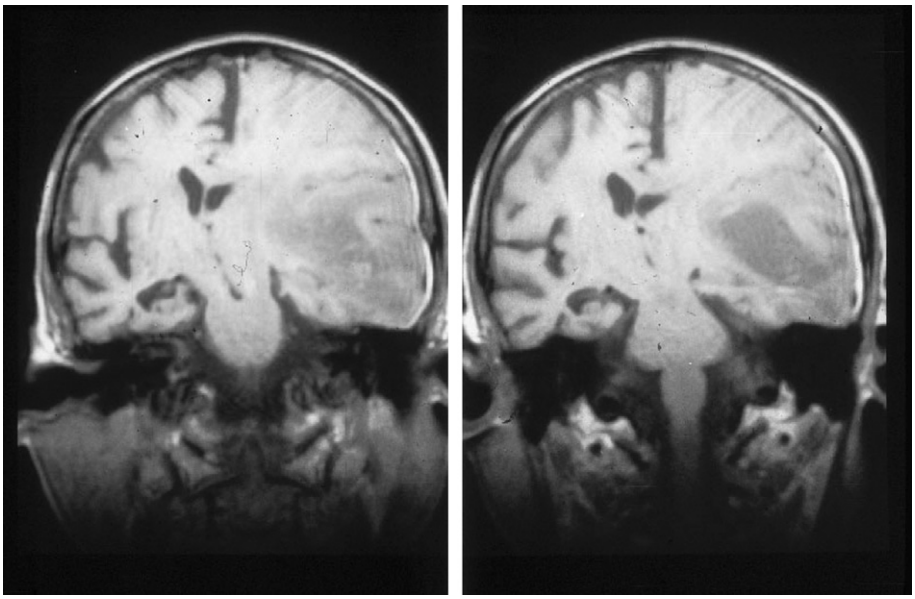

Fig. 5.8. Coronal MRI images from a patient with a large putaminal hemorrhage showing mainly horizontal displacement of central structures and patency of the perimesencephalic cisterns on the side of the mass. There is incipient hydrocephalus evident in the lateral ventricle opposite the mass. (With permission from Ropper, 1998).

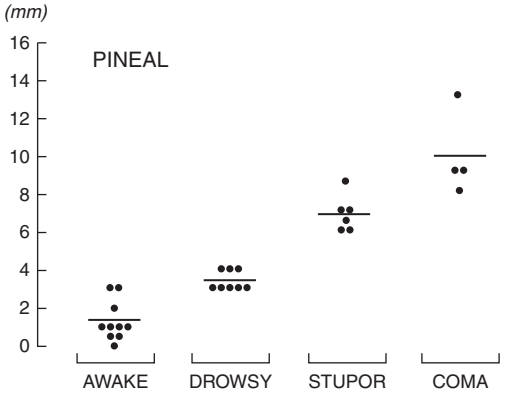

Fig. 5.9. Horizontal displacement from the midline of the pineal body in cases of acute unilateral cerebral masses. There is a graduated increase in horizontal shift with the level of consciousness. This is an extension of the formerly used idea of 'pineal shift' on anteroposterior skull X-rays. (With permission from Ropper, 1986.)

the relationship between the level of consciousness and septal displacement was poor; however, the series reported by Ross and colleagues (1989) showed more of a graduated increase in this measurement as the level of consciousness decreased.

5.6.4. Cerebellar–foramen magnum herniation

This was the deformation that Cushing emphasized early in the last century, to which he incorrectly attributed autonomic instability but which he correctly aligned with respiratory arrest. Like the faint uncal groove that may be seen in normal brains, a similar slight impression can be found on the inferior cerebellum as a result of its contiguity with the lip of the foramen magnum. On occasion, up to 2 cm of tongue-shaped projections of the cerebellum may dip below the foramen magnum and in a few normal specimens the tissue from the two sides meet in the midline (a cerebellar ectopia without Chiari malformation). In the other extreme, as pointed out by Howell (1959) and by others, true foraminal impaction of tissue from downward pressure may be so pronounced as to cause infarction and necrosis of inferior cerebellar tissue, even to the point of causing necrotic material to drop down into the lumbar subarachnoid space (Fig. 5.10). In reference to foraminal herniation, Howell (1959) stated: 'A progressive global impairment of consciousness, which is the dominant feature of upper brainstem compression, is no part of this syndrome. The patient may be alert one minute and dead the next.' In the above-cited MRI study by Reich and colleagues, about half of patients with transtentorial herniation also showed tonsillar herniation.

That foraminal herniation may be partly reversible was shown in the images presented by Onesti and colleagues (1997) in which resection of a massive hemispheral meningioma was followed by elevation of a portion of the inferior cerebellum back into the posterior fossa, and resolution of neck and occipital pain. Residual signs of cerebellar herniation are not subject to study because few such patients survive. Among the features produced by cerebellar herniation is a

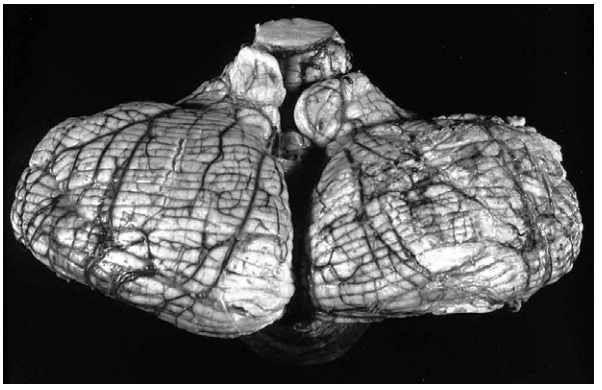

Fig. 5.10. Cerebellar tonsillar herniation with impressions made by the foramen magnum in a case of cerebral tumor.

flaccid quadriplegia, as occurred in one of our patients (Ropper and Kanis, 2000), and a hemiplegia ipsilateral to a cerebellar mass that is the result of compression of the pyramid (Kanis et al., 1994). The latter configuration is somewhat comparable to the Kernohan–Woltman phenomenon insofar as there is a horizontal displacement that compresses the ipsilateral motor pathways and causes a paradoxical hemiparesis.

5.6.5. Upward cerebellar herniation

This displacement is less commented on in the literature than the others. The problem occurs particularly with masses in the posterior fossa. In past decades, it was recognized largely by implication when an upward displacement of the pineal calcification was detected. Obstructive hydrocephalus is a common accompaniment. Few reports have attempted to make a correlation with a clinical syndrome, but one important paper by Cuneo and colleagues (1979) suggested that the premonitory signs were due to pontine compression (reactive but small pupils, asymmetric or absent caloric responses, and decerebration) followed by frank upward herniation that produced midbrain compression, reflected by a change from round and reactive pupils to anisocoria. Several instances have been reported of upward cerebellar herniation occurring immediately after ventriculostomy for obstructive hydrocephalus that was caused by a cerebellar mass, such as the case described by Kase and Wolf (1993). Differentiating the effects of the posterior fossa mass from the secondary effects of upward herniation is difficult.

5.6.6. Transfalcine herniation

This refers to displacement of the cingulate gyrus under the falx and into the contralateral frontal compartment of the skull as a result of pressure from a lesion in one anterior hemisphere. The dimensions of the opening under the falx membrane that allows movement of the cingulate and adjacent gyri have been mentioned earlier. Most of what can be said regarding this herniation pertains to occlusion of the anterior cerebral artery or its callosal branches, as discussed below. In other words, the clinical effects of tissue shifts across the frontal region without vascular occlusion are not at all clear. In the early literature it was suggested that a frontal syndrome of one sort or another emerged if there is no concurrent depression in the level of consciousness.

5.7. Secondary effects of herniation

5.7.1. Monovascular occlusive syndromes

Numerous examples are to be found in the pathology and radiology literature of hemorrhagic infarctions in the posterior and anterior cerebral artery territories that occur concurrently with transtentorial herniation (Fig. 5.11). Probably the earliest report of occipital infarction was included in Meyer's series (Meyer, 1920). On occasion, it is possible by angiography to identify compression of the proximal vessel at the tentorial edge by brain tissue.

In the case of posterior cerebral artery infarction, it is almost always the distal calcarine territory that becomes ischemic and, far less often, the medial temporal region is altered (Lindenberg, 1955). Usually, the vascular occlusion and infarction in the posterior regions is on the side of the supratentorial mass, but there are numerous examples in which solely the contralateral side or both sides are affected. One of the largest series of illustrative cases of secondary infarctions from herniation has been given by Sato and colleagues (1986). Of their nine patients, the contralateral occipital lobe was involved in two and there were additional areas of infarction in the posterior limb of the internal capsule and contralateral hippocampus in one patient each. Papadakis (1974) reported a derivative case of alexia without agraphia due to left occipital and callosal infarction.

Anterior cerebral artery occlusion, usually the result of herniated cingulate gyrus, results in limited infarction of the ipsilateral frontal lobe. Among the most instructive of such cases are the three reported by Rothfus and colleagues (1987) of callosal–marginal artery branch infarction. They noted that this vessel would be the most susceptible to compression of the branches of the anterior cerebral because it runs adjacent to the falx. A pathological study of a series of frontal lobe infarctions caused by cingulate herniation was given by Sohn and Levine (1967). Another paper

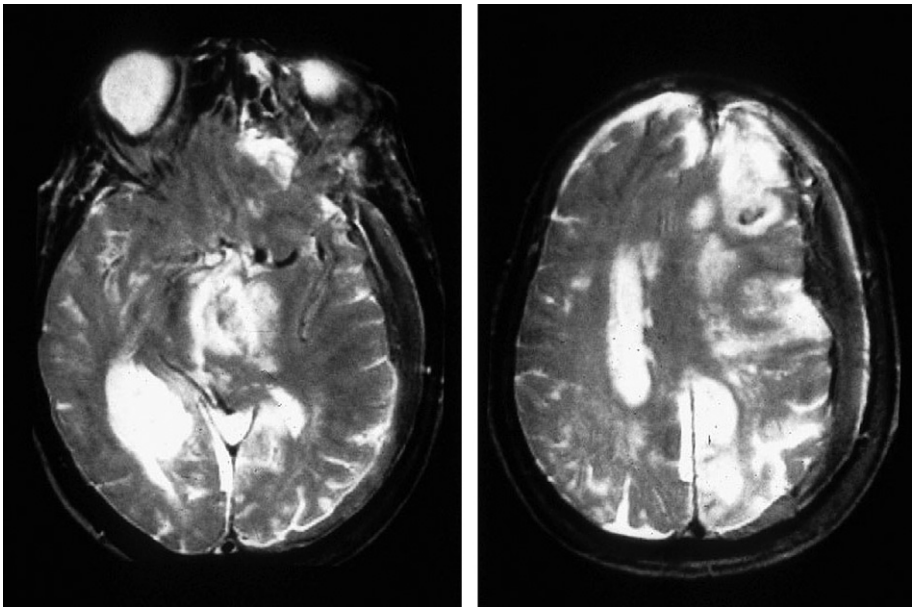

Fig. 5.11. MRI scans of brain shift from a massive left middle cerebral artery infarction showing secondary i) right and left posterior cerebral artery infarctions, ii) right anterior cerebral infarction, and iii) early contralateral hydrocephalus.

by Moore and Stern (1938) is of interest mainly because they made an implicit connection between occipital infarctions and brainstem ischemic–hemorrhagic lesions, a notion that has little support because the mechanisms differ. They did emphasize the hemorrhagic component of some occipital infarctions and made careful histologic studies.

The variability between individuals in the configuration of vessels and their relationships to the tentorial margins has already been mentioned and, conceivably, this may account for the inconsistent appearance of the strokes. There seems little doubt, however, that vascular occlusion requires genuine herniation of tissue from one dural compartment to an adjacent one. Patients who survive coma and transtentorial herniation may be left with strokes, mainly a hemianopia, but, despite the references given above, such examples are rare.

5.7.2. Obstructive hydrocephalus

Here, the problem is apparently that a large unilateral mass causes tissue shifts across the midline that ostensibly traps the contralateral lateral ventricle at the foramen of Munro or in the midportion of the ventricle. However, as pointed out incisively by Stovring (1977a), careful consideration suggests that hydrocephalus cannot be manifest in the ventricle on the side of the mass since it is compressed early during expansion of the lesion. Therefore, it is at least as likely that the third ventricle or aqueduct is compressed and that what appears to be unilateral hydrocephalus is actually a generalized hydrocephalus but with the inability of one ventricle to expand. Few pathological studies have been made.

5.7.3. Sixth nerve and other cranial palsies from a cerebral mass

This is a common but perplexing problem as alluded to earlier in the discussion of false localizing signs. In cases of raised intracranial pressure in which there is no tissue shift, either vertical or horizontal (e.g., in pseudotumor cerebri or sagittal sinus venous thrombosis) unilateral or bilateral sixth nerve palsies may result. It is difficult to conceive, however, how pressure alone could be the causative agent and it is presumed that some tissue shift occurs. Presumably, displacement of the brainstem, most probably downward, tugs on the cranial nerves in some way, but this is speculative. A similar theoretical problem pertains to the fourth nerve palsies that appear after head trauma.

In cases of herniation and brainstem compression, sixth nerve palsies are often obscured by the evolution of more prominent ophthalmoplegic signs. Lower cranial nerve palsies have also been described in cases of supratentorial tumors but there is no a priori reason to attribute them to herniation (Needham et al., 1970). In Collier's series of 20 tumor cases, there were six unilateral and six bilateral abducens palsies. He attributed the sign to posteroinferior displacement of the tentorium (sic), brainstem, and cerebellum. The series by Gessel (1961) mentioned in the introductory section

of this chapter can be consulted for the relative frequency of cranial nerve signs in a large collection of meningiomas.

5.7.4. Tissue displacements from bilateral supratentorial masses

This presents a special problem in that there is little or no horizontal shift and there may or may not be caudal displacement of central structures. One likely mechanism of coma is that bilateral masses act in a pincer-like manner to compress the diencephalon and upper midbrain above the tentorial plane (Fig. 5.12). There tends to be a more symmetric elongation and distortion of the brainstem than occurs in cases of a unilateral mass. Undoubtedly, bilateral or diffuse brain swelling or masses can push the upper brainstem downward through the incisura, i.e., cause central herniation. Balanced cerebral enlargement is more likely than a unilateral mass to be accompanied by sixth or fourth nerve palsies but one suspects that this may be because coma and brainstem compression do not supervene and hide the cranial nerve signs.

5.8. Persistent clinical effects of brainstem and diencephalic damage

In addition to the occipital and anterior cerebral artery territory infarctions discussed above, a number of curious and often singular persistent effects of transtentorial herniation have been reported. Among these is a peduncular hemiplegia from the horizontal Kernohan–Woltman displacement. A more extensive version is a locked-in syndrome that is due to peduncular necrosis on one side and capsular infarction on the other, as reported by Keane and Itabashi (1985). Similar compressions of the motor tracts in the posterior fossa have already been mentioned from our material.

Furthermore, patients may be left with any number of upper midbrain and pontine signs. Among these are internuclear ophthalmoplegia, vertical gaze palsy, and persistent pupillary changes, or other residual signs of oculomotor paralysis as recorded most extensively by Keane (1986), whose article should be consulted. Two notable cases described by Caplan and Zervas (1977) had persistent third nerve palsy, one of which was possibly central in origin.

One presumes that cases of persistent coma after herniation would provide instructive information regarding the nature of upper brainstem distortion with a mass. Interpretation of such material is clouded by the presence of the primary mass lesion or by diffuse traumatic injury to the brain. Nonetheless, there are instances on record in which persistent coma corresponds solely to an ischemic hemorrhagic lesion in the dorsal ventral brainstem that resulted from tissue shifts (Ropper and Miller, 1985).

5.9. Neuroradiological features of herniation

A substantial literature on this subject existed prior to the inception of CT and MRI scanning. Careful explications by Taveras (1961) using pneumoencephalography and numerous studies that used major vascular

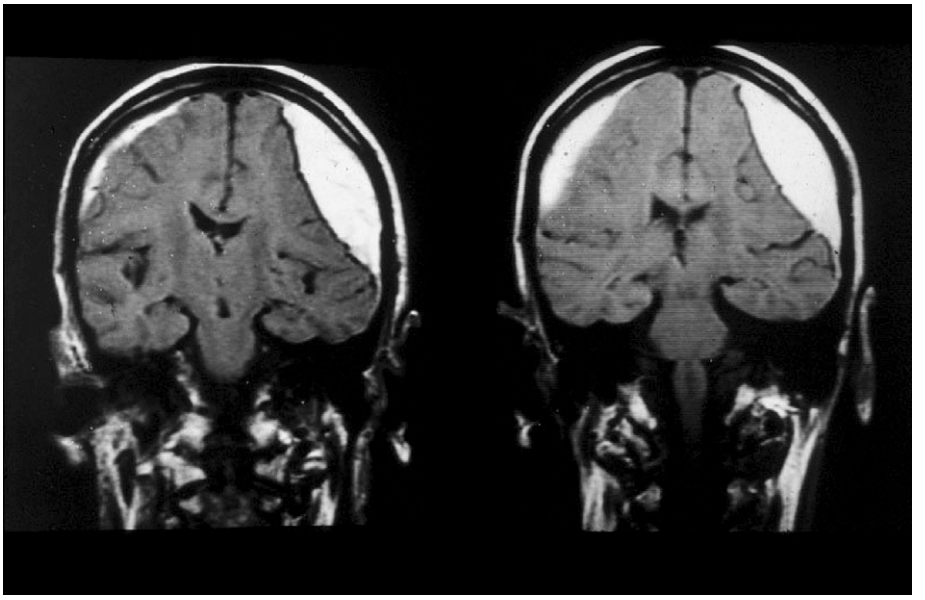

Fig. 5.12. Coronal MRI scans from a stuporous patient with bilateral subdural hematomas. There is little lateral shift but the diencephalon and midbrain are nonetheless compressed in a 'pincer-like' configuration. (With permission from Ropper, 1998).

structures as markers of displacement appeared in the middle of the last century. Prior to that time, the location of the pineal calcification was a staple of neuroradiological study, as already mentioned. Pia (1957) and also Lilja (1948) believed that there was a correspondence between the degree of herniation and the displacement of the pineal from the midline but at the same time they were among the first to point out that inferior displacement was a more important aspect. A summary of these early radiological studies is to be found in the monograph by Finney and Walker (1962) (see pp. 103–125 of that monograph).

Most of the anatomical displacements that can be detected by MRI and CT have been referred to in the previous discussion, particularly in reference to central herniation. The earliest changes have to do with obliteration of the cisterns that abut the upper brainstem at the incisura and also with compression of the suprachiasmatic cistern. Probably most relevant is the compression of the lateral perimesencephalic cistern on the side of the mass. Osborn (1977) described the early features of mass effect on tentorial structures and she suggested that encroachment on the lateral aspect of the suprasellar cistern by the displaced temporal lobe was a feature of impending transtentorial herniation. Stovring was of the opinion that the reverse pertained, namely that suprachiasmatic encroachment was an early sign and herniation was evidenced by a widening of the ambient and crural cisterns on the side of the lesion (Stovring, 1977b) (Fig. 5.13). Once the brainstem had been displaced horizontally and the contralateral cerebral peduncle flattened, herniation was considered to be actually occurring. However, Osborn concurred that the subarachnoid space between the ipsilateral free tentorial edge and the lateral midbrain expanded as this herniation was occurring. This opening up of the perimesencephalic cistern on the side of the mass (space of Bichat) has retained its importance as an early sign of tissue shift and reflects almost entirely horizontal translocation of the diencephalon well above the level of the tentorium. Once the midbrain has been slightly rotated and the perimesencephalic cisterns obliterated by medial temporal tissue, herniation is fully evident. Many neurosurgical reports emphasize the compression of these cisterns as a poor prognostic feature and rough correlations have been made with pupillary changes. Several demonstrations of the Kernohan–Woltman phenomenon have been made, one of the most instructive being the report of Cohen and Wilson (1990), which showed a lesion in the peduncle. These and related radiological changes are reviewed by Nguyen and colleagues (1989) from the perspective of CT anatomy and have the great advantage of pathological correlation.

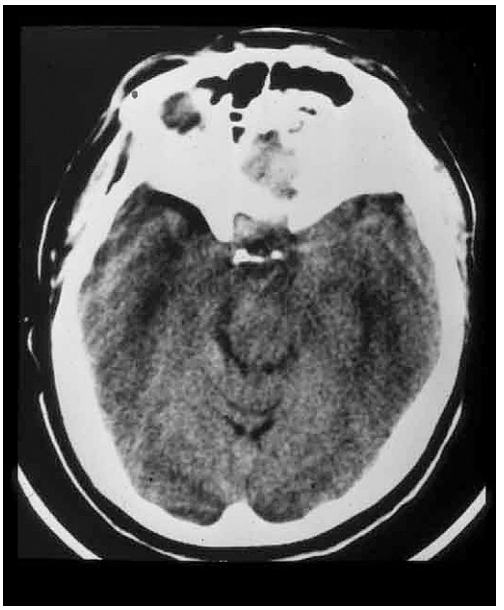

Fig. 5.13. CT scan from a stuporous patient with a large middle cerebral artery infarction and brain swelling showing enlargement of the perimesencephalic cistern on the side of the mass. See also Fig. 5.8 and text.

The eventual radiographic and MRI appearance of severe transtentorial displacements are an elongation and rotation of the upper brainstem and the complete disappearance of the interpeduncular and quadrigeminal cisterns. The rotational aspect of brainstem distortion was studied and quantified by Inao and colleagues (1993) using MRI; they found it to precede herniation in many cases.

5.10. Lumbar puncture and herniation

The risk of spinal tap in patients with a large cerebral mass or in cases of diffusely raised intracranial pressure has occupied the attention of neurologists for a century. The similar problem created by the effects of severe leakage or overdrainage of lumbar CSF on descent of the upper brainstem have already been discussed. In the case of lumbar puncture, it is conceptualized that removal of lumbar spinal fluid creates a pressure gradient from the supratentorial to infratentorial compartments and thus induces transtentorial or foramen magnum cerebellar herniation resulting in coma and respiratory arrest. Endless opinions have been expressed regarding this risk. In the past, papilloedema was felt to be a marker for risk but this has been largely supplanted by CT and MRI detection of a mass. The ubiquitous availability of cranial imaging has reduced both the need for diagnostic lumbar puncture and has reduced the risk by identifying a mass. That clinical deterioration can occur after lumbar puncture if there

is an intracranial mass is undoubted and a proximate relationship to downward herniation is likely but, quite often, coma occurs many hours or days after the lumbar puncture and a direct relationship is then not as clear.

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Chapter 6

The vegetative and minimally conscious states

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The term 'persistent vegetative state' (PVS) was originally introduced by Jennett and Plum (1972) to describe patients who recovered from coma with periods of wakefulness but without any sign of self or environmental awareness. This term was chosen to emphasize the dissociation between the still-viable vegetative functions (e.g., respiration, heart rate, blood pressure) and the complete loss of cognition. These authors went on to recommend that an absolute distinction be made between patients in PVS and those who inconsistently demonstrate signs of conscious behavior. Unfortunately, nearly three decades passed before this latter group was formally recognized (American Congress of Rehabilitation Medicine, 1995) and the term 'minimally conscious state' (MCS) was assigned to distinguish this condition from PVS (Giacino et al., 2002). Until this time, clinicians tended to lump patients in PVS and MCS together despite important diagnostic and prognostic differences between the two groups. Observational studies of diagnostic accuracy conducted prior to the publication of the MCS case definition reported rates of misdiagnosis ranging from 15% (Tresch et al., 1991) to 43% (Andrews et al., 1996), possibly reflecting inattention to the distinguishing features of these conditions.

The objective of this chapter is to review the salient scientific and clinical developments that have occurred over the last 10 years to influence the evaluation and management of patients with disorders of consciousness. Specifically, we review existing diagnostic guidelines, estimates of incidence and prevalence, recent pathophysiological findings from structural and functional neuroimaging studies, prognostic parameters, assessment methods, and medical management and conclude with recommendations for future research.

6.1. Diagnostic criteria

In coma, the eyes remain continuously closed and there is no evidence of coordinated or purposeful behavior. After 2–4 weeks, spontaneous or stimulus-induced eye-opening re-emerges. If the recovery of eye-opening is not accompanied by behavioral signs of cognitively mediated behavior, this signals the onset of the vegetative state (VS). The diagnostic features of VS were outlined by the Multi-Society Task Force on PVS, a multispecialty workgroup assembled by the American Academy of Neurology, following an exhaustive review of the world literature (Multi-Society Task Force on PVS, 1994). Although the focus of the Multi-Society Task Force was on PVS, the diagnostic criteria developed by the task force pertain to VS as well. The diagnosis is based on clinical findings obtained at the bedside. All three of the following criteria must be met to establish the diagnosis of VS:

1. No evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli;
2. No evidence of language comprehension or expression;
3. Intermittent wakefulness manifested by the presence of sleep–wake cycles (i.e., periodic eye-opening).

In addition to the above, autonomic functions are sufficiently preserved in VS to permit survival with

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adequate medical care, there is double incontinence, and cranial nerve and spinal reflexes are variably preserved. Movement of the head, limbs, and eyes is usually diminished in VS. In those who survive longer than 2–3 months, there is usually some resumption of spontaneous and elicited movement; however, this is always nonpurposeful or reflexive. Complex movement patterns (Plum et al., 1998), vocalizations (Jennett and Plum, 1972; Multi-Society Task Force on PVS, 1994) or emotional responses such as smiling and crying (Giacino and Kalmar, 1997) may occur in VS but these behaviors tend to occur infrequently and are independent of meaningful environmental interaction.

VS may be a transient, persistent, or permanent condition. Transient VS lasts less than 4 weeks and is often associated with a favorable outcome (Choi et al., 1994; Multi-Society Task Force on PVS, 1994). The term *persistent* is applied when VS lasts longer than 4 weeks, regardless of etiology. VS is considered permanent (i.e., irreversible) after 3 months following nontraumatic brain injury and after 12 months following traumatic injuries. The marked difference in the window of recovery between traumatic and nontraumatic VS is based on the literature review completed by the Multi-Society Task Force on PVS (1994). Approximately 35% of patients in traumatic VS at 1 month post-injury will recover consciousness during the next 11 months. In contrast, approximately 5% of patients in nontraumatic VS at 1 month will recover consciousness within 1 year. After 6 months in traumatic VS, there is still a 15% probability of recovering consciousness by 12 months. In nontraumatic VS, the probability of recovering consciousness after 6 months is near zero. There are, however, documented case reports of late recovery (Arts et al., 1985; Childs and Mercer, 1996) which suggest that these temporal guidelines should not be considered absolute.

Most patients recovering from coma or VS transition into the minimally conscious state before regaining higher-level cognitive functions. Unlike coma and VS, patients in MCS demonstrate minimal but definite behavioral evidence of self or environmental awareness. These behaviors are often subtle, occur inconsistently, and must be differentiated from reflexive or random behavior. In view of these behavioral characteristics, serial reassessment is usually required to accurately diagnose MCS. Specialized assessment instruments have been developed that incorporate standardized administration and scoring procedures to assist with differential diagnosis. Table 6.1 lists those measures that have demonstrated adequate reliability and validity.

Diagnostic criteria for MCS were originally proposed by the Aspen Workgroup (Giacino et al., 2002). The original criteria were subsequently refined and a case definition was published in *Neurology* after extensive review by the American Academy of Neurology, the American Congress of Rehabilitation Medicine, the American Association of Neurological Surgeons, the American Academy of Physical Medicine and Rehabilitation, and other organizations (Giacino et al., 2002). The diagnosis of MCS requires

Table 6.1

Standardized assessment instruments developed for use in patients with disorders of consciousness

Scale	Target setting	Target population	Principal author (year of publication)
Comprehensive Level of Consciousness (CLOCS)	ICU	Coma	Stanczak et al. (1984)
Coma-Near Coma Scale (CNC)	Inpatient rehabilitation unit	Coma/VS/MCS	Rappaport et al. (1992)
Full Outline of Unresponsiveness (FOUR)	ICU	Coma	Wijdicks (2005)
JFK Coma Recovery Scale (CRS)	ICU/Inpatient rehabilitation unit	Coma/VS/MCS	Giacino et al. (1991, 2004)
Sensory Modality Assessment Technique (SMART)	Inpatient rehabilitation unit	VS/MCS	Gill-Thwaites (2004)
Sensory Stimulation Assessment Measure (SSAM)	Inpatient rehabilitation unit	VS/MCS	Rader (1989)
Wessex Head Injury Matrix (WHIM)	ICU/Inpatient rehabilitation unit	Coma/VS/MCS	Shiel (2000)
Western Neuro Sensory Stimulation Profile (WNSSP)	Inpatient rehabilitation unit	VS/MCS	Ansell and Keenan (1989)

MCS, minimally conscious state; VS, vegetative state.

clearly discernible and reproducible evidence of one or more of the following behaviors:

1. Simple command-following;
2. Gestural or verbal yes/no responses (regardless of accuracy);
3. Intelligible verbalization;
4. Movements or affective behaviors that occur in contingent relation to relevant environmental stimuli and are not attributable to reflexive activity. While not limited to the following list, the behaviors described below provide sufficient evidence of contingent behavior:
   (a) Episodes of crying, smiling, or laughter in response to the linguistic or visual content of emotional but not neutral topics or stimuli;
   (b) Vocalizations or gestures that occur in direct response to the linguistic content of comments or questions;
   (c) Reaching for objects that demonstrates a clear relationship between object location and direction of reach;
   (d) Touching or holding objects in a manner that accommodates the size and shape of the object;
   (e) Pursuit eye movement or sustained fixation that occurs in direct response to moving or salient stimuli.

Disturbances of higher cognitive function, particularly aphasia and apraxia, may also limit behavioral responsiveness and should be considered before establishing the diagnosis of MCS.

The course of recovery from MCS is variable. Some patients recover from MCS within a few weeks while others show slow, gradual improvement across the first year post-injury. MCS may also exist as a permanent outcome. While the diagnosis of MCS is based on *reproducible* behavioral evidence of consciousness, emergence from MCS requires *reliable and consistent* demonstration of interactive communication or functional object use. Communication may occur through verbal responses, gestural means, or augmentative devices. To demonstrate functional object use, two different items must be utilized appropriately (e.g., comb brought to the head and toothbrush to the mouth).

6.2. Incidence and prevalence

Incidence and prevalence figures are difficult to estimate for VS and MCS because surveillance varies across settings (e.g., hospital, nursing home, private residence), diagnoses (e.g., head injury, cardiac arrest, stroke, dementia) and geographical regions (Jennett, 1997). In the USA, for example, the majority of patients in VS and MCS are transferred to long-term care facilities after a relatively brief hospitalization at a trauma center or inpatient rehabilitation facility. Even among those individuals admitted to inpatient rehabilitation programs, most are discharged to nursing homes or private residences within 2–3 months of the injury. Neither of these settings is equipped to monitor patients over time. Further complicating surveillance efforts, some individuals who are in VS at the time of hospital discharge transition to MCS, or emerge from MCS, while they are in custodial care and escape notice.

Accepting these constraints, the best estimates suggest that the annual incidence of VS at 1 month post-injury (excluding congenital and neurodegenerative causes) in the USA is 46 per million population (Jennett, 2002). At 3 and 6 months post-injury, these figures drop to 27 and 17 per million, respectively, because of mortality and recovery rates.

Prevalence figures are even more difficult to estimate because they are influenced by access to reimbursement, adequacy of care, and decisions to withdraw artificial nutrition and hydration (Beaumont and Kenealy, 2005). Prevalence estimates for VS are widely discrepant, ranging from 25 000–45 000 (Multi-Society Task Force on PVS, 1994) to 140 000–420 000 (Spudis, 1991). Moreover, these rates usually do not take survival time into account. The Multi-Society Task Force on PVS found that mean survival was 2–5 years for patients in VS at 1 month post-injury; however, mean survival was approximately 10 years for those alive at 1 year and increased to 12 additional years for those surviving at 4 years post-injury (Beaumont and Kenealy, 2005).

Because the diagnostic criteria for MCS have only recently been established, this condition is not yet recognized by standard classification systems such as the International Classification of Diseases (World Health Organization, 1992). Consequently, estimates of incidence and prevalence are constrained by the lack of a systematic coding and tracking process. Strauss and colleagues (2000) have provided the only empirically derived prevalence estimate for MCS published to date. These investigators extracted data from a large state registry used by the California Department of Developmental Services to track medical care and services administered to residents between the ages of 3 and 15. Using data from a standardized functional rating scale employed by the registry, operational definitions were established for VS and MCS, according to accepted diagnostic criteria. Of the 5075 individuals who met criteria for one of these two diagnoses, 11% were in VS and 89% in MCS. Extrapolating from US census data for the general adult population, the prevalence of MCS was estimated to be between 112 000 and

280 000. If accurate, these data suggest that MCS may be eight times more prevalent than VS (Multi-Society Task Force on PVS, 1994).

6.3. Pathophysiological profiles

The underlying pathophysiology of VS and MCS has been investigated using postmortem analyses as well as structural and functional neuroimaging techniques. Lesion profiles are largely determined by the primary mechanism of injury, although there is increasing evidence of important pathophysiological differences that appear to be specific to diagnosis, independent of injury mechanism.

6.3.1. Traumatic brain injury

Postmortem neuropathological analyses of patients who remain in post-traumatic VS until death have revealed distinct patterns of structural damage. One of the most common findings, noted in as many as 71% of cases, is diffuse axonal injury (DAI) associated with moderate to severe ischemic damage, usually involving the thalamus (80%) and arterial watershed areas (43%). In these cases, grade 2 and 3 DAI predominates as manifested by punctate lesions distributed throughout the corpus callosum and/or rostral brainstem (Adams et al., 2000). A second, less frequent profile has been identified in approximately 15% of cases. This lesion pattern is characterized primarily by focal brainstem lesions not accounted for by DAI. There is some evidence that patients with callosal and dorsolateral brainstem lesions who remain in VS for 2–3 months have a much lower probability of recovery of consciousness by 1 year than those without lesions in these locations. Kampfl et al. (1998) reported that the likelihood of VS at 1 year was 214 times higher in patients with callosal lesions and seven times higher in those with upper brainstem lesions. Both of the studies described above underscore the importance of DAI in post-traumatic VS.

The pathophysiology of post-traumatic MCS has only recently begun to be explored. Jennett and colleagues (2001) compared a group of 35 individuals diagnosed with VS to a second group of 30 individuals, all of whom were rated as severely disabled (SD) on the Glasgow Outcome Scale (GOS) (Jennett and Bond, 1975) until death. The SD group was divided into those who were mobile ($n = 9$), bed-bound ($n = 9$), or in MCS ($n = 12$) prior to death. The authors found no evidence of grade 2 or 3 DAI and no indication of thalamic damage in 50% of the SD group. In contrast, all of the patients in the VS group had moderate to severe DAI and thalamic lesions. In the MCS cases, grade 2 or 3 DAI was more frequent than in the SD cases (42% versus 22%) but considerably less frequent than in the VS group (71%). Thalamic lesions were also notably less prevalent in MCS (50%) relative to VS (80%). These findings suggest that MCS is characterized by greater sparing of cortico-cortical and cortico-thalamic connections, relative to VS.

Recent advances in functional neuroimaging technologies and novel applications of existing techniques have provided new insights into the pathophysiology of disorders of consciousness. Functional neuroimaging procedures such as positron emission tomography (PET) and functional MRI (fMRI) are beginning to make important contributions to diagnostic and prognostic assessment (see recent reviews by Giacino et al., 2006; Laureys et al., 2006; Owen et al., 2007). fMRI and PET ($H_2{}^{15}O$-PET) studies correlate changes in blood oxygen level and cerebral blood flow with neuronal activity and, in doing so, serve as a proxy for neuronal activation per se.

Laureys and colleagues (2002) investigated cortical processing of noxious somatosensory stimuli in a series of patients diagnosed with traumatic and non-traumatic VS by comparing changes in regional cerebral blood flow ($H_2{}^{15}O$-PET) and cerebral metabolism (FDG-PET). Although noxious stimuli activated midbrain, thalamic, and primary somatosensory cortices, these areas were found to be functionally disconnected from higher-order association cortices in all 15 cases studied. These results suggest that while pain messages are carried to primary cortical regions in VS, it is unlikely that these signals are consciously processed given the lack of downstream activation in association cortices.

PET activation studies have also been employed with patients in MCS. Using $H_2{}^{15}O$-PET, Laureys and others (2004) found differential activation patterns in an MCS patient who was exposed to no sound, frequency-modulated noise, infant cries, and the patient's own voice. Compared to the no-sound and random noise conditions, the spread of activation was much broader (encompassing multimodal association cortices) following presentation of the infant cries and the patient's own name. A second study (Boly et al., 2005) comparing responses to auditory stimuli in VS and MCS patients showed significantly greater bilateral activation of heteromodal frontal and temporal regions in the MCS patients. Because these regions are thought to mediate aspects of selective attention and self-awareness, these data were thought to be indicative of cognitive processing in the MCS group.

In order to most effectively define the degree and extent of preserved cognitive function in patients with DOC, some investigators have argued for a hierarchical approach to functional neuroimaging in which tasks progress sequentially from those that rely on

simple sensory processing to those dependent upon complex cognitive functions. For example, Owen and others (2005) used an fMRI paradigm to assess language functions by comparing cortical responses to 1) spoken sentences with acoustically-matched noise sequences, 2) degraded sentences with fully intelligible sentences, and 3) sentences with ambiguous (e.g., 'The *creak* came from a *beam* in the *ceiling*') versus unambiguous words. The authors illustrated this approach in a patient diagnosed with VS. After demonstrating activation in response to speech relative to signal correlated noise (presumably reflecting some perception of speech), a significant response was observed to speech of increasing intelligibility, suggesting that perceptual processes were recruited more strongly for intelligible versus unintelligible speech. A partially normal response was also noted to the ambiguous sentences, which was interpreted as evidence of at least partial preservation of semantic processing.

To rule out the possibility that semantic processes such as those described above were carried out in the absence of conscious awareness, a fourth level of cognitive complexity was added to the scanning hierarchy. At specific points during the scan, subjects were instructed to alternately perform mental imagery tasks involving either tennis-playing or navigating the rooms of the house in which they lived. The authors reported findings in one exceptional patient diagnosed with VS 5 months after sustaining a traumatic brain injury (Owen et al., 2006). When the patient was instructed to imagine playing tennis, activation was observed in the supplementary motor area, but when asked to imagine walking through the rooms of her house, activation shifted to the premotor cortex, parahippocampal gyrus, and posterior parietal cortex. Similar activation patterns were consistently observed in 34 healthy volunteers. Because the only difference between the conditions that elicited task-specific activation was in the instruction given at the beginning of each scanning session, the activation patterns observed were interpreted as a direct reflection of the intention of the patient, rather than an automatic process triggered simply by exposure to an environmental stimulus. It is important to note that the patient demonstrated visual fixation at the time of her first scan, suggesting that she may have been in the early stages of transition from VS to MCS, rather than VS per se. These findings illustrate the increasing role of functional neuroimaging procedures in identifying important pathophysiological differences in patients with similar behavioral presentations. While of uncertain clinical significance at present, extension of such neuroimaging research may lead to enhanced diagnostic accuracy and prognostic specificity. These tools may eventually enable clinicians to detect conscious awareness in patients who lack behavioral signs of consciousness on bedside examination and improve prediction of recovery of consciousness during VS.

6.3.2. Hypoxic–ischemic brain injury

Cardiac arrest, hypotensive crisis, asphyxia, and near-drowning are the most common causes of hypoxic–ischemic VS (Multi-Society Task Force on PVS, 1994). The signature neuropathological profile of hypoxic–ischemic VS is diffuse laminar cortical necrosis (Dougherty et al., 1981; Adams et al., 2000) in which neuronal loss increases progressively from the frontal to occipital poles, often sparing mesial occipital structures. Cortical necrosis is almost always accompanied by bilateral hippocampal, amygdaloid, and thalamic neuronal loss. Brainstem structures remain generally intact. Multifocal cortical infarcts involving arterial border zones can result in VS; however, the cortical lesions are almost invariably accompanied by widespread thalamic ischemia. In cases of VS in which the cortex is generally well preserved, diffuse thalamic involvement has been noted. Neuropathological findings on autopsy in the well publicized case of Karen Ann Quinlan, who remained in VS for 10 years, showed bilateral, symmetrical atrophic changes in the thalamic nuclei with relative sparing of brainstem, hypothalamic, and cortical structures (Kinney et al., 1994). In the case of Terri Schiavo, who was reportedly in VS for 15 years, microscopic examination findings from the autopsy report issued by the medical examiner revealed striking gradient loss of the cerebral cortex progressing from anterior to posterior regions, predominating in the watershed regions. The frontal and temporal poles and insular cortex were relatively well preserved. The basal ganglia and corpus striatum were barely discernible, having been replaced by extensive astrocytosis. The thalami were less involved and there was relative sparing of the medial portion. The lateral geniculate showed transneuronal degeneration and gliosis while the medial geniculate was largely intact. Wallerian degeneration was evident in the pyramidal tracts and there was reactive astrocytosis bilaterally in the hippocampi secondary to diffuse neuronal loss. In the brainstem, there was severe retrograde degeneration of the descending fiber pathways of the pons and no discernible Purkinje neurons in the cerebellum. The reticular activating system, locus ceruleus, median raphe nuclei, and medullary structures were relatively preserved. These findings represent typical changes associated with long-term survival in postanoxic VS.

Schiff and coworkers (2002) investigated the nature and extent of residual metabolic activity in three

patients diagnosed with hypoxic–ischemic VS using [^{18}F]-fluorodeoxyglucose PET. Two patients displayed behaviors not typically observed in VS. One patient uttered random but comprehensible single words while the other exhibited emotional responses tied to environmental events. Neither patient demonstrated purposeful movement, followed commands, visually tracked environmental stimuli or showed any form of communicative response. To investigate the relationship between these behaviors and the integrity of the underlying neural substrate, fMRI findings were co-registered to MRI to identify regions of preserved cortical and subcortical activity. Although global cerebral metabolic rates of glucose consumption averaged 44–65% of normal, there were isolated regions with metabolic rates ranging up to 80% of normal. In the two patients referred to above, these regions were well correlated with the unusual behavioral findings noted on bedside examination. These findings suggest that functional networks may remain partially viable in VS, despite the loss of consciousness.

There is some evidence that diagnosis is a stronger predictor of residual neurophysiology than etiology of injury. Laureys and others (Laureys et al., 2000, 2002; Boly et al., 2004) compared patterns of brain activation in a mixed group (i.e., traumatic, anoxic, vascular, encephalitic) of VS and MCS patients who were exposed to auditory and noxious stimulation while undergoing [$H_2{}^{15}O$]-PET. Both patient groups were compared to 15 controls. Conjunction and functional connectivity analyses were performed to investigate differences in activation between patients and controls within and across brain regions, respectively. Results indicated that patients in VS activated primary auditory and somatosensory cortices bilaterally. However, only MCS patients and controls activated higher-order association cortices and showed significant interactions between multimodal association cortices believed to be necessary for conscious processing. These results suggest that, although differences in injury mechanism play an important role in determining clinical outcome, the extent to which functional networks are retained appears to be a stronger determinant of level of consciousness.

6.3.3. Cerebrovascular disease

The effects of intracranial hemorrhage range from transient alteration in consciousness to permanent VS, depending on the location and type of hemorrhage (see Wijdicks, 1998 for a review). Subarachnoid hemorrhage usually does not lead to VS as blood tends to pool in the subarachnoid space and basal cisterns. If the volume of the hemorrhage is sufficient to increase intracranial pressure, or brainstem compression ensues, persistent or permanent VS may follow as a result of global ischemic changes. Large intraparenchymal, subdural, and epidural hemorrhages produce mass effect and midline shift, which impinge on hemispheric and reticular structures. Consequently, patients are initially comatose and may subsequently evolve into transient or long-term VS. Pontomesencephalic hemorrhages cause rapid loss of consciousness secondary to disruption of the paramedian segment of the reticular system. VS often follows as the result of reticulo-thalamo-cortical disconnection.

Castaigne and others (1981) described two neuropathological conditions arising from intracranial hemorrhage or infarction that result in behavioral syndromes consistent with MCS. Bilateral paramedian thalamic infarcts, which involve the intralaminar, parafascicular, median and central nuclei, initially produce transient disturbance in consciousness ranging from coma to delirium. Following recovery of consciousness, cognitive and behavioral sequelae usually include severe abulia characterized by infrequent speech, command-following, or purposeful behavior. When the area of infarction extends from the thalamus into the paramedian midbrain encompassing the thalamopeduncular arterial distribution, there is often abrupt onset of coma followed by hypersomnia, akinesia, and mutism. Because these disorders primarily result from a disturbance in behavioral initiation and drive, it is often possible to elicit command-following, intelligible verbalizations, or other signs of consciousness, albeit inconsistently, when sufficient sensory or pharmacological stimulation is provided (American Congress of Rehabilitation Medicine, 1995).

6.4. Prognosis and outcome

There is an extensive literature on prognostic indicators in disorders of consciousness. Because the positive and negative predictive value of these variables is generally unknown, outcome prediction at the level of the individual case is often unreliable. Moreover, many studies simply dichotomize outcomes as ‘favorable’ or ‘unfavorable’ and fail to capture salient aspects of functional capacity such as communication ability and degree of assistance required for self-care. Nevertheless, a number of clinical factors have been reliably shown to correlate with outcome in patients with VS and MCS. Most prognostic studies have focused on one of three outcome dimensions: mortality, recovery of consciousness and degree of functional disability.

6.4.1. Mortality

Prognostic studies of patients in acute coma have consistently found that low Glasgow Coma Scale scores (i.e., <5), bilaterally nonreactive pupils, hypotension, and advanced age increase risk of death. In patients with VS,

the largest compilation of data on survival was published by the Multi-Society Task Force on PVS (1994). This report included data on 434 adults and 106 children with traumatic brain injury and 169 adults and 45 children with nontraumatic brain injury (primarily anoxic brain injury and stroke). Mortality figures differ dramatically for patients with nontraumatic versus traumatic brain injury. The Task Force reported that 53% of patients in VS due to nontraumatic causes died within the first 12 months post-injury as compared to 33% of those with traumatic brain injury. Of those surviving up to 3 months, 46% of nontraumatic cases died by 12 months, as compared to 35% of traumatic cases. Mortality rates are considerably lower in children but the etiological disparity is maintained. After 1 month, 9% of traumatic cases ($n = 106$) and 22% of nontraumatic cases ($n = 45$) died within the first year. After 3 months, the trend reversed, with 14% of traumatic cases and 3% of nontraumatic cases dead by 12 months, but this is probably due to the greater number of surviving traumatic cases at this point. It is important to note that, after 1 year, mean survival time increases significantly and, with appropriate medical care, may approximate normal life expectancy.

6.4.2. Recovery of consciousness

Prognosis for recovery of consciousness is also substantially more favorable for patients in traumatic VS relative to those who sustain nontraumatic injury. Based on the data from the Multi-Society Task Force Report, in adults with traumatic brain injury who were unconscious at least 1 month, 33% recovered consciousness by 3 months post-injury, 46% by 6 months and 52% by 1 year. Approximately 35% of patients with traumatic brain injury who were still in VS at 3 months regained consciousness by 1 year. In the group that remained in VS for 6 months, 16% regained consciousness by 1 year. In the nontraumatic VS group, only 11% of those in VS at 1 month recovered consciousness by 3 months and 15% by 6 months. No patient with nontraumatic injury regained consciousness after 6 months post-injury.

Prognosis in children was only slightly more favorable. Of those children with traumatic brain injury who were unconscious at 1 month, 51% regained consciousness by 6 months and up to 62% of children with traumatic brain injury recovered consciousness at 1 year after injury. After nontraumatic injury, recovery of consciousness occurred mainly within the first 3 months (11%), but a very small percentage (2%) regained consciousness between 6 and 12 months.

In view of the prognostic data concerning disorders of consciousness, the American Academy of Neurology established a practice guideline for determining when VS should be considered permanent (Quality Standards Subcommittee, 1995). Table 6.2 summarizes the temporal parameters for permanent VS in adults and children.

Table 6.2

Temporal cut-offs for determination of permanent vegetative state

Type of injury	Length of time post-injury
Traumatic brain injury	After 12 months
Congenital malformations	After 3–6 months
Anoxia/stroke/other nontraumatic causes	After 3 months
Metabolic diseases	After 1–3 months
Degenerative diseases	After 1–3 months
Anencephaly	At birth

Adapted from: Quality Standards Subcommittee, American Academy of Neurology (1995). Assessment and management of persons in the persistent vegetative state. Neurology 45: 1015–1018.

There are important caveats to consider when utilizing the criteria for permanent VS. First, the subject pool assembled by the Task Force included a total of only 53 patients for whom follow-up data were available beyond 12 months post-injury (Bricolo et al., 1980; Alberico et al., 1987; Braakman et al., 1988; Grosswasser and Szabon, 1990; Levin et al., 1991). Of these, empirical outcome data were available for 26 subjects while data for the remaining 27 patients were obtained anecdotally. In addition, the duration of follow-up was highly variable, ranging from 14 months to 10 years. Second, the Task Force calculated the probability of recovery at 3, 6, and 12 months using the number of patients who were in VS at one month. Childs (unpublished work) has pointed out that this procedure does not take into account the number of patients who either die or regain consciousness between these assessment points (i.e., from 1 to 3 months, from 3 to 6 months, etc.), which may underestimate the probability of recovery at any point prior to 12 months. Third, there are well documented accounts of recovery from VS after 12 months post-injury (Arts et al., 1985; Childs and Mercer, 1996). These qualifications should serve as a reminder that, while recovery from VS is unlikely after the criteria for permanence are met, it is not absolute.

6.4.3. Recovery of function

The majority of prognostic studies involving patients in VS and MCS have included degree of functional disability as the primary outcome measure. Functional

disability scales generally incorporate ratings of self-care (e.g., feeding, toileting, grooming, dressing) and activities of daily living (e.g., housekeeping, use of public transportation) and are usually assessed during the subacute and postacute phases of recovery. The Task Force report described functional outcome using the Glasgow Outcome Scale (Jennett and Bond, 1975). After 3 months, adults in traumatic VS have a 19% probability of being severely disabled at 12 months and a 16% probability of achieving a moderate to good recovery. After 6 months, these rates fall to 12% and 4% for moderate disability and good recovery, respectively. Functional outcome is considerably worse after nontraumatic injury. For patients in VS at 3 months, the probability of severe disability at 12 months is 6% with a 1% chance of achieving moderate disability to good recovery. After 6 months, there is a 3% probability of severe disability. The Task Force did not find any nontraumatic cases recovering to moderate disability or good recovery after 6 months. Outcome in children is better at 12 months. After 3 months, children in traumatic VS have a 32% probability of moderate to good recovery and a 24% probability of severe disability.

A recently-completed multicenter study of the natural history of recovery from VS and MCS conducted by Whyte and colleagues (2005) found that rate of improvement over a two-week period on the Disability Rating Scale (DRS) (Rappaport et al., 1982) was highly predictive of functional outcome at 16 weeks post-injury. Specifically, those patients with better DRS scores at enrollment and faster rates of initial improvement tended to have better DRS scores at the 16 week mark. The combination of rate of DRS recovery, time between injury and enrollment and DRS score at enrollment accounted for nearly 50% of the variance in DRS scores at 16 weeks. These same three variables were also highly significant predictors of time until commands were followed.

Studies comparing functional outcome between individuals diagnosed with VS and MCS suggest that individuals in MCS show more rapid improvement, a longer period of recovery and significantly less functional disability at 12 months. Giacino and Kalmar (1997) investigated functional outcome on the DRS across the first year post-injury in patients diagnosed with VS or MCS. The VS and MCS groups were stratified further according to etiology of injury (i.e., traumatic or nontraumatic). Although both diagnostic groups presented with similar levels of disability at 1 month post-injury, outcome was significantly more favorable by 12 months in the MCS group, particularly after traumatic brain injury. The differences in outcome became progressively more apparent at 3, 6, and 12 months post-injury. The probability of a more favorable outcome (i.e., moderate or no disability) by 1 year was much greater for the MCS group (38%) than the VS group (2%) and only occurred in those patients with traumatic brain injury.

Giacino and Kalmar's findings were recently replicated and extended by Lammi and colleagues (2005) who followed 18 patients in traumatic MCS for 2–5 years after discharge from an inpatient brain injury rehabilitation program located in Australia. The authors found that 15% of their sample had partial disability or less at follow-up while 20% fell in the extremely severe to vegetative category. In comparison, Giacino and Kalmar reported that 23% of their sample had no more than partial disability at 12 months with 17% classified as extremely severe to vegetative. In both samples, the most common outcome was moderate disability which occurred in approximately 50% of patients. Of particular importance, Lammi et al. also noted that duration of MCS was not correlated with DRS outcome and that 50% of their sample had regained independence in activities of daily living at follow-up. Both of these studies suggest a clear separation between MCS and VS in course of recovery and eventual functional outcome.

6.5. Medical management

Patients with disorders of consciousness, particularly those with traumatic brain injury, are prone to a variety of medical problems that arise directly from damage to neural structures or represent secondary complications of the injury. Delayed recognition of these problems can slow the recovery course and, in some cases, may further compromise functional outcome. With the exception of seizure management, there is insufficient evidence to support treatment guidelines for injury-related medical problems.

6.5.1. Seizure

Post-traumatic seizures are arbitrarily divided into early seizures (those occurring within the first 7 days post-injury) and late post-traumatic seizures (those occurring later than 1 week after injury) (Schierhout and Roberts, 1998). Anticonvulsants have been shown to be effective in preventing early, but not late, post-traumatic seizures (Temkin et al., 1990, 1999), although there is evidence that prophylaxis is less effective in post-traumatic seizures (Chang and Lowenstein, 2003). If a late seizure occurs, aggressive anticonvulsant treatment is indicated as there is a high incidence of recurrence (Haltiner et al., 1997). A patient experiencing an isolated immediate seizure

(one within the first 24 hours) or an early seizure may still be a candidate for withdrawal of anticonvulsants (Yablon and Dostrow, 2001). However, if a patient has multiple early seizures or status epilepticus, it may be prudent to continue treatment with an anti-seizure medication. Anecdotally, withdrawal of seizure prophylaxis is occasionally associated with improvement in behavioral responsiveness in patients with post-traumatic alteration in consciousness. In patients who remain seizure-free for 2–5 years, the Quality Standards Subcommittee of the American Academy of Neurology recommended that consideration be given to withdrawing anticonvulsant medications when the patient meets all of the following additional clinical criteria: 1) single type of partial or generalized seizure, 2) normal IQ, 3) normal neurological examination, and 4) normalization of the EEG with treatment (Quality Standards Subcommittee, 1996).

6.5.2. Endocrinopathies

In traumatic brain injury, diabetes insipidus or the syndrome of inappropriate antidiuretic hormone (SIADH) may occur (Watanabe and Sant, 2001). Patients may also develop a deficiency of an isolated stimulating/releasing factor from the anterior pituitary, panhypopituitarism or a combination of anterior and posterior pituitary dysfunction. Growth hormone deficiency has recently been receiving intense investigation in patients with traumatic brain injury. Panhypopituitarism should be investigated in the setting of hypoarousal, hypotension, and hypothermia.

6.5.3. Hydrocephalus and ventriculomegaly

Ventriculomegaly (i.e., dilatation of the ventricles) is very common following acquired brain injury with incidence estimates as high as 77% (Jennett et al., 2001). Hydrocephalus refers to the accumulation of excess cerebrospinal fluid (CSF) within the head and is often but not always associated with dilatation of the ventricles, due to an abnormality of secretion, circulation, or absorption of CSF. The great majority of cases of hydrocephalus are the result of blockage within or at the outlets of the ventricular system (obstructive) or within the basal cisterns/subarachnoid space or arachnoid granulations (communicating). Communicating hydrocephalus occurs most frequently following intracranial hemorrhage, especially subarachnoid hemorrhage. These patients may benefit from a ventriculoperitoneal shunt. The most common reason for enlargement of the ventricles is volume loss secondary to encephalomalacia or atrophy (i.e., hydrocephalus ex-vacuo). This cause of ventriculomegaly is not treated with shunting. The distinction between atrophy and potentially treatable hydrocephalus cannot be made on the basis of conventional computed tomographic (CT) or magnetic resonance (MR) scanning alone. Physiological measurements of intracranial pressure and CSF outflow resistance may be helpful (Pickard et al., 2005).

6.5.4. Dysautonomia

Autonomic dysfunction can occur and may be typified by tachycardia, hypertension, diaphoresis, fever, and orthostatic hypotension. Hypertension, tachycardia, and increased cardiac output in the acute post-injury period result from the increased release of epinephrine (adrenaline) and norepinephrine (noradrenaline). In severe brain injury, hypertension may persist beyond the acute phase. This may be linked to injury to the brainstem, hypothalamus, and orbitofrontal regions (Whyte et al., 1998).

6.5.5. Cerebrospinal fluid leak

In patients with basilar skull fractures, CSF rhinorrhea can occur with fracture of the anterior cranial fossa and CSF otorrhea with middle cranial fossa fractures. CSF leakage may be intermittent and associated with position changes. If a sufficient quantity of the discharge can be collected, beta-2-transferrin is the confirmatory test for the presence of CSF. The leakage may resolve on its own. Occasionally, surgical intervention may be required to patch the defect. There is a risk of meningitis in patients with a communication to the outside world; however, prophylactic antibiotics are not recommended (Long, 1996).

6.5.6. Cranial nerve palsies

Multiple or isolated cranial nerve palsies may occur in patients with traumatic brain injury. An afferent pupillary defect can be a sign of optic neuropathy. In a cooperative patient, the cross-cover test can be helpful in detecting ophthalmoplegia. Exposure keratitis and corneal ulceration may occur as the result of facial nerve injury or diminished blinking associated with disturbance in consciousness. Lubrication and tarsorrhaphy can be helpful. In cases without recovery of function of the facial nerve, gold weight placement in the upper eyelid may be indicated to allow for eyelid closure.

6.5.7. Malnutrition

Protein calorie malnutrition can initially be treated with a nasogastric tube; however, the tube can only be used for a limited time because of the possibility

of nasal septum erosion, sinusitis or gastroesophageal reflux. Early placement of a percutaneous gastronomy tube for administration of tube feeding, hydration, and medication is often recommended. Some centers advocate open gastrostomy/jejunostomy tube placement as a means of being able to administer feedings to the jejunum to decrease the risk of reflux and aspiration of tube feedings. As behavioral responsiveness improves, bedside dysphagia evaluation and functional endoscopic examination of swallowing should be considered. The modified barium swallow remains the gold standard for evaluating the consistency of solids and liquids the patient may be able to tolerate, and to investigate the possibility of silent aspiration. Once the patient is able to meet his/her nutritional and hydration needs, as well as take any medications by mouth, the gastrostomy tube can be removed. It is generally recommended that a gastrostomy tube remain in place for at least 1 month prior to removal so that an adhesion can form between the stomach and abdominal wall to avoid a chemical peritonitis.

6.5.8. Occult fractures and heterotrophic ossification

It is not uncommon for occult fractures to be discovered as the patient's communication status improves and complaints of pain can be discerned. These fractures may not be discovered until the patient is in a rehabilitation setting. Heterotrophic ossification is a common complication of acquired brain injury. Heterotrophic ossification is the formation of mature lamellar bone in soft tissue sites outside the skeleton (Haran et al., 2004). Edema, erythema, pain, and limitation of joint motion may occur. Entrapment of a peripheral nerve may occur as well as lymphedema. Etidronate has been used to decrease the ossification of the matrix. Surgical excision may be indicated at some point to improve joint range of motion, release an entrapped nerve, or perhaps for hygiene purposes if limited joint range of motion impacts skin care. An elevated alkaline phosphatase level may be seen with active heterotrophic ossification. Calcification may be noted on X-rays but a triple-phase bone scan may be positive prior to detection of ossification on conventional X-rays.

6.5.9. Spasticity and contractures

Spasticity, which is defined as a velocity-dependent increase in muscle tone, is a frequent complication of prolonged disturbance in consciousness caused by the direct and indirect effects of motor system lesions, and by chronic immobility. Range of motion, positioning, and splinting interventions are routinely used in rehabilitation settings. While controlled studies have not been conducted (Leong, 2002), serial casting may help decrease spasticity and increase joint range of motion when performed by an experienced occupational or physical therapist. Oral antispasticity agents such as tizanidine, Lioresal, or Dantrium can be effective but side effects such as sedation, weakness, and worsening swallowing function are often encountered and may preclude their use. Botulinum toxin or chemical denerveration with phenol or alcohol blocks can be utilized without the risk of sedative side effects. Intrathecal baclofen pumps are used extensively in patients with spasticity of cerebral origin. Since the dose of administered baclofen is a fraction of the effective oral dose, weakness and sedation can generally be avoided.

6.5.10. Neurogenic bladder

Neurogenic bladder is common in patients with severe brain injury. Indwelling bladder catheters are initially used for urinary drainage. As early as possible, the catheter can be removed. Intermittent catherization can be done if needed to drain the bladder. Commonly, after indwelling catheter removal, there may be a period of detrusor hyporeflexia with urinary retention. There can also be detrusor sphincter dyssynergia. Usually, a hyper-reflexive neurogenic bladder will develop and patients may be incontinent at a lower volume of urine than they would normally experience the urge to void. Alpha-blockers such as tamsulosin are commonly used to facilitate voiding. The use of bethanechol to treat hypodetrusor is controversial at best. Complications such as urinary tract infections, bladder calculi, and urosepsis can occur. Limiting bladder distention to no more than about 400 ml of urine may help prevent an overdistended bladder with urethral reflux of urine and hydronephrosis.

6.5.11. Decubitus ulcers

Decubitus ulcers are a complication of prolonged immobilization as well as spasticity. Repositioning of the immobile patient every 2 hours should be performed. Pressure-relieving mattresses decrease the risk of ulceration and ankle/foot orthoses can prevent heel breakdown.

6.5.12. Persistent underarousal

Hypoarousal is a defining feature of disorders of consciousness; however, sedating medications such as anticonvulsants, benzodiazepines, antispasticity medications

and prokinetic agents such as metoclopramide should be considered as a contributing factor. Whenever possible, these agents should be tapered or discontinued (Giacino et al., 2002). There are numerous case reports suggesting that dopaminergic agents such as amantadine hydrochloride, bromocriptine, and methylphenidate may be helpful in improving arousal, attention, and initiation but no definitive prospective randomized controlled trials have been completed to date (Giacino, 2005).

6.5.13. Post-traumatic agitation and delirium

Post-traumatic agitation may develop during or shortly after emergence from MCS and is more commonly observed in patients with traumatic brain injury. Characteristic features typically include some combination of akathisia, aggressiveness, disinhibition, emotional lability, and post-traumatic amnesia (Sandel and Mysiw, 1996). Post-traumatic agitation frequently occurs in association with delirium in which fluctuation in arousal level is the defining feature. Evaluation for infection or hypothermia should be considered as these disorders may produce similar symptoms. Noxious stimuli such as bladder distension, fecal impaction, ingrown toenail, or decubitus ulcer should also be considered in the differential diagnosis. Medications such as trazodone, buspirone, anticonvulsants, or atypical antipsychotics should be considered in place of typical antipsychotics and benzodiazepines given their potential to decrease arousal, impair motor recovery, compromise cognition, and result in dependence.

6.6. Conclusion and future directions

Disorders of consciousness are arguably among the most enigmatic conditions encountered in medicine. Remarkably little is known about the neurophysiological mechanisms underlying these disorders and there are no existing treatment interventions proven to alter the pace or extent of recovery. These problems have been sustained, in part, by the nihilistic belief that little effort should be invested in the study of these patients because of the perception that they are beyond help (Fins, 2003). Recent initiatives to establish standards for clinical management and the development of novel assessment methods have begun to change the current climate and are expected to provide new insights into the underpinnings of normal and impaired consciousness.

The last decade has been witness to the crafting of more finely tuned diagnostic nosologies, the adaptation of cutting-edge neuroimaging technologies for use in patients with disorders of consciousness and improved strategies for medical management. Additional research is needed, however, to clarify the natural history of recovery from VS and MCS, elucidate the pathophysiology responsible for persistent impairment in consciousness, identify more reliable predictors of recovery of consciousness and function, develop more sensitive behavioral assessment tools, and establish novel, theory-driven approaches to treatment. In view of the clinical complexity, emotional toil, and costs associated with long-term care of this population, and the practical constraints associated with longitudinal research, the success of this endeavor will require cross-cutting, multidisciplinary collaboration among neuroscientists, neurologists, and neurorehabilitation professionals. The obstacles imposed by disorders of consciousness, although imposing, seem relatively minor when weighed against the potential benefits that an improved system of care offers to patients, families, and society at large.

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Chapter 7

Metabolic encephalopathies

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'Metabolic encephalopathy' was coined by Kinnier Wilson in 1927 to describe a clinical state of heterogeneous etiology wherein cerebral activity is impaired in the absence of parenchymal inflammation or gross structural abnormalities. Metabolic encephalopathy is not a diagnosis but a state of global cerebral dysfunction induced by systemic stress, and can vary in clinical presentation from mild executive dysfunction, to an agitated delirium, to deep coma with decerebrate posturing.

The ability for a neurologist to appropriately examine subtle impairments of consciousness is a mandatory skill. Patients with metabolic encephalopathy may have symptoms that are detectable only with formal tests of higher cognitive function. For example, mild executive dysfunction would elude the standard neurological assessment; therefore the earliest clinical manifestations of hepatic encephalopathy may escape detection, thus delaying diagnosis and treatment.

This chapter will focus on common causes of metabolic encephalopathy, and will outline, when relevant, the epidemiology, clinical presentation, laboratory and imaging findings, and management.

7.1. Hepatic encephalopathy

Hepatic encephalopathy (HE) is a potentially reversible neuropsychiatric clinical syndrome stemming from acute or chronic liver failure. Acute liver failure, a manifestation of impaired hepatocellular function, begins within 6 months from the onset of liver disease. Fulminant hepatic failure is a subset of acute liver failure and is a particularly catastrophic condition, characterized by rapid onset of hepatic encephalopathy, coagulopathy from hepatocellular dysfunction, and cerebral edema, and occurs within 8 weeks of the onset of liver disease. By contrast, the hepatic encephalopathy associated with chronic liver failure results from a longer (>8 months) process, most often due to portosystemic shunting, wherein venous blood destined to the liver is shunted into the systemic system without being 'detoxified' of its various nitrogenous wastes. Common causes of acute liver failure include viral hepatitis, drugs (e.g., paracetamol/acetaminophen, Ecstasy, idiopathic drug reaction), toxins, vascular disease (e.g., ischemia, Budd–Chiari syndrome, heat stroke, malignant hyperthermia) as well as Wilson's disease, lymphoma, Reye's syndrome, and the acute fatty liver of pregnancy. Common causes of chronic liver failure include alcoholic cirrhosis, nonalcoholic cirrhosis (e.g., Wilson's disease, viral hepatitis), transjugular intrahepatic portosystemic shunt (TIPS), and urea acid cycle impairment.

7.1.1. Clinical findings

The clinical presentation of acute and fulminant liver failure is often dramatic. Because confusion, delirium, and psychosis may precede obvious systemic features of liver failure, such as jaundice, the clinical picture of acute fulminant liver failure can often resemble drug intoxication or a condition of primary psychiatric etiology. The initial stages (stages I–II) are hyperkinetic and agitated and may be followed within hours by stupor with preservation of arousal (stage III), then coma (stage IV). By stage IV, cerebral

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edema is typically present and patients often have widened pulse pressure, bradycardia and decorticate or decerebrate posturing.

The classification of HE associated with portosystemic shunt is subdivided into minimal HE and overt (grade I–IV) HE. Minimal HE was previously dubbed 'subclinical hepatic encephalopathy'; however, the latter falsely implies a normal cognitive state: it diminishes the impact of the disease on the patient's quality of life and it underestimates the patient's functional disability (Ferenci et al., 2002). Minimal HE may have significant implications on fitness to drive or operate heavy machinery. The Portal–Systemic Encephalopathy (PSE) Syndrome Test is a bedside mental status assessment that measures a composite score from line tracing time, serial dotting, Trail Making A, Trail Making B, and Digit Symbol Test and was designed specifically to detect the impaired attention and visuomotor skills of minimal HE (Weissenborn et al., 2001).

The transition from grades I to IV of HE associated with chronic liver failure is more gradual than in acute liver failure and can follow a relapsing-remitting course according to inciting events such as intercurrent infection, protein load, gastrointestinal bleeds, constipation, or sedative use for example. Patients demonstrate apathy, slowness of thought, and brevity of speech. Impaired attention and concentration is almost universal. Mild, quiet confusion with progressive obtundation is more common than frank delirium (Young and DeRubeis, 1998). Table 7.1 summarizes some of the clinical features of HE across its spectrum of clinical severity.

7.1.2. Imaging

7.1.2.1. Structural imaging

Bilateral excessive deposition of manganese in the globus pallidi can be present in liver disease and viewed as T_1 hyperintensities on magnetic resonance imaging (MRI) (Zeneroli et al., 1991; Maeda et al., 1997). Although T_1 hyperintensities in the basal ganglia most often occur in association with liver disease and HE, they can also be seen following exogenous manganese toxicity and in the nonketotic hyperosmolar syndrome with hemichorea–hemiballism (see section on Hyperglycemia, below). T_1 hyperintensities in HE can also be found within the limbic system, within other areas of the basal ganglia, and along cerebral white matter tracts (Norton et al., 1994). Beyond supporting a clinical diagnosis of liver disease, these imaging characteristics are of questionable clinical usefulness. For example, there is no clear relationship between the MRI characteristics and the clinical severity of HE. Furthermore, following orthotopic liver transplant, the T_1 hyperintensities linger long after the clinical resolution of symptoms.

In acute hepatic encephalopathy, computed tomography (CT) imaging is a useful tool in grading cerebral edema. A CT grading system has been devised that quantifies: sulcal effacement; visibility of subcortical white matter; and degree of loss of the basal

Table 7.1

Neurological and neuropsychiatric abnormalities related to severity of cirrhosis-induced hepatic encephalopathy

	Grade I	Grade II	Grade III	Grade IV
Consciousness	Alert; mild inattention	Blunting	Stuporous but rousable	Coma
Behavior	Reversal of sleep pattern; irritable; depressed	Apathy; lethargy; disinhibition; anxious	Paranoia	–
Affect	Labile	Labile	Blunted	–
Cognition	Impaired visuomotor skills	Delirium	Too impaired to test	–
Neurological exam	Postural–action tremor, asterixis, multifocal myoclonus; ↑deep tendon reflexes	Frontal release signs (grasp; sucking); gegenhalten; dysarthria; ataxic gait; parkinsonism	Dilated pupils; nystagmus	Spasticity; clonus extensor plantar responses; decorticate; decerebrate, abnormal eye movements

Source: adapted from Lockwood, 2004.

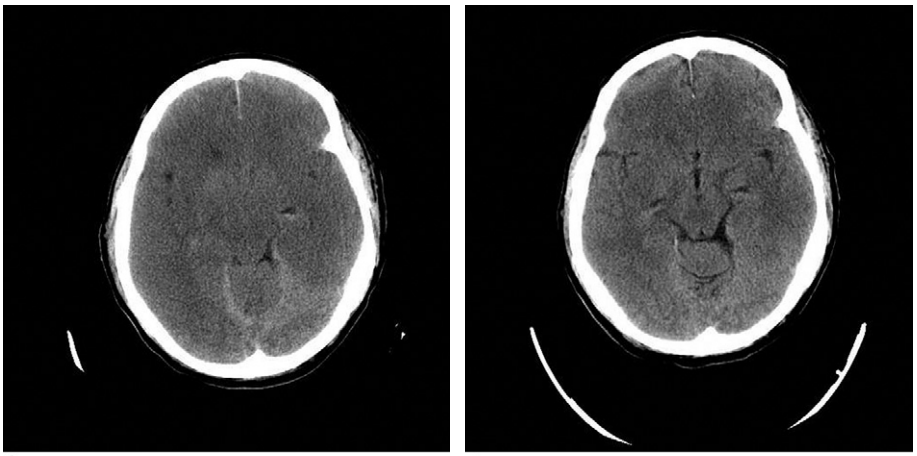

Fig. 7.1. Unenhanced CT of a 51-year-old patient in deep coma from acute fulminant hepatic encephalopathy following acetaminophen (paracetamol) overdose. The patient had lost all cranial nerve reflexes. **A.** The marked cerebral edema is characterized by loss of basal cisterns, blurring of the gray–white matter, diffuse sulcal effacement, and compression of ventricular system. **B.** The same patient 1 day after treatment with hypothermia and mannitol. The dramatic reduction of edema correlated with marked clinical improvement. The patient subsequently died as a result of other medical complications.

cisterns (Wijdicks et al., 1995) (Fig. 7.1). The grade correlates with clinical severity of coma and can be used to help guide appropriate intervention for managing raised intracranial pressure (ICP) from cerebral edema. Serial CT scans should thus be part of the management of acute hepatic encephalopathy.

7.1.2.2. Functional imaging

Functional imaging assesses the cerebral molecular changes of HE and has provided important insights into its pathophysiology. Magnetic resonance spectroscopy (MRS) measures concentrations of particular molecules within the brain. Values are expressed as ratios of compound-to-creatine (Cr). In HE there is a characteristic pattern of increased Glx/Cr (Glx represents glutamine concentrations and its increase is presumably as a result of the increased detoxification of astrocytic ammonia). Increases in Glx/Cr is the most reliable neurospectroscopic indicator of HE as Glx/Cr increases along with the severity of encephalopathy (Laubenberger et al., 1997) and normalizes within 1–2 months post-orthotopic liver transplantation (Naegele et al., 2000). MRS demonstrates a reduction of intracellular brain choline and myoinositol: two glia-derived osmosensitive molecules whose movement from the intracellular to the extracellular compartment is believed to represent a compensatory mechanism aimed at decreasing osmotic forces in response to cell swelling (Pasantes-Morales, 1996). To this end, astrocyte volume dysregulation, i.e., astrocytic swelling (Norenberg et al., 1991), has been implicated in the pathogenesis of HE (see section on Cell swelling, below). The neuronal marker *N*-acetylaspartate resonances remain normal in hepatic encephalopathy. MRS is not universally available and is expensive; however, it is an important research tool and, when available, its clinical usefulness may lie in its high sensitivity for minimal HE or in the detection of HE in a patient who has combined causes of impaired consciousness (Lockwood, 2004).

7.1.3. Neurophysiological tests

7.1.3.1. EEG

The triphasic wave represents the hallmark EEG finding in well developed forms of HE. Milder degrees of HE include a slowing of the dominant posterior rhythm (alpha slowing), with increased presence of theta (>4 but <8 Hz) and delta (4 Hz or less) frequencies. The most severe abnormality consists of delta waves alone, variably associated with epileptiform activity or epochs of suppression. The EEG pattern does not strictly correlate with ammonia levels (Demedts et al., 1973). Quantification of the various frequency bands is an effective way to classify the severity of encephalopathy (Van der Rijt et al., 1984).

7.1.3.2. Evoked potentials

In fulminant hepatic failure, absence of the N70 wave from median nerve somatosensory-evoked potentials may be used to differentiate those patients whose clinical outcome is poor, and who therefore need transplant, from those who may respond to medical management (Madl et al., 1994). In chronic hepatic

encephalopathy, both somatosensory evoked potentials and brainstem evoked potentials may be objective markers of disease severity. For example, a delay and prolongation of the N20, P25, N35, P45, N65, and P90 waves of the median nerve somatosensory evoked potential correlates with clinical severity (Yang et al., 1985; Chu et al., 1997). The P300 wave is an event-related brainstem auditory evoked potential that is generated when a sound-stimulus is delivered that is unlike others of a series of sounds (i.e., an aberrant or 'oddball' sound) and relies on the discriminative ability of the brain. In chronic hepatic encephalopathy there is an increase in the latency of this wave. The P300 is a sensitive test for grade I (Davies et al., 1990) but not for minimal hepatic encephalopathy (Senzolo et al., 2005).

7.1.4. Pathophysiology

The pathophysiology of HE is not known. Central to the current theory is raised arterial and brain ammonia (Butterworth, 2002). Ammonia is absorbed in the gut and is delivered to the liver for detoxification via portal circulation. Hepatocellular dysfunction (acute liver failure) or portocaval shunting (chronic liver failure) can raise arterial ammonia. As ammonia passes through the blood–brain barrier (BBB) it is taken up by astrocytes and metabolized into glutamine by the ATPase-dependent glutamine synthase.

Table 7.2 outlines the key features that support ammonia as a central figure in the generation of HE. There are, however, multiple other chemical and structural changes that contribute to the clinical presentation of HE and many of these have a complex relationship with each other and with ammonia. These include gamma-aminobutyric acid (GABA) transmission, the expression of the peripheral-type benzodiazepine receptor, cell volume dysregulation, reactive oxygen species, and oxidative stress, and protein tyrosine nitration of astrocytes.

Table 7.2

Substantiation of role of ammonia in hepatic encephalopathy (HE)

1. Marked elevation in serum and brain ammonia in HE
2. Neuropathological correlates consistent with exposure to ammonia
   a. Astrocyte swelling and brain edema in acute HE
   b. Alzheimer type II astrocytes in chronic HE
3. The presence of increased $^{13}NH_3$ concentrations using PET scanning
4. Magnetic resonance spectroscopy findings of elevated glutamine in HE
5. Lowering ammonia is the treatment of choice for HE

7.1.4.1. Ammonia and GABA transmission

One of the key roles of ammonia in HE is its relationship with central inhibitory neurotransmission (Jones and Lavini, 2002). The interplay between ammonia and GABA transmission is complex and incompletely understood and much of the evidence blends data from rat cell culture preparations, in vivo animal studies, and cultured human neurons.

There is now growing evidence that ammonia may enhance GABA transmission in at least three independent ways. The first is by ammonia-induced enhancement of $GABA_A$ receptor activation. Exposure of isolated rat cortical neurons to concentrations of ammonia that are present in HE enhances the $GABA_A$-mediated, inward chloride conductance (Takahashi et al., 1993). The relationship is dose-dependent but becomes sigmoidal at very high levels of ammonia. The second involves increasing the availability of GABA at the synaptic cleft. To this end, Norenberg's group has reported a reduction of GABA uptake by cultured rat astrocytes in the presence of ammonia at concentrations found in HE (Norenberg et al., 1985; Bender and Norenberg, 2000). The third involves ammonia-induced expression of astrocytic peripheral type benzodiazepine receptor (PTBR) (Butterworth, 2000). The PTBR is a multimeric complex with a voltage-dependent anion channel that spans the inner and outer mitochondrial membrane of astrocytes (Anholt et al., 1986; Basile and Skolnick, 1986; Itzhak et al., 1993). In contrast to the central-type benzodiazepine receptor, the PTBR is not found on neurons of the central nervous system (CNS), and its endogenous ligand is the diazepam binding inhibitor (DBI), not GABA (Papadopoulos and Brown, 1995). Brain homogenates of patients who died of cirrhosis associated with HE have increased densities of PTBR in the frontal cortex and caudate nucleus compared to age matched controls (Lavoie et al., 1990). Furthermore, in the portocaval-shunted rat – the animal model of portosystemic encephalopathy – there are increased binding site densities of the selective PTBR ligand, [^{3}H]-K11195, in several cortical and subcortical sites (Giguere et al., 1992; Desjardins et al., 1997). Interestingly, PTBR binding site densities were increased in other tissues, suggesting that the changes seen are due to a systemically active substance, such as ammonia (Rao et al., 1994; Butterworth, 2000). The role of PTBR in astrocytes is not fully known. Activation of PTBR promotes synthesis and release of the neurosteroids tetrahydroprogesterone (THP) and tetrahydrodeoxycorticosterone (THDOC),

both of which are powerful agonists of the GABA receptor complex. Injection of neurosteroids into normal mice induces sedation as well as expression of the characteristic Alzheimer type II astrocytes in the brain (Norenberg et al., 1997), two features common to hepatic encephalopathy.

Stimulation of PTBR also induces protein tyrosine nitration (PTN) of rat astrocytes (Schliess et al., 2002). PTN is present in rat astrocytes when exposed to ammonia or diazepam. PTN is an *N*-methyl-D-aspartate (NMDA)-mediated process that also involves generation of reactive oxygen species. That diazepam can induce PTN of the astroglial glutamine synthase supports the hypothesis that PTN may play a role in the generation of HE (Gorg et al., 2003).

7.1.4.2. Cell swelling

In acute fulminant liver failure there is marked astrocyte swelling, cytotoxic cerebral edema and raised ICP, which may result in fatal herniation. The degree of cell swelling has been shown to be related to levels of arterial ammonia and thus indirectly supports the glutamine–osmotic hypothesis. The latter posits that elevated levels of the osmotically active glutamine induces a hyperosmotic state, resulting in a shift of water into astrocytes (Brusilow and Traystman, 1986; Takahashi et al., 1991).

In chronic liver failure, the effects of cell volume change are believed to alter astrocyte function without causing changes in ICP. The ability of MRS to measure specific osmotically active substances has been invaluable in studying this phenomenon. Myoinositol is involved in cell volume regulation. It accumulates intracellularly in response to cell shrinkage and moves to the extracellular compartment in response to swelling. Changes in myoinositol are thus believed to represent a compensatory mechanism to buffer changes in cell volume and therefore abnormal levels of myoinositol may represent derangements in cell volume homeostasis (Haussinger et al., 1994, 2004). In cirrhotic patients with HE, MRS consistently shows depleted myoinositol. The depth of depletion correlates with severity of encephalopathy. Such spectroscopic changes have also been demonstrated in the rat model of portosystemic shunt (Moats et al., 1993) and following transjugular intrahepatic portosystemic shunt (TIPS) (Haussinger et al., 1994) and these abnormalities are essentially reversed following liver transplant (Ross et al., 1996). Not only is MRS a highly sensitive and specific diagnostic tool for hepatic encephalopathy (Haussinger et al., 1994) but the alteration in myoinositol pools have prompted some authors to suggest that subtle changes in astrocyte cell volume may be a crucial component of the clinical expression and severity of HE (Haussinger et al., 2000). How subtle changes in astrocytic volume produce encephalopathy is not known. Recent work on glial–neuronal signaling has shown that astrocytic calcium waves can have potent modulator effects on presynaptic glutamatergic release and disruption of these calcium waves alters such glutamatergic transmission (Araque et al., 1999; Araque and Perea, 2004; Perea and Araque, 2005). The term 'tripartite synapse' has been introduced to include the astrocyte as an important component of the standard synapse. Whether there are alterations in glial calcium waves associated with ammonia-induced astrocytic swelling is not known. Given the altered glial–neuron communication present in HE, future investigations into the effects of ammonia on astrocytic calcium waves may be of interest.

7.1.4.3. Manganese

Clearance of manganese is impaired in chronic liver failure and concentrations of manganese in brain parenchyma can be increased sevenfold (Butterworth et al., 1995). Manganese probably contributes to the expression of HE and the accumulation of manganese within the basal ganglia probably underlies the clinical features of parkinsonism (Layrargues et al., 1998). Manganese has been shown to increase expression of astrocytic PTBR in vitro (Hazell et al., 1999) and it induces the mitochondrial permeability transition (Rao and Norenberg, 2004). Thus manganese is a likely neurotoxin in HE having multiple mechanisms of actions, some of which may be synergistic with ammonia (Jayakumar et al., 2004).

7.1.4.4. Oxidative stress

Evidence for oxidative stress in the pathogenesis of HE stems from in vitro studies on cultured astrocytes. Although one should be guarded about extrapolating a clinical syndrome from such reduced preparations, it is rather compelling that the very molecules implicated in the pathogenesis of hepatic encephalopathy, i.e., ammonia, manganese, PTBR ligands and glutamine, have all been shown to generate free radicals in vitro, in addition to causing cell swelling (for detailed review see Norenberg et al., 2004). There is therefore at least an association of oxidative stress and HE.

7.1.4.5. Cerebral blood flow and glucose metabolism

Positron emission tomography (PET) has shown that patients with minimal HE have selective reduced glucose metabolism in the cingulate gyrus and frontal and parietal association areas. These areas correlated to the areas of the brain responsible for the deficits

seen on neurocognitive testing (Lockwood, 2002). Similar findings using single photon emission computed tomography (SPECT) confirm the anterior cingulate gyrus as being an important site of altered blood flow in HE (Iwasa et al., 2005).

7.1.5. Treatment

The management of acute and fulminant liver failure is orthotopic liver transplantation when treatment of the underlying disease (e.g., infection, drug overdose) proves unsuccessful. Guidelines have been developed for orthotopic liver transplantation for patients with fulminant liver failure (Steinman et al., 2001). These patients are frequently critically ill and often require intensive care management with invasive monitoring and ventilatory support. Successful management of life-threatening cerebral edema is critical for temporizing these patients prior to liver transplantation. Hypothermia has been used with some success in these patients (Jalan et al., 1999; Zwingmann et al., 2004). A single study comparing steroids and mannitol in the management of ICP in acute fulminant hepatic failure showed that in patients who receive mannitol the cerebral edema resolves more frequently with significantly greater survival than in those who receive dexamethasone (Canalese et al., 1982). More recently, hypertonic saline therapy has shown to reduce cerebral edema and ICP more effectively than mannitol (Murphy et al., 2004).

The definitive treatment for advanced chronic liver failure is orthotopic liver transplantation (Steinman et al., 2001). Management of the encephalopathy associated with chronic liver failure should target: 1) treatment of any intercurrent infection; 2) addressing and reversing any inciting triggers, e.g., treating active GI bleed, discontinuation of sedative medication; 3) restriction of subsequent dietary protein; and 4) lowering blood ammonia. Dietary protein intake of 1–2 g/kg/day is enough to maintain adequate nitrogen balance while reducing the risk of recurrent hepatic encephalopathy (Swart et al., 1988). The nonabsorbable disaccharide lactulose is a popular method of reducing ammonia production within the gut. Its mechanisms of action include: 1) acidification of gut lumen, thus reducing the uptake of ammonia; 2) increased uptake of ammonia by gut flora, which are thence passed in the stool; and 3) catharsis. In a double-blinded, placebo-controlled trial, L-ornithine-L-aspartate (OA) lowers arterial ammonia, with clinical improvement in cognitive test scores in patients with HE (Kircheis et al., 1997). The mechanism is not known but improvement of the urea cycle function has been suggested.

7.1.5.1. Other treatments

Flumazenil, an antagonist of the benzodiazepine recognition site located on the $GABA_A$ receptor, has garnered some attention in clinical practice but has failed to produce significant results. The small clinical improvement produced by flumazenil has been attributed to reversal of action of endogenous benzodiazepine molecules (endozepines), which are thought to have a contributory role in the pathogenesis of HE (Rothstein and Olasmaa, 1990).

Neomycin or rifaximin are antibiotics that target urease-producing bacteria. Both are considered effective at lowering serum ammonia (Williams and Bass, 2005). In rare cases neomycin can cause oto- or nephrotoxicity.

7.2. Uremic encephalopathy

Impairment of consciousness and other CNS abnormalities associated with kidney failure can be broadly categorized into those related to kidney failure per se and those resulting from the treatment of renal failure. Uremia is the clinical syndrome of renal failure, and its full expression is manifested in the context of multiple organ system dysfunction. Uremia is caused by two main mechanisms: 1) excessive accumulation of products of protein metabolism; and 2) loss of intrinsic kidney homeostatic and endocrine function. Uremic encephalopathy is the cerebral manifestation of uremia.

7.2.1. Epidemiology

It is difficult to determine the epidemiological profile of uremic encephalopathy. Its prevalence would follow that of end-stage renal disease. To this end, in the year 2003, 320 000 people with end-stage renal disease were treated with dialysis therapy in the USA. This number is projected to climb to 650 000 by the year 2010 and 2 million in 2030 (Szczech and Lazar, 2004). Such exponential growth is also expected in Europe (Lameire et al., 2005). Therefore the incidence and prevalence of uremic encephalopathy as well as the neurological complications associated with dialysis will continue to increase with time.

7.2.2. Clinical manifestations of acute and chronic uremic encephalopathy

Documentation of this condition dates back to the first century when Araetus the Cappadocian noted ‘they are very pale, inert, sluggish, without appetite, without digestion... their eyes become dim, dull, and rolling, hence many become epileptic; others are swollen, misty,

dropsical; and others again are filled with melancholy and paralysis' (Adams, 1836). In modern parlance, this refers to anorexia, malnutrition, extracellular fluid expansion, encephalopathy, and weakness. In his seminal text, Osler added psychosis, depression, insomnia, myoclonus, and focal and generalized seizures to the description of uremia (Osler, 1892).

Acute uremic encephalopathy is a florid neuropsychiatric illness whose clinical features range from subtle executive dysfunction to coma. Accordingly, early signs include reduced attention, impaired construction and writing, executive dysfunction, behavioral changes, and sleep disturbances. This can lead to an agitated delirium and coma. Hyperventilation may be present during periods of metabolic acidosis. Motor findings include generalized weakness, paratonia, multifocal myoclonus, action myoclonus, stimulus-sensitive myoclonus, tremor, and asterixis. Myoclonus is more prominent in uremia than in most other metabolic encephalopathies and it often responds to clonazepam. Asterixis is a periodic loss of muscle tone (i.e., negative myoclonus) and can be seen as a flapping of the wrists with the arms outstretched and wrists hyperextended. In bed-bound patients who are unable to assume this posture, asterixis can be identified by instructing the patient to hold the tongue out: periodic retraction of the tongue towards the mouth is considered analogous to asterixis. Similarly, flexion at the hips and knees bilaterally and placing the soles of the feet together (lithotomy position) can bring out asterixis as evidenced by periodic loss of adductor tone and 'flapping of the knees'. Asterixis can also affect truncal musculature and cause loss of balance and falls. Tetany from abnormal calcium homeostasis can also be seen. Seizures are not uncommon during acute uremic encephalopathy. These are usually generalized and occur in the anuric or oligarch phase. Less common are focal seizures, which may occur with or without an identified structural lesion. Uremic coma, uncommon now, is typically accompanied by Kussmaul breathing related to metabolic acidosis.

Compared to acute uremia, chronic uremic encephalopathy has a more insidious clinical presentation. Nevertheless, patients may have similar but less dramatic clinical findings. Chronic uremic encephalopathy is characterized by changes in mental status such as slowness of thought, apathy, flattening of affect, inattention, and constructional impairment. Headaches are not uncommon. Sleep disturbances and restless leg syndrome are common complaints in this patient population. Diffuse motor findings of tremor, myoclonus, and asterixis may be present. Prior to the advent of dialysis, uremic meningitis (i.e., meningismus, headache, and a lymphocytic pleocytosis on cerebrospinal fluid (CSF) examination with elevated opening pressure) was a feature of chronic uremia. Generalized convulsive seizures can occur in chronic uremic encephalopathy; however, this is typically seen at the very end stage of the disease and may be accompanied by stupor or coma (Glaser, 1974). With improved treatment strategies, seizures have become less common. The condition of posterior reversible leukoencephalopathy (described separately in this chapter) is often seen in patients with chronic renal failure and accelerated hypertension.

7.2.3. Pathophysiology of uremic encephalopathy

Derangement of a single neurotoxic metabolite is not responsible for the protean clinical features of uremic encephalopathy. Rather it is the cumulative effects of both the uncleared products of protein metabolism and the dysfunctional endocrine kidney that lead to brain dysfunction. A candidate neurotoxin must fulfill certain criteria: 1) its levels should be elevated in uremic encephalopathy; 2) there should be a direct or linear relationship between the concentration of toxin and degree of encephalopathy; 3) neurotoxicity should be demonstrated; 4) it should be dialyzable; 5) removal of the candidate neurotoxin should result in clinical improvement; and 6) altering its levels in experimental conditions should theoretically give rise to some observable neurological dysfunction. Thus far many substances have fulfilled some of these criteria but few have remained in the running as culprit molecules that produce uremic encephalopathy. Table 7.3 lists some of the many substances that have been considered as neurotoxins in uremic encephalopathy.

7.2.3.1. Guanidino compounds

Guanidino compounds (GC) are breakdown products of protein and amino acid metabolism, and four GCs (guanidinosuccinic acid (GSA), methylguanidine (MG), guanidine (G), and creatinine (CTN)) are particularly elevated in the serum, CSF, and brain tissue of patients with chronic uremia (De Deyn et al., 1995; Marescau et al., 1997). Under experimental conditions, intraperitoneal injection of these four GCs elicit either tonic–clonic convulsions or myoclonic twitches in adult mice. GSA was the most potent proconvulsive toxin, since it produced its effects at concentrations seen in humans with uremia (D'Hooge et al., 1993a). Guanidine and CTN produced convulsive seizure at higher concentrations, and CTN only produced myoclonic twitching.

In reduced preparations, all GCs can block the $GABA_A$ and glycine inhibitory currents, with GSA being the most potent compound and G, MG, and CTN less so

Table 7.3

Neurotoxic substances proposed in uremic encephalopathy

Neurotoxins	Levels	Possible clinical consequences	Proposed mechanisms of action
Guanidino compounds Guanidinosuccinic acid Methylguanidine Guanidine Creatinine	↑ in CSF and brain	Seizures; cognitive dysfunction	Activation of NMDA receptors Inhibition of $GABA_A$ and glycine transmission
Parathyroid hormone	↑ in serum	Levels are directly proportional to degree of encephalopathy	Altered cerebral calcium, in the presence of elevated PTH, may influence transmitter release and second-messenger signaling and alter metabolism
Urea	↑ in serum	Myoclonus in acute uremia	–
Aluminum	↑ in serum	Neurocognitive decline	–
Middle molecules (300–5000 kDa)*	↑ in serum	Unsubstantiated	–
Phenols	↑ in serum	Unsubstantiated	–
Amines, myoinositol, uric, oxalic acids	↑ in serum	Unsubstantiated	–

*Krishnan and Kiernan (2007) provide a critical review of the middle molecule hypothesis.

(De Deyn and Macdonald, 1990). The GC-induced convulsions in animal models were only partially blocked by benzodiazepines. Thus their proconvulsive mechanism may be more complex than just generalized disinhibition. To this end, recent evidence has shown that GCs may be an agonist at the NMDA glutamate receptor (D'Hooge et al., 1993b, 1996; Reynolds and Rothermund, 1995). A proposed mechanism of cerebral hyperexcitability thus includes the combined disinhibition via competitive blocking of $GABA_A$ and glycine receptors and activation of NMDA receptors (De Deyn et al., 2001). The possible role of nitric oxide (NO) and calcium-induced excitotoxicity has been proposed (De Deyn et al., 2003; D'Hooge et al., 2003). Based on animal studies, GCs may be implicated in the seizures and possibly myoclonus of uremic encephalopathy.

7.2.3.2. Urea

From studies in cat, acute elevation of serum urea induces myoclonus with associated epileptiform bursting in nucleus reticularis gigantocellularis and caudalis. This was abolished by either sectioning the spinal cord or from chemical paralysis, suggesting a reflex origin (Zuckermann and Glaser, 1972; also see Chadwick and French, 1979). The effects of urea in these acute studies followed a latency of 60 minutes, indicating that urea may exert neurotoxic effects indirectly. In the chronic uremic state, however, there is evidence *against* a significant role of urea in uremic encephalopathy, since dialyzing a patient against a high urea concentration dialysate (i.e., not changing serum urea levels) still results in clinical improvement.

7.2.3.3. Parathyroid hormone

Parathyroid hormone (PTH) has a central role in phosphate and calcium homeostasis. In uremia PTH secretion is stimulated 1) by the presence of uremia-associated PTH resistance, and 2) by decreased levels of serum ionized calcium. This leads to a relative excess of PTH. There is decent evidence that PTH is an important toxin in uremic encephalopathy; however, the mechanism is as yet unresolved. Uremic patients with normal serum PTH or parathyroidectomies have fewer EEG abnormalities than uremic patients with elevated PTH (Avram et al., 1979). Therefore, the EEG correlate of encephalopathy follows the serum PTH. In the animal model of uremia, dogs without parathyroidectomy (and thus higher PTH) had a higher percentage of <7 Hz frequencies on EEG, and had a higher concentration of brain calcium (Akmal et al., 1984). The elevation of brain calcium has been observed in the cerebral cortex and hypothalamus (Mahoney and Arieff, 1983).

It is reasonable to propose that alterations in brain calcium may lead to changes in either intrinsic membrane properties and/or alterations in transmitter release. The details of this, however, are not known in the case of uremic encephalopathy, and some challenge the suggestion that PTH and changes in brain calcium exert neurotoxic effects in uremia (Adler and Berlyne, 1985).

7.2.4. Encephalopathy related to treatment of uremia

7.2.4.1. Dialysis disequilibrium

An encephalopathic state can be induced by rapid dialysis. The so-called dialysis disequilibrium is a well described phenomenon that affects patients during or shortly after hemodialysis. The symptoms include headache, nausea, vomiting, restlessness, myoclonus, disorientation, and somnolence (Bolton and Young, 1990). In its most severe form, patients may experience organic psychosis, generalized seizures, stupor, or coma (Port et al., 1973).

Symptoms of dialysis disequilibrium are caused by shifts of water and subsequent cerebral edema. Changes in brain volume are probably very common following dialysis; in fact there is an average increase in brain volume of 3% following hemodialysis (Walters et al., 2001). These changes were in the absence of any neurological symptoms. There are two schools of thought about the molecular mechanism of dialysis disequilibrium: 1) cerebral edema is caused by the 'reverse' urea effect (Silver et al., 1992) and 2) cerebral edema is explained by the idiogenic osmoles hypothesis (Arieff et al., 1973). An in-depth critical analysis of these two theories is beyond the scope of this chapter; however, the reader is referred to an excellent review (Silver et al., 1996). The reverse urea effect got its name from the old neurosurgical practice of intravenous infusion of urea to reverse cerebral edema (an effect caused by the osmotic forces from urea). In the case of hemodialysis, the rapid *removal* of urea may cause brain swelling, hence the 'reverse' urea effect. In brief, compared to water, urea slowly moves across the BBB. Rapid hemodialysis sets up an osmotic gradient caused by the different concentrations of urea across the BBB. This leads to movement of water into the brain extracellular compartment and cerebral swelling. Increased brain water content does not occur if the concentration of urea in the hemodialysate is equal to that of the plasma. The idiogenic osmoles theory posits that dialysis induces the formation of intracellular osmotically active particles of uncertain chemical composition (idiogenic osmoles), which draw water across the BBB.

The movement of water and urea across the BBB is facilitated by proteins called aquaporins and urea transporters respectively. In the rat model of chronic uremia, there is both a significant reduction in brain urea transporter UT-B1 (Hu et al., 2000; Trinh-Trang-Tan et al., 2005) and a coincident increase in expression of brain aquaporins AQP-4 and AQP-9 (Trinh-Trang-Tan et al., 2005). These findings may provide a molecular basis to support the hypothesis of the 'reverse urea effect' in dialysis disequilibrium.

7.2.4.2. Dialysis dementia

Also known as dialytic encephalopathy, dialysis encephalopathy, or progressive myoclonic dialysis encephalopathy; dialysis dementia is an historically important, but currently uncommon, form of uremia-associated encephalopathy. Dialysis dementia is a progressive, multisystem, degenerative condition that can be fatal if not corrected early in its course (Alfrey et al., 1972; Burks et al., 1976). The abnormalities of speech and language that are seen in dialysis dementia differentiate it clinically from other forms of metabolic encephalopathy. Like other metabolic encephalopathies, patients with dialysis dementia can have impaired attention and memory, poor construction, impaired visuospatial function, myoclonus, asterixis, and seizures. Speech difficulties are seen in 93% of patients (Jack et al., 1983). Early problems include poor articulation and stuttering (Madison et al., 1977). Language can become nonfluent, like that seen in a Broca's aphasia, with associated word substitutions and omissions, agrammatism, and word-finding difficulties. These language deficits can also be manifest in writing. The EEG findings in dialysis dementia include very frequent (>50 times per recording session) frontal intermittent bursts of delta activity (Chokroverty and Gandhi, 1982), in addition to triphasic waves (Noriega-Sanchez et al., 1978) and paroxysmal bursts of spike and wave activity (Hughes and Schreeder, 1980).

The neurotoxic effects of aluminum are thought to cause dialysis dementia; however, the mechanism by which aluminum induces neurodegeneration remains elusive (Bolton and Young, 1990). The incidence of dialysis dementia has declined significantly since aluminum has been systematically removed from the dialysate; however, dialysis dementia still rarely occurs. The source of aluminum is probably oral ingestion of phosphate binders ($Al(OH)_3$). The treatment of dialysis dementia involves maximum reduction of aluminum exposure, which would include ensuring an aluminum-free dialysate as well as switching from $Al(OH)_3$ to $CaCO_3$ or oral phosphate binding therapy. Desferrioxamine, a chelating agent, has shown some promise in reversing the symptoms of dialysis dementia (Ackrill

et al., 1980; Arze et al., 1981; Milne et al., 1983a, b). Desferrioxamine also chelates iron and limits its availability and has also been associated with ocular toxicity. The risk–benefit ratio needs to be considered.

7.2.4.3. Wernicke's encephalopathy

Wernicke's encephalopathy is the triad of dementia, ophthalmoplegia, and ataxia and is caused by thiamine deficiency. Patients with chronic renal failure are at risk for Wernicke's encephalopathy if thiamine replacement is not given during dialysis. In addition, the cachexia, nausea, and vomiting that is present in some patients with chronic uremia may lead to dramatic reduction in oral thiamine intake (such as that seen in hyperemesis gravidarum). Ensuring proper replacement during dialysis and adequate nutritional status is necessary to prevent this debilitating condition.

7.2.5. EEG changes in uremic encephalopathy

Jacob et al. (1965) classified the electroencephalographic (EEG) changes associated with chronic renal failure into those changes caused by dialysis therapy and those not influenced by dialysis therapy. The most common findings of EEG changes not influenced by dialysis therapy include: 1) poor regulation and slowing of the background rhythm – in this case the alpha rhythm is replaced or mixed with slower 5–7 Hz rhythm and seen in almost all patients; 2) paroxysmal, high-voltage, slow (delta) synchronous bursts that are frontally predominant – seen in all patients with chronic renal failure and most of those with acute renal failure; 3) paradoxical response to eye opening with accentuation rather than suppression of the background rhythm – this can be seen in both chronic and acute renal failure and indicates a dysfunction of the ascending reticular formation; 4) abnormal arousal response characterized by bursts of synchronous bilateral delta waves. Hughes and Schreeder (1980) described a predominantly frontal, low amplitude rhythmic theta (3–6 Hz) rhythm in patients with chronic renal failure. Epileptiform activity is less commonly seen. Triphasic waves have been reported in chronic renal failure. Although less common with aggressive dialysis, frontal predominant triphasic waves with a fronto-occipital gradient can be seen in severe azotemia (Karnaze and Bickford, 1984), or decompensated chronic renal failure (i.e., sepsis, concomitant dialysis dementia), and is typically associated with reduced levels of consciousness that can range from somnolence to stupor and coma (Bolton and Young, 1990).

The most common EEG change during dialysis is a deterioration of the predialysis recordings (Jacob et al., 1965). This was described as an increase in amplitude and continuity of the delta waves, as well as further slowing of the background EEG activity. One of the biochemical underpinnings of this finding may be the 'reverse urea effect', since it was prevented by using dialysate with concentrations of urea that were equal to that of the patient's plasma.

7.3. Posterior reversible leukoencephalopathy syndrome

Coined by Hinchey et al. (1996), the posterior reversible leukoencephalopathy syndrome (PRLE or PRES; sometimes called reversible posterior leukoencephalopathy (RPL)) is a relatively recently described metabolic encephalopathy. In its initial description, patients with hypertension associated with renal disease, pre-eclampsia, or immunosuppressant therapy developed a syndrome of headache, altered mental status (from confusion to stupor or coma) and a variable combination of vomiting, seizures, and changes in visual perception (blurred vision, hemifield defects, visual neglect, visual hallucinations, or cortical blindness), reflecting the maximal involvement in the posterior cerebrum. Focal or generalized seizures are common but lateralized weakness is not.

Neuroimaging revealed a predominantly posterior, bilateral cerebral edema involving white matter structures, with variable involvement of brainstem and cerebellum. In these patients, symptoms as well as imaging findings resolved following the correction of hypertension or removal of immunosuppressive drugs, e.g., tacrolimus and ciclosporin. Since its initial description there has been a groundswell of case reports identifying other conditions associated with PRLE (Table 7.4). In general, therapy is targeted at managing hypertension, withdrawal of the offending agent and treating the underlying condition.

7.3.1. Pathophysiology of PRLE

The precise pathophysiology of PRLE is not entirely known; however, the combination of loss of cerebrovascular autoregulation and endothelial damage are thought to be two important factors. The end result of these two processes is vasogenic edema, with or without cytotoxic edema, and, regardless of the comorbid illness, the clinical presentations are similar.

Systemic blood pressures that approach or exceed the upper limit of the autoregulatory curve may induce vasodilatation of cerebral vasculature due to excessive systemic forces. This may produce a sausage-string pattern of alternating vasoconstriction and vasodilatation (Strandgaard et al., 1976) with an associated physical breakdown of the BBB and fluid extravasation. This is the basis of the vasogenic theory. In some cases

Table 7.4

Conditions associated with the posterior reversible leukoencephalopathy syndrome

Hypertensive encephalopathy (Hinchey et al., 1996; Schaefer et al., 1997)
Renal disease (Weingarten et al., 1994)
Vasculitis
SLE (Primavera et al., 2001)
PAN (Vora et al., 1992)
Endocrinopathy
Pheochromocytoma (de Seze et al., 2000)
Primary aldosteronism (Kaplan, 1963)
Hypoglycemic coma (Aoki et al., 2004)
Porphyria (Kupferschmidt et al., 1995)
Scorpion venom (Sofer and Gueron, 1990)
Cocaine, amfetamine use (Grewal and Miller, 1991)
Over-the-counter stimulants (Lake et al., 1990)
Eclampsia (Digre et al., 1993; Hinchey et al., 1996; Schwartz et al., 2000)
Thrombotic thrombocytopenic purpura (Bakshi et al., 1999)
Hemolytic–uremic syndrome (Taylor et al., 2000)
Hypercalcemia (Kaplan, 1998)
Immunosuppressive drugs
Ciclosporin A (Truwit et al., 1991; Schwartz et al., 1995)
Tacrolimus (Shutter et al., 1993)
Vincristine (Hurwitz et al., 1988)
Cisplatin (Ito et al., 1998)
Cytarabine (Vaughn et al., 1993)
Interferon-alpha (Hinchey et al., 1996)
Combination chemotherapy (Cooney et al., 2000; Shin et al., 2001)
Other drugs
Antiretroviral therapy in HIV-infected patients (Giner et al., 2002)
EPO (Delanty et al., 1997)
Granulocyte-stimulating factor (Leniger et al., 2000)
IVIg (Mathy et al., 1998; Doss-Esper et al., 2005)
Blood transfusion (Boughammoura et al., 2003; Heo et al., 2003)
Contrast media exposure (Sticherling et al., 1998)

Source: adapted with permission from Lamy et al., 2004.

of severe tissue edema, the raised tissue pressure is thought to result in reduced perfusion and local hypoxia (Ay et al., 1998). The cytotoxic theory posits that cerebral vasoconstriction in response to hypertension causes local hypoxic changes that alter the BBB permeability, leading to cytotoxic edema (Ito et al., 1997; Casey et al., 2000). The propensity of the structures perfused by the posterior circulation to be involved in PRLE is thought to be due to the differential sympathetic control of the posterior circulation as compared to the anterior circulation.

In patients receiving immunosuppressive therapy or those with pre-eclampsia, PRLE may manifest at blood pressures that are not at the extreme ends of the autoregulatory curve. Thus, intrinsic endothelial damage may play a significant role in the development of PRLE. Cytotoxic drugs may exert effects directly on vascular endothelium, resulting in breakdown in the BBB followed by vascular leakage and edema (Ito et al., 1998). In the case of pre-eclampsia, endothelial damage may be in response to circulating trophoblastic cytotoxic factors from the underperfused placenta (Roberts and Redman, 1993).

7.3.2. Imaging findings

MRI typically demonstrates bilaterally symmetric lesions, hyperintense on T2 and fluid attenuation inversion recovery (FLAIR), in the subcortical white matter of the parieto-occipital junction in both parietal and occipital regions. Frontal and temporal regions are sometimes also affected, as is the overlying neocortex. Often more than one vascular territory is involved. Edema can be a mix of cytotoxic and vasogenic types and diffusion-weighted images can be iso-, hypo-, or hyperintense. Apparent diffusion coefficient (ADC) maps can suggest infarction. There is mounting evidence that not all patients conform to the disease's descriptive moniker. In fact, the lesions of PRLE are not always posterior: over 80% of patients in one study had frontal involvement (Covarrubias et al., 2002). The lesions are at times irreversible. This finding has been facilitated by the use of diffusion-weighted MRI (DWI) and ADC maps. An area that is both DWI- and ADC-positive indicates vasogenic, and potentially reversible, edema. On the other hand, a DWI-positive and ADC-negative area indicates cytotoxic edema, such as that seen in infarction (Fig. 7.2) (Ay et al., 1998; Kinoshita et al., 2003; Lamy et al., 2004; Stott et al., 2005). To this end, persistent deficits have been reported in up to 25% of cases (Covarrubias et al., 2002).

Furthermore, microhemorrhage and infarct are not infrequently seen (Ay et al., 1998; Kinoshita et al., 2003; Stott et al., 2005). Finally, cortical gray matter can be involved (Kinoshita et al., 2003; Ahn et al., 2004; Stott et al., 2005). Until a novel mechanism is identified that accounts for the variable MRI findings (i.e., location and vasogenic with or without cytotoxic edema), the name PRLE, as imperfect as it is, will probably remain.

7.3.3. Therapy

For cases of PRLE related to accelerated hypertension, prompt lowering of blood pressure is indicated. Intravenous sodium nitroprusside and/or labetalol or sublingual

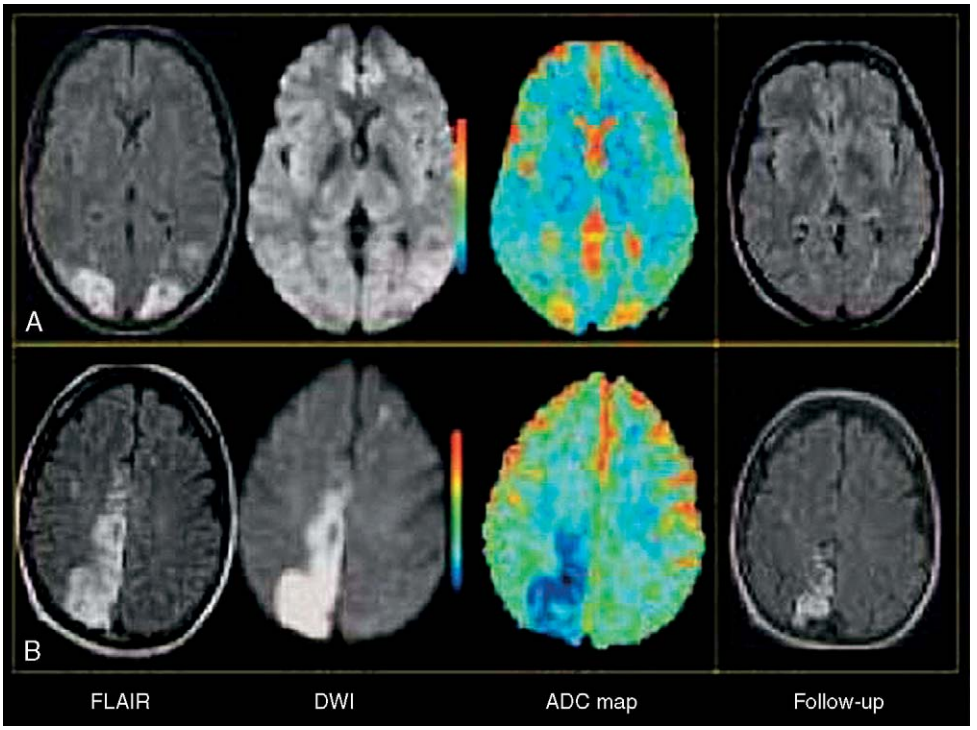

Fig. 7.2. Predictive value of ADC in posterior reversible encephalopathy syndrome. **A.** A 32-year-old woman with severe pre-eclampsia who presented with generalized seizures and cortical blindness. MRI was performed 1 day after onset. FLAIR showed cortical and subcortical hyperintensities with a posterior, bilateral, and symmetrical distribution. DWI ($b = 1000$ s/mm^2) showed a slight hyposignal in the posterior areas and ADC maps demonstrated increased ADC values in areas containing signal changes on FLAIR. This ADC–DWI pattern is consistent with the presence of vasogenic edema. The lesions are reversible, as confirmed by the 2-week follow-up FLAIR. **B.** A 30-year-old woman with eclampsia. She developed a motor deficit of the left lower limb 3 days after onset. A striking hyper intense signal was seen posteriorly in the right hemisphere on FLAIR and DWI ($b = 1000$ s/mm^2), with decreased ADC values. This pattern, similar to that of ischemic stroke, suggests the presence of cytotoxic edema. The 3-month follow-up FLAIR confirmed that most of the tissue was irreversibly damaged. With permission from Lamy et al., 2004.

nifedipine are most commonly used. A loading dose of phenytoin (15–20 mg/kg) or fosphenytoin (same dose in phenytoin equivalents) followed by a maintenance dose for a week is usually sufficient to prevent further seizures, as the disorder is usually self-limited in the uremic, hypertensive patient.

7.4. Pulmonary encephalopathy

Plum and Posner coined the term pulmonary encephalopathy – an encephalopathic state due to respiratory insufficiency often from mixed etiologies including hypoxemia, hypercapnia, respiratory exhaustion or fatigue, systemic infection, or congestive heart failure. Retention of CO_2 is the most common cause of the pulmonary encephalopathy, since its level most closely follows the CNS disturbance (Austen et al., 1957), although isolated hypoxia will also lead to impaired consciousness. Pulmonary encephalopathy is a potentially reversible condition and correction of the CO_2 and O_2 levels usually results in prompt recovery.

7.4.1. Clinical presentation

In general pulmonary encephalopathy may present with headache, ataxia, reduced vigilance, inattention, confusion, drowsiness, stupor, and coma. Funduscopic exam may reveal papilledema and absent spontaneous venous pulsations due to raised ICP. Motor signs include multifocal myoclonus and asterixis. Seizures are uncommon.

7.4.2. Etiologies of pulmonary encephalopathy

7.4.2.1. Hypoxia

7.4.2.1.1. Acute mountain sickness and high-altitude cerebral edema

Isolated hypoxia, or hypoxic hypoxia in the absence of combined hypoventilation and elevated CO_2, is often seen in people newly exposed to low partial pressure of oxygen, such as high-altitude recreationalists (mountain climbing, etc.). Risk factors include living above 900 m, increased length of time spent at altitude, exertion, and cardiopulmonary disease (Hackett and Roach, 2001).

Early signs of headache, nausea, fatigue, anorexia, and lassitude make up the syndrome of acute mountain sickness (AMS) (Singh et al., 1969). Worsening of symptoms of ataxia, delirium, and rarely seizures result from high-altitude cerebral edema (HACE), which is often associated with, and possibly exacerbated by, pulmonary edema (high altitude pulmonary edema; HAPE). HACE is considered to be an advanced form of AMS. The incidence of AMS/HACE is increasing as tourism takes more people higher. In 1991 in Summit County, Colorado, the incidence of AMS was 22% at altitudes of 1850–2750 m (7000–9000 feet) (Honigman et al., 1993) and 42% at altitudes of 3000 m (10 000 feet) (Dean et al., 1990). Symptoms typically begin within 12 hours of exposure to altitudes greater than 3000 m.

7.4.2.1.1.1. Neuroimaging

MRI findings in a small study of nine high-altitude recreationalists with HACE revealed subcortical white matter T2 hyperintensities, often of the splenium of the corpus callosum (Hackett et al., 1998). Based on the MRI characteristics the pathophysiology is thought to be vasogenic edema.

7.4.2.1.1.2. Pathophysiology

The pathophysiology of AMI/HACE is only partially understood.

Roach and Hackett (2001) outlined a schema wherein hypoxia and exercise leads to hypoxemia. A cascade of events thence increases BBB permeability and ultimately cerebral edema. In persons with insufficient cerebrospinal compliance, intracerebral pressure rises and symptoms of AMS/HACE will follow. Factors that likely combine to alter BBB permeability include: mechanical forces from increased cerebral blood flow; loss of autoregulation (Sutton and Lassen, 1979; Lassen, 1992); and increased cerebral perfusion pressure from elevated peripheral sympathetic activity (Duplain et al., 1999; Roach et al., 2000). Propranolol has been used to reduce the symptoms of AMS (Fulco et al., 1989) suggesting a role of enhanced sympathetic activity in the generation of symptoms. Oxidative damage from free radicals resulting in disruption of the BBB and AMS/HACE has been postulated (Askew, 2002). In support of this theory, *Gingko biloba* (Egb761 160 mg twice daily), a potent free radical scavenger, has been reported to prevent AMS (Roncin et al., 1996); however, this finding has not been reproduced subsequently (Chow et al., 2005).

7.4.2.1.1.3. Treatment

Hyperventilation-induced vasoconstriction at altitude may be a protective mechanism to reduce cerebral edema. The standard treatment and prevention of AMS/HACE involves acetazolamide and dexamethasone (Larson et al., 1982; Johnson et al., 1984). Immediate descent is, however, perhaps the most reliable and effective way of treating this condition.

7.4.2.1.1.2. Hypoxemic chronic obstructive pulmonary disease

Hypoxemic chronic obstructive pulmonary disease (COPD) can cause a chronic but reversible encephalopathic state. Patients with hypoxemic COPD who are treated with continuous oxygen supplementation over a 12-month period show improved problem-solving skills and motor learning as compared to a similar group of patients who only had night-time oxygen supplementation (Heaton et al., 1983). Neuropsychological studies on patients with hypoxemic COPD also demonstrate impaired verbal attainment, impaired deductive thinking and inattention. These cognitive deficits were associated with anterior cerebral hypoperfusion on SPECT imaging. Patients with nonhypoxemic COPD failed to demonstrate similar SPECT findings (Antonelli Incalzi et al., 2003). It is not known whether the neurocognitive changes or SPECT characteristics in this population of patients are reversible with long-term oxygen supplementation.

7.4.2.2. Hypercapnia

Hypercapnia is defined as arterial blood pressure of CO_2 (P_aCO_2) in excess of 60 mmHg.

The classic paper of Austen et al. (1957) describes the syndrome of headache, altered mental status, and papilledema related to pulmonary insufficiency, and the neurological manifestations of hypercapnia.

Symptomatic hypercapnia is usually due to an acute metabolic, pulmonary, or cardiac decompensation in a person with chronic pulmonary disease. Other syndromes of hypoventilation that can result in hypercapnia are listed in Table 7.5. The clinical presentation often includes headache, behavioral changes, and altered level of consciousness. Patients are inattentive and lethargic. Symptoms are often worse in the morning because of reduced respiratory drive during sleep and periods of hypoxia. Papilledema, cerebral vasodilation, and raised ICP are variably present. Generalized tremulousness, asterixis, and myoclonus of the upper limbs are typical motor findings in the metabolic encephalopathy associated with chronic hypercapnia. An early report concludes that, in patients with respiratory failure, the presence of asterixis is the most accurate predictor of cerebral dysfunction (defined as difficulty with memory, coherent thinking, serial subtractions, disorientation, and somnolence) (Kilburn, 1965). Furthermore, the combination of cerebral dysfunction, somnolence, asterixis, and

Table 7.5

Hypoventilation syndromes that may cause hypercapnia

Anatomical site	Clinical entity
Sensory	Loss of carotid sensitivity
Brainstem	Infarct; demyelination; tumor; sedative use; motor neuron disease; syringobulbia
Motor nerve	Acute inflammatory polyradiculoneuronopathy (Guillain–Barré syndrome); critical illness polyneuropathy
Neuromuscular junction	Myasthenia gravis; Lambert–Eaton myasthenic syndrome; botulism
Muscle	Congenital myopathy; inflammatory myopathy; critical illness myopathy
Chest wall	Restrictive lung disease; skeletal abnormalities of chest wall; obesity; circumferential burns
Alveolus	Primary alveolar hypoventilation; chronic obstructive pulmonary disease; central and obstructive sleep apnea.

tremors with arterial hydrogen ion concentration above 54.9 μEq/l (pH = 7.2) almost invariably precedes coma. In general, asterixis correlates with the degree of hypercapnia and acidemia. Those in respiratory failure without asterixis almost never demonstrate cerebral dysfunction (Kilburn, 1965). Seizures are infrequent in patients with asterixis and never occur in the absence of asterixis. The EEG findings in hypercapnia show generalized slowing.

7.4.2.2.1. Pathophysiology of hypercapnic encephalopathy

Although extensively studied, it is not clear how acute rises in CO_2 cause encephalopathy. The reader is referred to a critical discussion of this topic published in a previous volume of the *Handbook* (Ortiz Vasquez, 1979). Inspired CO_2 rapidly diffuses across all tissue membranes, including the CNS. The terms hypercapnia-induced encephalopathy or CO_2 narcosis may in fact be misnomers: the impairment of consciousness, neurocognitive changes, and movement disorders seen during hypercapnia may be due to CSF acidemia. Thus CO_2 would be imposing its effects on the CNS through its influence on CSF pH. The explanation of why people with severe metabolic acidosis remain alert while those with respiratory acidosis have impaired consciousness stems, in part, from the early work of Plum and Posner, who reported a proportionally greater drop in CSF pH relative to serum pH in respiratory acidosis than in metabolic acidosis. They proposed that, since bicarbonate moves slowly across the BBB in severe hypercapnia (Huang and Lyons, 1966), the CSF is buffered to a lesser degree than in metabolic acidosis, leading to a drop in CSF pH (Posner and Plum, 1967).

It is generally felt that the causes of impaired consciousness in hypercarbia are multifactorial: 1) compensatory cerebral vasodilation and increased cerebral blood flow occur in response to CSF acidosis with 2) associated vascular congestion and increased CSF pressure. In addition, CSF acidosis per se may impair neuronal excitability and neuronal metabolism (Borgstrom et al., 1976; Siesjo et al., 1976).

7.4.2.3. Carbon monoxide encephalopathy

Inhalation of carbon monoxide (CO) can induce both acute and delayed encephalopathy. With 245 times the affinity, CO competes with O_2 for the binding sites on hemoglobin and impairs tissue oxygen delivery. Neurological symptoms occur at 20–30% carboxyhemoglobin (COHb) and include dizziness, confusion, nausea, vomiting, pounding headache, and memory impairment. With increased COHb, ataxia, syncope, hallucinations, and depressed consciousness will follow, with rapid death occurring at 80% carboxyhemoglobin (Von Berg, 1999). The pathophysiology of acute CO encephalopathy is tissue hypoxia, which can cause endothelium and platelet activation from an NMDA-mediated generation of nitric oxide and peroxynitrite (Thom et al., 2004b). Survival of acute symptomatic CO exposure can lead to a period of lucidity, which then may be followed 2–3 weeks later by a delayed CO encephalopathy: the severity of which is directly related to the severity of the acute insult. Delayed CO encephalopathy is somewhat analogous to that seen following postanoxic brain injury and is characterized by recurrence of neurological symptoms such as language dysfunction, parkinsonism, urinary incontinence, and memory loss (Ginsberg et al., 1974; Choi, 1983; Kim et al., 2003). Magnetic resonance imaging findings of delayed CO encephalopathy demonstrate bilateral, confluent T2 white matter lesions that have reduced ADC values that suggest the presence of delayed cytotoxic edema. The progressive brain damage may also be due to an immune-mediated neutrophil activation, lipid peroxidation, and breakdown in cerebral vasculature (Thom, 1990; Thom et al., 2004a). Apoptosis and activation of cyclin-dependent kinases, invoked in hypoxic–ischemic encephalopathy, may also be relevant (Rashidian et al., 2005). Although hyperbaric oxygen therapy is often given for acute or delayed CO encephalopathy, its benefit is highly controversial (Scheinkestel et al., 2004).

7.4.2.4. Nitrogen narcosis

Although not an insufficiency of pulmonary function, nitrogen narcosis is an encephalopathic state affecting scuba divers, is brought on by breathing compressed air at depths greater than 30 m and is colloquially known as 'rapture of the deep' (Bennett, 1976; Tetzlaff and Thorsen, 2005). Behavioral changes include difficulty in problem solving, slowness of thought, giddiness, impaired judgment, and altered level of consciousness (Tetzlaff and Thorsen, 2005). EEG patterns show diffuse slowing (Pastena et al., 2005). The symptoms are believed to be due to increased concentration of nitrogen within hydrophobic tissue such as the lipid-rich myelin of the brain. Nitrogen narcosis can be avoided either by avoiding depths or by breathing a mixture of helium and oxygen. Treatment for this is ascent to a depth of 20 m (Szidon, 1993).

7.5. Pancreatic encephalopathy

Pancreatic encephalopathy is a rare and controversial CNS complication of pancreatitis with fewer than 30 reports in the literature.

7.5.1. Clinical presentation

The encephalopathy is characterized by mental confusion, visual and auditory hallucinations, psychomotor agitation and behavioral changes, delirium, stupor, and coma (Scharf and Levy, 1976; Estrada et al., 1979), and was first described by Rothermich and Van Haam (1941). Symptoms begin 2–5 days after the onset of the abdominal pains of pancreatitis. Although the disorder is usually monophasic, symptoms can fluctuate and follow a relapsing–remitting course along with recurrent pancreatitis over many years (Ruggieri et al., 2002).

7.5.2. Pathophysiology

Rothermich and Van Haam (1941) attributed the condition to a state of 'avitaminosis' of the pancreatic condition. Pancreatic encephalopathy does not appear to be related to alcoholism, vitamin deficiency, hypocalcemia, disseminated intravascular coagulation, or hyperglycemia (Young and DeRubeis, 1998). Vogel (1951) postulated a role of circulating lipase, since he was able to reproduce the scattered demyelinating lesions he described at autopsy in his patients who had pancreatic encephalopathy in rabbit brain by intracerebral injection of a preparation of lipase. Estrada et al. (1979) examined 17 young patients with non-alcohol-related pancreatitis and showed that, compared both to controls and to patients with nonencephalopathic pancreatitis, those with encephalopathy had significantly elevated CSF lipase. The controls and nonencephalopathic patients with pancreatitis had similar levels of CSF lipase. It was also shown that pancreatic encephalopathy was not related to the severity of the disease.

Elevated CSF lipase and increased permeability of the BBB were shown in a patient with pancreatic encephalopathy (Ohkubo et al., 2004). Whether lipase or other pancreatic enzymes leads to breakdown of the BBB is not known. However, in an animal model of acute pancreatitis, tumor necrosis factor and IL-6 are elevated, two cytokines that are known to cause capillary endothelial cell proinflammatory responses (Farkas et al., 1998). These cytokines may play a role in breakdown of the BBB and development of vascular edema. Whether this is present in humans with pancreatic encephalopathy is not known.

7.5.3. Imaging

Reports of the MRI findings in suspected pancreatic encephalopathy are scarce. A single case report describes increased white matter signals in pons, cerebellar peduncles and deep cerebral white matter that are partially reversible with resolution of the disease (Ohkubo et al., 2004). Diffusion positivity was described but mention was not made of the ADC correlate. This would be of interest as it would differentiate cytotoxic from vascular edema. There have been suggestions that fat emboli (Kincaid et al., 1982) or microthrombi may be part of the pathophysiology of pancreatic encephalopathy. These would presumably result in infarct, and thus give characteristic MRI findings.

The entity of pancreatic encephalopathy is controversial. Pancreatitis is common; however, the reports of pancreatic encephalopathy are few. This begs the question whether pancreatic encephalopathy is a unique entity. About 25% of patients with acute pancreatitis develop multiorgan dysfunction syndrome/multisystem organ failure, which is associated with a systemic inflammatory response syndrome (SIRS) – a condition frequently characterized by profound encephalopathy and increased systemic vascular permeability. SIRS encephalopathy surely accounts for some of the encephalopathy associated with pancreatitis. It is possible, indeed likely, that the encephalopathy associated with pancreatitis is both underrecognized and underreported. Further work, including systematic MRI, is needed in order investigate the presence of cytotoxic edema, which perhaps would not be expected in mild SIRS encephalopathy.

7.5.4. Management

There is no specific therapy aimed at treating pancreatic encephalopathy. Treatment of the underlying pancreatitis represents the standard of therapy and is beyond the scope of this chapter. In patients with pancreatitis, the diagnosis of pancreatic encephalopathy should be a diagnosis of exclusion if a new onset of encephalopathy develops. Instead, every effort should be made to unveil causes of the encephalopathic state such as those caused by: intercurrent infection, electrolyte derangements, toxic encephalopathy, cerebral infarct, other organ failure, sinovenous thrombosis, subdural hematoma, Wernicke's encephalopathy, or withdrawal seizures.

7.6. Hashimoto's encephalopathy

Lord Brain described an unusual case of a 40 year old man with a previous diagnosis of autoimmune thyroiditis who had multiple episodes of alternating hemiplegia, with visual disturbances and protracted confusional states associated with abnormal EEG, elevated thyroid antibodies, and normal thyroid function. The patient fully recovered with normalization of his laboratory findings (Brain et al., 1966). According to Brain, 'The association of the two disorders – the thyroiditis and the brain disease – suggests that antibody studies in other cases of unexplained encephalopathy might prove fruitful.' Brain was the first to describe what would later be dubbed Hashimoto's encephalopathy (Shaw et al., 1991). His prediction of an association between antibodies and the CNS manifestations of the condition was found to be accurate when patients with this condition were subsequently shown to have elevated serum antithyroglobulin antibodies (Shaw et al., 1991). The role of antithyroid antibodies and the CNS disease, however, remains both elusive and a source of ongoing controversy.

One of the main controversies surrounding Hashimoto's encephalopathy is that there are reports of up to 30% of healthy individuals with elevated antithyroglobulin antibodies (Hackett et al., 1960; Mariotti et al., 1992). Given the rarity of the disease, is it possible that Hashimoto's encephalopathy represents a coexistence of a very rare encephalopathy with a relatively common biochemical variation? Furthermore, it remains to be determined whether the antibodies present in Hashimoto's encephalopathy cause the neurological signs and symptoms or whether they are merely markers of the disease. Recently, Ferracci et al. (2003) reported that patients fulfilling the criteria for Hashimoto's encephalopathy had elevated CSF levels of antithyroglobulin antibodies, antithyroid peroxidase (antimicrosomal) antibodies, and circulating immune complexes: findings that were unique compared to controls. These antibodies were shown indirectly to have originated by intrathecal synthesis; therefore such findings may represent an important diagnostic test for Hashimoto's encephalopathy.

Reliable epidemiological data on this condition is lacking, given the preponderance of case reports or small case series related to this illness. The best estimate on the prevalence of Hashimoto's encephalopathy is 2.1/100 000 (Ferracci et al., 2004). Hashimoto's encephalopathy is present in the adult as well as the pediatric population (Vasconcellos et al., 1999).

7.6.1. Clinical presentation

There are two main presentations of Hashimoto's encephalopathy: 1) a 'vasculitic type' with multiple stroke-like episodes and 2) a 'diffuse progressive type' with predominantly neuropsychiatric symptoms and dementia (Chong et al., 2003). Both forms of Hashimoto's encephalopathy can share common features such as myoclonus, seizures, tremor, and fluctuating levels of consciousness. Confusion and acute cognitive decline are the most common features. Impairment of consciousness has been reported in up to 30% of cases (Ferracci et al., 2004). There are a number of case reports of isolated neurological or psychiatric features that were felt to be manifestations of Hashimoto's encephalopathy, such as bipolar affective disorder (Mussig et al., 2005), major depressive episode (Laske et al., 2005), subacute cerebellar syndrome (Passarella et al., 2005), and amnesia. Ferracci et al. (2004) state that, in a patient with an otherwise unexplained neurological condition, the presence of CSF antithyroid antibodies is confirmatory of a diagnosis of Hashimoto's encephalopathy. Other potential neurological complications of Hashimoto's encephalopathy include myoclonus, tremor, myelopathy, reversible stroke-like episodes, chorea, nystagmus, a cerebellar syndrome, and reversible amnesia. Any of these plus elevated serum antithyroid antibody levels represent criteria proposed by Ferracci et al. (2004). CSF antibody studies have not been routinely adopted by other workers.

Unexplained neurological symptoms that are unresponsive to standard therapy should prompt investigation for Hashimoto's encephalopathy. The 'typical' scenario is the patient with rapid or subacute onset neurocognitive decline with impaired consciousness (behavioral changes, confusion, dementia, delirium, seizures) with myoclonus (Shaw et al., 1991). This clinical phenotype resembles Creutzfeldt–Jakob Disease (CJD) (Seipelt et al., 1999). Establishing a diagnosis of Hashimoto's encephalopathy in such a patient will have enormous implications on the prognosis: CJD is universally fatal and Hashimoto's encephalopathy may

spontaneously remit or respond to immunotherapy. It may also obviate the elaborate and expensive infection control procedures that arise in the management of CJD.

7.6.2. Laboratory findings

CSF analysis in Hashimoto's encephalopathy is bland. There may be a slight lymphocytic pleocytosis but this is rare. CSF protein is usually elevated (Shaw et al., 1991). Patients are euthyroid (Shaw et al., 1991; Ferracci et al., 2003, 2004) or slightly hypothyroid (Shaw et al., 1991; Chong et al., 2003). CSF antithyroglobulin and antithyroperoxidase antibodies, and circulating immune complexes, should be elevated (Ferracci et al., 2003, 2004). CSF IgG index is normal, as is the CSF/serum albumin (Q_{alb}) (Ferracci et al., 2004).

7.6.3. EEG findings

EEG abnormalities are seen in the majority of patients with Hashimoto's encephalopathy (Ferracci et al., 2003, 2004). The severity of changes seen in the EEG in Hashimoto's encephalopathy varies according to the severity of the clinical features (Schauble et al., 2003). Typical EEG abnormalities seen in this condition include generalized slowing (Schauble et al., 2003), focal slowing (Henchey et al., 1995), frontal intermittent rhythmic delta activity (FIRDA) (Henchey et al., 1995), focal sharp waves (Ferracci et al., 2004), triphasic waves (Henchey et al., 1995; Schauble et al., 2003), and epileptiform discharges (Schauble et al., 2003).

7.6.4. Neuroimaging

The MRI findings in Hashimoto's encephalopathy are variable and nonspecific. In one review of the literature, half the reported cases demonstrate normal cerebral MRI (Chong et al., 2003). When present, MRI findings include subcortical white matter and cortical T2 changes that are reversible upon resolution of symptoms (Pozo-Rosich et al., 2002). In the largest prospective study 67% (6/9) of patients with Hashimoto's encephalopathy had normal MRI, while the remaining patients had nonspecific white matter changes (2/9) or cortical atrophy (1/9) (Ferracci et al., 2003). Conventional cerebral angiography has failed thus far to demonstrate abnormalities in Hashimoto's encephalopathy (Shaw et al., 1991). Results from SPECT studies have been variable. There is evidence of reduced perfusion in the cortex and basal ganglia in some patients (Forchetti et al., 1997; Chaudhuri and Behan, 2003). In one study that examined cerebral perfusion in patients with Hashimoto's thyroiditis who were then euthyroid with a normal neurological exam, there was an increased prevalence of subclinical brain perfusion abnormalities compared to normal controls (Zettinig et al., 2003). Ferracci et al. (2004), however, did not find SPECT abnormalities in their cohort of patients with Hashimoto's encephalopathy. Whether the abnormal SPECT results reflect a causal mechanism for cerebral dysfunction or a response to depressed cerebral activity (either clinically manifest or subclinical) is not known.

7.6.5. Pathophysiology

The encephalopathy does not result directly from thyroid disease. The proposed pathophysiologies of Hashimoto's encephalopathy include: autoimmune cerebral vasculitis (Thrush and Boddie, 1974; Shein et al., 1986), global hypoperfusion (Forchetti et al., 1997; Zettinig et al., 2003), brainstem vasculitis (Nolte et al., 2000), and primary demyelination (Mahad et al., 2005). No confirmed mechanism has been proven, because of the rarity of the disease and the paucity of neuropathological data. An immune-mediated process appears most compelling for the following reasons:

1. There is a strong association between previous autoimmune thyroiditis and Hashimoto's encephalopathy.
2. CSF autoimmune antibodies and circulating immune complexes are, thus far, specific for the condition of Hashimoto's encephalopathy (Ferracci et al., 2003, 2004).
3. Plasmapheresis has been shown to improve neurocognitive function (Boers, 2001; Nieuwenhuis et al., 2004; Hussain et al., 2005).
4. Intravenous immunoglobulin (IVIg) has been used with some benefit in the treatment of Hashimoto's encephalopathy (Jacob and Rajabally, 2005).
5. Alpha-enolase, a novel autoantigen, has shown to be present in patients with Hashimoto's encephalopathy, but not in patients with Hashimoto's thyroiditis (without Hashimoto's encephalopathy) or in patients with other neurological diseases. Its concentration varies according to the disease severity (Ochi et al., 2002). Alpha-enolase is also known to be present in other autoimmune diseases such as systemic lupus erythematosus with renal disease, antineuronal-cytoplasmic-antibody-associated vasculitis, and rheumatoid arthritis (Pancholi, 2001). Finally, autoantibodies directed at the amino terminal of alpha-enolase have been shown to be specific for Hashimoto's encephalopathy (Fujii et al., 2005).

7.6.6. Treatment

There is no consensus to the treatment of Hashimoto's encephalopathy. Because many case reports, including

a recent retrospective study, have used the presence of steroid-responsiveness as part of their diagnostic criteria for Hashimoto's encephalopathy, there may be a built-in bias towards the effectiveness of steroid therapy (Castillo et al., 2006). Lord Brain's original patient in 1966 improved spontaneously, without steroids. Furthermore, Ferracci's group failed to demonstrate a relationship between corticosteroid use and clinical benefit. Clearly, further work is required to determine the role of steroids in Hashimoto's encephalopathy. There are reports of some success with plasmapheresis or IVIg (see above).

Many still feel that it is unfortunate that Hashimoto's name is used in this clinical entity because 1) Hashimoto did not describe the syndrome and 2) to endocrinologists the name implies the existence of a concurrent thyroid dysfunction (for review see Fatourechi, 2005). Unlike myxedema and thyrotoxicosis, the CNS manifestations of Hashimoto's encephalopathy are not related to altered thyroid function. Other names such as 'encephalopathy associated with autoimmune thyroid disease', 'nonvasculitic autoimmune meningoencephalitis', or 'steroid-responsive encephalopathy associated with Hashimoto's thyroiditis' have been suggested. It has been suggested that until there is a better understanding of the pathophysiology and natural history of the disease, Hashimoto's encephalopathy remains a useful and appropriately inclusive name for this rare condition (Chong and Rowland, 2006).

7.7. Thyroid disorders

7.7.1. Actions of thyroid hormone

Thyroid hormones (thyroxine (T_4) and triiodothyronine (T_3)) bind nuclear receptors (TRs) in cells; in the brain these are mainly TRα receptors. TRs are present in most brain regions, including cerebral neocortex, hippocampus, thalamus, hypothalamus, cerebellum, and brainstem nuclei (Constantinou et al., 2005). Thyroid hormones play an important role in the maturation of the brain in all mammals. Genes regulated by thyroid hormone have been identified in neurons, astroglia, and oligodendrocytes, indicating their role in cell differentiation and development, myelination, migration, and signaling (Bernal, 2005). The hypothalamus and pituitary gland have beta-2 receptors; these receptors are involved in the negative feedback loop to control secretion of thyroid-stimulating hormone (TSH). Receptors have much greater affinity for T_3 than T_4 and, since T_4 is largely converted to T_3 in peripheral tissues, T_3 is the predominantly effective thyroid hormone. Activation leads to gene transcription within the cell; when the receptor is not occupied, there is an active suppression of gene transcription. This is probably produced by 'chaperone molecules' that act on the response element (Freeman and Yamamoto, 2002). Thyroid hormones also act at the level of the mitochondrion to stimulate oxidative metabolism. They also act on the cell membrane to affect the sodium–potassium pump (Boelaert and Franklyn, 2005).

7.7.2. Hyperthyroidism

7.7.2.1. Epidemiology

The overall yearly incidence of hyperthyroidism has been variably reported from different countries at between 0.5 and 0.012/1000 persons, combining overt and subclinical cases in population surveys (Vanderpump et al., 1995; Mostbeck et al., 1998; Soler Sole et al., 2003). Women almost always outnumber men. Thyroid storm (see later) is rare, with little epidemiological data.

7.7.2.2. Clinical manifestations of hyperthyroidism

Essentially, general features of thyrotoxicosis, regardless of cause, include warm, moist skin, tachycardia, nervousness, heat sensitivity, weight loss, increased appetite, tremor, muscular weakness (myopathy), and goiter (enlarged thyroid gland).

Most cases of hyperthyroidism are due to Graves' disease. Characteristics include widening of the palpebral fissure due to retraction of the upper lids. The upper lid lags with downward gaze. The ocular globes are displaced forward (proptosis). Ophthalmoplegia, due to deposits of mucopolysaccharide in extraocular muscles, causes tethering of the muscle, most commonly the inferior rectus, causing impaired upgaze (the differentiation from a nerve palsy can be made using the forced duction test).

The main hyperthyroid condition associated with impaired consciousness is 'thyroid storm'. There is an acute decompensation of the brain, thermoregulatory mechanisms, and cardiovascular and gastrointestinal–hepatic systems. The diagnostic criteria for thyroid storm are given in Table 7.6. In thyroid storm an agitated delirium, with tremor and restlessness with impaired attention and variably added delusions and hallucinations (organic psychosis), can evolve into apathy, then stupor to coma and/or generalized convulsive seizures.

7.7.2.3. Laboratory investigations

Thyroid function tests reveal elevated free T_4 and free T_3 concentrations with reduced serum TSH. EEG is not especially helpful as it is nonspecific, unless monitoring for seizures is deemed necessary.

Table 7.6

Diagnostic criteria for thyroid storm

Central nervous system effects		
Absent		0
Mild agitation		10
Moderate agitation	Delirium	20
	Psychosis	20
	Extreme lethargy	20
Severe	Seizure	30
	Coma	30
Thermoregulatory dysfunction		
99–99.9°F		5
100–100.9°F		10
101–101.9°F		15
102–102.9°F		20
103–103.9°F		25
>104°F		30
Cardiovascular dysfunction		
Tachycardia (beats/min)	90–109	5
	110–119	10
	120–129	15
	130–139	20
	>140	25
Congestive heart failure	Absent	0
	Mild: pedal edema	5
	Moderate: bibasilar crackles	10
	Severe: pulmonary edema	15
Atrial fibrillation	Absent	0
	Present	10
Gastrointestinal–hepatic dysfunction		
Absent		0
Moderate	Diarrhea	10
	Nausea/vomiting	10
	Abdominal pain	10
Severe	Unexplained jaundice	20
Precipitant history		
Absent		0
Present		10

Patients are assigned to the highest weighted description in each category and the results are tallied. When it is not possible to distinguish the effects of an intercurrent illness from those of severe thyrotoxicosis, the points are awarded to avoid thyroid storm and empiric therapy. An aggregate score of ≥45 is suggestive of thyroid storm; 25–44 of impending storm; and <25 makes thyroid storm unlikely. Source: from Burch and Wartofsky, 1993.

7.7.2.4. Management

Treatment involves: 1) reducing the secretion and actions of thyroid hormone, 2) treating the systemic complications, and 3) deactivating precipitants. Correcting the hormonal issue is primary; none of the other measures will be effective without this step. Propylthiouracil is the drug of choice as it reduces thyroid hormone synthesis and blocks the peripheral conversion of T_4 to T_3. Plasmapheresis and charcoal hemoperfusion, to remove thyroid hormone, have been used with some success in extreme cases.

The peripheral effects of thyrotoxicosis can be antagonized by beta-adrenergic blockers, especially propranolol and esmolol, and calcium channel antagonists, e.g., verapamil, to slow the heart rate.

Systemic treatment involves acetaminophen/paracetamol (acetylsalicylic acid should be avoided as it causes dissociation of thyroid hormones from protein binding sites) and cooling blankets to lower body temperature. Standard therapy for congestive heart failure, dehydration, and psychotic behavior should be used appropriately. Fluid and electrolyte balance should be carefully monitored and corrected; thiamine should be added to prevent Wernicke's encephalopathy.

Possible precipitants of thyroid storm include surgery, labor, and delivery, withdrawal of antithyroid drugs and radioiodine therapy. These measures should be considered carefully in the thyrotoxic patient. Definitive therapy may include thyroidectomy.

7.7.3. Hypothyroidism

Hypothyroidism relates to a deficiency of thyroid hormone or its actions on tissues. Goitrous (enlargement of the thyroid gland) hypothyroidism is the most common cause, while consumptive and central (due to deficiency of TSH) etiologies and tissue resistance to thyroid hormone are uncommon.

7.7.3.1. Epidemiology

Congenital hypothyroidism (cretinism) affects 1 in 3000–5000 neonates (Alm et al., 1984). There is a move to have thyroid blood tests carried out on every newborn. Clinical hypothyroidism overall occurs in about 2% and 0.2% of adult women and men, respectively, while asymptomatic hypothyroidism was found in 9.5% of a sample of the general population (Danese et al., 1996; Canaris et al., 2000). The incidence increases with advancing age. Some 99% of cases are primary, while only 1% are due to adrenal–pituitary causes with reduced TSH. Some symptomatic causes include thyroiditis, previous radiation to the neck, e.g., for tumor, and previous radioiodine therapy or surgery for overactive thyroid conditions.

7.7.3.2. Clinical features

Impaired consciousness is usually acute or subacute and is often precipitated by intercurrent infections or other serious systemic illness, cold exposure (hypothermia), medications that increase the metabolism of T_4 and T_3

(e.g., phenytoin, rifampin/rifampicin, amiodarone, and lithium) or sedative drugs, hypoglycemia, or withdrawal from thyroid replacement therapy.

Older women are the most likely group to present with myxedema coma. Features are like many metabolic encephalopathies, with sparing of cranial nerve functions. Deep tendon reflexes may show a prolonged relaxation phase. Coma can be preceded by nystagmus, muscle spasms, ataxia, and marked slowing of cognition. Clues that myxedema is the cause include the overall features of myxedema, including pale, doughy skin, periorbital swelling, swollen tongue, hypothermia, bradycardia, hypoventilation, and signs of pericardial effusion.

The neonate with cretinism shows prolongation of physiological jaundice, a hoarse cry, constipation, somnolence, and poor feeding. In the older child features are similar to those of adults.

7.7.3.3. Laboratory investigations

Specific tests include serum TSH (elevated) and T_4 (reduced). Hyponatremia, due to a syndrome of inappropriate antidiuretic hormone (SIADH), is common. Blood gas testing reveals elevated $P_{a}CO_2$ and low PO_2. Anemia and hypercholesterolemia are common. The EEG shows both suppression of voltage and slowing of background rhythms. The chest X-ray and echocardiogram can confirm the pericardial effusion.

7.7.3.4. Differential diagnosis

Myxedema coma can be mimicked by carbon dioxide narcosis, hypothermia, depression from medication, sepsis, severe emotional depression, and nephrotic syndrome.

7.7.3.5. Management

Myxedema coma is a medical emergency and demands thyroid replacement therapy, usually before confirmatory laboratory tests are back. Replacement therapy is instituted with either 500 μg of T_4 or liothyronine at 25 μg orally every 12 hours. Supplemental glucocorticoid, e.g., intravenous hydrocortisone 5 mg/h, should be given to prevent acute adrenal failure. Three times the daily maintenance dose of T_4 is given daily for 3 days if required, unless there are contraindications. Glucose solutions without saline should not be given, in view of poor free water clearance in hypothyroidism. Warming the patient, screening for infection, treating the pericardial effusion when indicated, e.g., pericardial tamponade, and treating hypotension with volume replacement or dopamine are other, often necessary, measures.

7.8. Acute adrenal failure

Adrenal failure is a medical emergency related to a deficiency of adrenal cortical hormones. Primary adrenal cortical failure affects both cortisol and aldosterone secretion, while secondary adrenal failure affects only cortisol secretion. Cortisol secretion is under the direction of the hypothalamic–pituitary axis while aldosterone is regulated by the renal–adrenal axis.

Cortisol acts on a cytoplasmic receptor; the cortisol–receptor complex moves into the cell nucleus to bind to specific DNA motifs that, in the presence of activator proteins, mediate anti-inflammatory and metabolic actions and effects on other endocrine glands. There are glucocorticoid receptors in the brain, including the hippocampus, neocortex, hypothalamus, and cerebellum (McEwen et al., 1986). Receptors in the hippocampus, when activated, may trigger apoptosis of neurons (Sapolsky et al., 1985). It should be noted that adrenocorticotropic hormone (ACTH), responsible for cortisol secretion by the adrenals, and its releasing hormone, corticotropin-releasing hormone (CRH), also have brain receptors. Aldosterone has a more limited action: increase in sodium retention and potassium excretion by the kidney.

7.8.1. Epidemiology

Primary adrenal failure has a prevalence of 4–11 cases per 100 000 population (Oelkers, 1996). Autoimmune adrenal damage accounts for most cases; some of these are associated with autoimmune polyendocrine syndromes. Other causes include infections (tuberculosis, fungal infections, cytomegalovirus, and human immunodeficiency virus), metastatic tumors, intra-adrenal hemorrhage (including meningococcemia), adrenoleukodystrophies, and adrenalectomy.

Secondary adrenal failure most commonly results from long-term corticosteroid usage with abrupt withdrawal or inadequate replacement at times of crisis, or less commonly from hypopituitarism of various causes.

7.8.2. Clinical features

Impaired consciousness ranges from an acute confusional state, either quiet or agitated, to coma. Cognitive changes may sometimes relate to central effects of ACTH, CRH, or a deficiency of cortisol on brain receptors. Hypotension, hypoglycemia, and the effects of cortisol on other endocrine glands or electrolyte disturbances (hyponatremia, hyperkalemia, hypercalcemia, and dehydration), as a consequence of relative cortisol deficiency, can also cause coma.

7.8.3. Treatment

Emergency therapy should be instituted as soon as the diagnosis of acute adrenal failure is considered: 100 mg hydrocortisone should be given intravenously every 6 hours. Hypotension, volume depletion, and hypoglycemia should be corrected. In cases of primary adrenal failure, the addition of a mineralocorticoid, such as fludrocortisone, is sometimes indicated. Investigation and treatment of underlying, reversible precipitants, such as infection, should be undertaken.

Maintenance replacement therapy should be undertaken once the patient is stable. Augmentation of corticosteroids at times of stress is advisable.

7.9. Electrolyte disturbances

Electrolyte disturbances are common causes of metabolic encephalopathy. Disruption of electrolyte balance is invariably secondary to other processes, whether iatrogenic or due to impairment of the organ function that regulates the particular electrolyte homeostasis. This section focuses on encephalopathies related to the disruption of sodium, calcium, magnesium, phosphate, and glucose homeostasis.

7.9.1. Sodium

7.9.1.1. Hyponatremia

7.9.1.1.1. Epidemiology

Hyponatremia is defined as a serum sodium concentration less than 135 mmol/l. It has a 1% incidence and a prevalence of approximately 3% among inpatients within general hospitals (Anderson, 1986). Hyponatremia reflects alterations in the body's water balance, which thus influences plasma osmolality. Hyponatremia can either be of the hypo-osmolar or iso-osmolar variety. Hypo-osmolar hyponatremia is more common and this group can be further classified according to volume status: isovolemic, hypovolemic, or hypervolemic hyponatremia. Hypo-osmolar hyponatremia is due to a relative excess of solvent to solute.

The most common causes of hyponatremic encephalopathy are related to thiazide diuretic use, or the administration of hypotonic fluids in hospitals (i.e., iatrogenic), especially in the post-operative period, and in conditions involving the presence of antidiuretic hormone (ADH) (i.e., drugs and SIADH). The use of hypotonic fluid administration in the post operative state is particularly risky due to SIADH from pain, nausea, and vomiting (Arieff, 1986; Fraser and Arieff, 1997). Accordingly, hypotonic intravenous fluids should never be used in this situation.

7.9.1.1.2. Clinical features

Clinical features associated with hyponatremia can be divided into those symptoms caused by hyponatremia per se, and those resulting from improper treatment of hyponatremia (i.e., the osmotic myelinolysis syndrome).

7.9.1.1.3. Acute and chronic hyponatremia

Severe hyponatremia, in and of itself, can lead to severe and permanent brain damage (Arieff, 1986). Clinical symptoms associated with hyponatremia typically occur following an acute drop in serum sodium. From the normonatremic state, symptoms commonly occur when serum levels drop below 125 mmol/l; however, severe symptoms have been reported at levels as high as 128 mmol/l. Acute-on-chronic hyponatremia can be symptomatic; however, the typical change in serum sodium sufficient to produce symptoms in acute-on-chronic hyponatremia is not known; it may be different from that seen from a normonatremic baseline and may vary from patient to patient. Symptoms of hyponatremic encephalopathy include headache, behavioral changes, and nausea and vomiting – symptoms similar to those seen in raised ICP. Focal neurological signs such as mono- or hemiparesis or ataxia have been reported and may be related to pre-existing structural lesions. EEG findings are typically nonspecific generalized slowing. Clinical symptoms are reversible with correction of the hyponatremia. Early symptoms may give way to an accelerated and what is often described as 'explosive' clinical decompensation characterized by depressed levels of consciousness, seizures, respiratory arrest, coma, decerebrate posturing, and death (Arieff, 1986; Soupart and Decaux, 1996). Thus diagnosis and appropriate treatment is paramount. Clinical symptoms of chronic hyponatremia may be similar to acute hyponatremia (Ayus and Arieff, 1999) and prompt management of this group is equally important.

If the adaptive mechanisms of the brain are not overwhelmed by hyponatremic stress, a relatively well tolerated state of chronic hyponatremia can be achieved. The arbitrary designation of 48 hours from the onset of alterations in serum sodium concentration denotes chronic hyponatremia. When present, the symptoms attributable to chronic hyponatremia are more subtle and may include dizziness, confusion, and lethargy. The presence of symptoms in this population may indicate an imperfectly adapted brain. Evidence of permanent brain damage from long-standing, chronic hyponatremia is lacking (Soupart and Decaux, 1996). In addition, animal studies have failed to demonstrate histological changes in long-standing, severe, chronic hyponatremia (Arieff, 1987; Verbalis and Martinez, 1991).

7.9.1.1.4. Pathophysiology of hyponatremic encephalopathy

Encephalopathy is due to the combined effects of hypo-osmolar stresses and the limitation imposed by the rigid bony caldarium on cerebral edema. In the presence of a hypo-osmolar extracellular milieu, osmotic forces drive water into the intracellular space. In the absence of brain adaptation, neurons and glia would swell immediately, resulting in cerebral edema. The brain, however, quickly responds by rapidly extruding electrolytes, then organic osmolytes, in a process known as regulatory volume decrease (Pasantes-Morales, 1996; Ordaz et al., 2004). The electrolytes include Na^+, K^+, and Cl^-, which reach an electrochemical balance within 2–3 hours. In vitro studies have shown that K^+ fluxes are regulated by Ca^{2+} and serine-threonine kinase (Pasantes-Morales et al., 2002). Organic osmolytes then move from the intracellular to the extracellular space in a delayed fashion over a period of 10 hours. These include glutamate, aspartate, glutamine, polyhydric alcohol, myoinositol, methylamine, taurine, and creatine. The majority of the organic osmolytes diffuse via leak currents (Pasantes-Morales et al., 2002); however, taurine and Cl^- move through tyrosine-kinase- and phosphoinositol-kinase-regulated transmembrane channels (Pasantes-Morales et al., 2002). Together, movement of electrolytes and organic osmolytes work to reduce the shift of water into the intracellular space and thus prevent cerebral edema. If the adaptive mechanisms are not overwhelmed, then within 48 hours a chronic, asymptomatic steady state may be achieved.

If the hypo-osmolar stress is severe and precipitous in onset, the adaptive mechanisms of regulatory volume decrease may be overwhelmed and the risk of symptomatic cerebral edema increases drastically. The threshold for symptomatic cerebral edema and herniation is lower in the young because of the lack of cerebral atrophy and relatively small amount of CSF space. By contrast, in the atrophic brain of the elderly a similar change in brain volume may be met with milder symptoms. The symptoms and signs of headache, coma, decerebrate posturing, and respiratory failure may be satisfactorily explained by raised ICP, herniation, and coning. However, subtle impairment of consciousness, lethargy, inattention, and seizure may indicate alterations in cerebral function due to neuronal swelling per se. Changes in cell volume represent a powerful stimulus for signal transduction and other metabolic processes (Pasantes-Morales, 1996) and, under experimental conditions, this can be produced by hypo-osmolar stresses. For example, in such conditions, rat cortical synaptosomes depolarize and release via synaptic-like exocytosis GABA and glutamate (Tuz et al., 2004) and noradrenalin (Tuz and Pasantes-Morales, 2005). If present in humans, this may alter cortical excitability and may be responsible for some of the clinical symptoms of hyponatremic encephalopathy.

The hypoxia theory promulgated by Arieff's group states that respiratory insufficiency is an important and critical sequela of acute symptomatic hyponatremia. The mechanisms include noncardiogenic pulmonary edema and respiratory insufficiency from CNS depression and have been reported in numerous studies (Arieff, 1986; Fraser and Arieff, 1990; Arieff et al., 1992; Ayus et al., 1992, 2000; Ayus and Arieff, 1995). There is no question that the presence of hypoxia worsens a pre-existing metabolic (hyponatremic) encephalopathy and that the mechanism is impairment of brain adaptability caused by dysfunction of brain sodium transport (Vexler et al., 1994). Controversy, however, stems from two observations: 1) there is a lack of supportive evidence from other research groups that hypoxia commonly plays an important role in hyponatremic encephalopathy (Karp and Laureno, 1993; Verbalis, 1993; Sterns et al., 1994); and 2) spontaneous hypoxia in the rat associated with severe symptomatic hyponatremia does not increase the risk of permanent brain damage (Soupart et al., 1997). There does not as yet appear to be a mutually agreed-upon explanation of the etiology or significance of hypoxia associated with hyponatremic encephalopathy. Confounding factors may include different patient populations in the various studies. There may also be limitations in the animal model of hyponatremic encephalopathy as regards to the nervous control of respiration or differences in pulmonary physiology. Regardless, the management (i.e., rate of sodium correction) of symptomatic hyponatremia does not differ in the presence or absence of hypoxia (Soupart and Decaux, 1996).

Estrogen status may be an independent risk factor for hyponatremic encephalopathy based on the report of a 25-fold increased rate of mortality and permanent brain damage in menstruant women compared to postmenopausal women or men who suffer from hyponatremic encephalopathy (Ayus et al., 1992). One proposed mechanism implicates the inhibitory effects of estrogen on the brain Na/K ATPase. This would presumably impair volume regulation and thus increase the risk of cerebral edema and induce other consequences of neuronal and glial swelling. Such a gender difference has not been reported in other studies (Sterns et al., 1986; Wijdicks and Larson, 1994).

7.9.1.1.5. Osmotic demyelination syndrome

The osmotic demyelination syndrome (ODS) is a potentially catastrophic complication of inappropriate correction of hyponatremia, most often chronic hyponatremia. During hyponatremia, the regulatory volume decrease functions to prevent cell swelling, rendering the cell in a relative state of dehydration. Following overly rapid and excessive correction of serum sodium, further cellular dehydration can set off currently unclear biological processes that result in demyelination of the pons and extrapontine structures (Fig. 7.3) (Sterns et al., 1986).

Why there is a predilection for the pons and selected extrapontine structures is somewhat of a mystery. It may relate to the 'grid-like' orthogonally arranged axons in these areas (i.e., juxtaposition of descending pontine fibers with crossing pontocerebellar fibers; the pencil fibers of the basal ganglia and the grid-like lateral geniculate body of the thalamus). What makes these areas vulnerable is not known; however, a relative physical impairment of diffusion of nutrients into these areas has been suggested.

ODS is an uncommon condition that affects mainly those who have serious underlying medical conditions (Adams et al., 1959; Sterns et al., 1986). Risk factors for ODS include alcoholism, poor nutritional status, liver transplantation, underlying liver disease, and hypokalemia.

7.9.1.1.5.1. Clinical findings in osmotic demyelination syndrome

The most commonly reported clinical findings in ODS relates to bulbar and long tract signs. These include horizontal gaze impairment or abducens palsies, dysphagia, dysarthria pseudobulbar palsy, and spastic tetraparesis (Sterns et al., 1986). There are fewer reports on the neurocognitive sequelae of ODS. These deficits are probably the result of both extrapontine involvement (e.g., cerebellum, lateral geniculate, external capsule, basal ganglia, cortex, subcortex), and possible involvement of the ascending reticular activation system. Disruption of arousal systems is felt to be responsible for the inattention, and poor speed of processing. Other indications of 'frontal' impairment include disinhibition, emotional lability, and executive dysfunction (Vermetten et al., 1999; Lee et al., 2003).

The outcome of the ODS is variable. A retrospective study examining the outcome of 44 patients with central pontine or extrapontine myelinolysis reports that, of the 34 patients available for follow-up, 32 survived. Of those 32, 11 had complete recovery, whereas 11 had neurological deficits but were independent and 10 had neurological deficits and were dependent in their activities of daily living. In this study, the best predictor of poor outcome was related not to the degree of dysnatremia, severity of radiological findings or severity of neurological findings related to myelinolysis but rather to the severity of other complications such as pneumonia, sepsis, and thromboembolic disease (Menger and Jorg, 1999).

7.9.1.1.5.2. Pathophysiology of osmotic demyelination syndrome

Early animal studies pinned the cause of ODS to the rapid change in serum sodium concentration in the chronic hyponatremic state (Laureno, 1980; Kleinschmidt-Demasters and Norenberg, 1981; Illowsky and Laureno, 1987) and descriptions in current medical textbooks still follow suit. It is generally accepted that exces-

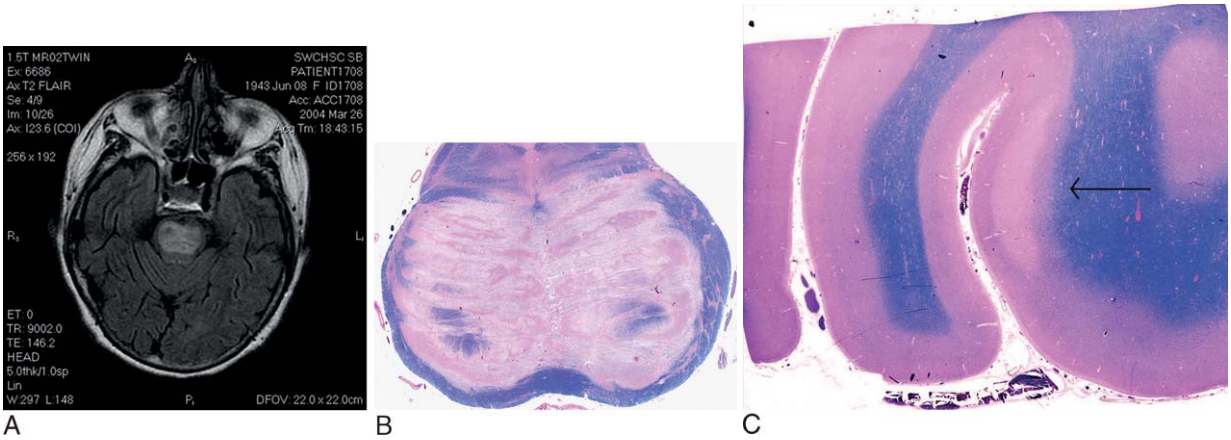

Fig. 7.3. Radiographic and pathological example of ODS. **A.** FLAIR MRI sequence demonstrates a large area of increased signal in the basis pontis in a patient whose serum sodium was corrected from 103 to 133 over 24 hours. **B.** Hematoxylin/eosin stain of a section through the pons in the same patient shows the classic 'batwing' appearance of pontine myelinolysis in the basis pontis, with sparing of the circumferential subpial white matter. **C.** A discrete, lentiform area of juxtacortical, extrapontine myelinolysis is seen in the same patient. Courtesy of Dr Juan Bilbao, Toronto, Ontario.

sive correction of sodium overwhelms the brain's regulatory volume increase capacity. The latter is the compensatory response of the brain to a hyperosmolar stress and functions to prevent cellular dehydration (Sterns et al., 1989; Lien et al., 1991; Verbalis and Gullans, 1993). How this dehydration status induces demyelination is not known. Glial activation and cytokine release have been implicated, together with breakdown in the BBB (for review see Kleinschmidt-Demasters et al., 2006). There is no doubt that inappropriate correction of hyponatremia is central to the pathophysiology of ODS but it must represent only a part of the underlying process. This is supported by the well known observation that ODS is relatively rare and typically occurs in a subset of patients, i.e., those with other serious medical comorbidities such as malnutrition, alcoholism, liver disease, etc. (Adams et al., 1959; Victor and Laureno, 1978; Wright et al., 1979). Thus an osmotic stress may be thought of as a required but perhaps not sufficient stimulus for ODS. According to one theory, patients at risk for ODS have impairment of glial energy utilization (i.e., energy debt) (Ashrafian and Davey, 2001). For example, severe malnutrition and liver failure may reduce glucose availability for the Na^+–K^+ ATPase. Reduced cellular energy levels may cause overactivity of mitochondria and increased production of free radicals, possibly resulting in apoptosis.

7.9.1.1.6. Treatment of hyponatremic encephalopathy

Soupart and Decaux (1996) have cogently outlined a rational approach to treatment of hyponatremia, and this review has used their Figure 3 as a guideline. The controversy surrounding the issue of treatment of hyponatremic encephalopathy arises from the sequelae of undercorrection and overly aggressive correction of serum sodium. Correcting the serum sodium too slowly in patients with hyponatremic encephalopathy may prolong periods of cerebral edema and increase the risk of permanent brain damage (Arieff, 1987). Overly aggressive treatment, however, is a risk factor for ODS. The literature is rife with conflicting reports on what rate and magnitude is appropriate. The best-evidence approaches to treatment of various hyponatremic states are summarized in the following paragraphs.

7.9.1.1.6.1. Treatment of acute hyponatremic encephalopathy

These patients are comatose with or without seizures and with serum sodium values <125 mmol/l and more commonly under 120 mmol/l. They are typically posterative, having received intravenous hypotonic fluids in the setting of SIADH or excessive thiazide diuretics. The duration of hyponatremia is considered acute if it is less than 48 hours, and is a medical emergency. Management of these patients should be undertaken in a monitored setting, with Foley catheterization to monitor urine output. Hypertonic saline (NaCl 3%, 0.514 mEq/ml) at an infusion rate of 1–2 ml/kg body weight/hour is recommended. This therapy will increase the patient's serum sodium by approximately 1–2 mmol/l/h. The target for this therapy is resolution of neurological symptoms, at which time hypertonic saline should be discontinued. The goal is not to achieve normonatremia. Arieff's group makes special mention of having a high index of suspicion for respiratory insufficiency and pulmonary edema and they advise endotracheal intubation and admission to an ICU setting for management of these very sick patients.

7.9.1.1.6.2. Treatment of symptomatic acute-on-chronic hyponatremia or hyponatremia of unknown duration

Again, the treatment algorithm depends on the presence of encephalopathy. These patients should also receive hypertonic saline at a rate no greater than that which results in a serum sodium change of 10–15 mEq/24 h. Resolution of symptoms is the target goal. In the presence of risk factors for ODS such as hypokalemia, liver disease, liver transplantation, alcoholism, or malnutrition, the lower rate is indicated (i.e., no more than 10 mEq/24 h). In these cases, serum sodium should be checked every 4 hours and urine output measured closely. In the presence of brisk diuresis and rapid increase in serum sodium, DDAVP and hypotonic saline should be administered over a 2-hour period (Soupart et al., 1994; Soupart and Decaux, 1996) to reduce serum sodium. The overall target remains a rate of change in serum sodium of 10–15 mEq/l/24 h until symptoms are relieved.

7.9.1.1.6.3. Treatment of chronic hyponatremic encephalopathy

Ayus and Arieff (1999) reported chronic hyponatremic encephalopathy with permanent brain damage in a population of postmenopausal women. This was an important finding as it showed that chronic hyponatremia is not always well tolerated. Whether some of these patients had acute-on-chronic changes in their serum sodium is not known and remains an important caveat. Nevertheless, aggressive therapy in such patients is necessary to prevent permanent brain damage. These authors recommend that symptomatic chronic hyponatremia should also be treated with a rapid but well monitored therapy of NaCl 3%, at 1–2 ml/kg body weight/hr for 4–5 h. Therapy should be stopped with symptom improvement. It should be recognized that

such chronically hyponatremic patients may be encephalopathic not from the hyponatremia but from an associated, related disorder (e.g., hypothyroidism, drug accumulation) or some intercurrent illness (e.g., infection).

7.9.1.1.6.4. Chronic asymptomatic hyponatremia

This population of patients is considered 'stable', in that rapid correction is not necessary. It is not, however, a normal state. Thus removal of offending agents or restriction of water is a reasonable approach as long as extracellular fluid contraction itself does not pose a risk to the patient.

7.9.1.1.6.5. Alternative treatments for hyponatremic encephalopathy

Urea is an effective treatment for symptomatic hyponatremia. Urea induces a sodium-retentive diuresis that reduces cerebral edema and raises serum sodium (Decaux and Soupart, 2003). Urea can also raise intracellular osmolytes, which may be protective against ODS (Silver et al., 2006). The rate of sodium change should remain 10–15 mEq/l/d. Vasopressin-2 antagonists have been introduced for treatment of hyponatremic encephalopathy. Caution is advised using these drugs since they can cause a brisk diuresis and rapid changes in serum sodium (Gross and Palm, 2000; Decaux and Soupart, 2003). Vasopressin antagonists may be useful in patients with extracellular fluid overload (cirrhosis, water intoxication, severe pulmonary edema). A recent study using the rat electrolyte-myelinolysis model provided evidence that pretreatment with the organic osmolyte myoinositol offered protection against myelinolysis following rapid correction of hyponatremia (Silver et al., 2006). Raising brain levels of myoinositol may improve hydration status and prevent cell shrinkage during rapid corrections of serum sodium in the rat. Whether this is a useful and safe prophylactic treatment for patients at risk for ODS remains a very interesting possibility.

7.9.1.2. Hypernatremia

Hypernatremia is defined as serum sodium >145 mEq/l. Symptomatic hypernatremia is almost universal at serum levels >160 mEq, above which 89% of patients have hypernatremic encephalopathy (Snyder et al., 1987). The clinical picture of hypernatremic encephalopathy includes nausea, lethargy, seizures, and coma (Arieff and Guisado, 1976). Tremor, chorea, and myoclonus are rarely seen (Sparacio et al., 1976). The two populations at highest risk for hypernatremic encephalopathy are the very young and very old. Gastrointestinal illness with vomiting and diarrhea coupled with a child's lack of access to water, or blunting of thirst in the elderly, increases this risk of developing hypernatremia (Finberg, 1973). Diabetes insipidus with blunted thirst similarly can have the same outcome. Any situation where ADH secretion is impaired or the thirst-response to ADH is impaired renders a patient at risk for hypernatremia (e.g., hypothalamic dysfunction from stroke, hemorrhage, tumor, etc.). Excess salt intake can affect all ages, and this has been reported in the context of salt-water emetics (Casavant and Fitch, 2003; Kupiec et al., 2004; Turk et al., 2005) and pica syndrome (Ofran et al., 2004). Administration of hypertonic (over-concentrated) baby formula is also a common cause of hypernatremia in babies. A recent review of the forensic literature reports that hypernatremia may occur in response to subdural hemorrhages from nonaccidental head injury in the young (Handy et al., 1999). The mortality of hypernatremia can be as high as 20%, with severe brain damage in 33%, in the pediatric population (Morris-Jones et al., 1967).

7.9.1.2.1. Pathophysiology of hypernatremic encephalopathy

Hypernatremic encephalopathy results from both alterations in brain parenchyma caused by raised serum sodium, as well as vascular sequelae (Arieff and Guisado, 1976). In response to a hyperosmolar stress, water is driven out of neurons and glia. Reduction of whole brain volume occurs, predominantly because of oligodendroglial shrinkage (Luse and Harris, 1961). Physical forces of volume loss can tear cortical bridging veins, resulting in subdural hematoma, subarachnoid hemorrhage, intracranial hemorrhage (Simmons et al., 1974), or petechial hemorrhage (Finberg, 1959; Luttrell and Finberg, 1959). Sinovenous thrombosis can also be reported. There is a paucity of studies examining MRI changes due to hypernatremia. Case reports have shown a number of interesting findings including isolated, transient cytotoxic edema of the thalamus (Hartfield et al., 1999), diffuse cerebral edema (Mocharla et al., 1997), and osmotic myelinolysis (Alorainy et al., 1999). During regulatory volume increase there is an intracellular flux of K^+ as well as increased levels of organic osmolytes, especially glutamine, glutamate, taurine, and myoinositol (Pasantes-Morales, 1996), and also many others. Movement of these solutes reduces the next flux of water out of the cells, thus reducing cell shrinkage. Symptoms probably occur when the adaptability of the brain is overwhelmed, causing cell shrinkage. The massive cerebral edema that has been reported in acute salt intoxication (e.g., salt-water-induced emesis) seems contrary to the 'cellular dehydration and shrinkage' hypothesis. It is possible that the hyperacute nature of the hyperosmolar stress elicits a different response from

what occurs in the more subacute or chronic state. Acute breakdown of the BBB with cytotoxic edema may supersede cellular dehydration. Alternatively, perhaps the treatment of severe hypernatremia in the presence of a compromised BBB resulted in edema (see below).

7.9.1.2.2. Treatment of hypernatremic encephalopathy

Over-rapid correction of hypernatremia can result in rapid reductions in extracellular osmolality. As a consequence of the slow movement of organic osmolytes out of the cells, the osmotic gradient drives water into the intracellular space and results in cerebral edema, seizures, and permanent brain damage. Reducing serum sodium at a rate of <0.5 mmol/l/h is thus recommended (Kahn et al., 1981).

7.9.2. Calcium

Extracellular calcium is held within a tight physiological range by the interactions of parathyroid hormone (PTH), vitamin D, calcitonin, magnesium, phosphate, and calcium. In response to minor drops in serum calcium, the parathyroid gland secretes PTH, which acts to increase serum calcium by stimulating calcium reabsorption from the kidney and by inhibiting renal phosphate reabsorption. PTH also stimulates the conversion of vitamin D from its inactive to its active form, which acts at the level of the gut to increase calcium reabsorption and, together with PTH, stimulates osteoclastic activity leading to increased calcium resorption from bone. Normalization of serum calcium feeds back to the parathyroid gland and inhibits PTH secretion. Hypomagnesemia reduces PTH secretion and diminishes renal response to PTH (Graber, 1995). Calcitonin works in the opposite direction to PTH: it inhibits osteoclast activity, stimulates osteoblast activity and reduces renal calcium and phosphate reabsorption.

Calcium circulates in either a bound or ionized form. The ionized fraction exerts the biological action of calcium. The neurological manifestations of abnormal calcium homeostasis depend on the severity and rapidity of progression of the calcium imbalance. Calcium is a ubiquitous cation that can have profound influences on neuronal processes, including alterations in membrane excitability and permeability, synaptic transmission, activation of second messenger systems, organelle function, and glial–neuronal interactions (i.e., the tripartite synapse).

7.9.2.1. Hypocalcemia

The common causes of hypocalcemia evoke their effects by inhibiting the PTH–vitamin D axis, by inducing redistribution of calcium or by inhibiting the effects of calcium.

7.9.2.1.1. Laboratory findings

Total serum calcium is made up of protein-bound, free ionized and complexed calcium. The range of normal total serum calcium is 2.12–2.62 mmol/l (8.5–10.5 mg/dl). Calcium concentration varies with serum albumin. For every 1 g/l drop in albumin, there is a 0.02 mmol/l (0.8 mg/dl) fall in calcium. Or:

$$\text{Corrected } [\text{Ca}] = \text{measured } [\text{Ca}] + \{(40 - [\text{albumin}]) \times 0.02\}.$$

This is an estimate and may vary during conditions where protein binding is affected, e.g., sepsis, rhabdomyolysis, cirrhosis, myeloma. It is thus important to measure the physiologically relevant serum ionized calcium. Symptomatic hypocalcemia is typically present when serum ionized calcium falls to less than 0.5 mmol/l (2 mg/dl; normal range 1.02–1.27 mmol/l (4.1–5.1 mg/dl)) or the total calcium drops below 1.8–1.875 mmol/l (7.0–7.5 mg/dl).

7.9.2.1.2. Clinical presentation

Hypocalcemic encephalopathy has long been present in the literature, with early reports describing neuropsychiatric manifestation of idiopathic hyperparathyroidism (Simpson, 1952). Symptoms include cognitive and behavioral changes, disorientation, confusion, hypomania, an agitated delirium, and chorea (Simpson, 1952; Hossain, 1970). In severe cases, obtundation and coma may result. Headache with papilledema can result from raised ICP (Katzman and Pappius, 1973). Seizures may also result from hypocalcemia. Seizures may be focal, generalized, convulsive, or nonconvulsive. EEG findings are likewise variable, with paroxysmal slowing, slowing of background rhythms, and focal and generalized spikes (Glaser and Levy, 1959; Rose and Vas, 1966). Generalized tonic–clonic seizures have been reported in association with kinesogenic paroxysmal dyskinesia in a patient with pseudohypoparathyroidism (Huang et al., 2005). A hypocalcemia-induced reversible encephalopathy and diffuse cerebral edema has likewise been reported in a patient with pseudohypoparathyroidism (Oechsner et al., 1996). Neuromuscular irritability, presenting with hyperreflexia, Chvostek and Trousseau signs and tetany are peripheral hallmarks of symptomatic hypocalcemia. Laryngeal stridor and spasm may compromise the airway. The reader is referred to an excellent discussion of tetany and the peripheral manifestations of hypocalcemia in a previous volume of this *Handbook* (Laureno, 1993).

7.9.2.1.3. Pathophysiology of hypocalcemic encephalopathy

It is not known how hypocalcemia alters CNS function in humans. In vitro experiments have shown that exposing rat hippocampal slices to a calcium-free solution modulates gap junction function and induces spontaneous neuronal activity (Valiante et al., 1995). Furthermore, small alterations in extracellular calcium can induce burst firing in individual hippocampal neurons via expression of intrinsic membrane properties (Wang et al., 2004). If present in humans, one could imagine these findings might contribute to the development of seizure or seizure propagation under conditions of severe hypocalcemia. The mechanism by which reduced serum calcium causes diverse neurocognitive dysfunction including impairment of consciousness is certainly multifactorial and probably includes alterations in both intrinsic membrane properties and synaptic function, and possibly also gap junction modulation or neuron–glia interaction.

7.9.2.1.4. Management of hypocalcemia

Symptomatic hypocalcemia must be treated. The presence of seizure or encephalopathy may necessitate intensive care monitoring and airway control. In addition to treating the hypocalcemia, specific therapies targeting the etiology of the hypocalcemia or other exacerbating factors are likewise important. For example, the concomitant treatment of hypomagnesemia will remove the hypomagnesemia-induced inhibition of PTH secretion (Graber, 1995). Initial therapy of 10–20 ml of 10% intravenous calcium gluconate (contains 93 mg of elemental calcium) should be administered over 10 minutes, to avoid cardiac conduction abnormalities. Patients taking digoxin should be closely monitored during intravenous calcium replacement for digitalis toxicity (Weiss-Guillet et al., 2003). A continuous infusion of 15 mg/kg will raise the serum calcium by 2–3 mg/dl. The aim of acute treatment is not to return to normocalcemic values but rather to reverse or improve the symptoms of hypocalcemia (Tohme and Bilezikian, 1993). In the presence of hypophosphatemia, calcium supplementation should be delayed until serum phosphate is reduced to <1.5 mmol/l (Weiss-Guillet et al., 2003) to prevent soft-tissue calcium phosphate precipitations. Oral supplementation of 1–2.6 g daily may be sufficient in presence of chronic stable hypocalcemia.

7.9.2.2. Hypercalcemia

Hypercalcemia is defined as total serum calcium levels >2.63 mmol/l; however, symptomatic hypocalcemia typically occurs at a serum level of 3 mmol/l (12 mg/dl). Early neuropsychiatric symptoms tend to occur at serum levels >3.0 mmol/l and severe CNS dysfunction is seen at serum levels >4 mmol/l (16 mg/dl).

7.9.2.2.1. Epidemiology

Hypercalcemia occurs in about 5% of patients with cancer and in 10–20% of patients with solid tumors (Spinazze and Schrijvers, 2006). The most common malignancies associated with hypercalcemia are multiple myeloma, breast, lung, kidney, and head and neck cancers. Malignant neoplasms and hyperparathyroidism account for approximately 70–80% of cases of hypercalcemia (Lafferty, 1991; Casez et al., 2001). Hypercalcemia has a prevalence of 0.5% of hospitalized patients (Fisken et al., 1981). There are numerous causes, ranging from metastatic tumors to bone, Paget's disease, excessive parathormone activity and hypervitaminosis D.

7.9.2.2.2. Pathophysiology

The precise way in which elevated serum calcium leads to the clinical presentation of encephalopathy is speculative. The term 'alterations in membrane stability' is often encountered in textbooks, but this seems vague and difficult to extrapolate to the clinical condition. It is not hard to imagine that alterations in calcium homeostasis can impact cerebral function given the ubiquitous nature of calcium, but the extent to which alterations in voltage gate calcium channels, presynaptic transmitter release, the inositol triphosphate system, intrinsic organelle function, cells volume, or glial–neuron signaling are affected by hypercalcemia is as yet unclear.

7.9.2.2.3. Clinical features

Early neuropsychiatric symptoms include cognitive impairment, mental slowing, and personality changes. Frank encephalopathy characterized by confusion, somnolence, stupor, and coma is typically reserved for those with severe hypercalcemia and usually with associated malignancy (Wang and Guyton, 1979). Seizures are not common. The catchy rhyme of 'groans, bones, stones, and psychic moans' is a medical school favorite for recalling the clinical constellation of abdominal pains, bone pains from metabolic disease, nephrolithiasis, and encephalopathy, respectively, associated with symptomatic hypercalcemia.

7.9.2.2.4. Management

There are four major components in the management of hypercalcemic encephalopathy. The first two are to disclose the etiology of the hypercalcemia and, in the case of acute hypercalcemia, to administer intravenous isotonic saline. These patients are in severe extracellular volume contraction and require 1–3 liters of isotonic saline over 1–4 hours if they have sufficient

cardiopulmonary reserve (Spinazze and Schrijvers, 2006). The third component relates to treatment of the underlying cause of hypercalcemia. For example, removal of offending agent, treatment of sarcoidosis, treatment of malignancy, or surgical excision of parathyroid adenoma may all contribute significantly or even cure the hypercalcemia. Finally, drugs that modulate calcium homeostasis should be instituted. Bisphosphonates will inhibit osteoclastic activity and inhibit renal calcium reabsorption and are the mainstay of treatment of recurrent hypercalcemia in malignancy (Spinazze and Schrijvers, 2006). A single dose of intravenous pamidronate 90 mg over 2–24 h is an acceptable regimen and normalizes serum calcium within 2 days in 70–90% of patients (Nussbaum et al., 1993). Zoledronate 4 mg or 8 mg single intravenous dose on a monthly basis has shown very good results for refractory hypercalcemia (Major et al., 2001). Calcitonin exerts its effects by inhibiting bone resorption and increasing renal excretion of calcium. A regimen of 8 IU/kg every 6 h for 5 days will achieve normocalcemia in a third of patients, and this will last for 1–2 days (Spinazze and Schrijvers, 2006). Calcitonin is often used in conjunction with bisphosphonates. Dialysis may be indicated for severe hypercalcemic encephalopathy with congestive heart failure or severe renal dysfunction.

7.9.3. Magnesium

7.9.3.1. Hypomagnesemia

Hypomagnesemia is defined as serum magnesium concentration <0.8 mmol/l (2.0 mg/dl). Neurological complications related to hypomagnesemia, however, typically manifest at concentrations <0.5 mmol/l (1.2 mg/dl). Because over 90% of total body magnesium resides in the intracellular compartment, serum magnesium levels fail to accurately reflect total body magnesium deficiency. Accordingly, a drop in serum magnesium may represent a profound total body magnesium deficit. Similarly, reduced total body magnesium may be present with normal serum concentrations. By contrast, in the rat model, diet-induced hypomagnesemia is not accompanied by a drop in intracellular magnesium (Standley and Cotton, 1996). Cerebrospinal fluid magnesium tends to be higher than that of serum because of its active secretion by the choroid plexus.

7.9.3.1.1. Epidemiology

Owing to its nutritional abundance, hypomagnesemia is rare in the otherwise healthy. Hypomagnesemia affects 4–47% of hospitalized patients (Ryzen et al., 1985; Croker and Walmsley, 1986; Whang and Ryder, 1990), with those suffering from critical illness at highest risk. The bulk of intracellular magnesium is complexed to adenosine triphosphate/diphosphate (ATP/ADP), DNA, RNA, and citrate, with only 5–10% in the ionized form. This is in contrast to the 60% unbound fraction in the plasma, which is under tight regulation by the kidney. Populations at highest risk for hypomagnesemia either lack adequate intake or have excessive loss of magnesium through the kidney. These include conditions of protein–calorie malnutrition, malabsorption, diabetic ketoacidosis (DKA), sepsis, diuretic use, alcohol abuse, hyperaldosteronism, and hypocalcemia (Olerich and Rude, 1994). Drugs known to cause hypomagnesemia include loop diuretics, aminoglycosides, cisplatin (Schilsky and Anderson, 1979), ciclosporin A (Hauben, 1996), amphotericin (Barton et al., 1984), tacrolimus (Nijenhuis et al., 2004), and cetuximab (Schrag et al., 2005).

7.9.3.1.2. Pathogenesis

The ways in which reduced serum magnesium leads to altered CNS function and encephalopathy are probably numerous; however, the precise mechanism is not known.

Magnesium plays an important role in the regulation of central NMDA, inducing a voltage-sensitive reversible block. NMDA receptor activation is one of the important mediators of excitatory transmission in the brain. Low magnesium may thus enhance glutamate excitatory transmission. Reduced intracellular magnesium has also been shown to influence potassium, calcium, and chloride channels (Kelepouris et al., 1993) and, at least in smooth muscle, magnesium has a modulatory effect on release of intracellular pools of calcium (Chiesi and Inesi, 1981). The hypomagnesium-induced inhibition of PTH may induce hypocalcemia; therefore, some of the clinical features of hypomagnesemia may in part be attributed to alterations in calcium homeostasis.

7.9.3.1.3. Clinical presentation

The clinical findings of hypomagnesemia are not unlike those of hypocalcemia. Peripheral manifestations include muscle cramps, hyperreflexia, and Chvostek sign. CNS symptoms include seizures, acute neuropsychiatric changes and impaired consciousness. Focal neurological features have also been described, including bulbar dysfunction (vertigo, dysphagia), athetosis, nystagmus, hemiparesis, and aphasia (Hall and Joffe, 1973; Hamed and Lindeman, 1978; Leicher et al., 1991).

7.9.3.1.4. Management

The clinical features of hypomagnesemia are reversible with proper treatment. In cases of severe hypomagnesemia (i.e., with seizures or other CNS features), parenteral magnesium sulfate (50% solution) given in divided doses, totaling 8–12 g of magnesium sulfate, is indicated. Monitoring of deep tendon reflexes and serum magnesium is

necessary, especially in the presence of renal failure. The often coincident hypocalcemia may necessitate calcium supplementation. Hypokalemia is also often present in hypomagnesemia; thus potassium replacement should be instituted when necessary. Ongoing magnesium supplementation in parenteral nutrition is important, especially in intensive care to prevent hypomagnesemia. Correcting underlying causes of hypomagnesemia (e.g., abstinence from alcohol) is likewise important.

7.9.3.2. Hypermagnesemia

Hypermagnesemia is defined as serum magnesium levels >1.05 mmol/l (2.4 mg/dl); however, clinical symptoms are usually manifest at serum concentrations >2–3.5 mmol/l (5–8 mg/dl). Hypermagnesemia is considered to be a highly underrecognized condition (Whang and Ryder, 1990).

7.9.3.2.1. Pathophysiology

Symptomatic hypermagnesemia is rare in the absence of renal failure. Typically it occurs in the context of excessive administration of magnesium-containing compounds (laxatives, cathartics, antihypertensives) in patients with impaired renal excretion. Cases of severe hypermagnesemia from Epsom salts have been reported in otherwise healthy individuals (Birrer et al., 2002). Magnesium is known to inhibit neuromuscular transmission and cause parasympathetic blockade (Rizzo et al., 1993). This would explain the profound weakness and autonomic dysfunction caused by hypermagnesemia. How elevated serum magnesium leads to altered levels of consciousness is less clear. Hypermagnesemia is known to alter glucose metabolism and reduce the metabolic rate in rat spinal cord (Szabo and Crosby, 1988), a finding that sparked interest in the possible use of induced-hypermagnesemia for neuroprotection following stroke. It is conceivable that impaired glucose metabolism may induce a generalized cerebral dysfunction resulting in encephalopathy; however, this is not proven. It has been shown that even high levels of serum magnesium fail to alter intracellular concentrations of magnesium, indicating that 1) intracellular levels of magnesium are under extremely tight control (Gee et al., 2001) and 2) encephalopathy and CNS depression caused by hypermagnesemia are probably due to the modulatory effects of extracellular magnesium on neuronal membrane excitability and not to changes in intracellular magnesium. At resting and hyperpolarizing potentials, the binding of extracellular magnesium to the NMDA channel renders it closed. Thus depression of excitatory glutamate transmission through the effect of magnesium at the NMDA receptor could theoretically contribute to hypermagnesemic encephalopathy.

7.9.3.2.2. Clinical presentation

Initial symptoms are usually due to the effects of magnesium on transmission at the neuromuscular junction. Thus weakness and loss of deep tendon reflexes are common early findings and most frequently occur at serum magnesium concentrations of 2.5–3 mmol/l (6.5–8.5 mg/dl). Diaphragmatic weakness from hypermagnesemia may cause respiratory insufficiency and hypercarbic encephalopathy, and is life-threatening. Lethargy, confusion and altered level of consciousness, leading to coma, represent the stepwise CNS manifestations of worsening hypermagnesemia. The encephalopathy from hypermagnesemia is probably due to both respiratory insufficiency and the effects of hypermagnesemia on neuronal excitability per se. The block of parasympathetic cholinergic transmission by hypermagnesemia can result in fixed, dilated pupils that mimic a brainstem stroke. This, together with paralysis, can create a clinical picture of 'pseudocoma' (Rizzo et al., 1993).

7.9.3.2.3. Treatment

Respiratory failure and cardiovascular collapse are the most life-threatening sequelae of severe hypermagnesemia; therefore aggressive supportive therapy including invasive monitoring, fluid resuscitation, and mechanical ventilation may be indicated. Calcium antagonizes the effects of magnesium, so 10 ml of a 10% solution can be given repeatedly to reverse the neuromuscular blockade. Enhancement of renal excretion using loop diuretics is reasonable as well. In patients with severe renal failure, dialysis may be needed to remove excess magnesium.

7.9.4. Phosphorus

7.9.4.1. Hypophosphatemia

The serum phosphate concentration is controlled by dietary intake, renal tubular reabsorption, and shifts between the intra- and extracellular compartments (Gaasbeek and Meinders, 2005). Thus hypophosphatemia may not represent changes in total body phosphate concentration but rather shifts from extra- to intracellular stores. Hypophosphatemia is defined as serum concentrations <2.5 mg/dl (0.83 mmol/l). Hypophosphatemic encephalopathy, however, is typically seen under conditions of severe hypophosphatemia, i.e., serum concentrations <1.5 mg/dl (0.5 mmol/l) (Knochel, 1977). Phosphate is primarily distributed in the intracellular space (intracellular:extracellular ratio of 100:1), where it is mostly found in its organic form (e.g., creatine phosphate and adenosine triphosphate) and is critical for cellular energy and enzyme processes (Gaasbeek and Meinders, 2005). 2,3-diphosphoglycerate, an intracellular phosphate store within red blood cells, is important for regulating

O_2 release to tissues from hemoglobin. In conditions of hypoxia, phosphate also stimulates anaerobic metabolism via activation of phosphofructokinase – a key enzyme in glycolysis (Siesjo and Nilsson, 1971). Complex mechanisms regulate phosphate homeostasis. Key players include parathyroid hormone and vitamin D, which stimulate intestinal absorption and stimulate resorption from bone. Vitamin D also inhibits renal losses of phosphate, whereas PTH can also stimulate phosphate excretion in the urine. Phosphatoins, a group of relatively newly described factors, also enhance phosphate excretion in the urine (for review see Gaasbeek and Meinders, 2005).

7.9.4.1.1. Epidemiology

The reported incidence of hypophosphatemia ranges from 0.2% (King et al., 1987) to 2.2% (Betro and Pain, 1972) among patients admitted to a general hospital. From a practical standpoint, the usefulness of these numbers is questionable, since the incidence is considerably higher among selected groups of patients, so it behoves the clinician to become familiar with the common risk factors predisposing patients to severe hypophosphatemia in order to initiate preventive or corrective therapy. For example, among alcoholic patients admitted to a medical ward the incidence has been reported to be 30.4% (Ryback et al., 1980) and in critically ill patients the prevalence has been reported as high as 80% (Barak et al., 1998). The causes of hypophosphatemia include conditions that alter intestinal absorption, renal reabsorption, and distribution between extra- and intracellular stores, or a combination thereof. The 'refeeding syndrome' is one of the main causes of acute symptomatic hypophosphatemia. The most common mechanism of hypophosphatemia is intracellular redistribution (Table 7.7). A combination of multiple factors typically contributes to severe hypophosphatemia. For example, in the critically ill patient with sepsis, mechanical ventilation, metabolic acidosis, volume expansion, and elevated catecholamines would all combine – via separate mechanisms – to lower serum phosphate. Similarly in the chronic alcoholic, poor nutritional status and vitamin D deficiency would influence intracellular shifts and urinary excretion (Territo and Tanaka, 1974; Knochel, 1977).

Table 7.7

Causes of hypophosphatemia

Intracellular redistribution	Re-feeding syndrome (chronic alcoholics, anorexia nervosa)
	Treatment of diabetic ketoacidosis
	Severe respiratory alkalosis (e.g., sepsis, anxiety, alcohol withdrawal, hepatic coma)
	Glucose infusions
	Mechanical ventilation
Increased urinary excretion	Hyperparathyroidism
	Vitamin D deficiency
	Renal tubular defects
	Volume expansion
	Metabolic acidosis
	Renal transplant
Decreased intestinal absorption	Severe malnutrition
	Vitamin D deficiency
	Steatorrhea
	Vomiting, diarrhea
	Phosphate-binding antacids

7.9.4.1.2. Clinical manifestation of hypophosphatemia

Neurological manifestations of hypophosphatemia are infrequent and only present when hypophosphatemia is severe. All levels of the nervous system can be affected. Hypophosphatemic encephalopathy can present as irritability, confusion, multifocal myoclonus, seizures, and coma (Prins et al., 1973; Knochel, 1977; Lee et al., 1978; Jansen and Velkeniers, 2003). Muscle weakness from a Guillain–Barré-like syndrome and myopathy are well documented (Knochel, 1977). Severe weakness from profound myopathy has been reported to involve the diaphragm, causing encephalopathy due at least in part to respiratory insufficiency (Newman et al., 1977; Aubier et al., 1985; Knochel, 1985). These features can be reversed with appropriate phosphate replacement (see below). Central pontine myelinolysis has been reported in association with severe hypophosphatemia (Michell et al., 2003; Falcone et al., 2004). Wernicke's encephalopathy has been reported in association with severe hypophosphatemia – this is of particular importance when standard therapy of Wernicke's encephalopathy fails to improve the symptoms of what is almost universally considered to be a thiamine-deficient state (Vanneste and Hage, 1986). The mechanism by which hypophosphatemia exerts its CNS effects are not known. It may be related to altered 2,3-diphosphoglycerate function and impaired oxygen delivery to neurons. This may give rise to local anoxia and reduced glucose oxidation and ATP production (Knochel, 1977). Severe hypophosphatemia may represent a pro-apoptotic milieu (Michell et al., 2003) and may therefore be analogous to what has been described in patients at risk for osmotic demyelination (Ashrafian and Davey, 2001).

7.9.4.1.3. Treatment of hypophosphatemia

A high index of suspicion for hypophosphatemic encephalopathy is needed in at-risk patients who develop altered levels of consciousness (e.g., during hyperalimentation of the malnourished, or hospitalized chronic

alcoholics). If patients are able to take fluids by mouth or gastric tube, then milk (which has a phosphate concentration of 0.9 mg/ml) is an appropriate supplement. Intravenous administration of 9 mmol of phosphorus in 77 mM NaCl over 12 h provides 4 mg/kg body weight and is also an appropriate therapy (Vannatta et al., 1981).

7.9.5. Glucose

7.9.5.1. Hypoglycemia

The human brain is almost entirely reliant on glucose for its energy source. The degree to which different brain regions are vulnerable to hypoglycemia is dependent on the local energy demand, and efficiency of glucose usage. For example, areas of higher cortical function (i.e., neocortex) have higher metabolic demands and thus display increased glucose utilization, whereas the cerebellar cortex has both a reduced demand and a more efficient glucose transport system (Agardh et al., 1981; LaManna and Harik, 1985).

7.9.5.1.1. Definition

Hypoglycemia is defined as serum glucose concentration <2.5 mmol/l (40 mg/dl). However, in patients with diabetes who have consistently high basal serum glucose, the neuroglycopenic symptoms can occur at normal, or even slightly high, levels. Likewise, patients with very tight glucose control often develop symptoms at lower serum glucose concentrations (Carroll et al., 2003). Severe hypoglycemia is differentiated from mild hypoglycemia by the inability of the person to self-correct with exogenous glucose or glucagon, thus requiring assistance in treatment.

Hypoglycemia is broadly classified into postprandial and fasting according to its etiology (Table 7.8). Epidemiological data on severe hypoglycemia in patients without diabetes is lacking. Most cases of severe hypoglycemia, however, involve patients with either type 1 or type 2 diabetes on insulin therapy (DCCT, 1997) or type 2 diabetes on sulfonylurea therapy (Shorr et al., 1997). Although the incidence of severe hypoglycemia in type 1 diabetes is significantly higher than that of type 2 diabetes, when matched for duration of insulin therapy the incidences are similar (Hepburn et al., 1993). In type 1 diabetes, severe hypoglycemia is common and potentially catastrophic, affecting approximately one-third of patients at least once per year. It is estimated that severe hypoglycemia is the cause of death in 2–4% of persons with type 1 diabetes (Laing et al., 1999).

In the diabetic population, risk factors for severe hypoglycemia include: length of time from diagnosis of type 1 diabetes; previous episodes of severe hypoglycemia; loss of awareness of hypoglycemic symptoms (i.e., impaired counter-regulatory hormone function); reduced C-peptide levels (i.e., well established insulin-requiring type 2 diabetes); and a history of low hemoglobin A1C (Frier, 2004). In diabetics, the glucagon response is essentially gone after 3 years, causing patients to be 'catecholamine-dependent', thus prolonging periods of hypoglycemia. Furthermore, previous hypoglycemic episodes result in increased neuronal glucose uptake, thus raising the threshold for sympathetic response to hypoglycemia (i.e., the counter-regulatory hormonal responses are triggered at relatively more hypoglycemic levels) (Carroll et al., 2003).

Table 7.8

Causes of hypoglycemia

Postprandial	Glucose-induced	
	Fructose-, galactose-, leucine-induced	
Fasting hypoglycemia	Hepatic disease	
	Excess endogenous insulin (insulinoma)	
	Exogenous insulin	
	Deficiency of growth hormone	
	Renal failure	
	Sepsis	
	Alcoholism	
	Drugs	
	Malnutrition	
	Heart failure	
	Tumors that secrete insulin-like growth factor (IGF)-1	Sarcoma Mesothelioma Hepatoma

Source: adapted from Young and DeRubeis, 1998.

7.9.5.1.2. Pathogenesis and pathology

Neuroglycopenic symptoms are related to activation of the counter-regulatory hormones, especially the catecholamine response. Severe symptomatic hypoglycemia occurs when counter-regulatory mechanisms are overwhelmed, and this is due to excessive insulin effect, diffuse hepatic dysfunction, or limited substrate for gluconeogenesis (Carroll et al., 2003). Failure to correct severe hypoglycemia in a timely fashion results in progressive impairment of consciousness, cerebral isoelectricity, and irreversible brain damage in an anatomical distribution best described as 'selective necrosis' (Auer et al., 1984b). Areas of the brain particularly susceptible to hypoglycemic brain damage include the medial subiculum, the crest of the dentate gyrus and dentate granule cells of the hippocampus, the superficial neocortical layers of the cerebral cortex, and the basal ganglia (Auer et al., 1984a, b, 1985a, b). Apoptosis has been implicated by the presence of hypoglycemia-induced expression of cytochrome c, caspase-3, and Bax (Ouyang et al.,

2000). Whether apoptosis contributes to cell death or whether it is merely an epiphenomenon of acute severe hypoglycemia remains to be firmly established (Ouyang et al., 2000; Auer, personal communication). The pathophysiological underpinnings of reversible and irreversible hypoglycemic encephalopathy are incompletely understood. It would be of great interest to disclose the biochemical and molecular events that represent the hypoglycemic tipping point – the point at which reversal of serum glucose fails to correct the clinical status and neuronal death ensues.

The EEG is a useful tool in predicting reversible and irreversible cerebral dysfunction in hypoglycemia. Table 7.9 summarizes the clinical-EEG correlation seen in hypoglycemic encephalopathy. Clinical somnolence correlates with the appearance of theta and coarse delta waves. Dominant delta waves correlate with stupor. With increased theta and delta activity, changes in cerebral monoamine (serotonin, noradrenaline (norepinephrine), dopamine) occur (Agardh et al., 1979). Plasma membrane ion channel functions become impaired (Agardh et al., 1982) and alterations in neuronal excitability contribute to the clinical picture of encephalopathy. With the onset of cerebral isoelectricity, the patient is invariably comatose. If uncorrected, selective neuronal necrosis will occur after 30 minutes of isoelectricity (Auer et al., 1984a). Diffusion-weighted sequences on MRI have revealed both symmetric and asymmetric focal cytotoxic edema in hypoglycemic coma that is potentially reversible if the patient is treated within a certain critical period (Aoki et al., 2004; Bottcher et al., 2005; Cordonnier et al., 2005).

Permanent hypoglycemic brain damage occurs in the context of prolonged energy failure and occurs after the onset of cerebral isoelectricity (Auer et al., 1984a; Auer, 2004). At the biochemical level this is manifested in alterations in the glycolytic pathway and tricarboxylic acid (TCA) cycle. This has been succinctly reviewed by Auer (2004). Briefly, in severe hypoglycemia, the end product of glycolysis, acetate, is severely reduced. Acetate feeds into the mitochondrial TCA and is condensed by oxaloacetate to form citrate, thus driving the TCA cycle. In the face of depleted acetate, there is a build-up of oxaloacetate. By the laws of mass action, the TCA cycle is driven 'to the left' through the aspartate–glutamate deamination pathway. Deamination of amino acids renders the neuron alkalotic (Pelligrino and Siesjo, 1981; Behar et al., 1985; Nagai et al., 1993). This highlights one of the important differences between ischemia and hypoglycemia: ischemia is associated with profound intracellular acidosis. In severe hypoglycemia, intracellular aspartate levels can increase to 1600% of control (Sandberg et al., 1986). Aspartate thence moves into the extracellular space and acts as a ligand at the NMDA receptor, leading to neuronal depolarization and increased levels of intracellular calcium, which represents an important step in excitotoxicity.

Although not completely known, the committed steps to cell death appear at least to involve mitochondrial swelling/dysfunction, nuclear DNA strand breaks, and a resistance of neurons to glucose. Hypoglycemia has been shown to induce mitochondrial depolarization and swelling through a Ca^{2+}-dependent process called mitochondrial permeability transition, which results in DNA fragmentation (Ferrand-Drake et al., 1999). DNA fragmentation activates poly (ADP-ribose) polymerase 1 (PARP1), an enzyme that combines NAD^+ and functions to repair DNA kinks and strand breaks (D'Amours et al., 1999). It is known that PARP1 is activated in severe hypoglycemia (Suh et al., 2003). Although PARP1 functions to repair DNA, overactivation of PARP1 will in fact lead to necrosis. Recent work has shown that the mechanism of PARP1-induced necrosis in hypoglycemia stems from its obligatory use and subsequent consumption of cytosolic NAD^+, a critical co-factor in the glycolytic pathway with glyceraldehyde 3-phosphate dehydrogenase (Ying et al., 2001, 2003; Alano et al., 2004). Because glycolysis relies on the presence of NAD^+ and ultimately donates carbon substrate to the mitochondrial TCA cycle, it has been hypothesized that

Table 7.9

Clinicoelectroencephalographic correlation of stages of hypoglycemia

Clinical	EEG	Blood glucose (mmol/l)
Normal	Normal	>3.5
Anxiety (adrenergic discharge)	↑ amplitude ↓ frequency (θ, δ waves)	2–3.5
Stupor	Δ waves	1–2
Coma, Cushing response (↑BP)	Flat	<1.36

Source: adapted with permission from Auer, 2004.

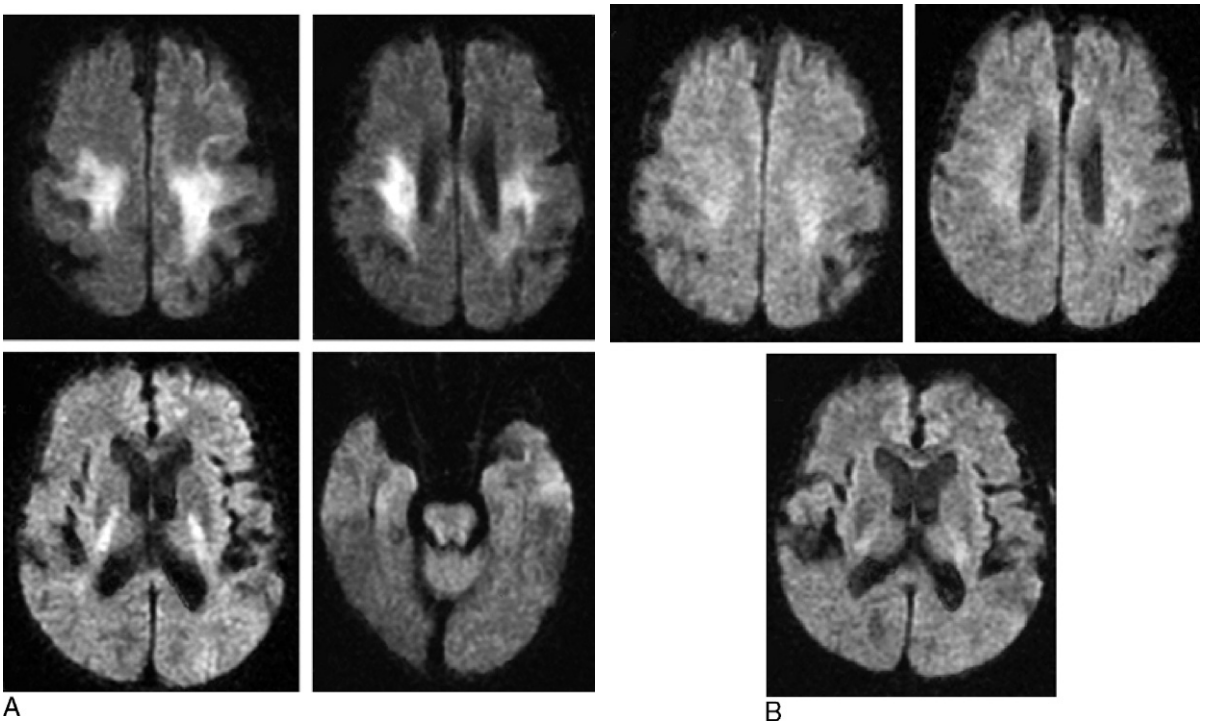

Fig. 7.4. A. 73-year-old woman in deep hypoglycemic coma (serum glucose 20 mg/dl; 0.5 mmol/l) with rolling eye movements, tetraparesis, and decerebrate rigidity to pain. DWI shows hyperintense lesions within the bilateral internal capsule, corona radiata, and frontoparietal cortex. Note that bilateral hippocampi do not disclose any hyperintensity lesions. **B.** DWI 10 days after glucose infusion showing regression of the hyperintensity lesions. The patient had complete neurological recovery. From Aoki T, Sato T, Hasegawa K et al. (2004). Reversible hyperintensity lesion on diffusion-weighted MRI in hypoglycemic coma. Neurology 63: 392–393, with permission from Lippincott Williams & Wilkins.

PARP1 overactivation in hypoglycemia obviates the neuron's ability to utilize glucose as an energy source (Suh et al., 2003), thus prolonging energy debt and resulting in cell necrosis.

7.9.5.1.3. Imaging findings

MRI in severe hypoglycemia has revealed signal changes involving cortical and subcortical structures. Interestingly, the MRI characteristics at first appear similar to acute ischemic brain damage. However, MRI changes from hypoglycemia may be reversible, as illustrated in Figures 7.4 and 7.5. Focal MRI abnormalities can be symmetrical or asymmetrical and do not follow vascular boundaries.

Table 7.10 compares the published case reports of DWI and ADC findings in severe hypoglycemia. Of interest, clinically relevant, permanent brain damage was present in all (3/3) cases in which DWI/ADC changes were present in the basal ganglia. This observation is in keeping with the T_1 and T_2-weighted MR changes described in a small group of patients with irreversible hypoglycemic brain damage (Fujioka et al., 1997). Thus DWI findings may offer important prognostic information. The temporal lobe and hippocampus are most often, but not always (7/11), affected. Deep white matter structures including the corona radiata, internal capsule, or corpus callosum were involved in 3/11 cases. The lack of thalamic and cerebellar changes seen on MRI from severe hypoglycemia probably correlates with the thalamic and cerebellar 'resistance' to hypoglycemia. Such findings are in contrast to what is seen following hypoxic–ischemic insults.

7.9.5.1.4. Clinical presentation

Cold perspiration, tachycardia, lightheadedness, headache and mild agitation are typical symptoms that precede more serious CNS dysfunction. There is a fairly orderly transition of clinical signs of altered consciousness associated with worsening hypoglycemia. Initial dysfunction of higher cognitive processes, such as attention, decision making, visuospatial skills, memory, hand–eye coordination, and speech, can give way to more overt confusion, lethargy, and stupor. Seizures, often generalized, are common in severe hypoglycemia and may

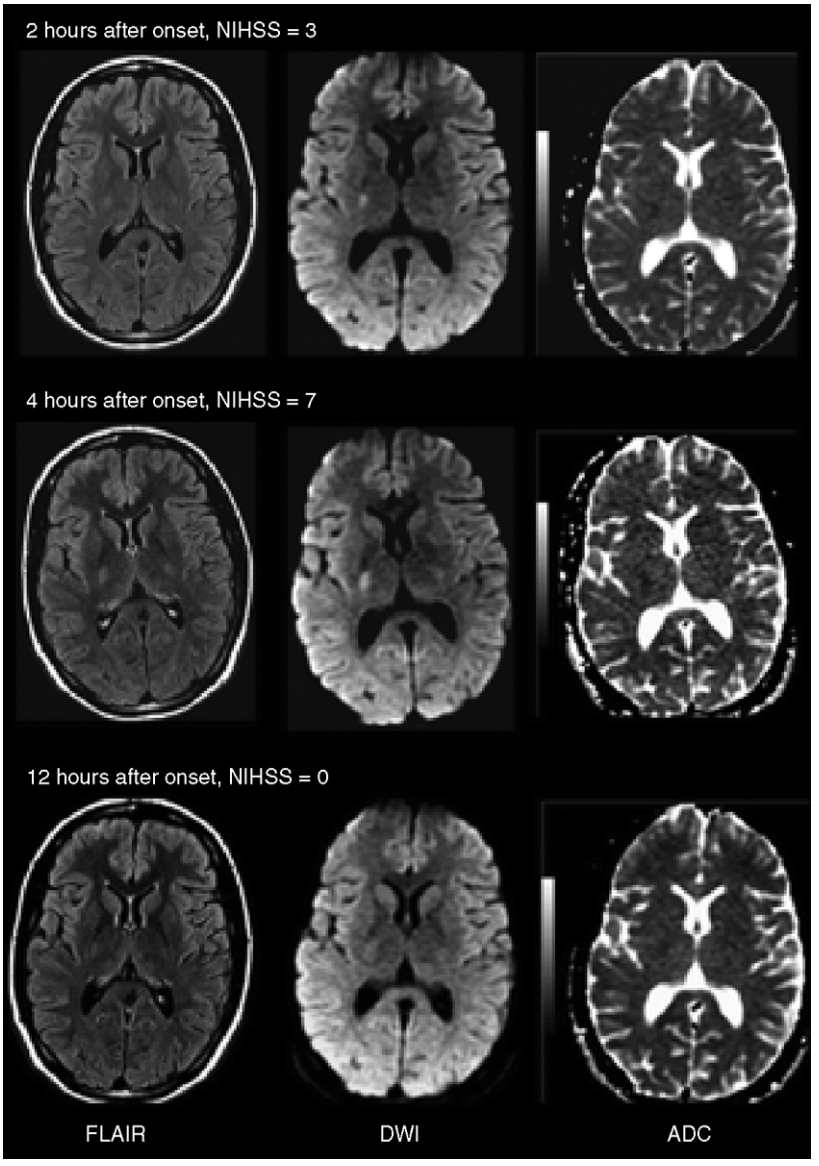

Fig. 7.5. 24-year-old woman with sudden-onset left hemiparesis from hypoglycemia resulting from insulinoma (glucose level of 2.2 mmol/l; 85.8 mg/dl). 2 hours after onset, the FLAIR image was normal while DWI showed a unilateral hypersignal in the right internal capsule with decreased ADC values (20% decreased). 4 hours after onset, a slight signal increase is seen on FLAIR images with a clear-cut signal increase on DWI. 12 hours after onset and treatment of hypoglycemia, the clinical symptoms had resolved and the MRI returned to normal. From Cordonnier C, Oppenheim C, Lamy C et al. (2005). Serial diffusion and perfusion-weighted MR in transient hypoglycemia. Neurology 65: 175, with permission from Lippincott Williams & Wilkins.

contribute to further impairment of consciousness both from ictal- and postictal-induced cerebral dysfunction, as well as cerebral edema, hypoxia, and excitotoxicity, especially in the presence of status epilepticus. Focal neurological deficits in hypoglycemia, although rare, are fairly well described in the literature, and can mimic stroke syndromes such as pure hemiplegia (Shirayama et al., 2004; Cordonnier et al., 2005) and middle cerebral artery stroke (Kossoff et al., 2001). In advanced, profound hypoglycemia, even cranial nerve reflexes, including the pupillary light reflex, can be abolished. Deficits can also be recurrent (Kossoff et al., 2001). Hypoglycemia is thus an important differential in a patient presenting with focal weakness or impaired consciousness with brainstem deficits (Aoki et al., 2004). Hypoglycemia-induced movement disorders including chorea and athetosis have been described (Newman and Kinkel, 1984). At its most extreme, severe hypoglycemia can present as coma with decerebration or decortication. This advanced state may nevertheless be reversible (Aoki

Table 7.10

Clinicoradiological correlation in hypoglycemic coma: summary of recent case reports

Study	Symptoms	Hypoxia?	Imaging	Location	Reversible?	Outcome
Boeve et al., 1995	Coma	No	T2 hyperintensities	Bilateral hippocampus	No	Seizure, amnesia
Finelli, 2001	Stupor	Not reported	DWI^+/ADC^-	Bilateral basal ganglia; hippocampus; temporal cortex	Not repeated	Death
Bottcher et al., 2005	Hemiparesis	No	DWI^+/ADC^-	Bilateral corona radiate; splenium corpus callosum	Yes	Recovery
Aoki et al., 2004	Coma, decerebrate	No	DWI^+/ADC^-	Bilateral corona radiate; internal capsule; frontoparietal cortex	Yes	Recovery
Chan et al., 2003	Encephalopathy; seizure	No	DWI^+/ADC^-	Bilateral (L>R) temporal/occipital lobes; frontoparietal cortex	No	Worsening seizure; death
Maekawa et al., 2005	Coma; decorticate	No	DWI^+/ADC^-	Bilateral occipital, hippocampi	Yes, after 14 days	Responds to commands
Cordonnier et al., 2005	Hemiparesis	No	DWI^+/ADC^-	Right internal capsule	Yes	Recovery
Yoneda & Yamamoto, 2005	Coma; decerebrate	Yes	ADC^-/SPECT	Entire hemisphere; basal ganglia. Global hypoperfusion sparing basal ganglia	No (laminar necrosis along cortical rim, day 21)	Death
Jung et al., 2005	Coma	No	DWI^+/ADC^-	Left frontal; bilateral parieto-occipital; posterior temporal cortices; insular cortex; bilateral basal ganglia	No	Persistent coma
Shirayama et al., 2004	Coma; hemiplegia	No	DWI^+	Pons	Yes	Recovery
Cho et al., 2006	Encephalopathy	No	DWI^+	Entire cortex, sparing bilateral dorsal frontal cortex and occipital poles	Not reported	–

ADC^-, reduced apparent diffusion coefficient; DWI^+, bright signal on diffusion-weighted MRI; SPECT, single photon emission computed tomography.

et al., 2004). It is therefore critical for serum glucose levels to be drawn in such patients prior to other investigations such as cranial imaging.

7.9.5.1.5. Treatment of hypoglycemia

A multidisciplinary approach is required for the treatment of hypoglycemia, and it can be separated into 1) education and prevention, 2) acute management, and 3) investigation of underlying cause.

In the diabetic population, patients need be educated on the warning signs of hypoglycemia and the effects of certain foods on serum glucose. Aggressive serum glucose monitoring with documentation in the form of a diary is very useful in plotting daily trends in serum glucose. Family members must be educated in the first aid management of severe hypoglycemia, and a designated storage of glucagon within the home should be established and all should be familiar with its use. First-aid bracelets are useful for emergency medical services teams or well informed good Samaritans. The benefits of aggressive glucose control should be balanced against the increased risk of severe hypoglycemia in patients with coexisting autonomic dysfunction or obligate beta-blocker use given their blunted neuroglycopenic symptoms. Such patients should closely monitor their serum glucose and err on the side of slightly higher basal glucose levels.

Severe hypoglycemia requires aggressive and sustained therapy and monitoring, particularly in sulfonylurea overdose given the long half-life of this oral hypoglycemic. Bolus intravenous administration of 50 ml of 50% glucose solution followed by ongoing 5% intravenous glucose maintenance to target euglycemia is the standard therapy for acute management of severe hypoglycemia. Insulin overdose may require 30% glucose solution as intravenous maintenance. Serum glucose should be monitored every half hour and maintenance intravenous glucose should continue until the patient is conscious and able to eat enough to replenish glycogen stores.

When the cause is not obvious, investigation of liver function and insulinoma are needed. Insulinoma requires surgery. Idiopathic postprandial hypoglycemia is best treated with small, frequent meals.

7.9.5.1.6. Future treatment: is there anything beyond glucose?

In uncomplicated severe hypoglycemia, intravenous glucose administration is an effective therapy and complete clinical resolution of hypoglycemic coma should be met without neurological sequelae. The presence of neurological sequelae following recurrent bouts of severe hypoglycemia may be due to an increased burden of hypoglycemia-induced cell death (Akyol et al., 2003). Regrettably, glucose is the only treatment available apart from supportive measures. As previously discussed, if treatment is delayed, establishing euglycemia may not reverse the clinical picture and severe permanent brain damage from selective neuronal necrosis is the rule. A neuroprotective intervention to inhibit this apparent 'point of no return' could theoretically rescue patients from profound and protracted hypoglycemia.

Provocative results from the rat model of hypoglycemia may suggest future treatments for hypoglycemic coma. As described above, overactivation of PARP1 may play a critical role in hypoglycemia-induced necrosis through its consumption of intracellular NAD^+, thus rendering the neuron unable to metabolize glucose. It stands to reason that providing an energy-producing substrate that bypasses the NAD^+-dependent pathway should theoretically restore ATP production and the energy status of the cell, and prevent or reduce cell necrosis. In fact this has been shown in cell culture (Ying et al., 2003).

Pyruvate is a key substrate of the mitochondrial TCA and does not require NAD^+ for its active metabolism. In vivo experiments by Suh and colleagues have shown that supplementing glucose therapy with pyruvate results in a 70–90% decrease in selective cell death in the CA1, dentate granule cell, subiculum, and perirhinal cortex regions of the hippocampus, compared to rats treated with glucose alone in the classic experimental conditions of hypoglycemic brain injury (Suh et al., 2005). The same study showed that neurocognitive function tested 6 weeks after is preserved in animals treated with pyruvate and glucose compared to glucose alone (Suh et al., 2005). The beneficial effects of pyruvate were also seen when given up to 2 hours after glucose administration. Thus in severe hypoglycemia, pyruvate supplementation can obviate the irreversible effects of PARP1 overactivation, reduce cell death, and improve neurocognitive function. The histological data with the behavioral correlate provides a compelling argument for pyruvate to be considered as adjuvant therapy along with glucose. There are as yet no data published that examine the effects of pyruvate in hypoglycemic coma in humans.

7.9.5.2. Hyperglycemia

Acute, symptomatic hyperglycemia typically occurs in the context of DKA or nonketotic hyperosmolar hyperglycemia (NKH) – two manifestations of severely decompensated diabetes. Impairment of consciousness is a common feature in NKH, less so in DKA.

Both conditions are potentially life-threatening and require diligent monitoring well beyond the point at which euglycemia is achieved.

7.9.5.2.1. Definition

Hyperglycemia is defined as serum glucose >7.8 mmol/l (140 mg/L). However, impairment of consciousness typically occurs when serum glucose values are >16.7 mmol/l (300 mg/dl) in DKA, and >33 mmol/l (600 mg/dl) in NKH (Arieff and Carroll, 1972). The principal defect in these patients is either lack of insulin or insulin resistance, both of which prevent cellular uptake and utilization of circulating glucose. In general, hyperglycemia can be heterogeneous in etiology with the common features of impaired 'insulin-effect' coupled with increased exogenous glucose, increased gluconeogenesis, or glycolysis.

7.9.5.2.2. Etiology and clinical features

Although hyperglycemia with impaired consciousness usually occurs in the at-risk population during a severe metabolic stress, such as infections, burns, inflammatory diseases, or steroid use, it can also occur spontaneously (Arieff and Carroll, 1972). Table 7.11 summarizes some common predisposing factors of nonketotic hyperglycemia.

Patients with NKH and DKA are invariably extracellularly volume-contracted with flat jugular venous pressure. Tissue turgor is reduced and mucus membranes are dry with soft, sunken eyeballs. Some of these findings may be difficult to appreciate in severely obese patients with NKH. Kussmaul breathing and breath with a fruity odor is caused by metabolic acidosis and expired acetone that is characteristic of DKA but not NKH. Neurological manifestations of symptomatic hyperglycemia occur more frequently in NKH than DKA. Impairment of consciousness follows a predictable course of confusion, lethargy, stupor, and coma (Arieff and Carroll, 1972). In NKH, focal neurological findings may be present and include hemiplegia, aphasia, and focal motor seizures (Venna and Sabin, 1981; Duncan et al., 1991; Hennis et al., 1992). Hemichorea–hemiballism (HC-HB) is a rare movement disorder complication of NKH. These patients tend to be women (Oh et al., 2002) and the neuroimaging correlates are reversible T_1-hyperintensities and T_2-hypointensities in the striatum (Lin et al., 2001; Oh et al., 2002). Local metabolic changes from selective hypoperfusion and reduced oxygen delivery to striatum have been implicated in HC-HB (Chang et al., 1996). In one study the presence of acanthocytosis correlated with HC-HB (Pisani et al., 2005).

Table 7.11

Common conditions causing nonketotic hyperglycemia

1. Serious systemic illness
   a. Unobserved dehydration
   b. Metabolic change (infection, inflammation, burns, myocardial infarction, Cushing's syndrome)
   c. Surgery or anesthesia
2. Reduction in carbohydrate tolerance with increased carbohydrate intake (e.g., burns, drug therapy plus parenteral hyperalimentation)
3. Inhibition of fat mobilization in ketosis-susceptible patients (e.g., propranolol therapy)
4. Inadequate insulin dosing

7.9.5.2.3. Epidemiology

The incidence of DKA is 4.6–8.0/1000 person-years among patients with diabetes, and that of NKH <1.0/1000 person-years (Fishbein and Palumbo, 1995). In one of the early prospective studies on NKH, the average age of patients was 62 years (Arieff and Carroll, 1972). Indeed, current clinical teaching usually categorizes NKH as a condition affecting the elderly, whereas DKA affects a relatively younger population. The explosion of childhood obesity and early-onset type 2 diabetes have been important observations with implications for the epidemiology of NKH (Vivian, 2006). For example, in the USA, there has been a tenfold increase in type 2 diabetes in the last decade, with 45% of children in pediatric diabetic clinics having type 2 diabetes (American Diabetes Association, 2002). Data on the incidence of NKH in the pediatric population is lacking; however, it probably follows the increased incidence of childhood obesity and type 2 diabetes. The largest study thus far – a retrospective analysis of pediatric type 2 diabetics over a 5-year period in a tertiary care center – reported an incidence of NKH of 3.7% (7/190), with a case fatality rate of 14% (1 death) (Fourtner et al., 2005). None of the patients in the study had the typical predisposing factors for NKH and all had NKH as their presenting symptom of type 2 diabetes. Characteristics of children with NKH include having a first- or second-degree relative with type 2 diabetes, obesity, African-American race, acanthosis nigricans, and absence of insulin autoantibodies (Morales and Rosenbloom, 2004; Carchman et al., 2005; Fourtner et al., 2005). The clinical outcome of death in the various case reports and case series ranges from 14–100% (Morales and Rosenbloom, 2004; Carchman et al., 2005; Fourtner et al., 2005); thus underscoring the potentially catastrophic nature of this subset of patients with NKH.

7.9.5.2.4. Laboratory values

Tables 7.12 and 7.13 summarize the diagnostic criteria for DKA and NKH, and other serum biochemical abnormalities that are typically present in NKH and DKA, with normal ranges for comparison.

7.9.5.2.5. Pathophysiology of impaired consciousness in hyperglycemia

Arieff and Carroll (1974) describe a clear relationship between increased serum osmolality and progressive degree of impaired consciousness in hyperglycemic encephalopathy. Alterations in electrical activity of the reticular activating system have been demonstrated following hyperosmolar stress (Tachibana and Yasuhara, 1986). Thus impairment of consciousness from severe hyperglycemia may localize to aberrations within the reticular activating system in addition to diffuse and cellular dehydration. A rapid rate of osmolar change is particularly effective in depressing consciousness (Arieff and Carroll, 1974). The metabolic acidosis per se does not cause altered levels of consciousness in DKA (Posner and Plum, 1967). Alterations in specific neurotransmitter systems that cause impaired consciousness have yet to be described. It is likely that multiple transmitter systems are involved. Seizures in NKH have been postulated as due to a decrease in GABA availability, because of glutamate shunting through the pentose phosphate shunt (Tiamkao et al., 2003).

Table 7.12

Laboratory diagnostic criteria for diabetic ketoacidosis (DKA) and nonketotic hyperosmolar hyperglycemia (NKH)

Parameter	Normal range	DKA	NKH
Plasma glucose (mmol/l)	4.2–6.4	>14	>34
Arterial pH	7.35–7.45	<7.30	>7.30
Serum bicarbonate (mmol/l)	22–28	<15	>15
Effective serum osmolality (mmol/kg)	275–295	<320	>320
Anion gap (mmol/l)	<12	>12	Variable
Serum ketones	Negative	Moderate to high	None to trace
Urine ketones	Negative	Moderate to high	None to trace

Source: from Chiasson JL, Aris-Jilwan N, Bélanger R et al. (2003). Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Can Med Assoc J 168(7): 859–866, by permission of the publisher. © 2003 CMA Media Inc.

Table 7.13

Other biochemical abnormalities associated with diabetic ketoacidosis (DKA) and nonketotic hyperosmolar hyperglycemia (NKH)

		Mean (standard deviation)	
Parameter	Normal range	DKA	NKH
Sodium (mmol/l)	136–145	134 (1.0)	149 (3.2)
Potassium (mmol/l)	3.5–5.0	4.5 (0.13)	3.9 (0.2)
Blood urea nitrogen (mmol/l)	2.8–7.9	11.4 (1.1)	21.8 (3.9)
Creatinine (μmol/l)	38–110	97.2 (8.8)	123.8 (8.8)
Free fatty acids (mmol/l)	0.4–0.7	1.6 (0.16)	1.5 (0.19)
Beta-hydroxybutyric acid (μmol/l)	<300	9100 (850)	1000 (200)
Lactate (mmol/l)	0.56–2.2	2.4	3.9
Insulin (pmol/l)	35–145	90 (10)	270 (50)
C-peptide (nmol/l)	0.26–1.32	0.25 (0.05)	1.75 (0.23)
Glucagon (ng/l)	50–100	580 (147)	689 (215)
Growth hormone (μg/L)	<5	7.9	1.1
Cortisol (nmol/l)	140–690	1609 (349)	1539 (490)
Catecholamines (ng/ml)	0.15–0.75	1.78 (0.4)	0.28 (0.09)

Source: from Chiasson JL, Aris-Jilwan N, Bélanger R et al. (2003). Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Can Med Assoc J 168(7): 859–866, by permission of the publisher. © 2003 CMA Media Inc.

Impairment of consciousness via cerebral edema can also occur following treatment of hyperglycemia. This can be seen in rapid correction of DKA and only very rarely during treatment of NKH. Initial studies suggest that elevated intracellular Na^+ and generation of additional 'idiogenic osmoles' (i.e., extra 'idiogenic osmoles' beyond the amount generated to maintain cellular volume during the adaptive phase of the hyperosmolar stress) are responsible for cerebral edema (Arieff and Kleeman, 1973, 1974). This would result in excess shift of water into neurons and glia. The need for generation of additional idiogenic osmoles has more recently been challenged (Silver et al., 1997). Regardless of the mechanism, close monitoring of these patients is needed as severe cerebral edema may be fatal. Sudden alterations of consciousness after correction of hyperglycemia should prompt cranial imaging to assess signs of edema.

7.9.5.2.6. Treatment

A detailed description of the management of NKH and DKA is beyond the scope of this chapter and the reader is referred to a recent review of this topic (Chiasson et al., 2003). The management principles of these disorders include 1) fluid replacement, 2) intravenous insulin therapy, 3) potassium replacement, 4) close monitoring of electrolytes and clinical state, and 5) treatment of the precipitating event.

Rapid extracellular fluid expansion is necessary, and – assuming adequate cardiopulmonary reserve – should be initiated by IV isotonic saline (0.9% NaCl) at 10–20 ml/kg (approximately 1–1.5 liters in an average adult) in the first hour. Ongoing IV physiological saline should be instituted at a rate of 4–14 ml/kg/h until serum glucose reaches 12–14 mmol/l, at which point 5% dextrose in 0.45% NaCl IV fluid should be given to help prevent cerebral edema (Arieff and Kleeman, 1973, 1974). IV insulin delivered by a pump at 0.1 U/kg/h should be started at the onset of fluid replacement. Insulin will reduce hyperglycemia by facilitating cellular uptake of glucose and by inhibiting glycolysis and gluconeogenesis. It will also arrest ketone production in DKA. Hypokalemia is usually present in severe hyperglycemia and is worsened by insulin therapy because of the intracellular shift of potassium caused by insulin. If serum potassium is <3.3 mmol/l at the outset, insulin should be withheld and 40 mEq of KCl should be added to the patient's IV fluids (Chiasson et al., 2003). Potassium replacement of 20 mEq/l IV physiological saline is typically used with potassium levels >3.3 mmol/l and <5.0 mmol/l. Thus careful monitoring of electrolytes is necessary and serum chemistries should be repeated every few hours until the patient is stable.

7.10. Idiopathic recurrent stupor: endozepine stupor

This rather curious syndrome is characterized by recurrent spontaneous stupor with associated fast EEG (beta frequency) that is responsive to the $GABA_A$ antagonist flumazenil.

7.10.1. Epidemiology

With only 30 cases reported, epidemiological features of endozepine stupor are clearly lacking. The largest study indicates a male preponderance (16:4 male: female) with involvement of both the young adult and elderly population (range 18–67 years) (Lugaresi et al., 1998). There are no obvious risk factors or common premorbid conditions; however, 30% (6/20) had some form of respiratory disease (obstructive sleep apnea, 3; chronic obstructive pulmonary disease, 3) (Lugaresi et al., 1998).

7.10.2. Clinical features

All patients have some impairment of consciousness which can range from stupor to coma. Dysarthria and ataxia are also common features and deep tendon reflexes are reduced (Tinuper et al., 1992; Chen et al., 1995; Lugaresi et al., 1998). Patients are usually amnesiac of the episode and of events hours to days preceding the attacks. The attacks can last 2–120 hours and their frequency is also variable. For example, in the study of Lugaresi et al. (1998), 9/20 patients had at some point more than 6 attacks per year. The attacks can occur at any time of the day and may be preceded by hours to days with fatigue, mental slowing, general malaise and behavioral disturbances such as combativeness or docility (Tinuper et al., 1992). Extensive investigations for other toxic or metabolic encephalopathies or exogenous benzodiazepine ingestion, by definition, should not disclose an alternative diagnosis. Between attacks there is no published evidence for any neurological sequelae.

7.10.3. EEG findings

Interictally, the patients have normal EEG findings. During the attacks, there is diffuse, low-amplitude, unreactive beta rhythm (13–16 Hz). Administration of intravenous flumazenil 0.5–2 mg or more reverses the abnormal EEG pattern to normal, reactive alpha rhythm (Fig. 7.6) and correlates with clinical improvement.

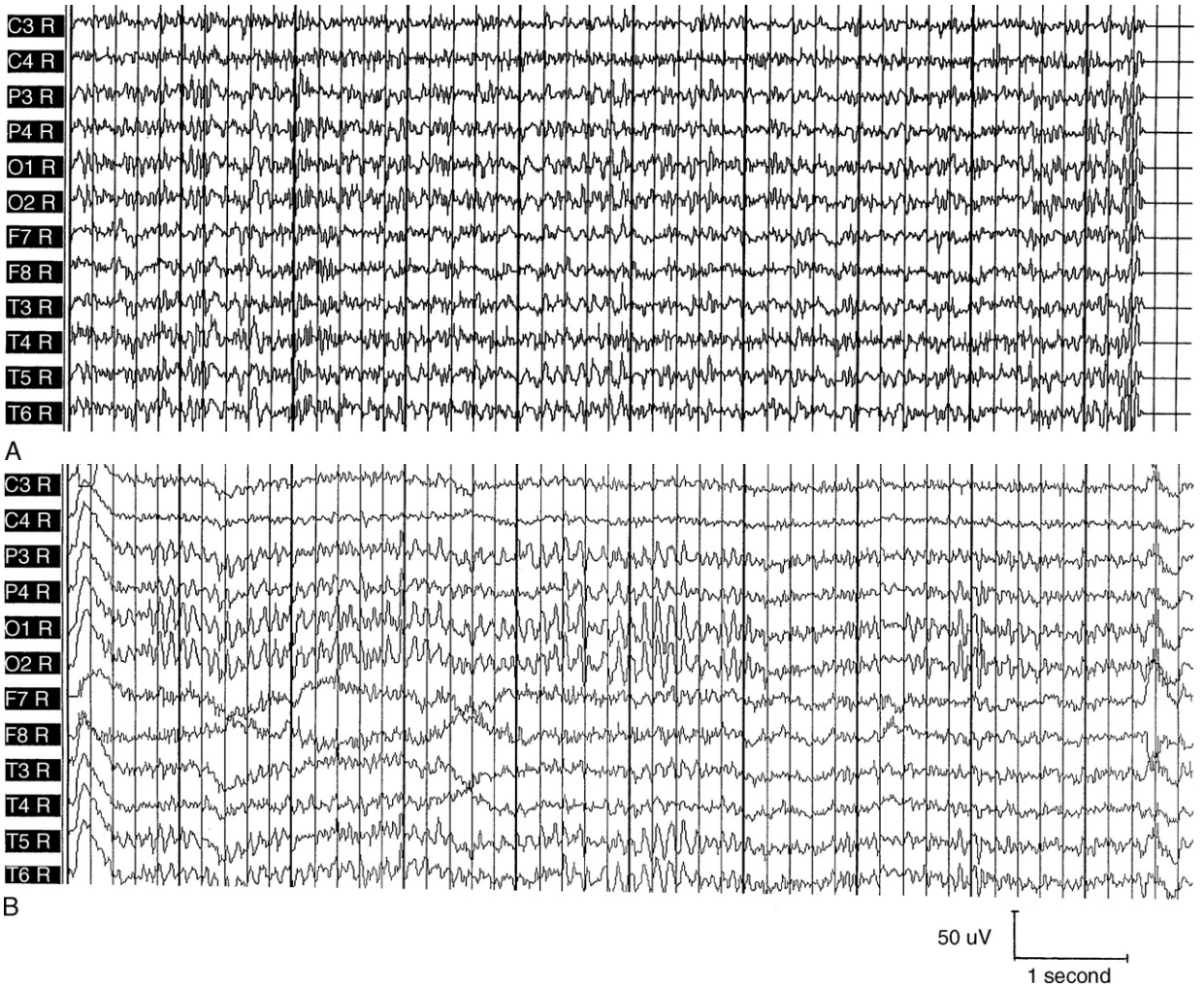

Fig. 7.6. EEG response to flumazenil in endozepine stupor. **A.** 49-year-old woman with a 20-year history of recurrent, episodic dysarthria and ataxia, and impaired consciousness. EEG tracing was obtained during an attack, prior to flumazenil administration. Note the diffuse, low-amplitude beta rhythm (16 Hz) and poorly formed occipital theta rhythm. **B.** Following intravenous flumazenil 0.5 mg administration, there is return of dominant alpha rhythm.

7.10.4. Pathophysiology

As the name would suggest, the sine qua non of endozepine stupor is the presence of elevated serum endozepine that coincides with the appropriate clinical picture. Endozepines are nonbenzodiazepine, nonprotein molecules that act as positive allosteric modulators of the $GABA_A$ receptor and have the same action on the CNS as exogenous benzodiazepines (Rothstein et al., 1992a). It is felt that, in the normally functioning nervous system, endozepine release is physiologically regulated by neurons and acts to modulate GABA-mediated neurotransmission (Rothstein et al., 1991; Cortelli et al., 2005). In the syndrome of idiopathic recurrent stupor, high-power liquid chromatography has shown that a subtype of endozepine molecule – endozepine-4 – is massively elevated during bouts of stupor (Rothstein et al., 1992b; Chen et al., 1995). At present there is no known cause for the episodic rise in serum endozepine-4 in these patients.

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Chapter 8

Nutritional disorders

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Nutritional disorders are those conditions related to a deficiency of one or more nutrients, either from dietary lack or a factor that diminishes absorption, accelerates excretion or metabolism, or otherwise antagonizes the action of the nutrient(s). (This chapter does not address 'inborn errors of metabolism', some of which reduce the activity of various vitamins and/or are responsive to large doses of vitamins, e.g., biotinidase deficiency, pyridoxine dependency, homcysteinuria, glutamic acid decarboxylase deficiency, propionic aciduria, and others. These are typically found in neonates and infants.) Most affected patients lack multiple nutrients. In addition to protein–calorie malnutrition and its attendant effects on maintenance, energy metabolism, and growth, the lack of specific vitamins, especially various B vitamins, and minerals produce a variety of syndromes. In North America and Europe, however, vitamin deficiency disorders occur most commonly in alcoholics, whose caloric intake is maintained. An epidemic of predominantly sensorineural axonal polyneuropathy, optic neuropathy (with cecocentral scotomas), dorsolateral myelopathy, and deafness occurred in Cuba in the early 1990s (Tucker and Hedges, 1993; Roman, 1994). This was similar to the amblyopia-neuropathy found in 'tobacco–alcohol amblyopia' and Strachan's syndrome (amblyopia, painful neuropathy, and orogenital dermatitis). Each is probably mainly due to B vitamin deficiencies, as features are commonly reversed with replacement therapy. Hypovitaminosis A has been associated with pseudotumor cerebri, flecked retina, and xerophthalmia (Panozzo et al., 1998). Those associated with impaired consciousness are underrecognized and typically acute, preventable, and treatable, but are associated with significant mortality and morbidity if neglected. They comprise Wernicke's encephalopathy (or Wernicke–Korsakoff syndrome), pellagra, refeeding syndrome, and Marchiafava–Bignami disease. These are reviewed in turn, as if they were pure entities. It should be recognized, however, that elements of these diseases can be combined and/or associated with other nutritional disorders that in themselves do not typically produce impaired consciousness. Pyridoxine deficiency, related to dietary deficiency or to antagonism by isoniazid (an antituberculous drug), is associated with a sensory neuropathy and may cause seizures. Pyridoxine is a co-factor in the enzymatic synthesis of gamma-amino butyric acid (GABA), an inhibitory neurotransmitter; its deficiency can produce seizures or status epilepticus. Beri-beri, probably due to single or multiple B vitamin deficiency, is characterized by a painful sensory neuropathy with impairment of large and small nerve fiber function with reflex loss and, less commonly, weakness. Coincidental vitamin A deficiency, usually in developing countries, can produce blindness due to retinal disease.

8.1. Wernicke's encephalopathy

8.1.1. Definition

Wernicke's encephalopathy is an acute brain dysfunction related to a deficiency of thiamine. The classic syndrome consists of the triad of ophthalmoplegia, ataxia, and disturbed mentation. Other features include hypothermia and features of a distal polyneuropathy.

8.1.2. Clinical features

Wernicke's encephalopathy should be suspected in any malnourished patient who develops central neurological symptoms, especially after being given a load of carbohydrates. However, it may not always be obvious that the patient is thiamine-deficient; the

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condition is more often missed in nonalcoholics than in alcoholics. Other conditions placing individuals at risk for Wernicke's encephalopathy include those with: starving or fasting, hyperemesis gravidarum, prolonged vomiting, gastric carcinoma, gastric bypass or partitioning operations for obesity, pancreatitis, prolonged administration of intravenous fluids, dialysis for renal failure (if not adequate supplementation), acquired immune deficiency syndrome (AIDS), and tolazemide administration in patients with transketolase deficiency (Young, 1998).

Only 16.5% of patients have all three of the classic features of encephalopathy, ocular abnormalities, and ataxia (Harper et al., 1986). More than one-third of patients show only abnormalities of mentation. The latter is most commonly an acute confusional state or delirium, with impaired attention, disorientation, and impaired memory and perception. Impairment of alertness can be more profound, including stupor and coma. Memory impairment may be due to the acute confusional state (memory is dysfunctional when patients are inattentive and cannot concentrate) but the more enduring memory problems of the Korsakoff state (see below) relate to damage to the medial dorsal nuclei of the thalamus (Victor et al., 1971).

Ocular findings include horizontal nystagmus in up to 85% of some series, followed by bilateral abducens palsies in 54% and conjugate gaze palsy in 45%; a smaller percentage may have bilateral internuclear ophthalmoplegia (Harper et al., 1986; De La Paz et al., 1992). Patients typically lose their vestibular ocular reflexes, including response to caloric testing (personal observation); this can be very helpful diagnostically. Pupillary reactions are spared, but the pupils may be small in diameter.

Ataxia is related to dysfunction and structural changes in the cerebellum's anterior superior vermis, affecting stance, gait, and lower limb coordination. However, in the acute phase, upper limb dysfunction may be due to vestibular nuclear damage.

Hypothermia should be emphasized as it is common and may be accompanied by hypotension, both due to hypothalamic disease (Philip and Smith, 1973).

Dysphagia, probably due to involvement of the dorsal nucleus of the vagus, can occur early in the course of Wernicke's encephalopathy and clears with administration of thiamine (Truedsson et al., 2002). The early, oral-pharyngeal phase is affected.

8.1.3. Epidemiology

Lindboe and Løberg (1989) conducted an autopsy study from a university hospital in Sweden. Of 6494 autopsies 52 (0.74%) showed features of Wernicke's encephalopathy. Of these 77% were alcoholics and 23% were not; among alcoholics men outnumbered women 4:1. A prevalence of Wernicke's encephalopathy was found in 2.8% of autopsies in an Australian study (Harper et al., 1989); this is close to that of American cities (Victor et al., 1971), although the studies differ in time. As autopsies are typically selective, and since many patients may survive for many years, it is not clear how these studies relate to the overall occurrence in the population. Clinical data are probably much less reliable in that only 20% of patients from the postmortem study of Harper et al. (1989) were diagnosed with Wernicke's encephalopathy or Korsakoff's psychosis during life.

About 80% of patients with Wernicke's encephalopathy will develop Korsakoff's psychosis; such patients suffer a severe amnestic–confabulatory state with inability to acquire new memories or to recall past events in the appropriate timing and sequence. Patients who do not receive prompt, appropriate treatment for Wernicke's encephalopathy (e.g., nonalcoholics in whom the condition is unlikely to be considered) are even more likely to develop Korsakoff's psychosis (Sands, 1987).

8.1.4. Pathology and pathogenesis

The gray matter structures surrounding the central cerebrospinal fluid pathways show swollen glia, microglial reaction, endothelial swelling, small hemorrhages, and macrophage accumulation (the latter three phenomena do not occur in the thalamus, for unknown reasons) in the acute stage; later these areas become shrunken and gliotic. The medial thalamus, the hypothalamus (especially and invariably affecting the mammillary bodies), the periaqueductal gray matter, and the floor of the fourth ventricle (including the vestibular, abducens, and vagal nuclei) are typically involved. In addition, the anterior superior vermis later shows atrophy and gliosis. The distribution fits nicely with the clinical features but the pathogenesis is not entirely agreed upon.

Wernicke–Korsakoff disease is due to thiamine deficiency. This has been well substantiated, in that thiamine administration in humans and in animal models can prevent the disease and its pathology. Furthermore, the mitochondrial and other metabolic derangements can be traced to a deficiency in phosphorylated thiamine, especially thiamine diphosphate, which is involved in coenzymes for many intracellular reactions. One of the most important involves alpha-ketoglutarate dehydrogenase in the Krebb's cycle (Butterworth and Héroux, 1989; Fig. 8.1). This leads to decreased adenosine triphosphate (ATP) production, increased lactic acidosis in the tissues, and decreased oxygen consumption, with the uncoupling of mitochondrial respiration. Cell death may arise from this. In addition, the recently discovered decreased activity

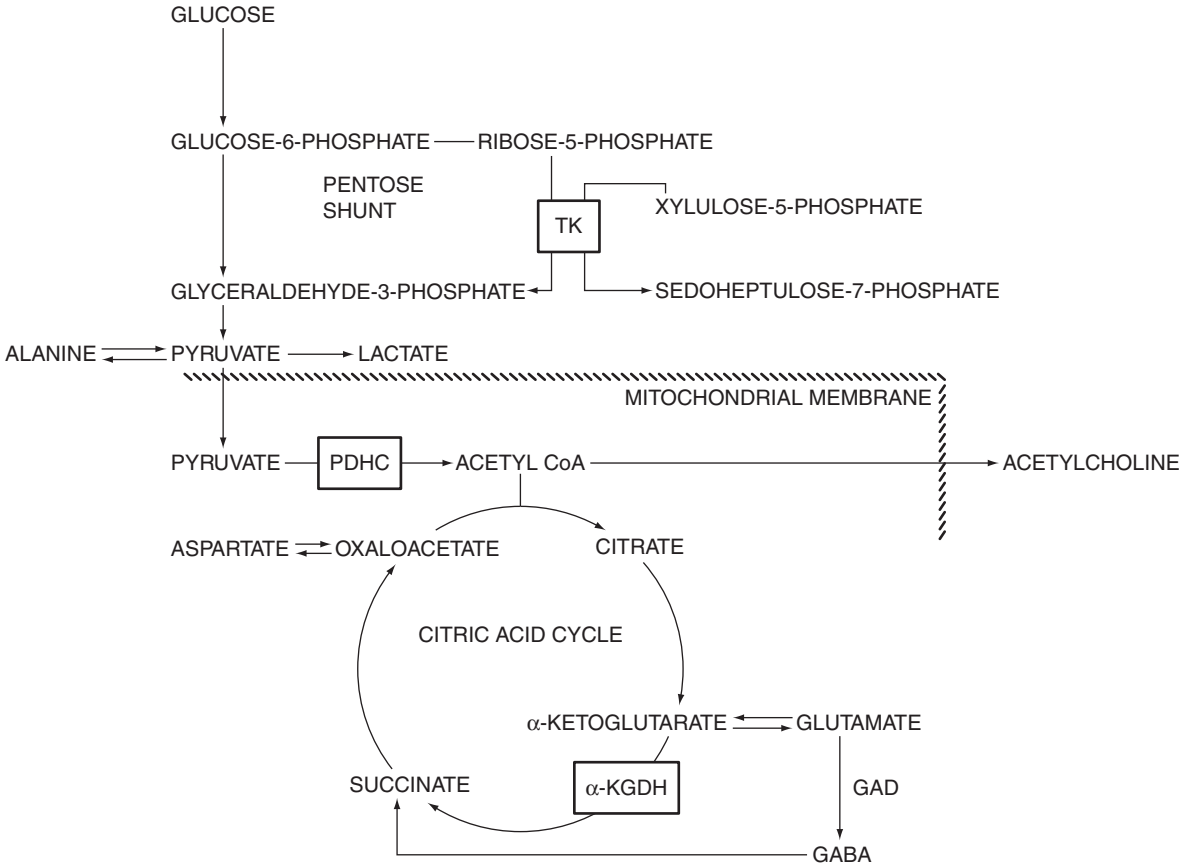

Fig. 8.1. Thiamine-diphosphate-dependent enzymes are implicated in brain glucose oxidation and pentose shunt pathway. Impaired activities of thiamine-diphosphate-dependent enzymes result in decreased synthesis of glucose-derived neurotransmitters (acetylcholine, glutamate, GABA) and, ultimately, a cellular energy deficit and lactic acidosis. PDHC, pyruvate dehydrogenase complex; α-KGDH, α-ketoglutarate dehydrogenase; TK, transketolase. With permission from Desjardins P, Butterworth RF (2005). Role of mitochondrial dysfunction and oxidative stress in the pathogenesis of selective neuronal loss in Wernicke's encephalopathy. Mol Neurobiol 31: 17–25.

of glutamate transporters in astrocytes leads to increased glutamate in the extracellular fluid, which could cause neuronal excitotoxic damage, by activation of *N*-methyl-D-aspartate receptors, causing massive calcium ion influx into neurons (Hazell et al., 2001). In addition there is evidence for apoptotic cell death in the medial thalamus. Because of microglial activation, there is the opportunity of oxidative damage to the neuropil as well (Desjardins and Butterworth, 2005). Thus there may be multiple, non-mutually-exclusive mechanisms for the neural and glial pathology in Wernicke–Korsakoff disease.

8.1.5. Diagnosis and management

Wernicke's encephalopathy should be considered in those at risk (see section 8.1.3) when any of the clinical features are presented. For in-hospital patients acute Wernicke's encephalopathy is commonly precipitated by intravenous glucose infusions; hence, suspect Wernicke's encephalopathy in anyone who loses consciousness or develops other clinical features of Wernicke's after such therapy. The clinical diagnosis usually suffices, especially if improvement follows thiamine administration.

Additional confirmatory evidence can be made by measuring increased serum thiamine, plasma pyruvate, decreased erythrocyte transketolase, or by characteristic magnetic resonance imaging (MRI) findings in the medial thalamus, hypothalamus, including mammillary bodies, and floor of the fourth ventricle using fluid-attenuated inversion recovery (FLAIR) (Koguchi et al., 2004) (Fig. 8.2).

Prevention cannot be overemphasized. Patients at risk for nutritional deficiency, including acquired immunodeficiency syndrome (AIDS) patients, should receive supplemental thiamine.

For any patient for whom Wernicke's is even a possibility, it is wise to administer thiamine 50 mg intramuscularly, along with 50 mg to each liter of intravenous solution. After this, thiamine can be given orally in 50–100 mg doses for the first week in hospital.

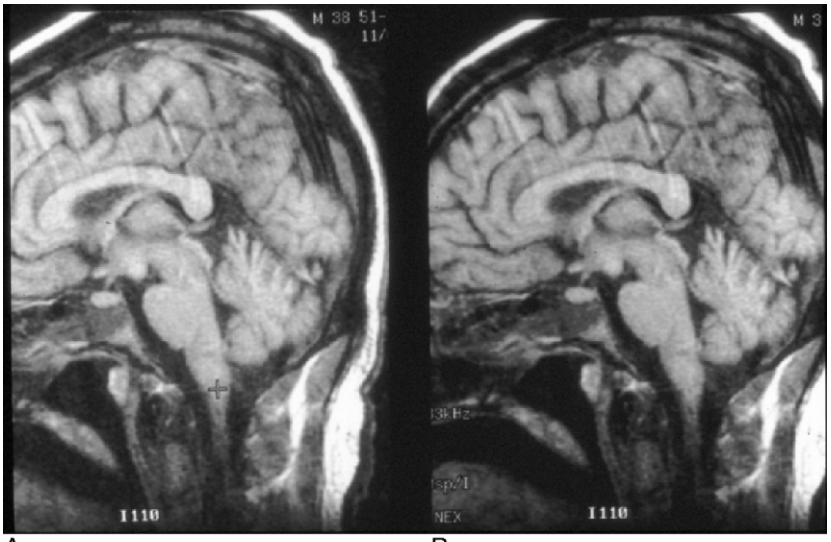

Fig. 8.2. Wernicke's encephalopathy: Sagittal MRI showing hyperintense signal in mammillary body on one side.

8.1.6. Outcome and prognosis

Outcomes may vary. Many patients are left with Korsakoff's state and are severely disabled; some do not recover from the ataxia of stance and gait. Almost all will regain ocular motility.

8.2. Pellagra

8.2.1. Definition

The term pellagra is derived from the Italian words *pele* (skin) and *agra* (rough), emphasizing the dermatological complications of the disease. However, gastrointestinal and neurological components are at least as vitally important. The condition is due to a deficiency of niacin or nicotinic acid, vitamin B_3, and is usually remembered by the 'three Ds': dermatitis, dementia, and diarrhea.

8.2.2. Clinical features and epidemiology

Primary pellagra, as a nutritional disorder, is rare in industrialized countries, but is found in developing countries where one of the main foods is maize or corn, in which niacin exists in a bound form that cannot be released into the gastrointestinal tract for absorption (Hegyi et al., 2004). In this form it is rare in children but is a disease of adolescents and adults. Secondary pellagra occurs in other countries when there is a problem with intake (alcoholics and AIDS patients), absorption (malabsorption syndromes), or processing. It can be found as a complication of Hartnup's disease or carcinoid syndrome: in the first condition tryptophan is poorly absorbed; in carcinoid the tumor cells convert tryptophan into serotonin, depleting the body of nicotinic acid. Isoniazid, an antituberculous drug, is an analog of niacin and can block its endogenous production, thereby producing pellagra. Other drugs that may interfere with the tryptophan–niacin pathway include: 5-fluorouracil, phenobarbital, hydantoins (notably phenytoin), 6-mercaptopurine, pyrazinamide, ethionamide, azathioprine, and chloramphenicol.

Neurological symptoms include acute confusional state (89%) of cases (Serdau et al., 1988). This fluctuates and is associated with clouding of consciousness, apathy, or stupor. Patients may be photophobic. Asthenia and emotional depression are common. Global memory loss, visual hallucinations, psychosis, and motor restlessness commonly occur as well. Terminally patients develop stupor, then coma. Other signs that may occur include paratonic rigidity, myoclonus (both spontaneous and stimulus-induced) affecting the limbs more than the face, ataxia, a sensorimotor polyneuropathy, and myelopathic features (the latter two features may be difficult to detect in the presence of the almost universally present encephalopathy). The neuropathy is associated with loss of deep tendon reflexes and muscular wasting, although poorly nourished patients are typically cachectic. Some patients may present with predominantly central nervous system features, without dermatological or gastrointestinal features. One case report describes isolated ataxia and myoclonus as sole features of a patient with pellagra (Sakai et al., 2006).

The dermatitis of pellagra is initially a tender or painful erythematous eruption on sun-exposed areas; it resembles sunburn and can blister or become exudative.

Patches can become pigmented. The dorsum of the hands and the butterfly area of the face (resembling lupus erythematosus) are commonly involved, as is the skin of the neck (Casal's necklace, after the physician who described it in 1762). Later the affected skin becomes rough and thickened. Glossitis and angular stomatitis are also found, the former contributing to nutritional deficiency. Gastrointestinal symptoms include anorexia, vomiting, and diarrhea with a malabsorptive state resulting from the mucosal damage.

8.2.3. Pathology and pathogenesis

The pathology in the central nervous system is 'central chromatolysis', similar to that produced in nerve cell bodies with axonal damage: distended cell bodies with the smaller-than-normal nucleus being displaced to the periphery (Fig. 8.3). The brainstem nuclei are predominantly involved, especially those of the pontine reticular formation. The cerebral cortex is less affected. The posterior horn cells and cells of Clark's column of the spinal cord may be affected.

Niacin's role in the nervous system is as a nicotinamide, in which it forms a component of various nucleotides involved in enzymatic oxidative–reduction reactions, e.g., nicotinamide adenine dinucleotide (NAD) or its phosphorylated form (NADP). Energy failure can thus develop in metabolically active and dividing cells. Tryptophan is a precursor for both niacin and serotonin. In addition, niacin plays a role in lipid metabolism, lowering serum concentrations of low-density and very-low-density lipoproteins, and facilitates reverse cholesterol transport. It also has antioxidative activity and antithrombotic effects (Williams and Ramsden, 2007).

8.2.4. Diagnosis

Diagnosis is primarily clinical, recognizing patients at risk who have some of the clinical features. The abrupt response to niacin administration is helpful in confirming the diagnosis. Some centers provide for serum niacin determination. Also low levels of urinary excretion of *N*-methylnicotinamide and pyridone indicate niacin deficiency.

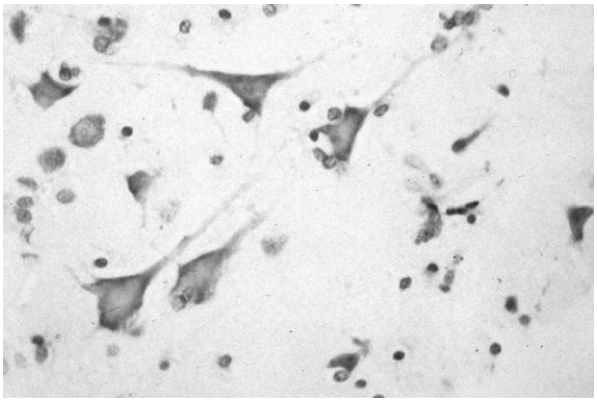

Fig. 8.3. Central chromatolysis (loss of Nissl substance, RNA) is apparent in cortical neurons (cresyl violet stain).

8.2.5. Management

Nicacin should be given along with other vitamins. Since vitamins B_2 and B_6 are involved in the synthesis of niacin from tryptophan, it is wise to give multiple B vitamins. Also, patients deficient in niacin may also be deficient in other B vitamins and nutrients.

8.3. Refeeding syndrome

8.3.1. Definition

'Refeeding syndrome' refers to a collection of neurological and systemic signs and symptoms that develop after an individual at risk is given nourishment containing carbohydrates. The condition was first recognized in malnourished prisoners of the Second World War, who developed heart failure and other problems when they were re-fed. The condition relates to shifts of electrolytes, including phosphate ion, intracellularly and profound changes in metabolic functions within cells. Although Wernicke's encephalopathy is not considered part of the syndrome, it sometimes complicates refeeding in malnourished patients.

8.3.2. Clinical features

The onset is typically delayed by several days from the time of onset of parenteral or enteral feeding. (Kaganski et al., 2005 found the mean time to be 10 days in a large group of elderly patients, but onset ranged from a day to more than 100 days.)

Neurologically, patients develop a nonspecific encephalopathy that includes disturbed consciousness ranging from delirium to coma, tetany, postural–action tremor, myoclonus (typically multifocal), and convulsive seizures. Profound muscular weakness, sometimes involving respiratory muscles, can also occur.

Systemically cardiac failure, due to acute cardiomyopathy, may develop. Rhabdomyolysis contributes to muscular weakness and renal impairment. Clotting deficiencies (related both to thrombocytopenia-impaired platelet contractility), hemolysis, superimposed infections (contributed to by white blood cell dysfunction) and, over a longer time, osteomalacia can occur. Elderly patients with severe hypophosphatemia have a higher mortality rate than those with less severe electrolyte disturbances (Kaganski et al., 2005).

The main risk factor appears to be undernutrition (e.g., patients with anorexia nervosa, persons with prolonged fasting, alcoholics, cancer victims, patients with dysphagia, postoperative patients, and those with intestinal bypasses for obesity) but the following conditions occur with greater frequency than in unaffected patients: sepsis, malignancy, diabetic ketoacidosis, and respiratory failure (Larsson et al., 1983; Haglin et al., 1999). Patients given intravenous glucose infusions are at greater risk (Kaganski et al., 2005) than those given enteral feedings.

8.3.3. Epidemiology

Hypophosphatemia, a reasonable marker of the refeeding syndrome or those at risk for it, occurs in between 3% and 42% of hospitalized patients but is highest in those with infections and the critically ill (Halevy and Bulvik, 1988). Kaganski et al. (2005) found that 14.1% of 2307 acutely hospitalized, elderly patients developed hypophosphatemia (serum phosphate $\leq$0.77 mmol/l), which was severe (serum phosphate $\leq$0.45 mmol/l) in 4.1%.

8.3.4. Pathogenesis

During starvation intracellular proteins and fats are metabolized; this results in a loss of intracellular electrolytes, including phosphate. During refeeding with carbohydrates, the increased insulin secretion drives phosphate intracellularly, with a relative switch from fat to carbohydrate metabolism. Other electrolytes, including magnesium, calcium, and potassium ions, also shift intracellularly. There is a relative paucity of phosphate for all its numerous intracellular purposes: generation of high-energy phosphate compounds (used as an energy source for numerous intracellular and cell membrane activities, including the sodium–potassium pump), glycolysis, generation of 2-3-diphosphoglycerate (involved in the dissociation of oxygen from hemoglobin: the deficiency limits oxygen release in capillaries), muscle contraction, leukocyte, and platelet function. The main result is an energy failure with all its resultant effects on brain, muscle, and heart; the ability to fight infection and to perform hemostasis is also impaired in the short term; problems with building proteins, bone, etc. are issues for the long term. Specific problems with hypophosphatemia, hypocalcemia, hypomagnesemia, and renal failure are dealt with in Chapter 7.

8.3.5. Diagnosis

The diagnosis can be made with the clinical features, especially multisystem dysfunction in the context of malnutrition (substantiated by low serum prealbumin concentration), and the presence of significant hypophosphatemia, hypomagnesemia, and hypokalemia. Even more importantly, it is wise to anticipate the development of the syndrome in high-risk patients, to pretreat with phosphate and thiamine, to begin refeeding gradually and to monitor electrolytes, especially serum phosphate. This should help to lessen mortality.

8.3.6. Management

Management of the established syndrome involves giving the depleted minerals and vitamins. There are no evidence-based guidelines for this, but phosphate supplementation should be given with serum concentrations of less than 0.5 mmol/l (1.5 mg/dl). A phosphate dose of 1–3 g/d in adults is usually needed with severe cases. Oral administration can be associated with gastric irritation and diarrhea. If given intravenously it is better to use saline or glucose rather than lactated Ringer's solution, as the latter contains ionic calcium, which can cause a precipitate with phosphate. Magnesium, potassium, and thiamine supplementation are also usually necessary or advisable.

8.4. Marchiafava–Bignami disease

8.4.1. Definition

Marchiafava–Bignami disease, the least understood of nutritionally related disorders, is an acute or subacute illness associated with demyelination or necrosis within the corpus callosum, in the context of alcoholism and/or nutritional deficiency. It must be differentiated from other causes of callosal lesions, including trauma (diffuse axonal injury), necrotizing hemorrhagic leukoencephalopathy, extrapontine myelinolysis related to rapid correction of hyponatremia, carbon monoxide poisoning, delayed hypoxic damage, status epilepticus with transient splenial lesions, multiple sclerosis, gliomas, infarction, or bleeding, lymphoma, and Binswanger's disease (Young, 1998).

8.4.2. Clinical–radiological features

Heinrich et al. (2004) suggest, based on a systematic review of all published cases, that there are two categories of presentation. Type A presents with impairment of consciousness (stupor or coma), pyramidal tract findings, and hypertonia. A few had convulsive seizures. Some had a prodromal period of cognitive impairment and gait disturbance. This group had a mortality of 21% within a mean of 15 days. Cognitive impairment, dysarthria, and disconnection syndromes

were noted in survivors but recovery from tetraparesis and gait dysfunction was the rule. Type A patients had hyperintense swelling, on T_2-weighted images, throughout the corpus callosum in the acute stage and tended to have T_1-hypointense cystic–necrotic callosal lesions on follow-up (Heinrich et al., 2004). Extracallosal (periventricular white matter or basal ganglia) lesions were noted in 47% of these cases.

The 'B type' lacked impairment of consciousness but had some cognitive impairment, gait disturbance, signs of interhemispheric disconnection, and limb hypertonia; however, seizures and pyramidal signs were less common than in the A group. Such patients had less prominent callosal lesions on CT and MRI, usually confined to the genu or splenium. None died and residual neurological handicaps were less marked than in the A group.

MRI has greatly facilitated the diagnosis of Marchiafava–Bignami disease (Hlaihel et al., 2005; Menegon et al., 2005). In the acute phase, conventional MRI shows decreased T_1 and increased T_2 signal, within the central portion of the corpus callosum, usually in the body, but the lesion can extend to the genu, splenium, or even into the surrounding white and gray matter structures (Fig. 8.4). The subcortical U-fibers are spared, but there may be cortical involvement. Hyperintensity on diffusion-weighted images (DWI) and FLAIR, with reduction in apparent diffusion coefficient (ADC), are more helpful in making the diagnosis. Recently, tensor imaging has allowed visualization of the disruption of fiber bundles within the body of the corpus callosum (Sair et al., 2006). Patients with more extensive lesions tend to do much worse than those with more limited lesions. After several weeks the DWI, FLAIR, and ADC changes disappear and are replaced by atrophy of the previously affected structures.

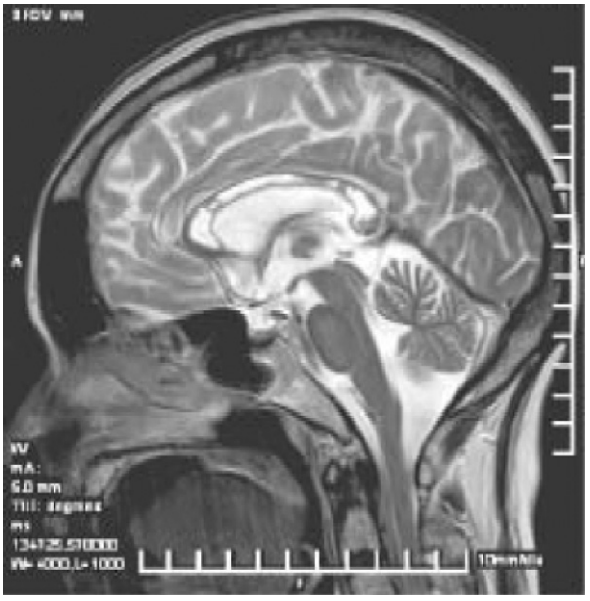

Fig. 8.4. T-2-weighted MRI with hyperintense signal in most of the central portion of the corpus callosum in a case of Marchiafava-Bignami disease (with permission from Goswani P, Medhi N, Sharma PK, et al. MRI findings in Marchiafava-Bignami disease with central pontine myelinolysis: a case report. Ind J Rafiol Imag 2006;16:4: 779–781.)

8.4.3. Pathology and pathogenesis

Autopsy cases typically reveal necrosis and cavitation of the central portion of the corpus callosum, with surrounding reactive gliosis. Neovascularization in the surrounding tissue is present if the patient has survived for a sufficient period. Extracallosal white matter lesions have been described in the corona radiata (but sparing the subcortical arcuate fibers and the internal capsules), the anterior and posterior commissures, the optic chiasm, the superior and inferior cerebellar peduncles, and the posterior columns of the spinal cord (Young, 1998). Neuronal loss in layers 3 and 5 of the neocortex probably relates to transsynaptic degeneration due to loss of commissural connections.

The pathogenesis and etiology are unclear. There is an incomplete association with alcoholism and most patients are malnourished. Some have proposed that the central portion of the corpus callosum is more vulnerable as it is more metabolically active (there is a higher rate of protein turnover). An analogy has been made with cyanide poisoning, in which similar callosal lesions occur, and metabolic (mitochondrial) dysfunction of oligodendroglia is proposed. Inflammatory mediators, including tumor necrosis factor (TNF)-alpha and interleukin-1, are expressed in the glial cells of the corpus callosum; these could be activated by various triggers, causing breakdown of the blood–brain barrier (Tchelingerian et al., 1993). In a rat glioma model, intravenous TNF injection was followed by callosal necrosis similar to that seen in Marchiafava–Bignami disease. However, intravenous injection of TNF by itself does not cause the lesion (Kido et al., 1991). This suggests that an initial lesion or blood–brain barrier disruption is needed for cytokines to play a role. Further work is clearly required.

8.4.4. Management

Since the etiology and pathogenesis are unknown, there is no specific prevention or treatment. It is reasonable to offer supportive care, nutritional supplementation, and prompt treatment of infections and inflammation. There are several case reports of milder cases with recovery after treatment with thiamine,

multivitamins, or steroids (Kinoshita et al., 2004; Staszewski et al., 2006). It is unclear whether there was direct benefit or whether milder cases without necrosis can recover spontaneously.

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Chapter 9

Coma induced by intoxication

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Intoxication is a frequent cause of coma, accounting for approximately 30% of all patients presenting to the emergency department with coma of unknown origin (Gallagher, 2002).

The prognosis of the patient is mainly determined by early diagnosis and appropriate therapeutic interventions and by the type of toxin. In this chapter a comprehensive approach of the comatose patient with suspected poisoning will be discussed. This survey, however, is not intended to be a substitute for consultation with a clinical toxicologist qualified in the diagnosis and treatment of poisoned patients.

9.1. Pathophysiology

Numerous substances are capable of producing coma and they can be classified into two groups: agents that produce coma through a direct effect on brain cells and agents with which coma is an indirect result of derangements involving other organ systems (Table 9.1) (Kostic and Dart, 2004).

Examples of direct-acting neurotoxins include agents that increase gamma-aminobutyric acid (GABA) effects such as benzodiazepines, alcohols, barbiturates, and gamma-hydroxybutyric acid (Chebib and Johnston, 1999). $GABA_A$ receptors are the primary mediators of inhibitory neurotransmission in the brain. The $GABA_A$ receptor is a pentameric structure composed of varying polypeptide subunits associated with a chloride channel on the postsynaptic membrane. Sedative–hypnotics alter the function of the chloride channel by increasing either its frequency or duration of opening. Indirect-acting agonists, such as benzodiazepines, require the presence of GABA to affect the channel. Other agents, such as barbiturates, can directly open the channel at high doses without the presence of GABA. This may explain the relatively high mortality seen with barbiturate overdoses compared to benzodiazepine overdoses. Many sedative–hypnotics, such as barbiturates, alcohols, and trichloroethanol, also decrease the effects of glutamate-mediated excitatory neurotransmission by interaction with the *N*-methyl-D-aspartate (NMDA) receptors (Zhu et al., 1997). Gamma-hydroxybutyric acid also has affinity for inhibitory presynaptic $GABA_B$ and opioid receptors. In addition, there is evidence to suggest that there are also specific gamma-hydroxybutyric acid receptor sites (Wong et al., 2004). Agents with anticholinergic properties, such as H_1 antihistamines, tricyclic antidepressants, and neuroleptics, induce coma by antagonism at the central muscarinic acetylcholine receptors. H_1 antihistamines and neuroleptics also produce central nervous system (CNS) depression due to inhibition of central histamine H_1 receptors (Simons and Simons, 1994; Parsons and Buckley, 1997; Bateman, 2005).

Opioids produce sedation by their effect on μ and κ receptors, which belong to the family of G-protein-coupled receptors and inhibit adenylate cyclase, so reducing the intracellular cyclic adenosine monophosphate content (Dhawan et al., 1996). These receptors also exert effects on ion channels through a direct G-protein coupling to the channel. By these means, opioids promote the opening of potassium channels and inhibit the opening of voltage-gated calcium channels. These membrane effects reduce both neuronal excitability and transmitter release, resulting in an overall inhibitory effect at the cellular level.

Cyanide causes direct neurotoxicity by binding to the ferric ions of cytochrome a_3, an integral component of the third and final cytochrome oxidase enzyme in the mitochondrial electron transport chain (Gracia

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Table 9.1

Nonexclusive list of substances that may be involved in coma due to poisoning classified according to their mechanism

Direct effect on the brain	Indirect effect on the brain
Anticholinergic agents	Antiarrhythmics
Barbiturates	Antihypertensives
Benzodiazepines	Carbon monoxide
Carbamazepine	Gases and fumes
Carbon monoxide	Insulin
Cyanide	Methemoglobin-forming agents
Ethanol	Oral hypoglycemic drugs
Ethylene glycol	
Gamma-hydroxybutyric acid	
Glutethimide	
H_1 antihistamines	
Hydrogen sulfide	
Lithium	
Monoamine oxidase inhibitors	
Methanol	
Neuroleptics	
Opioids	
Organophosphates	
Phenytoin	
Presynaptic alpha-2-receptor agonists	
Salicylates	
Selective serotonin reuptake inhibitors	
Trichloroethanol	
Tricyclic antidepressants	
Valproic acid	

and Shepherd, 2004). Once bound, the enzyme becomes inactivated and oxidative phosphorylation is blocked. Cells are thus deprived of their major energy source. The inhibition of oxidative phosphorylation results in widespread metabolic derangements. Adenosine triphosphate (ATP) is consumed by active cells but very little can be produced. Tissues quickly exhaust their supply of ATP. Furthermore, hydrogen ions that are generated by ATP hydrolysis begin to accumulate because they can no longer be recycled back into the process of ATP formation, resulting in metabolic acidosis. The result of these intracellular derangements is cellular dysfunction and ultimately cell death if cytochrome inhibition persists. Cyanide also induces cellular oxidative stress, possibly through inhibition of antioxidant enzymes such as catalase, glutathione dehydrogenase, glutathione reductase, or superoxide dismutase. Cyanide-induced lipid peroxidation occurs to the greatest extent in the brain, which explains the predominance of neurological findings in patients with cyanide poisoning. There is also compelling evidence that cyanide neurotoxicity is mediated by glutamate release, leading to increased cytosolic calcium and cell death.

Hydrogen sulfide's toxicity results from its potent inhibition of cytochrome oxidase, thereby interrupting oxidative phosphorylation. Like cyanide, hydrogen sulfide binds to the ferric moiety of cytochrome a_3 oxidase complex. The resulting inhibition of oxidative phosphorylation produces cellular hypoxia (Smith and Gosselin, 1979).

The second group of agents are those for which coma is an indirect result of derangements involving other organ systems. Examples of indirect agents include those causing hypoxia, such as methemoglobin-forming agents, or agents that decrease oxygen delivery to cells via hypoperfusion, such as antiarrhythmic and antihypertensive drugs.

Carbon monoxide (CO) is an example of a substance producing coma via a combination of systemic effects and direct cellular toxicity (Jaffe, 1997). CO's most obvious effect is binding to hemoglobin, rendering it incapable of delivering oxygen to the cells as the affinity for hemoglobin is 200–250 times greater than that of oxygen. Direct cellular toxicity is caused by cytochrome oxidase inactivation accompanied by ischemic–reperfusion injury. Animal studies suggest that CO poisoning may also cause glutamate increases in the brain, resulting in intracellular calcium release and neuronal cell death.

9.2. General approach during the first few minutes

9.2.1. Safety

Before any rescue attempts are undertaken, the rescuer's safety should be guaranteed. This is especially important for gas intoxications (e.g., CO, hydrogen sulfide) as there may still be gas present in the air. Some toxic agents (e.g., organophosphates) may be absorbed through the skin and mucosa and may intoxicate the health-care provider when in contact with the patient without taking protective measures. In case of an illegal drug overdose, the rescuer should always be alert for the presence of intravenous needles to avoid needle stick injuries.

9.2.2. Primary assessment and resuscitation

Irrespective of the cause of coma, primary assessment requires identification and treatment of life-threatening conditions (Advanced Life Support Group, 2001;

Mokhlesi et al., 2003; Hack and Hoffman, 2004; Huff, 2004; Greene et al., 2005; International Liaison Committee on Resuscitation, 2005a, b). The primary assessment should be repeated following emergency treatment and with any further deterioration in the patient's condition. The importance of these measures cannot be overemphasized. In many cases, coma induced by poisoning has a good prognosis provided secondary damage due to hypoxia, hypoperfusion and sepsis is avoided.

In order not to overlook life-threatening conditions a structured approach to the comatose patient is given below. However, as illustrated at the end of this section, management will often also be guided by the underlying etiology. The aim of the primary assessment is to identify and treat all immediately life-threatening conditions.

Key components of the primary assessment (ABCDE) are:

A. Airway and oxygen administration
B. Breathing
C. Circulation
D. Disability
E. Exposure.

9.2.2.1. A: Airway and oxygen administration

All agents causing CNS depression may compromise airway patency. Improper or nonaggressive airway management may lead to anoxic brain injury and/or aspiration. Airway patency may be assessed by evaluating the patient's verbal response to questions. A patient answering appropriately indicates an open airway, the presence of breathing and adequate cerebral perfusion. If the patient remains unresponsive, the airway should be opened with the head tilt–chin lift maneuver. However, if a neck injury cannot be excluded (see below), cervical immobilization should be maintained; the jaw thrust technique is the safest approach to control the airway. The mouth should be inspected for foreign bodies. Removing liquid (blood, saliva, and gastric contents) from the upper airway using a suction device may be necessary to clear the airway. However, this should be done cautiously if the patient has an intact gag reflex, as the suction device can provoke vomiting. Oropharyngeal airway cannulas are curved plastic tubes that fit between the tongue and the hard palate and are often helpful to improve or maintain airway patency in the unconscious patient. These devices should not be used in patients with preserved glossopharyngeal and laryngeal reflexes as insertion may cause vomiting and laryngospasm (International Liaison Committee on Resuscitation, 2005a, b). The recovery position may be used in unresponsive and spontaneously breathing patients to avoid airway obstruction by the tongue or mucus and vomit. Indications for orotracheal intubation in comatose patients are the presence of apnea or bradypnea related to deep coma and/or vomiting (International Liaison Committee on Resuscitation, 2005b). It should be noted that deep coma as such, often defined as the presence of a Glasgow Coma Scale (GCS) lower than 8, is not an absolute criterion for intubation (see examples at the end of this section) and that the score intended for head trauma has never been validated in intoxications (Chan et al., 1993). Once control of the airway has been achieved supplemental oxygen should be delivered.

9.2.2.2. B: Breathing

To assess breathing, one should maintain an open airway and subsequently look for chest movements, listen for breathing sounds and feel for expired air.

If there are signs of inadequacy, ventilation through a mask or an orotracheal tube is needed (Advanced Life Support Group, 2001). Respiratory depression and bradypnea may occur in opioids and sedative–hypnotic overdose. Hyperventilation is observed in poisoning with salicylates and during the initial stage of any cause of hypoxia such as CO and cyanide poisoning; if left untreated, these ultimately result in respiratory failure. Cheyne–Stokes respiration, defined as alternating hyperpnea and apnea, is rarely observed in poisoned patients; it rather indicates the presence of a structural lesion at the level of the midbrain, infection, cardiopulmonary disease, or other metabolic disorders.

Hypoxemia can easily be detected with pulse oximetry. However, one should realize that pulse oximeters are unable to detect hypercarbia, which may result from hypoventilation. Pulse oximeters are also totally unreliable in CO poisoning since the apparatus cannot distinguish between oxyhemoglobin and carboxyhemoglobin.

9.2.2.3. C: Circulation

The patient's hemodynamic status should be assessed by checking for an arterial pulse, ideally the carotid, for rate, rhythm, and character. Blood pressure should be measured and peripheral perfusion should be assessed using capillary refill time. Patients should be connected to a cardiac monitor, and urinary catheterization is necessary for all unconscious patients to follow urine output.

In case of cardiac arrest, resuscitation should be started at once. Cardiac arrest may be due to a direct toxic effect on the heart or a severe metabolic disturbance or may be secondary to a respiratory arrest.

Examples of drugs that can cause a cardiac arrest through a direct effect on the heart include the tricyclic antidepressants, chloral hydrate, and the phenothiazines. Calcium antagonists, beta-adrenergic antagonists, vasodilators, and any negative inotropic drug in overdose may also cause cardiovascular collapse leading to cardiac arrest. Particularly in young patients, resuscitation for a prolonged period should be considered as the poison may be metabolized or excreted during extended life support measures (International Liaison Committee on Resuscitation, 2005b).

Hemodynamic shock can impair consciousness due to reduced cerebral perfusion. Malignant tachyarrhythmias resulting in hypotension may be observed in intoxications with tricyclic antidepressants or theophylline. Bradyarrhythmias and hypotension may result from an overdose of beta-adrenoceptor antagonists, digoxin, and clonidine. Intravenous access has to be established and shock should be treated appropriately with, for instance, intravenous fluids and vasopressors to prevent secondary brain injury and other organ failures. Cardiovascular collapse following overdose with beta-adrenergic or calcium antagonists requires specific antidote therapy, e.g., glucagon and calcium (Dewitt and Waksman, 2004).

9.2.2.4. D: Disability

The initial neurological assessment should be a rapid evaluation of the Glasgow Coma Score and the pupils (size, equality and reaction to light). The AVPU (Alert/Verbal/Painful/Unresponsive) responsiveness scale provides a more rapid and simple alternative to the GCS in assessing consciousness level in most poisoned patients (Kelly and Upex, 2004). It should be noted that both scales are difficult to use in uncooperative patients, e.g., ethanol-intoxicated patients.

During this phase, the crucial question should arise whether the coma is really due to intoxication. Indeed, causes of coma may be of toxicological, metabolic, infectious, neurological with structural changes or psychiatric nature. Life-threatening conditions should be looked for, such as hypoglycemia, meningitis, epilepsy, and opioid poisoning, and treated appropriately. Hypoglycemia may result not only from insulin and oral hypoglycemic poisoning but also from intoxication with ethanol (more common in young children), paracetamol/acetaminophen, and salicylates. Confirming hypoglycemia can easily be done and should be routine in every comatose patient. Rapid bedside tests are available but it should be remembered that the apparatus may not always be accurate at lower glucose levels. Furthermore, diabetic patients may experience glycopenic symptoms at lower but still normal glucose levels (Boyle et al., 1988). The treatment of hypoglycemia is discussed below.

Signs of recent head trauma (e.g., abrasions, contusions and hematoma) or the presence of lateralizing or asymmetrical neurological findings should prompt an immediate search for a structural lesion. Bilateral orbital hematoma (raccoon eyes) and ecchymosis behind the ear (Battle's sign) may indicate a skull fracture. Focal findings on examination greatly reduce the likelihood of toxic etiology alone. One should always keep in mind that a patient may have more than one cause of coma. For instance, poisoning with CNS depressants may result in a fall, leading to a traumatic subdural hematoma.

The pupils may provide important information in establishing a diagnosis. Many medical textbooks state that, in coma caused by a toxic–metabolic process, the integrity of the pupillary light reflex remains intact. Exceptions include anoxia, hypothermia, and intoxication with anticholinergics, barbiturates, cholinergics, glutethimide, or opioids (Kostic and Dart, 2004). In a prospective study the loss of the light reflex and anisocoria were independent predictors for structural causes of coma, with sensitivity and specificity for loss of light reflex of 83% and 77% respectively (likelihood ratio 3.56) and for anisocoria of 39% and 96% respectively (likelihood ratio 9); this means, however, that in 23% of patients with coma of metabolic–toxic origin light reflex was absent (Tokuda et al., 2003). Pupils that are equal, pinpoint, and fixed may be observed in intoxications with opioids and organophosphates, and should be differentiated from pontine lesions. Equal, dilated, and reactive pupils can be seen in methylenedioxymethamphetamine (MDMA) and amfetamine users but may also result from metabolic disturbances or midbrain lesions. Equal, dilated, and fixed pupils may occur in anticholinergic poisoning but also in hypoxemia, hypothermia, and in the peri-ictal phase. Meningeal irritation should be checked if there are no contraindications to mobilization of the spine.

9.2.2.5. E: Exposure

The patient must be fully exposed to allow complete assessment, and the body temperature must be measured. Hypothermia is an important cause of coma. Factors predisposing to hypothermia are CNS depression and immobilization, which may be observed following an overdose with, for instance, sedatives. In the urban setting, alcohol intoxication is the most common predisposing factor to hypothermia. The mechanism by which ethanol predisposes to hypothermia is probably based on its depressive effects on the CNS, vasodilation and blunting of behavioral responses

to cold. Hyperthermia accompanying decreased consciousness may indicate the presence of a serotonergic syndrome, a neuroleptic malignant syndrome (NMS), or intoxication with CNS stimulants such as cocaine and amphetamines.

Important information can be obtained by contacting relatives and friends and by searching the patient's clothes for useful information such as medical cards and drugs.

At the end of the primary assessment the potential lethality of the overdose should be assessed. This requires knowledge of the substance, the time of intake and the dose. It often happens, however, that information about these three key elements is not available or not reliable, and in this case one should always keep a high suspicion of a potentially lethal intoxication.

9.2.3. Etiology-oriented approach

In a comatose patient with respiratory depression, etiological clues of a heroin overdose should immediately alert the rescuer to watch carefully for needles to avoid stick injuries. Initial airway management will consist of oxygenation and bag mask ventilation followed by administration of the antidote naloxone rather than immediately performing orotracheal intubation (see below).

A comatose, spontaneously breathing patient with a history of insulin-dependent diabetes mellitus should immediately prompt the rescuer to exclude hypoglycemia and, if needed, the intravenous administration of glucose (see below). Except for providing a patent airway, additional airway management maneuvers will usually not be needed.

Respiratory insufficiency in a patient with an organophosphate poisoning must be managed by immediate orotracheal intubation and appropriate antidotal treatment. Protective safety measures for the rescuer are very important as organophosphates may be absorbed through the skin.

CO poisoning poses an important safety risk to rescuers. Carrying a CO detector is an important safety measure. The mainstay of treatment of comatose patients from CO poisoning is attention to the airway and oxygenation: 100% oxygen should be provided as soon as possible by mask reservoir, followed if necessary by endotracheal tube, and the patient should be transferred to a hospital with hyperbaric oxygen therapy facilities (see below).

Most patients comatose from barbiturate poisoning require definite airway protection by orotracheal intubation and ventilatory support because of the expected prolonged, profound coma. Conversely, uncomplicated coma induced by benzodiazepines and/or alcohol can often be managed by providing oxygen and a free airway and positioning the patient in the recovery position under close monitoring. For benzodiazepines, the use of the antidote flumazenil can be considered under rare conditions (see below).

9.3. Secondary assessments

The secondary assessment should only be done once the immediately life-threatening conditions have been treated. In most cases, a complete history-taking and thorough clinical examination will result in identification of the substance taken (Olson et al., 1987). Important information can also be obtained by anamnesis of the patient's surroundings and by searching for, for example, (empty) drug blisters. Identifying the toxic substance by clinical examination requires profound knowledge of the different toxidromes.

9.3.1. Neurological examination

As part of the primary assessment, one should try to determine the cause of coma, as a rapid diagnosis may be important for the prognosis of the patient's neurological outcome. Subsequently, during the secondary assessment, a careful neurological assessment should be performed to further distinguish between a toxic–metabolic cause for coma and structural neurological causes, e.g., a cerebrovascular accident, or an epi- or subdural hematoma. At this stage, the role of a thorough neurological clinical examination is of pivotal importance. Examination of pupillary reactivity, motor responses to noxious stimuli and ocular movements are of paramount importance to differentiate between these two entities (Gallagher, 2002; Wolfe and Brown, 2002; Kostic and Dart, 2004).

As already mentioned above, pupil size and the reaction to light may provide valuable information. Dysconjugate gaze in the horizontal plane is normally observed in drowsiness and in various sedated states, including alcohol intoxication, with parallel ocular axes re-emerging when the patient awakens or slips deeper into coma. Dysconjugate gaze in the vertical plane, called skew deviation, generally results from pontine or cerebellar lesions. Sustained conjugate upward gaze is usually the result of hypoxic encephalopathy.

Focal or asymmetric findings in motor responses to a noxious stimulus should invoke a search for a structural lesion. There are, however, exceptions to this generalization. For instance, mass lesions of the brain may cause compression of the brainstem bilaterally resulting in bilateral and symmetric neurological deficit. Some toxic–metabolic conditions such as hyperosmolar nonketotic hyperglycemia or hypoglycemia

may produce focal deficits. Different metabolic demands in different brain regions and circulation defects have been suggested as the causes of hypoglycemia-related stroke-like episodes (Gold and Marshall, 1996). Focal neurological signs observed in hyperosmolar nonketotic hyperglycemia have been hypothesized to be secondary to effects of hyperosmolality on the brain resulting in focal regions of brain edema and reactivation of previously resolved neurological deficits.

The presence of oculocephalic and oculovestibular reflexes also helps in differentiating toxic from structural causes of coma. The oculocephalic reflex (doll's eye movements) implies conjugate eye movement away from the direction of rotation. This maneuver is strictly contraindicated when there is a possibility of cervical instability. The oculovestibular reflex, which involves cold water irrigation of the tympanic membrane, produces transient conjugate slow deviation of gaze toward the side of the stimulus (brainstem-mediated) followed by a quick saccadic correction back to the midline (cortically mediated). As the hallmark of a toxic–metabolic coma is a dissociation of findings, these reflexes should be paired with other findings such as pupillary reactivity. For instance, with respect to pupillary reactivity, this means that pupillary reactivity is dissociated from other neuraxis dysfunction in a fashion that is not characteristic of structural brain disease. Thus, in addition to symmetric findings, patients whose coma originates from a toxicological or metabolic cause typically have an intact and equal pupillary light reflex that may be paired with an absent oculovestibular response, an absent motor response to noxious stimuli, or hypoventilation requiring ventilatory support. This phenomenon of dissociation occurs with toxic–metabolic coma because other brainstem functions tend to be far more vulnerable to toxic and metabolic insult than are the pupillary light reflexes. It is important to note that, in contrast with coma caused by structural disease, in coma caused by a toxic–metabolic process there is symmetry in either response or nonresponse to provocative maneuvers.

Seizures caused by drugs and toxins are mostly of the generalized tonic–clonic variety unless there is underlying focal neurological disease or epilepsy. Seizures may result from a direct reduction of seizure threshold or from secondary events such as hypoxia. Toxin-induced seizures are most commonly caused by tricyclic antidepressants and sympathomimetic or anticholinergic agents. Seizures as part of an alcohol or benzodiazepine withdrawal syndrome are also frequently observed (Pétursson, 1994; Schuckit et al., 1995).

Clonus is caused by a variety of substances, most commonly sedative–hypnotics and anticonvulsants. Rigidity, clonus, hyperreflexia, and tremor are seen with lithium poisoning.

Serotonin syndrome and NMS typically have a motor component combined with altered mental status and hyperthermia. The key differences between the two syndromes are shown in Table 9.2. The serotonin syndrome is an adverse drug reaction resulting from excessive serotonergic neurotransmission following therapeutic drug use (rare when only one serotonergic drug is used), intentional self-poisoning or inadvertent interactions between drugs such as selective serotonin reuptake inhibitors, serotonin precursors such as tryptophan, serotonin agonists such as the triptans, serotonin releasers such as amphetamines, tricyclic antidepressants, and MAO inhibitors (Boyer and Shannon, 2005). NMS is an idiosyncratic reaction to antipsychotic agents. There are also case reports of other medications causing NMS, including venlafaxine, promethazine, metoclopramide, and prochlorperazine. NMS is believed to result from CNS dopamine receptor blockade or withdrawal of exogenous dopaminergic agonists. NMS can also develop in patients with Parkinson's disease following withdrawal of levodopa therapy. The probability of developing NMS is directly related to the antidopaminergic potency of the neuroleptic agent.

Table 9.2

Key differences between serotonin and neuroleptic malignant syndrome

Feature	Serotonin syndrome	Neuroleptic malignant syndrome
Neuroleptic drugs	0	+++
Serotonergic drugs	+++	0
Hyperactivity	+++	0
Clonus	+++	0
Tremor	+++	+
Shivering	+++	0
Hyperreflexia	+++	0
Rapid onset	+++	0
Leaden rigidity	0	+++
Bradykinesia	0	+++
Stupor/mutism	+	+++
Creatine phosphokinase activity	++	+++
Hallucinations	+	++
Hyperthermia	++	++

Source: adapted from Richards and Aronson, 2005.

9.3.2. Toxidromes

The identification of specific toxidromes may be helpful in establishing a diagnosis when the exposure is not well defined (Hack and Hoffman, 2004). These are grouped, physiologically based abnormalities of vital signs, general appearance, skin, eyes, mucous membranes, and pulmonary, cardiovascular, gastrointestinal, and neurological systems that are known to occur with specific classes of substances such as anticholinergic, cholinergic, sympathomimetic, and opioid agents (Table 9.3). The list of representative agents in the table is not exclusive. One should always remember that the actual clinical manifestations of an ingestion or exposure are far more variable than the syndromes described in the table.

Table 9.3

Toxidromes

Toxidrome	Mental status	Pupils	Vital signs	Other symptoms	Representative agents
Sympathomimetic	Hyperalertness Agitation Hallucinations Paranoia	Mydriasis	Hyperthermia Tachycardia Hypertension Tachypnea Hyperpnea	Diaphoresis Tremor Hyperreflexia Seizures	Cocaine Amphetamines Ephedrine Pseudo-ephedrine Phenylpropanolamine Theophylline Caffeine
Anticholinergic	Hyperalertness Agitation Hallucinations Delirium Mumbling speech Coma	Mydriasis	Hyperthermia Tachycardia Hypertension Tachypnea	Flushing Dry skin Dry mucosa Blurred vision Decreased bowel sounds Urinary retention Myoclonus Choreoathetosis Seizures	H_1 antihistamines Tricyclic antidepressants Antiparkinson drugs Antispasmodic drugs Phenothiazines Atropine Scopolamine Belladonna alkaloids
Hallucinogenic	Hallucinations Distortion of perception Depersonalization Agitation	Mydriasis (usually)	Hyperthermia Tachycardia Hypertension Tachypnea	Nystagmus	Phencyclidine LSD Mescaline Psilocybin Amphetamines (e.g., MDMA, MDEA)
Opioids	CNS depression Coma	Miosis	Hypothermia Bradycardia Hypotension Hypopnea Bradypnea	Hyporeflexia Lung edema Decreased bowel sounds Needle track marks	Opioids (e.g., heroin, morphine, methadone, oxycodone, hydromorphone) Diphenoxylate
Sedative/hypnotic	Confusion Sedation Stupor Coma Slurred speech Ataxia	Miosis (usually)	Hypothermia Bradycardia Hypotension Hypopnea Bradypnea	Hyporeflexia	Benzodiazepines Zolpidem Barbiturates Alcohol
	Combativeness interspersed with obtundation Sudden awakening	Variable			Gamma-hydroxybutyrate

(Continued)

Table 9.3

(Continued)

Toxidrome	Mental status	Pupils	Vital signs	Other symptoms	Representative agents
Cholinergic	Confusion Coma	Miosis	Bradycardia (initially tachycardia) Hypertension or hypotension Tachypnea or bradypnea	Salivation Urination Defecation (diarrhea) Diaphoresis Lacrimation Abdominal cramps Bronchoconstriction Bronchorrhea Muscle weakness and fasciculations Seizures	Organophosphates Nerve agents Nicotine Pilocarpine Physostigmine Edrophonium Bethanechol Urecholine
Serotonin syndrome	Confusion Agitation Coma	Mydriasis	Hyperthermia Tachycardia Hypertension Tachypnea	Tremor Myoclonus Hyperreflexia Clonus Diaphoresis Flushes Jaw stiffness Muscle stiffness Diarrhea	SSRIs, serotonin precursors (tryptophan), serotonin agonists (e.g., triptans), serotonin releasers (e.g., MDMA), MAOIs, tricyclic antidepressants, others (e.g., dextromethorphan, lithium)
Tricyclic antidepressants	Confusion Agitation Coma	Mydriasis	Hyperthermia Tachycardia Hypertension followed by hypotension Hypopnea	Seizures Myoclonus Choreoathetosis Arrhythmia Conduction disorders	Amitriptyline Nortriptyline Imipramine Clomipramine Desipramine Doxepin

Source: adapted from Burns and Schwartzstein, 2005.

9.3.3. Odors and skin

Odors can provide useful hints, e.g., alcohol may indicate ethanol intoxication. An odor of acetone may accompany diabetic ketoacidosis, chloral hydrate, or isopropyl alcohol poisoning; the scent of bitter almonds with cyanide; and a garlic-like odor with organophosphates and arsenic.

Central cyanosis is a sign of hypoxia but methemoglobinemia may also cause a similar color. The 'cherry pink' skin color of carboxyhemoglobin is not always obvious and its absence does not exclude serious CO poisoning. Anticholinergics, alcohol, cocaine, cyanide, and borates may produce a flushed pink skin. The presence of track marks is often indicative of intravenous drug use and resultant opioids or sympathomimetic toxicity. Cutaneous bullae (coma blisters) may be found not only in barbiturate, glutethimide, and other sedative overdoses but also in tricyclic antidepressant and CO poisoning.

Bruises and hematoma indicate a traumatic injury, which may be due to violence. In this context, it should be mentioned that some drugs (e.g., gamma-hydroxybutyrate, flunitrazepam, ketamine) may be used to assist a sexual assault because of their sedative, muscle relaxant and amnestic properties, and are therefore called 'date rape drugs'.

Patients who have been lying in coma for a long time on a hard surface may develop cutaneous bullae and rhabdomyolysis due to pressure necrosis of the skin and muscles. This particularly affects muscles in compartments, leading to compartment syndrome and renal failure. The agents most often implicated are CO, alcohol, opioids, barbiturates, or other CNS depressants. Therefore, all extremities of coma patients should be inspected for edema, color change, or vascular deficit. Diagnosis of a

compartment syndrome can be established by measuring compartment pressures. Some agents such as cocaine and ethanol may induce rhabdomyolysis by direct toxic effects on the sarcoplasmic reticulum.

9.4. Decontamination procedures

Decontamination procedures have to be considered in the treatment for the poisoned patient. The procedures briefly discussed here are based on the guidelines published by the American Academy of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists.

In case of a potentially lethal overdose or if the exact nature of the overdose is not known, one should always consider measures to prevent or reduce toxic drug levels. This may be achieved by reducing drug absorption and/or enhancing drug elimination. Methods used to decrease drug absorption in the gastrointestinal tract are activated charcoal, gastric lavage, whole bowel irrigation, and therapeutic emesis. Procedures enhancing drug elimination include multiple doses of activated charcoal, therapeutic diuresis, urinary alkalinization, hemoperfusion, and hemodialysis.

Before initiating these procedures, consultation with a clinical toxicologist is advisable. In comatose patients, emesis is prohibited and gastric lavage and the administration of activated charcoal are contraindicated unless the patient has a secured airway by means of an orotracheal tube with inflated cuff.

9.4.1. Reducing absorption

9.4.1.1. Skin decontamination

Skin decontamination should always be considered upon toxic exposure of the skin (Began, 2002). Removal of the clothes is an important measure to prevent direct effects and systemic absorption of certain toxins, e.g., organophosphates. In general, a copious amount of water is the decontamination agent of choice for skin irrigation. Soap should be added when adherent materials are involved.

9.4.1.2. Gastrointestinal decontamination

9.4.1.2.1. Activated charcoal

Charcoal works by adsorbing ingested drugs on to its large surface area, and adsorbs 10% of its own weight. In most instances, 0.5–1 g/kg is an appropriate initial dose of activated charcoal; doses of 1.5–2 g/kg should be used following particularly massive or dangerous ingestions. In vitro studies show that ideal activated-charcoal-to-drug ratios vary widely, but 10:1 is a representative value for many typical drugs and is therefore useful in theoretical consideration of optimal activated charcoal dosing. Substances such as alcohols, lithium, and iron are not effectively adsorbed by activated charcoal. Based on volunteer studies, the administration of activated charcoal should be considered if a patient has ingested a potentially toxic amount of a poison (which is known to be adsorbed to charcoal) up to 1 hour previously (American Academy of Clinical Toxicology/European Association of Poison Centres and Clinical Toxicologists, 2005). Although volunteer studies demonstrate that the reduction of drug absorption decreases to values of questionable clinical importance when charcoal is administered after 1 hour, the potential for benefit after 1 hour cannot be excluded and charcoal administration should therefore still be considered in intoxications with large doses of toxic substances where delayed gastrointestinal absorption is possible (e.g., tricyclic antidepressants causing delayed gastric emptying due to anticholinergic effect, sustained-release preparations). In this respect, one should bear in mind that, unless a patient has an intact or protected airway, the administration of charcoal is contraindicated because of the risk of lung aspiration. Activated charcoal is also contraindicated if its use increases the risk and severity of aspiration, e.g., ingestion of a hydrocarbon with a high aspiration potential. Patients who are at risk of gastrointestinal hemorrhage or perforation due to medical conditions or recent surgery of the gastrointestinal tract could be further compromised by single-dose activated charcoal. Presence of activated charcoal in the gastrointestinal tract may obscure endoscopic visualization, but intoxication with a corrosive is not a contraindication for activated charcoal when it is administered for co-ingested agents that are systemic toxins.

Multiple-dose activated charcoal therapy involves the repeated administration (more than two doses) of oral activated charcoal to enhance the elimination of drugs already absorbed into the body. Multiple-dose activated charcoal is thought to produce its beneficial effect by interrupting the enteroenteric and, in some cases, enterohepatic and enterogastric circulation of drugs (American Academy of Clinical Toxicology/European Association of Poison Centres and Clinical Toxicologists, 1999). Based on experimental and clinical studies, multiple-dose activated charcoal should be considered only if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. The use of multiple-dose charcoal in salicylate poisoning is controversial.

Finally when weighting the advantages of activated charcoal against its disadvantages, it should be stressed that there is no evidence from randomized controlled trials that the administration of activated charcoal improves clinical outcome.

9.4.1.2.2. Gastric lavage

Gastric lavage should not be employed routinely, if ever, in the management of poisoned patients (American Academy of Clinical Toxicology/European Association of Poison Centres and Clinical Toxicologists, 2004c). The results of clinical outcome studies in overdose patients are weighted heavily on the side of showing a lack of beneficial effect. Serious risks of the procedure include hypoxia, arrhythmias, laryngospasm, perforation of the gastrointestinal tract or pharynx, fluid and electrolyte abnormalities, and aspiration pneumonitis. In comatose patients without a gag reflex endotracheal or nasotracheal intubation should always precede gastric lavage. Contraindications for gastric lavage include ingestion of a strong acid or alkali, ingestion of a hydrocarbon with a high aspiration potential, or risk of gastrointestinal hemorrhage due to an underlying medical or surgical condition. In situations where the procedure may be a reasonable treatment option, e.g., recent overdose with a life-threatening toxin such as tricyclic antidepressants, lithium, and organophosphates, the clinician should carefully examine the risk–benefit ratio. Gastric lavage is usually followed by the administration of activated charcoal.

9.4.1.2.3. Whole bowel irrigation

Whole bowel irrigation cleanses the bowel by the enteral administration of large amounts of an osmotically balanced polyethylene glycol electrolyte solution, which induces a liquid stool. It reduces drug absorption by decontaminating the entire gastrointestinal tract by physically expelling intraluminal contents. Whole bowel irrigation should be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs, particularly for those patients presenting more than 2 hours after drug ingestion (American Academy of Clinical Toxicology/European Association of Poison Centres and Clinical Toxicologists, 2004b). It should also be considered for the removal of ingested packets of illicit drugs in body packers. However, in case of a ruptured cocaine packet, emergency surgery is required, whereas in case of a ruptured heroin packet, the patient may be treated by a continuous naloxone infusion awaiting spontaneous elimination. Whole bowel irrigation is contraindicated in patients with bowel obstruction, perforation, or ileus and in patients with hemodynamic instability or compromised unprotected airways. The concurrent administration of activated charcoal and whole bowel irrigation may decrease the effectiveness of the charcoal.

9.4.1.2.4. Emesis

Apomorphine and salt water are outdated and dangerous emetics, and should no longer be used.

Syrup of ipecac has been used to promote active vomiting (American Academy of Clinical Toxicology/European Association of Poison Centres and Clinical Toxicologists, 2004a). There is, however, no evidence from clinical studies that ipecac improves the outcome of poisoned patients and its routine administration in the emergency department should be abandoned. Ipecac may delay the administration or reduce the effectiveness of activated charcoal, oral antidotes, and whole bowel irrigation. Ipecac should not be administered to a patient who has a decreased level or impending loss of consciousness or who has ingested a corrosive substance or hydrocarbon with high aspiration potential.

9.4.2. Increasing elimination

Measures to increase elimination include therapeutic diuresis, urinary alkalinization, hemoperfusion, and hemodialysis.

Forced diuresis by administration of large volumes of isotonic fluids and diuretics to increase renal excretion of a drug or metabolite is of limited clinical value. It is not recommended because of potential volume overload and electrolyte abnormalities.

Urinary alkalinization to enhance excretion of weak acids is achieved by the administration of intravenous sodium bicarbonate to produce urine with a pH $\geq$7.5 and may be beneficial for compounds such as salicylates and phenobarbital/primidone (Proudfoot et al., 2004). Side effects of urinary alkalinization are alkalemia and electrolyte disturbances such as hypokalemia and hypocalcemia.

Invasive techniques such as hemodialysis and hemoperfusion are reserved for elimination of specific life-threatening toxins (Cutler et al., 1987). Hemodialysis is particularly suited for drugs or metabolites that are water-soluble, have a low volume of distribution, have a molecular weight $<$500 Da and have low plasma protein binding, e.g., methanol, ethylene glycol, lithium, and salicylates. Hemoperfusion involves the passage of blood through an adsorptive-containing cartridge (usually resin or charcoal). This technique removes substances that have a high degree of plasma protein binding. Charcoal hemoperfusion may be indicated for intoxications with carbamazepine, phenobarbital, phenytoin, and theophylline. There are limited data available on drug removal by continuous arteriovenous (CAVH) or venovenous (CVVH) hemofiltration. Hemofiltration has been used to enhance elimination of aminoglycosides, vancomycin, and metal–chelate complexes but the technique does not remove highly protein-bound drugs effectively. It may also be of benefit for intoxications with drugs that have a large

volume of distribution, tight tissue binding, or slow intercompartmental transfer.

9.5. Further diagnostic approach

9.5.1. Electrocardiogram

A 12-lead ECG should be recorded in all patients with a potential risk of cardiac effects from their overdose or if rhythm disturbances are observed on cardiac monitoring. The electrocardiogram should be examined for rate and rhythm disturbance, ST changes indicative of ischemia, atrioventricular block, QRS and QT interval prolongation and right axis deviation. For instance, prolongation of the QRS duration >100 ms and/or right axis deviation of the terminal 40 ms of the QRS complex (terminal S wave in lead I and elevated R wave in lead aVR) following tricyclic antidepressant intoxication is a sign of potential cardiac toxicity (Liebelt and Francis, 2002). Poisoning with cardiac glycosides can present with almost any type of rhythm disturbance but frequently express a bradycardic rhythm with atrioventricular block similar to intoxication with calcium channel or beta-blocking agents.

9.5.2. Blood and urine analysis

A glucose level should be obtained during the primary assessment to rule out hypoglycemia. Blood should be taken for complete blood count, renal and liver function, electrolyte tests, clotting studies, and osmolality. A creatine phosphokinase level should be obtained when rhabdomyolysis is suspected. The possibility of pregnancy should be ruled out in every woman presenting with coma. Hypokalemia may indicate salbutamol, theophylline, or salicylate poisoning. Raised osmolality suggests ethanol, methanol, ethylene glycol, or isopropanol poisoning. Arterial blood gases will help with quantifying any respiratory compromise and also indicate an acid–base disturbance. If an acidosis is present, a serum lactate level and calculation of the serum anion gap (anion gap = sodium − [chloride + bicarbonate], normal value 13 ± 4 mEq/l) will help to assess the type of acid–base disorder. Metabolic acidosis may result from poisoning with, for example, salicylates, paracetamol/acetaminophen, ethanol, methanol, and ethylene glycol but also from circulatory shock. Poisoning with CO or the presence of methemoglobin can be ruled out by measuring carboxyhemoglobin and methemoglobin levels respectively. As already mentioned above, pulse oximetry is unable to distinguish between oxyhemoglobin and carboxyhemoglobin because of their spectrophotometric similarities. Urinalysis can assist in the evaluation of ketosis, hemolysis, and renal injury. Microscopy of urine may reveal calcium oxalate crystals, suggesting ethylene glycol poisoning.

9.5.3. Toxicological testing

Toxicology screening on blood and/or urine may be ordered, depending on the clinical picture (Rainey, 2002; Wu et al., 2003). It is obvious that, when clinically indicated, therapy of a patient with suspected poisoning should never be postponed until the toxicological results are known. In practice, however, many clinicians, emergency physicians as well as neurologists, feel that toxicological testing is useful. When, for instance, doubt remains in a coma patient about the cause, toxicological data are also of great help when they are negative. This aspect is rarely studied. Furthermore, identifying the toxic substance will definitely influence therapy and prevent morbidity and mortality in a small percentage of patients. For instance, knowing that the coma is due to lithium poisoning may point to the necessity of hemodialysis. Finally for documentation and liability concerns, confirmation of a suspected poisoning with a toxicological analysis is preferred by most clinicians. A more important issue than whether or not to order tests is 'how' to order the tests. Clinicians treating patients with coma and suspected poisoning should know the limitation of a 'comprehensive tox-screen'. The number of drugs detected in a screen varies from laboratory to laboratory and can be falsely negative or reassuring. Moreover a comprehensive screen demands a lot of work in the lab and may not be cost-effective. In order to increase efficiency and reduce the cost of toxicological analysis it is very important that the clinician provides information on the suspected drugs and consults with the clinical toxicologist.

The possibility of (co-)intoxication with paracetamol/acetaminophen and salicylate poisoning should always be considered in a patient presenting with an overdose as these drugs are widely available, potentially lethal and treatable in the early phase of intoxication (Hartington et al., 2002). Salicylates by themselves can cause coma through cerebral edema; and paracetamol/acetaminophen and combination preparations with, for example, paracetamol/acetaminophen and codeine in massive overdose have also been associated with coma (Yip et al., 1994; Schiodt et al., 1997).

For some drugs and poisons, quantitative concentration measurements may be useful, as they may guide treatment (Table 9.4). For some coma-inducing substances such as anticonvulsants, lithium, and methemoglobin there is a good correlation between the

Table 9.4

Some examples of compounds for which quantitative analysis may be useful in guiding treatment

Anti-epileptics: carbamazepine, phenytoin, valproic acid
Carboxyhemoglobin
Digoxin
Ethylene glycol
Heavy metals: iron, lead, mercury
Lithium
Methanol
Methemoglobin
Paracetamol
Paraquat
Salicylates
Theophylline

concentration and the clinical symptoms. Levels of alcohol and benzodiazepines usually do not correlate well with depth of coma because of the large interindividual variability; chronic users, for instance, will exhibit CNS depression at significantly higher blood concentrations than nontolerant individuals. The problem with carboxyhemoglobin levels is that there is wide variation in clinical manifestations with identical carboxyhemoglobin levels and that particular carboxyhemoglobin levels are not predictive of symptoms or final outcome (Myers, 1984). Also for salicylates, the severity of toxicity poorly correlates with serum levels. Quantitative levels of tricyclic antidepressants also have little correlation with clinical symptoms and fail to predict the risk of seizures or ventricular dysrhythmias, and are therefore rarely indicated. Timing of measuring blood concentrations may be important; for example, concentrations measured during the absorption phase may lead to underestimation of the risk and to potentially fatal errors. Sometimes repeated drug concentrations should be determined to look for trends, as drug absorption in overdose may be delayed or erratic.

9.5.4. Radiography

A chest radiograph is indicated in patients presenting with coma to evaluate for an infectious source of coma or aspiration pneumonia.

Cranial computed tomography should be performed if a concern for an intracranial lesion exists or if cerebral edema is suspected, e.g., in paracetamol/acetaminophen-induced liver failure. If indicated, a lumbar puncture should be considered to rule out subarachnoid bleed, meningitis, or encephalitis.

9.6. Urgent specific antidotes

In this section, some of the most frequently used antidotes that may be considered in the initial management of comatose patients will be reviewed. Antidotes for, for example, cyanides, organophosphates, tricyclic antidepressants, and methemoglobin-forming agents are not discussed and the reader is referred to specialized textbooks in toxicology (Goldfrank et al., 2002). Normobaric oxygen (NBO) should be delivered to all comatose patients, and in case of CO poisoning the administration of hyperbaric oxygen (HBO) may be considered. The value of the antidotes dextrose, thiamine, and the opioid antagonist naloxone used as a 'coma cocktail' will be discussed below (Hoffman and Goldfrank, 1995). More recently the benzodiazepine receptor antagonist flumazenil has also been considered as an urgent antidote.

9.6.1. Hyperbaric oxygen

HBO involves exposing patients to 100% oxygen under supra-atmospheric conditions. This results in a decrease in the half-life of carboxyhemoglobin (COHb), from 40–80 minutes on 100% NBO to 15–30 minutes during HBO. HBO may be beneficial in preventing the late neurocognitive deficits associated with severe CO poisoning; however, the quality and results of clinical trials have varied widely (Clardy and Manaker, 2005; Phin, 2005).

A well-designed double-blind, controlled trial randomly assigned 152 patients with symptomatic CO intoxication within 24 hours of presentation to HBO or NBO (Weaver et al., 2002). Treatment was administered during three sessions in a hyperbaric chamber and 6 weeks after presentation cognitive sequelae were more common in the group treated with NBO (46 vs 25%). This advantage of HBO was maintained at 1 year following initial presentation. It is noteworthy that in 31% of the patients in the study by Weaver et al., CO intoxication was related to a suicide attempt.

Another study randomly assigned 343 patients without initial impairment of consciousness in a nonblinded way to either 6 hours of NBO or 2 hours of HBO at 2 atm (203 kPa) plus 4 hours of NBO (Raphael et al., 1989). No difference in mortality or in the incidence of delayed neurological sequelae was observed. However, critics of the study noted that many patients in the HBO group did not receive treatment until more than 6 hours from the time of poisoning, and patients were treated with only one HBO session.

Similar findings were noted in a double-blind, randomized trial of 191 patients with CO poisoning referred to a tertiary center, which failed to document

benefit for patients who received HBO (Scheinkestel et al., 1999). On the contrary, delayed neurological sequelae and poor performance on neuropsychiatric tests after 1 month were significantly more common among HBO-treated patients. It should be noted that, in this study, although people with all levels of CO were included, a high proportion (73%) of patients with severe CO poisoning was presented. Moreover, cluster randomization was used for patients presenting simultaneously, which may have engendered a risk of bias. Also, mean time interval to treatment was high (>6 h) and it is therefore possible that a significant proportion of the patients were treated at a time after CO exposure when HBO is unlikely to be effective.

Despite the uncertainty in identifying patients who will benefit from HBO therapy, most authorities favor HBO in the presence of COHb >25%, metabolic acidosis, a history of loss of consciousness, neurological or cardiovascular dysfunction, and in pregnant women with COHb >15% or evidence of fetal distress. All patients selected to receive HBO should have at least one treatment at 2.5–3.0 atm (253–304 kPa) as soon as possible to reverse the acute effects of CO intoxication, with possibly additional hyperbaric sessions directed toward limitation or prevention of delayed neurological sequelae.

9.6.2. Glucose and glucagon

Any patient with an altered mental status should be suspected of hypoglycemia. Clinical diagnosis of hypoglycemia is not easy. Symptoms may range from agitation to deep coma with diaphoresis and tachycardia. However, other neurological symptoms like decerebrate and decorticate posturing may occur and even focal signs with, for instance, hemiplegia. In most cases a glucose dose of 10–15 g in adults (as hypertonic glucose 50%) will be sufficient to reverse hypoglycemic coma; however, in some cases doses as high as 0.5–1 g/kg will be needed (e.g., in deliberate insulin overdose). Glucagon (adult dose: 1–2 mg) may be used as a temporizing measure in patients who have no intravenous access because it can be administered intramuscularly.

9.6.3. Thiamine

Although Wernicke's encephalopathy is rare, thiamine 100 mg (intravenously or intramuscularly) should be given in any patient with an altered mental state. Adverse effects seldom occur following administration of thiamine but hypersensitivity reactions have occurred, mainly after parenteral administration ranging in severity from very mild to (very rarely) fatal anaphylactic shock. It will only rarely immediately improve the mental state but its routine use reminds us of potential nutritional deficiencies in many patients, especially chronic alcoholics, who are at risk of Wernicke's encephalopathy. It should be remembered that administration of intravenous glucose to severely malnourished patients can exhaust their supply of thiamine and precipitate Wernicke–Korsakoff syndrome. Therefore glucose and thiamine should be given as a cocktail for comatose patients of unknown origin.

9.6.4. Naloxone

Naloxone is an antagonist with a high affinity for μ, κ, and δ opioid receptors (Howland, 2002a). It therefore antagonizes the opioid effects like sedation and the life-threatening respiratory depression that makes it of great value in cases of intoxication. It should be noted that it is less effective in poisoning with D-propoxyphene, pentazocine, and buprenorphine. It is a pure antagonist, which means that it does not produce opioid effects by itself and is specific for opioid poisoning.

It is a competitive antagonist, which implies that the dose needed to reverse the opioid effects will depend upon the amount of the opioid present in the poisoned patient, which is of course rarely known in acute poisoning.

Initially, and especially in the USA, naloxone was propagated in the 'coma cocktail' for diagnostic and therapeutic use in any patient with decreased consciousness. However, this indiscriminate use is questioned now because of the very poor yield of beneficial effects (only in about 3% of comatose patients) and since studies indicate that clinical diagnosis of opioid poisoning based on respiratory rate and pupil size is quite reliable (Hoffman et al., 1991). Therefore naloxone is only indicated now in coma and/or respiratory depression (rate <12/min) in patients showing signs of opioid poisoning. The side effects, such as pulmonary edema, are relatively rare.

However, potentially severe withdrawal problems may occur in opioid addicts. Therefore, when naloxone is used in potentially dependent patients, the use of incremental intravenous doses is recommended, based on the clinical response, such as reversal of respiratory depression and decreased consciousness. A practical starting dose in most adult patients is 0.05 mg, increasing to 0.4 mg, then to 2 mg, and finally to 10 mg (Howland, 2002a). If there is no response to 10 mg, then an opioid is unlikely to be responsible for the coma and/or respiratory depression.

Recurrent toxicity is common after an initial good response because the half-life of naloxone is short

(20–30 min), which obviates the need for a continuous infusion or a repeat bolus administration, e.g., after 15 minutes. Naloxone can also be administered by the intramuscular, subcutaneous, intralingual, and intratracheal routes.

9.6.5. Flumazenil

Flumazenil is a competitive antagonist of the benzodiazepine receptor in the CNS that facilitates GABAergic transmission, giving rise to the classic effects of benzodiazepines such as sedation, anxiolytic, anticonvulsive, and hypnotic properties (Howland, 2002b). Flumazenil will reverse such effects as sedation and also the anticonvulsant properties of the benzodiazepines. While the use of flumazenil is well established to counteract the effects of benzodiazepines used in diagnostic procedures such as endoscopy where benzodiazepines are used for sedation, its use in patients with acute poisoning is still the subject of debate.

Opponents of the use of flumazenil in patients with benzodiazepine poisoning stress that benzodiazepines rarely cause morbidity and mortality. The latter is often not due to respiratory depression (which is not always reversed by flumazenil) but to aspiration pneumonia that has already occurred prior to admission to the hospital. They emphasize the importance of the risk of inducing seizures, which can be due to co-ingested drugs such as tricyclic antidepressants or to the acute withdrawal provoked in patients chronically taking benzodiazepines.

Proponents of the use of flumazenil stress the benefit of avoiding procedures in the diagnostic work-up of a coma patient that carry their own risks (e.g., gastric lavage). Furthermore, they mention the benefits of avoiding the risks of endotracheal intubation and ventilation (Höjer et al., 1990).

Flumazenil is better avoided, or even contraindicated, in patients with a history of seizures or current treatment for seizures. History of intake or ingestion of substances capable of provoking seizures or provoking cardiac arrhythmias (e.g., tricyclic antidepressants, theophylline, carbamazepine, chloroquine, chlorinated hydrocarbons) is also a contraindication as is long-term use of benzodiazepines. Finally flumazenil should never be used in patients with abnormal vital signs.

If needed, flumazenil should be given slowly and by titration (0.1 mg/min in adults) without exceeding a total dose of 1 mg. Relapse of the sedation may occur after 20 or more minutes because of the rather short half-life of flumazenil.

In summary, many authors now agree that the indications for flumazenil in the overdose setting are pure benzodiazepine poisoning in individuals who are not tolerant of benzodiazepines and who have CNS depression, normal vital signs, normal ECG, otherwise normal neurological examination and no history of epilepsy (Gueye et al., 1996). Of course, such cases are rare in adults with benzodiazepine poisoning.

9.7. Disposition

All comatose patients should be closely observed with frequent controls of blood pressure, heart rate, respiratory rate, body temperature, GCS and pupils. Electrocardiographic monitoring is required in all patients intoxicated with potential cardiotoxic agents. Continuous pulse oximetry is recommended in comatose patients, since all agents causing CNS depression may compromise airway patency. Depending on end-organ toxicity, toxin characteristics, requirements for physiological monitoring and specialized treatment, and patient factors, admission to the intensive care unit is indicated.

In a retrospective study, a set of criteria was established to identify those poisoned patients needing intensive care unit admission without taking into account the specific toxin ingested (Brett et al., 1987). Criteria defining high-risk patients were needed for intubation, unresponsiveness to verbal stimuli, seizures, P_{CO_2} >45 mmHg, systolic blood pressure <80 mmHg, QRS duration >0.12 seconds, or any cardiac rhythm except normal sinus rhythm, sinus tachycardia, or sinus bradycardia.

Intensive care unit admission is always warranted for patients with expected serious toxic effects from an ingested poison. This is especially true for those toxins known to be deadly, such as calcium channel blockers, cocaine, cyanide, cyclic antidepressants, and salicylates. Indicators of toxicity should be identified for individual toxins so that high-risk patients may be closely monitored and aggressively treated.

The intensive care unit setting provides a nurse-to-patient ratio that allows for frequent or continuous monitoring of basic physiological parameters. Intensive care units are also best equipped to treat respiratory failure and hemodynamic shock. Extracorporeal methods for eliminating toxins and most antidotal therapy are also best performed in the intensive care unit.

Pre-existing medical conditions increase a patient's risk for developing toxicity and may therefore require intensive care unit admission. For instance, patients with underlying cardiac disease are more susceptible to myocardial ischemia from CO poisoning. Renal and hepatic disease may alter drug metabolism and elimination, resulting in prolonged toxicity.

9.8. Psychosocial approach

Most intoxications presenting to the emergency department result from an autointoxication. Therefore, psychosocial factors are significant in the evaluation and treatment of patients with toxicological emergencies (Gautieri and Brambill, 2002). The acute event of an intoxication offers the opportunity to initiate well-coordinated care management with particular attention to continuity and follow-up. Integrated health-care systems include formal and informal linkages to community-based health, mental health, substance abuse treatment, and social service agencies, all of which interact with interdisciplinary teams in their management of toxicological emergencies. Even with the highest levels of clinical and technological expertise applied in the diagnosis and treatment of poisoned or overdosed patients, successful outcomes may be compromised by inadequacies in aftercare and follow-up. Therefore, it is important to identify and cultivate appropriate referral resources for a wide range of continuing-care services.

Self-poisoning prompts immediate referral for further psychosocial, social, and psychiatric assessment and poses unique problems for the clinician, who must make appropriate assessment and management decisions (Hawton et al., 1998; National Institute for Clinical Excellence, 2004; Sinclair and Green, 2005). The assessor should at least have received specific training and have access to support from a psychiatrist (Skegg, 2005). Identifying risk factors for suicide can aid the clinician in employing preventive or early intervention strategies. Important risk factors for suicidal behavior include past history of suicide attempts, comorbid mental illness, substance intoxication, young age groups and absence of a social/family support network. Mental status examination for suicidal risk should focus on extrinsic factors such as current ideation, intent, lethality of the plan, and current life stressors, as well as intrinsic vulnerability factors such as comorbid mental illness, feelings of hopelessness, and impulsivity. Early detection and rapid intervention for patients at risk for suicide are the best means for preventing injury or death (Gunnell et al., 2004).

Appropriate interventions should also be offered to patients with hazardous or harmful alcohol drinking (Ritson, 2005). In general, health-care providers tend to have an overly pessimistic view of the benefits of treating alcoholism. However, this view is not in line with psychosocial interventional strategies, which have proved to be effective.

Optimal psychosocial care of patients with substance abuse is also quite challenging. A compassionate and nonjudgmental approach is important to gain their confidence and enhance the care rendered.

9.9. Summary and conclusions

Comatose patients with suspected poisoning are a challenge to the clinicians involved in the management of these patients. The approach of these patients should start with stabilization of vital parameters and the judicious use of antidotes. Clinicians should be very alert not only for specific clinical signs of acute poisoning but also for other causes of decreased consciousness. One should always be suspicious for associated traumatic injuries in poisoned patients. Thorough knowledge of toxidromes, clinical neurological examination, decontamination procedures, and toxicological testing are of major importance in the management of these patients. Therefore, early consultation between the neurologist and the clinical toxicologist is of utmost importance, as is communication with the toxicology laboratory. Attention should be paid to optimal psychosocial support of the poisoned patient, especially in autointoxications.

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Chapter 10

Ischemic stroke and anoxic–ischemic encephalopathy

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10.1. Ischemic stroke

While coma is common and expected with global brain ischemia, impairment of consciousness with regional ischemia (strokes) depends on dysfunction of specific brain regions involved in alertness and higher functions (Ch. 2). These structures can be affected directly by the lack of perfusion, by remote synaptic or metabolic suppression (diaschisis), by mass effect with herniation (Ch. 5), or by complications such as seizures, superimposed infections, respiratory or hemodynamic effects, metabolic derangements, or adverse effects of drugs.

10.1.1. Epidemiology

Over 70% of strokes are ischemic in almost all countries (Feigin, 2005). Internationally the incidence of stroke is age-dependent, considerably higher in those over 65 years and exponentially higher after 75 years of age (Feigin, 2005). The recent equivalence of age-dependent patterns across countries may relate to the increased incidence of hypertension and diabetes mellitus and longer life-expectancy in developing countries (Feigin, 2005). Despite the decline in the incidence of stroke in all age groups (Pajunen et al., 2005), the aging of the population has meant that the prevalence of stroke has not fallen and may increase. The incidence of ischemic stroke in North America and western Europe is roughly 250 per 100 000 persons per year. The incidence is higher in men than in women for those under 85 years of age, after which the rates are equal (Pajunen et al., 2005).

Closely related transient ischemic attacks (TIAs) are discussed separately, as they briefly and reversibly interfere with neurological function (even though they almost never cause loss of alertness/consciousness). TIAs have an annual incidence just less than that of stroke and are a strong predictor of stroke and death; this can be reduced if the underlying causes and risk factors are appropriately treated (Kleindorfer et al., 2005).

Strokes also occur in children, with an annual incidence of 2–6/100 000 (Lynch et al., 2002). Causes of acute ischemic stroke include prothrombotic states (e.g., protein C deficiency, high lipoprotein-a concentrations), post-varicella angiopathy, trauma-induced or spontaneous arterial dissection, and cardioembolism (deVeber, 2005).

Younger individuals at risk for stroke include those with polytrauma. The mechanism for stroke is most often traumatic dissection of the carotid or vertebral arteries in the neck (Blacker and Wijdicks, 2004). Strokes are often missed or recognized late in management as the patients may have impaired consciousness and movements from direct trauma to the brain, the use of sedatives and/or paralyzing drugs, or coincident limb fractures. Such ischemic stroke has a serious impact on both in-hospital mortality and long-term morbidity.

10.1.2. Significance

If we assume that the site damaged by a stroke cannot, in itself, recover, the effects on consciousness reflect not only the contribution of the affected part of the brain on alertness and cognitive function but also the dynamic mechanisms that operate once a stroke has occurred. Thus, although the anatomical lesion may be static, the effects on the patient often are not, but change over time, eventually reaching a plateau that may take 2 years or more to be realized.

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In-hospital mortality and severe disability are highest in those who present with impaired consciousness as part of the ischemic stroke syndrome (Baptista et al., 1999; Paciaroni et al., 2000) and is an independent predictor of outcome in those treated with thrombolysis in posterior circulation strokes (Tsao et al., 2005).

In the next section we shall consider the various vascular syndromes and their effects on consciousness and its components. These are summarized in Table 10.1.

10.1.3. Anterior cerebral artery ischemia

Infarction in the territory of both anterior cerebral arteries produces akinetic mutism, in which the patient makes little voluntary movement and is mute but is awake and fixates and follows with the eyes. The crucial anatomical regions are the anterior cingulate gyri and the anterior limbs of the internal capsules. Alternatively, lesions of the supplementary motor areas, even unilaterally, can produce temporary abulia, or profound lack of spontaneity. Infarction of the anterior and mid-portions of the corpus callosum results in a disconnection syndrome.

Acute ischemia in the middle cerebral artery territory of the dominant hemisphere can result in temporary unresponsiveness or decreased alertness (Fig. 10.1). This is not consistent across individuals but sometimes occurs. The mechanism is not understood but it may represent a temporary diaschisis for individuals whose left hemisphere is very dominant. The left cerebrum is dominant for language in almost all right-handers and in over 60% of left-handers. According to Gazzaniga (1998) the left hemisphere has many more functions and circuits than the right and functions as an 'interpreter' for much of our experiences. Thus, after basic alertness is regained, the patient with extensive left cerebral damage has limited awareness of various experiences, in that the internal verbal interpretation of conscious experience is lost.

Table 10.1

Vascular syndromes and their effects

Vascular territory	Alertness	Cognitive and other deficits
Anterior cerebral artery	Not usually affected if unilateral	Unilateral mesial frontal infarcts produce initial abulia, incontinence, contralateral forced grasping, and lower limb paresis. Bilateral mesial frontal or anterior internal capsular lesions are associated with akinetic mutism with various degrees of improvement. A disconnection syndrome may follow corpus callosum infarction
Middle cerebral artery	Transiently compromised in a minority of dominant hemisphere strokes. Consistently affected in bilateral strokes, until return of alertness and wake–sleep cycles in 2–3 weeks	Unilateral stroke affects dominant or nondominant hemisphere functions. Bilateral, extensive middle cerebral artery strokes produce vegetative state. Apraxia of eyelid opening in nondominant parietal strokes
Posterior cerebral artery	Bilateral, paramedian thalamic lesions → coma then hypersomnolence	Bilateral occipital lesions may produce Anton's syndrome, cortical blindness, visual agnosia, Balint's syndrome, phenomenon of blindsight. Thalamic lesions, especially paramedian, associated with enduring amnesia
Basilar artery	Top of the basilar syndrome associated with tegmental rostral brainstem ± thalamic damage → initial coma, may be permanent with thalamic and hypothalamic and midbrain damage. Extensive basilar thrombosis may lead to clinical brain death	Peduncular hallucinosis with rostral brainstem–hypothalamic lesions. Various ocular problems: Parinaud's syndrome, unreactive pupils, third nerve dysfunction, including bilateral ptosis. Locked-in syndrome with basis pontis infarction

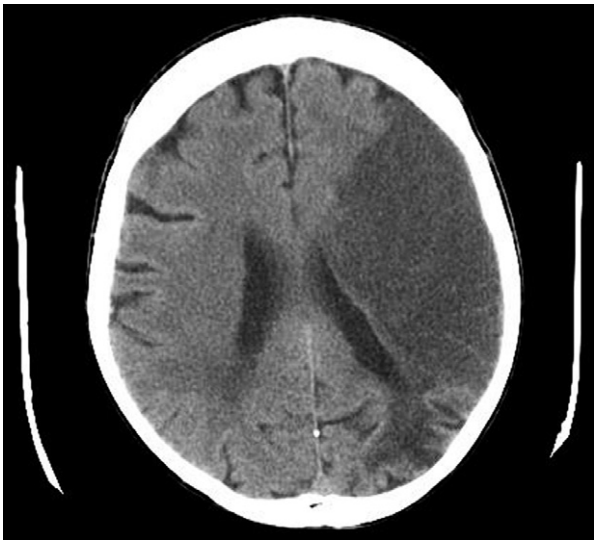

Fig. 10.1. Infarction in the dominant cerebral hemisphere of less than 24 hours' duration.

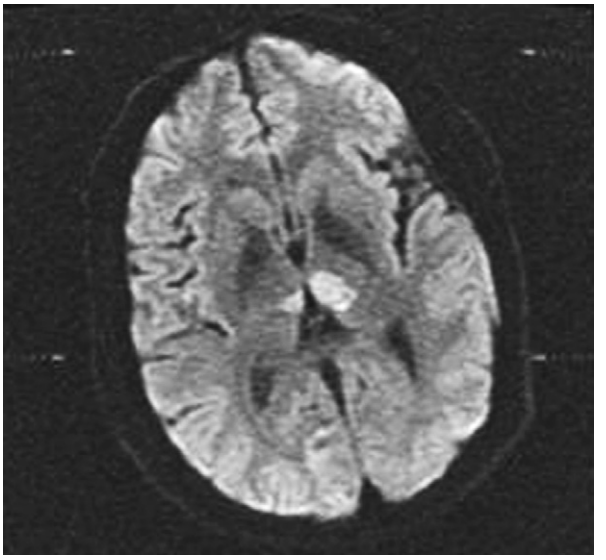

Fig. 10.2. Bilateral thalamic infarctions on fluid-attenuated inversion recovery (FLAIR) imaging within several hours of onset.

Bilateral internal carotid artery occlusion, either due to atherosclerosis or cardiogenic embolism, can cause sudden coma, initially resembling a metabolic encephalopathy, with preservation of brainstem reflexes (Kwon et al., 2002). With subsequent cerebral swelling and transtentorial herniation, the brainstem reflexes are lost in a few days and death occurs.

10.1.4. Posterior circulation ischemia

Ischemia within the basilar arterial system can produce impaired alertness at least initially with bilateral thalamic damage and especially with damage to the paramedian regions (Steinke et al., 1992). Following medial thalamic damage (Fig. 10.2), akinetic mutism, profound memory impairment, or altered behavior can evolve (Castaigne et al., 1981; Tatu et al., 1996). Unilateral paramedian thalamic infarction produces confusion, disorientation, and behavioral changes (Castaigne et al., 1981; Tatu et al., 1996). Ocular movement abnormalities are common, especially 'wrong way eyes' (a gaze palsy to the opposite side), skew deviation, and vertical gaze palsy (Steinke et al., 1992). Motor deficits do not occur unless there is extension into more caudal structures.

Bilateral rostral midbrain and pontine tegmental lesions are almost always associated with impaired alertness (Chase et al., 1968) but strokes rarely involve these regions selectively; thalamic damage is commonly associated. Damage to the rostral brainstem reticular formation is commonly associated with pupillary and ocular movement abnormalities, other cranial nerve abnormalities (typically bilateral), corticospinal deficits, and cerebellar dysfunction. The 'top of the basilar' syndrome that most commonly produces this picture is usually embolic in nature. The sources of emboli are either the proximal vertebrobasilar system or more proximal sites, especially the heart or arch of the aorta. Parvisi and Damasio (2003) showed in a careful magnetic resonance imaging (MRI) study that coma occurred acutely with ischemic strokes that involved the rostral pontine tegmentum bilaterally, with or without involvement of the midbrain. In addition to pontine reticular nuclei, the lesions involved the locus ceruleus, the dorsal raphe, the parabrachial nuclei, and white matter between these structures. The lesions interrupted important rostrally directed cholinergic, adrenergic, and serotonin pathways as well as the reticular formation itself. Since their patients were followed for only 1 week from the stroke, it is possible that the impairment of consciousness with pontine tegmental strokes is not permanent if the patient survives for a sufficient duration.

10.1.5. Multiple territory ischemia

Multiple territory infarctions are not uncommonly accompanied by impairment in alertness (Gootjes et al., 2005). Elderly, postoperative patients are at risk for multiple embolic strokes or watershed ischemia (in the end territories of the three major cerebral arteries) especially with cardiac surgery or if intraoperative hypotension occurred (Gootjes et al., 2005).

10.1.6. Pathogenesis of ischemic stroke and coma

Ischemic strokes cause death of tissue due to a marked reduction in vascular tissue perfusion. The threshold blood flow is about 20 ml/100 g/min for gray matter and 12.3 ml/100 g/min for white matter (Bristow et al., 2005). Some 80% of ischemic strokes relate to atherosclerotic changes in the carotid or vertebral arteries or their proximal arterial systems; about 20% result from cardiogenic emboli and a tiny percentage are due to hypotension, vasospasm, inflammatory change, intimal dissection from trauma, or other factors. Most ischemic strokes are due to distal embolism rather than in situ thrombosis. The extent of the ischemic damage is due to the anatomy of the vascular supply, especially whether collateral channels can ameliorate the lack of tissue perfusion. Deficiency of endothelial nitric oxide, elevations of body temperature, or serum glucose concentration each contribute to the severity of ischemic stroke (Beridze et al., 2004).

10.1.7. Diagnosis

MRI is superior to computed tomography (CT) scanning in identifying territories of stroke at an early stage (Gootjes et al., 2005). Abnormalities on diffusion-weighted MRI can be used to differentiate recent from old infarcts and from leukoaraiosis (Helenius et al., 2002). CT perfusion is an advance in allowing detection and quantification of regional blood flow shortly after a stroke (Maruya et al., 2005). These imaging techniques can determine the presence of a stroke and its anatomy immediately after the event.

10.1.8. Management

Patients who present with focal brain ischemia within 3 hours of onset are potential candidates for thrombolysis (Bassi et al., 2005). Usually this is attempted with intravenous recombinant tissue plasminogen activator (rTPA) at 0.9 mg/kg. Some patients, e.g., those with an extensive thromboembolus that occludes more than a few millimeters of the length of an artery, may be better treated with intra-arterial rTPA or even a mechanical extractor of the embolus (Wardlaw et al., 2003). Thus, there is urgency in patient evaluation and neuroimaging.

Determining the source of the stroke is important in preventing future infarctions. Most ischemic strokes are embolic in nature. Often the associated features will offer an indication of the source of the embolus, e.g., a history of prior vertebrobasilar transient ischemic events (visual symptoms such as transient teichopsia or diplopia) or cardiac events or risk factors (e.g., strokes in different vascular territories, evidence of systemic embolism, evidence of chronic or paroxysmal atrial fibrillation). This has implications for investigation and therapy.

Close observation, monitoring, and appropriate management in a stroke unit reduces mortality (Silva et al., 2005). Attention should be given to serum glucose and body temperature, as elevations of either can worsen stroke outcome (Silva et al., 2005).

The conventional wisdom of a dismal outlook for patients admitted to intensive care units for mechanical ventilation is incorrect. Of the 30% or so who survive, most had a good outcome (Barthel Index of 60 or more) (Santoli et al., 2001). However, patients with posterior circulation strokes and Glasgow Coma Scale (GCS) scores of 8 or less are unlikely to have good outcomes (Tsao et al., 2005).

Some patients with large hemispheric stroke (Fig. 10.3) are at risk for cerebral herniation and death. Decompressive craniectomy can be life-saving and often produces outcomes that are acceptable to patients and their families (Fraser and Hartl, 2005). Patients at high risk for herniation and brain death include those with CT evidence of midline shift and compression of the ambient cistern (Dominguez-Roldan et al., 2004).

Prevention of stroke in patients with TIAs or recurrence of stroke in victims of partial strokes depends on the underlying mechanism and risk factors. For arterial TIAs or strokes related to carotid atherosclerosis, surgery is of benefit to those with more than 70% stenosis

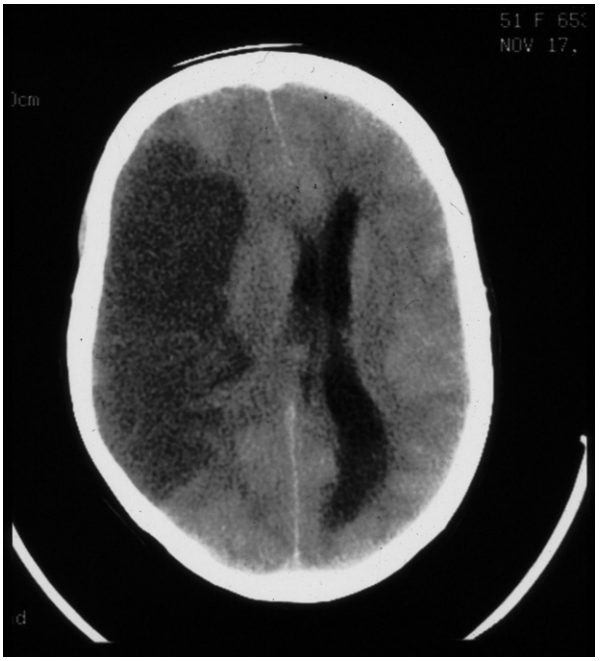

Fig. 10.3. CT scan reveals a large right middle cerebral artery territory infarction with swelling and midline shift, sufficient to produce coma.

of the symptomatic artery (Rothwell et al., 2003). Arterial stenting may be an option for selected patients who are not surgical candidates but trials thus far have not shown net benefit (Alberts et al., 2001). Surgery remains controversial for lesser degrees of stenosis but antiplatelet medication (aspirin, clopidogrel, ticlopidine, or aspirin–dipyridamole combination) has been shown to reduce the risk of stroke in those with TIAs and artery-to-artery strokes (Antithrombotic Trialists' Collaboration, 2003). Anticoagulants are usually necessary for prevention of cardiogenic emboli. Of course, correcting lipid abnormalities, stopping smoking, controlling hypertension and serum glucose, and reducing elevated serum homocysteine are worthwhile. Specific therapies for sickle cell disease, vasculitis, arterial dissection, and unusual arteriopathies such as moyamoya are needed; guidelines are being developed (deVeber, 2005).

10.2. Anoxic–ischemic encephalopathy

Anoxic–ischemic encephalopathy or postresuscitation encephalopathy refers to brain dysfunction due to transient circulatory arrest. Approximately 450 000 deaths in the USA can be attributed to sudden cardiac arrest, mostly due to coronary artery disease (Zheng et al., 2001) and associated with major cardiac disease risk factors (Zandbergen et al., 2001; Albert et al., 2003). Overall, about 33% of attempted cardiopulmonary resuscitation (CPR) efforts restore the pulse and blood pressure (Myerburg et al., 1980). However, the brain often suffers severe damage. The use of hypothermia has recently been shown to ameliorate both mortality and morbidity after CPR.

The neurologist is frequently asked to determine the neurological prognosis after CPR or hypothermic therapy. This needs to be done carefully, as decisions about the level of care are heavily dependent on the neurological conclusion. Establishing the prognosis with certainty is of fundamental importance; the sections below address this issue. Death without recovery of consciousness and the permanent vegetative state, in which there never will be any awareness (Ch. 6), constitute outcomes that few would accept; further intensive care unit support is futile. There are several indicators of poor prognosis but few exist for favorable recovery of awareness and independence.

10.2.1. Clinical factors and outcome

None of the following reliably discriminate patients with poor versus good outcomes: the time between collapse and initiation of CPR (anoxia time), the duration of CPR, the cause of the cardiac arrest (cardiac versus noncardiac), and the type of cardiac arrhythmia (ventricular fibrillation or tachycardia versus asystole or electrical–mechanic dissociation), elevated temperature, or high APACHE-2 score (Acute Physiology and Chronic Health Evaluation, a measure of severity of general health and acute illness that includes the GCS as a component). Even the duration of coma is not sufficiently reliable: 13–61% of patients in coma for 2 weeks may still recover consciousness.

Features of the neurological examination are more helpful. It should be realized that these examine primarily brainstem reflexes and other subcortical functions and do not really assess cerebral cortical function, the principal localization of awareness and all its components. As the large cell layers of the cerebral cortex are more vulnerable to anoxia–ischemia than subcortical structures, the inference is that, when the latter are seriously impaired, the cortex is even more devastated. The GCS on its own and the separate components of the GCS (best motor, verbal, and eye opening response), and brainstem reflexes (pupillary light reflexes, cornea reflexes, and spontaneous eye movements or oculocephalic reflexes), are useful, especially when very low (GCS) or absent (other variables). Of patients with GCS-scores $\leq$4 within the first 48 hours, 98% died or were still comatose after 2 weeks, whereas this occurred in 18% of patients with GCS-scores $\geq$10.

The results of studies of motor responses and brainstem reflexes have been summarized in two independent structured reviews (Zandbergen et al., 1998; Booth et al., 2004). Zandbergen et al. (1998) concentrated on variables with a 100% specificity (i.e., 0% false-positive rate) and found such values for absent motor responses and absent pupillary reactions to light on the third day, with zero false-positive rate (95% CI 0–7 and 0–12) and positive likelihood ratios of 16.8 (3.4–84.1) and 10.5 (2.1–52.4), respectively. The corresponding likelihood ratios computed were 9.2 (2.1–49.4) for absent motor responses and 3.4 (0.5–23.6) for absent pupillary reactions. False-positive rates for the absence of pupillary light responses within 24 hours after CPR vary from 18–36%, so this is not a reliable indicator of prognosis. However, in patients with absent pupillary responses or motor responses 72 hours after CPR the prognosis is invariably poor (Levy et al., 1985).

Although single seizures are poorly predictive, myoclonic status epilepticus (defined as spontaneous, repetitive, unrelenting, generalized myoclonus in face, limbs, and axial musculature in comatose patients) is invariably associated with in-hospital death or poor outcome (Wijdicks et al., 1994). In a postmortem study, this condition was associated with severe ischemic brain, brainstem, and spinal cord damage, indicating that death was due to anoxic–ischemic damage rather than to status epilepticus (Young et al., 1990).

10.2.2. Electrophysiological tests

Electrophysiological tests can be divided into electroencephalogram (EEG) and evoked/event-related potential studies.

Unfortunately, the EEG literature is confounded by different classification systems; for purposes of discussion EEG categories have been collapsed into two: malignant and benign/uncertain, to allow for comparisons and statistical analysis. This represents a condensation of the categories contained in several proposed classification systems (Young, 2000).

Most studies report intervals from CPR to EEG recording of less than 3 days, but there is considerable variation. Complete suppression (isoelectric EEG) or burst-suppression patterns containing generalized epileptiform discharges may have predictive power, but these have rarely been examined separately. Generalized suppression to 20 μV, burst-suppression pattern with generalized epileptiform activity, or generalized periodic complexes on a flat background are associated with outcomes no better than persistent vegetative state (Young, 2000). Most 'malignant' classifications include suppression, burst-suppression, alpha and theta pattern coma, and generalized periodic complexes combined; hence the predictive value of individual classifications has not been adequately addressed. The so-called alpha-coma pattern does not invariably herald a poor outcome. Further, serial or continuous EEGs may have more reliability and validity than single EEGs. The presence of EEG reactivity and variability are possibly favorable features for recovery of consciousness.

Somatosensory evoked potentials (SSEPs) are not as susceptible to drugs and metabolic derangements and are therefore more reliable than EEG. A total of 11 class III studies were identified. Bilateral absence of the N20 component of the SSEP with median nerve stimulation at the wrist has greater predictive value for poor outcome than EEG, with studies showing false-positive rates of 0%. One study reported a pooled likelihood ratio of 12.0 (95% CI, 5.3–26.6) for bilateral absence of N20 on SSEP in the first week (Zandbergen et al., 1998). The false-positive rate is essentially zero. The presence of the N20 response is not helpful in predicting outcome; many patients who fail to recover will have preserved N20 responses. Repeated testing should be considered when the N20 responses are present early in the course of post-cardiac-arrest coma: the N20 responses may disappear on repeat tests after showing initial preservation after cardiac arrest.

Other evoked (brainstem auditory and visual) and event-related potential tests have not been thoroughly tested for their prognostic value in anoxic–ischemic encephalopathy. In one series, the middle latency auditory evoked response was absent in all 13 patients who died or remained in a persistent vegetative state (sensitivity 34% (CI 19–49%), false-positive rate 0%).

The presence of late components (e.g., the N70 response) of SSEPs has been examined. The use of later responses (N35 and N70) for prediction of good outcome has been suggested. The preservation of responses to multiple event-related/cognitive-event-related potentials may prove useful in indicating favorable outcomes. There are insufficient data to analyze its merit in prognostication.

Induced hypothermia for comatose survivors of cardiac arrest is being increasingly used. Patients so treated are anesthetized and paralyzed with neuromuscular blocking agents to prevent shivering. At temperatures above 33°C, there is no profound effect on the EEG or SSEPs from the hypothermia alone, although the anesthetic agent profoundly affects the EEG (Young, 2000).

10.2.3. Neuroimaging

Preliminary studies suggest a role for MRI scanning (especially for diffusion-weighted and fluid-attenuated inversion recovery sequences) in helping to determine a poor prognosis after cardiac arrest (Martin et al., 1991; Torbey et al., 2000; Wijdicks et al., 2001) (Fig. 10.4). Diffuse cerebral cortical or cerebral white matter signal

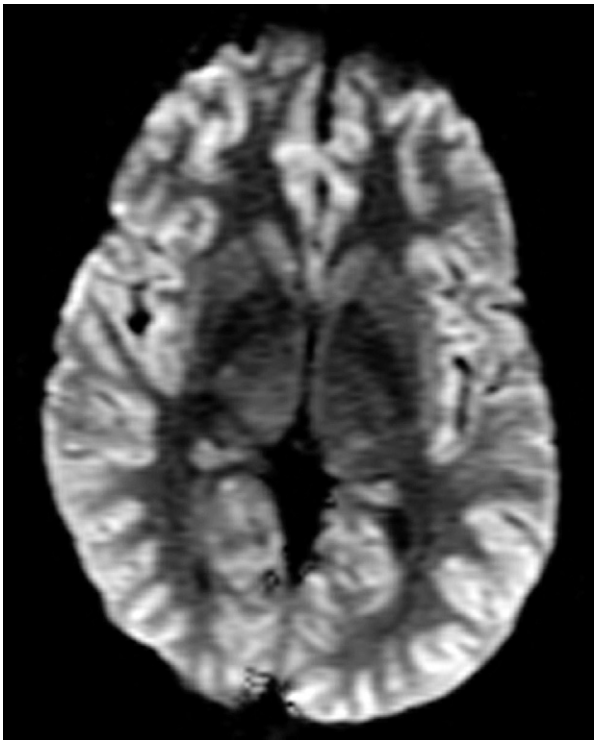

Fig. 10.4. Widespread cortical damage on MRI was confirmed at autopsy, which revealed widespread laminar necrosis.

is usually associated with a poor prognosis. The studies are small, however, and more work needs to be done to determine the sensitivity and false-positive rates.

10.2.4. Biochemical testing

Several studies investigated serum neuron-specific enolase (NSE), S100, cerebrospinal fluid, and creatine kinase brain isoenzyme as markers of brain damage in association with cardiac arrest. NSE is a gamma isomer of enolase that is located in neurons and neuroectodermal cells. NSE and S100 are not automated tests and are time-consuming. Thus there are logistical problems in obtaining these markers for prognostication. Because NSE is present in platelets, hemolysis increases the serum values.

In one class I study (Zandbergen et al., 2006) the 138 patients who had NSE serum concentrations of more than 33 μg/l between 24 and 72 hours did not recover conscious awareness. This confirmed earlier class III and IV studies (Fogel et al., 1997; Martens et al., 1998; Tiainen et al., 2003; Pfeifer et al., 2005). Thus, NSE should be a helpful prognostic indicator if logistical issues of timely biochemical testing can be overcome.

Serum astroglial S100 does not appear to be as reliably predictive as NSE, based on values measured within the first 2 days after cardiac arrest: the median false-positive rate was 2% (range 0–54%) in the four class III/IV studies that allowed this calculation (Fogel et al., 1997; Martens et al., 1998; Bottiger et al., 2001; Tiainen et al., 2003) and in Pfeifer et al., 2005; it was 5% in the class I study (Zandbergen et al., 2006).

Neither creatine kinase nor neurofilament protein in the serum or CSF seem sufficiently predictive of poor outcome: median false-positive rates are 10–15% (Sherman et al., 2000; Rosen et al., 2004).

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Chapter 11

Infectious etiologies of altered consciousness

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In every patient with altered consciousness there is always the concern that the disorder is due to infection. There is an urgency to diagnosing a central nervous system (CNS) infectious disease, as it is potentially treatable and the longer it goes untreated the greater the risk of neurological morbidity and mortality. The disorder of consciousness may be due to bacterial meningoencephalitis, viral encephalitis, tick-borne bacterial diseases, fungal meningitis or abscess, tuberculous meningitis, a brain abscess, or an epidural abscess. The disorder of consciousness may also be due to sepsis and an infectious encephalopathy, or the disorder of consciousness can follow an infection and be due to a parainfectious encephalomyelitis.

11.1. Bacterial meningoencephalitis

Bacterial meningitis begins as an acute purulent infection within the subarachnoid space. The multiplication and lysis of bacteria with the subsequent release of bacterial cell wall components in the subarachnoid space is the initial step in the induction of an inflammatory response that ultimately leads to the neurological complications of cerebral edema, obstructive and communicating hydrocephalus, seizure activity, stupor, and coma, and the cerebrovascular complications of arteritis, ischemic and hemorrhagic infarctions and septic venous sinus thrombosis.

The most common bacteria that cause meningitis, *Streptococcus pneumoniae* and *Neisseria meningitidis*, initially colonize the nasopharynx. From there bacteria are able to enter the bloodstream and avoid phagocytosis by neutrophils and classic complement-mediated bactericidal activity because of the presence of a polysaccharide capsule. Bacteria in the bloodstream can gain access to the cerebrospinal fluid (CSF) through the epithelial cells of the choroid plexus of the lateral ventricles. In addition, some bacteria, such as *S. pneumoniae*, can adhere to cerebral capillary endothelial cells through receptors on these cells and pass through or between cells to invade the CSF.

The CNS is an area of impaired host defense. Normal CSF contains few white blood cells and relatively small amounts of complement proteins and immunoglobulins. Bacteria are able to multiply rapidly. Phagocytosis of bacteria is further impaired by the fluid medium of CSF, which is less conducive to phagocytosis than a solid tissue substrate.

The multiplication and lysis of bacteria in the subarachnoid space leads to the release of bacterial cell wall components. Lipopolysaccharide molecules (endotoxins), a cell wall component of gram-negative bacteria, and teichoic acid and peptidoglycan, cell wall components of the pneumococcus, induce meningeal inflammation by stimulating the production of inflammatory cytokines and chemokines by microglia, astrocytes, monocytes, microvascular endothelial cells, and white blood cells in the CSF space. A large number of cytokines and chemokines (cytokines that induce chemotactic migration in leukocytes) are present in meningeal inflammation; the most thoroughly understood cytokines are tumor necrosis factor (TNF) and interleukin (IL)-1.

A number of pathophysiological consequences result from the presence of the inflammatory cytokines in CSF. TNF and IL-1 act synergistically to alter the permeability of the blood–brain barrier. The alteration in blood–brain barrier permeability during bacterial meningitis results in vasogenic cerebral edema and allows leakage of serum proteins and other molecules into the CSF, contributing to the formation of a purulent exudate in the subarachnoid space. The purulent exudate obstructs the flow of CSF through the ventricular system and

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diminishes the resorptive capacity of the arachnoid granulations in the dural sinuses. This leads to obstructive and communicating hydrocephalus and interstitial edema. The exudate also surrounds and narrows the diameter of the lumen of the large arteries at the base of the brain, and inflammatory cells infiltrate the arterial wall (vasculitis). This in combination with the alterations in cerebral blood flow that occur in this infection results in cerebral ischemia, focal neurological deficits, and stroke.

The inflammatory cytokines recruit polymorphonuclear leukocytes from the bloodstream and upregulate the expression of selectins on cerebral capillary endothelial cells and leukocytes, which allows leukocytes to adhere to vascular endothelial cells and subsequently migrate into the CSF. Neutrophils degranulate and release toxic metabolites that contribute to cytotoxic edema, cell injury, and death. The adherence of leukocytes to capillary endothelial cells increases the permeability of blood vessels, allowing leakage of plasma proteins into the CSF, further contributing to the inflammatory exudate in the subarachnoid space. The degranulation of leukocytes, and cerebral ischemia resulting from alterations in cerebral blood flow, cause cytotoxic edema. The combination of interstitial, vasogenic, and cytotoxic edema leads to raised intracranial pressure and coma. In addition, bacteria and the inflammatory cytokines induce the production of excitatory amino acids, reactive oxygen and nitrogen species (free oxygen radicals, nitric oxide, and peroxynitrite), and other mediators that induce massive apoptosis of brain cells.

11.1.1. Etiology

The most common causative organisms of community-acquired bacterial meningitis in adults ages 15–50 years are *S. pneumoniae* and *N. meningitidis*. The most important antecedent illnesses for pneumococcal meningitis are pneumonia, acute otitis media, and acute sinusitis. Several factors predispose to pneumococcal meningitis, including complement deficiency, hypogammaglobulinemia, splenectomy, head trauma with basilar skull fracture and CSF rhinorrhea, alcoholism, diabetes, and sickle cell disease. *N. meningitidis* initially colonizes the nasopharynx. The risk of invasive disease following nasopharyngeal colonization depends on both the virulence of the organism and host immune defense mechanisms, including the ability to produce antimeningococcal antibodies and the ability to lyse meningococci by both the classic and alternative complement pathways. Individuals with deficiencies of any of the complement components are highly susceptible to meningococcal infections. Less common causative organisms of bacterial meningitis in adults ages 15–50 years are *Listeria monocytogenes*, staphylococci, enteric gram-negative bacilli including *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, and *Pseudomonas aeruginosa*. Because of the profound reduction by vaccination in the incidence of invasive infections caused by *Haemophilus influenzae* type b, this organism is rarely a causative organism of bacterial meningitis, except in the elderly.

The most common organisms causing meningitis in a patient who has undergone a neurosurgical procedure, with the exception of a shunting procedure, are gram-negative bacilli and staphylococci. Coagulase-negative staphylococci and *Staphylococcus aureus* are the most common pathogens causing CSF shunt infections and meningitis that occurs as a complication of the use of a subcutaneous Ommaya reservoir for the administration of intrathecal chemotherapy.

The causative organism of bacterial meningitis in an immunocompromised patient can be predicted based on the patient's type of immune abnormality and the duration of immunosuppression. Patients with defects in cell-mediated immunity are most susceptible to CNS infections by microorganisms that are intracellular parasites, the eradication of which depends on an intact T-lymphocyte–macrophage system. *L. monocytogenes* is the most common cause of bacterial meningitis in patients with defective cell-mediated immunity. This includes patients with hematological malignancies, pregnancy, organ transplantation, cancer and cancer chemotherapy, human immunodeficiency virus (HIV) infection, and chronic corticosteroid therapy (Armstrong and Wong, 1982). Patients with defective humoral immunity are unable to mount an antibody response to a bacterial infection and are therefore unable to control infection caused by polysaccharide-encapsulated bacteria such as *S. pneumoniae* and *N. meningitidis*. Young age, old age, and congenital or acquired immunodeficiency states are associated with antibody deficiency or dysfunction. Congenital or acquired splenic dysfunction or a complement deficiency or dysfunction increases the risk of infection caused by polysaccharide-encapsulated pathogens (Overturf, 2003).

Recurrent bacterial meningitis occurs in patients with previous head trauma and a skull fracture or dural CSF leak, patients who have had a splenectomy, those with congenital defects such as meningomyelocele, those with deficiencies of any of the complement components or hypogammaglobulinemia, and those with a parameningeal focus of infection.

11.1.2. Clinical presentation

The classic triad of symptoms and signs of meningitis is fever, headache, and stiff neck. Bacterial meningitis may either present with a subacute presentation of

fever, headache, lethargy, and stiff neck that progresses over one to several days to a worsening disorder of consciousness, or may have a fulminant presentation and be progressive over several hours.

A stiff neck is the pathognomonic sign of meningeal irritation. Nuchal rigidity is present when the neck resists passive flexion. Kernig's and Brudzinski's signs are also classic signs of meningeal irritation. Kernig's sign is elicited with the patient in the supine position. The thigh is flexed on the abdomen and, with the knee flexed, the leg is then passively extended. When meningeal inflammation is present, the patient resists leg extension. Brudzinski described at least five different meningeal signs. His best known sign, the nape of the neck sign, is elicited with the patient in the supine position and is positive when passive flexion of the neck results in spontaneous flexion of the hips and knees (Feigin et al., 1992).

Seizure activity occurs in approximately 40% of patients. Seizure activity that has a focal onset is due to either focal arterial ischemia or infarction, cortical venous thrombosis with hemorrhage or focal edema. Generalized seizure activity and status epilepticus are due to fever, hyponatremia, anoxia from decreased cerebral perfusion, spread from a focal onset to a generalized tonic–clonic convulsion, or toxicity from antimicrobial agents.

Raised intracranial pressure is an expected complication of bacterial meningitis and is the major cause of obtundation and coma in this disease. The most common signs of raised intracranial pressure in bacterial meningitis are an altered level of consciousness and papilledema. A deteriorating level of consciousness in the patient with bacterial meningitis is most often due to increased intracranial pressure from cerebral edema.

11.1.2.1. Rash

The rash of meningococcemia begins as a diffuse erythematous maculopapular rash resembling a viral exanthema, but the skin lesions of meningococcemia rapidly become petechial. Petechiae are found on the trunk and lower extremities, in the mucous membranes and conjunctiva, and occasionally on the palms and soles. A petechial rash is characteristic of Rocky Mountain spotted fever. The rash of Rocky Mountain spotted fever consists initially of 1–5 mm pink macules that are often noted first on the wrist and ankles then spread centrally to the chest, face, and abdomen. The rash does not usually involve the mucous membranes. Petechial lesions in the axilla and around the ankles accompanied by lesions on the palms and soles of the feet are characteristic. The macules will initially blanch with pressure but after a few days they become fixed and turn dark red or purple. Diagnosis can be made by biopsy of the lesions and staining of the specimen with fluorescent antibodies to *Rickettsia rickettsii* (Hornick, 1988). The characteristic rash caused by an enterovirus consists of erythematous macules and papules on the face, neck, trunk, and to a lesser degree the extremities. Rarely the rash associated with enteroviral infection may become petechial in nature. Other infectious diseases that may manifest with a petechial, purpuric, or erythematous maculopapular rash like that of meningococcemia include West Nile virus encephalitis, bacterial endocarditis, echovirus type 9 viremia, and pneumococcal or *H. influenzae* meningitis. The location of the rash predominately on the trunk and lower extremities is typical of meningococcemia.

At least 50% of patients with acute bacterial meningitis develop neurological complications including cerebral edema, hydrocephalus, septic sinus venous thrombosis, arteritis, seizures, cranial nerve palsies (most commonly hearing impairment due to purulent labyrinthitis), septic shock, disseminated intravascular coagulation, renal failure, syndrome of inappropriate antidiuretic hormone secretion (SIADH), or rarely, central diabetes insipidus, cerebral salt-wasting syndrome, and adult respiratory distress syndrome.

11.1.3. Diagnosis

When the clinical presentation is suggestive of bacterial meningitis, blood cultures should be obtained and empiric antimicrobial therapy and adjunctive therapy initiated immediately. Blood cultures may identify the infecting organism in 50–80% of cases of bacterial meningitis (although this frequency varies with the causative organism) and they are more often positive in patients who have not received prior treatment with antibiotics. The initiation of therapy should not await a head computed tomography (CT) scan and a lumbar puncture. A cranial head CT scan prior to lumbar puncture is not absolutely indicated in all patients with bacterial meningitis. If any of the following are present in a patient with suspected bacterial meningitis, CT scan should be obtained prior to lumbar puncture: 1) focal neurological deficit; 2) new onset seizure; 3) papilledema; 4) abnormal level of consciousness; and 5) immunocompromised state (Tunkel et al., 2004). The clinical presentation may, however, rapidly become complicated by a deteriorating level of consciousness and seizure activity, and the appearance and management of these complications are better tolerated by the physician if neuroimaging has been obtained prior to lumbar puncture. Antimicrobial therapy for several hours prior to lumbar puncture does not

significantly alter the CSF white blood cell count or glucose concentration so that a diagnosis of bacterial meningitis is not suspected, and it is not likely to sterilize the CSF so that the organism cannot be identified by Gram's stain or grown in culture. The CSF white blood cell count increases after the initiation of antimicrobial therapy. The yield of CSF Gram's stain and culture may be diminished by antimicrobial therapy given for several hours prior to lumbar puncture but the increasingly available polymerase chain reaction (PCR), which detects nucleic acid of bacteria in CSF, is not affected by hours of antimicrobial therapy.

In bacterial meningitis, cranial CT cannot reliably predict who will and who will not herniate from lumbar puncture. In the patient with either an altered level of consciousness or papilledema, signs of increased intracranial pressure, a bolus dose of mannitol 1 g/kg body weight can be given intravenously and lumbar puncture performed 20 minutes later. Alternatively, the patient can be intubated and hyperventilated in addition to being treated with mannitol. If the clinician is concerned about a risk of herniation with lumbar puncture, lumbar puncture can be delayed while the patient is being treated with empiric antimicrobial and adjunctive therapy until either the patient stabilizes enough that lumbar puncture is safe or the organism is identified by blood culture.

The diagnosis of bacterial meningitis is made by examination of the spinal fluid. The classic CSF abnormalities in bacterial meningitis are as follows: 1) increased opening pressure ($>180\ mmH_2O$ in 90%); 2) a pleocytosis of polymorphonuclear leukocytes (>100 cells/mm^3 in 90%); 3) a decreased glucose concentration (<45 mg/dl and/or a CSF:serum glucose ratio of <0.31); and 4) an increased protein concentration. The CSF should be examined by Gram's stain and bacterial culture. Gram's stain is positive in identifying the organism in 60–90% of cases of bacterial meningitis. The probability of detecting bacteria on a Gram's stain specimen depends on the number of organisms present. The higher the CSF bacterial concentration, the more likely the smear is to be positive. CSF culture is positive in 80% of untreated patients. The yield on Gram's stain and culture is much lower in patients who have been pretreated with oral antibiotics. A broad-range PCR can detect small numbers of viable and nonviable organisms in CSF. When the broad-range PCR is positive, a PCR that uses specific bacterial primers to detect the nucleic acid of *S. pneumoniae*, *N. meningitidis*, *E. coli*, *L. monocytogenes*, *H. influenzae*, and *Streptococcus agalactiae* should be done.

11.1.4. Differential diagnosis

The differential diagnosis of a clinical presentation of fever, headache, and altered consciousness includes viral encephalitis, fungal meningitis, tuberculous meningitis, tick-borne bacterial infections, focal suppurative CNS infections, including subdural and epidural empyema and brain abscess, and subarachnoid hemorrhage. These disorders can all be distinguished from bacterial meningitis by the findings on neuroimaging and spinal fluid analysis. The typical CSF profile in patients with viral encephalitis is a lymphocytic pleocytosis with a normal glucose concentration, as contrasted with the polymorphonuclear pleocytosis and hypoglycorrhachia characteristic of bacterial meningitis. Patients with viral encephalitis, and especially those patients with herpes simplex virus (HSV) encephalitis, have parenchymal abnormalities on brain magnetic resonance imaging (MRI). Subdural and epidural empyema and brain abscess are readily visualized on MRI. Subarachnoid hemorrhage may present with the apoplectic onset of a severe headache and a sudden transient loss of consciousness followed by a severe headache. Nuchal rigidity is a frequent sign in subarachnoid hemorrhage. The hemorrhage may be visualized by CT scan. The presence of bloody CSF that does not clear between tubes 1 and 4 is characteristic of subarachnoid hemorrhage.

11.1.5. Treatment

Bacterial meningitis is initially treated empirically, after a single set of blood cultures is obtained and prior to CT scan and lumbar puncture. The choice of antibiotic for empirical antimicrobial therapy is based on the possibility that a penicillin- and cephalosporin-resistant strain of *S. pneumoniae* is the causative organism of the meningitis, and on the patient's age and any associated condition that may have predisposed the patient to meningitis. Empirical therapy in infants older than 1 month of age and in children and adults up to age 50 should include a combination of either a third- or fourth-generation cephalosporin plus vancomycin. Empirical therapy of bacterial meningitis in adults older than 50 years of age and in the immunocompromised patient should include the combination of a third- or fourth-generation cephalosporin plus vancomycin plus ampicillin. Prior to or with the first dose of antibiotic, dexamethasone should be administered. The dose of dexamethasone for adults is 10 mg intravenously every 6 hours for 4 days.

Once the bacterial pathogen is isolated and the sensitivity of the organism to the antibiotic is confirmed by in vitro testing, antimicrobial therapy is modified

Table 11.1

Recommendations for specific antibiotic therapy in bacterial meningitis

Microorganism		Antibiotic
Streptococcus pneumoniae	Penicillin-susceptible	Penicillin G or cefepime (or ceftriaxone or cefotaxime)
	Penicillin-tolerant (MIC 0.1–1 μg/ml)	Cefepime (or cefotaxime or ceftriaxone) or meropenem
	Penicillin-resistant (MIC >1 μg/ml)	Cefepime (or ceftriaxone or cefotaxime) plus vancomycin
Neisseria meningitidis		Penicillin G or ampicillin Cefepime for penicillin-resistant strains
Listeria monocytogenes		Ampicillin Add gentamicin for critically ill patient
Streptococcus agalactiae (group B streptococcus)		Ampicillin or penicillin G or cefotaxime
Gram negative Enterobacteriaceae (*Klebsiella*, *Escherichia coli*, *Proteus*)		Ceftriaxone or cefotaxime or cefepime
Pseudomonas aeruginosa		Meropenem or cefepime
Staphylococcus aureus	Methicillin-susceptible Methicillin-resistant	Nafcillin or oxacillin Vancomycin
Staphylococcus epidermidis		Vancomycin or linezolid
Haemophilus influenzae		Ceftriaxone or cefotaxime or cefepime

accordingly. Table 11.1 lists the recommended antibiotic therapy based on meningeal pathogen. Table 11.2 lists the recommended doses for the antibiotics commonly used in the treatment of bacterial meningitis. The results of a prospective, randomized, multicenter, double-blind trial of adjunctive dexamethasone therapy for bacterial meningitis in 301 adults in five European countries over a period of 9 years demonstrated that dexamethasone improves the outcome in adults with acute bacterial meningitis and reduces mortality (de Gans and van de Beek, 2002). The benefits were most striking in the patients with pneumococcal meningitis. Dexamethasone was administered in a dose of 10 mg, 15–20 minutes before or with the first dose of antibiotic, and given every 6 hours for 4 days. Previously, the efficacy of dexamethasone had been demonstrated in animal models of bacterial meningitis and in childhood meningitis, if begun with or before antibiotics. As stated earlier in this chapter, in bacterial meningitis it is not the pathogen itself that causes the neurological complications. It is the inflammatory response, and specifically the formation of the inflammatory cytokines initiated by the lysis of bacteria with the release of bacterial cell walls in the subarachnoid space that leads to the neurological complications. Dexamethasone exerts its beneficial effects by inhibiting the synthesis of the inflammatory cytokines and by decreasing CSF outflow resistance and stabilizing the blood–brain barrier.

Bacteria meningitis due to *S. pneumoniae*, *H. influenzae*, and group B streptococci is usually treated with intravenous antibiotics for 10–14 days. Meningitis due to *N. meningitidis* is treated for 5–7 days. Patients with clinically suspected meningococcal meningitis have to be isolated for the first 24 hours after initiation of antibiotic therapy and treated with ciprofloxacin (500mg) single dose or rifampin 600 mg every 12 hours for 2 days after they finish a course of intravenous antimicrobial therapy to eradicate nasopharyngeal colonization. Meningitis due to *L. monocytogenes* and Enterobacteriaceae is treated for 3–4 weeks. Gentamicin is added to ampicillin in critically ill patients with *L. monocytogenes* meningitis. Current recommendations are that all patients with pneumococcal meningitis have CSF re-examined 48 hours after antibiotic therapy has been initiated to determine if the CSF culture is negative. The CSF white blood cell count and glucose concentration is not used to monitor response to therapy.

Table 11.2

Recommended doses of antibiotics commonly used in the treatment of bacterial meningitis

Antibiotic agent	Total daily dosage (dosing interval in hours)
Ampicillin	Neonate: 150 mg/kg/d (q 8 h) Infants and children: 300 mg/kg/d (q 6 h) Adult: 12 g/d (q 4–6 h)
Cefepime	Infants and children: 150 mg/kg/d (q 8 h) Adult: 6 g/d (q 8 h)
Cefotaxime	Neonate: 100–150 mg/kg/d (q 8–12 h) Infants and children: 225–300 mg/kg/d (q 6–8 h) Adult: 8–12 g/d (q 4–6 h)
Ceftriaxone	Infants and children: 80–100 mg/kg/d (q 12 h) Adult: 4 g/d (q 12 h)
Gentamicin	Neonate: 5 mg/kg/d (q 12 h) Infants and children: 7.5 mg/kg/d (q 8 h) Adult: 5 mg/kg/d (q 8 h)
Meropenem	Infants and children: 120 mg/kg/d (q 8 h) Adult: 6 g/d (q 8 h)
Nafcillin	Neonates: 75 mg/kg/d (q 8–12 h) Infants and children: 200 mg/kg/d (q 6 h) Adult: 9–12 g/d (q 4 h)
Penicillin G	Neonates: 0.15–0.2 g/mU/kg/d (q 8–12 h) Infants and children: 0.3 mU/kg/d (q 4–6 h) Adult: 24 mU/d (q 4–6 h)
Rifampin/ rifampicin	Infants and children: 10–20 mg/kg/d (q 12–24 h) Adults: 600–1200 mg/d (q 12 h)
Vancomycin*	Neonates: 20–30 mg/kg/d (q 8–12 h) Infants and children: 60 mg/kg/d (q 6 h) Adults: 45–60 mg/kg/d (q 6–8 h)

*For intravenous vancomycin therapy, maintain serum trough concentrations of 15–20 μg/ml. Recommended peak levels 1 hour after intravenous administration, vancomycin 25 μg/ml. Intraventricular vancomycin administration: children 1–2 mg/d, adults 10–20 mg/d.

11.1.6. Postoperative meningitis in neurosurgical patients

The majority of cases of postoperative meningitis are caused by *S. aureus*, coagulase-negative staphylococci, aerobic gram-negative bacilli and streptococci. Empiric therapy for postoperative meningitis should include a combination of vancomycin and meropenem based on the possibility that methicillin-resistant *S. aureus* is the causative organism. Meropenem is added for Gram-negative coverage, including *P. aeruginosa*. When the results of culture and sensitivities are available, antimicrobial therapy can be modified accordingly.

11.1.7. Enterococcal meningitis

Even though enterococci are the second most common causative organisms of bloodstream infections in patients in the intensive care unit, they are relatively uncommon causes of CNS infections. Enterococci are part of the normal flora in the gastrointestinal tract. The most common conditions associated with enterococcal meningitis are external ventricular drains, epidural catheters, neurosurgical procedures, immunosuppressive therapy, gastrointestinal disease, and *Strongyloides* species hyperinfections. Most cases of enterococcal meningitis are caused by *Enterococcus faecalis* (Zeana et al., 2001). Vancomycin-resistant enterococcal infections are a major concern. Enterococci are naturally resistant to several antibiotics and have the ability to acquire resistance through the exchange of genetic material (Zeana et al., 2001). Linezolid has good CSF penetration and is generally well tolerated but prolonged therapy has been associated with thrombocytopenia. The usual dose of linezolid for enterococcal infections is 600 mg every 12 hours. Adverse effects include bone marrow suppression with thrombocytopenia, rash, liver function abnormalities, and renal insufficiency. There are also reports of patients with linezolid-resistant enterococcal infections. Quinupristin and dalfopristin are two semisynthetic streptogramin antibiotics that are combined in a 30:70 ratio and are bacteriostatic against enterococcus (Steinmetz et al., 2001; Williamson et al., 2002). Intravenous quinupristin/dalfopristin penetrates poorly into the subarachnoid space. The administration of quinupristin/dalfopristin by both the intravenous (7.5 mg/kg every 8 h) and intraventricular route (2 mg daily) was successful in eradicating vancomycin-resistant *Enterococcus faecium* ventriculostomy-related meningitis (Williamson et al., 2002).

11.2. Viral encephalitis

Viral encephalitis is due to an acute infection of brain parenchyma and presents with fever, headache, and an altered level of consciousness. There may also be focal or multifocal neurological deficits and focal or generalized seizure activity.

11.2.1. Etiology

Herpes simplex virus type 1 (HSV-1) is the most common cause of acute sporadic viral encephalitis. Humans acquire HSV infection from other humans.

Primary infection with HSV-1 usually occurs in the oropharyngeal mucosa and is typically asymptomatic. Symptomatic disease is characterized by fever, pain, and inability to swallow because of lesions on the buccal and gingival mucosa. The duration of illness is 2–3 weeks (Whitley et al., 1998). After primary infection, HSV-1 is transported to the CNS by retrograde axoplasmic flow of virus in the axons of a division of the trigeminal nerve. The trigeminal ganglion becomes colonized and the virus establishes latent infection in the ganglion. Reactivation of latent ganglionic infection with replication of virus leads to encephalitis with inflammatory and necrotizing lesions in the inferior and medial temporal lobes, the orbital frontal cortex, and the limbic structures (Stroop and Schaefer, 1986; Barnett et al., 1994). HSV-1 encephalitis may also be the result of primary infection from intranasal inoculation of virus with direct invasion of the olfactory bulbs and spread via the olfactory pathways to the orbital frontal and temporal lobes.

There are a number of arthropod-borne viruses (arboviruses) that can cause encephalitis. These include La Crosse virus, St Louis encephalitis virus, West Nile virus, Japanese encephalitis virus, eastern equine encephalitis virus, western equine encephalitis virus, Venezuelan equine encephalitis virus, dengue virus, Powassan virus, and Colorado tick fever virus. Japanese encephalitis virus is the most common cause of arboviral infections worldwide. In the USA, the La Crosse virus, St Louis encephalitis virus, and West Nile virus are the most common causes of arthropod-borne viral encephalitis. Predicting the etiological agent of mosquito-borne viral encephalitis depends on geographical location. La Crosse virus is endemic in the upper midwestern USA. The St Louis encephalitis virus is endemic in the midwestern and southeastern USA and western and eastern Canada. West Nile virus has spread throughout the USA from its beginnings in August 1999 in the New York City metropolitan area. Japanese encephalitis virus causes encephalitis in China, southeast Asia, northeast India, Nepal, and Sri Lanka. Eastern equine encephalitis virus is found along the eastern coast of the USA from Massachusetts to Florida and along the Gulf coast as well as in Minnesota and Texas. The western equine encephalitis virus is found throughout North America and the Venezuelan encephalitis virus is endemic in South America and a rare cause of encephalitis in the southwestern USA. Dengue virus causes dengue fever in Hawaii, Asia, Africa, the Caribbean, and Central and South America, and is transmitted by the bite of a mosquito. There is a short incubation period, with travelers to endemic areas becoming symptomatic shortly after they return home.

The arboviruses are inoculated into the host subcutaneously by a mosquito or tick bite and then undergo local replication at the skin site. A viremia follows and, if there is a large enough inoculum of virus, invasion and infection of the CNS occurs. Initial CNS infection by arboviruses appears to occur via cerebral capillary endothelial cells with subsequent infection of neurons. Virus spreads from cell to cell, typically along dendritic or axonal processes. Arboviral encephalitis is primarily a disease of cortical gray matter and brainstem and thalamic nuclei.

Rabies virus is primarily transmitted by the bite of a rabid animal but can also be acquired by inhalation of aerosolized virus in caves or in the laboratory. In North America, bats, dogs, and raccoons are the principal rabies vectors, with most human cases being caused by the bite of a bat. Rabies virus has also been transmitted from an organ donor to organ recipients (Srinivasan et al., 2005). The rabies virus replicates in muscle and binds to the nicotinic acetylcholine receptor at the neuromuscular junction. Virus moves by retrograde axonal transport to the CNS (Jackson, 2002).

A number of viruses acquired in childhood, in addition to HSV-1, may react to cause encephalitis. Epstein–Barr virus causes infectious mononucleosis. Encephalitis was the first described neurological complication of infectious mononucleosis (Connelly and DeWitt, 1994). In immunocompromised patients, the acquisition of or the reactivation of latent Epstein–Barr virus infection can cause a syndrome of altered mental status with or without focal neurological deficits (Patchell, 1994). Varicella zoster virus (VZV) causes chicken pox and then establishes latent infection in the CNS. The virus can reactivate to cause shingles or encephalitis. VZV encephalitis may follow the cutaneous eruption of shingles or occur in association with or following the eruption of a diffuse varicella-like rash. There is often a period of several months between the eruption of shingles and the clinical presentation of varicella zoster encephalitis. Human herpesvirus type 6 (HHV-6) is an infection acquired in childhood that is similar to VZV and establishes latent infection in the CNS, and can reactivate in the setting of immunosuppression. HHV-6 may cause an encephalitis with focal features resembling HSV-1 encephalitis or an encephalitis with multifocal areas of demyelination (McCullers et al., 1995; Kamei et al., 1997). Cytomegalovirus can cause encephalitis in immunosuppressed individuals and can be transmitted from organ donor to organ recipient.

Reactivation of a virus acquired in childhood, the JC virus, is the etiology of progressive multifocal leukoencephalopathy, a demyelinating disease occurring

in patients with severe cellular immunosuppression. The JC virus selectively infects and destroys oligodendrocytes, leading to a pattern of multifocal demyelination. Enteroviruses may cause encephalitis in persons who have hypogammaglobulinemia or agammaglobulinemia. Measles may cause either subacute measles encephalitis, which occurs most commonly in immunosuppressed persons, or subacute sclerosing panencephalitis, which presents after a latent period of several years or more after acute measles infection.

11.2.2. Clinical presentation

HSV-1 encephalitis begins with fever and hemicranial or generalized headache, followed by behavioral abnormalities, difficulty with memory, word finding difficulty and focal seizure activity and/or focal neurological deficits. Symptoms often take 2–3 weeks to reach maximal severity.

There are some similarities to and some differences from the clinical presentation of mosquito-borne viral encephalitis, depending on the specific virus. La Crosse virus is the most common cause of pediatric mosquito-borne viral encephalitis in the USA. Clinical manifestations of symptomatic infection range from a mild febrile illness to aseptic meningitis, a mild encephalitic illness, and severe encephalitis. Symptoms of a mild encephalitic illness usually begin with headache, fever, irritability, vomiting, and abdominal pain followed by increasing lethargy and behavioral changes or brief single seizures, or both. Symptoms last for 3–4 days and the child's condition improves over the next 3–4 days. La Crosse virus encephalitis may also have a fulminant presentation of fever, headache, disorientation, and seizures progressing to coma. Focal neurological deficits occur in 16–25% of children and focal and generalized seizures in 42–62% (McJunkin et al., 1998). St Louis encephalitis virus may cause a mild febrile illness with headache, an aseptic meningitis, or an encephalitis. The majority of symptomatic infections present as encephalitis, and adults older than 50 years of age are most commonly affected. Arboviral encephalitis, in general, is often preceded by an influenza-like prodrome of malaise, myalgias, and fever. In the case of encephalitis due to the St Louis encephalitis virus, this is followed by symptoms of headache, nausea, vomiting, confusion, disorientation, irritability, stupor, tremor, and occasionally convulsions.

West Nile fever begins 5–15 days after the bite of a mosquito carrying the virus with the sudden onset of fever, headache, backache, and myalgias. Patients may also complain of pharyngitis, conjunctival injection, diarrhea, nausea, vomiting, and abdominal pain. In about 50% there is a nonpruritic roseolar or maculopapular rash on the chest, back, and arms which lasts approximately a week (Asnis et al., 2000). Concomitant with or following these symptoms, patients may develop a coarse tremor in the upper extremities and symptoms of encephalitis. There also may be a mild carditis, hepatitis, or pancreatitis. Some cases of encephalitis are associated with an acute flaccid paralysis, a poliomyelitis-like syndrome. Western equine encephalitis virus infects horses and humans, and disease in horses may precede disease in humans. Inapparent infections with western equine encephalitis virus are more common than symptomatic cases. Like St Louis encephalitis virus and West Nile virus, infection with western equine encephalitis begins with an influenza-like prodrome of fever, malaise, myalgias, pharyngitis, and vomiting. As the disease progresses, lethargy, irritability, convulsions, or coma develop (Bale, 1993). Eastern equine encephalitis virus causes a severe encephalitis. There may be a short prodrome of fever, headache, and abdominal pain followed by neurological symptoms of confusion, somnolence, focal neurological deficits, seizures, and meningeal signs. The majority of patients have an abrupt onset of symptoms of encephalitis and a rapid progression from stupor to coma (Deresiewicz et al., 1997).

Japanese encephalitis virus infects the thalamus, brainstem, basal ganglia, substantia nigra, spinal cord, cerebral cortex, and cerebellum. The clinical presentation reflects the involvement of these areas. Encephalitis due to Japanese encephalitis virus is characterized by fever, vomiting, convulsions, and coma. During the acute illness, patients may have restricted eye movements, opsoclonus, upbeating nystagmus, cogwheel rigidity (due to lesions in the substantia nigra), or flaccid paralysis (due to lesions in the spinal cord).

Venezuelan equine encephalitis virus begins with fever, severe headache, myalgias, vomiting, and sometimes diarrhea. This is associated with or followed within a few days by convulsions, disorientation, drowsiness and lethargy, or stupor (Weaver et al., 1996).

The most important tick-borne causes of viral encephalitis in North America are Powassan virus and Colorado tick fever virus. The onset of encephalitis due to the Powassan virus is abrupt with headache, fever, and convulsions. The encephalitis may be associated with focal neurological signs and may thus mimic HSV encephalitis (Calisher, 1994). Infection with the Colorado tick fever virus is typically a biphasic illness. The onset of illness is characterized by fever, chills, severe headache, conjunctival injection, and nausea. A petechial or maculopapular rash may be seen. Defervescence may then occur, only to be followed by the recurrence of fever in 2–3 days with signs of encephalitis (Calisher, 1994).

Dengue fever begins as an acute febrile illness with rigors, headache, retroorbital pain, myalgias, arthralgias, rash, and fatigue. Most dengue infections result in relatively mild illness but some patients will have a course complicated by cerebral edema, hemorrhagic diathesis, hypoperfusion, hyponatremia, and liver and renal failure (Rigau-Perez et al., 1997).

Encephalitis may complicate chicken pox or cutaneous zoster eruption within days to months after the rash. It is due to acute viral infection. When encephalitis complicates chicken pox it is characterized by headache, fever, vomiting, seizures, and focal neurological abnormalities, including hemiparesis and ataxia. When encephalitis is associated with shingles or when it follows the cutaneous eruption of zoster by several months, it begins with headache but then patients develop confusion and may have focal neurological deficits.

When encephalitis complicates acute Epstein–Barr virus infection it presents with fever, headache, focal neurological deficits, an altered level of consciousness or seizure activity, or a combination of these.

In immunosuppressed patients, HHV-6 encephalitis presents with focal neurological deficits resembling HSV-1 encephalitis.

Cytomegalovirus causes two forms of encephalitis and both occur primarily in immunosuppressed individuals. In the diffuse micronodular form of encephalitis, there is the acute or subacute development of forgetfulness, memory impairment, and apathy. Cytomegalovirus also causes a ventriculoencephalitis, which is characterized by a rapidly fatal delirium with oculomotor palsies and nystagmus.

Classic rabies, due to the bite of a rabid dog, may present as either an encephalitic illness (the furious form) or a paralytic illness (the dumb form). There are three major cardinal features of furious rabies: fluctuating consciousness, phobic spasms, and autonomic dysfunction (hypersalivation, piloerection, cardiac arrhythmias, and dilated pupils). The dumb form of rabies presents with weakness in the bitten limb that progresses to generalized weakness. Rabies due to the bite of a bat presents with focal neurological deficits (hemiparesis or hemisensory deficits), choreiform movements, myoclonus, seizures, and hallucinations. Phobic spasms are not a cardinal feature of bat rabies (Hemachudha and Rupprecht, 2005).

11.2.3. Diagnosis

The diagnosis of HSV encephalitis is made by MRI, which demonstrates the characteristic abnormalities of HSV-1 encephalitis, and spinal fluid analysis. The characteristic MRI abnormality of HSV-1 encephalitis is a high-signal-intensity lesion on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images in the medial and inferior temporal lobe extending up into the insula. A normal T2-weighted and FLAIR MRI is evidence against the diagnosis of HSV-1 encephalitis. Examination of the CSF shows an increased opening pressure, a lymphocytic pleocytosis of 5–500 cells/mm^3, a mild to moderate increase in the protein concentration and a normal or mildly decreased glucose concentration. HSV nucleic acid can be detected by PCR on CSF. The PCR is most likely to be positive on days 3–10. If the CSF PCR is negative and it is in the first 24–72 hours from the onset of symptoms, the spinal fluid analysis should be repeated and the PCR performed again. Porphyrin compounds from the degradation of heme and erythrocytes may inhibit the PCR, and a false-negative HSV-1 PCR may be obtained from bloody or xanthochromic CSF specimens. CSF and serum samples should be obtained to determine if there is intrathecal synthesis of antibodies against HSV. Antibodies against HSV do not appear in the CSF until approximately 8–12 days after the onset of disease, and they can increase markedly during the first 2–4 weeks of infection. A serum:CSF antibody of less than 20:1 is considered diagnostic of HSV infection. There is also a characteristic EEG pattern in HSV-1 encephalitis consisting of periodic stereotyped sharp and slow-wave complexes that occur at regular intervals of 2–3 seconds and are expressed maximally over the involved temporal lobe. The periodic complexes are most often observed between the second and 15th day of the illness (Smith et al., 1975).

The laboratory diagnosis of arboviral encephalitis has been established by the Centers for Disease Control and Prevention (CDC) and is listed in Table 11.3.

Table 11.3

Laboratory diagnosis of arboviral encephalitis

Definitive diagnosis of arboviral encephalitis
One or more of the following:
Fourfold increase in antibody titer between acute and convalescent sera
Viral isolation from tissue, blood, or cerebrospinal fluid
Virus-specific IgM antibody in cerebrospinal fluid
Presumptive diagnosis of arboviral encephalitis
Stable increased antibody titer to arboviral virus
≥320 by hemagglutination inhibition
≥128 by complement fixation
≥256 by immunofluorescent assay
≥160 by plaque reduction neutralization test
or
Positive serum IgM capture enzyme immunoassay

The best way to make the diagnosis is to detect a fourfold or greater increase in viral antibody titer between acute and convalescent sera or to identify viral specific antibody in CSF. The detection of viral specific IgM antibody in serum only makes the diagnosis presumptive. The plaque reduction neutralization assay is the recommended test for detecting West Nile virus neutralizing antibodies in serum. In order to attribute the neurological illness to West Nile virus infection, one of the following criteria must be met: 1) West Nile virus IgM antibody in CSF detected by enzyme-linked immunosorbent assay (ELISA); 2) West Nile virus nucleic acid in CSF by PCR; 3) a fourfold increase in neutralizing immunoglobulin G antibody titer between acute and convalescent sera obtained 4 weeks later; or 4) isolation of the virus from the brain or spinal cord.

Examination of the spinal fluid in arboviral encephalitis demonstrates a lymphocytic pleocytosis, a normal glucose concentration and a moderately increased protein concentration. Polymorphonuclear leukocytes may predominate early in infection with a shift to a lymphocytic pleocytosis early in the disease course. The neuroimaging abnormalities of encephalitis are best detected by T_2-weighted and FLAIR MRI images. On these images there are often small areas of hyperintensities that are focal areas of encephalitis. Hyperintense lesions in the substantia nigra, basal ganglia, and thalamus on T_2-weighted images are seen in all the flavivirus infections (West Nile virus, St Louis encephalitis virus, and Japanese encephalitis virus). Eastern equine encephalitis virus may also cause areas of increased T_2 signal abnormalities in the thalamus and basal ganglia. Antibody tests for the flaviviruses may be negative in the early phase of the disease and become positive later.

The diagnosis of VZV encephalitis is suggested by neuroimaging evidence of large and small ischemic and hemorrhagic infarctions of the cortical and subcortical gray matter and white matter as well as spherical subcortical white matter lesions with a typical appearance of demyelination. The detection of VZV IgM antibodies in the CSF is more sensitive than the detection of VZV DNA by PCR. The diagnosis of encephalitis due to Epstein–Barr virus is made by the serology. Epstein–Barr virus DNA is found in peripheral blood latently infected mononuclear cells and may be detected in the CSF in any CNS inflammatory disorder.

Serology should be sent for rabies virus IgM and IgG if there is any possibility of exposure to a bat or the bite of a rabid dog.

11.2.4. Treatment

HSV-1 encephalitis is treated with intravenous acyclovir 10 mg/kg every 8 hours for 3 weeks. The therapy of arboviral encephalitis is primarily supportive care with management of the neurological complications of seizures and increased intracranial pressure. Ribavirin has been investigated for the therapy of La Crosse virus encephalitis and human intravenous immunoglobulin has been investigated for the treatment of West Nile virus encephalitis. VZV encephalitis is treated with intravenous acyclovir 10 mg/kg every 8 hours for a minimum of 14 days. HHV-6 variant A encephalitis is treated with foscarnet 60 mg/kg every 8 hours. HHV-6 variant B can be treated with either foscarnet 60 mg/kg every 8 hours or ganciclovir 5 mg/kg every 12 hours. Cytomegalovirus encephalitis is treated with a combination of ganciclovir and foscarnet. The dose of ganciclovir is 5 mg/kg intravenously every 12 hours for a minimum of 2–3 weeks followed by maintenance therapy of 5 mg/kg per day for an indefinite period. The dose of foscarnet is 60 mg/kg intravenously every 8 hours for a minimum of 2–3 weeks followed by maintenance therapy (60–120 mg/kg per day). Cytomegalovirus, like HHV-6, lacks the thymidine kinase for acyclovir; as such, acyclovir has no effect on cytomegalovirus or HHV-6 CNS infection. In approximately 70% of cases of viral encephalitis, an etiological organism cannot be identified despite the availability of PCR (Studahl et al., 1998). Empiric therapy with acyclovir is often initiated based on the possibility that an acyclovir-sensitive virus may be the causative organism of the encephalitis. Acyclovir-resistant HSV isolates have been identified in both immunosuppressed and immunocompetent persons. Patients with acyclovir-resistant HSV-1 encephalitis have been treated successfully with foscarnet or ganciclovir.

Because of the long incubation period, rabies virus infection is potentially treatable. The administration of postexposure prophylaxis with rabies vaccine and human rabies immune globulin can prevent infection after exposure.

11.3. Tick-borne bacterial infections

11.3.1. Etiology

Rickettsia rickettsii is transmitted by the bite of the American dog tick (*Dermacentor variabilis*), the Rocky Mountain wood tick (*Dermacentor andersoni*), *Amblyomma* ticks, or the common brown dog tick (*Rhipicephalus sanguineus*).

11.3.2. Clinical presentation

The illness begins with fever, malaise, headache, myalgias, and typically a rash. The rash begins with macules on the wrist and ankles that subsequently spread to involve the trunk, face, palms, and soles. The rash progresses from a maculopapular rash to a petechial then a purpuric rash. Of the patients, 100% have fever, 95% have malaise, 90% have frontal headache, 80% have myalgias, and 60% have vomiting. A disorder of consciousness, meningismus, conjunctivitis, renal dysfunction, respiratory failure, and myocarditis may develop during the course of the illness (Spach et al., 1993). In addition to a severe bifrontal headache and a disorder of consciousness, which is most often delirium or confusion, patients may also progress to coma. Pathologically brisk reflexes are often found on examination.

Two human ehrlichioses may present with fever and confusion. *Ehrlichia chaffeensis* infects mononuclear phagocytes in blood and tissue and causes human monocytic ehrlichioses. *Anaplasma phagocytophilum* causes human granulocytic ehrlichioses (anaplasmosis). *A. phagocytophilum* and *Borrelia burgdorferi* are both transmitted by *Ixodes* species ticks, and coinfection with *A. phagocytophilum* and *B. burgdorferi* can occur. The ehrlichias are small, gram-negative pleomorphic coccobacilli that cause a nonspecific febrile illness that on presentation resembles Rocky Mountain spotted fever. The most characteristic clinical features are high fever and intense headache with a disorder of consciousness ranging from mild lethargy to coma. Hyperreflexia may also be a finding on examination in patients with *A. phagocytophilum*.

11.3.3. Diagnosis

The tick-borne bacterial infections are difficult to diagnose. Serological analysis is not useful during the acute phase of Rocky Mountain spotted fever, PCR analysis is insensitive and diagnosis often depends on immunohistochemical analysis of skin biopsy specimens for *R. rickettsii* (Dumler and Walker, 2005). Serological diagnosis is still, however, recommended and acute and convalescent sera should be sent to detect an increase in antibody titers. Detectable antibodies may not be present in the acute sample, and sending the sample repeatedly on a weekly basis may detect antibodies. PCR assays and specific enzyme linked immunosorbent assays are increasingly available. Spinal fluid analysis in Rocky Mountain spotted fever may be normal or may demonstrate a mononuclear CSF pleocytosis. The CSF glucose concentration is usually normal. Spinal fluid analysis in human monocytic ehrlichiosis usually demonstrates a lymphocytic pleocytosis and a normal glucose concentration. Spinal fluid analysis in anaplasmosis may demonstrate a mild CSF pleocytosis (Sexton and Dasch, 2005).

Table 11.4 provides a list of the serological tests to aid in the diagnosis of viral and tick-borne bacterial encephalitis. Table 11.5 provides a list of the cerebrospinal fluid diagnostic studies for encephalitis.

11.3.4. Treatment

Rocky Mountain spotted fever is treated with doxycycline 100 mg intravenously every 12 hours for at least 7 days and until the patient has been afebrile for at least 48 hours. Human monocytic ehrlichioses and anaplasmosis are treated with the same regimen as Rocky Mountain spotted fever, i.e., (as above) doxycycline 100 mg twice daily for a minimum of 5–7 days and for at least 48 hours after defervescence.

Table 11.4

Serological tests for an infectious etiology of altered consciousness

IgM and IgG antibodies for
St Louis encephalitis virus
West Nile encephalitis virus*
Eastern equine encephalitis virus
Western equine encephalitis virus
Japanese encephalitis virus
Dengue virus
Epstein–Barr virus
Human herpesvirus type 6
Cytomegalovirus
Rabies virus
Human immunodeficiency virus
Tick-borne bacterial infection
IgG and IgM by indirect immunofluorescence for Rocky Mountain spotted fever
Lyme enzyme-linked immunosorbent assay (ELISA) – positive ELISA results should be confirmed by Western blot
Ehrlichial antibodies by indirect fluorescent antibody test (IFA)†

*West Nile virus IgM and IgG antibody titers that are positive by ELISA should be confirmed by the more specific plaque-reduction neutralization assay and cell culture.

†In addition to IFA for rickettsial and ehrlichial infections there are increasing numbers of ELISAs and flow immunoassays available, as well as polymerase chain reaction.

Table 11.5

Cerebrospinal fluid diagnostic studies for an infectious etiology of altered consciousness

Cell count with differential
Glucose and protein concentration
Stain and culture
Gram's stain and bacterial culture
India ink and fungal culture
Viral culture
Acid fast smear and *M. tuberculosis* culture
Antigens
Cryptococcal polysaccharide antigen
Histoplasma polysaccharide antigen
Polymerase chain reaction (PCR)
Broad-range bacterial PCR
Specific meningeal pathogen PCR
PCR for *Mycobacterium tuberculosis*
Reverse-transcriptase PCR (RT-PCR) for enteroviruses
PCR for herpes simplex virus type 1 and 2
PCR for West Nile virus
PCR for Epstein–Barr virus
PCR for varicella zoster virus
PCR for cytomegalovirus DNA
PCR for human immunodeficiency virus RNA
RT-PCR for rabies virus
Antibodies
Herpes simplex virus (serum:cerebrospinal fluid antibody ratio <20:1)
Arthropod-borne viruses
Borrelia burgdorferi
Coccidioides immitis complement fixation antibody
Rabies virus

11.4. Fungal meningitis

11.4.1. Etiology

Cryptococcus neoformans is the most common cause of fungal meningitis in immunocompetent and immunosuppressed individuals. Infection is acquired through direct exposure to pigeon droppings. *Histoplasma capsulatum* is a dimorphic fungus that is endemic to the Ohio and Mississippi River valleys. The fungus is acquired by inhalation. *Coccidioides immitis* is a dimorphic fungus that is endemic to the desert areas of the southwest, specifically California, Arizona, New Mexico, and Texas. Infection is acquired by inhalation of airborne arthroconidia. For all three of these organisms, initial infection is most often either asymptomatic or a limited pneumonitis with fever and cough. Dissemination of infection to the CNS results primarily in a meningitis.

11.4.2. Clinical presentation

The most common symptoms of fungal meningitis are headache, fever, and malaise, but nausea and vomiting, meningeal signs, altered mental status, and cranial nerve palsies may also develop.

11.4.3. Diagnosis

The diagnosis of cryptococcal meningitis is made by examination of the CSF, which demonstrates the following abnormalities: 1) normal or slightly elevated opening pressure; 2) lymphocytic pleocytosis; 3) elevated protein concentration; 4) decreased glucose concentration; and 5) positive cryptococcal antigen. The cryptococcal antigen is a highly sensitive and specific test and should be performed on all CSF specimens. *C. neoformans* can also be identified by India ink stain of CSF and grown in culture of CSF.

In meningitis due to *H. capsulatum,* examination of the CSF typically reveals a lymphocytic pleocytosis, although a predominance of polymorphonuclear leukocytes may also be seen. The CSF protein concentration is increased and the CSF glucose concentration is usually decreased. It is rare to identify the fungus on CSF India ink stain. The CSF culture, however, is frequently positive, as are blood, bone marrow, and urine cultures. The presence of the histoplasma polysaccharide antigen in CSF is a reliable indicator of CNS involvement; however, cross reactions with *C. immitis*, *C. neoformans*, and *Candida* have been reported (Christin and Sugar, 1997). The CSF histoplasma polysaccharide antigen is preferred to the CSF histoplasma antibody test for establishing the diagnosis.

The recommended test for the diagnosis of meningitis due to *C. immitis* is the complement fixation antibody test. The CSF complement fixation antibody test is reported to have a specificity of 100% and a sensitivity of 75% in the setting of active disease (Treseler and Sugar, 1990).

Measurement of (1→3) β-D-glucan (BG) derived from fungal cell walls has emerged as a diagnostic test for invasive fungal infections. The BG assay has a high predictive value for infections due to *Candida*, *Aspergillus*, or *Fusarium* species. Zygomycetes do not produce BG, and the BG produced by encapsulated *Cryptococcus* species is at low levels in infection. Medical sources of BG that can lead to a false positive result are: cellulose membranes used during hemodialysis result in significant increases in BG after dialysis, specific immunoglobulin products, cotton gauze and sponges used in surgery, and some drugs (crestin) are reported to contain BG (Ostrosky-Zeichner et al., 2005).

11.4.4. Treatment

A CNS fungal infection can be treated with either AmBisome (liposomal amphotericin) 5 mg/kg/day, Abelcet (amphotericin lipid complex) 5 mg/kg/day, or amphotericin B 0.7–1.0 mg/kg/day.

The addition of flucytosine 25 mg/kg four times daily to amphotericin is recommended for the treatment of cryptococcal meningitis because this leads to a more rapid sterilization of the CSF. Cryptococcal meningitis is treated in three phases: an induction phase, a clearance phase and with maintenance therapy. Generally after 2 weeks of therapy, if the patient is responding and the CSF culture is sterile, fluconazole 400–800 mg/day can be substituted for amphotericin B and flucytosine. The clearance phase is generally continued for at least 10 weeks, after which the dose of fluconazole is decreased to 100–200 mg daily.

The treatment of meningitis due to *H. capsulatum* typically requires a course of amphotericin to a target dose of 30 mg/kg. Itraconazole is often added and continued for long-term treatment.

The management of increased intracranial pressure is critical to a successful outcome from fungal meningitis and is often a recurrent problem. Intracranial pressure should be measured at the initial lumbar puncture and at the completion of induction therapy, and any time during the course of the illness when the patient has a change in mental status or a change in the neurological examination (gait abnormalities, pathologically brisk reflexes, cranial nerve abnormalities, visual changes). Increased intracranial pressure is best managed with a ventriculostomy during acute infection followed by a ventriculoperitoneal shunt. The practice of daily lumbar puncture to decrease CSF pressure by 50% and maintain CSF pressure at <300 mm/H_2O is impractical. Shunt revision should be done quickly in patients with deteriorating consciousness. Outcome has been demonstrated to be associated with the length of time between mental status changes and shunt revision (Lilliang et al., 2003). The longer the duration of symptoms at presentation, the less impact shunting will have on reversing neurological complications.

11.5. Tuberculous meningitis

11.5.1. Etiology

The majority of CNS tuberculous infections are caused by *Mycobacterium tuberculosis*. A person becomes infected by *M. tuberculosis* when they inhale aerosolized droplet nuclei containing tubercle bacilli. An immunocompetent adult with untreated *M. tuberculosis* infection has a 5–10% lifetime risk of disease and approximately 10% of immunocompetent persons with tuberculosis develop CNS disease (Udani et al., 1971). The neurological complications of tuberculosis meningitis are the result of a hypersensitivity reaction to the discharge of tubercle bacilli and tuberculous antigens into the subarachnoid space. This leads to the production of a purulent exudate that obstructs the flow of CSF through the basilar cisterns and the resorption of CSF by the arachnoid granulations, surrounds the cranial nerves, and surrounds and infiltrates the arterial walls of the blood vessels at the base of the brain. The result is communicating and obstructive hydrocephalus, ischemic and hemorrhagic infarctions, and cranial nerve palsies.

11.5.2. Clinical presentation

Tuberculous meningitis presents as either a subacute or chronic meningitis characterized by fever, headache, night sweats, and malaise or a fulminant meningoencephalitis with coma, raised intracranial pressure, seizure activity, and stroke.

11.5.3. Diagnosis

The most common abnormality on MRI scan is hydrocephalus and meningeal enhancement. The characteristic CSF abnormalities in tuberculous meningitis are an elevated opening pressure, a lymphocytic pleocytosis (10–500 cells/mm^3), a mildly decreased glucose concentration (20–40 mg/dl), and an elevated protein concentration. Early in infection the CSF may have a predominance of polymorphonuclear leukocytes, but lymphocytes become the predominant cell type within a few days. Spinal fluid should be examined by acid-fast smear and cultured. Positive smears are reported in 10–40% of cases. The growth of the organism is very slow. It may take 4–8 weeks for the culture to become positive. The PCR technique can detect *M. tuberculosis* DNA and mRNA in CSF. The patient should also have a tuberculin skin test and a chest X-ray. The Mantoux intradermal skin test may be falsely negative, even in the absence of immunosuppression and in association with a positive reaction to the common antigens used to determine anergy.

The lungs are the most common site of initial infection. The classic primary complex (Ghon complex) refers to Anton Ghon's observation from autopsy specimens that the primary lesion of tuberculosis is in the lung with secondary infection in the tracheobronchial lymph nodes (Ober, 1983). In addition to the 'primary complex' chest radiographic abnormalities suggestive of pulmonary

tuberculosis are hilar adenopathy, a miliary pattern, upper lobe infiltrates, and lobar consolidation (Kent et al., 1993).

The combination of symptoms of headache and low-grade fever with a shift in CSF white blood cells from a neutrophilic to a lymphocytic predominance, a mildly decreased glucose concentration, and an increasing protein concentration, and/or the development of hydrocephalus, is highly suggestive of tuberculous meningitis. The British Medical Research Council divides the clinical course of tuberculous meningitis into three stages (Medical Research Council, 1948). In the first stage, the level of consciousness is normal but patients are irritable and febrile. There are no focal neurological signs. Stage two is characterized by confusion, but not coma, and there may be headache, vomiting, and focal neurological deficits such as hemiparesis and a single cranial nerve palsy. In stage three, the patient is febrile and stuporous or comatose, may have focal neurological deficits from ischemic infarction, focal or generalized seizures, and multiple cranial nerve palsies (Medical Research Council, 1948).

11.5.4. Treatment

An important rule of management of tuberculous meningitis is to initiate therapy based on a strong clinical suspicion while awaiting the results of cultures of CSF, as outcome is affected by the clinical stage at the time therapy is initiated. Present recommendations are that treatment of tuberculous meningitis in adults be initiated with a combination of isoniazid (300 mg/day), rifampin/rifampicin (10 mg/kg/day, up to 600 mg/day), and pyrazinamide (25–35 mg/kg/day) for 2 months, followed by isoniazid and rifampin for an additional 9–12 months. Pyridoxine in a dose of 50 mg daily is added to this regimen to avoid peripheral neuropathy due to isoniazid-induced pyridoxine deficiency. Monthly liver function studies should be obtained in adults receiving isoniazid and rifampin. In patients with a high probability of a drug-resistant strain of *M. tuberculosis*, therapy is initiated with a combination of isoniazid, rifampin, pyrazinamide, and either streptomycin (1 g daily by intramuscular injection) or ethambutol (15–25 mg/kg/day) for 2 months. This is followed by isoniazid and rifampin to complete a 9–18 month course of therapy. During therapy the CSF should be monitored in order to demonstrate that the culture becomes negative. Therapy should be continued until cultures are negative for 6 months (Garcia-Monco, 2005). During pregnancy, streptomycin and pyrazinamide should be avoided (Garcia-Monco, 2005).

Treatment with dexamethasone appears to reduce mortality but not disability from tuberculous meningitis (Thwaites et al., 2004). No cases of severe hepatitis developed in the dexamethasone-treated group; thus, dexamethasone may improve outcomes by reducing the need to change the antituberculosis drug regimen. In review of the literature on adjunctive corticosteroid therapy for tuberculous meningitis from 1966–1996 using Medline, adjunctive corticosteroid therapy had a significant benefit in improving survival and reducing sequelae with stage 2 disease (drowsiness, single cranial nerve palsy, or hemiparesis), and less benefit in early disease or late disease (coma) and more benefit with longer regimens (4 weeks–2 months) (Dooley et al., 1997). Dexamethasone 8–12 mg per day, or prednisone equivalent, tapered over 6–8 weeks, is recommended. Isoniazid and pyrazinamide penetrate the CSF regardless of the degree of meningeal inflammation. Rifampin/rifampicin penetrates the CSF barrier more readily when inflammation is present, and streptomycin penetrates poorly in general.

11.6. Intracranial mass lesion

An intracranial mass lesion, either a brain abscess or an epidural abscess, as the etiology of a disorder of consciousness is readily demonstrated by neuroimaging. Empirical antimicrobial therapy includes a combination of a third- or fourth-generation cephalosporin with vancomycin and metronidazole until the organism, and its antimicrobial sensitivities, has been identified by Gram's stain and culture of the purulent collection obtained by aspiration or excision.

11.7. Postinfectious encephalomyelitis

Postinfectious encephalomyelitis is an acute monophasic, inflammatory, and demyelinating disorder of the CNS that occurs within days to weeks of a viral illness or a vaccination. Postinfectious encephalomyelitis, which is predominantly a disease of white matter, is distinguished from acute viral encephalitis, which is predominantly a disease of gray matter. The brainstem, basal ganglia, and thalami may also be affected.

11.7.1. Clinical presentation

Signs and symptoms of postinfectious encephalomyelitis usually begin within 2–31 days of a viral illness or vaccination and include symptoms of optic neuritis (which may be bilateral), visual field deficits, ataxia, hemiparesis, paraparesis, aphasia, movement disorders, and sensory deficits. There may be an altered level of consciousness ranging from lethargy to coma,

and focal or generalized tonic–clonic seizures. On neurological examination, signs of upper motor neuron disease, weakness, spasticity, and hyperreflexia predominate. There may be cranial nerve deficits due to involvement of the corticobulbar fibers to the motor nuclei of the cranial nerves in the brainstem. Maximal deficits are reached on the average in 4–5 days and then the patient begins to recover.

11.7.2. Diagnosis

On T_2-weighted and FLAIR magnetic resonance imaging, there are asymmetric areas of increased signal in the subcortical white matter, brainstem, cerebellum, and periventricular white matter. On T_1-imaging post gadolinium DTPA, the lesions enhance in a nodular, ring, or heterogeneous pattern. There may be lesions in gray matter as well. This is a monophasic illness; therefore, all lesions are in the same stage and partial resolution of existing lesions without new lesions during the recovery phase of the disease is critical in distinguishing postinfectious encephalomyelitis from other demyelinating diseases. CSF abnormalities include a mononuclear cell pleocytosis, an elevated protein concentration and a normal glucose concentration. Myelin basic protein and oligoclonal bands may be detected. Oligoclonal bands should not persist over time in the CSF of individuals with postinfectious encephalomyelitis.

11.7.3. Treatment

Therapeutic recommendations for postinfectious encephalomyelitis are complicated by the lack of double-blind, placebo-controlled clinical trials and the fact that postinfectious encephalomyelitis improves spontaneously. The most universally accepted therapy is intravenous methylprednisolone in a daily dose of 1000 mg/day for 3–5 days based on the experience with treating an acute exacerbation of multiple sclerosis. There are no firm guidelines on whether or not intravenous methylprednisolone therapy should be followed by an oral prednisone taper. Plasma exchange therapy was beneficial in a randomized sham-controlled clinical trial that involved a group of patients with inflammatory demyelinating diseases who had a severe clinical deficit and had failed to improve over a period of 2 weeks from the initiation of high-dose intravenous corticosteroid therapy (Weinshenker, 2001). There are a number of case reports of intravenous immunoglobulin therapy in acute disseminated encephalomyelitis (Nishikawa et al., 1999; Marchioni et al., 2002).

11.8. Summary

A disorder of consciousness may be due to any of a number of infectious diseases. Table 11.4 summarizes the recommended serological tests and Table 11.5 the recommended CSF diagnostic studies to determine an infectious etiology for the patient's altered consciousness. Often empiric therapy with a combination of a third- or fourth-generation cephalosporin, vancomycin, acyclovir, and doxycycline is initiated while awaiting the results of the spinal fluid analysis. In the patient with suspected viral encephalitis in whom a specific virus cannot be identified, empiric therapy with acyclovir, or foscarnet if the patient fails to respond to acyclovir, is reasonable. Empiric therapy for tuberculous meningitis should be initiated in the patient with a history of a headache of longer than 4 weeks' duration and now an altered level of consciousness, and a spinal fluid lymphocytic pleocytosis with a mildly decreased glucose concentration until another etiology can be determined. In the patient with altered consciousness with evidence of an inflammatory, demyelinating CNS disease, high-dose intravenous corticosteroid therapy should be given with a course of acyclovir for VZV infection as this may present as a demyelinating disorder. If the patient fails to improve on high-dose intravenous corticosteroid therapy, a course of plasma exchange is recommended.

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Chapter 12

Traumatic brain injury

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12.1. Epidemiology

Traumatic brain injury is the second most frequent cause of coma, second only to chemically induced coma. The spectrum of impairment in mental status due to head injury ranges from concussion through stupor to coma. Traumatic head injury is a major public health problem that affects up to 500 000 people in the USA each year. The incidence of traumatic head injury is estimated at 200/100 000 people and is the leading cause of accident-related death in the USA. Approximately 30–40% of traumatic brain injuries are considered moderate to severe and carry a mortality and serious morbidity rate of 10% (Rosenwasser et al., 1991; Shackford, 1997; Silvestri and Aronson, 1997).

Patient outcomes from severe head injury remain generally unfavorable but in the past few decades research and technological advances have improved overall patient outcomes to a certain degree. Some improvements include a better understanding of the pathophysiological changes that occur after brain injury, the wide availability of computed tomography (CT) scanning, the refinement of intensive care as a specialty, the improved resuscitation efforts in the field and recent research elucidating the cellular mechanisms of brain injury in an effort to prevent secondary brain injury. Also, improved monitoring during intensive care including intracranial pressure (ICP) monitors have helped to guide management and improve outcomes.

12.2. Classification of traumatic brain injury

In general, brain injury can be categorized as primary or secondary injury. Primary injury is the direct result of the initial trauma. Secondary injury is due to the evolution of the initial injury or to subsequent complications such as infection, hypoxia, hypotension, cerebral ischemia, cerebral edema, changes in cerebral blood flow, or increased ICP. Most people with severe traumatic brain injury will have a combination of diffuse and focal primary brain injuries and little can be done to repair the primary brain insult. The current management of traumatic brain injury is mostly aimed at preventing secondary brain injury. Another classification used often is open vs. closed head injury – the differentiating factor being whether or not the intracranial space is in communication with the environment. The risk of secondary infection and the need for surgical closure are key considerations distinguishing open head injury.

12.2.1. Primary brain injury

12.2.1.1. Concussion

A concussion is considered a mild traumatic brain injury and is described as an alteration of consciousness as a result of nonpenetrating traumatic injury to the brain with no gross or microscopic parenchymal abnormalities. It had been previously proposed that the patient must experience a brief loss of consciousness to be classified as having a concussion, but this definition has subsequently been revised. Currently, the only definite requirement to be classified a concussion is an alteration in mentation, such as confusion, amnesia, or loss of consciousness (Aubry et al., 2002).

Concussions have low morbidity and treatment is mainly supportive. A postconcussive syndrome commonly follows the injury and may linger for months. This syndrome consists of a collection of possible

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symptoms including headache, dizziness or lightheadedness, visual disturbances, anosmia, balance difficulties, difficulty concentrating, impaired judgment, emotional difficulties, personality changes, loss of libido, disruption of sleep/wake cycles, photophobia, and delirium. Treatment, again, is mainly supportive.

Although rare, one must also be mindful of the concept of a second impact syndrome where a person who suffers a second mild head injury while they are still symptomatic from their first one can develop malignant cerebral edema, which is refractory to all treatments and carries a 50–100% mortality (Schneider, 1973; Saunders and Harbaugh, 1984). There is a predilection for teenagers; this should be kept in mind when advising these patients and their parents.

12.2.1.2. Contusion

Cerebral contusions most commonly occur in areas where sudden deceleration of the head causes the brain to impact on bony prominences – namely, the temporal, frontal, and occipital poles. They show up as high-density areas on CT scans (Fig. 12.1). Often they enlarge and coalesce into frank blood clot, and with time usually develop perilesional edema. Cerebral contusions may occasionally not be well visualized on initial CT and appear more prominently on later imaging. Treatment of cerebral contusions is generally supportive with close neurological observation but, if the contusion generates significant deleterious mass effect, particularly a herniation syndrome, surgical decompression may be required.

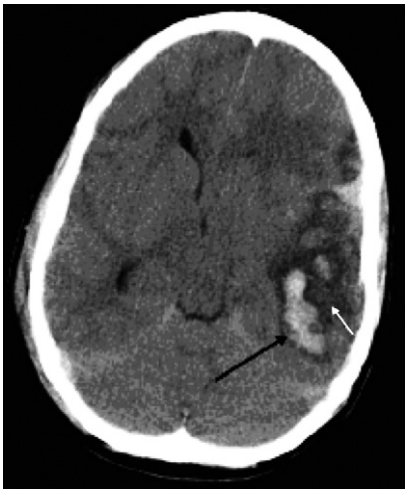

Fig. 12.1. Axial CT scan without contrast showing high-density area representing contusion (black arrow); hypodense areas (white arrows) represent perilesional edema.

12.2.1.3. Epidural hematoma

A traumatic epidural hematoma is a hemorrhage into epidural space and is commonly caused by the rupture of a meningeal artery. Other sources of bleeding include the meningeal veins or the cerebral sinuses. There is usually a concomitant skull fracture. Some 70% of epidural hematomas occur in the temporoparietal region (Miller and Statham, 1995) and 40% of all epidural hematomas occur in the 20 and younger population (Jennett and Teasdale, 1981) because of the less adherent dura of the younger person. The hematomas are classically lens-shaped or biconcave and do not cross suture lines (Fig. 12.2). Surgical evacuation is the mainstay of treatment.

The typical presentation of an epidural follows a head injury in a young person with a short period of unconsciousness. This is then followed by a lucid interval, then depressed consciousness, contralateral hemiparesis, and an ipsilateral dilated pupil. This classic

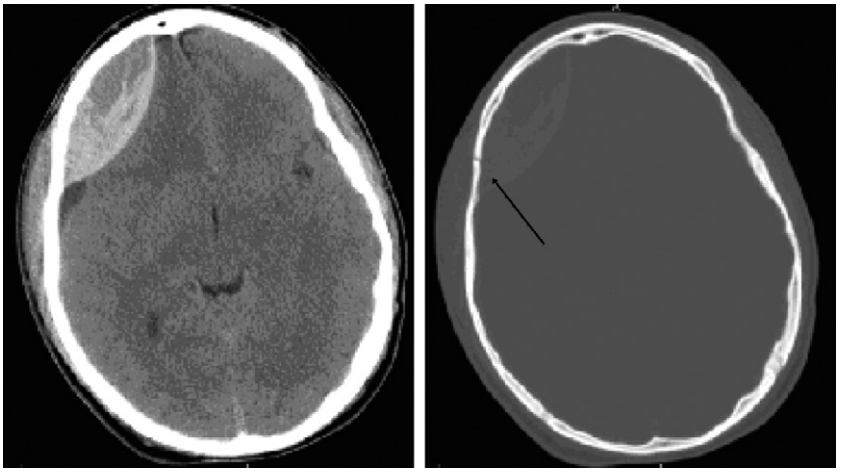

Fig. 12.2. Axial CT scan (left) in the brain windows show the high density lens-shaped epidural hematoma. Bone windows (right) show associated fracture (arrow).

presentation is infrequent and with only one-third presenting with the lucid interval (Munro and Maltby, 1941; Woodhall et al., 1941; Jamieson and Yelland, 1968; Kvarnes and Trumpy, 1978; Phonprasert et al., 1980; Bricolo and Pasut, 1984). Other traumatic intracranial lesions may occur concomitantly and may expand after the epidural hematoma is evacuated.

12.2.1.4. Subdural hematoma

This lesion is typically caused by high-speed injuries and results when a bridging vein that traverses the subdural space tears during a deceleration/acceleration-type force. On a CT scan, acute subdural hematomas are high-density lesions that are usually crescent-shaped (Fig. 12.3). Subdural hematomas can become more hypointense with time because of evolution of blood products. Acute subdural hematomas should be evacuated if they are causing a significant mass effect, midline shift, or effacement of the ventricles in association with neurological deficit. The mortality from an acute subdural hematoma is quite high, ranging from 50% to 90%, and can be as high as 90–100% in patients who are on anticoagulants (Kawamata et al., 1995).

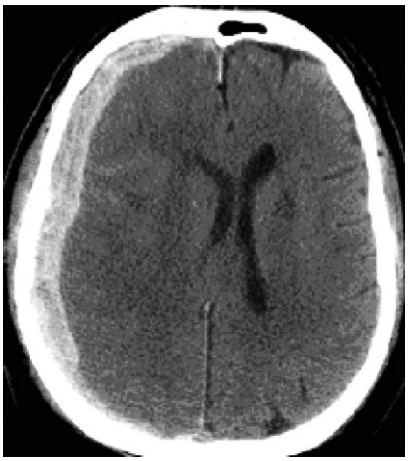

Fig. 12.3. Axial CT scan shows hyperdense crescentic lesion representing an acute subdural hematoma.

12.2.1.5. Diffuse axonal injury

Diffuse axonal injury is a common cause of deranged consciousness or coma in the absence of an intracranial space-occupying lesion. The mechanism of this injury involves rotational acceleration and deceleration and small hemorrhagic foci are seen in the corpus callosum, dorsolateral rostral brainstem, and gray/white matter junctions within the hemispheres. There is microscopic evidence of injury to the axons. Diffuse axonal injury is often accompanied by other primary brain injuries. Treatment of this injury is mainly supportive. CT scans may demonstrate punctuate hemorrhagic foci. Magnetic resonance imaging (MRI) well demonstrates characteristic abnormalities on T_2-weighted images that are pathognomonic (Fig. 12.4).

12.2.2. Secondary injury

Much of the management of moderate to severe traumatic brain injury is aimed at preventing secondary injury. Secondary injury develops after the initial impact damage and can be caused by delayed expansion of intracranial hematoma, cerebral edema, hypoxia, hydrocephalus, and elevated ICP. The final pathway of secondary injury is generally ischemia – inadequate blood supply and oxygenation to meet the metabolic demands of the brain tissue. The main goals in preventing secondary injury are to provide appropriate oxygenation and prevent

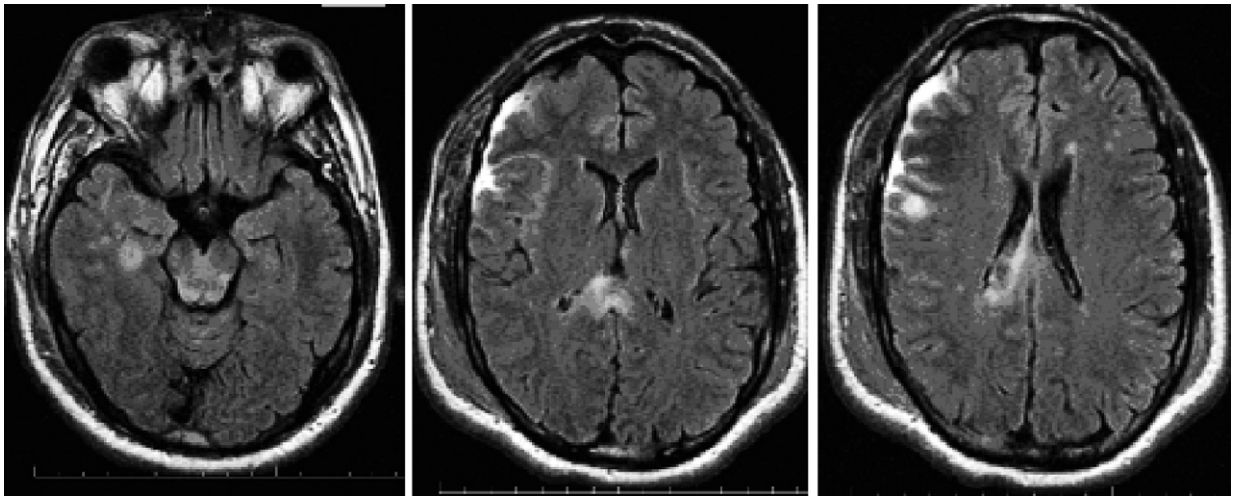

Fig. 12.4. Axial FLAIR MRI scans show foci of hyperintense regions in brainstem, corpus callosum, and gray–white junctions representing diffuse axonal injury.

increased ICP and poor cerebral perfusion pressure, which hinder adequate cerebral blood flow.

Delayed expansion of an intracranial hematoma is a common cause of neurological deterioration after head injury. Delayed epidural hematomas comprise up to 10% of all epidural hematomas in some series (Piepmeier and Wagner, 1982; Borovich et al., 1985). The incidence of delayed acute subdural hematomas is approximately 0.5% (Cohen and Gudeman, 1996). Delayed traumatic contusions have an incidence of 10% in patients whose Glasgow Coma Score (GCS) is <8 and usually occur within 72 hours of trauma (Cooper et al., 1979; Gudeman et al., 1979). These new contusions can also represent coalesced micro-contusions. The increased mass effect from these expanding lesions leads to increased ICP and/or herniation syndromes, which further compromises blood supply and subsequently results in more ischemia. Factors associated with the development of delayed hemorrhages include coagulopathies and hypertension.

Another aspect that can contribute to increased ICPs is the development of cerebral edema. There are two basic types of edema: 1) cytotoxic, which is the result of cellular and organelle dysfunction from ischemia, and 2) vasogenic, which is caused by the breakdown of the blood–brain barrier. Vasogenic edema allows extravasation of fluid into the interstitial spaces. Accumulation of more volumes into the intracranial space can increase ICP and decrease cerebral blood flow, which in turn can cause more edema – and a vicious cycle begins. Hydrocephalus can also contribute to delayed injury by increasing ICP. Obstruction of the absorption of cerebrospinal fluid (CSF) is a common cause of hydrocephalus, generally when blood products within the ventricular system disrupts the absorption by the arachnoid villi. Communicating hydrocephalus after traumatic brain injury is poorly understood but can respond to ventriculoperitoneal shunting in certain cases.

12.3. Principles of neurological examination in head trauma

Assessing the head-injured patient during an acute trauma often needs to be done rapidly and is often carried out in very chaotic situations. The following will attempt to describe the features of the general examination to assess craniospinal injuries and assumes that all other injuries in a trauma patient will be identified by other members of a trauma team.

Visual inspection of the cranium can provide valuable clues to injury type: periorbital ecchymosis (racoon's eyes), postauricular ecchymosis (Battle's sign), CSF otorrhea or rhinorrhea, or hemotympanum.

Table 12.1

The Glasgow Coma Scale

Points earned	Best verbal	Best motor	Best eye opening
6	–	Obeys commands	–
5	Oriented	Localizes to pain	–
4	Confused	Withdraws to pain	Spontaneous
3	Inappropriate	Decorticate	To speech
2	Incomprehensible	Decerebrate	To pain
1	None	None	None

The most extensively used assessment tool to classify the brain-injured patient is the GCS (Teasdale and Jennett, 1974) (Table 12.1). Its current use is based on eye opening (scored 1–4), verbal responsiveness (scored 1–5), and motor responsiveness (scored 1–6). The sum of the score allows classification of the patient's injury into severe (GCS 3–8), moderate (GCS 9–12), and mild (GCS 13–15). Those with a mild head injury have a much lower risk of death or disability (Stein and Ross, 1992). The probability of poor outcome increases with a lower GCS. Treatment modalities for those who present with moderate or severe head injury are aimed at secondary injury prevention.

The neurological examination is the most sensitive measure to follow a patient's in-hospital course. Serial examinations are vital to monitor improvement or deterioration, and prompt repeat imaging and/or intervention. In comatose patients (GCS <8), the neurological examination may not reveal deterioration, and invasive ICP monitoring may be required (see section on ICP, below).

12.4. Systemic sequelae of head trauma

Metabolic derangements in the setting of shock are a direct consequence of tissue hypoperfusion and secondary activation of the inflammatory response. The global physiological effects of shock are wide-ranging and beyond the scope of this text. It will suffice to say that tissue hypoperfusion and impaired oxygen delivery lead to tissue acidosis and a global inflammatory response characterized by proinflammatory cytokine release (TNF-α, IL-1β, IL-6, IL-8), complement activation, free radical formation, and neutrophil activation (Harbrecht et al., 2004). Neutrophil-mediated cytotoxicity is further enhanced by upregulation of the various surface adhesion molecules such as

ICAMs, VCAMs, and selectins. These events cause microvascular injury, coagulopathy, and end-organ damage. Because the brain is highly reliant on an intact blood–brain barrier and is exquisitely sensitive to edema, it is particularly vulnerable to the consequences of the shock state.

In a recent retrospective analysis of 81 blunt trauma patients with traumatic brain injury and GCS ≤ 8, the presence of hypotension and acidosis during the first 24 hours was associated with worse neurological outcome and discharge to an acute rehabilitation facility rather than home. Similarly, hypothermia and hypotension during this same period were found to correlate with a higher mortality rate (Jeremitsky et al., 2003). Once considered a promising neuroprotective strategy, hypothermia after head injury has been shown to increase infection risk without reducing neurologic morbidity (Shiozaki et al., 1999). Therefore, restoring normothermia, correcting acid–base disturbances and restoring tissue perfusion (with the goals of normovolemia, normotension, correction of base deficit and normalization of oxygen extraction) are essential goals in the medical care of the trauma patient. Because these issues must be addressed early, often in the operative setting, communication of these priorities to anesthesiologists and intensive care specialists is of utmost importance.

Of particular importance in the head-injured patient is rapid correction of coagulopathy. Persistent coagulopathy is a risk factor for ongoing hemorrhage and delayed hemorrhage from traumatic contusions and extra-axial hematomas (Oertel et al., 2002). Acute coagulopathy may be the result of tissue hypoperfusion but also can occur from head trauma alone. Both human and animal data suggests that this is a consequence of the release of procoagulant factors and a subclinical disseminated intravascular coagulation (Stein et al., 2002). One particularly potent procoagulant factor known to be present in high concentration in the brain is tissue thromboplastin; release of thromboplastin is thought to act in concert with a broader cytokine activation (TNF-α and IL-1) to precipitate a consumptive coagulopathy (Hoots, 1997). Support for this model comes from observations that brain-injured patients with low fibrinogen levels suffer a significantly higher mortality rate; similarly, serum levels of antithrombin, an endogenous anticoagulant, are inversely correlated with mortality in the acute brain-injured patient (Hoots, 1997). A large, multicenter prospective trial of antithrombin as a possible therapy for coagulopathy from brain trauma was terminated in 1995 for practical reasons; consequently, the practical usefulness of antithrombin in this setting remains uncertain. Other attempts to interfere with the coagulation cascade in the setting of acute brain trauma have not been systematically studied and therefore should not be undertaken.

At present, strategy for reversing coagulopathy is limited to factor replacement. In the severely head-injured patient, fresh frozen plasma should be considered presumptively, rather than waiting 20–30 minutes for coagulation panel results to be returned. Unless a herniation syndrome or other rapid neurological decline is occurring, neurosurgical interventions should await at least partial correction of coagulopathy. When fresh frozen plasma is ineffective in correcting a life-threatening coagulopathy, consideration should be given to the use of recombinant activated factor VII. Randomized, prospective trials of this therapy have not yet been undertaken; however, there is anecdotal evidence to suggest that recombinant factor VII is effective in rapidly reversing a variety of coagulopathies that are refractory to standard medical management (Park et al., 2003).

12.5. Management

12.5.1. General principles

Acute management of the trauma patient is a rapid process of stabilization, information gathering, and focused diagnostic investigation. In a tertiary care setting, this is best accomplished with concurrent care by multiple services, each attending to the patient in a prescribed and coordinated fashion, so that the overall process occurs as expeditiously as possible. The primary survey is the first step in assessment and treatment and should be completed in less than 1 minute, unless interventions are required. It is based on the mnemonic ABCDE.

12.5.1.1. Airway: ensure patent airway

In the awake patient, this can often be accomplished by eliciting verbal responses to basic questions, such as ‘What happened?’ In the stuporous or comatose patient, or a patient with significant facial or laryngeal trauma, intervention is often required to ensure a patent airway. Special attention should be given to the patient with hoarseness, a weak voice, or unexplained agitation; all are potential signs of an airway that is becoming compromised. Interventions to ensure a patent airway include: chin lift or jaw thrust maneuver (use the latter unless cervical spine injury has been ruled out), placement of an oral airway, rapid sequence intubation, placement of a laryngeal mask airway, cricothyroidotomy/tracheostomy, and jet insufflation.

12.5.1.2. Breathing: ensure adequate ventilation

Inspection, palpation, and auscultation of the lower neck and chest should be performed with the goal of identifying the following: tension pneumothorax, flail chest, open pneumothorax, and massive hemothorax (>1500 ml). Interventions that may be required at this point include needle thoracentesis and chest tube placement.

12.5.1.3. Circulation: ensure hemodynamic stability

Discovery and tamponade of exsanguinating hemorrhage, auscultation of the heart, and assessment of distal perfusion (pulses, extremity warmth, capillary refill) should be undertaken. The presence of shock requires consideration of all likely causes, including hemorrhage, tension pneumothorax (hopefully already discovered), pericardial tamponade, cardiac contusion, fat embolus (from long bone fracture), and neurogenic shock (from sympathetic denervation secondary to cervicothoracic spinal cord injury). Aggressive volume resuscitation should be undertaken concurrently with ultrasonographic investigation of the pericardium and abdomen.

12.5.1.4. Disability: assess degree of neurological impairment

This is typically expressed as a GCS score (Teasdale and Jennett, 1974). The presence of a fixed and dilated pupil should prompt an immediate CT scan of the head, administration of 1 g/kg intravenous mannitol (unless precluded by hemodynamic instability), and emergency neurosurgical consultation.

12.5.1.5. Exposure: remove all clothing

Log-roll patient and assess for penetrating trauma, obvious deformity, or spinal/paraspinal tenderness.

It is important to remember that each element in the above sequence should be addressed before proceeding to any of the subsequent steps. In a multidisciplinary setting, however, it is common for tasks to be divided, so that, as one team attends to the airway, another focuses on hemodynamic stabilization, and a third performs a rapid neurological examination.

Once the primary survey is accomplished and ventilation and perfusion are insured, a secondary survey should be undertaken. This involves a truncated history (using the AMPLE format), a rapid head-to-toe physical examination (including a more complete neurological examination), and focused diagnostic investigations. In the severely injured polytrauma patient, this will often include 'pan-scanning' CT investigations of head, neck, chest, abdomen, and pelvis. Head CTs should be performed in all patients with documented loss of consciousness or impaired consciousness on arrival. Focused CT investigations of the spine should be performed in all patients with significant mechanism of injury or spinal tenderness or sensorimotor deficits.

Occasionally, multiple injuries will be identified that require emergency surgical intervention. In this situation, coordination and cooperation between multiple surgical teams is essential, so that concurrent surgery can be undertaken without compromising access.

12.5.2. Medical management of head trauma

12.5.2.1. Seizure

Post-traumatic seizures are divided into two groups: early (seizures occurring up to 7 days postinjury) and late (those occurring more than 1 week postinjury). Because late-onset post-traumatic seizures are noted to occur rarely before 8 weeks postinjury, there is speculation that late post-traumatic seizure has a distinct pathophysiology from early post-traumatic seizure; inherent in this line of thought is the belief that microscopic or ultrastructural change underlies the development of late post-traumatic seizure and that this change takes time (latent period). Proposed mechanisms for the development of late post-traumatic seizure include: changes in relative neurotransmitter concentration, postsynaptic hypersensitivity, deposition of ferric ions at the site of contusion or hemorrhage, and a variety of other structural, electrical, and biochemical alterations. Recent experiments in mice have demonstrated not only short-term increases in hippocampal granule cell excitability after experimental blunt trauma but also a sustained decrease in thresholds for seizure activity as well as new mossy fiber sprouting in the dentate gyrus (Santhakumar et al., 2001). The generalizability of these findings to humans has yet to be demonstrated.

Because early post-traumatic seizure can usually be effectively treated in the hospital and because late post-traumatic epilepsy exacts a much higher cost on the patient in terms of quality of life, cognitive function, and economic and social well-being, the thrust of most research is appropriately directed at the prevention of late post-traumatic epilepsy.

An early post-traumatic seizure has a positive correlation with late post-traumatic seizure(s); 25% of patients who experience a seizure in the first week following head trauma will go on to develop a late post-traumatic seizure disorder. This correlation is supported by a number of shared risk factors for both types of seizures. Severity of injury, GCS <8, post-traumatic amnesia >24 hours, depressed skull fracture,

extra-axial hematoma, and intracerebral hematoma are all established risk factors for both early and late post-traumatic epilepsy (Jennett, 1974).

While early seizure prophylaxis does reduce the incidence of early post-traumatic seizure, it does not reduce the incidence of late post-traumatic seizure. In a large, prospective, randomized, controlled trial, Temkin et al. (1990) demonstrated that, among patients with serious head injury, phenytoin started within 24 hours of injury significantly reduced the incidence of early post-traumatic seizure by 73% but did not reduce the incidence of late post-traumatic epilepsy (27% in phenytoin group vs 21% in placebo group, $p > 0.2$). These results were borne out by a meta-analysis of 10 randomized, controlled trials, which found a pooled relative risk of early seizure of 0.34 among patients given prophylaxis compared with control patients. Rates of mortality, neurological disability, and late seizures remained unaffected (Schierhout and Roberts, 2000). Therefore, early seizure prophylaxis should be instituted for a limited time with the goal of preventing seizure during the acute recovery phase of head injury.

The decision to initiate early prophylaxis is typically based on either the occurrence of a seizure or high clinical suspicion of seizure risk. A retrospective study of 1868 consecutive admissions (excluding penetrating trauma or pre-existing seizure disorder) found an early seizure frequency of 5.8%. Conditions associated with increased seizure frequency included alcohol abuse (odds ratio (OR) 4.17), subdural hematoma (OR 3.34), and contusion (OR 1.83). Interestingly, neither skull fracture nor severe head injury (GCS <8) were found to be independent risk factors in this multivariate analysis. However, other studies have found these to be positive predictors of early and late seizure (Jennett, 1974; Annegers et al., 1980; Dalmady-Israel and Zasler, 1993). Some practitioners advocate prophylaxis of these higher-risk patients, while others defer pharmacotherapy until a seizure has occurred. There is no conclusive evidence to show that either strategy is superior.

Long-term seizure prophylaxis is reserved for patients who demonstrate late post-traumatic epilepsy. The particulars of pharmacotherapy remain highly variable, with no studies demonstrating clear benefits of one drug over another for this indication. Anticonvulsant therapy is largely guided by individual patient preference and side effect profiles. Seizure focus localization and resection can be undertaken in medically refractory cases.

12.5.2.2. Nutrition

For patients whose mental status or injuries prevent them from maintaining an adequate oral caloric intake, consideration should be given to nutritional intervention within the first 2–3 days of hospitalization. While all brain trauma patients will experience a degree of hypermetabolism and hypercatabolism, adequate nutritional supplementation can reduce the severity of these processes and prevent acute metabolic sequelae, such as ketoacidosis. A recent randomized study comparing a standard enteral nutrition protocol (slow advancement of the infusion rate over 1–2 days) with immediate full-dose tube feeds found a decreased infection rate but no difference in long-term neurological outcome among the patients receiving early full nutritional support (Taylor et al., 1999). Thus, in patients who may be extubated and recover mental status within the first few days of hospitalization, it is reasonable to defer gastric or intestinal tube placement until hospital day 2 or 3. Metabolic parameters such as bicarbonate, anion gap, and electrolytes should be closely followed during this period, and nutritional support instituted if significant derangements occur. The decision to employ enteral versus parenteral nutrition depends on the nature of the injury, the presence or absence of ileus, vascular access, and other factors. Generally, enteral nutrition is favored, as it is less expensive, helps to maintain the integrity of the gut, requires fewer adjustments, and does not carry a risk of line sepsis. In patients with skull base fractures, it is essential to make sure that no fracture line extends through the anterior cranial fossa before attempting nasogastric tube placement; nasogastric tube placement in the setting of anterior fossa fracture can lead to intracranial passage of the feeding tube, with catastrophic outcome. If an anterior fossa fracture exists, an orogastric tube should be placed instead.

In the neurotrauma population, enteral and parenteral nutrition are comparable with respect to energy expenditure, protein intake, and serum albumin and transferrin levels (Borzotta et al., 1994). If parenteral nutrition is required because of ileus or abdominal trauma, a central line should be placed and total (rather than partial) parenteral nutrition instituted. If tube feeds are attempted, but not tolerated, total parenteral nutrition should be instituted without delay, as tube feed intolerance for 1 week is associated with a higher incidence of septic shock (Young et al., 1987a). There is no evidence that total parenteral nutrition causes increased ICP in the head-injured population, a concern initially raised by animal models but not borne out in human trials (Young et al., 1987b).

One small, randomized study supports the use of enteral nutrition containing glutamine and probiotics (*Lactobacillus johnsonii*); this regimen was shown to reduce infection rate, intensive care unit length of stay and duration of mechanical ventilation (Falcao de Arruda et al., 2004).

12.5.2.3. Hyponatremia

Hyponatremia is common after traumatic brain injury and should be dealt with aggressively to prevent cerebral edema and worsening intracranial hypertension. Most cases are due to syndrome of inappropriate antidiuretic hormone secretion (SIADH), cerebral salt wasting, or a combination of the two. The precise mechanism of SIADH after brain trauma is uncertain; it is thought to occur as a result of injury to the posterior pituitary or the pituitary stalk which causes increased release of vesicles containing vasopressin. SIADH results in a euvolemic or hypervolemic hyponatremia. Cerebral salt wasting is caused by increased levels of atrial natriuretic peptide (ANP), which in turn causes increased urinary salt loss and therefore a hypovolemic hyponatremia. While ANP is found within neurons, post-traumatic release of the hormone by the brain is not thought adequate to account for the observed natriuresis in cerebral salt wasting cases; current speculation centers on an undefined central stimulation of cardiac release of ANP (Donati-Genet et al., 2001).

While proper long-term management of these conditions is distinctly different (fluid restriction for SIADH, electrolyte replacement for salt wasting), the acute management of hyponatremia after trauma is relatively simple. If hyponatremia persists and is severe (serum Na <125) after adequate volume resuscitation with normal saline, adult patients can be started on a 3% saline drip at 40 ml/h. Electrolytes should be checked every 6 hours to monitor for overrapid correction, which risks central pontine myelinolysis. Because it is a continuous infusion, hypertonic saline will usually cause gradual improvement in the serum sodium, even in patients with post-traumatic SIADH. Typically, post-traumatic SIADH and cerebral salt wasting both have a natural course of a few days to a week, so hypertonic therapy can be stopped once sodium values have normalized. Excess volume is autodiuresed by the patient after the acute phase of treatment. If the hyponatremia persists beyond 1 week, a more comprehensive work-up, with serum and urine electrolytes and calculation of FeNa, should be undertaken. Fluid restriction is generally avoided as primary therapy in the SIADH trauma population because of the concerns about hypovolemia and hypoperfusion discussed earlier in this chapter. However, if hypertonic saline is ineffective in correcting low sodium in a patient at risk for intracranial hypertension, then fluid restriction can be employed sooner. Finally, if hyponatremia is accompanied by hypotension, hyperkalemia, or other signs of hypoadrenalism, a cortisol level and/or ACTH stimulation test should be performed.

12.5.3. Intracranial pressure monitoring and management

Prevention and treatment of prolonged intracranial hypertension is essential to ensuring a good neurological outcome after trauma. In spite of a general agreement on this central fact, there is still a great deal of controversy on how to best monitor and treat patients with elevated ICP. There are two widely accepted means of monitoring ICP: the fiberoptic ICP monitor (or 'bolt') and the ventriculostomy. The former has an advantage of causing minimal violation of brain tissue and therefore minimal risk of iatrogenic intracerebral or extra-axial hemorrhage. The latter requires passage of a ventricular catheter a few millimeters in diameter through cerebral cortex and white matter, into the lateral ventricle. If correctly placed, the ventriculostomy catheter sits with its tip at the foramen of Monro, away from any choroid plexus that might clog its apertures. Once placed, the ventriculostomy catheter is hooked up to an external ventricular drainage system, which collects CSF from the patient. The process of placement carries with it a 6.5% risk of intracerebral or extra-axial hemorrhage, although most of these hemorrhages are small and clinically occult (Wiesmann and Mayer, 2001). Risk of ventriculitis increases by approximately 1–2% each day (Park et al., 2004). So long as the catheter is patent and the lumen of the ventricle has not been effaced by a mass lesion or edema, ICP can be managed by elevating or lowering the burette of the external ventricular drainage system (typically between 5–15 cm above the external auditory meatus), allowing drainage of CSF and lowering ICP. This is the principal advantage of ventriculostomy over the ICP monitor: the fiberoptic bolt can measure ICP but does not offer a means of therapeutic intervention beyond usual medical therapy. The choice of bolt versus ventriculostomy is still largely one of practitioner preference. However, when there is significant risk of post-traumatic hydrocephalus, either because of intraventricular hemorrhage or posterior fossa mass effect causing aqueductal obstruction, then external ventricular drainage is clearly the better choice. Noninvasive ICP monitoring, such as tympanic membrane displacement, is still experimental and imprecise; it should not be employed as a primary monitoring technique in the acutely head-injured patient.

Initial management of rising ICP requires ruling out an expansile mass lesion. This can be accomplished with an urgent CT scan of the head. If expanding epidural, subdural, or intracerebral hematoma is noted, then consideration should be given to surgical evacuation. If hydrocephalus is noted, then consideration should

be given to ventriculostomy. Once these conditions have been ruled out or addressed, the management of elevated ICP becomes more complicated. At this stage, elevated ICP is most commonly the result of cerebral edema and/or 'blossoming' contusions. The goal of medical therapy is to maintain ICP and cerebral perfusion within an acceptable range and thus avert the need for surgical intervention (decompressive craniectomy and/or debridement of contusions).

The armamentarium of medical therapies is usually employed in a step-wise fashion, roughly outlined in three tiers below. Any patient requiring continuous ICP monitoring and therapy from tiers 2 or 3 should be managed in an ICU setting with 24 hour neurosurgical consultation available.

Tier 1 Loosen cervical collar, elevated head of bed to 30°, normalize serum sodium (3% NaCl at 30–40 ml/h in the adult, monitor electrolytes every 6 h or more frequently), minimize intrathoracic pressure (i.e., lowest positive end-expiratory pressure possible), and strive for normocarbia.

Tier 2 Mannitol 0.25–1.0 g/kg intravenously as required for ICP >22 in the adult, monitor serum osmolality every 6 h. Once serum osmolality exceeds 320 mosmol/l, the utility of mannitol is limited and it may contribute to further breakdown of the blood–brain barrier and additional increases in ICP, as well as acute tubular necrosis. Mild hyperventilation to an arterial P_{CO_2} of approximately 30 may be used for brief (<15 min) periods, but no longer, as it can result in cerebral vasoconstriction and ischemia.

Tier 3 Barbiturate therapy: this remains controversial. Generally, aggressive dosing of pentobarbital is used until burst suppression on EEG is achieved. Barbiturate burst suppression is typically reserved for patients with elevated ICP who have failed maximal medical measures for ICP control. In a patient in whom meaningful recovery is deemed possible, consideration should also be given to surgical decompression when appropriate before barbiturate coma is induced. Because burst suppression temporarily ablates all neurological function (including, occasionally, pupillary light reflexes), the utility of the neurological examination is lost once this level of therapy is pursued. Clearance of high doses of pentobarbital from the body may take days or weeks, depending on the duration of the therapy. The use of alternative agents, such as Diprivan, to induce burst suppression and lower ICP may also be considered but as yet lack definitive evidence of efficacy.

The concept of cerebral perfusion pressure (CPP) is a paradigm that has become widely adopted in the hour-to-hour, minute-to-minute management of elevated ICP. This is based on the idea that the critical parameter for brain survival is adequate cerebral blood flow to meet the metabolic demands of the brain. Cerebral blood flow can be difficult to measure so CPP is used essentially as its surrogate. Blood flow is dependent on the perfusion pressure and is related to ICP in this manner: CPP = Mean arterial pressure − ICP. Cerebral autoregulation allows only a small change in the cerebral blood flow with large swings in systemic blood pressure. In a head-injured person recent evidence suggests that, as long as the CPP remains above 60, the small changes in CPP are less detrimental than elevated ICP (Juul et al., 2000). The aim then is to maintain CPP >60 with volume resuscitation and pressors and treat elevated ICP aggressively using the abovementioned methods.

12.5.4. Surgical intervention for head trauma

12.5.4.1. Supratentorial extra-axial hematoma

Subdural and epidural hematomas can be the most urgent of traumatic intracranial lesions. Among all patients with acute subdural hematomas, mortality is over 50%. This is most probably due to the high shear forces required to tear bridging veins; the incidence of other significant intracranial pathology (i.e., contusion, deep hemorrhage, brainstem injury) among patients with subdural hematoma is high. Epidural hematomas have a lower mortality rate but a high propensity for rapid deterioration. Therefore, patients with either diagnosis should be rapidly evaluated and transferred to a setting in which neurosurgical intervention is available if needed.

Once the presence of epidural or subdural hematoma is established by radiographic imaging, the decision of whether or not to take a head-injured patient to the operating room is largely clinical. A clot of a given size and location may represent an emergency surgical condition in one patient but in another patient might be more appropriately managed nonoperatively. The decision to operate requires consideration of a number of variables and must often be made expeditiously. No guidelines can account for every scenario but the following statements account for most of the usual, basic considerations.

1. A patient with depressed consciousness, confusion, active deterioration, or focal neurologic signs referable to mass effect from the clot should undergo craniotomy and clot evacuation. If the patient is comatose or unresponsive, this should be done as an emergency.

2. In patients who are awake and without neurological signs (i.e., asymptomatic or with only headache), the decision to operate should be based on the size of the clot, the degree of symptomatology (i.e., mild versus intolerable headache), and medical suitability for surgery and anesthesia. Some authors have advocated regarding a clot width of more than 1 cm as an indication for surgery. However, many would argue that, in a patient with significant medical comorbidities and/or minimal mass effect (e.g., the patient with baseline cerebral atrophy), some hematomas larger than 1 cm are more appropriately managed without immediate surgery. Clot location should also be considered; mass lesions in proximity to the medial temporal lobe carry a much higher herniation risk than high-convexity lesions and should therefore prompt earlier consideration of surgical evacuation.
3. Coagulation status must be considered. Only in a patient with rapid deterioration or a herniation syndrome should surgical evacuation proceed before this has been adequately addressed.
4. In patients who are deemed stable for conservative management, hematomas should be followed radiographically. Typically, a patient with a nonoperative extra-axial hematoma will undergo a follow-up head CT 24 hours after the injury; in patients with epidural hematoma or sizeable subdural hematoma, this will be followed with another head CT 2–3 days later. If patients are radiographically and clinically stable, they may be discharged from the hospital after 1–3 days. After discharge, clot size can be followed with monthly or bimonthly investigations. Typically, younger patients with minimal atrophy will resorb the clot over time. Older patients and patients with more generous subdural spaces are likely to demonstrate transformation of the clot into a hypodense, chronic-appearing subdural collection. After this maturation process is complete, drainage of this collection can proceed with a less invasive, two-burhole technique.

The surgical procedure for acute subdural and epidural hematomas is relatively straightforward. Typically, a Mayfield clamp is used to immobilize the head. A generous craniotomy is performed. In the case of a subdural hematoma, the boundaries of the craniotomy should include the entire clot, as well as any associated contusions which may require debridement. Care is taken not to injure parasagittal bridging veins during the dural opening. Clot is evacuated with suction and irrigation. Bleeding dural or cortical vessels are cauterized or tamponaded with Gelfoam. If extensive edema is noted, consideration should be given to craniectomy (described below). In the case of epidural hematoma, the craniotomy should extend inferiorly to the floor of the middle cranial fossa, so that if a proximal tear in the middle meningeal artery is found, it may be cauterized, and the foramen spinosum accessed, if necessary.

12.5.4.2. Posterior fossa hematoma

Posterior fossa hematoma, whether intra-axial or extra-axial, carries with it the possibility of clot expansion and secondary brainstem compression or obstructive hydrocephalus. Both conditions can be rapidly fatal. While non-operative management is appropriate in some of these patients, they must be monitored very closely for signs of deterioration. If clot expansion is noted, they must be rapidly decompressed. Surgery is usually via a midline suboccipital craniotomy or craniectomy. In the case of extra-axial hematoma, the source of the bleeding is usually venous. During surgery, care is taken not to disturb any fracture lines which overlie a dural sinus, since perturbation of tenuous clot can precipitate rapidly fatal hemorrhage. When obstructive hydrocephalus is the only secondary effect (i.e., when brainstem compression is absent), surgery can often be forestalled or avoided by placement of a ventriculostomy.

12.5.4.3. Cerebral contusion and intracerebral hemorrhage

Contusional injury can be the result of rapid deceleration or a direct blow to the head. In the case of the former, coup and contrecoup injuries are often seen. The spectrum of contusions ranges from a barely perceptible hyperdensity at the frontal or temporal pole to severe and multiple hemorrhages involving the cortical surface and/or deep structures. The natural history of moderate-sized to large contusions is to expand, or 'blossom', in the 3–5 days after the initial injury. Head CTs performed after this period often look dramatically worse than studies performed at admission. Blossoming corresponds to ongoing hemorrhage or worsening edema, both of which have a deleterious effect on ICP. Therefore, comatose patients with contusions must have an ICP monitor or a ventriculostomy. Anecdotally, the blossoming phenomenon is most dramatic in alcoholics and patients with coagulopathy. In these patients, close clinical and radiographic monitoring is particularly important, as they can deteriorate 2 or even 3 days after an injury.

Surgical intervention for cerebral contusion centers on reducing mass effect. The spectrum of approaches ranges from medical management to debridement

and, in severe cases, lobectomy or craniectomy. Debridement of contusions remains a controversial topic. Many advocate for aggressive debridement of contusions, with the rationale that contusional injury results in inflammatory penumbra with secondary hypoperfusion and resultant tissue damage. By removing the inciting, nonviable focus of this reaction, the size of this penumbra is thought to be reduced and therefore total tissue loss minimized. Others argue that contused brain may still harbor function and that resection of brain matter should be limited to those situations in which ICP control is essential. There are no rigorous studies to support one approach over the other.

There are two types of craniectomy that may be performed to reduce ICP after severe head trauma: bifrontal craniectomy and hemicraniectomy, both with wide decompressive durotomy. The choice of which to pursue is based on the nature of the injury. Bifrontal craniectomy is used in the setting of severe contusional injury to both frontal poles; hemicraniectomy is used as the setting of severe unilateral contusions or massive edema after evacuation of a hemispheric subdural hematoma. Craniectomy appears to be effective in reducing ICP and improving long-term outcomes in patients with post-traumatic cerebral edema; in a 1998 study of 35 consecutive bifrontal craniectomies compared with matched historical controls, Polin et al. (1997) demonstrated a good recovery or moderate disability in 37% of craniectomy patients versus 16% of medically managed controls. Risk factors for poor outcome included ICP values more than 40, admission GCS <6, and craniectomy performed more than 48 hours after injury. These findings are consistent with other studies and support early craniectomy for anticipated intractable post-traumatic edema in patients with GCS >6 on admission. For patients with GCS <6 at the scene and at admission, prognosis for meaningful recovery is poor; for these patients, most advocate ending the ICP management algorithm at barbiturate therapy.

Intracerebral hemorrhage after head trauma is less common than surface contusion and usually implies a severe mechanism of injury. When significant hemorrhage into deep structures is seen, particularly if it is out of proportion to extra-axial or surface lesions, then additional investigation to rule out aneurysm, arteriovenous malformation or tumor is necessary. This is typically accomplished with CT angiography and/or MRI. Except in select circumstances, surgical evacuation of traumatic deep hemorrhage is usually avoided. Because accessing the clot requires damaging overlying cortex and white matter, neurological outcome is often worsened by surgical intervention. Exceptions to this rule include threatened herniation and significant mass effect with a relatively superficial clot location. To date, experience with minimally invasive, stereotactic evacuation of this type of hematoma is limited to a few case series and case reports (Fadrus et al., 1998). Further study is needed before any conclusions can be drawn about the role of stereotactic clot evacuation in improving long-term outcome in this setting.

12.5.4.4. Depressed skull fracture and frontal sinus fracture

Depressed skull fracture is defined by the presence of a bony fragment that has been displaced inward by a distance at least as great as the thickness of the skull at that location. Surgery is indicated to repair underlying dura, if lacerated, to elevate the bone and decompress underlying cortex, and to prevent cosmetic deformity. If the fracture is open, the patient should be started on broad-spectrum, meningitis-dose prophylactic antibiotics such as ceftriaxone on admission. Compound fractures should be repaired by reconstruction of the fragments, if possible. Depressed skull fractures are associated with post-traumatic epilepsy. All skull fractures through the inner table of the frontal sinus require exploration, exenteration of the sinus and placement of a pericranial graft over the defect to prevent mucocele development. Patients should receive preoperative and perioperative antibiotic prophylaxis.

12.5.4.5. Penetrating brain trauma

The treatment of penetrating brain trauma should focus on hemostasis and infection control. If vascular injury is suspected, an angiogram should be obtained. Post-traumatic pseudoaneurysm carries a high incidence of repeat hemorrhage and demands surgical treatment, if demonstrated. If no treatable vascular lesion is identified, wounds should be explored and copiously irrigated. Dissection into white matter and deeper structures is ill-advised. Retained missiles, if deep, should not be retrieved. Dura should be reapproximated whenever possible. Investigations into more minimal debridement with less attention to dural closure have been shown to result in a 10–15-fold increase in post-traumatic meningitis (Carey, 2003). As with any significant head trauma, management of intracranial hypertension requires vigilant monitoring and treatment, as described above.

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Chapter 13

Seizures and impairment of consciousness

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A seizure is an abnormal synchronized, paroxysmal discharge of brain neurons. Seizures may arise from one part of the brain (partial or focal onset seizures) or virtually simultaneously from both hemispheres from the onset (generalized seizures). Epilepsy is diagnosed when a patient has a tendency for recurrent, unprovoked seizures. Focal-onset seizures have characteristic ictal semiologies depending on where they arise from and where they spread to within the brain. Generalized seizures typically have no warning, as consciousness is lost at the onset; their defining clinical features are mainly the motor activities, including cessation of activity, that accompany them.

13.1. Classification of seizures and their clinical–electroencephalographic features

The Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) has established the most commonly employed classification scheme for seizures (Commission on Classification and Terminology of the ILAE, 1981), epilepsies, and epileptic syndromes (Commission on Classification and Terminology of the ILAE, 1989). This has allowed for a consistent and stable terminology among researchers and clinicians as well as serving as a template for educating other physicians and their patients. The ILAE classification of seizures is given in Table 13.1.

13.2. Partial seizures

The ILAE classifies seizures as partial (Table 13.1) if their initial semiology (signs and symptoms) or electroencephalogram (EEG) suggests onset is from activation of only part of one cerebral hemisphere. They are classified as generalized if their initial semiology or EEG suggests more than minimal activation of both hemispheres simultaneously.

Partial seizures are subdivided into three groups: those in which consciousness is preserved (simple partial), those in which it is impaired (complex partial), and those in which the semiology evolves to secondary generalized activity (secondary generalized partial seizures).

13.2.1. Simple partial seizures

By definition consciousness, meaning alertness and global awareness, is preserved in simple partial seizures. The aura is the subjective experience/awareness of a seizure and is, therefore, a feature of focally originating or partial seizures. Whether elementary sensory, complex hallucinations of any modality, affective change, or another feature related to the involved system, the aura has four principal characteristics that differ from ordinary conscious experience (Alvarez-Silva et al., 2006): 1) it is typically sudden, evolves quickly, and is brief (typically seconds to a minute or two); 2) the experience is passive: the aura is 'imposed' without the conscious will or participation of the person; 3) it is an intense experience that intrudes upon conscious awareness and captures attention; 4) it has a 'strange' quality that is unlike ordinary experience and is out of context with ongoing activity. Unlike psychotic hallucinations or delusions, the epileptic aura is not incorporated in to the person's belief system or world view. These features are helpful clinically in recognizing auras and differentiating them from psychoses and other pathological experiences. They also give some insight into the

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Table 13.1

International League Against Epilepsy classification of seizures

1. Partial seizures
   - A. Simple partial seizures
     1. With motor signs
     2. With somatosensory or special sensory
     3. With autonomic symptoms or signs
     4. With psychic symptoms
   - B. Complex partial seizures (beginning as a simple partial seizure *or* with impairment of consciousness at onset)
     1. With no other features
     2. With features as in simple partial seizures
     3. With automatisms
   - C. Partial seizures evolving to secondary generalized seizures
2. Generalized seizures
   - A. Absence seizures (typical or atypical)
   - B. Myoclonic seizures
   - C. Clonic seizures
   - D. Tonic seizures
   - E. Tonic–clonic seizures
   - F. Atonic seizures
   - G. Combinations
3. Unclassified epileptic seizures

Source: with permission of the International League Against Epilepsy from Commission on Classification and Terminology of the ILAE, 1981.

mind–brain's ability to discriminate the 'forced' experience of a seizure imposing itself on consciousness from the ongoing, orderly processing of the brain or from nonepileptic phenomena.

Partial (focal) onset seizures can be associated with various somatosensory, special sensory, motor, autonomic, psychic, behavioral, or even negative symptoms (e.g., aphasia). Ictal sensory symptoms arise when a sensory area of the brain is involved in the seizure discharge. Elementary sensations perceived during a seizure include somatosensory, visual, auditory, olfactory, and gustatory. Numbness, tingling, and pain are all examples of somatosensory symptoms. Visual features can include unformed elementary visual images such as flashing lights or spots arising from activation of the occipital lobe. Olfactory features, with ictal involvement of the mesial anterior temporal lobe involvement, are commonly an unpleasant odor, such as burning tires. Vertiginous sensations may arise from involvement of the posterior superior region of the temporal lobe. Auditory hallucinations from the primary auditory area are relatively rare and are usually reported as a roaring noise or buzzing sound.

Motor activity seen during a seizure can consist of one or any combination of different movements during the ictus. Elementary motor movements such as tonic, clonic (with or without 'Jacksonian march'), tonic–clonic, dystonic, postural, myoclonic, negative myoclonic, atonic, astatic, and versive movements, and vocal utterances, can all be seen. Epilepsia partialis continua is a term used to describe a focal motor seizure of long duration, typically hours to days but occasionally lasting much longer. These commonly involve facial or arm twitching and are poorly responsive to antiepileptic medications (Nakken et al., 2005). The most common cause is a structural lesion or infection, although focal motor seizures are sometimes seen in metabolic disorders, including hypoglycemia or nonketotic hyperglycemia (Singh and Strobos, 1980). Focal inhibitory seizures may cause negative symptoms (ictal negative phenomenon) such as weakness, without any prior motor activity (AbouKhalil et al., 1995; So, 1995; Noachtar and Lüders, 1999). Rarely, focal inhibitory seizures have been demonstrated to cause nonconvulsive status with protracted negative symptoms (Matsumoto et al., 2000). The sensation of vertigo, smells, epigastric rising sensation, déjà vu, and visual distortions are all common. Autonomic features associated with seizures are due to involvement of the hypothalamus (usually with seizures from mesial temporal or orbital frontal lobes), diencephalon, and brainstem during or around the time of the ictus (Reis and Oliphant, 1964). The classic 'epigastric aura', a rising sensation or butterflies in the stomach or throat, frequently with nausea, is mainly seen with seizures originating from the temporal lobe. Cardiovascular (arrhythmias, blood pressure fluctuations), gastrointestinal, sudomotor, vasomotor, and thermoregulatory abnormalities can all be seen in seizures of focal (usually mesial temporal lobe) or generalized origin. Psychic manifestations/experiential phenomena usually implicate the limbic system, variably with neocortical regions. Aphasia, apraxia, or alexia may be seen as an ictal or postictal event with seizures involving the dominant hemisphere.

13.2.1.1. EEG features

Fewer than one-third of simple partial seizures have an abnormality on ictal scalp EEG (15% of nonmotor and 33% with motor semiology) (Devinsky et al., 1988; Sirven et al., 1996). The lack of EEG correlation during the seizure is probably due to the small area involved in generating abnormal electrical activity and the fact that scalp electrodes are not sensitive enough to detect these small changes. Partial seizures, especially those that impair level of consciousness, commonly have focal, lateralized interictal spikes on EEG, although

bitemporal discharges may occasionally be seen. Ictal discharges may cause a paroxysmal change in the EEG that predominates in one region of the recording. Focal or lateralized rhythmical spikes or spike–slow-wave discharges are commonly seen that increase and decrease in amplitude as well as frequency (Fig. 13.1) (Blume et al., 1984). Attenuation of the background or rhythmical slow waves that change in amplitude and frequency may also indicate ictal activity during partial-onset seizures.

13.2.2. Complex partial/dyscognitive seizures

Complex partial seizures (Engel, 2001) are associated with impairment of memory and, variably, other higher cognitive functions, often with associated automatic behaviors or automatisms. The aura, if one occurs, relates to the site of origin – often from mesial temporal lobe structures and their connections (Theodor et al., 1983). Common auras include rising visceral sensations, fear, or olfactory hallucinations,

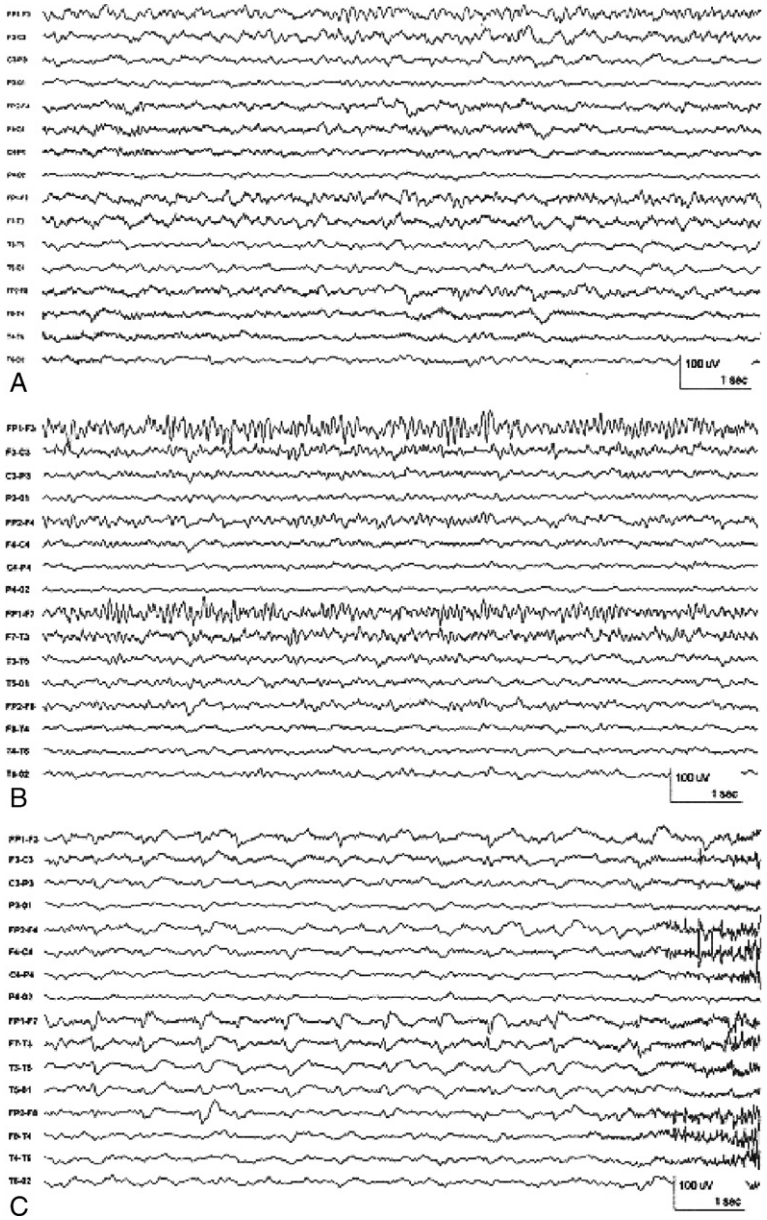

Fig. 13.1. A. The focal onset of left frontal temporal seizure activity (rhythmical spikes/sharp waves). **B.** Evolution of ictal activity (changes in amplitude and frequency). **C.** Repetitive left frontal temporal sharp waves follow cessation of ictal activity. From Brenner RP (2004). EEG in convulsive and nonconvulsive status epilepticus. J Clin Neurophysiol 21: 319–331, with permission from Lippincott Williams & Wilkins.

or more complex experiential phenomena such as micropsia (images shrinking), macropsia (images enlarging), or dysmnesic experiences such as déjà vu or jamais vu, in which there is an unnatural feeling of familiarity or strange unfamiliarity, respectively. Occasionally, memory can be selectively affected if the seizure remains localized to the hippocampal regions. If one hippocampus is previously damaged, a seizure restricted to the remaining intact one may produce a brief amnestic spell, analogous to the syndrome of 'transient global amnesia'.

Automatisms, for which the patient is almost always amnestic, are most commonly simple, e.g., eye blinking, swallowing, or lip smacking; however, more complex automatisms such as eating, walking, or fumbling with buttons may be seen. Some extratemporal sites of seizure onset do not have the classic findings seen in complex partial epilepsy of temporal lobe origin.

Complex partial seizures typically last from 30 seconds to several minutes and are followed by a period of postictal lethargy and confusion. This state can last minutes to hours and be associated with paranoia and agitation; however, lethargy is usually a prominent feature.

Complex partial seizures of medial or orbital frontal lobe origin tend to be brief and have complex motor automatisms such as kicking or thrashing. Sexual automatisms and various degrees of vocalization may be seen.

Frontal lobe seizures are often bizarre, leading to the erroneous diagnosis of pseudoseizures (Saygi et al., 1992). Stereotyped patterns strongly suggest the diagnosis of epileptic spells and not pseudoseizures. Interictal and ictal scalp EEGs are often not helpful in diagnosis since the ictal focus is often deep within the frontal lobe and commonly not detectable on the recording (Williamson et al., 1985; Laskowitz et al., 1995).

Complex partial seizures occasionally cause cardiac arrhythmias including supraventricular tachycardia, sinus tachycardia, sinus bradycardia, sinus arrest, atrioventricular block, and asystole (Phizackerley et al., 1954; Blumhardt et al., 1986; Kiok et al., 1986; Devinsky et al., 1997). These arrhythmias are reported more frequently when seizure origin is from the temporal lobes than from extra-temporal sites (Phizackerley et al., 1954; Blumhardt et al., 1986; Kiok et al., 1986; Devinsky et al., 1997). Arrhythmias seen during seizures are probably related to autonomic dysfunction during the ictus and possibly indicate involvement of the insular cortex (Reis and Oliphant, 1964). Seizure-induced arrhythmias may contribute to the increased risk of sudden death in epilepsy patients (Earnest et al., 1992).

13.2.3. Secondarily generalized seizures

These seizures commonly begin as either an identifiable simple partial seizure (motor event or nonmotor aura) or a complex partial seizure but they may also quickly generalize without warning. The video and electrographic analysis of secondary generalized seizures shows a fairly predictable pattern of motor events (Theodore et al., 1994). The tonic–clonic movements are often more asymmetric than with primary generalized seizures. The tonic phase consists of spasms in axial muscles causing tonic posturing of the body. This phase typically lasts for 10–30 seconds and a 'cry' is often heard at the beginning, as air is forcefully expired against a closed glottis. The clonic phase follows and consists of clonic movements that decrease in frequency, become less symmetric, and eventually cease. These motor events typically last 1–2 minutes and during them apnea, cyanosis, and dysautonomia are common. Following the seizure there is typically a postictal state of stupor or lethargy, incontinence, and loss of pharyngeal muscle tone. Airway obstruction and aspiration may occur.

Secondary generalized tonic–clonic seizures usually show focal spike-and-slow-wave or slow-wave discharges indicating their focal origin. The discharge subsequently spreads and becomes synchronous generalized spike-and-wave activity similar to primary generalized tonic–clonic seizures. Occasionally secondary generalization occurs rapidly, hampering electrographic identification of a focal onset.

13.3. Primary generalized seizures

13.3.1. Absence seizures

Absence seizures, primary generalized seizures in which motor activity is not a predominant feature, have impairment of consciousness as their defining feature. However, there is a spectrum of impairment across patients, with some patients remembering some events during the attack, some showing considerable interaction with their environment and others simply arresting in their activity.

Typical absence seizures begin in childhood and are commonly associated with idiopathic epilepsy. These brief spells, often described as 'staring spells', usually last 2–10 seconds and may occur hundreds of times per day. Cessation of activity and failure to respond to external stimuli occur. Simple automatisms such as eye-blinking, facial movements, fine clonic movements of the face, arms and fingers, and rocking are common. The more complex automatisms seen in complex partial seizures rarely occur in typical absence seizures.

Occasionally the child may continue a complex task such as walking or riding a bicycle (perseverative automatism). Unlike generalized tonic–clonic seizures there is no postictal confusion and there is return of normal cognition immediately after the event. Absence seizures may be provoked in the office setting and during EEG by hyperventilation.

Atypical absence seizures occur with symptomatic epilepsies in which a widespread brain disorder is associated; such patients almost always have baseline cognitive impairment. Atypical absence spells are longer in duration, commonly 10–25 seconds, and the motor automatisms are more complex than with typical absence seizures. Postictal confusion and lethargy are present and of variable duration.

Absence seizures are electrographically characterized by generalized symmetric spike-and-slow-wave discharges at 3 cycles per second. These discharges may slow to 2.5 or 2 Hz when seizures persist for more than a few minutes. They may also be provoked by hyperventilation during the EEG. Atypical absence seizures usually demonstrate a slower and more irregular EEG pattern (Penry et al., 1975; Holmes et al., 1987; Camfield and Camfield, 2002).

13.3.2. Primary generalized tonic–clonic seizures

By definition, these seizures begin virtually simultaneously in both hemispheres, without warning and with abrupt coma; the motor manifestations are synchronous. Similar to secondary generalized seizures, tonic activity is followed by clonic jerks and tongue biting; incontinence may occur. These seizures are sometimes associated with other seizure types (such as myoclonic or absence seizures), which may occur around the same time as the tonic–clonic seizure. The postictal encephalopathy is similar to that seen in secondary generalized seizures.

13.3.2.1. EEG features

In primary generalized tonic–clonic seizures there is an initial attenuation of the background rhythm, sometimes preceded by a generalized spike-and-wave discharge. This is followed by low-voltage, fast activity that evolves in character by increasing in amplitude and decreasing in frequency to eventually become the classic generalized spike-and-wave pattern. During the tonic phase of a tonic–clonic seizure the EEG is obscured by muscle artifact. The subsequent clonic phase consists of an alternating pattern of repetitive muscle artifact and identifiable spike-and-wave seizure activity. Following the clonic phase there is a period of postictal suppression of the EEG (Fig. 13.2).

13.3.3. Myoclonic seizures

Myoclonus is defined as a brief, shock-like jerk of a muscle group. In generalized myoclonic seizures the myoclonic jerks happen bilaterally and synchronously; however, in focal onset seizures myoclonic jerks of

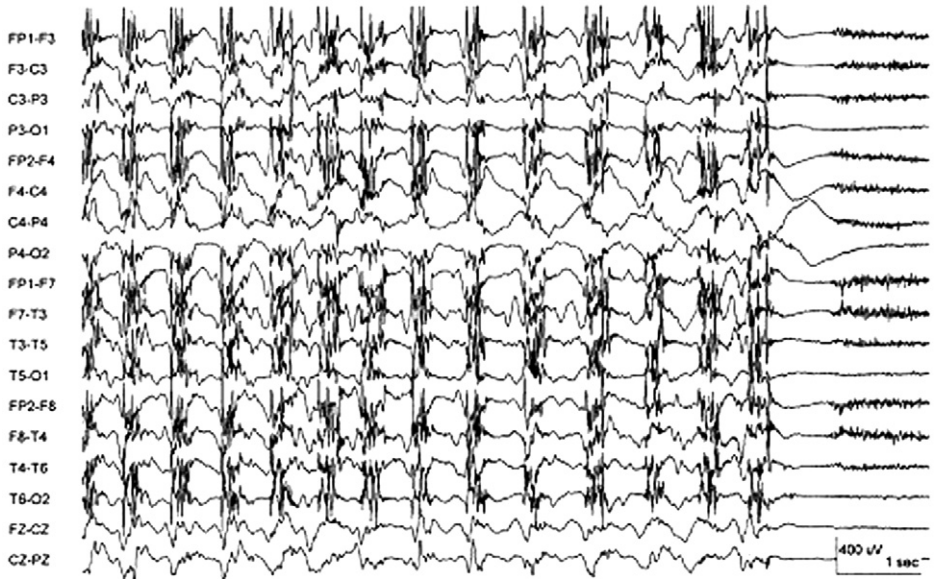

Fig. 13.2. Generalized spike-and-wave activity with superimposed, repetitive, muscle artifact seen during the clonic phase of a generalized tonic–clonic seizure. There is postictal EEG background suppression. From Brenner RP (2004). EEG in convulsive and nonconvulsive status epilepticus. J Clin Neurophysiol 21: 319–331, with permission from Lippincott Williams & Wilkins.

epileptic origin may be unilateral. Generalized myoclonic seizures can occur in trains where multiple 'jerks' happen consecutively. Typically myoclonic seizures are so brief that there is no impairment in level of consciousness even though they represent a generalized seizure. These seizures are commonly associated with other seizure types such as generalized tonic–clonic or absence seizures. Juvenile myoclonic epilepsy is an example of an epilepsy syndrome in which myoclonic seizures are associated with generalized tonic–clonic and absence seizures (Asconape and Penry, 1984).

13.3.4. Other generalized seizure types

In neonates and infants clonic seizures represent the epileptic equivalent of the adult generalized tonic–clonic seizures. They are usually multifocal, migratory, and associated with some degree of postictal confusion (Gastaut et al., 1963). Tonic seizures also begin early in life and are associated with tonic contraction of axial muscles with flexion or extension of appendicular musculature, as infantile spasms (Benbadis et al., 2001). Atonic seizures or 'drop attacks' may be mild and just involve partial loss of postural muscle tone, causing a head drop. More severe atonic seizures can result in sudden unpredictable falls from loss of all postural muscle tone, sometimes causing severe traumatic injury.

13.3.5. EEG patterns in myoclonic, atonic, clonic, and tonic seizures

Myoclonic seizures are often characterized electrographically by brief generalized, paroxysmal, symmetric polyspike and slow wave discharges (Asconape and Penry, 1984). The ictal EEG during clonic seizures shows high amplitude polyspike-and-wave discharges followed by low amplitude slowing (Gastaut et al., 1963). Tonic seizures may show low-voltage fast activity followed by semirhythmic delta (Benbadis et al., 2001).

13.4. Epilepsy syndromes

An epileptic syndrome involves a complex of signs and symptoms that define a unique epilepsy condition. Commonly patients fit the defining criteria for a certain epileptic syndrome, which may help, for example, in choosing effective antiepileptic drug therapy or for counseling on prognosis and genetics. A detailed discussion is beyond the mandate of this chapter; good discussions can be found elsewhere (Lerman and Kivity, 1975; Engel, 2001; Galanopoulou and Lado, 2004).

13.5. Epidemiology of seizures and epilepsy

The annual incidence for unprovoked seizures is between 20 and 96 per 100 000 and the incidence of epilepsy is between 12 and 67 per 100 000 depending on age and sex. The incidence of epilepsy is highest in ages younger than 5 years. The incidence remains somewhat stable, at about 15 per 100 000, from ages 25–54, increasing again, however, in older age groups (Annegers et al., 1999). Hence, the peak times for developing epilepsy are during childhood and young adulthood and again late in life. The prevalence of epilepsy is around 6.8 cases per 1000 individuals and increases with age to approximately 15 cases per 1000 in individuals over 75 years of age (Hauser et al., 1991). Complex partial seizures are the most common single type referred to epilepsy centers.

It is beyond the scope of this chapter to discuss genetic influences on epilepsy, but excellent reviews can be found in other genetic epidemiological studies (Ottman et al., 1988, 1989, 1998; Ottman, 1997; Gardiner and Lehesjoki, 2000).

13.6. Pathophysiology of seizures

Mechanisms of epileptogenesis are beyond the mandate of this chapter. Interested readers should consult Morimoto et al. (2004) for working hypotheses.

Those regions of the brain that are most plastic, i.e., involved in the dynamic functions involved in awareness, are the most vulnerable to epileptic processes (Bernardo, 2006). On a cellular basis, neuronal excitability is regulated by intrinsic and synaptically driven excitatory and inhibitory processes. Intrinsic membrane factors are those controlling conductances of various ions, either passive or voltage-dependent; these are responsible for the various membrane currents that determine the excitability and firing patterns of neurons. Neuronal interactions involve excitatory amino acids (glutamic and aspartic acid, which can act on *N*-methyl-D-aspartate (NMDA), non-NMDA, and metabotropic receptors), responsible for cationic currents, and gamma-aminobutyric acid (GABA) A and B receptors, which, when activated, cause the neuron to be hyperpolarized by increasing chloride and potassium conductance, respectively. Other neurotransmitters and neuromodulators, glial buffering, and gap junctions (electrotonic coupling) also play roles in neuronal excitability.

The initiation and spread of abnormal excitation depends on the 'bursting neurons' in the neocortex or hippocampus, especially if they are tightly coupled synaptically with other neurons. For seizures to evolve these downstream 'generator' cells provide a powerful excitatory influence on connected 'follower' neurons.

If this excitation breaks through the inhibitory surround provided by other neurons and glia, the seizure spreads to a variable extent to other brain regions, producing features of the seizure. Manifestations of the seizure depend on the functional anatomy of the involved structures.

13.6.1. Pathophysiology of impairment of consciousness in various seizure types

It is useful to think of consciousness as being composed of both alertness and awareness. Alertness depends on the function of the ascending reticular activating system in the rostral brainstem tegmentum and posterior hypothalamus and their interactions with the thalamus, including the thalamic reticular nuclei and cerebral hemispheres (Moruzzi and Magoun, 1949). Coma, an unarousable unconscious state, results when this system is rendered dysfunctional. This is distinct from sleep, in which the orderly inhibition of this system can be overcome by stimulating the sleeping person, or by spontaneous awakening. Awareness is a higher function, but rests on alertness being intact. Awareness is primarily a cerebral cortical function. Individual cortical functions, e.g., the primary visual reception area, are represented in discrete modules but for further processing and awareness of the significance of stimuli, and motivated responses, numerous cortical areas are functionally integrated. Seizures alter awareness by disrupting the integrated functioning of the brain. This 'model' of brain functions allows us to understand impairment of consciousness or its components in epileptic seizures.

In complex partial/dyscognitive seizures, more complete loss of awareness is associated with widespread, bilateral EEG changes, usually slow waves. Single photon emission tomographic (SPECT) and positron emission tomographic (PET) studies performed on humans with complex partial seizures have shown altered diminished regional blood flow in the mesial temporal regions and ipsilateral thalamus when done interictally (Yune et al., 1998; Newberg et al., 2000). Ictally, however, regional blood flow is increased in these structures, while diminished blood flow is seen in widespread areas of the frontal and parietal neocortex, including heteromodal areas bilaterally (Rabinowicz et al., 1997; Chang et al., 2002; McNally et al., 2003). The 'network inhibition hypothesis', which arose from these observations, proposes that the excitatory effects of the mesial temporal lobe seizure spread to the thalamus and the thalamus then produces widespread inhibition of the cerebral cortex (Fig. 13.3) (Blumenfeld and Taylor, 2003). This could certainly account for the loss of awareness and memory

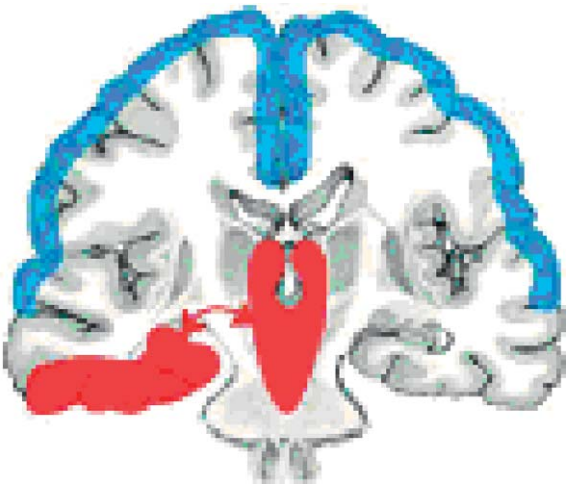

Fig. 13.3. This illustrates the network inhibition hypothesis, in which excitation spreads from the mesial temporal region to the thalamus; then the thalamus produces widespread inhibition in the neocortex. With permission from Blumenfeld H, Taylor J (2003). Why do seizures cause loss of consciousness? Neurosci Update 9: 301–310.

mechanisms that occur in complex partial seizures (Yamauchi, 1998; Norden and Blumenfeld, 2002). Postictal amnesia is thought to arise from involvement of the hippocampal structures (Bancaud et al., 1994).

Generalized convulsive seizures, whether primary or secondary generalized, appear to interfere with similar brain regions to produce loss of consciousness, both alertness and awareness (Ackerman et al., 1986). Interestingly, the seizure discharge is not universal or homogenous throughout the brain (McIntyre et al., 1991; Blumenfeld, 2003). Recent SPECT studies by Blumenfeld and Taylor (2003) using patients undergoing electroconvulsive therapy have shown relative increases in regional blood flow in frontal and parietal cortices bilaterally, the thalamus, and upper brainstem. This, again, could account for the loss of consciousness; the relative lack of involvement of the primary motor cortex is compatible with other studies that suggest the generalized tonic and then clonic movements relate to involvement of subcortical structures, especially the brainstem reticular formation (Gale, 1992; Faingold, 1999).

13.6.2. Absence seizures

Blumenfeld (2005) proposes that, although absence seizures are classified as generalized, the impairment of consciousness associated with them is not an all-or-none phenomenon.

In studies of absence seizures (a generalized seizure), spike-and-wave bursts with a paroxysm longer than 3 seconds have been shown to produce observable

impairment of functioning (Goode et al., 1970). It has also been shown that impairment of consciousness is most pronounced in the middle stages of a paroxysm and less so during the initial and terminal stages (Shimazono et al., 1953; Goldie and Green, 1961). The spike discharge seems to be initiated by a reticular discharge at the thalamic level and the slow-wave component seems to be related to a bihemispheric inhibitory effect on the cortex (Yamauchi, 1998). Slow spike wave (<3 Hz episodes, as seen in the Lennox–Gastaut syndrome) may not be associated with observable impairment of consciousness. Very prolonged absence attacks, i.e., absence status, are variable in the degree of impairment of consciousness or memory; only mild impairment may occur.

Functional imaging studies of blood flow and metabolism of patients during absence attacks have been highly variable (Blumenfeld and Taylor, 2003). However, EEGs show a predominance in the frontal lobes bilaterally, with variable but relative sparing of the posterior cerebrum. Blumenfeld (2005) proposes that the impairment in consciousness in absence seizures relates to the involvement of frontal heteromodal or association cortex, and related subcortical structures interfere with normal information processing. This seems a plausible explanation and would explain the variability in consciousness found in these patients.

13.7. Status epilepticus

Any seizure type (Table 13.1) may manifest as status epilepticus. The Working Group on Status Epilepticus (1993) defined status epilepticus as more than 30 minutes of either continuous seizure activity or two or more sequential seizures without full recovery of consciousness in between. Lowenstein et al. (1999) proposed the generally accepted operational definition of status epilepticus as ≥5 min of a) continuous seizures or b) two or more discrete seizures between which there is incomplete recovery of consciousness. This practical definition is based upon clinical and experimental research showing neuronal damage associated with status epilepticus and that increased seizure duration leads to the ictal activity becoming more refractory to standard medical treatment. However, epileptic brain damage does not usually occur until at least half an hour (Fig. 13.4).

A complete discussion of status epilepticus is beyond the scope of this chapter, but excellent writings on its various aspects can be found in: Aminoff and Simon, 1980; Meldrum, 1983, 1986; Siesjo et al., 1983, 1986; Nevander et al., 1985; Bertram and Lothman, 1990; Hauser, 1990; Lothman, 1990; Jope et al., 1991; Towne et al., 1994.

13.7.1. Classification of status epilepticus

We divide status epilepticus into convulsive (CSE) or nonconvulsive (NCSE) and further subdivide these categories into generalized or focal (partial) activity. When generalized activity evolves into nonconvulsive or 'subtle convulsive activity' the patient may have only slight twitching of the limbs or face, or jerking eye movements. There may eventually be no obvious motor activity despite generalized EEG activity (electromechanical dissociation). In secondary generalized convulsive epilepticus the EEG at onset shows focal activity that secondarily generalizes. However, the EEG during primary and secondary generalized convulsive status epilepticus may look similar if not recorded early enough to catch the onset. As stated previously, focal seizure activity may also cause status epilepticus and have convulsive or nonconvulsive properties. The EEG is frequently helpful in making the correct diagnosis in regards to status epilepticus.

Treiman et al. described five identifiable electroencephalographic stages that they thought occurred sequentially during the course of secondary GCSE. They did not find evidence that these patterns occurred sequentially during primary GCSE (Treiman et al., 1990; Treiman, 1993, 1995):

Stage 1	Discrete seizures
Stage 2	Merging seizures with waxing and waning amplitude and frequency of EEG rhythms
Stage 3	Continuous ictal activity
Stage 4	Continuous ictal discharges punctuated by low voltage flat periods
Stage 5	Periodic epileptiform discharges on a 'flat' background.

Clinical manifestations associated with each stage have been described but are highly variable. Some of this variability may be due to the fact that the medications used to treat status epilepticus may cause a clinical-EEG dissociation. Classically, the originally tonic–clonic convulsions become less prominent clonic activity then intermittent and rare clonic activity. In the final stage (stage 5) coma ensues without other manifestations of seizure activity. Other researchers have not consistently found this sequential pattern but have noted similar EEG appearances. Generalized convulsive status epilepticus may evolve to nonconvulsive status epilepticus, or terminate with appropriate therapy.

13.7.2. Consciousness in status epilepticus

13.7.2.1. Absence status epilepticus

Absence status epilepticus occurs mainly in younger patients with idiopathic generalized epilepsy, especially

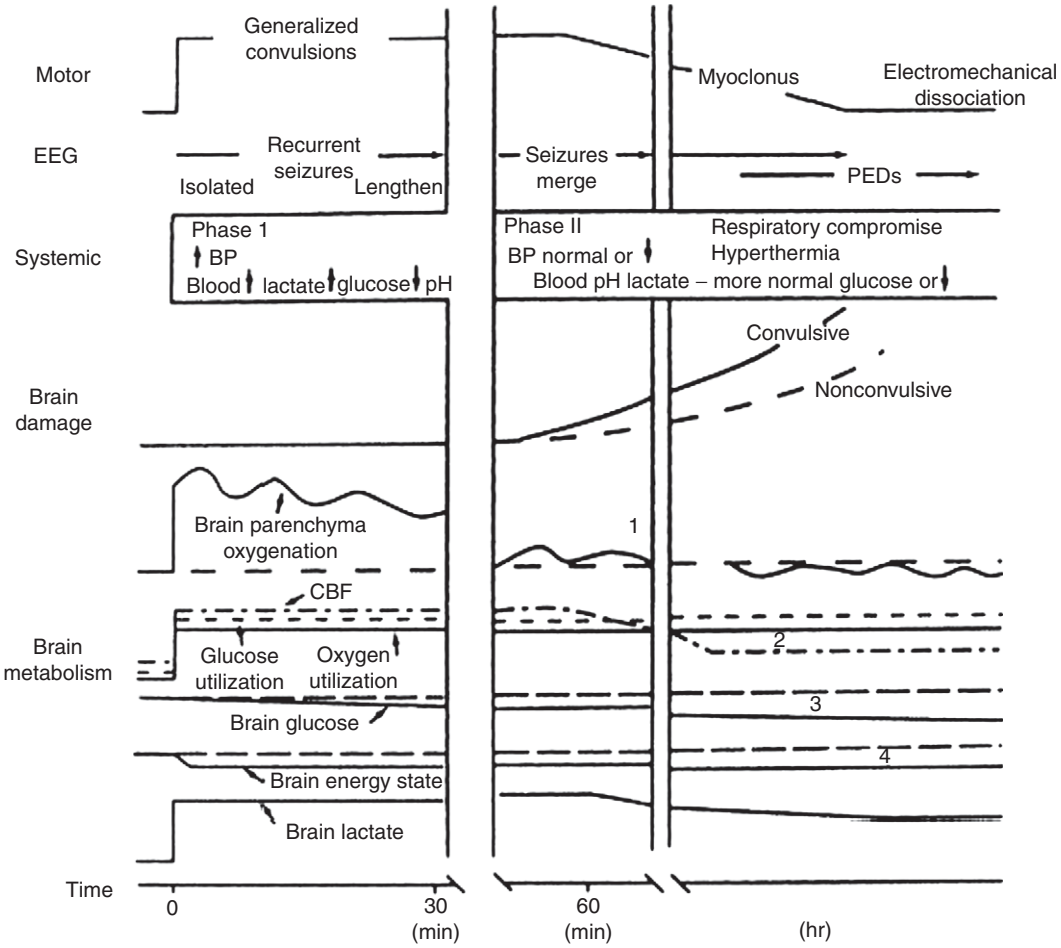

Fig. 13.4. An overview of the systemic and neurophysiological changes during status epilepticus. During phase I, increased cerebral metabolic demand is satisfied by systemic derangements (e.g., increased blood pressure, increased glucose). During phase II there is failure of cerebral autoregulation and different systemic derangements that lead to decreased cerebral blood flow with failure to meet cerebral metabolic demands. With permission from Lothman E (1990). The biochemical basis and pathophysiology of status epilepticus. Neurology 40: 13. Copyright © 1990 by AAN Enterprises, Inc.

the subtypes with perioral myoclonus and 'phantom absence and generalized tonic clonic seizures' and de novo in the elderly as 'spike-and-wave stupor' (Shorvon and Walker, 2005).

Impairment of consciousness is highly variable from patient to patient and may show variability in various attacks in the same patient. In the typical case the patient responds but is confused and slow to respond, or may respond only after repeated requests. Severe cases show stupor and a state similar to akinetic mutism, lacking in spontaneity and following with the eyes. Memory for the event is also variably impaired. Sometimes there is a fair degree of recall. Motor phenomena during the attack, e.g., myoclonus of the facial muscles, especially those around the eyes, is common. Some patients may be immobile and expressionless but some appear perplexed or even agitated. If speech is uttered it is often nonfluent, hesitant, and monosyllabic. Automatisms are rare, in contrast to complex partial status epilepticus. Episodes can end abruptly, e.g., on their own or after administration of a rapidly acting drug such as lorazepam or intravenous valproate.

13.7.2.2. Myoclonic status epilepticus

Myoclonic status epilepticus in patients with idiopathic epilepsy is rare but has been reported in patients with juvenile myoclonic epilepsy. Video-EEG shows brief, repetitive bursts of polyspike-and-wave discharges associated with myoclonic movements (Badhwar et al., 2002). Generalized myoclonic status epilepticus with coma following cardiopulmonary arrest is almost uniformly fatal (Young et al., 1990; Wijdicks et al., 1994). Though some controversy has existed in the past, EEG patterns demonstrate that these motor

events are probably seizures. Spikes, sharp waves, or triphasic waves, commonly in a burst-suppression pattern, correlate with generalized myoclonic movements. This neocortical activity represents irreversible neuronal damage and occurs prior to electrocerebral silence. This activity will abate on its own and needs to be treated with paralytics only if it is disruptive to the family.

As described previously, simple partial seizures commonly do not appear on EEG. Simple partial status epilepticus may be associated with a normal EEG or waxing and waning semi-rhythmic frequencies, focal spike, or spike-and-wave discharges occurring repetitively. These seizures may cause nonconvulsive or convulsive status epilepticus (epilepsia partialis continua).

Complex partial status epilepticus may present in a fugue or twilight state, often with wandering, or with a more depressed level of consciousness. Patients are typically amnestic for the event. Intermittent automatisms may give a clue to the ictal nature of the spell; sensory (hallucinations) affective disturbances (fear) may occur near the onset.

Nonconvulsive status epilepticus (NCSE) is a more controversial term but in general is accepted as meeting the definition of status epilepticus by involving a change in mental status or behavior (lasting more than 30 min) without prominent convulsive activity. The term seems to be increasingly used for nonconvulsive seizures in an intensive care unit (ICU) or emergency room setting. Surveys of comatose patients in general ICUs reveal that at least 8% are in NCSE (Young et al., 1996; Towne et al., 2000); the subgroup with structural brain lesions has the highest incidence, at over 10% (Young et al., 1996). At least 14% of patients who remain comatose after treatment for convulsive status epilepticus are in NCSE (DeLorenzo et al., 1996). An EEG showing ongoing focally originating or generalized ictal activity is required for definitive diagnosis. Facial myoclonus or 'epileptic nystagmus', as clinical clues, occur in fewer than 10% of such cases. NCSE is associated with substantial mortality when etiology is an acute medical illness and when severe mental status impairment is present (Shenker and Fountain, 2003). The mortality rises almost exponentially with seizure duration (Young et al., 1996). The corollary is that patients at risk of NCSE should have continuous EEG monitoring (Claassen et al. (2004) have shown that 48 hours is an optimal duration) and that seizures should be treated vigorously. Continuous EEG (cEEG) also serves to monitor the effectiveness of therapy. Approximately 8% of patients undergoing EEG for unexplained coma in general ICUs will have electrographic evidence of nonconvulsive status epilepticus (Towne et al., 2000). However, in neurological ICUs the incidence of nonconvulsive seizures and status is probably higher and may be between 30% and 40% in certain populations (Jordan, 1993; Hirsch, 2004). Acute structural brain lesions that cause coma are much more likely to cause seizure activity than metabolic encephalopathy, and cEEG is a useful tool for detecting NCSE in this patient population (Bleck et al., 1993; Young and Doig, 2005).

NCSE in obtunded or comatose patients can be difficult to diagnose. This is probably an underrecognized cause of hypoactive delirium in the ICU setting (Jordan, 1993; Towne et al., 1994; Hirsch, 2004). It may evolve from generalized tonic–clonic seizures, as described previously, and can be associated with a variety of other disorders. Subtle motor movements may or may not be seen. The EEG pattern may show focal or generalized epileptiform activity occurring continuously or intermittently.

There are no universally agreed criteria for electrographic NCSE; however, Young et al. (1996) have proposed criteria for nonconvulsive seizures that can reasonably be used for defining NCSE (Table 13.2). Some common EEG patterns seen during monitoring for status epilepticus are more controversial as to whether or not they represent ictal phenomena. Periodic lateralized epileptiform discharges consist of lateralized spike or sharp wave activity occurring every 1–2 seconds. Alone, they are considered by most to represent an interictal pattern with an increased

Table 13.2

Proposed criteria for a nonconvulsive seizure

GUIDELINE: To qualify at least *one* of primary criteria 1–3 and *one or more* of the secondary criteria, with discharges >10 seconds

Primary criteria

1. Repetitive generalized or focal spikes, sharp waves, spike-and-wave or sharp-and-slow wave complexes at >3/second.
2. Repetitive generalized or focal spikes, sharp waves, spike-and-wave or sharp-and-slow wave complexes at <3/second *and* secondary criterion 4.
3. Sequential rhythmic waves and secondary criteria 1, 2 *and* 3 with or without 4.

Secondary criteria

1. Incrementing onset: increase in voltage and/or increase or slowing of frequency.
2. Decrementing offset: decrease in voltage or frequency.
3. Postdischarge slowing or voltage attenuation.
4. Significant improvement in clinical state or baseline EEG after antiepileptic drug.

Source: with permission from Young et al., 1996.

risk for acute seizures to develop (Jordan 1999a, b; Claassen et al., 2001). It is important to recognize that the presence of periodic lateralized epileptiform discharges on an EEG usually indicates acute brain injury from a source other than a seizure.

13.8. Management of seizures

13.8.1. Is it a seizure? Differential diagnosis

Although a seizure is in the differential diagnosis of a paroxysmal event, there are many other conditions that need to be considered. Movement disorders including paroxysmal dyskinesias, non-epileptic myoclonus, tremors, spasms, and many others may all mimic an epileptic spell. Toxic and metabolically induced movements, e.g., multifocal myoclonus, tremor, and asterixis, may also be mistaken for seizures. In children 'breath-holding spells' in association with crying are also common causes of intermittent loss of consciousness. Brainstem release phenomenon, migraine, and transient vascular events may also be confused with epileptic spells. Syncope, especially when a myoclonic component is present, is commonly mistaken for an epileptic event. In rare circumstances a seizure may trigger syncope-like spells, as in the ictal bradycardia syndrome. During the seizure bradycardia is induced by the ictal activity causing hemodynamic instability leading to loss of consciousness (Reeves et al., 1996). Psychogenic spells/pseudoseizures account for approximately one-half of paroxysmal non-epileptic spells. Some features that suggest psychogenic origin include asynchronous limb movements, opisthotonus without passing out, side-to-side head shaking, vocalization in the tonic–clonic phase, and closed eyes during the convulsive activity (Devinsky et al., 1997; Reuber and Elger, 2003). Prolactin levels have been shown to be elevated following complex partial and generalized tonic–clonic seizures (Abbott et al., 1980; Dana-Haeri et al., 1983; Aminoff et al., 1984). However, the utility of this in differentiating epileptic from non-epileptic spells has been questioned (Shukla et al., 2004). Video-EEG monitoring is commonly required for characterizing spells to determine if the origin is epileptic or non-epileptic. Studies indicate that 9.4% of patients with psychogenic spells also have coexisting epileptic spells, so the presence of psychogenic spells does not completely rule out the diagnosis of true epilepsy (Benbadis et al., 2001).

13.8.2. Investigations: clinical diagnostic tests for seizures

These include EEG, neuroimaging, lumbar puncture, and biochemical tests. These are discussed in turn.

13.8.2.1. The role of electroencephalography in seizures

Since its inception in 1929 the EEG has been used extensively in the diagnosis of suspected seizures and has been invaluable in the characterization of epilepsies. EEG patterns for various seizure types have been discussed earlier. Continuous EEG monitoring is commonly employed in epilepsy units to classify seizures and to check for nonepileptic events. cEEG is increasingly utilized in the ICU for the detection of non-convulsive seizures and in the treatment of status epilepticus.

13.8.2.2. Neuroimaging in seizures

Most patients suspected of having a seizure or epilepsy require an imaging study; however, when to obtain this depends on many factors. Adult patients with their first spell should have a head computed tomography (CT) scan or magnetic resonance imaging (MRI) scan depending on clinical history. Patients with new focal neurological findings or who have prolonged awakening after a seizure should have an emergency head CT scan to evaluate for intracranial hemorrhage, mass lesion, or hydrocephalus. Critically ill patients may also need an MRI scan, which is more sensitive and specific for most causes of provoked seizures in hospitalized patients. Previously investigated patients with a history of epilepsy do not typically need new brain imaging if they return to their baseline neurological examination. Most patients suspected of focal or partial epilepsy should have an MRI during their evaluation to look for symptomatic causes of epilepsy. However, not all patients suspected of having a seizure or epilepsy need brain imaging. Examples include children with typical absence epilepsy or benign rolandic epilepsy with a normal neurological examination. These patients may have classic ictal semiology and EEG patterns.

The choice of imaging modality depends on many factors. Ultrasound is the first choice in neonates and young infants, although CT scan is commonly employed. In emergency situations in the adult population head CT is the preferred imaging modality because of its availability. This can be done quickly from the emergency room and is highly sensitive for blood, calcium, and for evaluation of the basal cisterns. Occasionally seizures may cause effacement of gyri and enhancement on CT scan (and other imaging modalities). Head CT scans are less sensitive and specific than MRI for detecting structural lesions; therefore MRI remains the imaging modality of choice for epilepsy. It has high sensitivity and specificity for detecting mesial temporal sclerosis, small tumors, encephalitis, leukoencephalopathies, cortical dysplasia, stroke, and anoxic injuries. As MRI is becoming more widely available, we are

beginning to image patients with this modality in the acute peri-ictal period and are finding areas of signal abnormalities after acute seizures. Diffusion-weighted, standard T_2-weighted and fluid-attenuated inversion recovery imaging on MRI have shown signal changes with acute seizures (Kawahara et al., 2004). MRI scans can also show abnormalities in the apparent diffusion coefficient (ADC) map after acute seizures. These may disappear over time and be associated with return to a normal neurological examination. Increased ADC reflects extracellular edema and ADC mapping may be useful for predicting the reversibility of brain damage due to status epilepticus (Wartenberg et al., 2004).

SPECT is not indicated for the majority of patients with epilepsy but has an important role in the investigation of surgical candidates (Andersen et al., 1990; Spencer, 1994). It localizes seizure activity better than other neuroimaging modalities. Studies have shown that approximately 50% of patients with temporal lobe epilepsy have hypoperfusion in the affected temporal lobe on interictal imaging and 90% have increased perfusion on ictal imaging (Bauer et al., 1991; Marks et al., 1992; Ho et al., 1994). PET is considerably more expensive than SPECT but is still commonly employed to look for ictal hypermetabolism and interictal hypometabolism. Magnetic resonance spectroscopy, magnetic resonance relaxometry, receptor PET studies and magnetoencephalography are newer techniques being studied. Functional MRI, which uses very rapid scanning techniques to detect alterations in blood oxygenation, has recently been studied in patients with epilepsy (Detre et al., 1995).

13.8.2.3. Lumbar puncture

A lumbar puncture may be required in patients with acute seizures. Patients suspected of having meningitis or encephalitis will require cerebrospinal fluid (CSF) evaluation. Failure to wake up, fever, rash, nuchal rigidity and certain abnormalities on neuroimaging all indicate that a lumbar puncture may be needed to rule out treatable causes of provoked seizures. An imaging study is typically required prior to lumbar puncture since the seizure may have been provoked by a mass lesion in the brain. CSF evaluation is used mainly to evaluate for central nervous system infection or bleeding but there are many other less common disease processes that may be found. Examples include neoplastic, inflammatory or metabolic, and toxic abnormalities. An epileptic pleocytosis may be seen following a flurry of seizures. The CSF is clear and colorless with normal opening pressure, normal glucose, and mildly increased protein. Maximum leukocyte count has varied between different studies with some reporting up to 80 cells/mm^3 and others a maximum of 12 cells/mm^3 within 72 hours of convulsions (Schmidley and Simon, 1981; Devinsky et al., 1988). It is estimated that approximately 11% of patients have an epileptic pleocytosis after a 'flurry' of seizures, either focal or generalized (Devinsky et al., 1988). In general more than 12 cells/mm^3 suggests a cause other than the seizure flurry and appropriate investigations should be done.

13.8.2.4. Other laboratory tests

During acute seizures laboratory screening for metabolic and toxic etiologies may be helpful. Uremia, hyponatremia, hypocalcemia, hyper- or hypoglycemia, and other metabolic abnormalities can all lower the seizure threshold. A toxicology screen for illicit and prescribed medications (e.g., theophylline) may also be helpful. Elevation of creatine kinase may occur after seizures and detection helps differentiate epileptic from non-epileptic spells. Markedly elevated levels also indicate a threat to kidney function and necessitate institution of nephroprotective measures.

13.8.3. Treatment of seizure disorders

The principles of therapy and the use of antiepileptic drugs and other treatments, including surgery, are beyond the scope of this chapter. Excellent reviews can be found in a number of articles and reviews (Bergey, 2005; Hitiris and Brodie, 2005, 2006; Hunt and Morrow, 2005; Kanner and Balabanov, 2005; Leppik, 2005; Patsalos, 2005; Perucca, 2005, 2006; Guerrini and Parmeggiani, 2006; Loscher et al., 2006; Pellock, 2006).

Status epilepticus requires special therapeutic consideration. Key articles and reviews include: Rashkin et al., 1987; Giroud et al., 1993; Jagoda and Riggio, 1993; Ramsay, 1993; Shorvon, 1994; Kinoshita et al., 1995; Krishnamurthy and Drislane, 1996; Lowenstein, 1998; Treiman et al., 1998; Hovinga et al., 1999; Naritoku and Mueed, 1999; Treiman, 1999; Uberall et al., 2000; Claassen et al., 2002; Mayer et al., 2002; Shenker and Fountain, 2003; Mirsattari et al., 2004; Bleck, 2006.

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Chapter 14

Syncope

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Syncope is a common presenting symptom, with an incidence rate for first occurrence of 6.2 per 1000 person years (Soteriades et al., 2002). Syncope accounts for 3% of emergency presentations and 1% of hospital admissions (Kapoor, 1990). It is generally associated with a low mortality and has a bimodal distribution. The first peak occurs in the adolescent and early adult years, which is predominantly neurocardiogenic in origin, with a second peak in the sixth and seventh decade generally reflecting arrhythmias from underlying structural heart disease. Presentations are often dramatic and can occur without warning, involving transient loss of consciousness and postural tone, generally for relatively short periods (seconds to minutes) with spontaneous recovery. It is variously described by patients and can often be associated with presyncopal episodes in which the patient believes they will lose consciousness but manages to avoid doing so. This chapter will focus principally on cardiac causes for syncope, in particular arrhythmic and neurocardiogenic syncope and their diagnosis and management.

14.1. Etiology

The etiology of syncope is complex and varied (Table 14.1). In a general population, syncope is most probably related to neurocardiogenic or 'vasovagal' syncope and resolves after a single episode. It is most commonly associated with disorders of the cardiovascular system; however, disorders of the neurological system or both systems may also cause syncope. Accordingly, it is often neurologists and cardiologists who investigate, diagnose, and manage syncope. Specifically, cardiovascular causes for syncope include mechanical or structural heart disease such as aortic stenosis or hypertrophic obstructive cardiomyopathy, cardiac arrhythmias, and neurally mediated syncope, of which neurocardiogenic syncope is the most common. Although it is arguable, neurocardiogenic syncope, along with other forms of reflex syncope (blood phobia, micturition syncope, etc.) and its autonomic variants such as postural tachycardia syncope, inappropriate sinus tachycardia, and primary or secondary autonomic failure, are often seen by cardiologists within the spectrum of the vascular portion of cardiovascular causes of syncope, even though they clearly fall squarely in between a purely cardiac or purely neurological cause.

The diagnosis of syncope can, however, be difficult, as demonstrated in a large patient case series of 433 patients examining the causes of syncope in patients presenting to emergency departments or the primary care setting (Kapoor, 1990). The cause of syncope was found in only 60% of cases. Of those who were diagnosed, the cause was found to be cardiac in 90.2% of cases, with vasomotor and reactive syncope the most common causes (50.4%). This included diagnosed neurocardiogenic syncope with and without a clinical precipitant, which accounted for 28% of patients, and orthostatic hypotension in 16.9%. Arrhythmias accounted for 34.3% of causes, with a high incidence of ventricular tachycardia (19.3%). As this study was performed before the use of prolonged monitoring strategies, the investigations were biased towards assigning a diagnosis of tachyarrhythmias from asymptomatic ventricular ectopy on Holter monitoring. It is likely that bradyarrhythmias, which are more often infrequent and intermittent, were underdiagnosed. This series demonstrates that syncope is most often a cardiovascular disorder and that

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Table 14.1

Etiologies of syncope

Cardiovascular		Noncardiovascular
Arrhythmias		**Neurological**
Bradycardia	Sinus bradycardia/pause	Seizure disorder
	AV block	Cerebrovascular accident
Tachycardia	Supraventricular	Autonomic neuropathy (idiopathic, secondary to diabetes, Parkinson's disease, etc.)
	Ventricular	
Mixed	Tachy-brady syndrome	
	Torsade de pointes	
	Long QT syndrome	
	Brugada syndrome	
Obstructive cardiac lesions		**Endocrine**
Left ventricular	Aortic stenosis	Hypoglycemia
	Hypertrophic cardiomyopathy	
	Subvalvular web	
	Mitral stenosis	
Other	Intracardiac tumors	
Vasomotor		**Miscellaneous**
Neurocardiogenic (vasovagal)		Pulmonary embolism
Postural tachycardia syndrome (postural tachycardia syncope)		Psychogenic
Postural hypotension		
Carotid sinus hypersensitivity		
Situational syncope (blood phobia, micturition, cough, swallowing, etc.)		

AV = atrioventricular.

vasomotor and arrhythmic disorders predominate in those patients who are ultimately diagnosed. The diagnosis of syncope is, however, difficult, stemming from the transient nature of the presentation, the large number of etiologies and the lack of a gold standard for diagnostic evaluation.

14.2. Pathophysiology of syncope

14.2.1. Cerebral perfusion

Regardless of the etiology, syncope results from insufficient cerebral blood perfusion. Gravity and the loss of blood volume due to both venous distention and loss of fluid through dependent capillaries compromise the heart's ability to perfuse the brain when upright. These challenges are overcome by a complex of reflexes, particularly baroreflexes, that include vasoconstriction of resistance and capacitance vessels in the periphery as well as autonomically mediated sinus tachycardia when needed. These mechanisms are exhaustible and their decline can be gradual or abrupt, even in the nonpathological state, leading to syncope. Cerebral perfusion is largely dependent on arterial blood pressure within the autoregulatory range assuming that blood gases remain constant. At pressures outside the autoregulatory range (<60 mmHg), cerebral flow is greatly influenced by chemical changes in the blood, in particular the $P_{a}CO_2$ (Hainsworth, 2004). Recent evidence suggests that syncopal individuals may have more pronounced changes in cerebral vessel and systemic reactivity to hypocapnia, predisposing them to cerebral hypoperfusion and syncope (Hainsworth, 2004).

14.2.2. Neurally mediated syncope

Neurally mediated syncope is a group of disorders, the most common of which is neurocardiogenic or vasovagal syncope (Grubb, 2005a). They are considered arbitrarily as cardiac causes of syncope and typically managed by cardiologists. These disorders occur secondary to a transient failure of the reflex mechanisms that maintain cerebral perfusion and ultimately consciousness in the face of orthostatic stress. Episodes are generally self-limited once the patient reaches a recumbent posture and accordingly generally have a benign prognosis (Grubb, 2005a). In a large population study on the incidence of first presentations of syncope, neurocardiogenic syncope accounted for 22% (Soteriades et al., 2002). Other disorders in this group include carotid sinus hypersensitivity and situational syncope, which can occur with venipuncture or blood phobia and after bodily functions such as urination, defecation, swallowing, or coughing. Carotid sinus hypersensitivity is defined as

syncope or presyncope resulting from an extreme reflex response to carotid sinus stimulation (Gregoratos et al., 1998). Situational syncope is also believed to stem from the same mechanism with abnormalities of local reflexes. The carotid sinus reflex has two components: a cardioinhibitory component associated with bradycardia and a vasodepressor component causing peripheral blood pooling resulting in hypotension. Orthostatic hypotension is also often considered a form of neurally mediated syncope. Unlike vasovagal syncope where reflexes are intrinsically normal with the exception of the infrequent incidents causing syncope, orthostatic hypotension reflects generalized loss of reflex compensation to maintain cerebral perfusion upon assuming the upright posture. This may be primary (e.g., Shy–Drager syndrome or multisystem atrophy) or secondary to inhibition of these reflexes by pharmacotherapy. Similarly, dysautonomias such as postural tachycardia syndrome (POTS) are also considered as neurally mediated causes of syncope. Patients with POTS typically have exaggerated sinus tachycardia upon standing associated with minimal hypotension (Kenny et al., 1986). These patients more typically experience presyncope than syncope and often complain of chronic fatigue.

The pathophysiology of neurocardiogenic syncope is currently incompletely understood, but is probably multifactorial (Mosqueda-Garcia et al., 2000). The current hypothesis integrates a predisposition to excessive pooling of blood in peripheral venous capacitance vessels, leading to a decrease in central blood volume. This venous pooling results in a hypercontractile cardiac state that is believed to activate left ventricular mechanoreceptors or 'C' fibers, which normally respond to ventricular stretch (Chen-Scarabelli and Scarabelli, 2004). This increases afferent input to the medullary vasodepressor center in the midbrain, which produces hypotension, bradycardia, and ultimately syncope. In association with these reflexes there is also believed to be an imbalance or 'misfire' in the sympathetic and parasympathetic responses to these stimuli such that there is excessively increased sympathetic activity prior to vagal withdrawal, which is then followed by reflex hypervagotonia leading to syncope (Grubb, 2005b). Peripheral monitoring of sympathetic neural traffic has demonstrated abrupt withdrawal of sympathetic activity in conjunction with an increase in vagal tone (Morillo et al., 1997). The mechanism of this is not well understood (Donadio et al., 2007). This response is also believed to be induced by afferent input from other nerves such as cranial nerves, cardiopulmonary baroreceptors, and genitourinary and gastrointestinal receptors (Kapoor, 2000; Brignole et al., 2001a; Chen-Scarabelli and Scarabelli, 2004). In a study of hemodynamic responses prior to neurocardiogenic syncope, hypotension occurred first in the majority of patients (71%), with bradycardia occurring first in 14% (Julu et al., 2003).

14.2.3. Cardiac arrhythmia

Syncope can be caused by either bradyarrhythmias or tachyarrhythmias, which cause syncope by decreasing cerebral perfusion. In syncopal patients in whom a diagnosis can be made, bradyarrhythmias are the more common arrhythmic cause, especially in the elderly. With cardiac arrhythmias, it is the heart rate change which is most important in determining the severity of symptoms, not the absolute heart rate. Accordingly, symptoms are often most pronounced at the beginning of an arrhythmia. The ability of the peripheral vasculature to adapt to a sudden change in cardiac output secondary to an arrhythmia strongly influences the severity of the symptoms. In addition, bradyarrhythmias often begin with a pause followed by an increase in sinus or escape rate, increasing cardiac output, and cerebral perfusion. The majority of sustained or nonsustained arrhythmias are surprisingly well tolerated. In addition, tachyarrhythmias may initiate a neurocardiogenic syncopal response. Many arrhythmias that lead to syncope are transient, with resolution of the etiology before coming to medical attention. This makes a diagnosis elusive, although less so with the recent development of prolonged monitoring technologies.

14.3. Investigations in syncope

The key first step in the investigation of syncope is to accurately separate benign non-life-threatening causes such as vasovagal syncope from malignant, life-threatening causes such as ventricular arrhythmias (Soteriades et al., 2002). Although this may appear obvious, an incorrect diagnosis of syncope can have unnecessary life-altering consequences such as loss of job, inability to drive, and inappropriate therapeutic intervention. The association of physiological abnormalities with an episode of spontaneous syncope, often electrocardiographic monitoring in a medically supervised facility, constitutes a gold standard investigation for the diagnosis of cardiovascular syncope (Brignole et al., 2001a). Unfortunately this is difficult to achieve in clinical practice. In cases where the diagnosis is not evident on history and clinical examination, it may not be achieved in as many as 50% of cases. This is because of resolution of symptoms or the transitory nature of the episodes, which cannot be adequately investigated by current means (Linzer et al., 1997a). A thorough understanding is therefore required of the efficacy and utility of the investigational tools for syncope to institute the appropriate management.

In general, investigations in syncope can be categorized into three tiers (Krahn et al., 2004). The first tier is performed at the time of the episode in an attempt to provide a baseline, ideally make a diagnosis, and direct future investigations. This includes a history, physical examination, an electrocardiogram (ECG), and short-term electrocardiographic monitoring, as well as discretionary echocardiography and electroencephalography (EEG). The second tier of investigations involves provocative testing in an attempt to reproduce an episode or prodrome. These investigations require clinical acumen as they create an 'artificial' physiological stress to reproduce symptoms which in itself can be misleading. These investigations include head-up tilt, electrophysiological testing, and sleep-deprived EEG. Finally the third tier involves long-term monitoring in the hope of correlating the physiological parameter being recorded with a syncopal or presyncopal episode. This includes increasing duration of electrocardiographic monitoring by hospital-based telemetry (hours to days), Holter monitoring (24–72 hours), an external loop recorder (2–8 weeks), or an implantable loop recorder (18–24 months). This strategy of investigation relies on the recurrence of syncope and is therefore limited by delay in diagnosis depending on time to recurrence and the risk of recurrence including injury and life-threatening ventricular arrhythmias. Accordingly, a management plan is then derived from the investigational results and clinical impression.

14.3.1. Tier 1: investigations immediately postsyncope

14.3.1.1. History and physical

History and physical examination is not an investigation tool per se; however, it is the most important means of arriving at a clinical diagnosis or providing important direction for investigations. In a review by Linzer et al. (1997a) of six studies of syncope, history and physical examination alone resulted in the diagnosis in 45% of cases. A study (Sarasin et al., 2001) in 650 patients presenting to the emergency room with syncope demonstrated that electrocardiography in addition to standardized clinical evaluation was able to diagnose the cause of syncope in up to 76% of cases. Common symptomatic and clinical examination findings associated with different causes of syncope are presented in Table 14.2. Often, however, presentations of syncope can be nebulous, especially if the syncopal event is unwitnessed, or associated with trauma or retrograde amnesia. Despite these limitations, it is the history that often dictates the successive management. In the assessment of the life-threatening potential of the syncopal event, it is essential to note a past history of myocardial infarction or congestive

Table 14.2

Clinical findings associated with different etiologies of syncope compared with seizure

	Arrhythmia	Neurocardiogenic	Seizure
History			
Prodrome	Short in duration Palpitations	Generally minutes in duration Warm Diaphoresis Loss of vision	Aura Todd's palsy
Duration of syncope	Seconds to minutes	Usually <60 s	Variable
Epileptiform movements	Almost never	Infrequent	Always
Recovery time	Seconds to minutes	Minutes	Minutes to hours with associated amnesia
Presyncope	Occasionally	Frequent	Rare
Posture	None	Usually upright	None
Palpitations	Occasionally	Occasionally	None
Examination findings			
Postural blood pressure drop	Not present	Often present	Not present
Signs of obstructive cardiac etiology	No	No	No
Evidence of structural heart disease	Frequent	No	No
Neurological deficit	No	No	Frequent
Maneuvers			
Valsalva	No effect	No effect	No effect
Carotid sinus massage	May see bradycardia	May see bradycardia	No effect

heart failure, as causes such as cardiac arrhythmia need more consideration.

Prodromal symptoms also give clues as to causation; a prodrome can last from seconds to several minutes. Neurocardiogenic syncope is typically preceded by diaphoresis, nausea, headache, blurring of vision, and presyncope. A patient can often avert an episode when the prodrome occurs, by adopting a recumbent posture. Episodes typically occur when upright or seated and do not occur if the patient is recumbent. Neurocardiogenic syncope can also present in clusters of syncopal episodes and then remain quiescent for years (Grubb, 2005a). This clustering is not well understood. The prodromal symptoms can be attributed to decreased blood pressure. Other causes of hypotension in association with syncope can therefore also have similar prodromes. Stokes–Adams attacks, described originally in patients with bradycardia secondary to atrioventricular node block (Adams, 1827; Stokes, 1846), are classically a sudden collapse with minimal or no prodromal symptoms. Patients regain consciousness within seconds to minutes and often suffer trauma with an episode. This abrupt onset and recovery history often occurs in the context of underlying structural heart disease and is due to transient hypotension secondary to bradycardia or tachycardia (Alboni et al., 2001). Therefore, investigations should be tailored towards an arrhythmic cause for syncope.

Palpitations experienced prior to syncope or presyncope may be indicative of 'tachy-brady' syndrome in association with sinus node disease and poor sinus node recovery after an episode of atrial fibrillation. The palpitations may also be secondary to a ventricular arrhythmia. A recent review suggested that neurocardiogenic syncope may be more easily diagnosed on historical grounds than arrhythmic syncope (Colman et al., 2004). A seizure disorder as distinct from syncope is suggested from epileptiform movements in association with an episode, urinary or fecal incontinence, tongue biting, prolonged impairment of conscious state, retrograde amnesia, preceding aura distinct from prodromal hypotensive or vagal symptoms, and subsequent Todd's paresis postictally (Kellinghaus and Kotagal, 2004). Additionally, seizure disorders may be precipitated by repetitive stimuli such as a strobe light. While historical clues are helpful in making the distinction between neurogenic and cardiogenic causes of syncope, this is not absolute. Observer accounts of the onset of symptoms can be very helpful, since syncope with secondary seizure or seizure with subsequent loss of consciousness may be difficult to distinguish. Cardiogenic syncope can present with symptoms such as tonic–clonic movements similar to seizure disorders secondary to cerebral hypoxia from hypotension (Lempert et al., 1994). A recent study, however, proposed a historical scoring system which can reliably differentiate syncope secondary to seizure disorder from other etiologies based on initial clinical assessment (Sheldon et al., 2002). The diagnostic questions and historical point scoring are presented in Table 14.3. Interviewing an observer is often the key in the diagnosis of syncope, since retrograde amnesia is common for prodromal events and duration of unresponsiveness.

The physical examination, like the history, provides important information to guide further investigations to diagnose and manage syncope. While the examination is often noncontributory, orthostatic intolerance is easily diagnosed by assessing lying and standing blood pressure

Table 14.3

Diagnostic questions differentiating seizure disorder from syncope

Question	Diagnostic score for positive response
At times do you wake with a cut tongue after your spells?	2
At times do you have a sense of déjà vu or jamais vu before your spells?	1
At times is emotional stress associated with losing consciousness?	1
Has anyone ever noted your head turning during a spell?	1
Has anyone ever noted that you are unresponsive, have unusual posturing or have jerking limbs during your spells or have no memory of your spells afterwards?	1 for any positive response
Has anyone ever noted that you are confused after a spell?	1
Have you ever had lightheaded spells?	−2
At times do you sweat before spells?	−2
Is prolonged sitting or standing associated with your spells?	−2

Diagnostic score ≥ 1, diagnosis: seizure disorder.
Diagnostic score < 1, diagnosis: syncope.
Source: adapted from Sheldon et al., 2002.

(instantaneous and delayed standing blood pressure). Physical evidence of structural heart disease, in particular potential obstructive lesions such as aortic stenosis, hypertrophic cardiomyopathy, or intracardiac tumors, enables diagnosis and direct management. Furthermore, physical evidence of ischemic heart disease or congestive heart disease suggests consideration of an arrhythmic cause for syncope, which is potentially life-threatening and amenable to intervention. If a seizure disorder or stroke is suspected, a neurological examination is also potentially useful to screen for Todd's palsy or residual deficits.

In addition to routine physical examination, carotid sinus massage can be performed and can increase the diagnostic yield of the examination. This maneuver is potentially diagnostic of carotid sinus hypersensitivity. This neurally mediated form of syncope occurs when pressure is applied to the carotid sinus, leading to bradycardia or atrioventricular heart block secondary to stimulation of an overactive baroreflex. During massage, it is important to monitor the patient both electrocardiographically and hemodynamically. The physician should auscultate for carotid bruits prior to performing massage. The presence of bruits is a contraindication to the performance of carotid sinus massage. The risk of neurological complication in association with carotid sinus massage is 0.28% (Davies and Kenny, 1998).

The normal response to carotid sinus massage is a slowing of the sinus rate, with a 3 second pause representing the upper limit of normal. Therefore, a positive test is described as a pause greater than 3 seconds (cardioinhibitory response), or a drop in blood pressure of $\geq$50 mmHg (vasodepressor response) not associated with the cardioinhibitory response. An abnormal response to carotid sinus massage is relatively nonspecific and can be observed in patients with syncope from other causes, especially in the elderly. Carotid sinus hypersensitivity should only be diagnosed when a positive response to carotid sinus massage reproduces symptoms or there is strong clinical suspicion that the response reflects the underlying cause for syncope. In addition, there is evidence to suggest performance of carotid sinus massage in the upright position enhances the sensitivity of the test (Sugrue et al., 1986) and that performing the test immediately after raising the patient yields the highest sensitivity (Farwell and Sulke, 2005).

14.3.1.2. Electrocardiogram

A key initial step in patients with syncope is to establish the presence or absence of structural heart disease and/or abnormal electrocardiogram (Brignole et al., 2001a). Using this distinction, the former group more commonly has an arrhythmic cause for syncope, requiring further investigation that should be considered urgent. The latter group typically has a neurogenic or neurocardiogenic cause, in which further investigations may not be required. While the abnormal ECG is important in the assessment of the syncopal patient, it is contributory in only 5% of cases (Linzer et al., 1997b; Pires et al., 2001). Electrocardiographic abnormalities in association with syncope are presented in Table 14.4. Despite the modest diagnostic yield, electrocardiographic examination is recommended in all patients with syncope. The

Table 14.4

Electrocardiographic abnormalities in syncope

Conduction abnormalities	Arrhythmias	Arrhythmogenic syndromes	Other
Between atrium and ventricle	**Bradyarrhythmias/pauses**	QT prolongation (congenital or acquired)	Q waves indicative of previous myocardial infarct
1st degree heart block	Sinus bradycardia (<50 beats per minute)	Brugada syndrome	Electrocardiographic evidence of LVH
2nd degree heart block	Sinus pauses (>3 s)	Pre-excitation syndrome	
Wenckebach (Mobitz type I)	Junctional bradycardia		
Mobitz type II	Ventricular escape rhythm (associated with 3rd degree heart block)		
3rd degree heart block			
Intra-ventricular	**Tachyarrhythmias**		
Right or left bundle branch block	Supraventricular		
	Ventricular		
Bifascicular block	**Tachy-brady or sick sinus syndrome**		

LVH = left ventricular hypertrophy.

most common electrocardiographic diagnoses include ventricular tachycardia, bradyarrhythmias and, less commonly, acute myocardial infarction. Conduction disturbances such as first-degree heart block, bundle-branch block, and sinus bradycardia may suggest a bradycardic cause for syncope. In contrast, previous myocardial infarction or left ventricular hypertrophy in association with hypertrophic cardiomyopathy may be associated with ventricular tachycardia.

14.3.1.3. Myocardial imaging

Myocardial imaging in syncope is important to diagnose underlying structural heart disease. Again, while important, these investigations rarely suggest a cause for syncope. Routine imaging with echocardiography and radionuclide ventriculography are associated with a 1–3% diagnostic yield (Kapoor et al., 1982; Recchia and Barzilai, 1995). The most common and important use of cardiac imaging is to detect structural heart disease secondary to ischemic heart disease or significant ventricular impairment from other causes. These findings should alert the physician to the possibility of more malignant causes for syncope such as ventricular arrhythmias and accordingly a more aggressive investigation strategy.

14.3.1.4. Exercise stress test

The role of exercise stress testing in investigating syncope has not been well studied to date. The diagnostic yield in undifferentiated cases of syncope is probably less than 1% (Kapoor, 1990). The most efficacious use of the exercise stress test therefore is in the patient with exertional symptoms or to investigate for occult ischemic heart disease when necessary. Exclusion of significant aortic stenosis or hypertrophic obstructive heart disease is mandatory prior to stress testing.

14.3.1.5. Neurological investigations

Neurological testing is covered extensively in other portions of this handbook. Neurological investigations are low-yield tests in undifferentiated syncope and appear to be overused in recent retrospective studies of patients presenting with syncope (Pires et al., 2001; Dolz et al., 2004). Testing should be directed at assessment of patients where the history and physical examination raise suspicion regarding seizure, or cardiovascular testing is negative and symptoms are recurrent. Specifically, the EEG is not a useful investigation when used indiscriminately in syncope (Gendelman et al., 1983; Kapoor et al., 1983; Davis and Freemon, 1990); however, it is efficacious if used in patients with symptoms and signs of a seizure disorder (Linzer et al., 1997a). Case series investigating the use of brain imaging with computed tomography (CT) scan and magnetic resonance imaging (MRI) have demonstrated utility only when there are focal neurological signs or a witnessed seizure. In an assessment of emergency presentations with transient loss of consciousness, the diagnostic yield of CT scans was only 4% (Day et al., 1982). Carotid Doppler is often used inappropriately to investigate syncope, as posterior cerebral circulation transient ischemic attacks can rarely cause drop attacks (loss of postural tone), typically different from syncope in most patients. Anterior circulation assessment at best infers potential for posterior circulation disease. It is currently unclear if transcranial Doppler imaging can diagnose significant posterior cerebral circulation abnormalities that may lead to drop attacks (Linzer et al., 1997a).

14.3.1.6. Laboratory blood investigations

Blood testing should only be performed if indicated by the history and examination. Routine use of such tests as measurement of electrolytes, full blood count, glucose level, thyroid function testing and serum markers of myocardial infarction is not recommended in the investigation of undifferentiated syncope (Kapoor, 2000; Link et al., 2001).

14.3.2. Tier 2: provocative tests

14.3.2.1. Head-up tilt test

The head-up tilt test seeks to recreate the physiological conditions believed to be associated with neurocardiogenic syncope. It uses a motorized tilt-table with a foot rest to which the patient is gently strapped. The tilt-table provides an orthostatic stress to the patient, typically to 60–80° with subsequent venous pooling and the accompanying hemodynamic changes to simulate an episode of syncope in susceptible individuals (Kenny et al., 1986). Tilt angles less than 60° appear to provide insufficient orthostatic stress to diagnose neurocardiogenic syncope (Fitzpatrick et al., 1991). Testing is performed with continuous hemodynamic and electrocardiographic monitoring, including during intravenous insertion, a common trigger of vasovagal attacks. The optimal duration of orthostatic provocation appears to be 30–45 minutes (Fitzpatrick et al., 1991; Benditt et al., 1996) and involves a predominant period of drug-free orthostatic stress and a second, shorter stage in which there is administration of a pharmacological provocative agent. These agents are designed to enhance the physiological orthostatic stress and increase test sensitivity. The two most common agents are isoproterenol and nitroglycerin. Isoproterenol is a beta-2 agonist that is positively chronotropic and inotropic but is also a peripheral

vasodilator enhancing peripheral venous pooling. Nitroglycerin is a vasodilator that principally dilates venous capacitance vessels and thereby increases orthostatic stress during upright tilt. Unlike isoproterenol which is given intravenously, nitroglycerin can be administered intravenously (Raviele et al., 1994) or sublingually (Aerts et al., 1997). The dosage of isoproterenol generally ranges from 1–3 μg/min with decreased specificity at higher doses (Natale et al., 1995). The dosage is often titrated to hemodynamic response. The dosage may be instituted with the patient supine after a negative head-up tilt and the patient re-tilted head-up for 5–15 minutes (Almquist et al., 1989). In contrast, nitroglycerin is used at the end of a prolonged tilt with the patient still upright (Raviele et al., 1995), with a sublingual dose of 300–400 μg tablets. The intravenous form is started while supine for 5 minutes and then runs for 10 minutes at 80° at increments of 0.86 μg/kg/h per stage (Raviele et al., 1994). Other less commonly used pharmacological agents include edrophonium (Lurie et al., 1993), clomipramine (Theodorakis et al., 2003), and adenosine (Shen et al., 1996).

The addition of a provocative agent to tilt-table testing increases sensitivity and accordingly diagnostic yield but decreases specificity (Sutton and Bloomfield, 1999). The diagnostic yield of a drug-free tilt test is approximately 50%, and the rate of positive tilt testing in normal subjects ranges from 5–15% (Natale et al., 1995; Petersen et al., 2000). The false-positive rate increases with pharmacological provocation from 5–15% up to 50% (Natale et al., 1995; Raviele et al., 1995). Nitroglycerin may be useful in guiding therapies in neurocardiogenic syncope (Kurbaan et al., 1999). Accordingly, the optimal tilt-table test should include a 30–45 minute drug-free period to optimize diagnostic yield and specificity, followed by provocative challenge. A positive response to head-up tilt can be divided into four types, summarized in Table 14.5, based on specific patterns of heart rate and blood pressure changes during syncope (Sutton et al., 1992). These classifications are designed to aid interpretation of the result. In practice it can be difficult to classify patients as responses may be categorically intermediate.

In addition to its utility in neurocardiogenic syncope, tilt-table testing is a useful investigation in the diagnosis of orthostatic hypotension, postural orthostatic tachycardia syndrome (POTS), psychogenic syncope, hyperventilation syndrome, carotid sinus syncope, and in the differential diagnosis of convulsive syncope. Recent guidelines on the diagnosis of orthostatic hypotension include a fall in systolic blood pressure of >20 mmHg or diastolic blood pressure of >10 mmHg within 3 minutes of the patient being tilted to 60° head-up tilt position (Consensus Committee of the American Autonomic Society and the American Academy of Neurology, 1996). Similarly, POTS can be diagnosed during head-up tilt by demonstrating a rise in heart rate of >30 beats/min (or maximum heart rate of 120 beats/min) in the absence of hypotension but in association with symptoms characteristic of an episode such as presyncope, dizziness, and fatigue (Grubb et al., 1997). Psychogenic syncopal patients generally exhibit certain atypical features during head-up tilt such as sudden dramatic syncope and prolonged recovery with normal hemodynamics, which enables differentiation from neurocardiogenic syncope (Petersen et al., 1995). Hyperventilation syncope can similarly be diagnosed during head-up tilt by associated use of a capnogram (Naschitz et al., 1997). As previously discussed, prolonged cerebral hypoxia secondary to hypotension can mimic epilepsy, which can be demonstrated during head-up tilt. Finally head-up tilt may provide a positive diagnosis for carotid sinus hypersensitivity when carotid sinus massage is performed during a head-up tilt despite a nondiagnostic supine carotid sinus massage.

Table 14.5

Vasovagal syncope responses induced by head-up tilt testing

Response type	Heart rate during syncope	Blood pressure response
Type I: Mixed response	≥40 beats/min or falls to <40 beats/min for <10 s ± asystole for <3 s	Blood pressure drop before heart rate drop
Type IIA: Cardioinhibitory response	<40 beats/min for >10 s or asystole for >3 s	Blood pressure drop before heart rate drop
Type IIB: Cardioinhibitory response	<40 beats/min for >10 s or asystole for >3 s	Blood pressure drops to <80 mmHg systolic at or after rapid drop in heart rate
Type III: Pure vasodilator response	Heart rate does not change or drops <10% from its peak	Blood pressure drops and precipitates syncope

14.3.2.2. Electrophysiological testing

Electrophysiological testing in the diagnosis of syncope is generally reserved for use after noninvasive tests such as Holter monitoring or head-up tilt-table testing are negative or inconclusive in patients with structural heart disease and/or an abnormal electrocardiogram (Klein et al., 1995). This is because of the invasive nature of the investigation and a low diagnostic yield in patients with structurally normal hearts and a normal electrocardiogram (Linzer et al., 1997b). An electrophysiological study is performed in a cardiac procedure laboratory with X-ray and hemodynamic monitoring capabilities, and trained nursing and technical staff. Surface electrodes are sited in the normal chest and limb positions on the patient and intracardiac electrode catheters are placed under X-ray guidance through the femoral vein to the right atrium, right ventricle, and near the atrioventricular node (bundle of His) in the heart. Programmed stimulation is performed from the intracardiac electrodes in the right atrium and right ventricles and the effects are monitored to assess cardiac impulse formation and conduction. This allows the assessment of sinus and atrioventricular node function and the diagnosis of bradyarrhythmias and tachyarrhythmias. The diagnostic yield of electrophysiological studies in patients with structural heart disease is as high as 50% (Linzer et al., 1997b). In patients with syncope and an abnormal electrocardiogram, electrophysiological studies had a diagnostic yield of 34% in a review of 14 studies (Linzer et al., 1997b). Unfortunately electrophysiological studies have a relatively low sensitivity for diagnosing bradyarrhythmias (Fujimura et al., 1989), which are relatively common causes in both these patient cohorts, especially if conduction abnormalities are present on the surface electrocardiogram. Patients at an increased likelihood for a bradycardic cause for syncope may require further investigations such as an implantable loop recorder (Krahn et al., 1995), which will be discussed subsequently.

Electrophysiological studies are an important investigation in the diagnosis of ventricular tachycardia as the cause for syncope; other important diagnoses are supraventricular tachycardia and bradyarrhythmias. Accordingly an electrophysiological study is considered positive in syncope if it demonstrates sustained monomorphic ventricular tachycardia, prolonged corrected sinus node recovery time of >550 ms, prolonged HV conduction >75 ms, spontaneous or induced infra-Hisian block and supraventricular tachycardia with hypotension (Linzer et al., 1997b). It is important to note that polymorphic ventricular tachycardia or ventricular fibrillation in response to programmed ventricular stimulation is nonspecific and therefore noncontributory to the diagnosis of syncope. Signal averaged electrocardiograms have a relatively high sensitivity and specificity for predicting inducible monomorphic ventricular tachycardia by demonstrating low-amplitude late potentials on the surface electrocardiograph (Steinberg et al., 1994). However, the utility of signal averaged electrocardiography independent of electrophysiological studies has not been demonstrated in the diagnosis of syncope secondary to ventricular tachycardia.

Syncope occurring in a patient with underlying structural heart disease and severe left ventricular dysfunction is associated with a higher incidence of ventricular arrhythmia and a poor prognosis (Kapoor, 2000) and necessitates an aggressive investigational and management strategy. Consideration in these patients should be given to an implantable cardiodefibrillator (ICD) as recent studies in patients with left ventricular ejection fraction of less than 35% have clearly demonstrated a survival benefit in those receiving ICDs for primary prevention (Klein et al., 1999; Moss et al., 2002). The prognosis of patients with ventricular impairment remains poor even in association with a normal electrophysiological study (Link et al., 1999). Accordingly less electrophysiological studies are performed in these patients as ICDs are increasingly implanted prophylactically.

14.3.3. Tier 3: association of an event with cardiac rhythm monitoring

14.3.3.1. Electrocardiographic monitoring

Short-term electrocardiographic monitoring via three or in some cases 12 surface electrodes is the most common initial investigation in patients who present with syncope. Typically this occurs in the emergency room or primary care setting with telemetry and central monitoring. Strictly speaking it is a tier 1 investigation performed immediately after the syncopal event. The diagnostic yield however is generally low. One patient series reported a diagnostic yield of 6.9% (Kapoor, 1990). Bradycardia or atrioventricular block was observed in 40% of patients, tachycardia in 43%, and acute myocardial infarction in 17%. The observations on electrocardiographic monitoring must be correlated with clinical presentation, as findings may be unrelated if observed in the absence of symptoms. The likelihood of another syncopal episode occurring during the monitoring period is the major limiting factor. Presyncope is a more common event during ambulatory monitoring but is less likely to be associated with an arrhythmia (Kapoor, 1992; Krahn et al., 2001a). Additionally, the ubiquity of presyncope as a symptom in the community makes its utility as a surrogate for syncope relatively uncertain. A review

of studies utilizing 12 or more hours of ambulatory monitoring with Holter monitoring demonstrated a correlation of 4% between symptoms and arrhythmias (Linzer et al., 1997b). The overall diagnostic yield of ambulatory or Holter monitoring was 19%. In these studies of Holter monitoring, symptoms were not associated with arrhythmias in 15% of cases. The causal relationship between the arrhythmia and syncope was uncertain. Uncommon asymptomatic arrhythmias such as prolonged sinus pauses, atrioventricular block (such as Mobitz type II block), and nonsustained ventricular tachycardia can provide important contributions to the diagnosis, often instigating further investigations to rule out structural heart disease and other precipitating factors. While these observations necessitate prompt attention, it is important to interpret the results in the clinical context of the syncopal presentation so common causes of syncope such as neurocardiogenic syncope are not unduly excluded. It is also important to understand that normal ambulatory electrocardiographic monitoring does not exclude an arrhythmic cause for syncope. If the pretest probability is high for an arrhythmic cause, then further investigations such as electrophysiological studies or prolonged monitoring (see below) are required. One study has investigated extending the duration of ambulatory Holter monitoring to 72 hours. In this study an increase in the number of asymptomatic arrhythmias detected was observed but not the overall diagnostic yield (Bass et al., 1990).

Ambulatory electrocardiographic or Holter monitoring for 24–48 hours is useful in syncope where an arrhythmic etiology is historically suggested or in unexplained syncope in a patient at increased risk for arrhythmic syncope (i.e., underlying structural heart disease or abnormal baseline electrocardiogram).

14.3.3.2. External loop recorder

The external loop recorder is an event monitor that endeavors to correlate physiological symptoms to recorded cardiac rhythms. The loop recorder continuously records and stores an external modified limb lead electrocardiogram with a 4–18 minute buffer. The patient then activates the event button after symptoms occur and there is then storage of the preceding 3–16 minutes and proceeding 1–2 minutes of cardiac rhythm (Fig. 14.1). The device then is 'frozen' so the stored electrocardiograms can be downloaded and subsequently analyzed. This system can be worn for weeks or even months at a time. The recording device is similar in size to a pager and 2 chest leads are attached to the chest by electrodes (Fig. 14.2, left). These electrodes need to be removed during showering. The batteries must be changed weekly. The recorded event can then be downloaded and analyzed remotely by a dial-in method to a base station or simply when the device is returned. The rhythm strip obtained can occasionally be difficult to interpret, especially with respect to localizing P waves.

Other issues with this technology include compliance when there are long intervals between recurrences. This often manifests as electrode and skin-related problems impairing subsequent recording of cardiac rhythm. A study by Linzer et al. (1990) reported on the usage of external patient activated loop recorders in 57 patients with syncope and nondiagnostic history and ambulatory electrocardiographic monitoring. A diagnosis was achieved in 14 of 32 patients with recurrent symptoms. Reasons for nondiagnosis in the remaining 18 patients included device malfunction, patient noncompliance, and inability to activate the recorder. Other studies have also reported similar findings (Brown et al., 1987; Cumbee et al., 1990) and demonstrated that loop recorders are complementary to 24-hour ambulatory electrocardiographic monitoring. The diagnostic yield for external loop recorders in these three referral studies (Brown et al., 1987; Cumbee et al., 1990; Linzer et al., 1990) ranged from 24–47%, with highest yields in patients with palpitations. A more recent study (Sivakumaran et al., 2003), which prospectively randomized patients with syncope and presyncope to either 48-hour Holter monitoring or external loop recorders, demonstrated a significantly greater diagnostic yield with the external loop recorder (21% vs 55%). The device- or patient-related failure in the external loop recorder arm was relatively high at 24%, which limits their diagnostic efficacy in some patients (Gula et al., 2004).

An external loop recorder is indicated in syncopal patients in whom an arrhythmic cause for syncope is suspected. The patient needs to be motivated with frequent syncope likely to recur within 4–6 weeks, since the major limitations of external loop recorders are infrequency of episodes and patient compliance with external electrodes.

14.3.3.3. Implantable loop recorders

The implantable loop recorder (ILR) is a relatively recent investigational tool in undiagnosed syncope. It is ideally suited to patients with infrequent recurrent syncope thought to be secondary to an arrhythmic cause. Similar to the external loop recorder, it is designed to correlate physiology with recorded cardiac rhythms but unlike the external loop recorder it is implanted and therefore devoid of surface electrodes and accompanying compliance issues. The ILR also

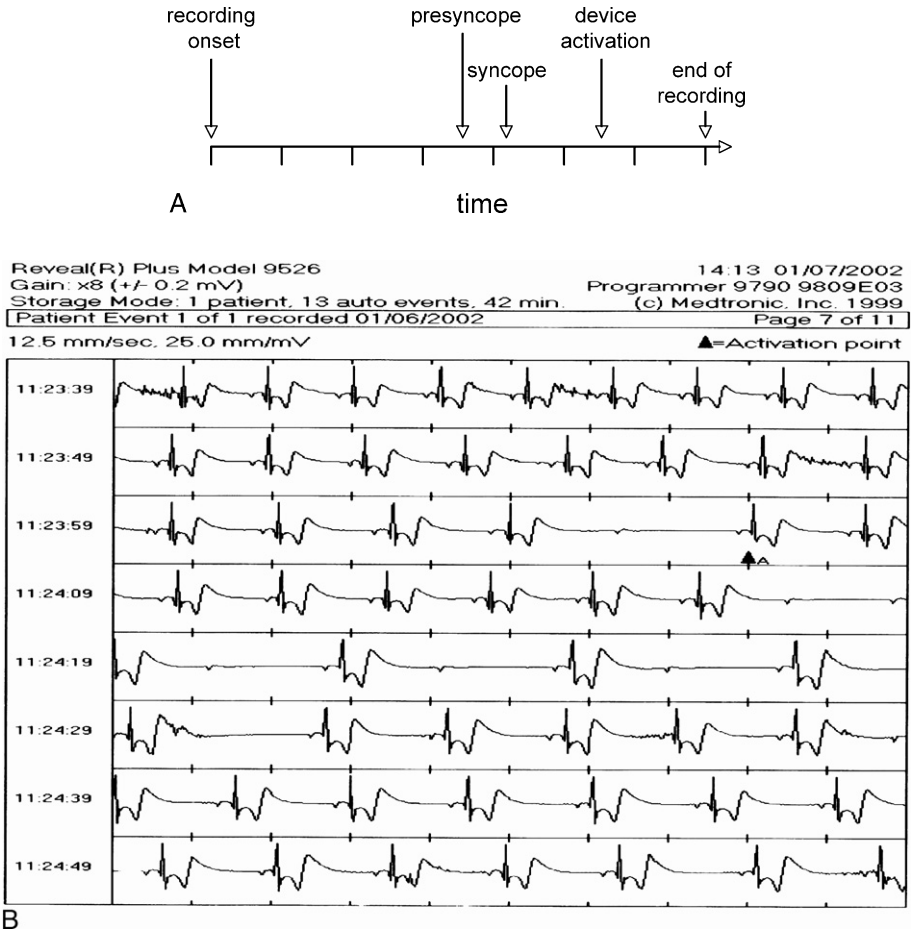

Fig. 14.1. Time line of a typical syncopal event recorded on a loop recorder. **A.** Schematic of the sequence of events. **B.** A single lead ECG rhythm strip is shown from an implantable loop recorder. Note sinus rhythm with normal AV conduction, followed by loss of conduction with small p waves without QRS complexes. After a 3 second pause, the device automatically stores a 2 minute rhythm strip, with activation marked by an A (arrow). Profound bradycardia leads to loss of consciousness. Note that the absence of sinus node acceleration after the blocked P waves raises the possibility that increased vagal tone is contributing, although the lack of PR interval prolongation leads to attributing the AV block to a primary bradycardia. The device was activated externally by the patient 3 minutes later (not shown). Syncope has resolved with implantation of a pacemaker.

monitors for much longer than an external loop recorder. Currently the ILR has a pair of sensing electrodes 3.7 cm apart on a small elongated recording device that is 6 cm long, 2 cm wide, and 0.8 cm thick, weighing 17 g (Fig. 14.2, center). The battery life is 18–24 months. The device can be implanted in the left chest under the subcutaneous tissues with local anesthetic and antibiotic prophylaxis.

Prior to implantation, cutaneous mapping should be performed to optimize the sensed signal to avoid T wave oversensing, which can falsely be recorded as a high rate episode. An adequate signal can be obtained anywhere in the left hemithorax (Krahn et al., 1997). The recorded bipolar electrocardiograph signal is stored in the device as 21 minutes of uncompressed or 42 minutes of compressed signal. Generally a compressed signal is used because its quality is marginally different from the uncompressed signal and this maximizes memory capability. Once an episode is recorded (i.e., a presyncopal or syncopal event occurs) the memory is 'frozen' by the patient or a relative applying a non-magnetic hand held applicator (Fig. 14.2, right). The episode is then downloaded after interrogation with a pacemaker programmer (Medtronic 9790). The ILR has programmable automatic detection of high and low heart rate episodes and pauses.

Currently there are several studies establishing the efficacy of ILR in the diagnosis of syncope (Krahn et al., 1998, 1999, 2001b, 2002). The largest of these studies is a multicenter study of 206 patients (Krahn et al., 2002). The majority of patients had undergone noninvasive and invasive testing including head-up tilt and electrophysiological studies. The etiology of syn-

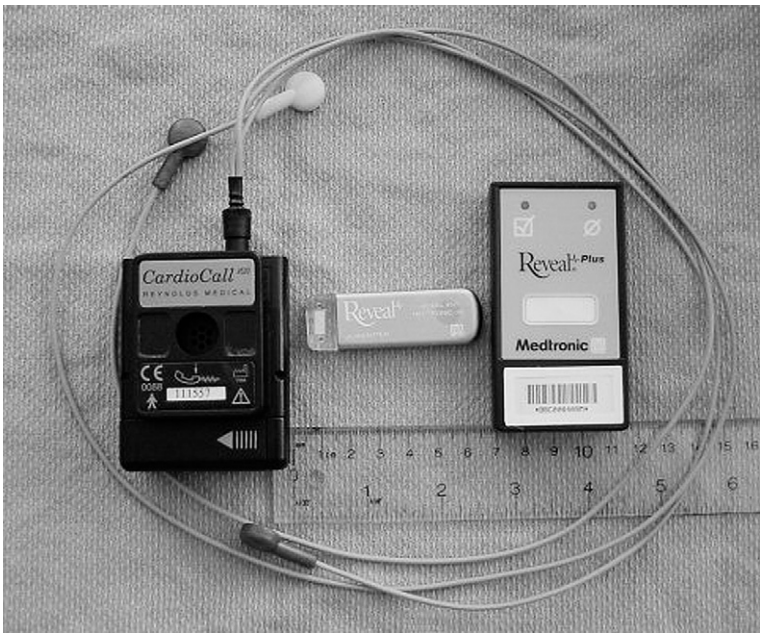

Fig. 14.2. Photograph of the external (left, with electrodes) and implantable (center) loop recorder with external activation device (right), which is applied over the implantable loop recorder post-event.

cope was arrhythmic in 22% of patients, sinus rhythm with exclusion of arrhythmia as a cause in 42% and 22% of patients had no further syncope or presyncope. Bradycardia was the most commonly detected arrhythmia (17% vs 6% tachycardia) usually leading to pacemaker implantation. From this study 4% of patients failed to properly activate the device and thus did not establish a symptom rhythm correlation.

Further recent studies have highlighted the potential utility of ILR in the diagnosis of syncope. In a group of patients with ongoing seizures despite anticonvulsant therapy, Zaidi et al. (1999, 2000) performed cardiac assessment including head-up tilt testing, carotid sinus massage in all patients, and implantation of ILR in 10 patients. Interestingly, two of the 10 patients with an ILR had marked bradycardia preceding a seizure; one due to sinus pauses, the other due to heart block. Importantly this study suggested that seizures that are atypical in presentation may have a cardiovascular cause in as many as 42% of cases and cardiovascular assessment, including long-term cardiac monitoring with an ILR, may play a role in select patients with atypical seizures.

In recent studies (Brignole et al., 2001b; Moya et al., 2001) from the International Study on Syncope of Uncertain Etiology (ISSUE) investigators, ILRs were implanted in three different groups of syncopal patients to assess cardiac rhythm during syncope after conventional testing. The first arm examined the cardiac rhythm in head-up tilt patients with unexplained syncope. This arm of the study suggested that head-up tilt testing is poorly predictive of rhythm findings during syncope and that bradycardia is a more common arrhythmia than previously recognized. In the second arm ILRs were implanted in patients with unexplained syncope in whom electrophysiological testing was negative and the baseline electrocardiogram demonstrated a bundle branch block. This study confirmed that negative electrophysiological testing does not exclude intermittent complete atrioventricular block during follow-up in this population. The third arm of this study examined implantation of an ILR in a cohort of patients with unexplained syncope, moderate structural heart disease and a negative electrophysiological testing. The ILR revealed a low incidence of ventricular arrhythmias in this cohort and no sudden cardiac death during 18 months of follow-up.

14.4. Diagnostic algorithm for syncope of unknown cause

An algorithm to approach a syndrome such as syncope will inherently oversimplify the approach to unusual presentations. Clinical acumen in applying an algorithm should rely on the principles of probability arising from the history and assessing the potential risk of sudden death from suspected ventricular arrhythmias. Blind application of diagnostic algorithms will lead

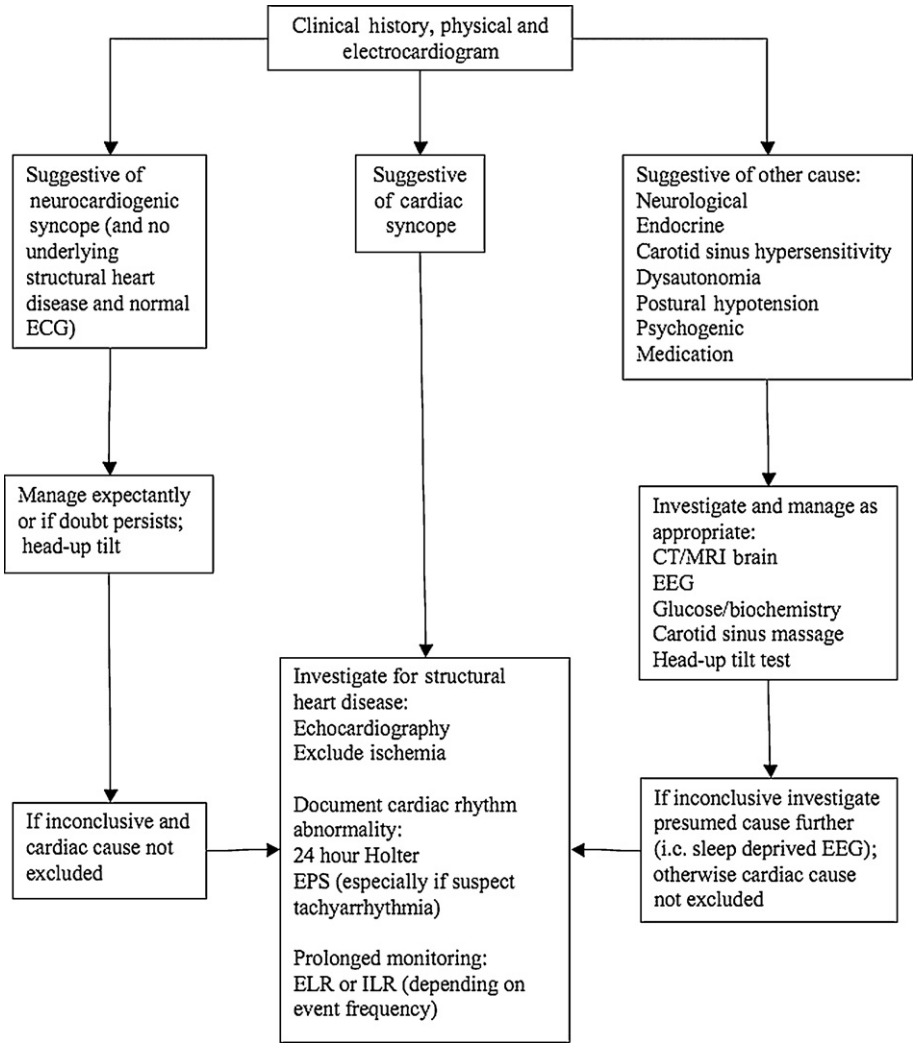

Fig. 14.3. Investigational and diagnostic algorithm for syncope. CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalogram; ELR, external loop recorder; EPS, electrophysiological study; ILR, implantable loop recorder; MRI, magnetic resonance imaging.

to mistakes. From the data presented in this chapter, a concise framework for an approach to investigating and diagnosing syncope (with particular emphasis on cardiac causes) is presented in Figure 14.3.

14.5. Management of syncope

In general, once a cause for syncope has been identified, therapy is readily identified and usually successful in preventing recurrence. A management plan is devised that incorporates lifestyle measures to avoid syncope and pharmacological or device management to treat and prevent syncope.

14.5.1. Neurally mediated syncope

Conservative management is particularly useful with neurally mediated syncope. Reassurance is important as this condition is benign and often anxiety-provoking in the patient and relatives. Education regarding sufficient intake of fluids to maintain blood volume is important, especially in warm weather. This should be a minimum of 2 liters, and often 3 liters in warm weather or during activity, with the addition of salt to food. Avoidance of precipitants whenever possible is important; patients should learn to recognize their prodrome and stop what they are doing and sit or lie

down. Support stockings may also be useful in those who have to stand. In addition, tilt training can be performed to improve venous return, which can be achieved with a tilt-table or leaning against a wall in a safe environment (Kinay et al., 2004). Aversion maneuvers involving isometric exercise are also helpful to increase venous return when presyncope occurs.

The literature on pharmacological therapy for neurally mediated syncope is characterized by multiple small to medium-sized trials with conflicting results that are often inadequately controlled. Beta-blockers are the most common initial pharmacological treatment as it is believed that they reduce mechanoreceptor activation and block the initiating effects of circulating catecholamines and thereby decrease syncope (Brignole et al., 2001a). Randomized trials have shown conflicting results regarding the efficacy of beta-blockers in neurocardiogenic syncope above that of placebo (Madrid et al., 2001; Flevari et al., 2002). Furthermore beta-blockers may even worsen syncope by their negative chronotropic effects and atrioventricular blocking effects (White and Tsikouris, 2000). Alpha-blockers, which increase peripheral resistance and decrease peripheral vascular capacitance to increase venous return, have also been studied (White and Tsikouris, 2000). Midodrine is an alpha-blocker that has been demonstrated to be effective in several small, randomized clinical trials (Ward et al., 1998; Perez-Lugones et al., 2001; Kaufmann et al., 2002). Selective serotonin reuptake inhibitors have also been used to treat syncope and have been shown to be efficacious in one randomized trial (Di Girolamo et al., 1999). The mineralocorticoid fludrocortisone promotes renal reabsorption of sodium to increase blood volume and blood pressure. An initial trial of its use in children (Scott et al., 1995) was encouraging; however, this was not reproduced in a more recent study (Salim and Di Sessa, 2005). Disopyramide is a class I antiarrhythmic agent with anticholinergic and negative inotropic effects that was found to be ineffective in treating neurocardiogenic syncope (Morillo et al., 1993). Finally anticholinergic agents such as scopolamine have been used successfully in some patients with neurocardiogenic syncope (White and Tsikouris, 2000). Despite encouraging small studies, pharmacotherapy for neurocardiogenic syncope has been inconsistent and disappointing in its results. It remains a largely empiric exercise in patients, influenced by the resting blood pressure and the presentation of the patient. In our experience, beta-blockers are used most frequently in the elderly or patients with hypertension on peripheral-acting antihypertensives. Fludrocortisone is used most often in the young patient with low resting blood pressure. Alpha-agonists are used as second line because they require three or four times a day dosing.

Permanent pacing has also been studied in the treatment of neurocardiogenic syncope that is associated with asystole or relative bradycardia (predominant cardioinhibitory response). However, the pathophysiology of neurocardiogenic syncope is characterized by varying degrees of peripheral vasodilatation (vasodepressor response) and therefore pacing alone is generally ineffective. The current studies indicate there is some evidence that dual-chamber pacing may be effective if there is a pronounced cardioinhibitory component demonstrated during head-up tilt or prolonged monitoring (Di Girolamo et al., 1999). Permanent pacing is generally reserved for patients who fail more conservative measures. In addition, patients with a cardioinhibitory response to carotid sinus massage and a history consistent with carotid sinus hypersensitivity also appear to benefit from permanent pacing (Kenny et al., 2001). Their response to pacing is generally better than that of neurocardiogenic syncope patients.

14.5.2. Arrhythmic syncope

Once an arrhythmia is diagnosed, therapy is usually successful. Bradyarrhythmias are effectively treated with permanent pacing with symptom resolution. This is distinct from the bradyarrhythmia associated with neurocardiogenic syncope and prominent vasodepressor response, as previously discussed. Antiarrhythmic drug therapy, catheter ablation, and ICDs are effective treatments for syncope in association with tachyarrhythmias. Trial data have demonstrated the benefits of ICD implantation in patients with structural heart disease, syncope, and inducible ventricular arrhythmias at electrophysiological testing (Link et al., 1997). Furthermore, recent large-scale randomized trial data have shown that the prophylactic implantation of an ICD in patients after myocardial infarction with an ejection fraction less than 30% carries a lower mortality; however, a decrease in arrhythmic syncope has not been demonstrated (Moss et al., 2002).

14.6. Conclusion

Syncope is a common and troublesome presenting symptom in the community. The etiology is complex, varied and, for common cardiovascular causes such as neurocardiogenic syncope, incompletely understood. The diagnosis and management can therefore be difficult, particularly if not evident after an initial assessment. A careful history and physical examination followed by directed testing yields to a diagnosis in the majority of patients. Results of testing require

clinical judgment since most tests suffer from sensitivity and specificity that are modest at best. Recent advances in the area of long-term rhythm monitoring have enabled better understanding of cardiac syncope and its response to treatment.

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Chapter 15

Altered consciousness associated with brain neoplasms

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15.1. Epidemiology

Coma is the ultimate disorder of consciousness, and any process causing a change in mental status can culminate in coma. After back pain in adults and headache in children, altered mental status is the second most common neurological symptom in patients with systemic cancer and intracranial neoplasm (Clouston et al., 1992; Antunes, 2002). Altered mental status, including seizures, afflicts 17.1% of the adult cancer population and 15.3% of children with cancer (DiMario and Packer, 1990; Newton, 1999; Antunes, 2002).

In a study exploring the causes of altered mental status in a cancer population, two-thirds of the patients developed confusion during hospitalization and the remaining third were admitted to hospital for confusion. Serial neurological examination of these patients revealed that encephalopathy reached its maximum degree upon initial neurological evaluation in 91% of patients and ultimately improved in 67% (Tuma and DeAngelis, 2000).

Patients with cancer are predisposed to alterations in mental status due to several medical and surgical factors. We will discuss the unique etiological factors of altered mental status for the cancer patient population although other typical culprits may also play a role.

15.2. Etiology

Neurological symptoms arise from disruption of neural function due to mass effect exerted by the tumor and peritumoral edema, obstructive hydrocephalus, ischemia, and toxic inhibition of local neuronal activity secondary to metabolic abnormalities (Weissman, 1988) (Table 15.1). Alterations in consciousness include both the level of consciousness and/or its quality during the clinical course of brain tumors, which is related to secondary effects of increased intracranial pressure (ICP); pressure gradients, compartmental shifts, brain herniation, and vascular changes; or the primary effect of compressive or destructive tumors involving eloquent cortex. Changes in higher cognitive functions can be due to focal and site-specific manifestations of a tumor's compressive or destructive effects. Depressed consciousness usually represents the presence of ICP due to secondary brainstem compression or direct involvement of the reticular activating system by the tumor itself, such as coma from thalamic or brainstem gliomas (Thapar et al., 1995).

15.3. Mass effect

Intracranial neoplasms are usually sufficiently slow-growing to allow some adaptation of the brain to the changes associated with increased ICP. In the absence of trauma, approximately 34% of patients with coma have mass lesion among admissions to the medical intensive care unit (Bates, 1993). The presenting symptoms of brain tumors are related to the sudden or indolent decompensation of the brain's adaptive mechanisms. Indolent decompensation may result from a slowly expanding mass. Sudden deterioration may be due to intracerebral hemorrhage associated with tumor, tumor necrosis with swelling, rapid tumor growth, or hydrocephalus, all of which may lead to brain herniation (Ropper, 1986, 1989; Posner, 1995). After the patient is stabilized and administered corticosteroids and/or mannitol, the presence of a structural lesion that may need immediate surgical intervention should be investigated.

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Table 15.1

Etiology of altered consciousness associated with brain neoplasms

Mass effect
Edema
Hemorrhage
Hydrocephalus
Involvement of eloquent areas
Stroke
Infections
Leptomeningeal tumor spread
Seizure
Coma following neurosurgery
Paraneoplastic involvement of central nervous system
Treatment-related
Chemo/radiotherapy
Miscellaneous
Drugs
Multiple organ failure
Hypoxia
Electrolyte disorder
Environmental

15.3.1. Intracranial hemorrhage

In pathological and radiological studies, the frequency of intracranial hemorrhage (ICH) with intracranial neoplasms ranges from 1.4% to 15% (Wakai et al., 1982; Kondziolka et al., 1987; Thapar et al., 1995; Schrader et al., 2000). From another perspective, the frequency of finding underlying intracranial neoplasms in ICH ranges from 0.8% to 7.4% (Albert, 1986; Husain et al., 1987; Misra et al., 1988; Jones and Blumbergs, 1989; Asari et al., 1992; Salcman, 1992; Cheng and Lin, 1997; Ahola et al., 1998; Erten et al., 1998; Taylor et al., 1998; Schrader et al., 2000). Three-quarters of tumor-related ICH are supratentorial, and 20% of hemorrhages associated with neoplasm rupture into the ventricular system (Schrader et al., 2000).

ICH can be intratumoral, intraparenchymal, subarachnoid, or subdural. Primary brain tumors are mostly associated with intratumoral hemorrhage (67%) followed by intraparenchymal (15%), subarachnoid (15%), and subdural (2%) (Wakai et al., 1982). Subarachnoid and subdural hemorrhages are more common with meningiomas (Kohli and Crouch, 1984).

In a review of tumor-associated ICH, the leading causes were metastases of extracerebral origin (36%) followed by glioblastoma multiforme (30%) and benign primary intracranial neoplasms, excluding meningiomas (18%). Malignant melanoma was the most common cause of hemorrhage among various metastatic tumors (Fig. 15.1) (Maiuri et al., 1985; Schrader et al., 2000). Metastases of choriocarcinoma are unique in that they directly erode cerebral vessels to produce hemorrhage (van den Doel et al., 1985; Salcman, 1992; Kidd et al., 1998).

Naturally, the suspicion of tumor-related ICH is greater in patients with known neoplastic disease; however, ICH as the earliest manifestation of an intracranial neoplasm has been reported to be between 9% and 58% (Jellinger, 1980; Wakai et al., 1982; Schrader et al., 2000; Licata and Turazzi, 2003). An irregular shape and an atypical location can hint at an intratumoral and/or intraparenchymal hemorrhage. A heterogeneous appearance with solid areas of blood, multiple hemorrhages, and a ring-shaped hemorrhage can also point towards that diagnosis. Peritumoral edema is an important feature in the differential diagnosis because it is only rarely seen in the acute phase of spontaneous intracerebral hemorrhage while it is a very common feature in expanding, space-occupying lesions such as tumors. High and low densities in the center surrounded by punctuate hemorrhages in its periphery and enhancement after administration of contrast agent are typical of ICH associated with neoplasm (Schrader et al., 2000).

There should also be high suspicion of a tumor-related ICH in the following cases: if hemorrhages are found in an atypical location, e.g., subcortical or close to dural membranes such as the falx or the tentorium; if they are located close to major cerebral veins or sinuses; if they are calcified, with multiple hemorrhages; in young people without any apparent cause for ICH such as hypertension or vascular malformation; if there is contrast enhancement within the hematoma or in its periphery; and if there is disproportionately large edema after acute stroke (Schrader et al., 2000; Tung et al., 2003).

Magnetic resonance imaging (MRI) is clearly superior to computed tomography (CT) scanning for the work-up of patients with acute ICH. Hemorrhagic neoplasms undergo changes in their appearance that can be categorized into three distinct intensity patterns or stages. Stage 1 is characterized as iso- or hypointensity on short TR sequences and as hypointensity on long TR sequences; stage 2 as developing hyperintensity on both short and long TR sequences, without evidence of a well-defined black rim; and stage 3 as a hyperintense lesion with a well-defined black rim on long TR sequences (Destian et al., 1989). However, CT is more practical in comatose patients, as an immediate diagnosis is necessary (Kazner et al., 1980; Schrader et al., 2000; Licata and Turazzi, 2003). Fast-growing and highly vascularized neoplasms with an irregular and fragile vascular architecture are most frequently associated with ICH (Liwnicz et al., 1987; Cheng et al., 1997).

In general, volume of the hematoma, neurological status (Glasgow Coma Score) on admission, intra-

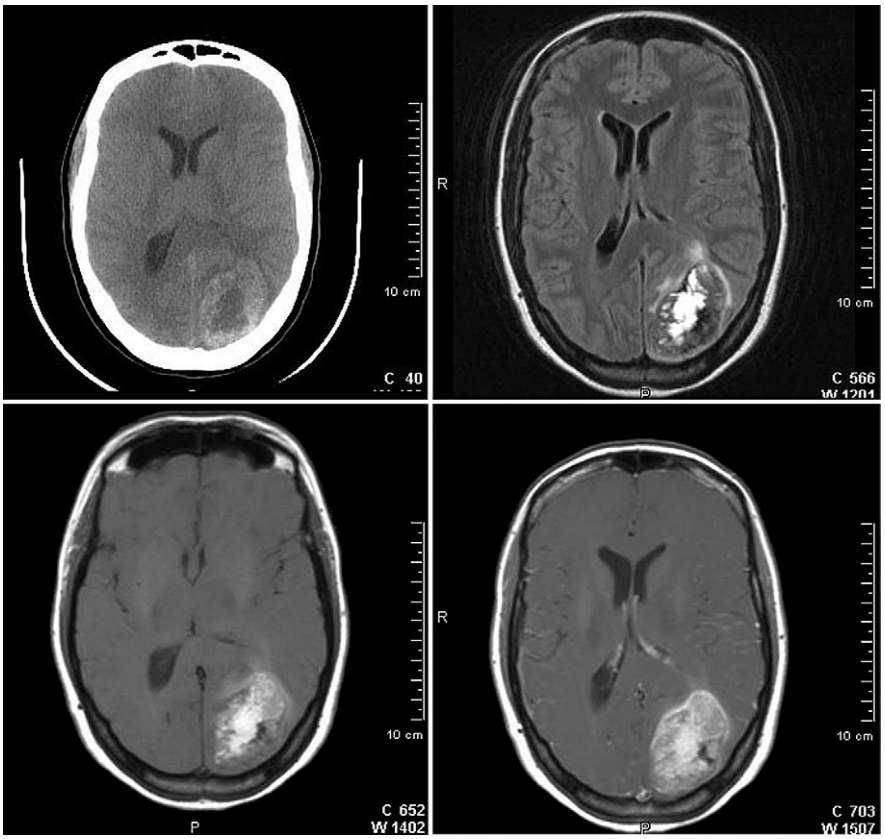

Fig. 15.1. CT and MRI (FLAIR, unenhanced and enhanced T_1-weighted images) reveal a left parietal melanoma metastasis with hemorrhage.

ventricular extension of the clot and/or hydrocephalus, subarachnoid extension, association with anticoagulation and relative edema are associated with poor outcome in spontaneous ICH. The methods for managing ICH are broadly divided into two categories: medical and surgical interventions (Pouratian et al., 2003). In one series, 36% of patients with ICH associated with tumor were somnolent and 28% comatose. Of the patients, 8% were not operated on because of poor clinical condition and died; an additional 12% died despite surgery (Schrader et al., 2000). Decompressive surgery has been recommended and authorities stress the importance of complete tumor resection where safe resection is possible since recurrent ICH occurs in all types of tumors (Iwama et al., 1992). Additionally, resection of hematoma may decrease hemorrhage-related edema formation (Hoff and Xi, 2003).

Recombinant activated factor VIIa is a hemostatic agent for the treatment of bleeding episodes in patients with hemophilia A or B, life-threatening hemorrhage associated with massive trauma, anticoagulant-related bleeding, liver failure, and other medical situations in which life-threatening hemorrhage is not responsive to conventional therapeutic interventions. Patients with traumatic brain injury respond to recombinant activated factor VIIa administration with an improvement in their coagulation profile and a decrease in bleeding (Dutton et al., 2004). Early administration of recombinant activated factor VIIa in patients with intracranial hemorrhage has demonstrated better results (Stein and Dutton, 2004). Although there is no case series for use of recombinant activated factor VII in ICH associated with tumor, a recent report demonstrated control of tumor-related hemorrhage during surgery with recombinant activated factor VII in a pediatric population (Heisel et al., 2004).

15.3.2. Pituitary apoplexy

Pituitary tumor apoplexy refers to the abrupt onset of a severe headache frequently coupled with nausea, vertigo, visual disturbance, meningismus and/or a decreased level of consciousness. Endocrine abnormalities associated with hypopituitarism, pressure transmitted to the brainstem or hypothalamic compression may account for a diminished level of consciousness (Verrees et al., 2004). Cortical irritation from extension of hemorrhage into the brain parenchyma may elicit seizures (Piotin et al., 1999).

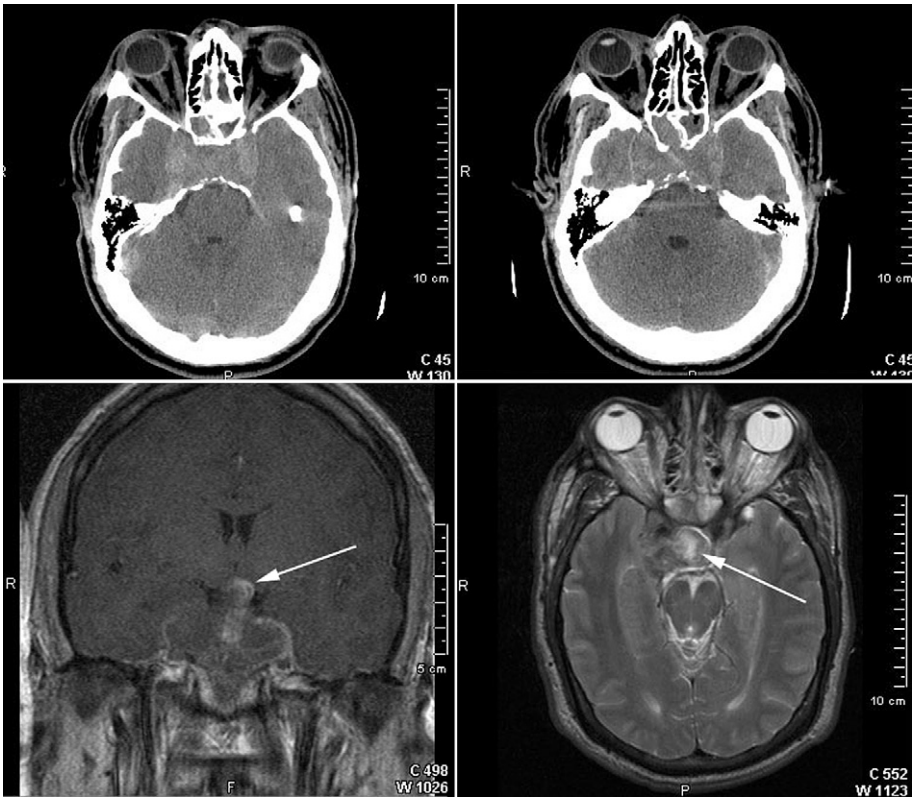

Fig. 15.2. Axial CT and coronal T_1-weighted and axial T_2-weighted images show a pituitary macroadenoma with apoplexy (arrows).

CT or MRI demonstrates sellar and/or suprasellar abnormalities that are consistent with hemorrhage and necrosis (Fig. 15.2). Pituitary adenomas comprise approximately 10% of intracranial tumors (Shimon and Melmed, 1998); the reported incidence of apoplexy in these lesions ranges from 0.6% to 27.7%; adenomas are 5.4 times more likely to bleed than other intracranial tumors (Mohanty et al., 1977; Wakai et al., 1981; Mohr and Hardy, 1982). Some 38 patients (6.8%) had a major attack manifested by disturbances of consciousness, hemiparesis, loss of vision, or ocular palsy (Wakai et al., 1981). Altered consciousness is present in 10–20% of patients and usually presents with other symptoms. Displacement of diencephalic structures from tumor expansion may result in varying degrees of impaired consciousness. Occlusion of the internal carotid artery is rare but may account for symptoms (Rosenbaum et al., 1977). If typical localizing signs and symptoms are absent, the condition may be misinterpreted as postoperative confusion or any of the toxic–metabolic encephalopathies (Cardoso and Peterson, 1984; Bills et al., 1993; Wiesmann et al., 1999; Tang-Wai and Wijdicks, 2002).

Treatment requires immediate therapy with corticosteroids and urgent surgical decompression. The definitive treatment for pituitary tumor apoplexy is surgery for decompression of compressed cavernous and/or suprasellar structures, especially in cases in which visual acuity or field defects, decreased level of consciousness, or progressive deterioration of visual or oculomotor abilities are present (Epstein et al., 1971; Rovit and Fein, 1972; Laws and Ebersold, 1982; Ebersold et al., 1983; Cardoso and Peterson, 1984; Onesti et al., 1990; da Motta et al., 1999; Lange et al., 1999). The clinical improvement of stupor seen after the treatment with corticosteroids or surgical decompression may be due to either a decrease in pituitary edema reducing pressure on the diencephalon or treatment of pituitary failure leading to hypoadrenalism (Cardoso and Peterson, 1984; Bills et al., 1993; Bonicki et al., 1993).

15.3.3. Brain edema

Brain edema is one of the most important factors contributing to morbidity and mortality associated with brain tumors (Thapar et al., 1995). As the brain tumor grows, peritumoral edema develops, causing further compromise to the closed system. Several distinct pathophysiological forms of brain edema have been

identified. The most widely used classification separates edema into three categories: vasogenic, cellular, and hydrocephalic/interstitial (Klatzo, 1967; Fishman, 1975).

Vasogenic edema, the type mostly associated with tumors, is due to increased capillary permeability. Cellular edema can also be seen with tumors secondary to disturbed metabolic conditions. Interstitial edema related to transependymal cerebrospinal fluid (CSF) deposition is generally associated with hydrocephalus, which may be related to an intracranial mass.

Intracranial tumors showing contrast enhancement are associated with local breakdown of blood–brain barrier. Alterations in capillary endothelium is the main mechanism for the breakdown of the blood–brain barrier and changes include lack of tight junctions (occludin, claudin, ZO-1 and 2), wide gap junctions, increased number of endothelial vesicles, endothelial proliferation, surface infolding of endothelial cells, and irregular basal lamina (Long, 1970, 1973; Grieg, 1989; Papadopoulos et al., 2001). Metastatic tumors retain the morphological features of capillaries in the tissue of origin (Long, 1979).

Concentration of free fatty acids is increased in peritumoral edema as a result of membrane breakdown (Baethmann et al., 1980). Oxidative metabolism of arachidonic acid, which is a major membrane fatty acid, produces prostaglandins and leukotrienes via the cyclooxygenase and lipoxygenase systems, respectively. Inflammatory infiltrate may produce prostaglandin E_2 through a cyclooxygenase-2 (COX-2) pathway, which has a role in tumorigenesis and peritumoral brain edema (Shinonaga et al., 1988; Shibata, 1989; Machein and Plate, 2000; Badie et al., 2003; Nathoo et al., 2004; Schneider et al., 2004). Leukotrienes, especially leukotriene C_4, are found to be high in brain tumors and level of expression correlates with the grade of tumor (Black et al., 1986). Several studies have confirmed the importance for vascular endothelial growth factor in tumorigenesis, neovascularization, and edema production (Connolly, 1991; Goldman et al., 1993; Strugar et al., 1995).

Although all aforementioned mechanisms may represent potential targets for antiedema therapies, corticosteroids have remained the standard treatment since they were first used for treating peritumoral edema in 1957 (Kofman et al., 1957; Galicich et al., 1961; Hedley-Whyte and Hsu, 1986; Fishman, 1992; Heiss et al., 1996). Their mechanism of action is not well understood but they may produce their antiedema effect by reducing the permeability of tumor capillaries. The indications for steroids, magnitude of benefit, dosage schedule, and duration of treatment are still controversial and generally empirical. There are only a few small prospective data on brain metastases regarding the dose and duration of their use (Horton et al., 1971; Vecht et al., 1994; Wolfson et al., 1994). Neurological response to dexamethasone is related to the reversal of ultramicroscopic features of cerebral edema, axonal distortion, and myelin disruption (French, 1966). Corticosteroids are usually indicated in any brain tumor patient with symptomatic peritumoral edema (Koehler, 1995). Steroids also provide a safer form of operative treatment. From a mechanistic point of view, the best neurological response to corticosteroids is expected in patients with vasogenic edema rather than other forms of cerebral edema (Posner, 1995). The benefit of steroids on brain edema was greatest in brain metastases, then glioblastomas, and least in other tumors (French, 1966). Patients with symptoms of raised ICP respond better than those with focal deficits from direct tumoral pressure and those with recent onset or progressive focal deficits benefit more than those with longer disease duration (Sarin and Murthy, 2003).

Dexamethasone is usually used because it has relatively little mineralocorticoid activity and possibly a lower risk of infection and cognitive impairment than other corticosteroids. The usual starting dose is a 10 mg load, followed by 16 mg a day in two to four doses, although there is evidence that lower doses may be as effective (Vecht et al., 1994; Vecht and Verbiest, 1995). In view of the definite increase in toxicity with daily doses more than 24 mg and inconclusive dose-response data, daily doses beyond 24 mg are not recommended outside clinical trial settings (Sarin and Murthy, 2003).

Despite their usefulness, corticosteroids are associated with a large number of side effects (Koehler, 1995). The frequency of these complications can be reduced by using the lowest possible doses (Vecht and Verbiest, 1995). Three complications of corticosteroid therapy are of particular concern to brain tumor patients: gastrointestinal complications, steroid myopathy, and *Pneumocystis carinii* pneumonitis (Wen and Marks, 2002). Because of the high complication rate of corticosteroids, corticotropin-releasing factor and COX-2 inhibitors have been tried as a better solution for treatment of brain edema; however, dexamethasone remains the most effective medicine in current practice (Villalona-Calero et al., 1998; Hariharan et al., 2000; Portnow et al., 2002; Khan et al., 2004).

Virtually all patients with features of raised ICP receive medical decompressive therapy, which consists of corticosteroids with or without mannitol (Sarin and Murthy, 2003). Mannitol is generally reserved for severe neurological manifestations or when a rapid

reduction in the raised ICP is desirable, such as in impending cerebral herniation. The conventional dose is 0.75–1.00 g/kg (intravenous infusion of a 20–25% solution) followed by 0.25–0.50 g/kg every 3–5 h (Frank, 1993). Although no clinical trials have directly studied different dosage schedules and durations of treatment with mannitol in brain tumors, data from head injury trials show better outcome with higher doses in subdural hematoma (Cruz et al., 2001). Animal experiments suggest that a rapid rate of infusion reduces ICP more effectively than a slow infusion (Roberts et al., 1987). Serum electrolytes should be monitored with mannitol use and corrected when required. Some recent small studies suggest an antiedema effect and symptomatic relief with boswellic acids in patients with brain tumors and radiochemotherapy-induced leukoencephalopathy (Janssen et al., 2000; Streffer et al., 2001).

In case of impending brain herniation, prompt decompressive surgery is usually necessary to revive such patients.

15.3.4. Hydrocephalus

CSF pathway obstruction may be due to intraventricular localization of tumor or secondary compression or distortion of extraventricular or cisternal CSF pathways from expanding intraparenchymal lesions (Thapar et al., 1995).

Obstructive hydrocephalus occurs in approximately 80% of posterior fossa tumors. Although tumor removal may relieve the obstruction and obviate the need for postoperative treatment, external ventricular drainage and/or endoscopic third ventriculostomy and/or ventriculoperitoneal shunt may be required for persistent or progressive hydrocephalus in about 25–30% of cases. The perioperative management of the associated hydrocephalus remains controversial (Schijman et al., 2004).

Hydrocephalus associated with supratentorial intraventricular tumors is managed primarily with temporary external CSF drainage followed by tumor surgery and postoperative assessment of ventricular size and tolerance of drainage withdrawal. Shunt insertion may be necessary only if compartmentalization or drainage dependency is manifest (Cedzich et al., 1992).

15.4. Eloquent location

Tumors centered in, infiltrating, or producing pressure upon centers of alertness may cause decreased level of consciousness. These include thalamic gliomas, brainstem gliomas, hypothalamic gliomas, and bilateral cortical lesions (Chalela and Kasner, 2003).

15.5. Cerebrovascular complications

In an autopsy study, 14.6% of systemic cancer patients had cerebral infarctions or hemorrhages (Graus et al., 1985). Although less common than hemorrhagic complications, stroke/transient ischemic attack syndromes may be the initial manifestation of 3% of brain tumors (Kondziolka et al., 1987). Reversible neurological deficits were described as ‘transient tumor attacks’ (Ross, 1983). Meningiomas (especially skull base), pituitary adenomas, and gliomas may cause ischemia (Ross, 1983; Salcman, 1990). The pathophysiology may be obstruction of vessels by encasement of tumor, arterial steal, radiation-induced vasculopathy, chemotherapy-related vascular injury or hypercoagulation, disseminated intravascular coagulation, or nonthrombotic endocarditis in systemic cancer (Thapar et al., 1995; Shaffrey et al., 1999; Rogers, 2003; Yeh and Lin, 2004). Although very uncommon, embolic occlusion of vessels by clumps of tumor with resultant hemorrhagic infarction has been observed in cardiac myxomas and other metastatic tumors (Thapar et al., 1995).

Cerebral intravascular coagulation is a syndrome that is progressive, culminating in coma. The pathophysiology is widespread fibrin occlusion of small vessels in the brain, by definition unassociated with nonbacterial thrombotic endocarditis. Widespread vessel occlusion results in diffuse infarctions and encephalopathy. There is no specific treatment other than supportive management (Rogers, 2003).

Venous thrombosis is another complication of brain tumors due either to coagulopathy (most commonly associated with hematological malignancies) or direct infiltrative or compressive effects of tumor (particularly seen with neuroblastoma, lung cancer, and lymphoma). The superior sagittal sinus is commonly affected; symptoms are related to severity of occlusion, rate of recanalization, and associated hemorrhagic infarcts. When suspected, it may be confirmed with MRI or angiography (Shaffrey et al., 1999). Treatment should be tailored to the individual case. Treatment of cerebral sinus thrombosis with anticoagulants has been controversial. Anticoagulants may prevent new venous infarcts, neurological deterioration, and pulmonary embolism but may also promote hemorrhages. On evidence-based review, anticoagulant treatment for cerebral sinus thrombosis appears to be safe and is associated with a potentially important reduction in the risk of death or dependency (de Bruijn and Stam, 1999; Stam et al., 2002; Masuhr et al., 2004).

Brain tumors metastatic to leptomeninges can produce cerebral infarctions due to tumor growth into Virchow–Robin spaces resulting in vessel thrombosis or spasms (Klein et al., 1989; Herman et al., 1995).

15.6. Infections

Central nervous system (CNS) infections are still a major cause of morbidity and mortality among patients with cancer (Pruitt, 2003). Approximately 17% of CNS infections have an underlying malignancy (Pruitt, 1997). Infections seen in brain tumor patients differ from other common infections in that causative bacterial organisms have low pathogenicity and are usually multiple in meningitis. Common signs and symptoms of meningismus may be missing. Unless quickly recognized and treated, the course is rapid and prognosis is poor (Pruitt, 2003; Schiff and Wen, 2003). Hematological malignancies account for 25% of CNS infections in patients with cancer, and another 16% arise in the setting of primary CNS tumors (Pruitt, 1997). Neutropenia and systemic sepsis are the predisposing conditions for patients with systemic cancer, while skin-derived organisms such as *Staphylococcus aureus* or *Staphylococcus epidermidis* account for infections in patients with primary CNS tumors. Use of corticosteroids renders patients immunocompromised and makes them more prone to infections. Bone marrow transplantation and implantation of Gliadel® chemotherapy wafers are recently becoming more of an etiological factor in CNS infections and formation of space-occupying abscesses (Fig. 15.3) (Graus et al., 1996; Subach et al., 1999; McGovern et al., 2003). Focal deficits associated with contrast-enhancing lesions may represent brain abscess, either bacterial or from atypical organisms such as *Aspergillus*, *Toxoplasma*, *Mycobacterium*, or *Nocardia* species. Multifocal progressive deficits without enhancement are consistent with multifocal leukoencephalopathy; JC virus is the etiology in immunocompromised patients. Stroke-like syndromes may be caused by infective-endocarditis-related infectious emboli, *Listeria* species, varicella-associated vasculitis, or septic emboli from fungal sepsis with *Aspergillus* or *Candida* species. Not uncommonly, investigations for a suspected CNS infection may lead to diagnosis of a lymphocytic meningitis. Major causes of aseptic meningitis are viruses, partially treated bacterial meningitis, mycoplasmas, and fungi (Pruitt, 2003; Schiff and Wen, 2003). Among the viral etiologies, herpes simplex encephalitis may be underestimated in cancer patients and is potentially fatal if untreated (Schiff and Rosenblum, 1998).

Diagnosis of CNS infections in brain neoplasms can be very challenging; high clinical suspicion leads to diagnosis. Neuroimaging, lumbar puncture, and even brain biopsy may be necessary to narrow the differential

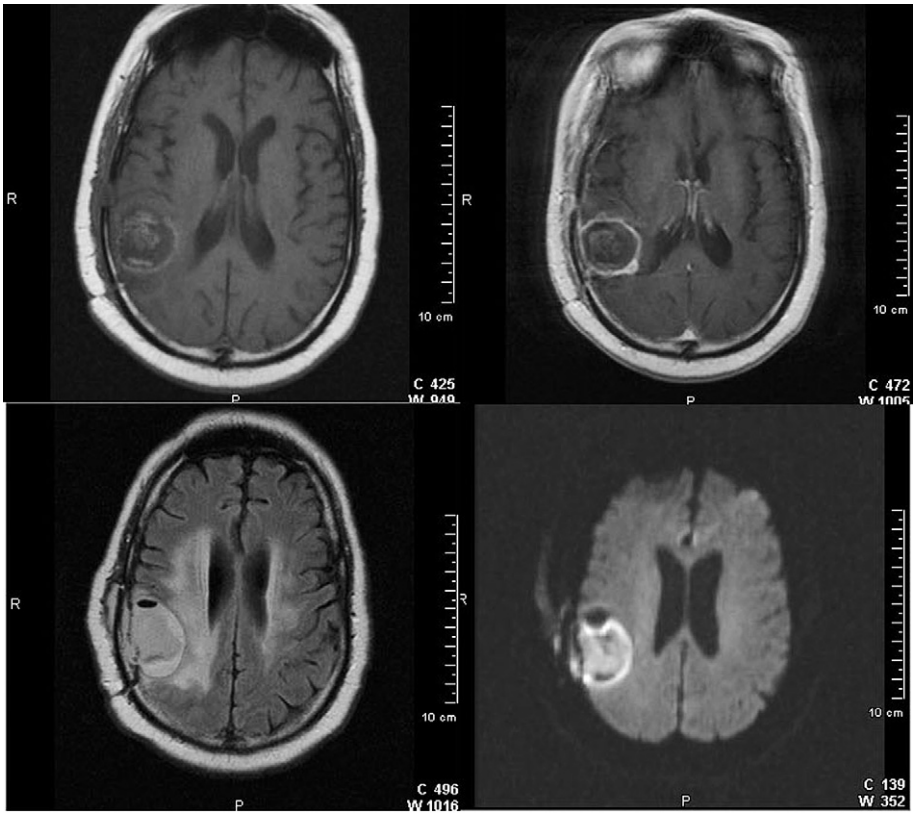

Fig. 15.3. Right posterior temporal abscess after Gliadel® implantation. Note abscess is ring enhancing in post-contrast TI-weighted images, hyperintense in diffusion-weighted images (DWI), and intracavitary air in FLAIR and DWI.

diagnosis. Many noninfectious entities, such as drug treatment complications, radiation effects, recurrent tumor, and paraneoplastic syndromes, may mimic CNS infections. Surgery is indicated if an abscess is present. In most clinical situations, empirical antimicrobial therapy is started immediately to prevent delay in treatment (Pruitt, 2003). The use of MRI and polymerase chain reaction analysis of CSF for herpes simplex virus nucleic acid sequences may permit more rapid diagnosis and treatment (Schiff and Rosenblum, 1998).

15.7. Leptomeningeal neoplasm

Neoplastic meningitis affects between 0.8% and 8% of patients with cancer (Gonzalez-Vitale and Garcia-Bunuel, 1976; Posner and Chernik, 1978). Between 40% and 60% of patients with leptomeningeal spread of tumor have altered level of consciousness (Newton, 1999). Meningeal cancer may impair consciousness by causing obstructive hydrocephalus: multifocal parenchymal involvement, vascular involvement in Virchow–Robin spaces with multiple cortical vein thrombosis or arterial occlusion, diffuse brain edema, metabolic dysfunction, or space-occupying lesions (Young, 1998). Communicating hydrocephalus can also be a sign of leptomeningeal metastases, because meningeal tumor often impairs CSF absorption. The most common clinical picture is encephalopathy; however, cranial nerve deficits are helpful in differential diagnosis of other encephalopathies. The main differential diagnosis is infection. Neuroimaging is helpful when it reveals diffuse, thick, partially nodular enhancement of the leptomeninges or cauda equina roots on contrast-enhanced MRI. However, the most useful test is CSF analysis. Enhancement in a pattern consistent with the patient's clinical findings is often considered sufficient evidence of leptomeningeal metastases to justify initiation of treatment, even if CSF cytological studies are negative.

Prognosis is poor and treatment is usually palliative if widespread systemic cancer is present; fixed focal deficits and cranial nerve dysfunction also augur poor prognosis. Intrathecal chemotherapy and focal palliative radiation treatment can be used in selected cases. Leukemia, medulloblastoma, and germinoma are exceptions that can be treated definitively with craniospinal irradiation (Chang and Maor, 2003). In most primary brain tumors, neoplastic meningitis is associated with progression to coma and death (Grossman and Moynihan, 1991; Young, 1998).

CSF diverting procedures may relieve severe symptoms related to hydrocephalus, including severe papilledema with threatened loss of vision, stupor, or coma, with repeated plateau waves. Seeding of the intraperitoneal cavity usually is not a concern (Posner, 1995).

15.8. Seizures

Seizures in patients with cancer may be due to intracranial neoplasm, chemotherapy-related metabolic disturbance or infections. Seizures account for 60% of acute mental status changes in children with cancer (DiMario and Packer, 1990). Focal seizures are related to location of tumor and infiltration of cerebral cortex; low-grade gliomas are more likely to cause seizures than high-grade gliomas. Tumors with recent bleeding are more epileptogenic. Frontal lobe lesions are more commonly responsible for status epilepticus. Strokes and infectious and neoplastic meningitis may cause seizures (Young, 1998).

Intracranial neoplasms may be the underlying cause of status epilepticus in 6% of patients (Lowenstein and Alldredge, 1993). Prolonged convulsions with impaired consciousness constitute generalized convulsive status epilepticus. Although a patient with convulsions is easily recognized, some patients who have been in generalized convulsive status epilepticus may progress to have minimal or no apparent motor activity but still show seizures on an electroencephalogram (EEG). The incidence of subsequent nonconvulsive status can be as high as 14% (DeLorenzo et al., 1998).

Nonconvulsive status epilepticus is more common than previously appreciated in patients with intracranial tumors (Broderick and Cascino, 1987; Drislane, 1994). However, it may also represent 6% of altered mental status in patients without brain metastases in cancer patients (Cocito et al., 2001).

The patient with nonconvulsive status epilepticus can exhibit a wide variety of clinical manifestations, including coma, confusion, somnolence, altered affect, fugue states, aphasia, abnormal autonomic/vegetative symptoms, delusions, hallucinations, and paranoia (Kaplan, 1996; Krumholz, 1999). The condition should be considered in the differential diagnosis of coma; 8% of patients in coma are in nonconvulsive status epilepticus (Towne et al., 2000). Mortality of SE is approximately 22% (Towne et al., 1994). Treatment should be started promptly (Bleck, 1999; Provencio et al., 2001; Bassin et al., 2002).

Treatment starts with basic life support. Benzodiazepines, usually either diazepam or lorazepam, remain the first-line control for acute status epilepticus. Diazepam is given at a dose of 10–20 mg; lorazepam is given in 2 mg increments at approximately 3 min intervals. If seizures have not terminated after 8 mg of lorazepam, another agent should be started.

Midazolam bolus (0.1–0.3 mg/kg) followed by continuous infusion (0.05–2.0 mg/kg/h) rapidly controls seizures that have not responded to traditional first-, second-, and even third-line agents. However,

benzodiazepines have a high failure rate (69%), which may necessitate addition of a second-line anticonvulsive drug, usually phenytoin (Mayer et al., 2002). Phenytoin alone is only used as a second-line agent after a faster-acting benzodiazepine has been tried. Pentobarbital, in a loading dose of 5–12 mg/kg followed by an infusion of 1–10 mg/kg, is effective in producing coma and achieving burst suppression on EEG for 12–24 hours before attempting to taper medications. Propofol is fast-acting, highly lipid-soluble, and has little propensity to accumulate. An initial dose of 3–5 mg/kg is followed by a maintenance dose of 1–15 mg/kg/h, as required for seizure control. Abrupt discontinuation of infusion has been associated with recurrent seizures (Bassin et al., 2002). Inhalational anesthesia may be beneficial, especially in children, who may not tolerate side effects of propofol such as acidosis (Baumeister et al., 2004; Mirsattari et al., 2004).

15.9. Coma following surgery

Postoperative complications that may cause altered level of consciousness are diverse: coma affected 2% of patients in a series of intraaxial tumor resections (Brell et al., 2000). When a patient does not recover from anesthesia or is not progressing as anticipated, an immediate CT is done to evaluate presence of a structural lesion: hematoma, hydrocephalus, edema, tension pneumocephalus and/or infarction. Non-structural abnormalities that may impair the level of consciousness include electrolyte imbalance, particularly hyponatremia associated with syndrome of inappropriate antidiuretic hormone secretion (SIADH) or cerebral salt wasting syndrome, pain medications, diabetes insipidus, or hormonal changes associated with manipulation of the pituitary gland or stalk. Seizure, stroke, and vasospasm could be included in the list.

The most important step is to stabilize the patient and rule out any structural lesion that may need emergency surgical intervention. Investigating other possible causes should follow.

Increased ICP is a common problem after intracranial tumor resection. In a retrospective study of 514 consecutive patients whose ICP was monitored after elective supratentorial or infratentorial surgery, 18.4% of patients with supratentorial and 12.7% of patients with infratentorial tumors had a postoperative sustained ICP elevation exceeding 20 torr. Risk factors for postoperative ICP elevation are resection of glioblastoma in 27.2% of cases, repeat surgery in 42.9% of cases, and protracted surgery (>6 h) in 41.7% of cases. A total of 52.8% of patients with elevated ICP had an associated clinical deterioration. The most common findings on CT is brain edema (21%) and bleeding in the tumor bed (17%). Some 15% with raised ICP and clinical deterioration undergo reoperation (Constantini et al., 1988). Another risk factor for postoperative ICP is the partial resection of tumor, a foreign-body-like effect exerted by tumor and necrotic debris (Ciric et al., 1987; Fadul et al., 1988; Chang et al., 2003). A recent study identified the risk of postoperative hematoma as associated with a large amount of intraoperative blood loss and elevated ICP. Most hematomas occur within 24 hours after surgery and in this time period deterioration is more severe than with hematomas that occur later (Zetterling and Ronne-Engstrom, 2004). Damage to major arteries during resection of tumor is a rare but life-threatening complication of surgery that requires immediate control of bleeding endovascularly or surgically (Chaloupka et al., 1996; Raymond et al., 1997; Laws, 1999).

15.10. Radiation-related coma

Radiation is one of the major modalities in the treatment of intracranial neoplasms. Side effects may arise from damage to endothelium and thrombosis (Hopewell and Wright, 1970).

Acute encephalopathy is a syndrome of patients with raised ICP or large tumor and more common with large dose fractions. This syndrome occurs within hours after first dose of radiation and is related to increased vasogenic edema. It responds to corticosteroids (Young et al., 1974; Sheline et al., 1980; Leibel and Sheline, 1987; Bruner et al., 1998). The routine use of small fractions of radiation and prophylactic use of corticosteroids has rendered this complication rare.

Focal encephalopathy may follow high-dose radiation treatment; the brainstem is often affected. Symptoms begin 8–12 weeks after radiotherapy. Diffuse CNS demyelination or direct injury to oligodendroglial cells, causing focal demyelination, may be present in this early delayed encephalopathy (Lampert and Davis, 1964; Monro and Mair, 1968; Fukamachi et al., 1982; Packer et al., 1993; Kleinschmidt-DeMasters, 1995; Bruner et al., 1998). Cerebral space-occupying cysts following radiation therapy are another cause of decreased level of consciousness after radiation treatment (Lee et al., 2004).

Late delayed encephalopathy (radionecrosis) begins several months after radiotherapy and is associated with vascular damage and necrosis (Burger et al., 1979). Sclerotic damage to the wall of the capillaries results in porosity with progressive destruction of the blood–brain barrier and an extensive fibrinoid

coagulative degeneration predominantly of the white matter. This typically forms a hard mass with ill-defined contours (Littman et al., 1977; Lorenzo et al., 1978; Bruner et al., 1998). It may accompany life-threatening hematoma (Woo et al., 1987; Lee et al., 2004).

The most common long-term toxicity of cranial radiotherapy is encephalopathy; clinical findings consist of progressive memory deficits, apathy, mental slowing, lack of concentration, urinary urgency or incontinence, and gait disturbances. Diffuse radiation leukoencephalopathy is another outcome that can progress to coma (DeAngelis et al., 1989); radiological findings comprise cerebral atrophy and white matter lesions (Constine and Konski, 1988; Stylopoulos and George, 1988; Corn and Yousem, 1994; Surma-aho and Niemelä, 2001). In addition to the classic white matter lesions, gray matter lesions, blood–brain barrier disruption, and hemosiderin deposition also were frequently demonstrated (Chan et al., 1999). Peterson et al. (1995) detected MRI abnormalities in both the gray and white matter in all six of the patients with radiation necrosis whom they examined, and found multifocal punctate (<601 cm) or ring enhancement on the MR images of cranial irradiation to brain tumors. Gray matter lesions were characteristically seen as a disruption of the gray matter by hyperintense lesions on T_2-weighted images. This is consistent with the reported histological descriptions of coagulative necrosis involving the cortex and white matter (Peterson et al., 1995).

The principal differential diagnosis of radionecrosis is tumor recurrence. The mass effect may necessitate surgical resection if unresponsive to medical management with corticosteroids.

15.11. Paraneoplastic encephalomyelitis

Paraneoplastic encephalomyelitis refers to a disorder with symptoms of multifocal nervous system involvement with cellular infiltrates and neuronal death and signs of inflammation demonstrated by CSF studies, biopsy, or radiological studies (Dalmau et al., 1992; Dalmau and Posner, 1997; Gultekin et al., 2000; Bataller and Dalmau, 2003). Paraneoplastic encephalomyelitis is usually associated with small cell lung cancer, and serum and CSF are commonly positive for anti-Hu antibodies (Dalmau et al., 1992). In one clinical syndrome of paraneoplastic encephalomyelitis, paraneoplastic limbic encephalitis, stupor or lethargy is present in 12% of patients (Gultekin et al., 2000). Another paraneoplastic syndrome, diffuse encephalomyelitis with brainstem involvement, may alter consciousness (Reddy and Vakili, 1981; Dalmau et al., 1991). There is no specific treatment for paraneoplastic diseases; immunosuppression and treating the underlying malignancy may ameliorate the symptoms (Gultekin et al., 2000; Keime-Guibert et al., 2000; Graus et al., 2001).

15.12. Altered mental status and coma from chemotherapy

The list of chemotherapy agents that can produce encephalopathy, seizures, focal neurological deficits and coma is extensive (Table 15.2). Many, but not all, drugs are excluded from the brain by the intact blood–brain barrier. Some agents cross the intact blood–brain barrier to produce neurotoxicity, others get in when the blood–brain barrier has been disrupted by the presence of metastatic disease and other agents may produce CNS neurotoxicity indirectly through mechanisms such as alteration of coagulation parameters or electrolytes. Some of the more common causes are discussed here. The interested reader is referred to more definitive reviews (Posner, 1995; Wen, 2003; Hammack, 2005).

Methotrexate, an inhibitor of dihydrofolate reductase, affects DNA and RNA synthesis as well as homocysteine metabolism. It achieves significant CNS concentrations when administered intrathecally or in very high intravenous doses. High-dose intravenous methotrexate can produce encephalopathy, stupor, coma and seizures within 1–2 days of administration. The pathogenesis is poorly understood; recovery is usually complete and rapid, and patients can be re-exposed to the agent without further symptoms. Intrathecal methotrexate produces aseptic meningitis that can be accompanied by lethargy. Rarely, administration of intrathecal methotrexate produces acute encephalopathy, focal neurological deficits, coma, or death (Wen, 2003). A gradually progressive leukoencephalopathy may be seen as a chronic complication of either intrathecal or high-dose intravenous methotrexate, particularly in combination with whole-brain radiotherapy and most commonly when radiotherapy has preceded methotrexate.

Ifosfamide is an alkylating agent related to cyclophosphamide. Large doses of ifosfamide, commonly used for sarcomas and hematological malignancies, produce CNS dysfunction in 20–40% of patients. The clinical spectrum ranges from confusion, with or without seizures, to aphasia or mutism, to coma (DiMaggio et al., 1994). Neurological dysfunction has been attributed to the production of chloroacetaldehyde, a metabolic by-product of ifosfamide that shares structural similarity with metaldehyde, which is known to be epileptogenic. Benzodiazepines may be helpful in

Table 15.2

Adverse effects of chemotherapy

Seizures	Encephalopathy (acute or subacute)	Encephalopathy (chronic)	Cerebrovascular complications
Methotrexate	Methotrexate	Methotrexate	Cisplatin
Cisplatin	Cisplatin	Ara-C (intrathecal)	Doxorubicin (intra-arterial)
Vinca alkaloids	Vinca alkaloids	5-fluorouracil + levamisole	Mitomycin C
Mechlorethamine	Mechlorethamine	BCNU (intra-arterial or high-dose intravenous)	L-asparaginase
Nitrosourea (intra-arterial or intracavitary)	Procarbazine	Interferon	Interleukin-2
Chlorambucil (high-dose)	Levamisole	Ifosfamide	Erythropoietin
Busulfan (high-dose)	Cytarabine	Fludarabine	Danazol
Cyclophosphamide	Fludarabine	Cisplatin (intra-arterial)	Estramustine
5-fluorouracil	Gemcitabine	Interleukin-2 (intrathecal)	
Cytarabine	Hydroxycarbamide		
Fludarabine	Pentostatin		
Gemcitabine	Chlorambucil		
Pentostatin	Thiotepa (high dose)		
Dacarbazine	Ifosfamide		
Temozolomide	Hexamethylmelamine		
Ifosfamide	Cyclophosphamide		
Etoposide (VP-16)	Etoposide		
Paclitaxel	Paclitaxel		
Docetaxel	Docetaxel		
Levamisole	Pyrazoloacridine		
Metronidazole	Doxorubicin (intrathecal only)		
L-asparaginase	Nitromidazoles		
Interferon	Plicamycin		
Interleukin-2	Thalidomide		
Erythropoietin	Interferon		
Leuprolide	Interleukin-2		
OKT3	Interleukin-3		
	Interleukin-6		
	Interleukin-11		
	Tumor necrosis factor-alpha		
	Tamoxifen		
	Mitotane		
	Corticosteroids		
	OKT3		
	L-asparaginase		

Source: adapted with permission from Hammack JE (2005). Neurologic complications of chemotherapy and biologic therapies. In: D Schiff, BP O'Neill (Eds.), Principles of Neuro-Oncology. McGraw-Hill, New York.

truncating an episode, although the syndrome is typically self-limited (Simonian et al., 1993). Thiamine and methylene blue have been reported to be helpful as well (Buesa et al., 2003; Turner et al., 2003).

Cisplatin may cause encephalopathy as a secondary effect on renal tubules with hypomagnesemia or hypocalcemia, from SIADH or from water intoxication related to prehydration. However, it rarely directly produces CNS dysfunction manifesting as cortical blindness, seizures, or other focal dysfunction within a few hours of intravenous administration. The clinical picture resembles reversible posterior leukoencephalopathy and recovery is usually rapid and complete (Hammack, 2005).

Like methotrexate, the antimetabolite cytarabine (cytosine arabinoside, ara-C) penetrates the CNS when administered intrathecally or in high systemic doses. Very high-dose intravenous cytarabine is sometimes used for hematological malignancies and occasionally produces a distinctive clinical picture of cerebellar

dysfunction, somnolence, and encephalopathy that may culminate in coma. Increasing cumulative dose and pre-existing renal dysfunction are risk factors for developing this syndrome, which usually improves following discontinuation of drug. Seizures and encephalopathy are also rare complications of intrathecal cytarabine.

The biological agent alpha-interferon may produce severe CNS toxicity, particularly in the elderly, those with pre-existing (sometimes undiagnosed) brain lesions and prior recipients of cranial irradiation. Somnolence, headache, encephalopathy, and seizures may be seen. Although these are usually reversible, permanent deficits and dementia have been reported (Meyers et al., 1991). The pathophysiology is unknown.

L-asparaginase is an enzyme that hydrolyzes L-asparagine, an amino acid that normal cells can produce but some tumors (notably acute lymphocytic leukemia) cannot. L-asparaginase produces both diffuse encephalopathy and cerebral venous thrombosis. The encephalopathy, which sometimes progressed to coma, is seldom seen now that lower doses of the agent are used; it may have been secondary to hepatic dysfunction. L-asparaginase additionally depletes serum factors related to coagulation and fibrinolysis, occasionally resulting in thrombotic or hemorrhagic CNS complications. Most commonly seen is cerebral venous or dural sinus thrombosis, manifesting as headaches, seizures, focal neurological deficits, and papilledema. Treatment includes discontinuation of the drug; some physicians will prescribe heparin if hemorrhage is absent.

The alkylating agents chlorambucil and busulfan may cause encephalopathy and seizures when given in high doses. The intravenous use of procarbazine, which has been largely abandoned, also was capable of producing severe encephalopathy. High intravenous doses of BCNU, or BCNU administered intra-arterially, also cause confusion, seizures, focal deficits, and permanent encephalopathy.

The neurological toxicity of the vinca alkaloids such as vincristine is primarily peripheral, namely neuropathy. However, vincristine can produce CNS toxicity through several mechanisms. It can cause SIADH with secondary encephalopathy. Rarely it directly produces seizures and encephalopathy. Finally, inadvertent intrathecal injection of vincristine produces a fatal encephalomyelopathy.

Fludarabine is a purine analog used for chronic lymphocytic leukemia and lymphoma. It can cause both acute and delayed chronic CNS neurotoxicity including seizures, cortical blindness, persistent vegetative state, and coma. MRI and histopathology suggest that demyelination is at least part of the mechanism. These complications were more common in the past when higher doses of this agent were used (Wen, 2003).

Interleukin-2 is an immunomodulatory and antineoplastic cytokine that increases capillary permeability. Patients with brain metastases or primary brain tumors may experience increased peritumoral edema and consequent symptoms upon receiving interleukin-2. It may also produce dose-related encephalopathy and rarely focal deficits in patients without underlying brain disease; these symptoms usually resolve following drug discontinuation (Hammack, 2005).

Pentostatin is a purine analog used in hairy cell leukemia. It can produce dose-dependent seizures, leukoencephalopathy, and coma (Cheson et al., 1994).

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Chapter 16

Abnormal conscious state and coma in transplant recipients

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Organ transplantation is a therapeutic option for many end-stage diseases. Over the last decades, improvements in surgical techniques and immunosuppressive treatment have increased the survival of transplant recipients. Neurological complications occur frequently among these patients and contribute substantially to mortality and morbidity after transplantation. The major neurological complications that occur in these patients are encephalopathy, stroke, seizures, and infectious diseases of the central nervous system (CNS). Several of these complications are associated with an abnormal conscious state.

The underlying causes of an abnormal conscious state or coma in transplant recipients depend on the preoperative state of the patient, the type of transplantation, the use of immunosuppressive drugs, rejection causing dysfunction of the graft and the behavior of the patient after organ transplant. Organ transplantation is such a major surgical procedure that some altered state of awareness is expected in the immediate postoperative aftermath; however, encephalopathy after operation may also be due to rejection causing dysfunction of the graft. In the longer term, neurological complications are more likely to be associated with chronic use of immunosuppressant medication. A decrease of consciousness in the transplant population may be secondary to transplantation itself, to structural lesions or to neither transplantation nor structural lesions. This chapter discusses the most commonly encountered causes of coma and other states of altered awareness in the transplant population.

16.1. Pretransplantation

Neurological consultation may be required before transplantation since neurological diseases may be important in the selection of patients. These conditions include cerebrovascular or neurodegenerative diseases but also an abnormal state of consciousness. The most common example of such a situation is a patient with acute liver failure awaiting liver transplantation. Liver failure of acute onset can be due to a variety of causes such as metabolic disturbances, drugs, and viruses but also can be idiopathic (Albrecht and Jones, 1999; Sass and Shakil, 2005). Acute liver failure may result in hepatic encephalopathy, which is a complex syndrome of symptoms ranging from minimal changes in personality or altered sleep pattern to deep coma (Sass and Shakil, 2005). In patients with liver failure other causes for abnormal state of consciousness should be evaluated as well, such as renal failure with uremia, electrolyte disturbances, hypoglycemia, hypoxia, alcohol withdrawal delirium or intoxication, and endocrine disorders. Hepatic encephalopathy can be separated into four clinical stages ranging from stage 1, indicating subtle changes, to stage 4, indicating coma (Table 16.1). Asterixis is often present in the early stages; extrapyramidal symptoms such as muscular rigidity and tremor may occur. Liver transplantation is the only effective treatment for fulminant hepatic failure, although the outcome in patients reaching grade 3 or 4 encephalopathy is often unfavorable (Daas et al., 1995).

16.2. General assessment of altered consciousness

Definitional clarity of neurological syndromes in sick patients in transplant units is quite a challenge. Some patients are agitated or have their eyes closed and cannot be aroused with pain stimuli. Some may display

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Table 16.1

The clinical stages of hepatic encephalopathy[1,2]

1. Mild confusion, euphoria or depression, decreased attention, mental slowing, untidiness, slurred speech, irritability, reversal of sleep pattern, possible asterixis
2. Drowsiness, lethargy, gross mental slowing, obvious personality changes, inappropriate behavior, intermittent disorientation, obvious asterixis
3. Somnolent but rousable, unable to perform mental tasks, persistent disorientation, amnesia, occasional attacks of rage, incoherent speech, pronounced confusion, asterixis probably absent
4. Coma

excessive sleepiness. This condition is known by the purely descriptive term hypersomnia but may be the most difficult condition to assess accurately. Several patients may have sleep deprivation and may need time to recover from a major surgical event. In many patients after transplantation, metabolites from prior administrative sedative drugs could still play a considerable role in dampening of arousal.

An acute confusional state is equally difficult to define but should probably only be considered if it lasts more than 2–3 consecutive days. In this state, agitation and acute disorientation are commonly associated with hallucinations. Acute confusional state could be due to many causes; most clinically relevant and common causes are shown in Table 16.2. More specifically in transplant recipients, an acute confusional state can be precipitated by withdrawal of barbiturates or alcohol, neurotoxicity from immunosuppressive agents, and the use of high-dose corticosteroids at the time of treatment of rejection. It could be due to nonconvulsive status epilepticus, but mostly if a confusional state follows immediately after a single generalized tonic–clonic seizure. An acute confusional state is very common in patients who have had a liver transplantation for alcoholic liver disease (Buis et al., 2002). In approximately half of such patients, an acute confusional state is seen that appears as early as 3 days after transplantation, on average 10 days after transplantation, and is less common after 1 month after transplantation. Increased serum levels of ammonia and brain atrophy on computed tomography (CT) scan predisposes to postoperative confusion in these patients.

Table 16.2

Most common or important causes of post-transplantation delirium

Orthotopic liver transplantation for alcoholic liver disease
Calcineurin inhibitors (cyclosporine, tacrolimus)
Cardiac transplantation
High dose corticosteroids
Wernicke's encephalopathy due to total parenteral nutrition

Table 16.3

Most common or important causes of post-transplantation stupor or coma

Central pontine myelinolysis
Intracerebral hematoma (aspergillus infection)
Hemolytic-uremic syndrome in bone marrow transplantation
Acute rejection in orthotopic liver transplantation, renal transplantation
Accumulation of anesthetic and sedative agents

Stupor or coma emerges when a more severe involvement of level of consciousness is present. Eye opening is not or barely seen with pain stimuli and many of the patients have no withdrawal to pain. The acute presence of stupor or coma in a liver transplantation patient is almost always serious and is probably due to a structural cause (Wijdicks, 1995; Wijdicks et al., 1995; Ardizzone et al., 2006). The differential diagnosis tailored towards the most common causes is shown in Table 16.3. Stupor is not infrequently due to central pontine myelinolysis (Fig. 16.1) (Wijdicks et al., 1996a; Fraser et al., 2005; Ardizzone et al., 2006; Kumar et al., 2006). The structural abnormalities seen in transplant patients often involve bihemispheric lesions or a massive lesion compressing the opposite hemisphere (Fig. 16.2) (Wijdicks et al., 1995).

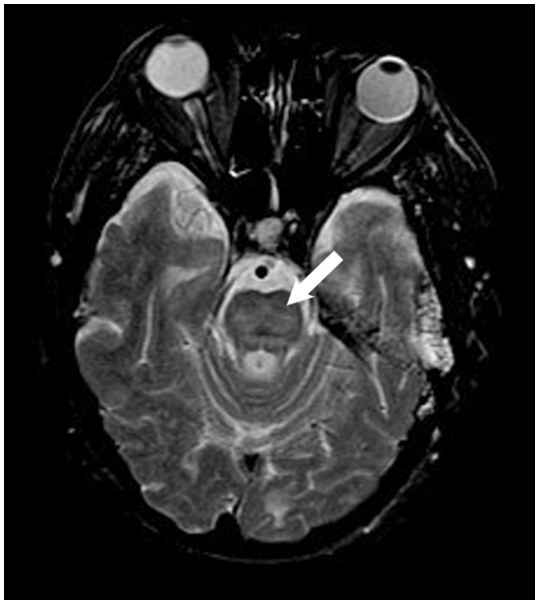

Fig. 16.1. Central pontine myelinolysis. T_2-weighted MRI image of batlike hyperintensity in the pons (arrow) consistent with central pontine myelinolysis in a patient after organ transplantation with an abnormal conscious state.

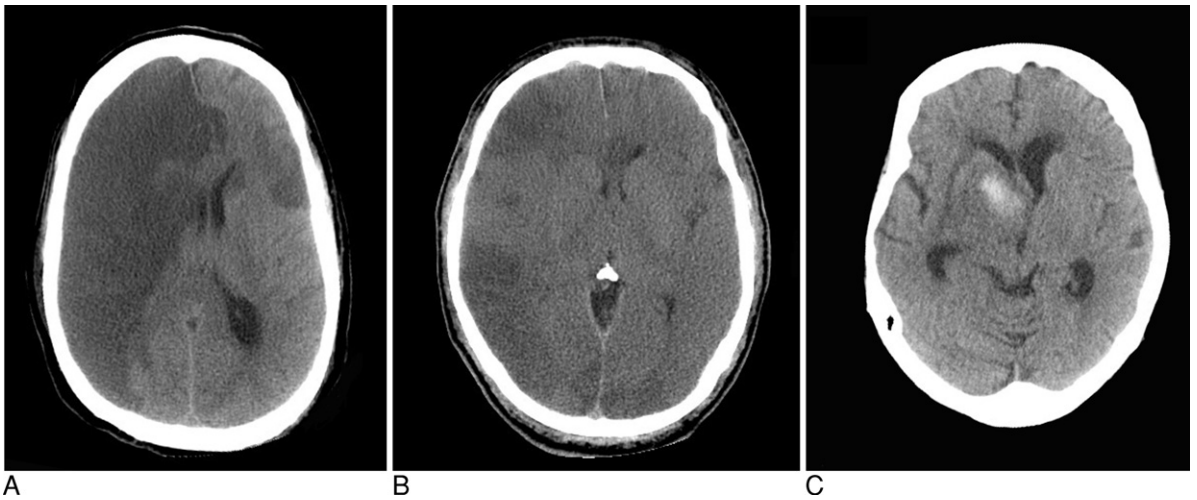

Fig. 16.2. Cerebrovascular complications in patients with an abnormal conscious state and coma after heart transplantation. **A.** CT showing large evolving subacute infarct involving the right frontal, temporal, and parietal lobes with subfalcine herniation and partial uncal herniation; there are additional smaller areas of infarction in the left hemisphere. **B.** CT showing massive cerebral edema throughout both cerebral hemispheres with loss of gray/white differentiation; there are extensive patchy areas of low-attenuation changes throughout both cerebral hemispheres in a watershed distribution. **C.** CT showing hemorrhage in the right basal ganglia.

Brain death, a comatose state with loss of all brain function, is fortunately uncommon in transplant recipients. It often makes the organ recipient an organ donor. The clinical diagnosis of brain death can be established in patients who had a heart–lung transplant with massive infarction of both hemispheres (Andrews et al., 1990; Jarquin-Valdivia et al., 1999; Malheiros et al., 2002; Perez-Miralles et al., 2005). The prolonged presence on cardiopulmonary bypass has caused significant ischemic damage to multiple territories of the brain (Fig. 16.2). After liver transplantation, loss of brain function can be a consequence of significant hypoxic–ischemic damage due to hypovolemic shock, but this is a rare condition (Wijdicks, 1995). In patients with fulminant hepatic failure transplanted as an emergency the cause is likely cerebral edema; preoperative edema may have progressed despite grafting (Wijdicks, 1995).

An unusual circumstance is a condition termed akinetic mutism. In this variant of a vegetative state, awareness is lost and patients do not speak but may visually track persons in the room. Although typically considered a major structural insult to the brain, it has been described in cyclosporine and OKT3 neurotoxicity (Bronster et al., 1995; Pittock et al., 2003). Akinetic mutism may also occur after radiation and chemotherapy in bone marrow recipients (Devinsky et al., 1987).

16.3. Organ failure or graft rejection

Acute failure of the graft results in a serious, life-threatening condition in heart, lung, liver, and bone marrow transplantation. Renal rejection results less commonly in critical illness. In general, primary graft failure prolongs intensive care unit stay and is associated with high additional mortality (Pascual et al., 2002; Neuberger, 2005; Hunt, 2006; Naeem et al., 2006; Perez-Simon et al., 2006; Webber et al., 2006). Hyperacute rejection of heart graft occurs typically within minutes to hours after graft implantation and will essentially always result in loss of the heart graft (Hunt, 2006). Primary acute liver graft dysfunction occurs in 5–10% of patients and is manifested by progressive encephalopathy with development of hepatorenal syndrome, systemic lactic acidosis, and severe coagulopathy increasing the risk of intracranial hemorrhage (Neuberger, 2005). In cadaveric liver transplants liver graft rejection is typically about a week after transplantation, without an identifiable cause (Hwang et al., 2006). This ‘seventh-day syndrome’ is characterized by sudden failure of a liver graft and has not been reported after living donor liver transplantation. The mortality associated with primary liver graft dysfunction is 40–50% even after retransplantation (Neuberger, 2005; Hwang et al., 2006).

Chronic failure, graft-versus-host disease, is the most common and severe complication among patients surviving >100 days after allogeneic bone marrow transplantation (Ma et al., 2002). Most frequently recognized neurological complications of graft-versus-host disease include myasthenia gravis, polymyositis, and polyneuropathy (Solaro et al., 2001; Ma et al., 2002; Krouwer and Wijdicks, 2003). CNS angiitis has been reported on rare occasions and is capable of producing a highly variable neurological syndrome that

poses diagnostic and therapeutic challenges (Ma et al., 2002). In patients with CNS angiitis, confusion is combined with other neurological symptoms, such as seizures and limb paresis. Magnetic resonance imaging (MRI) shows multifocal or confluent white matter signal changes (Ma et al., 2002; Krouwer and Wijdicks, 2003). The differential diagnosis includes progressive multifocal leukoencephalopathy and leukoencephalopathy due to irradiation, cytosine arabinoside, and cyclosporine (Re et al., 1999). Cyclosporine neurotoxicity characteristically results in reversible changes in the parieto-occipital white matter and is discussed below (Wijdicks, 2001). Infectious etiologies should be excluded by cerebrospinal fluid analysis and brain biopsy may be necessary to confirm the diagnosis (Czartoski, 2006).

16.4. Electrolyte disturbances and uremia

Electrolyte disturbances occur frequently in transplant recipients but rarely lead to seizures, decreased level of consciousness, or confusional state (Wijdicks et al., 1996b; Tsinari et al., 2004; Rubin et al., 2005; Montas et al., 2006). Electrolyte disturbances have been related to neurological complications during the first 3 months after transplantation in children after hematopoietic stem cell transplantation (Rubin et al., 2005). The direct relation between (subtle) electrolyte disturbances and complications remains unclear. Severe electrolyte disturbances and in particular rapid changes in sodium values (below 125 mmol/l) are known to contribute to increased vulnerability to seizures and may cause altered consciousness and increased risk for other metabolic disturbances (Decaux and Soupart, 2003). Sodium levels should be corrected slowly because of the risk of central pontine myelinolysis (Fig. 16.1). Hypernatremia occurs frequently in patients after liver transplantation and may also result in decreased level of consciousness (Powner, 2004).

Failure of the kidney graft may result in uremic encephalopathy (Pascual et al., 2002). When renal failure is part of multiple organ failure, hypertension, hypotension, hypoxia, or nutritional status may also play a part in the degree of alertness in a patient. Acute renal failure is one of the most common complications of orthotopic liver transplantation, with an incidence ranging from 12% to 64% (Wei et al., 2006). The diagnosis of uremic encephalopathy is often complicated by the coexistence of other metabolic illnesses that may contribute to clouding of the sensorium. The symptoms of uremic encephalopathy, although dependent on the magnitude of renal failure, are most pronounced with a rapid development of uremia (Brouns and de Deyn, 2004); with treatment and recovery, mental status function is often reattained in the reverse order of loss.

16.5. Structural lesions

Global cerebral ischemia occurs relatively frequently in patients after heart transplantation (Fig. 16.2) (Andrews et al., 1990; Jarquin-Valdivia et al., 1999; Malheiros et al., 2002; Perez-Miralles et al., 2005). Patients who fail to awaken after heart transplantation may have had marked intraoperative hypotension or have been resuscitated for intraoperative asystole or ventricular fibrillation. In many patients after heart transplantation, global cerebral ischemia is not attributable to the heart transplantation itself but is rather more directly related to the preoperative or postoperative cardiac dysfunction (Perez-Miralles et al., 2005). The postoperative care of heart transplantation is complicated and can be associated with perioperative cardiac arrest, hypovolemia, and hypotension (not uncommonly associated with overtitration of vasodilators). Mechanical support of the circulation has been associated with global cerebral ischemia (Boehmer and Popjes, 2006). In patients with postanoxic encephalopathy, CT brain shows diffuse brain edema.

Pure anoxic injury may be most common in patients after lung transplantation, particularly because oxygenation is impaired as a result of pulmonary hemorrhage, infection, and pulmonary edema from reperfusion injury to the pulmonary graft (Wong et al., 1999).

Postanoxic encephalopathy after liver transplantation is infrequent but if present it is commonly caused by cardiac complications. Retrospective case-series showed an incidence of 1–2% anoxic injury in patients undergoing liver transplantation (Wong et al., 1993; Singh et al., 1994; Bronster et al., 2000a; Agildere et al., 2006). The most common cause of postanoxic encephalopathy was in-hospital cardiorespiratory arrest shortly after transplantation (mean of 10 days after transplantation). Fulminant hepatic failure may also result in brain edema, which may rapidly lead to brain death from tissue shift followed by global ischemia due to massively increased intracranial pressure impeding entry of arterial blood flow (Wijdicks, 1995).

Long-standing graft-versus-host disease may be associated with the development of a form of cerebral angiitis causing areas of infarction (Ma et al., 2002), and has been discussed above.

Cerebral infarction caused by emboli fragments from a residual atrial thrombus occur in 7–20% of patients after cardiac transplant (Andrews et al., 1990; Jarquin-Valdivia et al., 1999; Malheiros et al., 2002; Mayer et al., 2002; Perez-Miralles et al., 2005). A decline of consciousness can be caused by infarction

of strategic areas such as the thalami or by massive infarction of both cerebral hemispheres. In many of those patients, CT or MRI scan readily shows the devastating ischemic injury (Fig. 16.2). Cerebrovascular disorders after heart transplantation are predominantly reported during the first 3 months, probably because of the accumulation of triggering factors in this period.

Cerebrovascular disorders also predominate in patients with impairment of consciousness after bone marrow transplantation (Antonini et al., 1998; Solaro et al., 2001; Krouwer and Wijdicks, 2003; Sostak et al., 2003; Rubin et al., 2005). In patients after bone marrow transplantation most cerebrovascular events are cerebral hemorrhages (subarachnoid hemorrhage, subdural hematoma, and intracranial hematomas) related with long-lasting thrombocytopenia. The prevalence of intracerebral hematoma ranges from 0.8% in one prospective clinical study of early neurological complications after allogeneic bone marrow transplantation in 115 patients with leukemia to 32.2% in a recent article focusing on 58 patients with various intracerebral hematomas detected at autopsy (Antonini et al., 1998; Solaro et al., 2001; Krouwer and Wijdicks, 2003; Sostak et al., 2003; Rubin et al., 2005). The incidence of ischemic strokes in patients after bone marrow transplantation with leukemia ranges from 0.3% to 3.3% (Antonini et al., 1998; Solaro et al., 2001; Krouwer and Wijdicks, 2003; Sostak et al., 2003; Rubin et al., 2005).

Sudden loss of consciousness in a liver transplant patient is typically due to catastrophic intracerebral hematoma (Wijdicks et al., 1995). Intracerebral hematoma is especially common in patients after liver transplantation with coagulopathy and bacterial sepsis syndrome, but fungal infections are notorious. An overwhelming *Aspergillus* infection may present with coma due to a massive intracranial hematoma. In a group of eight patients with intracranial hemorrhage after orthotopic liver transplantation bacteremia or fungemia was found in five (62%) (Wijdicks et al., 1995).

Central pontine myelinolysis has emerged as a cause of a decreased level of consciousness after liver transplantation (Fig. 16.1) (Buis and Wijdicks, 2002; Fraser et al., 2005). Dysarthria, dysphagia, ophthalmoplegia, and quadriparesis might be absent at first and become more apparent when the level of consciousness improves (Kumar et al., 2006). Tremor and even katatonia, ataxia, or a full-fledged akinetic rigid syndrome can be seen if extrapontine locations (thalamus) are involved (Buis and Wijdicks, 2002). The outcome of central pontine myelinolysis after liver transplantation can be surprisingly good.

16.6. Seizures

Seizures occur frequently in the transplantation population and are more frequent in the pediatric population than in adults (Wong et al., 1993; Wijdicks, 1995; Wszolek and Steg, 1997; Antonini et al., 1998; Grigg et al., 1998; Jarquin-Valdivia et al., 1999; Bronster et al., 2000a; Solaro et al., 2001; Krouwer and Wijdicks, 2003; Sostak et al., 2003; Domhan et al., 2005; Perez-Miralles et al., 2005; Rubin et al., 2005; Ardizzone et al., 2006). The most commonly identified underlying causes for seizures in transplant recipients include metabolic and electrolyte derangements, drugs (especially cyclosporine and OKT3), hypoxic–ischemic injury, cerebral structural lesions, and CNS infections.

The prevalence of seizures differs with the type of transplant. The reported prevalence of seizures in patients after bone marrow transplantation is approximately 20% (Antonini et al., 1998; Krouwer and Wijdicks, 2003; Sostak et al., 2003). About one-third of patients with seizures after bone marrow transplantation will have generalized seizures without either focal neurological signs or neuroradiological changes (Antonini et al., 1998; Krouwer and Wijdicks, 2003; Sostak et al., 2003). Busulfan during the preparatory regimen and cyclosporine toxicity during graft-versus-host disease prophylaxis and treatment are frequently considered to be responsible for seizures in transplanted patients (see below).

Reported seizure rates in the liver transplantation recipients differs between studies (3–42%) (Wong et al., 1993; Wijdicks et al., 1996b; Wszolek and Steg, 1997; Bronster et al., 2000b; Agildere et al., 2006). Seizures in the liver recipient often occur as a result of focal brain injury; however, metabolic abnormalities may predispose these patients to seizures.

Seizures have been reported in 2–43% of heart transplant recipients (Andrews et al., 1990; Grigg et al., 1998; Malheiros et al., 2002; Perez-Miralles et al., 2005; Webber et al., 2006). Most of these patients have an identifiable cause to explain the occurrence of seizures (Grigg et al., 1998). In the heart transplant population three clinical subgroups of seizures after heart transplantation can be distinguished (Grigg et al., 1998): first, seizures associated with postoperatively acquired focal neurological deficits, usually acquired within 24 hours after operation; second, seizures associated with posterior reversible encephalopathy syndrome, which is discussed in detail below; finally, seizures associated with severe graft rejection.

Rejection of renal graft is also associated with seizures (Wszolek and Steg, 1997; Agildere et al., 2006; Montas et al., 2006). Cerebral infarction and posterior reversible encephalopathy syndrome are the most

common causes of seizures after renal transplantation (Wszolek and Steg, 1997; Agildere et al., 2006; Montas et al., 2006).

16.7. Neurological infectious diseases

CNS infections in the transplant population can be caused by receipt of an infected organ or associated neutropenia and use of immunosuppressive drugs. Viral reactivation and opportunistic infections are the most frequent causes (Czartoski, 2006). Over the last decades, effective antimicrobial prophylactic strategies have led to a decline in the incidence of several opportunistic pathogens (Singh, 2003). As a consequence, the spectrum of infections in transplant recipients has evolved from traditional infections to newer complications. Opportunistic pathogens in the current era are likely to differ in their clinical presentation, time of onset and/or antimicrobial susceptibility from those of a decade ago (Singh, 2003). An important change in epidemiology is emerging invasive fungal infection (Marr et al., 2002). In children following bone marrow transplantation, adenovirus is increasingly being recognized as a significant pathogen (Walls et al., 2003). When disseminated adenovirus infection occurs in these children, reported mortality rates are as high as 60% (Walls et al., 2003). The increased incidence of specific pathogens in the transplant population probably reflects multiple factors, including changes in hosts at risk but also improvements in diagnostic methods. Although systemic studies are lacking, neurological infectious diseases are still causing substantial morbidity and mortality, especially among allogenic bone marrow recipients.

In patients after transplantation, signs and symptoms of infection are often not present in early phases. It is important to realize that classic symptoms and signs of CNS inflammation as neck stiffness and changes in mental status might not develop at all. Cranial nerve palsy may be present, especially in infections with varicella zoster virus (Czartoski, 2006). Meningoencephalitis in transplant recipients can be caused by fungal, viral, or bacterial agents; parasitic CNS infections are relatively rare (Walker et al., 2006). Clues to the causative agent can be found in history (travel history), animal contacts (*Bartonella henselae* and *Toxoplasma gondii*), food exposure (*Listeria monocytogenes*) and (pre-) transplant serology combined with serology of the donor (herpes viruses, in particular cytomegalovirus and Epstein–Barr virus) (Czartoski, 2006).

In evaluating a transplant recipient with clinical signs of meningoencephalitis, time after transplantation is important, since infection with cytomegalovirus or Epstein–Barr virus is most frequent in the first 6 months after transplantation (Fishman and Rubin, 1998). In patients with cytomegalovirus or Epstein–Barr virus infection, MRI of the brain may reveal a communicating hydrocephalus with abnormal T_2 signal of the periventricular white matter (Fig. 16.3). After the first period of 6 months, patients can be divided into patients with good transplant results, who are at increased risk of infections with ordinary infectious agents such as *Streptococcus pneumoniae*, and patients with poorer transplant results, who will need treatment with severe immunosuppressant agents, with a high risk of opportunistic CNS infections (Fishman and Rubin, 1998).

Allogenic bone marrow recipients are especially susceptible to infectious CNS diseases (Antonini et al., 1998; Solaro et al., 2001; Sostak et al., 2003; Czartoski, 2006). This susceptibility is probably related to the combination of neutropenia and impairment of cell-mediated immunity due to the use of immunosuppressive drugs. In a follow-up of 71 allogeneic bone marrow recipients 14 months after transplantation, CNS infections were seen in 11% of the patients and constituted the most common complication (Antonini et al., 1998). Typically, infectious complications occurred more frequently in patients with severe graft-versus-host disease and extended immunosuppression. The most common identified organism causing CNS infectious disease in this study was *Aspergillus*.

Infectious CNS diseases have been reported in approximately 10% of liver recipients (Wong et al., 1993; Wijdicks et al., 1996b; Wszolek and Steg, 1997; Bronster et al., 2000a; Agildere et al., 2006). Infections in liver recipients may occur in the context of either cerebral hemorrhage or a systemic infection with subsequent neurological involvement. Autopsy studies have shown that *Aspergillus* is the most frequently encountered pathogen within the CNS (Boon et al., 1991; McCarron and Prayson, 1998). Primary viral infections of the CNS are infrequent; however, infection with cytomegalovirus may uncommonly cause fulminant systemic failure, with secondary involvement of the CNS. Infection by agents such as *Coccidioides immitis*, *Cryptococcus neoformans*, and *Histoplasma capsulatum* are common in solid organ transplant recipients but rare in allogenic bone marrow recipients (Czartoski, 2006).

An evolving brain mass is another manifestation of CNS infection in the transplant population. Only bilateral lesions, lesions with extensive mass effect or lesions with strategic localization will cause a decrease of consciousness. Most infectious cerebral mass lesions are due to fungi or *Toxoplasma gondii*; however, differentiating between infectious and neoplastic processes can be difficult.

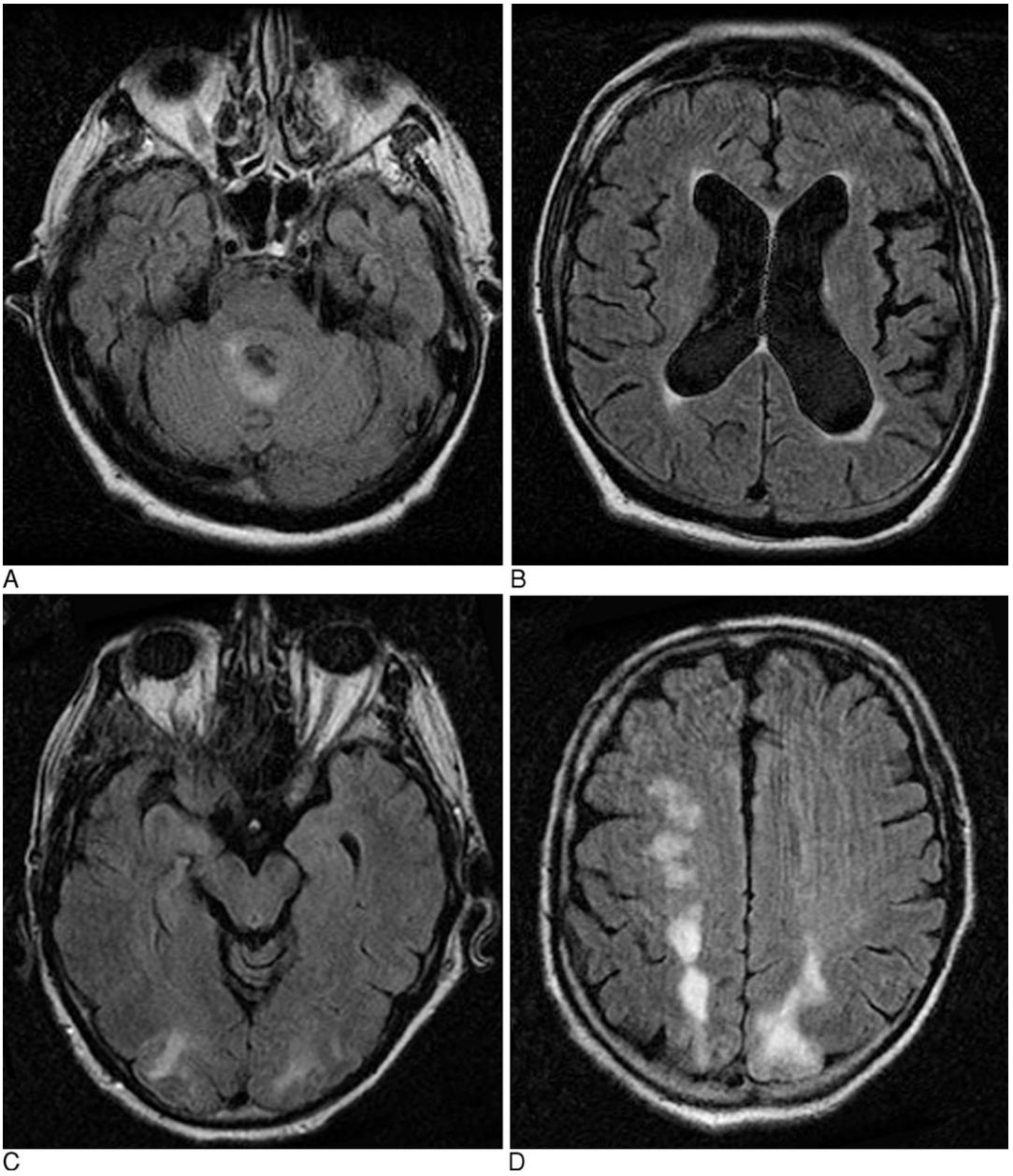

Fig. 16.3. Two patients with abnormal conscious state after transplantation with hyperintensities on FLAIR-weighted MRI. **A, B.** Patient with generalized cytomegalovirus infection and abnormal conscious state; MRI shows hydrocephalus with abnormal signal of periventricular white matter surrounding the 4th ventricle with extension into the dorsal midbrain on the right. **C, D.** Patient with abnormal conscious state after heart transplantation due to cyclosporine neurotoxicity; MRI shows abnormal patchy signal within the subcortical white matter, predominately in the parieto-occipital regions bilaterally and extending into the posterior frontal regions. There is no associated mass effect, associated restricted diffusion, or abnormal enhancement, which is all consistent with posterior reversible encephalopathy syndrome.

Patients after transplantation are at risk for neoplasms. The CNS accounts for 24% of all extranodal post-transplantation lymphoproliferative disorders (Mihalov et al., 1996; Kauffman, 2006; Su et al., 2006). Post-transplant lymphoproliferative disorders represent a heterogeneous group of abnormal lymphoid proliferation related to Epstein–Barr virus reactivation that arises after transplant. Post-transplantation lymphoproliferation with CNS involvement has been reported in a few cases (Nozzoli et al., 2006). Recurrent hematological malignancy should be considered in the differential diagnosis of neurological infectious

diseases in patients with bone marrow transplantation after hematological malignancy.

Progressive multifocal leukoencephalopathy typically presents with subacute neurological deficits and an altered mental status (Aksamit, 2006). Seizures occur in a high percentage; CT shows patchy or confluent hypodense areas in the white matter. MRI shows hypointense lesions on T_1-weighted images and hyperintense lesions on T_2-weighted images. Spinal fluid detection of JC virus is specific but incompletely sensitive.

16.8. Accumulation of sedation

Accumulation of sedation after transplantation is a common cause of failure to become fully alert in all transplantation types. Commonly used drugs such as midazolam and propofol may have different pharmakinetics in transplant patients. Midazolam, although relatively short-acting in comparison with other sedative agents, can have prolonged activity if a liver graft is not functioning fully; it is highly protein-bound and therefore pre-existing low protein levels may increase its sedative effect. Propofol is dependent for its clearance on hepatic blood flow and cardiac output. If both are disturbed, awakening from propofol may be unexpectedly prolonged. Opioids are commonly used after cardiac transplantation and may cause a significant decrease in responsiveness.

16.9. Immunosuppressive toxicity

The most serious problem in the transplant population is the neurotoxicity of immunosuppressive drugs. Cyclosporine and tacrolimus are typically used as part of a postoperative regimen (Wijdicks et al., 1994; Wijdicks, 2001). In general, CNS symptoms induced by these drugs occur early after transplantation and may or may not correlate with blood levels of the neurotoxic drugs. The prevalence of neurotoxicity remains unknown but there is some indication that it is decreasing. Some of the more newly developed drugs (e.g., sirolimus) may not have any significant neurotoxicity (see below) (Maramattom and Wijdicks, 2004).

The clinical presentation of cyclosporine neurotoxicity is characterized by tremulousness and restlessness in all patients (Shah, 1999; Wijdicks, 2001). In many patients, there is a beginning of a fine tremor with many components of an essential tremor followed by visual hallucinations involving kaleidoscopic configurations and the development of a language or speech abnormality. In some patients, articulation is less precise, as if the patient is speaking with a foreign accent. When these symptoms are not recognized, neurotoxicity may become severe, may include cortical blindness, and may progress to a single generalized tonic–clonic seizure or lapse into a decreased level of consciousness. All these symptoms are reversible if recognized early. Cyclosporine neurotoxicity is often triggered by intravenous administration of the drug (Shah, 1999). Extensive clinical use has confirmed that tacrolimus is a key option for immunosuppression after transplantation (Scott et al., 2003); however, neurotoxicity has commonly been reported (Wijdicks, 2001).

Posterior reversible encephalopathy syndrome is most commonly seen in patients with hypertensive encephalopathy, eclampsia, renal failure, uremic encephalopathy or use of immunosuppressants (Stott et al., 2005). It is considered the characteristic imaging presentation of cyclosporine neurotoxicity with subcortical and deep white matter changes consistent with vasogenic edema found predominantly in parietal and occipital lobes (Fig. 16.3). It is not always possible to differentiate the cause (immunosuppressive drug toxicity vs hypertensive encephalopathy) on the basis of imaging (Wennberg, 1998; Besenski et al., 2005). Many patients with cyclosporine or tacrolimus neurotoxicity do not have severe hypertension and a significant increase in mean arterial blood pressure is a feature that typically occurs 1 month after transplantation, far beyond the interval of maximal risk for neurotoxicity.

Newer drugs such as sirolimus have not been associated with neurotoxicity (Maramattom and Wijdicks, 2004). Sirolimus is a new agent related to tacrolimus, but its mechanism of action differs. In a review of 202 transplant recipients treated with sirolimus from 2001–2004, there was no evidence of neurotoxicity with sirolimus therapy after 18 months follow-up (Maramattom and Wijdicks, 2004).

Neurotoxicity in bone marrow transplantation has somewhat specific features. The frequent use of antineoplastic agents such as busulfan, methotrexate, BCNU, and cisplatin may increase the risk (Verstappen et al., 2003). In some patients, this may already become apparent during the initial preparatory stages. For example, busulfan can cause generalized tonic–clonic seizures, methotrexate can cause a leukoencephalopathy and ifosfamide can cause hallucinations, mutism, and coma.

16.10. Management

The approach to an abnormal conscious state and coma in transplant recipients is based on several factors. As noted in the introduction, underlying causes of an abnormal conscious state or coma depend on the preoperative state of the patient, the type of transplantation,

the use of immunosuppressive drugs, rejection causing dysfunction of the graft and the behavior of the patient after organ transplant. Definitional clarity of the neurological syndrome is provided by a profound general assessment of altered consciousness and subsequent neurological examination. If neurological examination is unable to localize to a certain area of the brain or document typical herniation syndromes, one is left with the assessment of a patient with a decreased level of consciousness and multiplicity of causes.

Recent laboratory values should be obtained and should, at least, include electrolyte panel, full liver and renal function, arterial blood gas, and possibly antiepileptic drug levels.

The chart should be scrutinized for sedative drugs and the time remaining to clearance should be calculated, assuming full elimination after obtaining metabolic half-life. Serum levels of cyclosporine or tacrolimus should be studied. A marked increase in cyclosporine, OKT3, or tacrolimus may potentially indicate the development of toxicity; however, many transplant surgeons titrate towards increasing plasma levels, and this should not be misinterpreted as indicative of toxicity. One should realize, however, that many of the drugs that potentially can cause neurological manifestations can be actually measured in serum, but serum levels do not correspond well with clinical manifestations.

Neuroimaging is helpful in detecting structural lesions and may provide clues about infectious CNS diseases and neurotoxicity. Typical lesions in the posterior occipital lobes such as are found in the posterior reversible encephalopathy syndrome may not be present and are most commonly seen in patients who have had seizures or have progressed to coma with pathological motor responses (Fig. 16.3). A normal MRI appearance is a frequent finding in patients with neurotoxicity due to calcineurin inhibitors. It has remained puzzling that all MRI sequences may even be normal in patients who are mute or aphasic because of neurotoxicity.

Cerebrospinal fluid examination should be obtained if meningitis is suspected but should be deferred until neuroimaging, either CT or MRI, has been performed to exclude a mass lesion. An electroencephalogram might be considered to detect nonconvulsive status epilepticus, but this is a highly unlikely explanation except in patients with a waxing and waning level of consciousness with preceding seizures. Nuclear studies, such as positron emission tomography, have been found to be useful to document diminished uptake, particularly in OKT3 neurotoxicity (Bronster et al., 2000a).

The management of an acute confusional state should characteristically include haloperidol and lorazepam. These drugs should only be administered after potentially triggering medication or other factors have been eliminated. A major source of contention is whether to discontinue cyclosporine or tacrolimus. It is prudent to maintain the dose for 3 days and await improvement. Targeting at a somewhat lower dose may be very successful. However, discontinuation is imperative when coma or seizures have occurred. Switching to another immunosuppressive agent has been associated with an increased risk of rejection, but switching to mycophenolate mofetil or sirolimus should be strongly considered if neurotoxicity has been particularly severe.

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Chapter 17

Pregnancy and coma

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Patients in the prime of life become comatose as the result of a somewhat different spectrum of disorders than older individuals. Perhaps the least affected adult group is pregnant women. The pregnant state occupies only a small percentage of many women's adult life but represents a critical treatment challenge to caregivers as it presents two major therapeutic goals: the preservation of the mother and the preservation of the fetus. These patients may have different 'priorities' and vulnerabilities to disease, as well as variable vulnerability to administered treatments. Legal considerations regarding the protection of the fetus, and decisions on abortion of the fetus in these circumstances, are largely beyond the scope of this chapter. Nonetheless, such considerations are of prime importance in the subsequent therapeutic decision-making.

The conditions that may put a pregnant woman in coma, for the most part, are those to which young individuals are vulnerable. These include trauma, seizure, organ failure, or toxic or metabolic dysfunction. Still others are unique to pregnancy, such as eclampsia and HELLP (**H**emolytic anemia, **E**levated **L**iver enzymes, and **L**ow **P**latelet count) syndrome. Other conditions are more frequent in women, e.g., cerebral venous sinus thrombosis and pituitary apoplexy. The unique aspects of coma in pregnancy center, then, around two general principles: unusual causes of coma particular to, or favored by, pregnancy, and specific differential concerns regarding treatment of mother and fetus. This chapter will review the subject from these vantage points, organized by topic and cause, e.g., vascular and hematological (including eclampsia), seizures, metabolic disorders, endocrine abnormalities, infections, organ-specific failures, hydrocephalus, drugs, and trauma.

17.1. Overview of coma in pregnancy

In common with coma in any age group and either sex, the state of eyes-closed unconsciousness can be brought about by structural involvement of midline brainstem arousal systems or widespread bihemispheric structural or functional disorganization. Diffuse central nervous system (CNS) disruption by toxic–metabolic infectious or ictal disorders may occur in pregnancy as it may in the nonpregnant state. The immediate challenges include stabilization of vital systems (e.g., **A**irway, **B**reathing, **C**irculation), while initiating investigation into the cause. For the most part, the critical nature of a comatose state almost always overshadows concerns regarding the morbidity of investigations that would otherwise be important in the awake and stable pregnant woman. For example, management of headache would rarely involve head computed tomography (CT) scanning, and even head magnetic resonance imaging (MRI) is often avoided. Conversely, in coma with pregnancy, the high morbidity and mortality mandate rapid and precise investigation of cause and virtually no investigation would be categorically denied (e.g., spiral CT, invasive cerebral angiogram, even brain biopsy). When the mother's life is at stake from a potentially reversible cause of coma, priority is routinely accorded to the mother's rather than the fetus's life. Intensive, potentially morbid investigation would, therefore, be undertaken to save the mother even at great risk to the fetus. Table 17.1 lists the more frequent causes of coma in pregnancy.

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Table 17.1

Causes of coma in pregnancy

Head and abdominal trauma
Thrombotic-ischemic stroke
Antiphospholipid antibody syndrome
Cerebral venous sinus thrombosis
Deep cerebral venous thrombosis
Postpartum cerebral angiopathy
Carotid and vertebral artery dissection
Amniotic fluid embolism
Air embolism
Subdural hematomas
Moyamoya disease
Cerebral vascular malformations and aneurysms
Pre-eclampsia/eclampsia
Subarachnoid hemorrhage
Coagulopathies during pregnancy
Hemolysis, elevated liver function tests, and low platelets (HELLP syndrome)
Thrombotic thrombocytopenic purpura (TTP)
Choriocarcinoma
Seizures and status epilepticus
Drug toxicity in pregnancy
Metabolic causes of coma
Hyperglycemia
Hypoglycemia
Wernicke's encephalopathy
Acute intermittent porphyria
Endocrine disturbances in pregnancy
Sheehan's syndrome
Pheochromocytoma
Infections and infestations
Maternal hydrocephalus in pregnancy
Organ-specific decompensations
Cardiac abnormalities
Peripartum cardiomyopathy
Acute renal failure
Acute fulminant liver failure
Acute fatty liver of pregnancy (AFLP)
Pulmonary disease and failure in pregnancy
Venous air embolus
Toxic pulmonary edema
Congenital pulmonary abnormalities

17.2. Vascular and hematological complications of pregnancy

17.2.1. Stroke in pregnancy

Stroke often encompasses bland cerebral infarction with intracranial hemorrhages, whether intracerebral, subdural, or epidural. Previous literature cites incidence rates for ischemic strokes with pregnancy or in the puerperium ranging from 5 to 210 per 100 000 deliveries (Huggenberg and Kesselring, 1958; Barnes and Abbott, 1961; Lorincz and Moore, 1962; Goldman et al., 1964; Carroll et al., 1966; Cross et al., 1968; Amias, 1970; Srinavasan, 1983; Simolke et al., 1991). Using a mean incidence of 1 cerebral infarction per 3000 pregnancies, derived from prior series, and the Rochester, Minnesota Data Bank incidence of 3.5 ischemic strokes per 100 000 population, the likelihood of cerebral infarction was estimated to be 13 times the risk in the nonpregnant woman (Wiebers, 1985). Shortcomings of this approach were the use of estimates from series of pregnancies at single-referral academic institutions, with their attendant selection bias. More recent estimates by Sharshar et al. (1995) are derived from public maternity units, some of which belong to academic hospitals. Further, studies conducted prior to 1965 assumed that cerebral ischemia was due only to cerebral infarction and did not necessarily distinguish among bland stroke, intracerebral, and subarachnoid hemorrhages. A retrospective review coupled with prospective study in 63 public maternity units (accounting for 348 295 deliveries) uncovered an incidence of 4.3 per 100 000 deliveries of nonhemorrhagic strokes in women (95% confidence interval, 2.4–7.1) (Sharshar et al., 1995). Nonetheless, recent data suggest that pregnancy does not significantly increase the risk of nonhemorrhagic stroke (Wiebers and Whisnant, 1979; Awada et al., 1995; Grosset et al., 1995; Lidegaard, 1995; Sharshar et al., 1995; Jeng et al., 2004).

Kittner et al. (1996) and Sharshar et al. (1995) speculate that specific causes of stroke include rapid hormonal changes in the postpartum period and significant falls in blood volume, resulting in cerebral infarction. The great majority are due to arterial occlusions, accounting for 60–80% of ischemic strokes (Wiebers, 1985), which predominate from the second trimester through the first week postpartum. The first month postpartum is the period of greatest risk for intracranial venous thrombosis (Wiebers, 1985; Grosset et al., 1995). Eclampsia and chronic hypertension also favor intracranial hemorrhages. Stroke in pregnancy increases the maternal death risk by 8.5% (Biller and Adams, 1986). As noted in Table 17.2, rarer causes of stroke include pituitary apoplexy, intracranial tumors, abscess, systemic lupus erythematosus, demyelinating disease, thrombocytopenic purpura, and inflammatory processes. Some other pregnancy-specific etiologies include amniotic fluid embolism (Donaldson, 1989), peripartum cardiomyopathy (Homans, 1985), and postpartum cerebral angiopathy. Other changes in the last trimester and first weeks of pregnancy include hypercoaguable states, with rises in clotting factors VII, VIII, IX, and X, fibrinogen, and plasminogen and falls in antithrombin III, protein C, and protein S (Schafer,

Table 17.2

Causes of stroke in pregnancy

- I. Arterial occlusive disease
  - A. Thrombotic cause
    1. Atherosclerotic
    2. Fibromuscular dysplasia
    3. Arterial dissection
    4. Homocystinuria
    5. Moyamoya disease
  - B. Embolic source
    1. Cardiac
       a. Peripartum cardiomyopathy
       b. Mitral valve prolapse
       c. Rheumatic heart disease
       d. Endocarditis (bacterial and non-bacterial)
       e. Paradoxical embolus
       f. Atrial fibrillation
- II. Peripartum cerebral angiopathy
- III. Cerebral venous and sinus thrombosis
  - A. Hypercoagulable state
  - B. Infectious
- IV. Drug abuse: cocaine and others
- V. Hypotensive disorders
  - A. Watershed infarction
  - B. Sheehan's pituitary necrosis
- VI. Hematological disorders
  - A. Lupus anticoagulant
  - B. Thrombocytopenic purpura
  - C. Sickle cell disease
  - D. Protein C, protein S, antithrombin III deficiency
- VII. Arteritis
  - A. Systemic lupus erythematosus
  - B. Infectious arteritis (syphilis, tuberculosis, meningococcal)
  - C. Cerebral angitis
  - D. Takayasu's arteritis
- VIII. Intracerebral hemorrhage
  - A. Eclampsia and hypertensive disorders
  - B. Venous thrombosis
  - C. Metastatic choriocarcinoma
  - D. Arteriovenous malformation
  - E. Vasculitis
  - F. Cocaine abuse
- IX. Subarachnoid hemorrhage
  - A. Aneurysm (saccular, mycotic)
  - B. Arteriovenous malformation
  - C. Eclampsia
  - D. Vasculitis
  - E. Metastatic choriocarcinoma
  - F. Venous thrombosis
  - G. Cocaine abuse
- X. Other
  - A. Carotid cavernosus fistula
  - B. Dural vascular malformation

Based on Digre and Varner (1993) and Donaldson (1991) with permission.

1985; Finley, 1989; Knepper and Giuliani, 1995). Estrogens may increase blood viscosity (Schafer, 1985). Thrombus formation is also promoted by a rise in cardiac output of 30–50% and of blood volume during pregnancy. A review of these findings is given by Bódis et al. (1998). Table 17.2 outlines the causes of stroke in pregnancy (from Donaldson, 1991; Digre and Varner, 1993; Bódis et al., 1998).

High altitude may also increase blood viscosity but the clinical effects of this, and whether there is an increased risk of stroke, is unknown (Kametas et al., 2004). Pregnancy at high altitude may be associated with intrauterine growth restriction and pre-eclampsia. At sea level, these have been linked to increased hematocrit and blood viscosity.

Stroke may induce coma by involvement of brainstem structures or by means of bilateral cerebral hemisphere involvement directly or with consequent edema. There may be further transtentorial or brainstem herniation contributing to coma. Investigation typically involves head CT or MRI imaging and investigation of the cause of stroke (e.g., cardiac echo, carotid duplex, coagulopathy studies).

17.2.2. Antiphospholipid antibody syndrome

Previously known as the lupus anticoagulant or anticardiolipin antibodies, the 'antiphospholipid syndrome' is seen with recurrent venous thromboses of limbs and organ systems as well as with cerebral artery occlusions. The syndrome may result in recurrent abortions with fetal death, and with severe pre-eclampsia. Similar to the pathogenesis of pre-eclampsia–eclampsia, endothelial damage, platelet activation, and thromboxane-mediated vasoconstriction as well as platelet activation and inhibition of protein C–protein S and antithrombin III activity have been invoked (Huong et al., 1993).

It may present with any cerebral infarction pattern of thrombotic occlusion, cerebral venous occlusion, recurrent pregnancy loss, or thrombocytopenia. These may involve encephalopathy, raised intracerebral pressure, migraine-like headache, ischemic optic neuropathy, amauroses, or other ocular events. It is an unusual hypercoagulable state affecting arterial and venous systems.

At least three antibodies have been implicated: lupus anticoagulant, anticardiolipin antibody, and anti-B_2 glycoprotein I. Typical screening assays are the Russell viper venom titer, kaolin clotting time, and partial thromboplastin time.

Thrombosis is treated with long-term anticoagulation, occasionally also with immunosuppression with corticosteroids.

17.2.3. Cardiac causes of stroke in pregnancy

17.2.3.1. Peripartum cardiomyopathy

It is not clear if peripartum cardiomyopathy is specific to pregnancy or appears because of physiological stresses during pregnancy. It is defined as an unexplained cardiac failure in the period ranging from the last month of pregnancy through the first 5 months postpartum. It may cause coma through global cerebral hypoperfusion or by strokes (see section 17.2.1). With a high mortality and high recurrence rate in subsequent pregnancies (Elkayam et al., 2001; Fett, 2002), the prevalence is 1 per 3000–4000 pregnancies in the USA but rises to one in 350 pregnancies in Haiti. The cause has not been clearly established, but autoimmune mechanisms and viral infections have been implicated. The thromboembolic mechanism involves a fall in ejection fraction, predisposing to thrombus formation in the left ventricle and hence embolic stroke, which may affect up to 10% of patients (Carroll et al., 1966; Simolke et al., 1991). With pregnancy-induced risks for venous thrombosis and the raised endothoracic pressure from Valsalva maneuvers during labor and delivery (Kozelj et al., 1999), there may be routing of an embolism, paradoxically through a patent foramen ovale.

Clinical presentations are as loss of consciousness or as an embolic stroke. Investigation is with a cardiac echo. Treatment involves anticoagulation.

17.2.3.2. Heart valve abnormalities

Cardioembolic strokes are a common cause in pregnancy and the puerperium of stroke and hence, occasionally, of coma (Jaigobin and Silver, 2000; Witlin et al., 2000). Prosthetic heart valves or chronic atrial fibrillation are recognized causes of cardioembolic stroke during pregnancy, peripartum, and the postpartum period. Women with cardiac abnormalities such as tetralogy of Fallot may be at increased risk of fetal loss and may pass on congenital abnormalities to their offspring. There may be left ventricular dysfunction, severe pulmonary hypertension, and pulmonic regurgitation with right ventricular dysfunction with sudden cardiac death (Veldtman et al., 2004). Although rare, it carries a mortality of up to 50% (Dias and Sekhar, 1990).

Another mechanism is the generation of thrombi in the pelvis and peripheral veins, which can result in pulmonary emboli. With the Valsalva efforts during childbirth, there is a resultant rise in right atrial pressure that may open an otherwise physiologically closed foramen ovale, permitting thrombus propagation to the lung.

Diagnosis involves echocardiography and, often, anticoagulation.

17.2.4. Cerebral venous thrombosis

Cerebral venous thrombosis consists of occlusion of cerebral veins resulting in pressure back-up that leads to cerebral edema and decreases anterograde arterial circulation and thus brain tissue perfusion. This can result in bland, ischemic infarcts with variable hemorrhagic transformation. Infarction is in the distribution of venous drainage and not, therefore, of a classic arterial pattern, a clue to the diagnosis. Presentation is usually acute but may occasionally be more insidious. There may be acute neurological deficits and seizures. When not presenting with catastrophic stroke (and hence coma), some present with intense headache and papilledema, resembling pseudotumor cerebri. Occasionally, psychosis and encephalopathy are presenting features. In addition to coma, akinetic mutism has been reported. One large series cites headache in 82%, papilledema in 56%, focal deficits in 42%, seizures in 39%, and coma in 31% (Biousse and Bousser, 1999). Exact causes are unknown but abnormalities encountered include increased fibrinogen and platelet adhesiveness and a fall in fibrinolytic activity and platelet count, although other studies failed to replicate these findings. Causes of venous sinus thrombosis are given in Table 17.3. Cerebral venous thrombosis may also be caused by pressure on the sagittal sinus, prothrombotic states, dehydration, or trauma and, more rarely, factor V Leiden, sickle cell disease, prothrombin mutations, antiphospholipid antibody syndrome, antithrombin III deficiency, and resistance to activated protein C (Biousse and Bousser, 1999). These hypercoaguable factors predispose to venous thrombosis rather than arterial clot. The process may affect cortical veins, the sagittal, petrosal, straight, or transverse sinuses and also cause CNS hemorrhage. Imaging with MRI or CT may reveal clot within the confluence of sinuses producing a bright triangle or ‘delta sign’ on

Table 17.3

Possible causes of cerebral venous thrombosis

Dehydration
Sepsis
Trauma
Eclampsia
Antithrombin III, protein C or S, factor V Leiden deficiencies
Leiden mutation
Sickle cell disease
Antiphospholipid antibodies
Parenchymal nocturnal hemoglobinuria
Prothrombinase gene mutation
Hemocystinuria

MRI. MRI and CT venograms now facilitate diagnosis but the 'gold standard' remains conventional angiography (Biousse and Bousser, 1999).

With a clear diagnosis, heparin has been used in a randomized prospective trial where eight of 20 patients recovered completely, while there were three deaths in the placebo group and only one complete recovery (Einhaupl et al., 1991). There is an absolute risk reduction of 70% with heparin (de Bruijn et al., 1999).

Newer techniques using vacuum catheters and recombinant tissue plasminogen activator administered endovascularly produce more rapid unblocking of occlusion than systemic anticoagulation. In one series, 80% of patients were living independently at 3 years although residual problems included headaches, weakness, visual field defects, and seizures (Breteau et al., 2003).

The deep venous system includes internal cerebral veins and basal veins (vein of Rosenthal) or the great cerebral vein (of Galen), which collect blood passing through the walls of the ventricles and basal cisterns, converging on the internal cerebral, basal, and great veins, draining the choroid plexi, striatum, thalamus, corpus callosum, periventricular white matter, limbic system, diencephalon, cerebellum and rostral brainstem, and the occipital lobe. Hence, thrombosis of this deep venous system precipitates severe diencephalic disturbance with confusion or coma with long tract signs or coma associated with abnormal pupillary reflexes and eye movements. The outcome is often long-term sequelae or death (Ameri and Bousser, 1992).

Radiological features show ischemia involving limbic structures, the visual cortex and sparing of the subcortical white matter. Paramedian bilateral arterial infarcts may occur with venous congestion producing irregular borders rather than the sharper margin of arterial infarction. Diffusion-weighted MRI will reveal cerebral venous congestion with hemorrhage appearing to spread from the midline, outwards. MR angiography/venography may distinguish deep cerebral venous thrombosis from bithalamic lesions due to other causes (Bell et al., 1994).

Treatment involves intravenous unfractionated heparin followed by oral anticoagulation for 6 months or longer (Ameri and Bousser et al., 1992). However, cerebral venous thrombosis is usually multifactorial, prompting further investigation and treatment of other underlying causes, e.g., inherited or acquired thrombophilia.

In a cohort of 624 cerebral venous thrombosis patients, prognosis was better than previous reports, with 8% deaths. Worse prognosis occurred in males, coma, age >37 years, intracranial hemorrhage and infection, or cancer (Ferro et al., 2004).

17.2.5. Postpartum cerebral angiopathy

Postpartum cerebral angiopathy typically represents a reversible narrowing of large and medium-sized cerebral arteries occurring in pregnancy and the puerperium. Although characterized as benign, there may be nonhemorrhagic strokes and/or intracranial hemorrhages (Geocadin et al., 2002). The mechanism of vasospasm has not been fully elucidated but intimal hyperplasia, circulating endothelial factors, and sympathomimetic medications have been implicated (Geraghty et al., 1991; Singhal, 2004). Postpartum cerebral angiopathy typically appears after a normal pregnancy (in contrast to pre-eclampsia/eclampsia) and is defined as a reversible clinicoradiological syndrome of a posterior watershed leukoencephalopathy usually associated with hypertension, similar to a syndrome seen outside of pregnancy under a number of names (Blecic et al., 1993). Case reports note therapeutic benefit from magnesium, steroids, and relative hypertension (Garner et al., 1990; Ursell et al., 1998; Singhal, 2004). The literature often does not clearly differentiate postpartum cerebral angiopathy from postpartum, unheralded eclampsia. Postpartum cerebral angiopathy is distinguished from hypertensive watershed infarcts by its reversibility (Ferro et al., 2004).

17.2.6. Amniotic fluid embolism

Amniotic fluid embolism is a highly morbid, albeit rare cause of stroke, causing up to 30% of maternal deaths (Tuffnell, 2003). Amniotic fluid embolism is produced by amniotic fluid trapped in uterine veins that is subsequently forced into the maternal circulation, producing acute hemodynamic collapse. This in turn produces disseminated intravascular coagulopathy (DIC) which may induce focal cerebral hypoperfusion, thrombosis, or hemorrhage, and focal neurological signs. Rarely, amniotic fluid embolism may pass via a patent foramen ovale.

With air embolism, pulmonary and cardiovascular symptoms predominate. In addition to the focal deficits seen with amniotic fluid embolism, there may be direct arterial blockage by bubbles of air, entering the venous circulation usually during cesarean section delivery. Cardiovascular collapse is induced by pulmonary capillary occlusion but larger bubbles may pass to the brain via pulmonary or cardiac shunts to cause stroke (Muth and Shank, 2000).

17.2.7. Cerebral vascular malformations and aneurysms

Cerebral angiomata may rupture during pregnancy causing coma but there are reports of complete

regression (De Wilde et al., 1987). In a series of 32 cases, the authors determined that the relative frequencies of arteriovascular malformations (AVMs) and arterial aneurysms was the same for pregnant and nonpregnant women (Velut et al., 2000). Pregnancy does not increase the risk of first bleeding of AVMs but the risk of re-bleeding is increased (Velut et al., 2000). Vascular malformations are more likely to bleed because of age rather than parity, with the mean maternal age at rupture greater for arterial aneurysms than for AVMs, as it is in the general population. AVMs rupture more frequently in the second and third trimesters, while labor and delivery are not particularly high-risk periods.

Diagnosis is established with head CT angiography or MRI angiography. Treatment usually involves surgical clipping or endovascular coiling of the aneurysm. Some authors suggest that ruptured arterial aneurysm or AVM be managed as in nonpregnant women, and that no fetal extraction is warranted unless it occurs at the very end of pregnancy (Velut et al., 2000). Nonruptured AVMs are treated after delivery and managed in the same way as a nonruptured arterial aneurysm.

17.2.8. Subarachnoid hemorrhage

Subarachnoid hemorrhage is usually caused by rupture of an aneurysm or AVM allowing blood under pressure to pass into the subarachnoid space. Presenting symptoms usually are severe headache, vomiting, focal neurological signs, neck stiffness, and coma.

Aneurysmal subarachnoid hemorrhage accounts for about 4% of all maternal deaths. Over a 23-year period, it was third among nonobstetric causes. In a series of 37 patients, pregnancy per se had no effect upon the occurrence of hemorrhage (Barno and Freeman, 1976). Conversely, others have repeated a fivefold increase in the rupture of intracranial aneurysms during pregnancy (Wiebers, 1988) and a fourfold increase in hemorrhage rate from AVM (Robinson et al., 1974). Over a 10 year period in England and Wales it was found to be a leading cause of other indirect maternal death (60 patients) (Selo-Ojeme et al., 2004). The incidence of rupture of cerebral aneurysms increases throughout pregnancy and early into the postpartum period, reaching a maximum of 55% in the third trimester (Kittner et al., 1996).

Subarachnoid hemorrhage from ruptured intracranial aneurysms in pregnancy (Mosiewicz et al., 2001) can be successfully managed by clipping or coiling, allowing the pregnancy to proceed to term. With coma or brainstem damage, cesarean section may be necessary. There are no differences in the clinical course of subarachnoid hemorrhage between pregnant and nonpregnant patients, but subarachnoid hemorrhage during pregnancy may be confused with eclampsia (Mosiewicz et al., 2001).

17.2.9. Choriocarcinoma

Metastatic choriocarcinoma is a rare cause of subarachnoid, subdural, or intracerebral hemorrhage (Weir et al., 1978). It is induced by trophoblastic invasion of blood vessels resulting in aneurysmal dilatation and rupture. A diagnostic aid is the elevated level of beta-human chorionic gonadotropin (β-hCG). It appears in 1 in 50 000 pregnancies and in 1 in 30 in other pregnancies, and often produces brain metastases (Fox et al., 1990).

17.2.10. Rarer causes of intracranial hemorrhage

Other rare causes of intracerebral hemorrhage include drug-abuse-induced DIC, septic emboli, bleeding diatheses, and moyamoya disease.

17.2.10.1. Subdural hematomas

Subdural hematomas are usually seen after head trauma, often in anticoagulated patients, e.g., in patients with artificial heart valves.

Occasionally, intracranial subdural hematomas may be a life-threatening complication of spinal anesthesia (Yildirim et al., 2005). Postpartum cerebral angiopathy should be considered the differential diagnosis of recurrent intracranial hemorrhagic stroke in young women (Ursell et al., 1998).

17.2.10.2. Moyamoya disease

Moyamoya in Japanese means ‘puff of smoke’. It is produced in response to large vessel cerebral occlusions, presenting with unilateral or bilateral carotid stenosis. In compensation, collateral vessels form into a myriad of small vessels with a tangled appearance producing the angiographic appearance of a ‘puff of smoke’.

More than 50 times more likely to occur in women, it also favors those on oral contraceptives and those who smoke. Presenting features include seizures, intracerebral hemorrhages, and bland infarctions, as well as headaches. Diagnosis is made by the typical angiographic appearance. The etiology of hemorrhage is the aneurysmal thinning of blood vessels in the setting of atherosclerotic disease. Although bland strokes are more common in children, hemorrhages occur more frequently in adults. Treatment with warfarin or aspirin increases the risk of hemorrhage. Encephalomyosynangiosis surgery may improve cerebral perfusion and neurological function, but not morbidity or mortality, in a small number of patients (Wityk et al., 2002).

Moyamoya disease has been described as worsening in the third trimester of pregnancy, presenting with intracranial hemorrhage. An underlying risk factor is hypertension. Komiyama et al. reported 30 pregnant women patients with moyamoya disease, four with transient cerebral ischemia but all with full recoveries. There was one intraventricular hemorrhage at 30 weeks gestation, with poor outcome. Some patients with moyamoya may have vaginal deliveries without neurological sequelae (Komiyama et al., 1998). Pregnant patients with moyamoya are optimally delivered by cesarean section, thus preventing hyperventilation-induced cerebral ischemia and hypertension during labor. In effect, hyperventilation, hypoventilation, hypercapnia, and hypothermia must all be avoided (Williams et al., 2000).

17.3. Evaluation of stroke in pregnancy

The diagnostic evaluation of stroke in pregnancy is similar to that of the nonpregnant woman. With shielding of the uterus, head CT produces a uterine exposure of <1 mrad, below the threshold that would cause fetal harm (Schwartz, 2002). Animal studies have failed to show damage to fetuses from MRI scanning, but some studies (Tyndall and Sulik, 1991) uncovered ocular abnormalities at twice the expected rate when MRI was used during mid-gestation. Other mice studies (Heinrichs et al., 1988) showed a decreased fetal crown–rump length, but no such findings have yet been found in humans. A clinical consensus indicates that magnetic resonance angiography and venography may be safe in late pregnancy but possibly dangerous in the first two trimesters. Gadolinium crosses the placenta, with unknown effects. For diagnosing vasculitis and cerebral venous thrombosis, conventional angiography is essential. It may also uncover aneurysms underlying subarachnoid hemorrhage and offers a nonsurgical option for ruptured aneurysms (Schwartz, 2002). Angiography also exposes the fetus to <1 mrad if carefully performed. Intravenous contrast with iodine has a slight risk of fetal hypothyroidism when used in the third trimester (Mas and Lanny, 1998).

Echocardiography may uncover a patent foramen ovale or right to left shunt (Mas and Lanny, 1998).

There has been an evolution in the surgical thinking of the treatment of intracranial hemorrhage during pregnancy. Previously, bed rest followed by surgery after delivery was favored. More recently, surgical intervention has been more active, treating the ruptured hemorrhage during pregnancy. Current thinking suggests that rupture of AVM or aneurysm during pregnancy should be treated no differently from the nonpregnant state, with intervention based on neurosurgical criteria. With Hunt and Hess grades I–III, immediate surgical intervention is recommended, avoiding hypotensive therapy. Hypothermia has been used safely. Many surgeons favor treating asymptomatic aneurysms only if they are above 7 mm. Contemporary neurosurgical approach to AVM rupture involves resection of accessible lesions on the premise that morbidity is lower from surgery than the risk of bleed. Conversely, others favor waiting because the bleeding risk from AVMs is lower than that of aneurysms. Despite these concerns for lesion rupture, vaginal delivery is still advocated unless obstetric indications exist for cesarean section. When surgery occurs before the third trimester, vaginal delivery is often attempted. If, however, the bleed occurs in the second trimester, cesarean section may be performed followed by surgical intervention. Treatment of raised intracranial pressure may involve corticosteroids, and diuretics are generally avoided. Similarly, mannitol may be passed through to the fetus. Vasospasm has been managed successfully with hypervolemic treatment and hypertension. There is concern with the use of nicardipine and nimodipine (calcium channel blockers) to decrease vasospasm, because of fetal acidosis and hypoperfusion, with teratogenicity demonstrated in animals (Dias and Sekhar, 1990).

17.4. Pre-eclampsia/eclampsia

17.4.1. Definition

Pre-eclampsia is defined by pregnancy-associated hypertension and proteinuria, often with arm or facial edema. Hypertension characterizes pre-eclampsia. Hypertension may be 'relative', as blood pressures that would not be alarming in an older population may result in cerebral ischemia, edema, hemorrhage, or vasospasm. Even modest increases in blood pressure (e.g., 140/70 mmHg) have been implicated. More recently, absolute measurements of at least 140/90 mmHg 6 hours apart define hypertension (American College of Obstetrics and Gynecology, 2002). Sheehan and Lynch (1973) noted that about 50% of patients had convulsions with systemic blood pressures between 160 and 195 mmHg. Proteinuria is defined as a urinary protein exceeding 300 mg/24 h or 30/dl on urine sample (American College of Obstetrics and Gynecology, 2002). The pathological edema typically involves the face and upper limbs, unlike that usually seen in pregnancy, which confines itself to the ankles. Severe pre-eclampsia is present when one of the following features occurs: 1) blood pressure ≥160 mmHg systolic or ≥110 mmHg diastolic on two occasions at least 6 hours apart during bedrest; 2) proteinuria >5 g/24 hours or 3^{+}–4^{+} by dipstick; 3) urine output <400 ml/d; 4) thrombocytopenia or hemolysis; 5) cyanosis or pulmonary

edema; 6) upper quadrant pain; or 7) cerebral dysfunction/visual disturbances (American College of Obstetrics and Gynecology, 2002).

All features of the triad may not be universally present to make the diagnosis. The defining feature of eclampsia is the appearance of a convulsion or coma, and it may not be correlated with the severity, or indeed the presence, of all three features of pre-eclampsia. Seizures may occur in the absence of edema, proteinuria, or even with mild hypertension, and up to 20% of patients may lack one of the cardinal features (Porapakkam, 1983).

Eclampsia has an incidence of 0.05–0.20% in developed countries, rising to 1% in developing countries, and is a leading cause of maternal death (Sibai, 1989). In pre-eclampsia a typical triad of hypertension, proteinuria, and edema define the condition. A number of systemic disorders may accompany the syndrome: pulmonary edema, hepatic dysfunction, oliguria, hemoconcentration, and thrombocytopenia with and without coagulopathy. The neurological manifestations, in addition to headache, include confusion, visual disturbances, raised intracranial pressure with cerebral edema, infarction, and hemorrhage. Eclampsia is present when seizures or coma supervene, usually with some of the heralding features of pre-eclampsia (Cunningham et al., 1993; Douglas and Redman, 1994).

Although there are many purported mechanisms thought to underlie eclampsia, more recent work centers on three: 1) hematological abnormalities with vascular damage activation by neutrophils, macrophages, and T-cell lymphocytes interacting with platelets, complement, and the coagulation system; 2) endothelial damage from impaired prostaglandin metabolism; and 3) arterial or vasospasm (Roberts and Redman, 1993; Sibai et al., 1995; Easton et al., 1998). Consequent neuropathological changes may involve cortical, subcortical, and brainstem regions with small, medium, and large hemorrhages, bland infarcts from vasospasm, and cerebral edema that favors the posterior more than the anterior watershed zones (Sheehan and Lynch, 1973; Donaldson, 1989). MRI and CT head scans may demonstrate these pathologies (Raroque et al., 1980; Crawford et al., 1985; Schwartz et al., 1992; Sibai, 1992).

Eclampsia may be classified according to time of presentation. If seizures occur before labor, it is antepartum; if seizures appear before 28 weeks gestation, then it is early antepartum eclampsia. Intrapartum eclampsia represents seizures after labor has started, while postpartum eclampsia refers to convulsions after delivery of the fetus and placenta. Several large series attest to the fact that eclamptic seizures not infrequently occur postpartum. In one series, 44% were postpartum, 12% after the first 48 hours, and 2% more than a week after delivery (Douglas and Redman, 1994). Another series describes 48% of patients with postpartum eclampsia after 48 hours (Sibai, 1989). Postpartum eclampsia carries a worse prognosis and is often accompanied by adult respiratory distress syndrome and DIC (Phelan, 1991).

17.4.2. Pathophysiology

CNS damage largely arises from the loss of cerebral autoregulation of blood pressure. When the autoregulatory curve and plateau have been exceeded, there is loss of vasoreactive protective effects. This is thought to affect the posterior watershed zone in particular because of a deficient sympathetic nervous system investing the basilar artery circulation (Sheehan and Lynch, 1973; Will et al., 1987; Call et al., 1988; Garner et al., 1990; Qureshi et al., 1996; Schobel et al., 1996; Naidu et al., 1997; Williams and Wilson, 1999; Zunker et al., 2000). Hypertensive changes are transferred to extravascular tissues in the form of hypertensive exudation through vessel walls, hemorrhage, and edema. This may be further complicated by vasospasm. Abnormalities of the coagulation cascade may also cause DIC and bleeding diatheses. HELLP is a frequent, highly morbid confounder of pre-eclampsia/eclampsia (Sullivan et al., 1994; Sibai et al., 1995; Barton and Sibai, 1996; Isler et al., 1999).

In eclamptic pregnancies, there is thought to be a faulty transformation of the placental vascular system. In pre-eclampsia, the cytotrophoblastic migration through the decidua to the inner third of the myometrium fails and there is lack of transformation of the spiral arteries to a pregnant 'low-pressure' system. Further, mitochondrial defects may underlie the impaired invasion (Widschwendter et al., 1998). This uteroplacental arterial insufficiency leads to release of inflammatory factors and cytokine production among producing signals that excite a generalized maternal inflammatory response. These factors are thought to interfere with the usual downregulation of the immune system that normally keeps inflammatory reactions at bay, part of the dynamic referred to as the 'maternal–fetal genetic conflict' (Haig, 1993). One such neuropeptide, neurokinin B, may have a striking pressor effect and is elevated in pre-eclampsia and pregnancy-induced hypertension (Page et al., 2000).

17.4.3. Neurological clinical features

Seizures may start focally but typically become generalized in the form of a convulsion. There may be psychosis, strokes, paralysis, aphasia, coma, and blindness. Raised intracranial pressure results in a clinical and

radiological picture of hypertensive encephalopathy, with posterior leukoencephalopathy. Imaging may show infarction, edema, hemorrhage, and evidence of herniation or hydrocephalus. Hemorrhagic lesions range from the small punctate to large hematomas, affecting the cortical mantle, subcortical white matter, and deeper intracerebral structures. The typical serpiginous subcortical white matter edema has a predilection for the posterior watershed zone and the tips of the occipital lobe (Digre and Varner, 1993). It may also affect the interior watershed zone. Cerebral edema is largely reversible with resolution of the process, occurring typically within days, but larger hemorrhages clearly may lead to permanent sequelae. Following seizures, the patient may have a severe headache (Sibai et al., 1995; Qureshi et al., 1996; Naidu et al., 1997).

17.4.4. Investigation

With focal neurological signs, imaging is important to provide information on which of the many pathological processes produced by eclampsia is at play. For example, whether edema or bland infarction are occurring, or conversely whether small or large hemorrhages are present. Urine testing may reveal proteinuria, electrolytes may show raised uric acid levels, blood smear may reveal abnormal red blood cells and chest X-ray show pulmonary edema or adult respiratory distress syndrome.

17.4.5. Management

The cornerstone to management is aggressive treatment of hypertension, usually managed by obstetricians but occasionally necessitating management in an intensive care unit. Agents typically used have included hydralazine, labetalol, and nifedipine. Magnesium sulfate has demonstrated effect in forestalling recurrent seizures and reversing the presumed vasospastic process, without strictly speaking acting as an anticonvulsant. The Eclampsia Trial Collaborative Group (1995) compared the recurrence rate of seizures in 1682 women with eclampsia in the developing world. One arm provided diazepam as an intravenous bolus of 10 mg over 2 minutes followed by infusion of 40 mg and 500 ml normal saline over 24 hours. Phenytoin was given intravenously as a 1 g load followed by 100 mg every 6 h for 24 h. This study showed a 52% lower incidence of recurrent seizures after magnesium sulfate compared to diazepam. There was a 67% decrease with magnesium sulfate compared to phenytoin. The Parkland Memorial Trial revealed that 10 of 1089 pre-eclamptic women treated with phenytoin had a seizure (Pritchard et al., 1984), while none of 1049 patients on magnesium sulfate had a seizure (Lucas et al., 1995), but women included in the study largely had pregnancy-induced hypertension without other signs of pre-eclampsia, and phenytoin levels were in the sub- or low therapeutic range.

17.4.6. Prognosis

When untreated, about 10% of eclamptic women have repeated seizures. Intracerebral hemorrhage leads to 15–20% of deaths from eclampsia, usually with hypertension. Recurrent eclampsia may occur in up to 21% of women (Chesley et al., 1976; Sibai et al., 1985; Sibai et al., 1986; Douglas and Redman, 1994; Lamy et al., 1996; Lanska and Kryscio, 1998).

17.5. Seizures and status epilepticus

Secondarily generalized seizures and, much more infrequently, idiopathic generalized seizures may evolve into status epilepticus, in which seizure activity is said to be present for at least 30 min without return to cognitive baseline. Because of the high morbidity of the condition, many advocate diagnosing status epilepticus after only 20, 10, or even 5 min (Lowenstein et al., 1999).

The effect of pregnancy on seizure control in women with epilepsy is highly variable. Epidemiological studies have revealed an increase in seizure frequency in some, a decrease in others, and no significant variation in most. A slight tendency towards increased seizures in patients with poor seizure control has been noted, while patients with infrequent seizures (i.e., <1/year) may see no aggravation (Schmidt, 1982; Schmidt et al., 1983). Pregnancy diminishes therapeutic blood levels of most antiepileptic drugs by 50% in total concentration and somewhat lesser decrease for the unbound moiety. One exception is the increase in unbound valproate levels. Lamotrigine levels may decrease strikingly because of markedly enhanced clearance, even in early pregnancy (Pennell, 2003).

The highest morbidity in status epilepticus occurs with convulsive status epilepticus, with management directed towards immediate control of seizures while investigating the underlying causes. Because of the urgency in treating convulsive status epilepticus, the antiepileptic drug armamentarium generally used is the same, with use of diazepam, lorazepam, phenytoin, barbiturates, or anesthetic agents if necessary. Treatment in a neurological intensive care unit, preferably with EEG monitoring should seizures persist, offers optimal outcomes. The diagnosis and treatment of nonconvulsive status epilepticus, dependent on EEG for diagnosis, is less urgent, with treatment often being less ‘aggressive’ because of the lesser perceived morbidity. Lightly obtunded or confused patients can usually be managed

without barbiturates or anesthesia. Patients in coma either because of status epilepticus or in association with status epilepticus may warrant more vigorous therapy with intravenous agents. There is little evidence to suggest that any of these treatment modalities pose particular dangers to the fetus.

Seizures and status epilepticus may occur with a number of inciting etiologies. Frequent ones are the exacerbation of an underlying epilepsy, usually, as noted above, because of decrease in antiepileptic drug levels. Any new intracranial structural abnormality such as infarctions, hemorrhages, infections, abscess, tumors, and vascular malformations may also result in seizures and hence status epilepticus. Eclampsia is associated with hypertension (see above) and may have typical MRI imaging abnormalities showing watershed distribution, pontine or larger hemorrhages, and/or edema, which may involve the occipital lobes. Other clinical features may be present (see above). Outside the context of eclampsia, other causes should be sought with cerebral imaging, looking for a structural abnormality.

Prognosis for stopping seizures is good. Status epilepticus in general carries a worse prognosis with acute symptomatic causes and a better prognosis when due to antiepileptic drug noncompliance with epilepsy. Data specific to pregnancy are scant.

17.6. Coagulopathies during pregnancy

17.6.1. HELLP syndrome

Hemolysis, elevated liver function tests, and low platelets have been recognized for over 30 years as complications of pre-eclampsia/eclampsia. The HELLP syndrome was delineated by Weinstein in 1982 as an entity separate from severe pre-eclampsia. Current thinking about this entity varies from characterizing it as 'misdiagnosed pre-eclampsia' at one end to a 'unique variant' of pre-eclampsia/eclampsia on the other (Weinstein, 1982; MacKenna et al., 1983). There is no universal consensus regarding whether some or all of these components must be present, nor the degree of elevation or fall in individual tests to diagnose the syndrome. For thrombocytopenia, cut-off values range from 75 000/mm^3 to 279 000/mm^3. Many large series define platelet counts as being $<$100–150 000/mm^3; AST abnormality as being above 40–70 U/l; and LDH exceeding 600 U/l.

Some 30% of patients with eclampsia may develop HELLP postpartum; most within 48 hours, but some up to 7 days postpartum. An excellent overview with decision and treatment pathways is provided in Barton and Sibai, 2004.

Typical presenting complaints include right upper quadrant or epigastric pain, nausea and vomiting, and malaise. It characteristically affects older pregnant women, multiparous women, and patients with pre-eclampsia, usually before 31 weeks of pregnancy. There is usually marked weight gain and generalized edema. Many patients may show no evidence of absolute or relative hypertension (see pre-eclampsia/eclampsia). HELLP may be distinguished from acute fatty liver of pregnancy (AFLP) by the frequent absence of proteinuria. Additionally, liver function abnormalities are generally worse in HELLP.

A number of disorders enter the differential diagnosis for HELLP. Laboratory investigation should include complete blood count, coagulation work-up, peripheral smear, serum electrolytes, and liver function tests.

17.6.1.1. Pathophysiology

A microangiopathic hemolytic anemia with hemolysis is characteristic of HELLP, believed to arise from fibrin deposition on a damaged intima. Peripheral smears may reflect the presence of burr cells, echinocytes, triangular cells, and spherocytes. This microangiopathic hemolytic anemia may also be seen in other disorders such as renal disease, eclampsia, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura (TTP) (Barton and Sibai, 2004). HELLP is typically an afebrile illness with elevated liver enzymes, while TTP often has fever and targets the kidney. Hereditary TTP may be caused by homozygous or double heterozygous ADAMTS-13 deficiency. The typical pentad of clinical and laboratory TTP features include: microangiopathic hemolytic anemia with fragmented erythrocytes (schistocytes) in a peripheral blood smear, thrombocytopenia, renal dysfunction, fever, and usually fluctuating neurological signs and symptoms. It is thought that the intravascular platelet clumping with high shear stress in the microcirculation causes thrombocytopenia, ischemic renal, neurological and other organ dysfunction, and the fragmentation of red blood cells in partially obstructed capillaries and arterials.

Hemolytic–uremic syndrome (HUS) described in five children (Gasser et al., 1955) highly resembles TTP and, while TTP is diagnosed in adults predominantly with neurological symptoms, HUS is characterized in children with renal failure. Distinctions are not universally accepted and authors often refer to 'TTP/HUS'. HUS is often seen with hemorrhagic colitis from verocytotoxin-producing *Escherichia coli* and nowadays called diarrhea-positive or D-plus (Lämmle et al., 2005).

17.6.1.2. Management

HELLP syndrome often follows a fulminant course with rapid morbidity for mother and fetus warranting

urgent hospitalization and observation. Therapy is aimed at correcting the coagulopathy, treatment of hypertension, prophylaxis with magnesium sulfate and investigation of possible liver hematomas, if suspected. Appropriate evaluation of the fetus is essential, and women are often delivered if more than 34 weeks along in gestation. If less, then glucocorticoids may be administered followed by delivery within 2 days. There is no universal consensus, however, on these guidelines. There have been at least five randomized trials suggesting some improvement in hematological or hepatic picture (Barton and Sibai, 2004). Treatment also involves appropriate analgesia and platelet transfusions.

Referred pain to the shoulder may reflect a subcapsular hepatic hematoma. Treatment of subcapsular hematoma, if ruptured, may involve massive blood transfusions, along with treatment with fresh frozen plasma and/or platelet concentrates, close monitoring of hemodynamic status, intravenous magnesium sulfate and consultation with surgery. Vaginal delivery is usually possible. With cesarean section, platelet transfusion and subfascial drains, when appropriate, can decrease morbidity. Because a number of syndromes resemble each other, i.e., HELLP, AFLP, HUS, and TTP, complete evaluation is essential as optimal treatments for the individual problems vary.

In addition to eclampsia with HELLP syndrome, other hematological conditions including sickle cell disease, disseminated intravascular coagulation and TTP may be precipitated by pregnancy or appear in the postpartum period, and can recur in subsequent pregnancies (Pinewte et al., 1989).

17.6.2. Thrombotic thrombocytopenic purpura

TTP is a rare syndrome characterized by thrombocytopenia, microangiopathic hemolytic anemia, fever, renal dysfunction, and fluctuating neurological abnormalities. TTP peaks in the second to fourth decades and is associated with pregnancy, infections, autoimmune disorders, and malignancy. Some 10–25% of patients with TTP are pregnant or in the postpartum period (Ezra et al., 2004). The central phenomenon is that of systemic endothelial cell damage. The relationship between TTP and pregnancy is unclear and some believe that pregnancy precipitates TTP (Egerman et al., 1996; Ezra et al., 1996; Proia et al., 2002). Typically patients may present or be diagnosed during pregnancy or the postpartum period, while a second group has chronic relapsing forms of the disease, occasionally precipitated by pregnancy. Pregnancy does not adversely affect survival but preterm delivery and intrauterine fetal death from placental infarction are frequent complications. Coma is rarely encountered but lethargy and confusion may occur. In a series of 10 patients, one mother and a third of the fetuses died.

Hereditary TTP may have VWF-cp deficiency with the *ADANTS-13* gene, causing a severely deficient proteinase activity.

17.6.2.1. Treatment

Evidence of treatment effects for TTP are largely level IV (Allford et al., 2003). Plasma exchange and fresh frozen plasma replacement in the 1970s improved survival from 10% to 80%, probably prohibiting a randomized study with controls not receiving plasma therapy (Byrnes and Khurana, 1977). The number of plasmic exchange procedures and treatment duration varies greatly among patients. Other treatments have included vincristine, corticosteroids, and other immunosuppressive medications, occasionally with splenectomy in refractory and relapsing cases (Ruggenenti and Remuzzi, 1996; Moalke and Chow, 1998; George, 2000; Rock, 2000). Plasma-refractory TTP patients may be treated with more intensive plasmic exchange, e.g., twice daily (Veltman et al., 1995; Crowther et al., 1996; Aqui et al., 2003).

17.7. Metabolic causes of coma

17.7.1. Glucose derangements

Hyper- and hypoglycemia in the setting of diabetes and its treatment may occur in pregnancy and peripartum. Destablization of diabetes to the point of coma in pregnancy is rare but may arise from avoidance of medications because of concern by the mother of their effects on the fetus. Morning sickness leading to vomiting up medications and food, or pregnancy-induced alterations in insulin resistance, may also destabilize diabetes control. Vomiting and dehydration may lead to hypernatremia as well as hypochloremic alkalosis, while lower gastrointestinal dysfunction, profuse diarrhea, or even purgative abuse may lead to hypokalemia, cardiac dysrhythmia, and cerebral ischemic coma. Other electrolytic disturbances are even rarer (Evers et al., 2002).

Treatment principles follow those of diabetic hyper- or hypoglycemia.

17.7.2. Wernicke's encephalopathy

Wernicke's encephalopathy is characterized by confusion, eye movement disorders and nystagmus, ataxia, and occasionally coma. Hyperemesis gravidarum may deplete body thiamine stores even in a well-nourished woman in 3–6 weeks, and more rapidly in malnourished women or alcoholics. Wernicke's encephalopathy

may be precipitated by intravenous glucose. Rapid correction of hyponatremia may independently precipitate central pontine myelinolysis. Rapid, intravenous thiamine repletion is essential, and eye movement abnormalities may disappear within the day. With malabsorption, parenteral thiamine repletion daily for 7–10 days may be required (Lamon et al., 1979; Reuler et al., 1985; Fraser, 1988; Kaplan et al., 1988; Kanaan et al., 1989; Mumford, 1989; Donaldson, 1991).

17.7.3. Acute intermittent porphyria

Acute intermittent porphyria is due to an autosomally dominant inherited abnormality of heme biosynthesis with toxic accumulation of aminolevulinic acid and porphobilinogen.

Acute intermittent porphyria can be precipitated in women during menarche, perimenstrually and with pregnancy as well as by a number of porphyrinogenic drugs. Clinically, porphyric crises can produce acute axonal polyneuropathy with paralysis resembling Guillain–Barré syndrome, severe pain, autonomic dysfunction with tachycardia and constipation, and psychosis, occasionally with coma, often from seizures. Precipitants include fasting, surgery, or an acute febrile illness (Kaplan et al., 1988; Kanaan et al., 1989; Donaldson, 1991).

Treatment is aimed at reversing fever, stopping offending medications and treating with intravenous hematin to break the porphyric crisis. In pregnancy, both glucose and hematin therapy have been used in the acute therapy of acute intermittent porphyria. The manufacturers of hematin counsel against infusion in pregnancy. The effects of hematin in pregnancy are unknown (Lamon, 1979).

Seizures or status epilepticus during porphyric crises are best managed with benzodiazepines and chronically with the few antiepileptic drugs that do not precipitate porphyria, such as gabapentin, levetiracetam, or vigabatrin.

Prognosis for remission of the individual attack is good but recurrence is typical, often with accumulating neurological deficits.

17.7.4. Endocrine disturbances in pregnancy

Most underlying endocrine disorders predating pregnancy improve but some can worsen. Thyrotoxicosis may rarely decompensate, as may stress associated with pregnancy on an incipient Addisonian state, or a state of hyperadrenocorticalism (Cushing's disease and syndrome). Many moderate or severe endocrinopathies, however, impair fertility and consequent pregnancy.

Pituitary apoplexy associated with increased vascularization and enlargement of the partum pituitary may result in prepartum infarction or hemorrhage, or more typically postpartum end-circulation ischemia, typically after massive maternal hemorrhage.

Coma may supervene from electrolyte or metabolic disturbance, cerebral edema, or seizures.

Detailed treatment is aimed at the individual endocrine dysfunction and is beyond the scope of this chapter.

17.7.5. Sheehan's syndrome

Sheehan's syndrome consists of a fall in a number of circulating hormones following necrosis of the anterior pituitary in the setting of hypotensive hypovolemia with postpartum hemorrhage. It is thought that, in pregnancy, the pituitary is particularly vulnerable because of its hyperplasia and increased metabolic demand, with a chronically borderline blood supply. Sheehan's syndrome may occur in 3–4% of pregnant patients with hemorrhagic collapse on retrospective survey (Sheehan, 1937; Hall, 1962; Moszkowski, 1973).

Typical features include fatigue, hypothyroidism and altered level of consciousness but the diagnosis is often made more than 10 years after postpartum hemorrhage. Problems arise not from acute hypopituitarism but rather if the woman becomes pregnant in the setting of prior pituitary infarction, necessitating hormone replacement therapy. In contrast, acute pituitary apoplexy represents a clinical syndrome of abrupt infarction, hemorrhage or necrosis, typically within a pituitary adenoma or occasionally in a normal pituitary gland. Representing a true emergency, it has a high mortality, typically from compression of the hypothalamus impairing consciousness or from acute failure of adrenal function. Pituitary apoplexy is rare in women and is rarely described in pregnancy. Patients present with severe frontal, retro-orbital, or diffuse headache, meningisms, and vomiting, resembling subarachnoid hemorrhage. There may be ophthalmoplegia, ptosis, and pupillary defects. Bilateral third nerve palsies are typical (Grimes et al., 1980).

A cornerstone of management is the acute substitution of cortical steroids intravenously, but surgery may be required to relieve hypothalamic compression or optic nerve compromise (Grimes et al., 1980).

17.7.6. Pheochromocytoma

Pheochromocytoma is a tumor of chromaffin tissue in the adrenal gland and along the developmental pathway of the adrenals; 10% are malignant. These tumors secrete endogenous catecholamines, including

epinephrine (adrenaline), norepinephrine (noradrenaline), dopamine and their metabolites (vanillyl mandelic acid and metanephrine). These catecholamines lead to hemodynamic instability with acute hypertensive crises (Pomares et al., 1998; Bullough et al., 2001). In general, pheochromocytomas account for 0.3–1.9% of secondary causes of hypertension but remain a rare cause in pregnancy. There are case reports of undiagnosed pheochromocytoma that has been successfully managed with epidural anesthesia, magnesium infusion, and cesarean section (Harper et al., 1989; Pomares et al., 1998). It remains difficult to diagnose because of the pleomorphic clinical features and the other clinical conditions for which it has been mistaken (see other causes of hypertension) (Daly and Landberg, 1992). It has been recommended that, if pheochromocytoma is confirmed before 24 weeks' gestation, the tumor be excised. Decisions on progression of the pregnancy must then be made. After the 24th week, the pregnancy is usually continued under adrenergic blockade until the fetus is mature. Cesarean section is encouraged to avoid further rises in pressure. Diagnosis is usually made with imaging, using CT or MRI as well as MIBG scintigraphy scanning when clinical features are unclear. In addition to surgery, 1–132 MIBG has been used. Occasionally, pheochromocytomas may be familial or may be seen in association with medullary thyroid carcinoma, parathyroidomas as part of multiple endocrine neoplasia type 2 (MEN 2), von Hippel–Lindau disease, and type I neurofibromatosis. Extramedullary tumors are usually malignant. In some cases, metyrosine has been helpful in controlling blood pressure (Schenker and Grant, 1982; Woodward et al., 1997; Hermayer and Szpiech, 1999).

17.8. Infections and infestations

There appears to be mild immunosuppression during pregnancy, thought possibly to be associated with changes in circulating maternal steroids and possibly having a protective effect in the 'maternal–fetal' immunological graft versus host reaction. There is a slight increase in vulnerability to certain systemic infections and hence septicemia, but these rarely induce coma. Meningitis and encephalitis can rarely occur but do not vary significantly from the nonpregnant state.

Occasionally, parasitic infestations can result in coma in pregnancy and even be mistaken for eclampsia. At least four cases of cysticercosis with seizures or coma during pregnancy are described (Suarez and Iannucci, 1999). Coma was produced by unilocular cysts near the third ventricle producing acute hydrocephalus. Treatment was successful with intraventricular drainage.

17.9. Organ-specific decompensations occasionally leading to coma

17.9.1. Acute renal failure in pregnancy

Acute renal failure is a serious but rare complication of pregnancy (Pertuiset and Grunfeld, 1994) and is usually seen with hemorrhagic or septic shock but may also be seen in severe pre-eclampsia. Other pregnancy-associated causes are microangiopathic hemolytic anemia, malignant hypertension, scleroderma, vasculitis, transplant rejection, hemolytic uremic syndrome, infections, malignancies, and drug toxicity. With HELLP there may be endovascular thrombosis, lumen occlusion, hyperperfusion with a fall in glomerular filtration and renal failure, sometimes with acute tubular necrosis (Lakkis et al., 1996). Thus renal failure is induced by a fall in glomerular filtration rate and indirectly from ischemia-induced tubular necrosis (Thadhani et al., 1996). Most acute renal failure in HELLP syndrome resolves (Sibai et al., 1993; Selcuk et al., 2000; Abraham et al., 2001, 2003). It may be caused by DIC, but more rarely it occurs with mesangial proliferative glomerular nephritis, primary Sjögren's syndrome, malaria, multicystic dysplastic kidneys, milk–alkali-syndrome-induced hypercalcemic acute renal failure, and toxins such as metamizol. Mesenteric cysts may cause acute renal failure. Necrotizing fasciitis and group A streptococcus can cause toxic shock syndrome. In utero exposure to nonsteroidal anti-inflammatory drugs may produce neonatal renal failure.

17.9.2. Acute fulminant liver failure

Acute fulminant liver failure may occur prepartum or postpartum in the setting of eclampsia or HELLP syndrome but also from unrecognized peripartum cardiomyopathy. Severe hepatic dysfunction may also arise from acute viral hepatitis. Acute fatty liver and HELLP syndrome predominate in the third trimester, presenting as jaundice, coagulopathy, and a rise in liver enzyme concentrations. They are often complicated by hypercoaguable states and DIC with evidence of intravascular and thrombocytopenia in HELLP syndrome. Other clinical features include pruritus, acholic diarrhea, and jaundice. Hepatic failure may also arise from chronic hepatitis-B-virus-related cirrhosis. Patients with worsening liver function despite early delivery and patients with encephalopathy coagulopathy, hypoglycemia, and other significant problems should be considered for urgent liver transplantation (Riely, 1994; Locarnini and Cunningham, 1995; Castro et al., 1999; Sheikh et al., 1999; Paternoster et al., 2004).

17.9.3. Acute fatty liver of pregnancy

AFLP is rare and affects about 1 in 7000–16 000 pregnancies (Reyes et al., 1994; Castro et al., 2000), typically occurs in the third trimester of pregnancy and manifests as microvesicular fatty infiltration of the liver, hepatic failure, and encephalopathy (Mabie, 1991; Sibai et al., 1994). Maternal mortality is about 18% with neonatal mortality ranging from 7% to 58% (Mabie, 1991; Reyes et al., 1994; Usta et al., 1994). Most cases are diagnosed in the antepartum period but a significant minority postpartum. The commonest symptoms are nausea and vomiting (75%) but malaise, jaundice, and epigastric pain are typical features. Associated morbidity and mortality include DIC, acute tubular necrosis, and pulmonary edema. Maternal death occurs in about 10%, within a month of delivery. Fetal loss is somewhat higher. It is usually a monophasic illness (Fesenmeier et al., 2005). The clinical and laboratory findings of AFLP are similar to those with pre-eclampsia, HELLP, and pancreatitis but hypoglycemia is found in about 50% of patients. There is no definitive treatment for AFLP aside from supportive measures for the associated morbidities until the disease regresses. In some cases, liver transplantation is recommended (Rolfes and Ishak, 1985; Reyes et al., 1994; Usta et al., 1994; Castro et al., 2000).

17.10. Pulmonary disease and failure in pregnancy

17.10.1. Acute respiratory failure

Typically, respiratory failure has been divided into hypoxic respiratory failure and reactive airways disease with hypercapnic–hypoxic respiratory failure, usually seen with bronchial asthma (Deblieux et al., 1996).

Acute respiratory failure in pregnancy is a significant cause of maternal morbidity and mortality, accounting for more than 30% of maternal deaths (Hollingsworth and Irwin, 1992). Major causes include: thromboembolism, amniotic fluid embolism, venous air embolism, and adult respiratory distress syndrome (ARDS). Pulmonary involvement may be the earliest indicator of severe disease. Therapeutic approaches involve treating the underlying disease and managing hemodynamic, ventilatory, and other multisystem problems while attempting to avoid complications (Deblieux and Summer, 1996) (see below).

Pulmonary injury may be expressed in ARDS caused by the same pathophysiology, with abnormal pulmonary capillary permeability causing accumulation of fluids in the lungs. Clinical features are nonspecific and are those of respiratory distress, including tachycardia, tachypnea, and dysphonia. The patient may be cyanotic. Auscultation reveals crackles in lung bases. Investigation fails to show evidence of congestive heart failure. Chest X-rays are highly variable, from minimal interstitial infiltrate to white-out of the lungs. ARDS criteria include 1) identifiable risk factors, 2) respiratory distress, 3) exclusion of cardiogenic pulmonary edema, 4) bilateral opacification on chest X-ray, and 5) P_{aO_2} F_{iO_2} <200. Pregnancy produces particular challenges in that specific risk factors are difficult to identify (Gurman et al., 1990; Deblieux and Summer, 1996).

Pathophysiology involves systemic or pulmonary insults that injure the endothelial lining and activate neutrophils, which in turn lead to release of oxygen-free radicals, metabolites, and proteinases, further worsening the cascade of damage to the capillary endothelium. There is consequent capillary leak, leading to vascular resistance, pulmonary edema, a fall in lung compliance, and intrapulmonary vascular shunting. After the 30th week of pregnancy, relative hypervolumemia may exacerbate ARDS and outcome (Collop and Sahn, 1993).

ARDS mortality is affected by comorbid illnesses, multiorgan system failure, and duration of ventilation, ranging from 30% to 70% despite advances in critical care. Differentiating among sepsis, ARDS, and systemic inflammatory response syndrome may be difficult (Gattinoni et al., 1991).

Treatment is directed at sepsis, protecting against alveolar distention and fluid overload, and ensuring oxygenation. ARDS is not a homogeneous disease but often has a mixed picture of affected and normal alveoli, enabling prophylaxis of overextension by restricting tidal volumes to 6–8 ml/kg, and the lowest level of positive end-expiratory pressure (Gattinoni et al., 1991).

Aspiration pneumonia is also a significant cause of maternal morbidity and mortality, arising from reduced consciousness during labor and delivery, the rise in intragastric pressure from compression by the pregnant uterus, delayed gastric emptying, and some relaxation of the esophagus. The worse prognosis is proportionate to the amount of aspirated matter, along with the acidity of aspirate. Most cases show early pulmonary infiltrates on chest X-ray progressing to a picture of ARDS. Prognosis ranges from a mild reversible picture lasting 4 days to sudden death (Rodrigues and Niederman, 1992; Clinton and Niederman, 1993).

Management is directed at prevention, use of regional anesthesia, avoiding oral feedings, use of H_2 blockers, and use of supportive care incorporating antibiotics, mechanical ventilation, and preventing hypoxia (Rodrigues and Niederman, 1992; Clinton and Niederman, 1993).

17.10.2. Venous air embolus

Venous air embolism may arise during delivery, abortion, labor, and other interventions. It represents the entry of air into the subplacental venous sinuses, which travels to the heart, blocking blood flow to the lungs often with the creation of a blood–air interface, causing microemboli, platelet injury, and inflammatory white cell response leading to ARDS (Hollingsworth and Irwin, 1992).

Classical clinical features include shortness of breath, rapid breathing and heart rate, hypotension, and sweating, with a distinctive cardiac murmur. Treatment is aimed at supportive pressure and pulmonary support, usually for 2–3 days. Nonetheless, death may occur with relatively small amounts of infused air, while survival has been seen after more than 1.5 liters of infused air (Hollingsworth and Irwin, 1992; Lowenwirt et al., 1994).

17.10.3. Toxic pulmonary edema

Pulmonary edema may arise from the use of selective and nonselective beta-2-adrenergic agents. Symptoms include tachycardia, tachypnea, chest pain, shortness of breath on exertion, orthopnea, basilar crackles, and chest X-ray findings of fluid overload. These clinical features typically appear 1–2 days after the use of beta-adrenergic agents and are thought to arise from cardiac toxicity, a fall in colloid osmotic pressure, fluid overload, and increased capillary permeability. Treatment is directed at stopping the offending agent and supportive care, with symptoms resolving usually within a day (Hollingsworth and Irwin, 1992).

17.10.4. Congenital pulmonary abnormalities

One series of pregnant women with complex pulmonary atresia revealed high miscarriage and termination rates along with neonatal deaths. Whether pregnancies occurred before or after radical repair, there were thromboembolic complications with pulmonary embolism, arrhythmias, heart failures, and left ventricular failure. The others concluded that surgical repair decreases fetal complications and that those with mild symptoms may have successful pregnancies (Neumayer and Somerville, 1997).

17.11. Maternal hydrocephalus in pregnancy

Hydrocephalus is the accumulation of cerebrospinal fluid in the cerebral ventricles causing their dilation. Hydrocephalus may be ‘communicating’, due to inadequate cerebrospinal fluid absorption, or obstructive when there is blockage of the passage of cerebrospinal fluid from the lateral to the 3rd and 4th ventricles.

Aside from obstructive lesions, causes of maternal hydrocephalus in pregnancy include aqueductal stenosis (Bódis et al., 1998; van Loenen et al., 2004; Watanabe et al., 2005). Treatment for the baby involving delivery with vacuum extractor, or by cesarean section, resulted in good outcomes.

With long-standing shunts for hydrocephalus there may be malfunction from the increased intra-abdominal pressure–Valsalva maneuvers during labor and delivery. Shunt malfunction may occur in about 50%, with surgical intervention needed in 10%. There may be symptoms from a rise in intracranial pressure, abdominal pain, and seizures. Further risks are premature deliveries and abortions. Cesarean section has been useful in cases of preterm delivery (Sova et al., 2001).

17.11.1. Prognosis

With acute hydrocephalus, consciousness typically improves in the absence of cerebral infarction. Even without surgical decompression most ocular palsies resolve, but some residual field defects may persist as may panhypopituitarism (Sova et al., 2001).

17.12. Head and abdominal trauma and coma

Traumatic injuries in pregnancy are the leading cause of nonobstetric maternal mortality in the USA, with motor vehicle accidents accounting for up to 3900 fetal losses per year (Dobo and Johnson, 2001; Weiss et al., 2002). Most women died from internal injuries of the abdomen, thorax, and pelvis. There were increased morbidities, premature delivery, higher rate of abruption, and low birth weight at delivery, with fetal outcome dependent on gestational age rather than on injury type/mechanism or severity of injury. Abdominal trauma and pregnancy have been reported to raise the maternal serum alpha fetoprotein and cause staining of the amniotic fluid from prior intrauterine hemorrhage, a finding also seen after physical abuse (Romem and Romem, 2003). A consequence of trauma in pregnancy may be sepsis in pregnancy, or even miscarriage (Paccagnella et al., 1994).

In coma following head trauma, investigations are centered on the anatomical and pathophysiological causes of coma of the mother. Imaging can reveal cranial fractures, displacement of cerebral contents, cerebrovascular compromise, intracranial hemorrhage and the features and progression of raised intracranial pressure. In these circumstances, management (from investigation through treatment) largely follows the

pathway used for nonpregnant patients. With stabilization of vital systems and CNS compromise, some attention can be directed at fetal health, seeking obstetric consultation for evaluation of the viability of the fetus and guidance regarding safety of use of medications electively used in management, when issues of mortality and significant morbidity are less critical. A similar stratagem can be used in the acute intensive care unit management of coma in pregnancy for other causes such as toxic–metabolic or infectious etiologies.

17.13. Anesthetic considerations in pregnant women with severe neurological disease

Although general anesthesia permits complete ventilatory control, there are dangers of neonatal depression, hypertension, and gastric aspiration. Some anesthetic agents favored include volatile anesthetics, intravenous narcotics, nitrous oxide, or propofol. Volatile agents may vasodilate, helpful with vasoconstrictive disorders; however, with moyamoya disease there may be a steal phenomenon. As a result, many favor the use of propofol (Gin, 1994; Abboud et al., 1995; Furuya et al., 1998; Sato et al., 1999; Williams et al., 2000).

Labor-induced hypocapnia and hyperventilation may be prevented by epidural anesthesia, allowing vaginal delivery (Fisher and Prys-Roberts, 1968).

17.14. Medical, legal, and ethical issues in maternal brain death

There are reports of maintenance of maternal brain function to permit in utero fetal maturation. Because of the unique problems posed by the coexistence of two distinct organisms so mutually dependent, maternal brain death poses ethical, medical, and legal issues regarding attempts to preserve fetal viability. The case of the Erlanger baby, the challenging bioethical case of whether a pregnant brain-dead woman should carry her child to full term, framed the international debate (Lane et al., 2004).

Medical issues are dominated by the consideration that progressive organ failure is inevitable. A predictable scenario of cardiovascular instability, sepsis, pituitary failure, and cardiac arrhythmias is well recognized. The optimal time for delivery is thought to be about 32 weeks of gestational age but viability has been pushed backwards to 28 weeks. In absolute terms, maternal support after brain death has reached 107 days (Bernstein et al., 1989).

The central ethical theme is that there must be a hope of success. Since the raised duration of somatic maternal support is unknown, all such efforts remain experimental. The treating and deciding parties must address the issues of the need to respect the person following brain death, a person's right to die with dignity, and the person's right to autonomy. The controversy centers around whether the mother's or the fetus's interests are paramount. Lane et al. (2004) and Finnerty et al. (1999) address three issues: 1) the subject as a terminally ill but autonomous being, with the maternal wishes in an advanced directive prevailing, 2) the view that the mother has no autonomy, with the right to the fetus predominating, and 3) viewing the mother as a voluntary organ donor.

In legal terms, with the mother dead, her rights do not prevail. The rights of the fetus in part derive from its gestational age. In many European countries, a fetus less than 13 weeks gestational age has no legal rights – in Austria, Belgium, France, Germany, and Sweden. There are limited rights in Denmark, the UK, Greece, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, and Switzerland. The fetus has a right to life from conception in the Republic of Ireland (Sheikh and Cusack, 2004).

The major consideration in extending maternal life support after brain death is the likelihood of a viable fetus. The parties involved, including family and medical and legal experts, must reach a consensus and, with immediate family, the wishes of the mother are paramount.

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Chapter 18

Psychogenic unresponsiveness and nonepileptic seizures

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Psychogenic unresponsiveness has been described in medical writings in the form of nonepileptic seizures since the middle of the first millennium BC (Wilson and Reynolds, 1990). In the late 20th century and early 21st century, we increasingly have had at our disposal powerful tools to help better understand and visualize neuroanatomy coupled with neurophysiology. Functional neuroimaging and electrophysiological assessments provide enhanced neurobiological examination, with better spatial and temporal resolution in brain processes. Along with the neurological examination, neurologists, neuroscientists, and other physicians may employ the use of these tools to evaluate patients with alterations in level of consciousness. The technologies used to assess neurophysiology, however, still do not have the power to distinguish conscious from unconscious, volitional from involuntary, feigned from unfeigned in individuals.

18.1. Terminology and manifestations of psychogenic unresponsiveness

We introduce psychogenic unresponsiveness, describing various manifestations, including catatonia and psychomotor retardation, fugue states, panic attacks, dissociation, and psychological nonepileptic seizures. In this chapter, we then take the better known characteristics of nonepileptic seizures to provide further information on epidemiology, diagnosis, physiology, inheritance, and treatment of a representative disorder of psychogenic unresponsiveness.

Nonepileptic seizures resemble epileptic seizures presenting as sudden, involuntary, time-limited alterations in behavior, motor activity, autonomic function, consciousness, or sensation. However, unlike epilepsy, nonepileptic seizures do not result from epileptogenic pathology and are not accompanied by an epileptiform electrographic ictal pattern. Patients with nonepileptic seizures are often misdiagnosed, disabled, and difficult to treat. Nonepileptic seizures can present in the same manner as any epileptic seizure and patients with nonepileptic seizures may appear to be unconscious during their events (Gates et al., 1985). For the purposes of this chapter, we will use the nonepileptic seizures presenting as a partial complex or a generalized seizure, during which the patient has a change in level of consciousness as the model of psychogenic unresponsiveness. For clarification, we provide definitions of various other alterations in conscious states.

18.1.1. Dissociative states

Dissociation is both a mechanism and a disorder. It is characterized in the DSM-IV definition as 'a disruption in the usual integrated functions of consciousness, memory, identity, or perception of environment' (Task Force on DSM-IV, 1994). Dissociation occurs in a variety of neurological and psychiatric disorders, ranging from temporal lobe epilepsy to post-traumatic stress disorder, to dissociative disorders, to nonepileptic seizures (Dikel et al., 2003; Dietl et al., 2005). Some dissociative episodes are thus due to ictal manifestations of abnormal neuronal firing, and others due to anxiety based defense responses to physical and psychological trauma (Sivec and Lynn, 1995). The World Health Organization diagnostic categorization

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of dissociation suggests a mechanistic relationship to psychological etiology related to 'trauma, insoluble or intolerable problems or disturbed relationships' (World Health Organization, 1992). Along with acute and chronic post-traumatic disorders, dissociation occurs in affective disorders and in certain personality disorders. Dissociation in nonepileptic seizures may lead to the misdiagnosis of epilepsy, with the reporting of amnesia and with electroencephalogram (EEG) abnormalities found in some patients having dissociative episodes (Jawad et al., 1995). While the patient may report being 'unconscious' during an ictus, the term 'loss of consciousness' means different things to doctors and to patients (Gloor, 1986). Many patients with nonepileptic seizures actually present with a dissociative alteration in consciousness, rather than loss of consciousness, and this amnestic report must not be equated with an epileptic event.

Other dissociative symptoms include depersonalization and derealization, referring to a disturbance of feeling about the self or the surrounding world, respectively. Autoscopy refers to the 'out of body experiences' where an individual reports standing outside his or her body and looks down on it. Déjà vu and jamais vu represent amnestic dislocations, with déjà vu most commonly occurring in anxiety disorder. The dissociative symptoms of the temporal lobe epilepsy aura are more vivid and often repetitive than those of the psychologically associated symptoms (Trimble, 2001).

As is the case with dissociation, alterations in consciousness are found in catatonic states and may be associated with cerebral dysfunction or toxic metabolic states, or due to psychogenic causes. Among the psychiatric diagnoses, catatonia is often associated with schizophrenia; however, catatonia occurs in severe affective disorders also. Catatonia is a disturbance of motor behavior with psychological or neurological etiologies, which manifests as rigid immobility for extended periods of time, or as agitated purposeless motor activity (Task Force on DSM-IV, 1994). Medically emergent forms of catatonia can be found in neuroleptic malignant syndrome, associated with antipsychotic use. Primavera et al. emphasized the necessity of using EEG in the acute catatonic patient, finding seizures in four patients and nonconvulsive status epilepticus in one in their series of 29 patients (Primavera et al., 1994).

Panic attacks present as paroxysmal episodes with autonomic symptomatology, including a combination of tachycardia, palpitations, hyperventilation, dyspnea, diaphoresis, angina, tremulousness, presyncope, visual changes, and 'an impending sense of doom'. They may occur in stressful situations or sporadically, once they have been entrained apart from the feared stimulus. Differentiating seizures from anxiety, with the overlap between ictal fear and panic symptoms, can be difficult. Clinically, however, the diffuse symptoms of anxiety differ from the 'dreamy state' and automatisms described by Hughlings-Jackson (Hogan and Kaiboriboon, 2003) and the epigastric rising sensation reported in temporal lobe epilepsy prior to loss of consciousness, and personality measures of anxiety are higher in nonepileptic seizure patients than in patients with epilepsy (Owczarek, 2003).

18.1.2. Conversion disorders

Symptoms in conversion disorders are defined as 'a loss of, or alteration in, voluntary motor or sensory functioning suggesting, but not explained by, a neurological or general medical condition. Psychological factors are judged to be associated with the development of the symptom, and the symptom is not intentionally produced or feigned, as in Malingering' (Task Force on DSM-IV, 1994). Conversion disorders may occur in the presence of neurological disease, and the two are not mutually exclusive. Briquet's syndrome (somatization disorder) is a more chronic, stable form of 'hysteria' that may present with numerous somatic complaints, various neurological symptoms, and a history of abnormal illness behaviors (Guze, 1975; Wetzel et al., 1994). The nonepileptic seizures that are described as types of conversion disorders or as dissociative phenomena are usually considered as unconscious processes.

In contrast, malingering, which makes up a small subset of nonepileptic seizure patients and is not considered to be a psychiatric illness, is thought of as a conscious process of deception. Malingering using epileptic-like symptoms has been documented in the medical literature for over a century (MacDonald, 1880; Hammond, 1948). The DSM-IV categorizes malingering in 'additional conditions that may be a focus of clinical attention', defining it as the intentional production of false or exaggerated symptoms, motivated by external incentives (Task Force on DSM-IV, 1994). Examples of when malingering is used include to get out of military service, jail, work, or a difficult social situation, but it is most often discovered in settings of obtaining drugs or compensation.

Episodic dyscontrol is a condition of repeated paroxysmal episodes of rage and violence, which often occur sporadically without precipitant and are relatively short-lived (Gordon, 1999). Similarly, individuals diagnosed with 'intermittent explosive disorder' may be amnestic of the events that result in serious assaults towards people or property destruction (Task Force on DSM-IV, 1994). Episodic dyscontrol and

intermittent explosive disorder are found in boys in urban areas, often with a family history of violence (Gordon, 1999). Intermittent explosive disorder may be confused with epilepsy, with the transient change in consciousness, the response to antiepileptic/mood stabilizing drugs, some association with a history of head injury and an abnormal EEG with nonspecific slowing in a third of patients in one series (Drake, 1985; Olvera, 2002).

18.1.3. Consciousness

Consciousness has been described as 'the subjective awareness of something', having 'limited awareness of [its] processes; it perceives the products of cognition' (Devinsky, 1997). Proponents of a hippocampal/medial temporal lobe based, modular memory theory argue that awareness is always present with declarative memory (episodic or semantic memory) (Moscovitch, 1995). In contrast, certain precepts and nonconscious behaviors, as in procedural memory, are fully unconscious (or inaccessible to consciousness). The interaction between procedural and declarative knowledge is seen in hypnosis and implicit memory, which are posited as examples of the individual's operational cognitive unconscious, where innate and overlearned behaviors may use declarative memory while being inaccessible to consciousness (Kihlstrom, 1987).

From a neurophysiological perspective, consciousness is state-dependent, requiring the forebrain to be in an operational state that is conducive to the representation of images, thoughts, and emotions, and is characterized by general depolarizations and readiness of cortical and thalamic networks (McCormick, 2002). A disruption of consciousness in epilepsy is associated with abnormal synchronized oscillations of activity that disrupt normal neurological function (McCormick and Contreras, 2001).

Consciousness in epilepsy has been conceptualized as bidimensional with axes of level of consciousness and content of consciousness (Monaco et al., 2005). In a study that compared semiology of nonepileptic seizures to temporal lobe epilepsy, patients with temporal lobe epilepsy had a disordered level of consciousness while patients with nonepileptic seizures showed self-directed consciousness disturbances. Awareness and arousal were not disordered during the ictus in the patients with nonepileptic seizures (Oana, 1998). Conversion disorders frequently present as alterations of sensory, motor, or behavioral functions and may result from nonconscious elements of mind associated with restriction of conscious awareness.

While the underlying neuroanatomy in pathophysiological alterations of consciousness is documented, the role of neurobiological factors in psychogenic unresponsiveness and consciousness itself is less well understood. Along with mediation of nonverbal, visuospatial, and topographic perception, the right hemisphere has functional correlates of corporeal awareness or the bodily sense of self (Devinsky and D'Esposito, 2004a). The prefrontal cortex has been proposed as a substrate for inhibitory mechanisms altering attention and awareness in conversion reactions (Sierra and Berrios, 1999). Right hemispheric dysfunction may impair recognition of the body's sense of self (e.g., anosognosia), and conversion disorders have been associated with right hemispheric laterality (Devinsky and D'Esposito, 2004b). Brain abnormalities, such as stroke, vascular malformations, infections, and traumatic brain injury, are found in almost one-quarter of patients with lone nonepileptic seizures and in over 90% of patients with mixed epilepsy and nonepileptic seizures (Reuber et al., 2002). Right hemispheric structural lesions or electrophysiological abnormalities were found in 71% of patients with nonepileptic seizures (Devinsky et al., 2001). These findings bring together functional neuroanatomic connections between consciousness, an individual's awareness of self and conversion symptoms, manifesting as nonepileptic seizures. Theories on the etiology of conversion symptoms range historically from psychodynamic to neuroanatomical. A unified theory acknowledges that environmental influences, in the presence of macroanatomic or distributed network brain abnormalities in the vulnerable individual, may contribute to the development of psychogenic unresponsiveness and conversion disorder.

18.2. Epidemiology of nonepileptic seizures

Of the 1% of the US population diagnosed with epilepsy, 5–20% have nonepileptic seizures (Gates et al., 1991). It is estimated that 10% of those with nonepileptic seizures have mixed epileptic/nonepileptic seizures (Lesser et al., 1983). The incidence of nonepileptic seizures has been estimated to be 3.03 per 100 000 (Szaflarski et al., 2000) and the prevalence of nonepileptic seizures is estimated to be up to 33 per 100 000 (Benbadis and Hauser, 2000). Patients with nonepileptic seizures are usually women (≈80%) and are usually between 15 and 35 years old (≈80%) (Shen et al., 1990), although children and the elderly can develop nonepileptic seizures. The patients, their families, and society bear an enormous cost if psychiatric care is not provided or if inappropriate neurological therapy is instituted. Although nonepileptic seizures are not responsive to treatment by antiepileptic drugs, most patients with nonepileptic seizures

receive unnecessary antiepileptic drugs and only half pursue recommended psychiatric follow-up (Krahn et al., 1997). Antiepileptic drugs are ineffective for and may worsen nonepileptic seizures (Krumholz et al., 1980, Oto et al., 2005). In some cases, potentially dangerous invasive diagnostic studies, toxic parenteral medications or emergency intubation are administered. It is estimated that up to 50% of patients admitted to an intensive care unit from the emergency department in status epilepticus in fact have pseudostatus as one manifestation of nonepileptic seizures (Reuber et al., 2003). Any patient in status nonresponsive to immediate treatment should have their diagnosis reviewed. Diagnostic and therapeutic challenges are complicated by the 10% rate of co-morbid nonepileptic seizures and epileptic seizure. Misdiagnosis and mistreatment of nonepileptic seizures as epileptic seizures cost an estimated $110–920 million annually on diagnostic evaluations, inappropriate administration of antiepileptic drugs, and emergency department use (Martin et al., 1998).

18.3. Diagnosis

A number of instruments are used to assist in the diagnosis of nonepileptic seizures. After conducting a thorough history, mental status, and neurological examination, clinicians may utilize neurophysiological, neurohumoral, and neuropsychological tests to assist in the diagnosis of nonepileptic seizures.

18.3.1. Bedside/clinical examination

The neurological examination is fundamental. Plum and Posner described the neurological signs associated with the various central nervous system lesion levels (Plum and Posner, 1980). Levels of consciousness range from alert through lethargic, obtunded, and stuporose to comatose. Observing the verbal responses, respirations, pupils, ocular movement, and motor function forms the basis of the assessment of the patient who is unresponsive. The patient with psychogenic unresponsiveness typically has a normal neurological examination. Patients with pre-existing neurological deficits may have legitimate, focal neurological findings (Lowe et al., 2001).

Conscious patients with conversion disorder and nonepileptic seizures may reveal the possibility of nonepileptic seizures by the nature of their comments. Descriptions of attacks and their effects on others (e.g., ‘It took six of them to hold me down’ or ‘They told me my heart stopped three times’, etc.), a fixed somatic idealization of their episodes, and an earlier ambiguous illness history with other possible somatoform disorders all may lead the alert clinician to consider a broad spectrum of diagnoses. On examination, such patients may reveal ambiguous or anomalous physical findings such as anesthetic patches, bizarre visual field defects or other abnormal movements (e.g., psychogenic dystonia).

During the ictus, some signs of nonepileptic seizures include geotropic eye movements, in which the eyes deviate downward to the side toward which the head is turned (Henry and Woodruff, 1978). Eyelids are typically closed at the onset of nonepileptic seizures and for a longer duration, as compared to temporal lobe epilepsy or frontal lobe seizures (20 s vs ≈2s, respectively) (Donati et al., 2005). Along with ictal eye closure, weeping is associated with nonepileptic seizures (Bergen and Ristanovic, 1993; Flügel et al., 1996). Postictal nose rubbing and postictal cough are found in temporal lobe epilepsy but not in nonepileptic seizures (Wennberg, 2001). Pelvic thrusting has been reported to occur as commonly in frontal lobe seizures as it does in nonepileptic seizures. Nonepileptic seizures and frontal lobe seizures differ, however, in that frontal lobe seizures are rarely associated with the overtly sexualized, often prolonged display seen in some cases of nonepileptic seizures (Geyer et al., 2000).

It was once thought that absence of physical injury sustained during a seizure was a diagnostic indicator differentiating nonepileptic from epileptic seizures; however, more than half of all patients with nonepileptic seizures actually have an associated physical injury (Kanner, 2003). Nonepileptic seizure patients may have urinary incontinence and may injure themselves during the ictus. Tongue biting, self-injury, and incontinence are commonly associated with generalized seizures; however, two-thirds of patients with nonepileptic seizures report one of these three signs typically associated with epileptic seizure (de Timary et al., 2002). Trimble described patients with rug or floor burns on their cheeks or bodies as being pathognomonic for nonepileptic seizures (Trimble, 2001).

18.3.2. EEG findings

A common concern with psychiatric nosology is that psychiatric diagnoses have no physiological correlate. Fortuitously, nonepileptic seizures are the exception to the rule, with diagnosis validated by neurophysiological testing, video EEG, clearly aiding in establishing the diagnosis. Capturing the patient’s event, where the behavior is visually observed while co-registered with simultaneous EEG, allows neurobehavior to be coupled with EEG rhythms. The absence of ictal patterns during the behavioral event yields the diagnosis

of nonepileptic seizures in many cases. Thus, video EEG is the gold standard in nonepileptic seizures diagnosis.

No other mental disorder, including other forms of conversion, dissociative, mood, anxiety or psychotic disorders, has the reliable neurophysiological diagnostic correlate that exists with nonepileptic seizures. Aggregate data from dexamethasone suppression/corticotropin-releasing hormone tests are used in depression and post-traumatic stress disorder research but do not reliably establish the diagnoses in individual patients (Baghai et al., 2002; Yehuda et al., 2004). Motor evoked potentials and somatosensory evoked potentials have been used in conversion paralysis and anesthesia, respectively, for assisting diagnosis in small case series (Levy and Mushin, 1973; Morota et al., 1994). Structural and functional neuroimaging reveal volumetric reductions and perfusion deficits in mood and anxiety disorders in aggregate data. This is highly variable, however, in individual cases (Kanner, 2004; Talbot, 2004).

EEG sensitivity and specificity increases with repeated tracings (Salinsky et al., 1987). While seizures associated with impaired consciousness (e.g., generalized convulsive and nonconvulsive seizures) are associated with typical, widespread ictal EEG abnormalities, some focal seizures may not show features of seizures with scalp electrodes (Ramsay et al., 1993). The limitation of video EEG is the same as that of routine EEG, i.e., simple partial seizures and frontal lobe seizure may not show ictal patterns using scalp electrodes. Without video EEG, neurologists' ability to differentiate an epileptic seizure and nonepileptic seizure by history has a specificity of 50% (Deacon et al., 2003).

Other disorders of consciousness, such as delirium and coma, can be distinguished from epilepsy and nonepileptic seizures by electrographic patterns. Slowing and low voltages are reflected on the tracing in these neurophysiological altered states, whereas stereotyped ictal focal and generalized patterns appear in epilepsy. Nonepileptic seizures, on the other hand, have a normal background before, during, and after the events, thus giving a normal neurophysiological correlate to the behavioral disorder.

18.3.3. Neuroimaging

Neuroimaging allows in vivo visualization of central nervous system lesions causing alterations of consciousness. No static and no functional neuroimaging abnormalities have yet been found associated with causes of nonepileptic seizures. Abnormalities on structural neuroimaging neither confirm nor exclude epileptic seizure or nonepileptic seizures. A lack of abnormality on single-photon emission computed tomography (SPECT) studies report an average sensitivity of 72% for nonepileptic seizures and an average of 59% specificity for epileptic seizures (Cragar et al., 2002). Case reports exist describing patients with other forms of sensory or motor impairment (Vuilleumier et al., 2001). Patients with astasia–abasia motor conversion disorder had left temporal hypoperfusion abnormalities on SPECT; however, this has not been seen in nonepileptic seizures (Yazici and Kostakoglu, 1998).

18.3.4. Neurohumoral

Serological measures have been helpful in differentiating epileptic seizures from nonepileptic seizures. Prolactin is secreted from the anterior pituitary and is inhibited by tuberoinfundibular dopaminergic neurons in the arcuate nucleus of the hypothalamus (Gerstik and Poland, 2004). Dopamine agonists induce a marked reduction in epileptic activity and many dopamine antagonists (antipsychotics) decrease the seizure threshold and increase prolactinemia (Wyllie, 2001). Trimble found that elevated serum prolactin in patients with generalized seizures helped distinguish epileptic seizures from nonepileptic seizures (Trimble, 1978). A number of studies have since been conducted measuring prolactin in nonepileptic seizures and, with a lack of elevation of prolactin, the average sensitivity to nonepileptic seizures was 89% (Cragar et al., 2002). Further, prolactin epileptic versus nonepileptic seizure studies have since shown that serum levels are elevated on average in 88% of generalized tonic–clonic seizures, in 64% of temporal complex partial seizures and in 12% of simple partial seizures. False positives for epilepsy include treatment with dopamine antagonists and some tricyclic antidepressants, breast stimulation, and syncope, and false negatives occur with use of a dopamine agonist or with status epilepticus, because prolactin has a short half-life and may attenuate in postictal release (Bauer, 1996) (Table 18.1). Prolactin also does not rise after frontal lobe seizures. The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology recently published their report on the use of serum prolactin in differentiating epileptic from nonepileptic seizures. The authors reviewed the prolactin seizure literature and concluded that a twice normal relative or absolute serum prolactin rise, drawn 10–20 minutes after the onset of the ictus and compared against a baseline nonictal prolactin, is a useful adjunct in the differentiation of generalized tonic–clonic or complex partial seizures from nonepileptic seizures (Chen et al., 2005).

Table 18.1

Sensitivity and specificity of procedures in differentiating nonepileptic seizures from epileptic seizure

Procedure/observation	Sensitivity for NES (unless otherwise indicated) (%)	Specificity for NES (unless otherwise indicated) (%)	Reference
Induction			
Hypnotic seizure induction	77	95	Barry et al., 2000
Saline provocation	91	100	Slater et al., 1995
Semiology			
Ictal cognitive assessment (memory testing)	54	100	Bell et al., 1998
Preictal pseudosleep	56 (per patient) 23 (per seizure)	100 (per patient) 100 (per seizure)	Benbadis et al., 1996
Eyelid closure	82 (average)	98 (average)	Multiple (Alhalabi and Verma, 1994; DeToledo and Ramsay, 1996)
Pelvic thrusting	26	89	Geyer et al., 2000
– with thrashing	78	89	
Absence of upper and lower extremity in-phase movements and absence of vocalizations at beginning or end of seizure	96	96	Gates et al., 1985
No postictal headache	96	38	Ettinger et al., 1999
No fatigue	52	100	Ettinger et al., 1999
Functional neuroimaging			
SPECT	72 (average) lack of abnormal in NES	59 (average) abnormal in ES	Varma et al., 1996; Ettinger et al., 1998
Prolactin level*			
Lack of elevation in prolactin	93	69	Ehsan et al., 1996
For generalized tonic–clonic seizures – elevation	60 (pooled)	96 (pooled)	Multiple (Chen et al., 2005)
For complex partial seizures – elevation	46 (pooled)	96 (pooled)	Multiple (Chen et al., 2005)
Psychological testing			
MMPI (Wilkus rules)	90	80	Wilkus et al., 1984
MMPI-2 (Derry rules)	92	94	Derry and McLachlan, 1996
Neuropsychological testing			
Negative response bias on CVLT	61	91	Bortz et al., 1995

Studies included using Cuthill and Espie's inclusion criteria of having to have a nonepileptic seizure group and a control group of people with epilepsy (each $n \geq 10$) and using video EEG.

*Prolactin level elevations yielded a positive predictive value of 99.6% and a negative predictive value of 11.2% for generalized tonic–clonic seizures (pretest probability of epileptic seizure 95%, assuming specificity 96% and sensitivity 60%) and a positive predictive value of 99.6% and negative predictive value of 8.6% for complex partial seizures (pretest probability of epileptic seizure 95%, assuming specificity 96% and sensitivity 46%) Chen et al., 2005.

CVLT, California Verbal Learning Test; ES, epileptic seizures; MMPI, Minnesota Multiphasic Personality Inventory; NES, nonepileptic seizures; SPECT, single-photon emission computed tomography.

Source: modified from Cuthill and Espie, 2005, Cragar et al., 2002, and Chen et al., 2005.

Other serum measure studies to differentiate generalized tonic–clonic from nonepileptic seizures have included the use of elevations in peripheral white blood count (Shah et al., 2001), cortisol (Pritchard et al., 1985), creatine kinase (Wyllie et al., 1985), and neuron-specific enolase (Rabinowicz et al., 1996); however, Willert et al. discussed the limited discriminative power of these serological tests in differentiating epileptic seizure from nonepileptic seizures (Willert et al., 2004). Ictal heart rate on electrocardiographic monitoring is higher and a change in ictal heart rate is associated with epileptic but not nonepileptic seizures (Donati et al., 1996; Opherk and Hirsch, 2002; Oliveira et al., 2004). Capillary oxygen saturation on pulse oximetry is lower for epileptic than for nonepileptic seizures (James et al., 1991). Consistent with this hypoxemic state in epileptic

seizure, while no formal study of blood gas determinations have been published, the editors have used them and found that convulsive epileptic seizures are associated with a profound mixed metabolic–respiratory acidosis, while this does not occur in nonepileptic seizures.

18.3.5. Neuropsychological

A number of studies describe the cognitive, emotional, personality, and psychomotor differences between the epileptic and nonepileptic seizure groups. Cragar et al. reviewed the literature on adjunctive tests for diagnosing nonepileptic seizures and reported sensitivity and specificity of the different measures (Cragar et al., 2002). A summary of their findings noted that nonepileptic and epileptic seizure patients did not differ on intelligence tests or on neuropsychological measures consistently. Both nonepileptic and epileptic seizure groups had cognitive deficits when compared to normal controls, and nonepileptic seizure patients tended to perform better than patients with epileptic seizure on various neuropsychological tests. Other study findings suggest the following.

18.3.5.1. Intelligence measures and cognitive testing

Comparing patients with nonepileptic seizures to those with epileptic seizures, Binder et al. found no significant differences on tests of intelligence or learning and memory, including the Wechsler Adult Intelligence Scale – Revised, Wisconsin Card Sort Test, or Rey Auditory Verbal Learning Test. Control subjects were significantly superior to the nonepileptic and epileptic seizure groups (Binder et al., 1998). Bortz et al. studied the California Verbal Learning Test results in patients with nonepileptic and epileptic seizures and suggested that 'failure to explicitly recognize words following repeated exposure' may be reflective of a negative response bias and psychological denial in patients with nonepileptic seizures (Bortz et al., 1995).

18.3.5.2. Psychomotor measures

Kalogjera-Sackellares and Sackellares (2001) evaluated patients with nonepileptic seizures compared to matched normal controls and found reduced motor speed and grip strength in the nonepileptic seizure patients. Dodrill and Holmes (2000) reported that patients with nonepileptic seizures performed better than epileptic seizure on measures from the Halstead-Reitan Battery, with differences between Tactual Performance Test, Seashore Tonal Memory, and Trail-making Part B. While finger tapping and grooved pegboard differed between controls compared to nonepileptic seizure and epileptic seizure groups, Binder et al. did not find differences between the epileptic seizure and nonepileptic seizure groups on these measures (Binder et al., 1998).

18.3.5.3. Motivational measures

Motivational tests include the Portland Digit Recognition Test (PDRT), the Test of Memory Malingering and others and are used to detect inadequate performance on neuropsychological testing. The presence of unconscious psychological stress is hypothesized as an explanation for variable effort in patients with nonepileptic seizures (Swanson et al., 2000). Binder et al. (1994, 1998) found that patients with nonepileptic seizures performed more poorly than patients with epileptic seizures on the PDRT. The authors noted that frank malingering occurs rarely in nonepileptic seizures and the poorer performance may reflect a lack of the psychological resources necessary to persist with a challenging neuropsychological battery.

18.3.5.4. Personality testing

The majority of the Minnesota Multiphasic Personality Inventory (MMPI/MMPI-2) studies in nonepileptic seizures report the 'conversion V' profile, with elevations in scales 1 (Hs – hypochondriasis) and 3 (Hy – hysteria), and depressions in scale 2 (D – depression) (Cragar et al., 2002). Cragar et al. also reported an average sensitivity of 70% and specificity of 73% to nonepileptic seizure diagnosis using MMPI-2 decision rules. The dramatic personality of patients with nonepileptic seizures was illustrated in a blinded pilot study of artwork drawn by patients with epileptic and nonepileptic seizures (Anschel et al., 2005). An 80% positive predictive value for nonepileptic seizures existed if subjects used 10 or more colors to draw their seizures. Galimberti et al. administered the Cognitive Behavioral Assessment psychometric battery to patients with lone nonepileptic seizures, mixed epileptic/nonepileptic seizures, and epileptic seizure controls. The Cognitive Behavioral Assessment, which assesses personality characteristics and emotional adjustment, is comprised of scales rating introversion/extroversion, neuroticism, psychoticism, state–trait anxiety, psychophysiological distress, and depressive and other anxiety symptoms and found that the mean scores on the Psychophysiological Distress Scale for the nonepileptic seizure and the epileptic/nonepileptic seizure groups were higher than the mean scores of the epileptic seizure control group (Galimberti et al., 2003). The Rorschach did not differentiate between patients with nonepileptic and epileptic seizures (Ferracuti et al., 1999). Krawetz et al. evaluated family functioning in patients with epileptic seizures and nonepileptic seizures and their families. They found that individuals with nonepileptic

seizures viewed their families as being more dysfunctional, particularly in the area of communication, whereas family members of patients with nonepileptic seizures reported 'roles' as being dysfunctional (Krawetz et al., 2001).

In summary, patients with epileptic and nonepileptic seizures perform worse on a number of neuropsychological measures, compared to healthy controls; however, there are few differences between epileptic and nonepileptic seizure groups on tests that would reliably differentiate epileptic from nonepileptic seizures. The impairments are thought to be due to at least three factors: 1) both the epileptic seizure and the nonepileptic seizure patients were on antiepileptic drugs, which may affect cognition; 2) structural lesions in the epileptic seizure patients and in some of the nonepileptic seizure patients with epileptic seizures; and 3) emotional factors contributing to cognitive impairment in the nonepileptic seizure group (Swanson et al., 2000). Psychologically, patients with nonepileptic seizures appear to have personalities with anxiety, cognitive, and somatic distress, with difficulties in expression and communication of that distress to family and others.

18.4. Genetics – future directions

There is no information on genetic associations with nonepileptic seizures or conversion disorders. Ljungberg (1957) studied the inheritance patterns of 381 patients with hysteria, 135 (35.7%) of which had 'fits'. Morbidity risk for hysteria among parents, siblings, and children of propositi with hysteria was calculated to be 6–7% for females and 2–3% for males, compared to 0.5% for the general population. Other large case studies include 215 cases of hysteria, 105 of which presented with motor convulsions and 104 presented with unconsciousness (Sethi and Narottam, 1976). In this study 21 females (9.7%) had a family member with a history of hysteria, 13 of which had the mother affected. While this does not support direct genetic inheritance in conversion disorders, it may lend support to a multifactorial model of genetic, environmental, and epigenetic mechanisms (LaFrance and Barry, 2005).

The 5′ promoter region of the serotonin transporter gene (*5-HTTLPR*) has received much attention with gene–environment interactions and temperamental traits in patients with depression (Mann et al., 2000). The homozygous short arm allele is observed in one-third of somatoform disorder populations, such as fibromyalgia (Belous et al., 2001; Cohen et al., 2002). Case-control incidence/prevalence studies in families with nonepileptic seizures, would be helpful. We are assessing the frequency of homozygous short arm allele of the *5-HTTLPR* gene, which may yield insights into the contribution of genetic factors in nonepileptic seizures.

18.5. Basic sciences and animal work

Animal models for conversion disorder, hysterical reactions, or nonepileptic seizures do not exist. A few authors have written about mass hysteria and collective panic and the similarities to a herd's stampede in a theoretical fashion (Schmidt, 1966; Boss, 1997). Histories of sexual abuse and trauma are associated with nonepileptic seizures, dissociation, and conversion disorder (Sar et al., 2004) and post-traumatic stress disorder is often the underlying diagnosis in patients with nonepileptic seizures (Bowman and Markand, 1996). Biological models for dissociation and post-traumatic stress disorder exist, with freezing responses in rodents in the presence of a predator (Scaer, 2001). Scaer describes the repetitive movements when emerging from immobile states as 'almost seizure-like motor activity' as a truncated fight/flight response. Animal work using ferrets for studying thalamocortical networks and local neocortical circuits may yield a neurocellular understanding of the excitatory depolarized states and inhibitory networks that may underlie consciousness (Sanchez-Vives and McCormick, 2000). The difficulty of finding a conversion animal model is acknowledgment that unconscious processes are still poorly understood in humans, let alone in animals without lexical communication abilities.

From a basic science perspective, no serum or cerebral spinal fluid laboratory or physiological measure confirms conversion disorder. A study of hypothalamic–pituitary–adrenal axis hormone levels in controls, epileptic seizure, and nonepileptic seizure patients showed an elevation of serum prolactin, thyrotropin, growth hormone, and cortisol postictally after a grand mal or complex partial seizure, but not after nonepileptic seizures, in comparison to baseline serum hormone levels obtained at the same time on a seizure-free day (Rao et al., 1989). Based on the work of McEwen (2000, 2001) on post-traumatic stress disorder, the hypothalamic–pituitary–adrenal axis, and temporal lobe structures, one of us (WCL) proposed an allostatic link between childhood abuse and corticotropin-releasing factor in nonepileptic seizure patients (LaFrance and Barry, 2005). A pilot trial comparing patients with psychogenic movement disorders to patients with nonepileptic seizures is in the initial phases. The study is designed to evaluate potential physiological measures possibly predisposing an individual to psychogenic movement disorders or nonepileptic seizures (Voon and Lang, 2005).

18.6. Treatment

Presently, no randomized, double-blind, placebo-controlled trial has been completed for treatment of nonepileptic seizures. Numerous case reports and case series and a few open-label trials using psychotropic medications, cognitive behavioral therapy (CBT), group psychotherapy, hypnosis, family therapy, and paradoxical therapy have been published (LaFrance and Devinsky, 2004; LaFrance and Barry, 2005). Amytal interviews have been used for diagnosis of psychogenic unresponsiveness; however, their usefulness in treatment of nonepileptic seizures and other conversion disorders is undetermined (Krishna et al., 1995; Fackler et al., 1997).

Reports of successful treatment approaches for patients with nonepileptic seizures have included matching the appropriate form of psychotherapy to the underlying psychological history and diagnoses (Rusch et al., 2001). Communication and collaboration between neurology, psychiatry, and psychology in the process of diagnosing and treating the patient with nonepileptic seizures is an essential part of the multidisciplinary approach needed to assess and manage these patients. A model of treatment has been proposed, comprising accurate diagnosis with video EEG by the epileptologist, presenting the diagnosis to patients and their family, constructing a problem list of precursors, precipitants, and perpetuating factors, and prescribing psychotropics, discontinuing antiepileptic drugs in lone nonepileptic seizures or adjusting appropriately in mixed epileptic/nonepileptic seizures (LaFrance and Devinsky, 2002). While no single treatment has been shown to treat all nonepileptic seizure patients, various models are being systematically tested. A pilot randomized controlled trial (RCT) of CBT for nonepileptic seizures is being conducted based on an open-label CBT trial in the UK (Goldstein et al., 2004) and a pilot RCT of a selective serotonin reuptake inhibitor (SSRI) is being conducted in the US based on an open label trial of an SSRI (LaFrance et al., 2007).

Reuber et al. found that 71% of patients with nonepileptic seizures continued to have episodes and half remained on disability in longitudinal follow up (Reuber et al., 2003). Prognostic indicators for remission of nonepileptic seizures include having a shorter duration of seizures from symptom onset to diagnosis (less than 1 year) and having 'catatonic'-type spells as compared to 'thrashing' spells (Selwa et al., 2000). Kanner et al. found that nonepileptic seizures persisted in patients who had a combination of affective disorder, personality disorder, and a history of chronic abuse (Kanner et al., 1999).

18.7. Summary

Psychogenic unresponsiveness presents in a variety of manners, including dissociative states, catatonia, conversion disorders, and episodic dyscontrol. As we grow in our neuroanatomical and neurophysiological understanding of consciousness, this may be a window into better understanding of psychogenic unresponsiveness. A large body of literature exists on nonepileptic seizures, a neuropsychiatric disorder that manifests as unresponsiveness in many patients. Nonepileptic seizure is an ideal disorder that can be further studied as a model for better understanding of psychogenic disorders.

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Chapter 19

Coma in childhood

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Coma is an important and common clinical problem in pediatric practice. The comatose state in children (a term used for those <20 years of age) can result from trauma or a wide variety of nontraumatic causes. The principles of management in children are similar to those in adults and are still based on the seminal approach of Plum and Posner (1966).

19.1. Age-dependent factors

The *APOE* ε2 allele apparently provides resilience after injury and the ε4 allele increases vulnerability to injury in adults; the contrary may be the case in children, suggesting differences between the adult and developing brain (Blackman et al., 2005). We are not aware of other age-dependent biological factors that influence the occurrence of coma in children. However, there are some clinical observations of interest. Zimmerman et al. (1978) and Obrist et al. (1979) proposed that diffuse brain swelling was more common in children than in older subjects. Bruce et al. (1981) described a group of young children who developed severe brain swelling (malignant brain edema) and raised intracranial pressure (ICP) from minor head injury and suggested an age-dependent susceptibility. They attributed the raised ICP to cerebral hyperemia (increased cerebral blood flow), an opinion not shared by Sharples (1994).

19.2. The differential diagnosis of coma

We have not encountered hysteria or malingering manifesting as apparent coma in the pediatric age group, perhaps because these are recognized by 'front-line' professionals. The occurrence of blinking (often subtle), resistance to eye opening with a normal Bell's phenomenon (upward deviation of the eyes when the eyelids are opened against resistance), presence of nystagmus on cold caloric testing, an otherwise normal neurological examination and a normal electroencephalogram (EEG) should suggest these diagnoses.

The assessment of consciousness is very dependent on motor responses. Hence, a child with total generalized loss of motor function may mistakenly be considered to be comatose.

19.3. The causes of coma

19.3.1. General

It is clinically useful to classify causes into 1) those generally associated with structural changes in the brain (macroscopic anatomic abnormalities are present and these may be focal or generalized/diffuse; correspondingly, clinical, radiological, and electroencephalographic findings may be focal or generalized/diffuse) and 2) those with predominant metabolic dysfunction (macroscopic anatomical abnormalities are often absent; however, anatomical abnormalities may be present in some disorders, in which case they often have a regional or diffuse distribution that may be etiology specific; correspondingly, clinical, radiological, and electroencephalographic features often mirror anatomic and biochemical dysfunction) (see Table 19.1). A number of factors contribute to coma due to metabolic disorders, and cerebral edema is common in these conditions (Greene, 1994; Morris and Coulthard, 1994; Mowat, 1994; Surtees and Leonard, 1994), especially in diabetic ketoacidosis. Thus, metabolic causes of coma can be associated with structural changes in the brain. Conversely, any of the causes listed under the structural category can result in or associate with metabolic derangement; for example, inappropriate

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Table 19.1

Causes of coma in childhood

I. Those with predominant structural lesions (anatomic abnormalities are usually present)
  A. Focal (focal features present)
    i. Accidental/nonaccidental head injury (NAI is most common under 1 year of age)
    ii. Vascular (presentation at any age – etiology dependent)
      a. Arteriovenous malformation
      b. Migraine
      c. Embolism
      d. Hypertensive encephalopathy
      e. Arteritis
      f. Associated with congenital heart disease (including postoperative)
      g. Polycythemia/thrombocythemia
      h. Homocystinuria
      i. Venous thrombosis
    iii. Mass
      a. Hematoma (see (i), (ii)(a), (ii)(d) above)
      b. Abscess (note association with congenital cyanotic heart disease, sinusitis)
      c. Others (rarely present with coma at an early stage)
    iv. Intracranial infection (presentation at any age)
      a. Meningitis (focal signs usually due to vasculitis)
      b. Encephalitis
      c. Postinfectious acute demyelinating encephalomyelopathy (acute disseminated encephalomyelitis) – diagnosis by MRI
      d. Other
    v. Metabolic disturbance (example: hypoglycemia may present with focal weakness or seizures)
  B. Diffuse (diffuse signs)
    i. Accidental/NAI (NAI is most common <1 year of age)
    ii. Intracranial infection, including postinfectious acute disseminated encephalomyelitis (any age)
    iii. Anoxia/diffuse ischemia (any age; cause-dependent)
      a. Cardiorespiratory arrest
      b. Severe prolonged shock/hypotension
    iv. Complications of malignancy (of disease or treatment)
    v. Complications of bleeding disorders
    vi. Vascular
      a. Venous thrombosis
      b. Diffuse arteritis
      c. Hypertensive encephalopathy
    vii. Inborn errors of metabolism affecting the brain primarily (example: leukodystrophies; mitochondrial cytopathies; most commonly present in infancy or early childhood)
    viii. Electrolyte disturbance associated with central pontine myelinosis (a diagnosis facilitated by MRI)
    ix. Acute necrotizing encephalopathy of childhood (a diagnosis typically made on MRI scan)
    x. Hydrocephalus/shunt dysfunction

II. Those with predominant metabolic dysfunction (anatomical abnormalities, if present, are usually potentially reversible and the principal derangement is metabolic/toxic; CNS features are usually diffuse but may rarely be asymmetric or focal)
  A. Fluid–electrolyte acid–base disturbance (any age, but infants are at high risk)
    i. Hypernatremia
    ii. Hyponatremia
    iii. Acidosis
    iv. Alkalosis
    v. Water intoxication
    vi. Inappropriate antidiuretic hormone
    vii. Diabetes insipidus
    viii. Rapid correction of dehydration, electrolyte or acid–base imbalance (*Note:* risk of central pontine myelinosis)

B. Infection – septicemia (encephalopathy of sepsis)
C. Poisoning (numerous agents; bimodal age distribution: 1–5 years and 13–20 years)
D. Hepatic
E. Renal failure
F. Respiratory failure
G. Endocrine
   i. Hypoglycemia (ketotic and nonketotic)
   ii. Diabetes mellitus (an important and common disorder) and ketoacidosis
   iii. Hypothyroidism
   iv. Other, including adrenal insufficiency
H. Inborn errors of metabolism (primarily systemic; long list! Presentation typically in neonatal period, infancy, and early childhood). Some examples:
   i. Urea cycle
   ii. Congenital lactic acidosis syndromes
   iii. Intermittent maple syrup urine disease
   iv. Mitochondrial cytopathies
   v. Carnitine palmitoyltransferase deficiency, etc.
I. Hypothermia/hyperthermia
J. Nutritional deficiencies
K. Iatrogenic
   i. Rapid correction of fluid, electrolyte, renal, acid–base derangement
   ii. Parenteral nutrition
   iii. Pediatric phosphate enema
L. Toxic
   i. Burns
   ii. Intussusception

III. Either, or not classifiable; status epilepticus (which may have a variety of causes)

Note: The above disorders may be associated with secondary metabolic disturbance. The distinction between focal and diffuse clinical presentations may be useful but these represent a clinical continuum. Typically, anatomical abnormalities are demonstrated on neuroradiological studies. EEG may exhibit focal or generalized/regional abnormalities and pattern may be informative.
Note: Typically, clinical features are 'diffuse'; anatomical abnormalities may or may not be seen on neuroradiological studies but if present may be 'diagnostic' (as in mitochondrial disorders); EEG findings are generalized although the patterns may be informative.
Caution: The above list is not meant to be exhaustive and reflects a personal approach to classification.
CNS, central nervous system; EEG, electroencephalogram; MRI, magnetic resonance imaging; NAI, nonaccidental injury.

antidiuretic hormone secretion or diabetes insipidus can complicate intracranial infection or traumatic brain injury. Some causes of coma such as cardiac arrest (hypoxia–ischemia) not only produce structural change in the brain but also cause systemic metabolic dysfunction, including hematological, renal, and hepatic dysfunction, which contribute to the comatose state.

19.3.2. Epidemiology of nontraumatic coma

19.3.2.1. Specific information

The causes of coma are influenced by geography, race (ethnic background) and season. The relative causes of coma in published series will also be influenced by referral and ascertainment biases. Table 19.2 lists the causes of nontraumatic coma from two recent series, one from the 'former Northern NHS region of England' (Wong et al., 2001) and the other from Chandigarh, India (Bansal et al., 2005) and from an older series of cases from Winnipeg, Canada. Neonates were excluded. Infections (systemic, respiratory, and central nervous system (CNS)) were responsible for 38% of cases in the series of Wong et al. (2001) but the authors did not stratify the causes. They found *Neisseria meningitides* to be the commonest identified pathogen. Wong et al. found the incidence of nontraumatic coma to be 160 per 100 000 children per year under 1 year of age (neonates excluded) compared to <40 per 100 000 children per year for those between 2 and 16 years. The higher incidence resulted from a relatively greater percentage of congenital and infective causes for coma in infants. The congenital causes included CNS and cardiac malformations and complications of surgical treatment for these conditions. The fall in maternally acquired passive immunity may explain the slightly higher incidence of infective causes in those <1 year old. Coma due to diabetic ketoacidosis was the first presentation of diabetes mellitus in seven of eight

Table 19.2

Relative causes of nontraumatic coma (%)

Diagnosis	Wong et al. (2001) $n = 283$	Bansal et al. (2005) $n = 100$	Seshia (1985) $n = 177$
I. Infection	38	60	29
i. Bacterial meningitis	NS	16	18
ii. Tuberculous meningitis	NS	19	–
iii. Encephalitis	NS	21	11
iv. Cerebral malaria	NS	2	–
v. Other	NS	2	–
vi. Systemic sepsis	NS	–	1.5
II. Toxic	10	3	7
III. Metabolic	5	11	10
i. Inborn error	2	NS	1
ii. Acquired	3	?11	9
IV. Anoxia-diffuse ischemia	5	4	26
V. Epilepsy/status epilepticus	9	10	15
VI. Intracranial vascular	NS	7	6
VII. Other	9	5	1.5
VIII. Unknown	14	–	1

NS, not specified.

diabetic children. Medium-chain acyl-CoA dehydrogenase deficiency, an inborn error of fatty acid oxidation, was the commonest inborn error of metabolism (three of six cases).

19.3.2.2. Infective causes in North America

Rickettsial infections occur in certain parts of North America, as do Lyme disease and arborvirus infections, often seasonally. There have been clusters of western equine encephalitis during some years in Manitoba, Canada (Medovy, 1976; Seshia et al., 1977). West Nile virus encephalitis spread to the North American continent in 1999, resulting in the 'largest epidemic of neuroinvasive west Nile virus ever reported' since then (Hayes, 2005). Clusters of cases of west Nile virus encephalitis have occurred in (several provinces of) Canada in the summer months, especially between 2002 and 2005; although the majority of cases have been adults, Yim et al. (2004) reported four children with west Nile virus infection, a condition that must be considered in children who present with encephalitic or hepatic symptoms in affected areas.

19.3.2.3. Tropical causes

Cerebral malaria and Japanese encephalitis are common in India, Africa, and south-east Asia and typically occur in cluster or epidemics during the monsoon season when the mosquito population is high, although cases of malaria can be seen throughout the year in endemic areas (Crawley et al., 1996, 2001; Baruah et al., 2002; Solomon et al., 2002; Njuguna and Newton, 2004). Serious epidemics of Japanese B encephalitis have been recurring in various parts of India in recent years. Other protozoal (example: amebiasis) and parasitic infections also have a geographical predilection. Tuberculous meningitis remains as frequent and important a cause of coma in India now as 30 years ago (Bharucha and Bharucha, 1973; Bansal et al., 2005). In western countries, including North America, tuberculous meningitis must be considered in immune-compromised patients (such as those with human immunodeficiency virus (HIV) infection). Intracranial infection (tuberculous meningitis, bacterial meningitis, and viral encephalitides) accounts for over 60% of cases of nontraumatic coma in developing countries (Sofiah and Hussain, 1997; Bansal et al., 2005) (Table 19.2). Global travel and immigration have become common. Hence, one may encounter 'tropical' causes of coma in Western countries.

19.3.2.4. Changes in frequency of causes of nontraumatic coma

There has been a considerable change in the relative frequency of the causes of coma in central Canada over the past two decades (personal experience): bacterial meningitis is now rare and the majority of cases we now see are in aboriginal children. Reye's syndrome was a common entity but has almost disappeared in developed countries.

When Reye's syndrome occurs, a metabolic cause should now be suspected. Coma related to intractable epilepsy and status epilepticus is now rare, probably because of better compliance (through education) of those on anticonvulsants and good first-response teams. For these reasons, viral encephalitis, hypoxia–ischemia, and acquired metabolic/toxic causes are relatively more common causes of nontraumatic coma in our region. Status epilepticus, usually febrile (not due to an intracranial infection), is a common cause of coma that resolves within 6–8 hours. Inborn errors of metabolism are uncommon causes (Table 19.2), especially in those over 1 year of age.

Mycoplasma pneumoniae encephalitis is now considered to be responsible for 5–10% of acute childhood encephalitis in Europe and North America and may present with a clinical picture of encephalitis or acute disseminated encephalomyelitis (Bitnun et al., 2003). Postinfectious acute disseminated encephalomyelitis is being increasingly recognized by magnetic resonance imaging (MRI).

We are not aware of recent population-based studies from developed countries that reflect these trends.

19.3.3. Inborn errors of metabolism

We include under this heading disorders that affect the brain primarily and traditionally have been considered to be neurodegenerative (neurometabolic) diseases, and those that have striking systemic abnormalities (such as the aminoacidopathies). Some forms of leukodystrophy (leukoencephalopathy) may be unique to certain ethnic groups. Cree leukoencephalopathy, a rapidly progressive autosomal recessive disorder, affects North American Cree and Chippewayan populations with a gene defect at the EIF2B5 locus and can present during infancy as coma triggered by infection (Fogli et al., 2002). Some inborn errors of metabolism may be overrepresented in certain populations (see, for example, Haworth et al., 1991).

19.3.4. Other causes

Sickle cell disease and betathalassemia predispose to stroke (Kirkham and DeBaun, 2004; Prengler et al., 2005), an important cause of coma. These disorders occur more frequently in certain ethnic groups (south-east Asian, Chinese, Mediterranean, Middle-Eastern, African, and some south Asian). Since many residents in Western countries are of these ethnic origins, clinicians must recognize them as at risk for complications, take preventive measures wherever possible and investigate those who present with stroke accordingly.

There are also geographically 'distinctive' causes of poisoning. Thus, accidental or suicidal poisoning with organophosphate insecticides (anticholinesterase) is common in developing/tropical countries, probably because they are commonly used and available (Verhulst et al., 2002). One must therefore be familiar with the unique causes of coma in one's geographical region.

19.3.5. Is the cause always identified?

A cause for nontraumatic coma could not be established in two of a series of 177 cases (Seshia, 1985) and in 14% of 283 episodes of nontraumatic coma in the study of Wong et al. (2001). In Wong et al'. s series, an infective cause was suspected in 50% of the unknown group, a metabolic cause in 25% and other causes in 15% but these causes could not be established with certainty.

19.3.6. Traumatic coma

The incidences of traumatic brain injury (TBI) and nonaccidental injury (NAI) have decreased in our region. Nonaccidental or inflicted head injury refers to deliberately inflicted head injury in the spectrum of child abuse.

19.3.7. The neonate

We are not aware of any systematic studies on coma in the neonate. The principles of approach are the same as for older children. However, ocular movements and pupillary responses are often difficult to assess. The neurological examination is influenced by the gestational age and, in our experience, frequently confounded by depressant drugs given for sedation. Many ill neonates are ventilated. Important causes of coma include inborn errors of metabolism, hypoxic–ischemic encephalopathy, intracranial infection (e.g., herpes simplex encephalitis, HIV encephalitis in high-risk groups), intracranial hemorrhage, and maternal drug ingestion or administration (especially narcotics). In an as yet unpublished retrospective review of suspected neonatal brain death (Hahn, personal communication), the etiologies were hypoxic–ischemic encephalopathy 70%, intracerebral hemorrhage 18%, and inborn errors of metabolism 12%.

19.3.8. Clinical clues to etiology

In most cases, the history will provide a clue to the cause and there may be an obvious coma-provoking antecedent event. In others, the diagnosis will have to be teased out from the history, examination, or investigations. Pyrexia should suggest an infective cause. However, infants with intracranial or systemic infections may be

hypothermic because of unstable temperature control, associated shock, or drop in body temperature during transportation and an infective process must be excluded in such cases (Seshia et al., 1977). There are many causes for cardiorespiratory arrest in children (Seshia et al., 1979; Kirkham, 1994) and these include cardiac disease, near drowning, choking on food, or aspiration. Defects of beta-oxidation (typically very-long-chain acyl CoA dehydrogenase deficiency) must be excluded where the etiology of the acute life-threatening event is uncertain (Gregersen et al., 2004). Fever may trigger metabolic decompensation and episodes of coma in those with inborn errors of metabolism (Surtees and Leonard, 1994).

Although traditionally considered to present in the neonatal period or infancy, inborn errors of metabolism may present at any age, including adult (Saudubray et al., 1990; Batshaw, 1994; Poggi-Travert et al., 1994; Surtees and Leonard, 1994; Scriver et al., 2001; Gaspari et al., 2003; Menkes and Wilcox, 2006). Failure to thrive and symptoms and signs of neurodevelopmental dysfunction may precede the acute encephalopathy. There may be parental consanguinity or a family history of similar disorder and the clinical course may be punctuated by episodes of coma. Multifocal and myoclonic seizures are common. Children with leukodystrophy can present in coma; features of adrenal crisis can complicate adrenoleukodystrophy (Stephenson et al., 2000; Espay et al., 2002).

Episodic coma may also be due to nonaccidental poisoning (Dine and McGovern, 1982). Exogenous poisoning occurs most frequently in adolescents and occasionally in toddlers. Hence, when the cause of coma is not apparent, the history must include information about drugs and substances in the home(s) of the care-giver(s).

A child with an established diagnosis of epilepsy who presents in coma may be in nonconvulsive status epilepticus.

19.4. Assessment

The approach to the comatose child has been discussed by several authors (Gordon et al., 1983; Seshia, 1985; Kirkham, 2001; Michelson and Ashwal, 2004).

19.4.1. General principles

The assessment and management of a child in coma requires a multidisciplinary coordinated team approach with each member of the team being assigned a specific responsibility especially when coma is complicated by poor cardiorespiratory function, shock, or status epilepticus, all of which must be rapidly addressed. In these situations, measurements of arterial blood pressure, central venous pressure, urinary output and core body (rectal or esophageal) temperature are essential and the ICP may also need to be monitored. Simultaneously, hypoglycemia must be excluded (and if present treated) and hematological, biochemical and acid–base status assessed and derangements corrected. Evidence of internal and external injuries must be sought and hypothermia/hyperthermia treated. Raised ICP must be anticipated. Decerebration, an important clue to raised ICP, should not be mistaken for epileptic seizures (Brown et al., 1973). Any clinical suspicion of raised ICP and brain shifts should be treated urgently (see below), the ICP and cerebral perfusion pressure (CPP) monitored and a computed tomography (CT) scan done promptly. An EEG may also need to be done urgently if nonconvulsive status epilepticus is suspected and continuous EEG monitoring may be necessary in some cases. Focal seizures suggest a focal structural lesion and if the child is febrile the cause is probably infective. The occurrence of multifocal or myoclonic seizures in a comatose child favors a metabolic cause or global hypoxia–ischemia.

Once these initial steps are taken, a detailed history is taken and examination completed. In our experience, the cause of coma is often apparent when these are done well and conversely a diagnosis is often missed when the history and examination are incomplete. The history and examination also guide the choice of further investigations and management. These can be completed by one individual within 15 minutes. Fragmentation should be avoided.

Ideally, staff in the front line (nursing stations/hospitals in remote communities and first-line responders) must have basic skills and knowledge about the initial management of the comatose child. Telephone and tele-medicine links are becoming available in many parts of the world (major thrust in countries like India) and hence pediatric expertise can be made immediately available to remote communities, optimizing the crucial initial management of the critically ill child.

19.4.2. General examination

The pulse, temperature, respiration, and blood pressure should be recorded and all major vessels palpated. Fever suggests infection. An undiagnosed coarctation of the aorta may be the cause of hypertension in the upper limbs and an associated ruptured intracranial aneurysm responsible for coma (one of us encountered such a case). Eden et al. (1977) discussed hypertension in acute neurological disease; they suggested that 1) seizures, retinal hemorrhage and pulmonary edema could occur secondary to hypertension, 2) hypertension often occurred with brainstem dysfunction, 3) it was often paroxysmal or persistent

and 4) it frequently occurred with electrolyte and fluid disturbance. A CT scan should be done as an emergency in any child with hypertension to exclude an intracranial cause or identify structural changes (such as posterior reversible leukoencephalopathy) secondary to hypertension (an MRI with magnetic resonance angiography/venography (MRA/MRV) will clearly provide better brain definition and may be necessary if the CT scan is unhelpful). Elevation of systemic blood pressure in response to elevated ICP, the Cushing's response, is an adaptive mechanism for maintaining CPP. Clinical and neuroradiological data, ICP, and CPP will help to distinguish the Cushing's response from non-CNS causes of hypertension.

The presence of bruising would suggest accidental or NAI or a hematological disorder. Meningococcal or rickettsial infection, where prevalent, are often associated with 'characteristic' petechiae. In infants, the head circumference should be measured and compared with previous values, the anterior fontanelle assessed, the sutures checked for separation, scalp veins observed for distention, and head auscultated for bruit. Transillumination, a simple bed-side test, can also be done. Evidence for dysraphism should be sought, especially over the occipital and lumbosacral regions since a sinus in one of these areas may be a clue to meningitis.

The length and weight must be taken, especially if the cause of coma is not apparent, and compared to previous values if possible, for clues to failure to thrive, a finding that may suggest an inborn error of metabolism. The external features may be diagnostic of a specific syndrome.

One should assess for meningeal irritation but these signs may be absent in infants or those critically ill or deeply comatose from meningitis or subarachnoid hemorrhage. Hence, meningitis must always be considered in such infants.

The chest and abdomen must be examined. Hepatomegaly and splenomegaly may suggest a metabolic disorder and a cardiac lesion could be responsible for a stroke.

19.4.3. Neurological examination

A neurological examination cannot be performed if the child has received neuromuscular blocking drugs or high doses of anticonvulsants or anesthetic agents for the treatment of refractory status epilepticus. The administration of anticonvulsants in therapeutic doses does not confound the neurological examination (Seshia et al., 1983). Interobserver agreement is good for most of the variables used in assessing comatose children (Yager et al., 1990; Seshia et al., 1991; Newton et al., 1995).

19.4.3.1. Grading of coma

The Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974) has been widely used to assess the severity and depth of coma in adults and children. Many of the responses in the GCS require an adult level of neurodevelopmental function and cannot be easily graded in those under 3 years of age (Simpson and Reilly, 1982; Yager et al., 1990). There are several modifications of the GCS for use in children (for tests of interobserver variability comparing several of these scales, see Yager et al., 1990 and Newton et al., 1995). The 0–IV scale had the best interobserver agreement. One modification of the GCS was found to have good interrater agreement (Tatman et al., 1997) and has been endorsed by the British Paediatric Neurology Association (Kirkham, 2001). Scales modeled after the GCS (Tables 19.3 and 19.4) have two components:

1. Individual scaled responses for eye opening, verbal response, and motor 'behavior'. A number of clinical factors can confound assessment: swollen eyelids

Table 19.3

Revised Simpson–Reilly Scale

A. Eye opening	
Spontaneous	4
To speech	3
To pain	2
None	1
B. Best verbal response	
Oriented	5
Words	4
Vocal sounds	3
Cries	2
None	1
C. Best motor response*	
Obeys commands	6
Localizes pain	5
Withdraws to pain	4
Abnormal flexion (to pain)	3
Extension (to pain)	2
None	1
Age-dependent best aggregate score	
Birth–6 months	9
6–12 months	12
1–2 years	13
2–5 years	14
>5 years	15

*Note: Simpson and Reilly (1982) described a 14-point pediatric scale corresponding to the then 14-point adult Glasgow Coma Scale (GCS). We have modified the motor responses in the Simpson–Reilly Scale to correspond to the current 15-point (with 6 instead of 5 motor categories) adult GCS.

Source: with permission from Simpson D, Reilly P (1982). Paediatric coma scale [letter to the editor]. Lancet 2: 450.

Table 19.4

Modified Glasgow Coma Score

	>5 years	<5 years
Eye opening		
E4	Spontaneous	As older child
E3	To verbal stimulus	As older child
E2	To pain	As older child
E1	No response to pain	As older child
Verbal (not used in intubated children; use 'grimace' instead)		
V5	Orientated	Alert, babbles, coos, words or sentences to usual ability
V4	Confused	Less than usual ability or spontaneous, irritable cry
V3	Inappropriate words	Cries to pain
V2	Incomprehensible sounds	Moans to pain
V1	No response to pain	No response to pain
VT (go to 'grimace')	Intubated	Intubated
Grimace (use in intubated children regardless of age)		
G5	Spontaneous normal facial/oromotor activity, e.g., sucks tube, coughs	
G4	Less than usual spontaneous ability or only responds to touch	
G3	Vigorous grimace to pain	
G2	Mild grimace or some change in facial expression to pain	
G1	No response to pain	
Motor		
M6	Obeys commands	Normal spontaneous movements or withdraws to touch
M5	Localizes to pain stimulus	As older child
M4	Withdraws from pain	As older child
M3	Abnormal flexion to pain	As older child
M2	Abnormal extension to pain	As older child
M1	No response to pain	As older child

*Pain as nail bed pressure with pencil.

Source: from Tatman A, Warren A, Williams A et al. (1997). Development of a modified paediatric coma scale in intensive care clinical practice. Arch Dis Child 77: 519–521, with permission from the BMJ Publishing Group.

and aphasia can influence eye opening; aphasia and intubation can affect the verbal response; and limb injuries can modify motor responses. Deafness, from intracranial infection or blood in the ears, will interfere with response to verbal stimuli. Scoring in these situations is unreliable. Tatman et al. (1997) suggested that a grimace score (Table 19.4) was more reliable than the verbal score in intubated children.

2. The summed score. To sum or not to sum? It is common place to describe a patient's comatose state solely by the summed score (example: GCS = 3, 8, or 15). Summed scores cannot be equated with clinical assessment. Several authors have cautioned against such usage and emphasized the importance of describing each response separately and supplementing the GCS with other clinical data (Teasdale et al., 1979; Price, 1986; Hennes et al., 1988; Starmark et al., 1988; Yager et al., 1990; Seshia, 1994). We would encourage the use of a child-oriented scale (Tables 19.3 and 19.4) rather than the adult GCS so that scoring is age-appropriate. We recognize that a summed score enables first-line responders, paramedical, emergency, and intensive care staff to provide each other with some idea of coma severity. However, summed scores as the sole descriptor of a child's comatose state should be discouraged, especially in the presence of confounding factors. In these situations, it would be best to describe the severity of coma on a 0–IV scale.

19.4.3.2. Ocular findings

The fundi must always be examined. Retinal hemorrhages strongly suggest intracranial hemorrhage and the possibility of NAI must be considered. Papilledema may be seen early in the comatose state (Pagani, 1969; Brown et al., 1973) but is rare. Raised ICP is unlikely in the presence of venous pulsations (Levy, 1978). The absence of venous pulsation is not helpful.

The 'behavior' of the eyeballs at rest is informative. Focal nystagmus often with slight quivering of the eyelids may suggest status epilepticus. Persistent ocular deviation may be due to hemispheric or brainstem

dysfunction or epileptic in origin. Ophthalmoplegia, ocular bobbing, convergent or divergent spasms, episodes of lid retraction and spontaneous blinking usually suggest brainstem dysfunction (Seshia et al., 1977). Overt nystagmus can be seen with barbiturate or phenytoin poisoning. Extraocular movements should be tested with the doll's eye maneuver (if not contraindicated in those with head/neck injury) and the ice water caloric test. Testing in neonates is unreliable (Seshia, personal communication). Ocular findings provide information about site and cause of dysfunction. In general, abnormalities of lateral gaze result from structural rather than metabolic dysfunction. Impaired upward gaze strongly suggests central herniation and is a finding that must be acted upon with alacrity. Ophthalmoplegia, although usually suggestive of a structural brainstem lesion, can occur with phenytoin poisoning (Spector et al., 1976) and in myasthenia gravis.

The corneal reflex tends to be abolished bilaterally in those in deep coma (Seshia et al., 1977). The reflex can be absent unilaterally in those with hemispheric disturbance (Ross, 1972) or with pontine lesions.

The pupils should be assessed at rest and the reaction to light, direct and consensual, noted. Pupillary responses correlate with the severity of coma (Seshia et al., 1977). Preserved pupillary responses despite other features of brainstem dysfunction may favor a metabolic or toxic cause. Disorders of neuromuscular transmission must be excluded in those who have well preserved pupillary responses despite impaired extraocular movements. The occurrence of a unilaterally fixed and dilated pupil is evidence of transtentorial herniation and urgent intervention is required. The abrupt occurrence of bilaterally fixed and dilated pupils is also an equal emergency, reflecting central herniation. The inadvertent use of topically administered sympathomimetic or anticholinergic agents or poisoning with barbiturates, sympathomimetics, or anticholinergics can also produce fixed and dilated pupils. Structural pontine lesions are uncommon in children and poisoning with narcotics, phenothiazines, ethanol, valproic acid, barbiturates, or anticholinesterases should be considered when the pupils are very small (Mitchell et al., 1976; Steinman et al., 1979; Verhulst et al., 2002).

19.4.3.3. Motor system findings

Muscle tone should be assessed and responses to a supraorbital painful stimulus checked. Limb withdrawal to local stimuli, including over the finger tips or sternum, may reflect spinal reflex. Decorticate and decerebrate patterns are often asymmetrical and may be intermittent; they are often provoked by stimulation; in infants, decerebration may be preceded by bicycling/paddling movements of the limbs (Brown et al., 1973). Neither should be mistaken for epileptic seizures. Decerebration is usually a reflection of raised ICP and central herniation. Decortication and decerebration can result from metabolic, toxic, and structural 'causes' of coma (Greenberg and Simon, 1982). Focal weakness usually implies a structural lesion, although it may be transient as in Todd's paralysis after focal status epilepticus or occur in metabolic coma. Dystonia or dyskinesia in a comatose child without antecedent history of a neurometabolic disease should suggest phenothiazine or phenytoin poisoning. Rarely, metabolic diseases such as glutaric aciduria type I and mitochondrial cytopathy may present acutely as coma with extrapyramidal signs, precipitated by systemic illness.

Flaccidity and areflexia are grave signs in a comatose child. A lower motor neurone/neuromuscular disorder, the effect of neuromuscular blocking agents, or high levels of depressant drugs should be excluded as causes. Therapeutic doses/levels of anticonvulsants do not cause areflexia or severe hypotonia.

19.4.3.4. Respiration

Abnormal respiratory patterns help in localizing site of dysfunction and assessing the 'rostral–caudal' progression of the effects of supratentorial lesions. These patterns include: 1) normal; 2) Cheyne–Stokes – the site of dysfunction is generally deep in the cerebral hemispheres or diencephalons, rarely in the upper pons; 3) central neurogenic hyperventilation – the site of dysfunction is the brainstem tegmentum; 4) apneustic from mid- or low pontine dysfunction; 5) ataxic from dysfunction in the medulla; and 6) apnea from medullary dysfunction. The majority of the causes of coma in children affect the brain diffusely and unilateral supratentorial structural lesions in children are very uncommon; hence, we rarely found abnormalities of breathing useful in assessing clinical course (Seshia et al., 1977) and ataxic or apneustic respiration or apnea frequently occurred with no warning. However, when a particular pattern is present it may suggest the site of dysfunction and therefore a cause. We have seen cases with Leigh's syndrome (in most cases a mitochondrial cytopathy) with central neurogenic hyperventilation and apneustic and ataxic respiration because of brainstem or medullary involvement without cerebral edema.

19.4.3.5. Blood pressure

Those dealing with comatose children should be familiar with the age-dependent values of normal blood pressure. Hypertension in the comatose child has been discussed earlier. Hypotension and inability to maintain normal blood pressure may be due to shock/sepsis or to central causes.

19.4.3.6. Temperature regulation

Systemic or CNS infections are more often the cause of hyperpyrexia than a primary neurogenic cause. Anticholinergic poisoning can cause fever. Hypothermia strongly suggests sepsis/shock. A rare cause of hypothermia is inadequate warming during transfer. Temperature and blood pressure regulation are lost in severe hypothermia or brain death.

19.5. Investigations

Investigations have to be tailored to the individual case and the clinician's diagnostic considerations. Furthermore, the history may have provided information about pre-existing conditions (e.g., an inborn error of metabolism, diabetes mellitus, epilepsy) that may predispose to coma. In these situations, investigations and management are directed to the cause.

19.5.1. General

The initial assessment should have included a complete blood count, blood gases, acid–base state, and urine examination, and a general battery of blood-based biochemical tests such as electrolytes, sugar, creatinine, calcium, phosphate, lactate, ammonia, alanine aminotransferase (ALT), and more specific hematological tests if warranted.

19.5.2. Tests for infection (sepsis, meningitis, encephalitis)

If the data suggest sepsis then blood and urine cultures should be done and treatment with the most appropriate antibiotic started. If meningitis is suspected then a lumbar puncture should be done and the cerebrospinal fluid (CSF) examined appropriately. Where the diagnosis is uncertain, it is always prudent to send a CSF specimen for lactate and save a sample for special biochemical or viral studies that may be needed. The blood glucose should be determined near simultaneously with the CSF collection. Kneen et al. (2002) found CSF analyses to be incomplete in a high percentage of those who had lumbar punctures, an experience not unique to their center. A CT scan should be performed if focal signs are present or raised ICP is suspected. If a CT is not immediately available, one of us (SSS) recommends a lumbar puncture after the administration of mannitol (0.5 g/kg) provided there are no signs of brain shift, an approach also advocated by Kirkham (2001). Kneen et al. (2002) and Riordan and Cant (2002) have discussed the safety, risks, and role of lumbar puncture in those suspected of having CNS infection. They emphasized that a normal CT scan does not exclude raised ICP, as did Cabral et al. (1987). Both concluded that the information from lumbar puncture in those suspected of having meningitis was potentially helpful, and inappropriate or unnecessary antibiotic use would be avoided, minimizing the risk of creating antibiotic resistance. Where a lumbar puncture seems contraindicated, the most appropriate therapeutic agent(s) should be started (Singhi et al., 2001), if necessary in consultation with the local infectious disease expert. The blood may need to be examined for malarial parasites and the CSF for the tuberculosis bacillus or fungi in the appropriate locales. Molecular diagnostic tests on blood or CSF can be diagnostic in *N. meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Mycobacterium tuberculosis*.

19.5.3. Toxicology screen

If a specific history is not obtained, and the cause of coma is not apparent (especially in a teenager or toddler), a toxicology screen should be done. Most screens test for a wide variety of commonly used/abused drugs and substances.

19.5.4. Neuroimaging

CT scan is now generally readily available on an emergency basis in most centers and is usually the first imaging of choice. A CT scan with and without contrast should be done when the cause of coma is not apparent or when the history and examination suggest focal, regional, or diffuse brain dysfunction (e.g., focal seizures, hemiparesis, etc.). The test should be supplemented with CT angiography/venography if a vascular cause is suspected. When there are extrapyramidal or brainstem signs or evidence of diffuse brain dysfunction, then MRI is preferred. Most centers can offer an MRI (under controlled ventilation) on an emergency basis, but if this is not possible then a CT can be done first. An ultrasound of the head at the bedside in a critically ill neonate is both convenient and often useful as an initial imaging modality in this age group but even in neonates an MRI is necessary to define brain structures.

MRI has helped to define acute disseminated encephalomyelitis and acute necrotizing encephalopathy of childhood (Mizuguchi et al., 1995) as important 'syndromes' in which coma (often triggered by a nonspecific illness) is an important clinical presentation; some cases of the latter entity may reflect mitochondrial cytopathies or as yet unknown inborn errors of metabolism. Hence, an MRI (supplemented by MRA/MRV if needed) is necessary when the cause of coma cannot be established

or if a neurometabolic disorder is suspected. MR spectroscopy (MRS) of the brain (and muscle) can be diagnostic in tumors and neurometabolic disorders. MRS data can provide information about brain metabolites after injury and findings may be predictive of outcome (Shutter et al., 2004).

CT and MRI have complementary roles in the assessment of TBI and NAI. CT has high sensitivity and specificity for diagnosing acute intraparenchymal, subdural, subarachnoid, and epidural hemorrhages. Lesions requiring urgent surgical intervention are thus readily recognized. CT is unreliable for detecting diffuse axonal injury and MRI should be done if diffuse axonal injury is suspected. MRI is also more sensitive for detecting lesions of different ages, as may occur with NAI (Datta et al., 2005). Additional investigations for spinal, abdominal, chest, and limb injuries may need to be conducted. Internal organ injury must be suspected when traumatic brain injury is complicated by hypotension.

It is best to discuss the clinical situation with a neuroradiologist so that the most appropriate test is done and the techniques tailored to the case, a cost-beneficial approach.

19.5.5. Conventional EEG

An EEG (ideally polygraphic in the neonate and with video if there are involuntary movements) is essential in diagnosing nonconvulsive status epilepticus. Seizures occur in a substantial percentage of comatose patients, regardless of underlying cause (Seshia et al., 1977; Johnston and Seshia, 1984; Tasker et al., 1991; Kirkham, 2001). Kivity and Lerman (1992) described children with the syndrome of benign childhood epilepsy with occipital paroxysms whose initial onset was with abrupt and prolonged loss of consciousness; the manifestations of epilepsy were subtle deviation of the eyes. For these reasons, a conventional EEG is an essential test in comatose patients. EEG patterns may provide a clue to the nature of the process or cause (such as herpes simplex encephalitis). Serial EEGs can help with prognostication. Discussion with a clinical neurophysiologist will ensure optimal testing for the problem at hand.

19.5.6. Continuous EEG (with or without video) monitoring

Continuous EEG monitoring is becoming increasingly common in the management of comatose adults (Young and Doig, 2005) but we are not aware of comparable data in children. Continuous EEG monitoring becomes essential in those whose (continuing) coma cannot be readily explained, who have refractory status epilepticus, when subjects are sedated or treated with neuromuscular blocking agents, and during neurointensive treatment for refractory status epilepticus or raised ICP. Clinicians should be aware that clinical and electrographic seizures can elevate ICP and provoke brain shifts (Minns and Brown, 1978; Brooks et al., 1982).

19.5.7. Other tests

These will be based upon the considered causes. They include cardiac assessment if a cardiac disorder is suspected; metabolic/enzyme studies on blood, urine and CSF for specific metabolic disorders; and examining tissue histologically for enzymes or genes for specific neurometabolic disorders. A skeletal survey should be done when NAI is suspected or in those who have retinal hemorrhages without a hematological cause. Special hematological studies may be required in those who have strokes (Hutchinson et al., 2004; Sebire et al., 2005). Testing for viruses, fungi, and acid-fast bacilli require input from an infectious disease/laboratory specialist.

19.5.8. Evoked potentials

Visual, auditory, and somatosensory evoked potentials do not provide specific information about the cause of coma. They can give information about site of dysfunction.

19.5.9. Serum biomarkers

Serum biomarkers such as serum neuron-specific enolase (NSE), S100B, and myelin basic protein (MBP) were studied by Berger et al. (2005) in children with traumatic and NAI (inflicted and noninflicted traumatic brain injury). Concentrations of NSE and S100B were increased in both groups compared to controls. Serum MBP was increased only in those with intracranial hemorrhage. Peak levels occurred at mean periods of 22–53 hours in those with NAI. The authors felt that elevated serum biomarkers could prompt physicians to exclude NAI. Serum biomarkers have also been used as potential predictors of outcome.

19.6. Management

19.6.1. General

The general principles have been discussed. The safety and specificity of naloxone is such that it can be used as a therapeutic and diagnostic test in suspected drug-induced coma (Krenzelok, 2002). Organ injuries and spinal fractures must be suspected in those with traumatic brain injury and cases managed accordingly during transfer.

19.6.2. Seizures

We have recently discussed the treatment of status epilepticus (Prasad and Seshia, 2006) in which we emphasized the importance of pre-hospital management (Fig. 19.1). Metabolic derangements may contribute to seizures and must be identified and treated. Nonepileptic motor phenomena such as decerebration should not be mistaken for seizures. The longer a seizure lasts, the more difficult it is to control (Working Group on Status Epilepticus, 1993; Meldrum, 1999) and relative refractoriness may develop to drugs such as diazepam (Kapur and MacDonald, 1997). A benzodiazepine (diazepam, midazolam, or lorazepam) is generally the first drug of choice (Status Epilepticus Working Party, 2000; Mitchell, 2002; Riviello and Holmes, 2004; Prasad and Seshia, 2006). The benzodiazepine is followed by either phenobarbital (if the child is febrile) or phenytoin/fosphenytoin if afebrile. Phenytoin may be ineffective when the child is febrile. The two drugs can be used together if either one alone is ineffective. Phenobarbital is an easy, effective, and affordable drug to use, especially in developing countries (Kwan and Brodie, 2004). If seizures/status epilepticus are/is refractory, then the initial step is to confirm the epileptic nature of the event with EEG monitoring and exclude a metabolic cause. In the appropriate circumstance, such as neonates or young infants, a trial of pyridoxine, biotin, or folinic acid may be considered. If a metabolic cause is excluded then our approach is intravenous midazolam or pentobarbital infusion under EEG monitoring. The sensitivity of $GABA_A$ receptors to pentobarbital is preserved even though that of diazepam may be reduced with prolonged seizures (Kapur and MacDonald, 1997; MacDonald and Kapur, 1999). Propofol's use has been questioned (Niermeijer et al., 2003). Valproic acid can be used intravenously in those who have been on the oral drug before but should not be used in those suspected of having a metabolic disorder. The cause of the refractory status epilepticus must be determined. Large doses of pyridoxine are required if the cause is isoniazid poisoning (Caksen et al., 2003). Faulty compliance, metabolic disorders, and intracranial infection are important triggers for refractory status epilepticus.

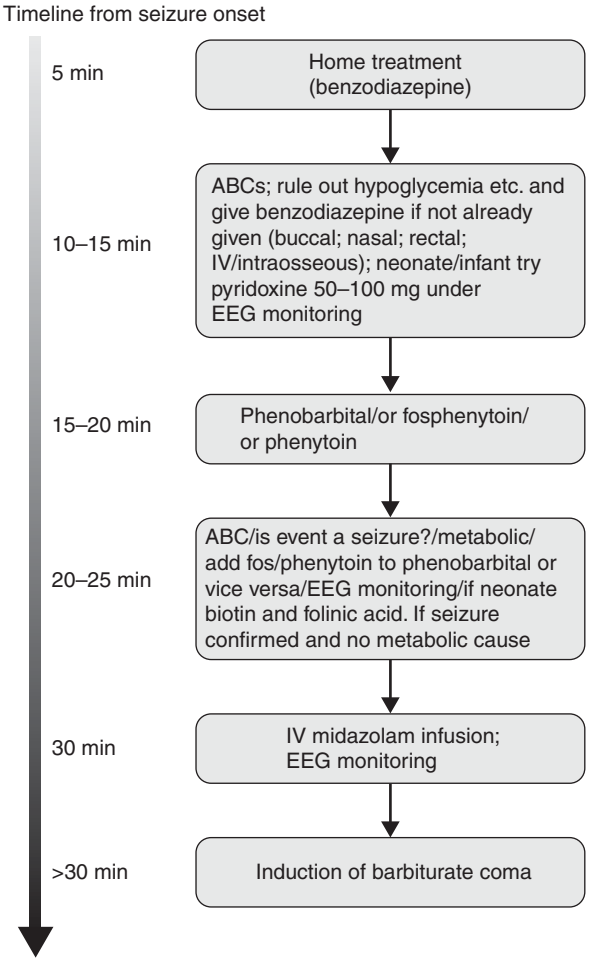

Fig. 19.1. Treatment of epileptic seizures. Note: these recommendations are in keeping with those in the literature; please see text for details. Please consult pediatric drug dosage handbooks, and most recent references available, for doses and side-effects. Modified from Prasad and Seshia, 2006.

19.6.3. Intracranial pressure monitoring

19.6.3.1. Traumatic coma

Under the auspices of several societies, including the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Societies (Society of Critical Care Medicine et al., 2003), the data on the management of severe TBI in children were reviewed in an evidence-based manner and suggestions made on various facets of care. For most aspects, there were insufficient data for treatment standards or guidelines. We provide a summary of the recommendations that are practical and reflect best practice at this time. Readers are encouraged to review the document in its entirety. We have included additional information wherever necessary. Figures 19.2 and 19.3 have been modified from the original to reflect our practice.

1. The evidence to monitor and treat raised ICP has been best established for severe traumatic brain injury in adults. Forsyth et al. (2004) felt that studies conducted to that time lacked randomization

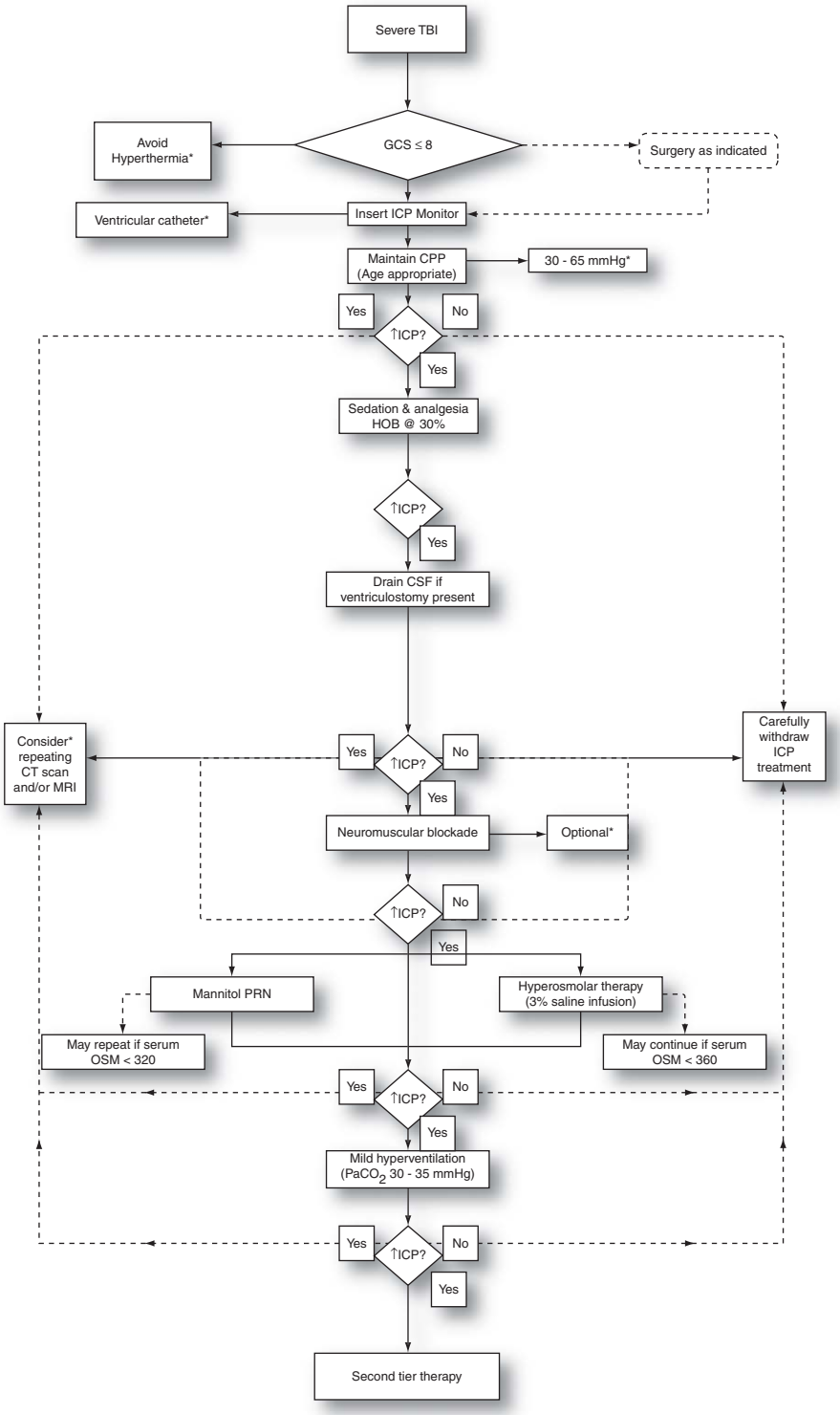

Fig. 19.2. Treatment of raised intracranial pressure in pediatric traumatic brain injury. Asterisked information represents our additions. CPP, cerebral perfusion Pressure; CSF, cerebrospinal fluid; CT, computed tomography of the head; GCS, Glasgow Coma Scale; HOB, head of bed; ICP, intracranial pressure; MRI, magnetic resonance imaging; OSM, osmolarity; PRN, as needed; TBI, traumatic brain injury. Modified from Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents (2003). Chapter 17. Critical pathway for the treatment of established intracranial hypertension in pediatric traumatic brain injury. Pediatr Crit Care Med 4(Suppl.): Figure 1, p. S66, with permission from Oregon Health Sciences University, Portland, OR.

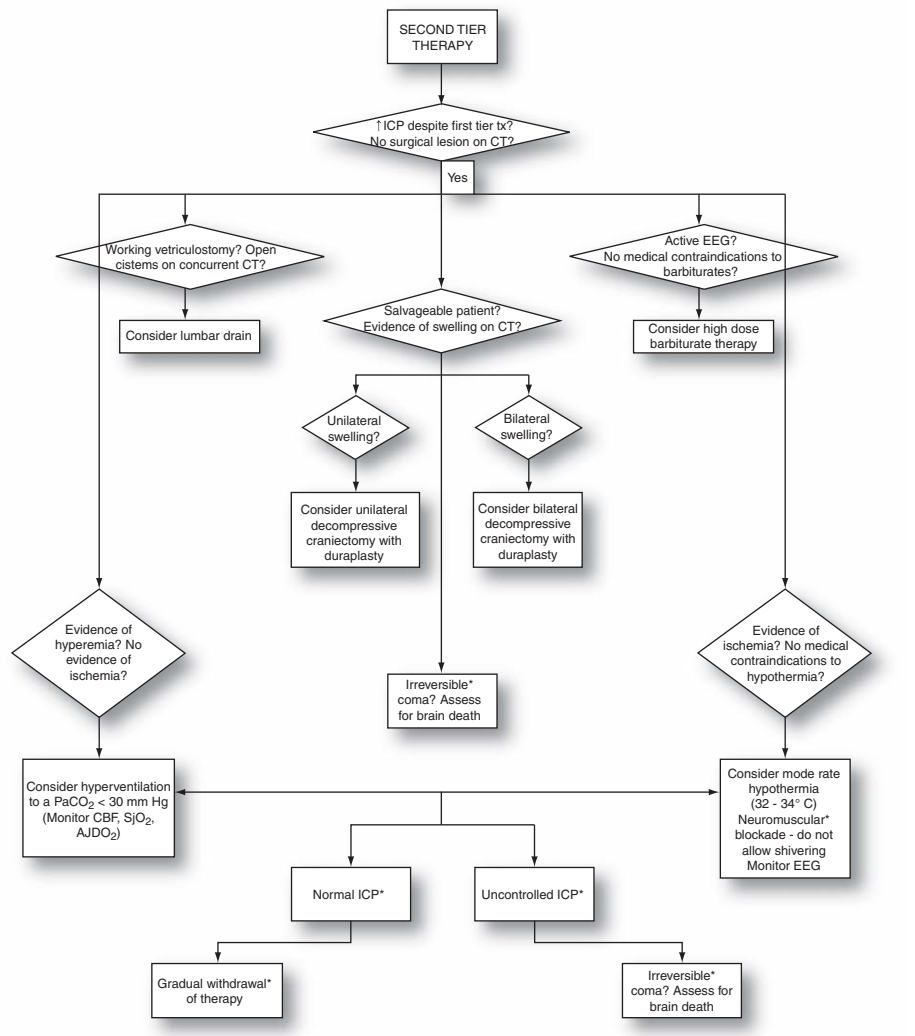

Fig. 19.3. Second tier treatment of raised intracranial pressure in pediatric traumatic brain injury. Asterisked information represents our additions. $AJDO_2$, arterial–jugular venous difference in oxygen content; CBF, cerebral blood flow; EEG, electroencephalogram; SjO_2, jugular venous oxygen saturation. Modified from Guidelines for the Modified from the Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents (2003). Chapter 17. Critical pathway for the treatment of established intracranial hypertension in pediatric traumatic brain injury. Pediatr Crit Care Med 4(Suppl.): Figure 2, p. S67, with permission from Oregon Health Sciences University, Portland, OR.

and none met the criteria for a Cochrane-type review.

2. The presence of open fontanelles or sutures in an infant does not preclude the development of intracranial hypertension or negate the utility of ICP monitoring. A normal initial CT does not exclude raised ICP (see also Tasker et al., 1990).
3. The Society for Critical Care Medicine et al. (2003) suggested (a) monitoring children with a GCS of 8 or less (i.e., deep coma; severe traumatic brain injury), (b) an ICP of 20 mmHg as the upper threshold for treatment, treatment being started at lower pressures if there was evidence of brain shift, and (c) maintaining the CPP above 40 mmHg in children. The authors pointed out that ICP monitoring 'allows the judicious use of interventions such as hyperosmolar therapy, sedatives, paralytics, barbiturates, and ventilatory management. This may avoid potentially harmful, overly aggressive treatment.' They suggested that a ventricular catheter connected to an external strain gauge was the most accurate, low-cost, and reliable method of monitoring ICP and allowed

for therapeutic CSF drainage. Other methods were also discussed.

These data on the management of ICP in children mirror information in adults. Chambers et al. (2005) suggest that CPPs of 53, 63, and 66 mmHg should be the minimum to strive for in those aged 2–6 years, 7–10 years, and 11–16 years respectively. There is little information on the effective CPP in those <2 years of age. The range is probably between 40 mmHg in the term newborn and 53 mmHg in the 2-year-old, and 30–40 mmHg in preterm infants.

19.6.3.2. Nontraumatic coma

The ICP is raised in children suffering nontraumatic coma from a variety of causes that include intracranial infection, hepatic encephalopathy, diabetic ketoacidosis, and inborn errors of metabolism (Brown and Habel, 1975; Rebaud et al., 1988; Tasker et al., 1988a, b; Minns et al., 1989; Minns, 1991; Greene, 1994; Mowat, 1994; Surtees and Leonard, 1994; Kirkham, 2001; Jalan, 2003; Mukherjee et al., 2003; Toftengi and Larsen, 2004). We are not aware of any randomized control trials or guidelines on monitoring ICP in nontraumatic coma. Hence, there is considerable inter- and intracenter variability in practice (personal observation; Segal et al., 2001). However, since raised ICP occurs in a number of medical situations in which children are comatose from infective or metabolic causes, we suggest that the recommendations established for the management of severe traumatic brain injury be adopted: ICP should be monitored in all those who are deeply comatose with a GCS of <8, those who show clinical features of brain swelling/brain shifts with higher summed GCS scores, those at risk for raised ICP, and those heavily sedated or treated with neuromuscular blocking agents.

19.6.4. Measures to treat raised ICP

The general principles of management have changed little since Lundberg (1960) discussed ICP monitoring and raised ICP. The objective is to keep the ICP <20 mmHg but counter brain shift and reduce CPP if these occur at lower ICPs.

19.6.4.1. General measures

These include avoiding overhydration (hence, monitoring central venous pressure is important), head end of the bed slightly elevated, head in the midline, avoiding mechanical obstruction to venous outflow from the head and minimizing unnecessary stimulation supplemented if clinically necessary by sedation and neuromuscular blocking drugs (in which case, ICP and EEG monitoring are essential). The P_aO_2 should be maintained at 100 mmHg. Hypotension, defined as systolic blood pressure below the 5th percentile for age or by clinical signs of shock, should be corrected. The mean arterial blood pressure should be maintained with inotropic agents if necessary to keep the CPP at age-appropriate values.

19.6.4.2. Body temperature

Fever, usually defined as core body temperature >38.3°C, can impair consciousness (Young, 1998), provoke seizures, precipitate coma in those with inborn errors of metabolism, elevate ICP (Stocchetti et al., 2005a), and contribute to brain damage through a number of processes (Busija et al., 1988; Reith et al., 1996; Mickley et al., 1997; Ginsberg and Busto, 1998). Hence, hyperthermia should be avoided and body temperature normalized. Several studies suggest target core temperatures of 32–33°C (see Zygun et al., 2003 and references cited by Nortje and Menon, 2004) in those with severe or refractory raised ICP. Gender may influence the effects of hypothermia; Suzuki et al. (2003) found that post-traumatic hypothermia (33°C) significantly reduced 'short-term histopathological outcomes' in male rats but not in female rats (Suzuki et al., 2003). We are unaware of comparable clinical data.

19.6.4.3. Use of sedation and neuromuscular blockade

Sedation and neuromuscular blockade can facilitate mechanical ventilation and management of raised ICP but should be used for precise and sound clinical reasons. Neuromuscular blockade prevents the shivering that occurs with hypothermia. Continuous infusion of propofol is not recommended.

19.6.4.4. Hyperventilation

The P_aCO_2 should not be reduced below 35 mmHg. Mild hyperventilation (P_aCO_2 30–35 mmHg) should be considered for raised ICP refractory to sedation, analgesia, neuromuscular blockade, and CSF drainage or hyperosmolar therapy. More aggressive hyperventilation (P_aCO_2 <30 mmHg) may be considered for refractory ICP. Cerebral blood flow, jugular venous oxygen saturation, or brain tissue oxygen monitoring must be done to detect cerebral ischemia that may occur from lowering P_aCO_2 excessively. Vigorous hyperventilation may be necessary for a brief period when there is acute deterioration/evidence of brain shift. Stocchetti et al. (2005b) have also reviewed this topic. They point out that hyperventilation in this situation really refers to hypocapnia (P_aCO_2 <40 mmHg) attained by increasing alveolar ventilation. Hyperventilation is most effective when the

raised ICP is due to increased cerebral blood volume from vasodilatation (an occurrence after traumatic brain injury in children and young adults). They also suggest that the general consensus is not to hyperventilate traumatic brain injury patients below a P_aCO_2 of 30 mmHg, unless the circumstances are exceptional. They draw attention to correcting P_aCO_2 target values for altitude and body temperature. Stocchetti et al. (2005b) also emphasized the adverse systemic effects of prolonged hyperventilation.

19.6.4.5. Ventricular catheter drainage

If a ventricular catheter is used to monitor ICP then drainage of CSF is the quickest and best method of reducing ICP promptly.

19.6.4.6. Hyperosmolar therapy

Administration of 3% hypertonic saline (0.1–1.0 ml/kg body weight per hour given on a sliding scale) or mannitol (0.25–1 g/kg of body weight as a bolus; strength is not specified in the document but 25% is cited in most publications) is effective. Serum osmolarity should be maintained below 320 mosmol/l with mannitol whilst levels of 360 mosmol/l are tolerated with 3% hypertonic saline. They work best in vasogenic and interstitial edema and may be contraindicated in the presence of vasodilatation (our opinion). Both agents are associated with rebound. Hypertonic saline can cause hematological and biochemical derangements and central pontine myelinosis (Doyle et al., 2001). The use of higher concentrations of hypertonic saline has been described but not yet subject to critical review. Miller et al. (1992) felt that patients with focal brain injury and 'less than adequate CPP' with relative preservation of autoregulatory function responded best to mannitol.

19.6.4.7. Furosemide

Miller et al. (1992) found that furosemide potentiated the effect of mannitol. Furosemide may, in some situations, be as effective as mannitol or hypertonic saline in reducing ICP without their cerebral blood flow or volume load effect. It may be of benefit in those who are overhydrated or in cardiac failure.

19.6.4.8. Barbiturates

High-dose barbiturate (pentobarbital or thiopental) therapy can be considered in 'hemodynamically stable patients with salvageable severe brain injury and refractory intracranial hypertension'. Hemodynamic monitoring is essential. Barbiturates should be used if the ICP fails to respond to initial measures, if frequent or continuous doses of hyperosmolar agents are required, or if side-effects occur with their use. Barbiturates are especially useful when seizures complicate coma and raised ICP. Barbiturates may be particularly effective when there is intracranial hyperemia such as in young patients with diffuse brain injury (Miller et al., 1992). The infusion has to be titrated to the ICP and the CPP. Marshall et al. (1978) suggested an initial load of 3–5 mg/kg. Subsequent doses are dependent on the following: 1) ICP <20 mmHg, 2) CPP that is age-appropriate, 3) mean arterial blood pressure that is age-appropriate, and 4) blood levels of 20–40 mg/l. Continuous EEG monitoring is essential. It is not necessary to ensure burst suppression on the EEG unless lower doses are insufficient to control ICP and provided there are no adverse systemic effects.

19.6.4.9. Corticosteroids

Steroids should not be used for the treatment of head-injured patients unless there is a specific reason to do so. Steroids may have a role in some forms of meningitis.

19.6.4.10. Decompression craniectomy

Decompression craniectomy should be considered in the treatment of severe TBI/refractory intracranial hypertension, including those with NAI. We would extend this recommendation to those with refractory raised ICP from medical coma. Common sense would dictate that the procedure be done when the patient is still considered salvageable. Winter et al. (2005) have also reviewed the topic.

19.6.4.11. How long to treat?

Definite suggestions were not provided in the 2003 recommendations. Therapy for raised ICP is carefully and gradually discontinued when the ICP has been <20 mmHg for 24 hours, there has been no evidence of brain shifts and the ICP is not elevated by suctioning, change of position, coughing, etc. Failure to control ICP <40 mmHg despite neurointensive measures is a grave sign and one associated with a very poor outcome. Smith and Madsen (2004) have described 'wean guidelines' used in their institution.

19.6.5. Antiseizure prophylaxis

Prophylactic antiseizure treatment 'may be considered. . .to prevent early post-traumatic seizures' in those at high risk for seizures following head injury (and by extension to those comatose from medical causes). The drug best studied is phenytoin. However, phenytoin need not be given if the child is already on a barbiturate, unless clinically necessary.

19.6.6. Nutritional support

Nutritional status is critical to recovery. One should replace 130–160% of resting metabolism expenditure after traumatic brain injury (and by extension after medical coma) beginning by 72 hours with full replacement by 7 days.

19.7. Outcome

19.7.1. Nontraumatic coma

As in other areas, pioneering work was done in adult nontraumatic and traumatic coma. One of us reviewed pediatric aspects in 1994 (Seshia, 1994) and discussed the role of clinical and investigative variables in prediction. The author considered clinical assessment to be the gold standard, an opinion also expressed by Bansal et al. (2005). The importance of a multivariate approach was emphasized. Trubel et al. (2003) and Michelson and Ashwal (2004) also reiterated the value of clinical data in predicting outcome and the importance of using 'aggregate' information. In general, the probability of long-term neurodevelopmental dysfunction is high in those with bacterial/tuberculous meningitis, those who have suffered a hypoxic–ischemic insult, in those comatose for >96 hours (not confounded by treatment), those in higher grade of coma, those with brainstem signs, and those exhibiting decorticate or decerebrate posturing. In addition, certain EEG and evoked potential patterns, some findings on CT/MRI scans, ICP >40 mmHg refractory to treatment, and those with severe systemic derangements have a higher probability of an adverse outcome. Those who have suffered a metabolic or toxic encephalopathy have a relatively good outcome provided the secondary effects of the cause are minimized and systemic complications avoided. Although one may be able to prognosticate relatively early in the comatose state (Seshia, 1994), serial assessments minimize inaccurate predictions. The early emergence of the vegetative state is a bad prognostic sign (Gillies and Seshia, 1980). A classification of outcome, using both neurological and developmental criteria, has been discussed in an earlier publication (Seshia, 1994). In our opinion, although one avoids giving predictions on long-term outcome till at least 1 year after the insult, a fairly accurate assessment of outcome can be made within 3 months of the insult. However, children who have suffered nontraumatic coma must be given the benefit of aggressive multidisciplinary assessment and rehabilitation measures for at least a year after which further strategies for management can be adopted based upon state and need.

19.7.2. Traumatic coma

In general, we find that the outcome in children from traumatic coma is far better than the initial assessment might suggest provided the secondary consequences of traumatic brain injury have been minimized. Refractory raised ICP (>40 mmHg) predicts an adverse outcome. We suggest that all children who have suffered traumatic brain injury be given the benefit of vigorous rehabilitation measures for at least 1 year after traumatic brain injury at which time a fairly accurate prediction of long-term outcome can be made and further strategies for management adopted. On the other hand, the outcome from NAI is often poor despite less severe initial neurological signs, likely reflecting differences in the mechanisms of injury between direct and nonaccidental trauma. Barlow and Minns (1999) found that reduced CPP influenced outcome after NAI. Severity of injury and lower socioeconomic status are important predictors of an adverse outcome (Robertson et al., 2001; Anderson et al., 2004; Campbell et al., 2004; Hawley et al., 2004; Odebode and Abubakar, 2004). Children with even moderate or mild head injury are at relatively high risk for behavioral and cognitive dysfunction but are often not followed up (Hawley et al., 2004). Barlow et al. (2004, 2005) discussed the outcome from NAI and emphasized the occurrence of long-term behavioral and cognitive dysfunction in this group and the importance of proactive multidisciplinary rehabilitation measures. Radiological findings can contribute prognostic information in NAI (Bonnier et al., 2003).

Evoked potentials, serum biomarkers and MRS have been used to assist with prediction but space does not permit further discussion.

19.7.3. The persistent vegetative state

Persistent vegetative state in children has been discussed by Gillies and Seshia (1980), Jennett and Plum (1972), and the Multi-Society Task Force on PVS (1994). Children in this state exhibit sleep–wake cycles but are unaware.

19.7.4. The minimally conscious state

Children in the minimally conscious state exhibit some awareness but are otherwise severely handicapped (Giacino et al., 2002; Ashwal, 2003).

19.7.5. Brain death

The criteria for brain death, for adults and children, have been recently discussed (Canadian Neurocritical

Care Group, 1999; Wijdicks, 2001, 2002; Banasiak and Lister, 2003; Canadian Council for Donation and Transplantation, 2003; Isaacs, 2003).

19.7.6. Rehabilitation measures in those who have recovered from coma

The importance of a multidisciplinary approach is now recognized. A number of strategies have been used in an open-label fashion. To our knowledge, none has been subject to critical review for efficacy. Space does not permit further discussion. In general, time and labor-intensive approaches to improve all aspects of cognition, speech, special senses, and motor function give some rewards.

19.7.7. How can an adverse outcome be minimized?

Preventing causes of coma (traumatic or nontraumatic) has yielded the best dividends. These measures include immunization against infective causes (especially high-risk populations such as aboriginal children in Canada), prevention of head injury, the use of helmets and seat belts, educating those on antiepileptic drugs about the dangers of poor compliance, educating the public about the mechanisms of NAI, identifying and helping families where children may be at risk, anticipating coma in those at risk (e.g., for inborn errors of metabolism), treating the cause of coma promptly, and preventing the cascade of secondary adverse mechanisms through well trained rapid first-response teams.

All children who have suffered an acute brain insult, traumatic or nontraumatic, should be followed up for at least 1 year to ensure that behavioral and cognitive disturbances are detected and remedial measures instituted early.

19.8. Summary

Several advances have improved our understanding and management of coma in children. These include recognition of a number of inborn errors of metabolism, progress in the prevention, diagnosis, and treatment of infective diseases, prevention of head trauma, MRI, continuous EEG monitoring, and an emerging consensus on the management of raised ICP.

Acknowledgment

One of us has written a chapter on this subject before (Seshia, 1985). The fundamental principles of approach to the comatose child have not changed significantly since then. Hence, substantial portions of the current chapter are similar to the one published earlier. The subject matter of this chapter was given as an invited presentation by one of us (SSS) at the 8th Asian Oceanian Congress of Child Neurology, 7–10 October 2004, New Delhi, India. We thank Dr V. Chernick and Dr A. N. Prasad for their suggestions. We are particularly grateful to Drs Nancy A. Carney, David P. Adelson, and Patrick M. Kochanek for reviewing Figures 19.2 and 19.3.

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Chapter 20

Management of the comatose patient

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Management of coma demands truly immediate action. The recognition of a probable cause, triage, and treatment of coma very often represent medical or surgical emergencies that do not allow any delays in diagnosis or treatment implementation. Examples include intoxications and poisonings, diabetic ketoacidosis or hyperosmolar coma, acute pituitary necrosis, fulminant hepatic failure, meningitis, basilar artery occlusion, nonconvulsive status epilepticus, and cerebellar hematomas, to mention just a few. Prompt intervention in those circumstances can avert death and preserve neurological function.

This chapter will focus on providing an organized summary of the main priorities in the treatment of patients with coma. Initially, we will review concepts on supportive care that must be provided on arrival to the emergency department and subsequently in the intensive care unit. Subsequently, we will discuss aspects of management according to the underlying cause of coma, with specific emphasis on those diagnoses that are more likely to be encountered by practicing clinicians.

20.1. General supportive care

When the brain is acutely injured, as is the case in coma, any additional insult will directly worsen outcome and reduce the potential for functional recovery. Avoiding secondary neurological insults from hypoxia or ischemia must be a priority from the time of initial evaluation in the field (Chesnut et al., 1993). Rapid assessment of airway, breathing effort, and effective circulation must define whether immediate endotracheal intubation, ventilatory assistance, or cardiac resuscitation measures are needed prior to transportation to the emergency department. Taking notice of the status of the patient when first found comatose (e.g., vital signs, breathing pattern, pupillary function, motor responses) and the surrounding circumstances (e.g., presence of empty medication bottles, toxic substances, needles, etc.) may be invaluable for the ascertainment of the cause of coma. The use of a Glasgow Coma Scale sum score of 8 to determine the need for intubation is a common practice. However, this approach has not been scientifically validated and, although useful for the training of paramedics, it cannot be employed dogmatically.

Any degree of hypoxia demands oxygen supplementation and arguably most, if not all, comatose patients should receive oxygen until their respiratory function and adequacy of oxygen supply can be more thoroughly evaluated. Hypotension requires immediate therapy with resuscitation fluids and drugs when indicated. Conversely, hypertension unless extreme (i.e., blood pressure above 240/140) is best left untreated until its cause may be assessed. Hypertensive encephalopathy is almost never responsible for unexplained coma; instead, elevations of blood pressure may be often the physiologic response to increased intracranial pressure (ICP) and compromised cerebral perfusion. Thus, emergency treatment of high blood pressure in these cases may precipitate preventable brain ischemia.

20.2. Priorities of care in the emergency department

Upon arrival in the emergency department, the patient must be reassessed to ensure that vital signs are stable and a more detailed systemic and neurological examination must be performed to decide if emergency neurosurgery is indicated. Careful documentation of this examination is crucial to define a baseline status which will be used for comparison with future serial examinations.

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It is prudent to administer 50 ml of 50% dextrose intravenously to all patients with coma of unclear cause. Concomitant infusion of 100 mg of thiamine should be given to prevent the risk of precipitating acute Wernicke's encephalopathy, especially in malnourished patients. Some textbooks recommend adding a dose of naloxone to this 'coma cocktail'; this is a useful measure but can be safely delayed until a more comprehensive evaluation has been completed and signs supportive of the suspicion of opiate intoxication are recognized. Similar reasoning applies to the use of flumazenil in patients with suspected benzodiazepine overdose.

20.2.1. Airway safety and gas exchange: indications for intubation and mechanical ventilation

Intubation is indicated in patients with hypoxia (pulse oximetry <90%) or clear risks of aspiration (e.g., vomiting with poor gag and cough reflexes). However, it is important to highlight that not all patients with depressed levels of consciousness require intubation for airway protection. This misconception is responsible for many unnecessary intubations, especially in trauma units handling large numbers of patients. A typical example is a patient who presents with alcohol intoxication or isolated seizures from alcohol withdrawal. In the absence of profuse vomiting or concomitant oxygenation problems, they can be safely supported without resorting to endotracheal intubation. Noninvasive devices (BiPAP mask) may have a role, although their value has not been systematically studied. Intubation may also be safely withheld in patients with large hemispheric strokes and Cheyne–Stokes breathing pattern. Conversely, patients with severe traumatic brain injury, status epilepticus requiring therapy with barbiturates or anesthetics, mass lesions with signs of herniation, suspected intoxications with evidence of hypoventilation, or suspicion of basilar artery occlusion must be treated as an emergency with mechanical ventilation. Pulmonary edema may result from excessive central sympathetic outflow (neurogenic pulmonary edema) or cardiopulmonary toxicity caused by several drugs (e.g., barbiturates) and poisons (e.g., carbon monoxide, cyanide). When severe, pulmonary edema demands invasive ventilation with application of adequate levels of positive end-expiratory pressure.

Analysis of arterial blood gases is an essential component of the initial evaluation of any comatose patient. Not only may it provide helpful clues to determine the cause of coma but it also may disclose the presence of acidosis and hypercapnia that demand immediate correction to reverse their deleterious impact on ICP. Mechanically ventilated patients must be monitored with serial blood gases to ensure they are properly oxygenated and normocapnic. Induced hypocapnia should be reserved for patients with raised ICP or clinical and radiological signs of herniation. Therapeutic hyperventilation is best used for short periods and especially as a bridge to more definitive forms of treatment for cerebral edema.

20.2.2. Evaluation and management of circulatory problems

Supporting adequate cerebral perfusion is a priority in patients with acute neurological disorders (Chesnut et al., 1993; Ling and Neal, 2005). Regardless of the nature of the initial brain insult, preventing secondary hypoxic–ischemic insults due to insufficient supply of oxygenated blood to sustain the metabolic demands is crucial to improve the chances of recovery. Cerebral perfusion pressure (calculated in practice by substrating ICP from mean arterial pressure) should ideally remain above 60 mmHg (Dandapani et al., 1995) but in most comatose patients the ICP will not be monitored and the focus will be on the systemic blood pressure measurements. Sudden and profound hypotension must be avoided by providing adequate hydration, carefully monitoring for arrhythmias, and reversing the effect of drugs with hypotensive effects (e.g., opiates, benzodiazepines, carbon monoxide, cyanide) when possible.

All comatose patients must have a 12-lead electrocardiogram (ECG) within minutes of their arrival in the emergency department and must be monitored continuously by cardiac telemetry. The possibility or recurrent arrhythmias is obvious in patients resuscitated after a cardiac arrest. But potentially fatal arrhythmias may also occur as a complication of various other causes of coma, such as drug poisonings, subarachnoid hemorrhage (McLaughlin et al., 2005), thyroid storm, and severe hypothermia. Arrhythmogenic drugs, most notably phenytoin, should be used with caution in these patients. Patients with tricyclic antidepressant toxicity and widening of the QRS interval should be given an infusion of sodium bicarbonate as emergency treatment.

The decision to treat acute hypertension must be made only after comprehensive evaluation of the status of the comatose patient and should never be rushed. Treatment is appropriate in cases of intraparenchymal hemorrhage, especially when the mean arterial pressure is greater than 145 mmHg (Dandapani et al., 1995). Current guidelines recommend lowering the mean arterial pressure below 130 mmHg (Broderick et al., 1999) but this has not been formally validated. More aggressive blood pressure therapy may be reasonable in patients

with very large hemorrhages in whom any expansion of the hematoma can be fatal or when an underlying vascular anomaly (ruptured aneurysm, arteriovenous malformation) is suspected. Keeping the systolic blood pressure below 160 mmHg is typically advised after subarachnoid hemorrhage until the ruptured aneurysm is secured because higher blood pressure has been found to be associated with greater risk of rebleeding in some series (Juvela, 2003). However, the true value of this strategy to prevent aneurysm re-rupture has never been validated in prospective controlled studies (Mayberg et al., 1994). It may also be prudent to lower very elevated blood pressure in the presence of extensive cerebral edema, although the perception that hypertension may exacerbate brain edema lacks solid scientific foundations and would only apply to vasogenic edema. In most other cases of coma, it is usually safe to withhold blood-pressure-lowering drugs. Intermittent intravenous doses of labetalol (10–20 mg every 10–15 min up to 300 mg/d) and continuous infusion of esmolol or nicardipine are reliable agents in most situations. In comatose patients, sodium nitroprusside should ideally be reserved for refractory cases, since it may result in accumulation of cyanide.

20.2.3. Management of body temperature

Achieving and maintaining normothermia should be the aim in all comatose patients. Extreme hypothermia may cause coma and the methods and rate of rewarming will depend on the degree of hypothermia (see 'Treatment of specific causes of coma', below). Therapeutic hypothermia has been consistently shown to have neuroprotective effects in laboratory animals, including models of brain trauma, large ischemic infarctions, and brain hemorrhages (Green et al., 1992; Koizumi and Povlishock, 1998; MacLellan et al., 2004). Early application of mild hypothermia (target temperature 32–34°C) after cardiac arrest followed by rapid recovery of effective circulation was associated with significant improvements in neurological outcome in two highly influential trials (Bernard et al., 2002; Hypothermia after Cardiac Arrest Study Group, 2002). Further research is needed to establish the long-term prognosis of patients treated with hypothermia, the optimal duration of hypothermia, and the ideal method of induction (Holzer et al., 2005). Yet, this intervention may soon become a standard part of resuscitation efforts and should be used whenever possible within 6 hours of cardiopulmonary resuscitation in patients who remain comatose.

Hypothermia is a promising intervention that is currently being tested for the treatment of various other acute neurological injuries, but proof of safety and efficacy is necessary before clinical application is prescribed to comatose patients other than those with postresuscitation encephalopathy. The disappointing results of a large randomized trial of hypothermia in patients with coma after traumatic brain injury underscore the need to wait for the data from ongoing clinical studies before promoting the use of hypothermia in the clinical arena.

Most institutions use surface water cooling mattresses covering the patient's trunk with additional ice packs in the axillas; cooled intravenous fluids and gastric lavage with ice water are also used if needed. Shivering can be treated with propofol or the combination of buspirone and meperidine (De Georgia et al., 2004) but the successful control of this response is often challenging. Intravascular cooling systems have been introduced in European countries (De Georgia et al., 2004) but their superiority over less invasive strategies remains to be fully established. This comparison is currently being tested in clinical trials in the USA and Australia.

20.2.4. Rational use of laboratory studies

Priorities when ordering tests in a patient with coma of unknown cause have to be defined. Certain studies are required in all patients and must be ordered as soon as the patient arrives in the emergency department. Many others are only indicated in some situations or when a specific diagnosis is suspected. A 'shotgun' approach is not cost-effective and may create unnecessary confusion. The best plan after obtaining basic laboratory tests (including arterial blood gases and measured serum osmolality), a computed tomography (CT) scan of the head, and an ECG is to reflect on the available information and then proceed with further testing. Certain causes of coma require specific tests that are needed urgently to prevent further morbidity. These include lumbar puncture in suspected bacterial meningitis or encephalitis, cerebral angiogram in patients with possible basilar artery occlusion, and electroencephalogram (EEG) when status epilepticus is suspected.

Table 20.1 summarizes the tests that should be ordered during the initial evaluation of all comatose patients. Table 20.2 lists the most common optional tests and the particular instances in which they must be considered.

There are a few optional tests that deserve a more detailed discussion:

20.2.4.1. Lumbar puncture

Lumbar puncture should be performed in any stuporose or comatose patient with fever. A delay may prove fatal in these cases. However, brain imaging should be

Table 20.1

First-line laboratory studies in the assessment of comatose patients

Glucose
Electrolytes (Na, K, Cl, CO_2, Ca, PO_4, Mg)
Creatinine, BUN
Aspartate transaminase, alanine transaminase
Complete cell count
PT, PTT
Arterial blood gases (including HbCO)
Measured serum osmolality
CT scan of the head without contrast
Electrocardiogram

obtained first to minimize the risk of precipitating or exacerbating a pressure gradient that may result in brain herniation (van Crevel et al., 2002). Cerebrospinal fluid analysis must include measurement of protein and glucose levels, cell counts, stains and bacterial cultures, and polymerase chain reaction (PCR) for viruses when these are suspected. It is advisable to save some fluid for potential future testing when new information becomes available at a later time.

20.2.4.2. EEG

The indication of EEG in a comatose patient with witnessed seizures is obvious. However, the clinical manifestations of status epilepticus may be very subtle or even totally absent. These cases of nonconvulsive status epilepticus are difficult to recognize and can only be reliably diagnosed by EEG. The test should be ordered urgently in any patient with previous history of seizures and unexplained coma, regardless of whether convulsive movements have been observed at any time during the presentation. EEG should also be considered in patients with intracerebral hemorrhage, subarachnoid hemorrhage, and traumatic brain

Table 20.2

Optional laboratory studies often used in the assessment of comatose patients

Diagnostic test	Indication
Specific drug levels*	Suspected overdose
Anticonvulsants	History of epilepsy
Acetaminophen/paracetamol	Suicidal attempt; liver failure
Salicylates	Anion gap metabolic acidosis with respiratory alkalosis
Tricyclic antidepressants	History of depression; wide QRS; antimuscarinic signs
Lithium	History of bipolar disorder; large output of diluted urine
Urine and serum toxicology screen;† see Table 20.3 for details	Suspected intoxication
Cyanide level	Suspected poisoning
Serum ammonia	Porto-systemic shunt
Serum lactic acid, urinary ketones	Anion gap metabolic acidosis
Thyroid hormones	Suspected thyroid storm; myxedema
Cortisol, ACTH	Addisonian crisis; pituitary apoplexy
Special coagulation studies	Venous sinus thrombosis; DIC
Lupus serology	Suspected lupus cerebritis; systemic signs of lupus flare
Blood cultures	Sepsis; meningitis
Peripheral blood smear	Anemia; signs of hemolysis; suspected TTP
Microscopic urine analysis	Suspected ethylene glycol intoxication
Cerebrospinal fluid analysis‡	Meningitis; encephalitis; ADEM
Electroencephalogram	Status epilepticus; secondary seizures
Brain MRI	Structural lesions
Brain MR venography	Venous sinus thrombosis
Cerebral angiogram	Basilar artery occlusion; ruptured aneurysm; AVM; suspected cerebral angiitis
CT scan or MRI of brain with contrast	Tumors; inflammatory or infectious lesions

*Partial list of most frequently overdosed drugs in patients presenting with coma.
†By gas chromatography and mass spectrometry.
‡Cell count, protein and glucose levels, Gram stain, Indian ink, cultures, and may consider oligoclonal bands, cryptococcal antigen, polymerase chain reaction for herpes virus, etc.
ACTH, adrenocorticotropic hormone; ADEM, acute demyelinating encephalomyelities; AVM, arteriovenous malformation; CT, computed tomography; DIC, disseminated intravascular coagulation; MRI, magnetic resonance imaging; TTP, thrombotic thrombocytopenic purpura.

injury when there is a perceived discrepancy between the depth of the depression of consciousness and the severity of the primary diagnosis (Vespa et al., 1999; Dennis et al., 2002). It may also be useful to obtain an EEG recording in comatose patients with normal brain imaging and no major metabolic abnormalities or exposure to toxins. Apart from epilepsy, EEG lacks the ability to provide a specific diagnosis. Nonetheless, the presence of triphasic waves should indicate the need for further evaluation focused on metabolic disorders (Brenner, 2005). And while EEG cannot determine prognosis in isolation, patterns of burst-suppression or alpha coma in patients with hypoxic–ischemic injury denote severe brain damage and a poor chance of meaningful recovery (Brenner, 2005; Young et al., 2005).

20.2.4.3. Magnetic resonance imaging

The introduction of magnetic resonance imaging (MRI) has markedly reduced the number of patients with uncertain etiology of coma but MRI is not diagnostic in all cases. It is essential for the diagnosis of viral encephalitis, venous sinus thrombosis, or acute demyelinating encephalomyelitis. The advent of diffusion-weighted imaging has added a new dimension to this imaging modality by allowing it to disclose areas of cytotoxic edema very shortly after their inception. As a consequence, MRI is far more sensitive than CT scan in delineating the extent of brain damage following cardiopulmonary resuscitation (Arbelaez et al., 1999; Torbey and Bhardwaj, 2002). It may also demonstrate the presence of cortical injury caused by status epilepticus often unrecognizable on CT scan. MRI discloses typical lesion patterns in Wernicke's encephalopathy and osmotic dysmyelination that are very difficult to distinguish with CT scan, making MRI essential for the early diagnosis of these conditions (Suzuki et al., 1996; Chua et al., 2002). It offers better depiction of the characteristic pallidal lesions produced by carbon monoxide toxicity and the basal ganglia changes induced by cyanide, although these changes are typically delayed (Rachinger et al., 2002).

20.2.4.4. Toxicology screening

Any clinicians likely to deal with toxicological emergencies should have a basic knowledge of the screening techniques used at their institution or know how to contact a toxicologist when urgently needed. In a comatose patient, a toxicology screening may be used to confirm or exclude the diagnosis of poisoning, identify and quantify the responsible toxic agent, grade the severity of the intoxication for prognostic purposes, and monitor the clearance of the toxic agent over time or after acute treatment. It may also have important forensic implications.

The first step in the process of ordering a toxicology screen is writing the request and sampling the specimens correctly. When known, the suspected drug or poison should be noted in the request or conveyed to the laboratory. This helps focus the testing, saving time and cost. In many hospitals, urine is screened for recreational drugs (opiates, cocaine, amphetamines, cannabinoids, benzodiazepines) almost routinely in patients presenting with unexplained altered level or content of consciousness. Also, ethanol levels are quantified in the serum. These tests have a rapid turnaround time and offer valuable information to guide acute management. Most other techniques, however, offer much more delayed results. High cost and prolonged processing time are clearly the most relevant disadvantages to be considered when deciding whether to order these tests. In acute cases, urine ($\geq$ 20 ml) and serum ($\geq$ 5 ml) should be sent to the laboratory in all cases. Whole blood ($\geq$ 10 ml) may also be required to check for carboxyhemoglobin, methemoglobin, and evidence of cholinesterase inhibition. Gastric fluid ($\geq$ 10 ml) is only useful when intoxication has occurred by oral ingestion and must be obtained before the patient receives any medications via gastric tube. Other specimens such as hair and saliva are typically not helpful for acute intoxications.

Routine toxicology screening for a patient with unexplained coma generally begins with *nonseparation methods* (i.e., tests that identify classes or groups of drugs without further characterization or quantification), such as the spot test described above for recreational drugs and immunoassays employing on-site testing kits. Results are available promptly and the techniques are relatively inexpensive. However, the information provided by these tests is neither comprehensive nor detailed enough to firmly guide management. Cross-reactions may produce false-positive results (e.g., false positivity for amphetamines in a patient taking decongestants containing ephedrine derivatives) or give rise to confusion (e.g., high levels of carbamazepine or phenothiazines may be wrongly identified as low therapeutic concentrations of tricyclic antidepressants). Conversely, the lack of cross-reaction among all the members of a drug family may generate false-negative results (e.g., certain opiates including fentanyl and meperidine). Additionally, it is not possible to distinguish between overdose and therapeutic dose (e.g., of opiates, benzodiazepines, etc.) since, at best, the results provided by immunoassays are semiquantitative (by comparing the findings with spectral databases). Thus, a positive result by a nonseparation method should ideally be confirmed by more accurate techniques.

Separation methods constitute the preeminent tool of analytic toxicology. They allow reliable recognition and precise quantification of specific drugs or toxic agents. Although many techniques exist, gas chromatography–mass spectrometry is the most efficient and widely used, at least in large centers (Maurer, 2004). A comprehensive gas chromatography–mass spectrometry screen can detect a very extensive panel of toxic substances and drugs (Table 20.3). However, there are exceptions that must be kept in mind. Solvents such as ethylene glycol, LSD, chloral hydrate, pesticides, and valproic acid can only be detected after special pretreatment of the sample, which will only be performed if screening for one of these substances is specifically requested. Some other substances cannot be detected by gas chromatography–mass spectrometry, most notably digoxin, lithium, and arsenic. Upon specific request, levels of these substances must be measured separately using other individual techniques.

20.3. Treatment of specific causes of coma

Even when the specific nosologic diagnosis remains undefined, by the time the patient is admitted to the intensive care unit the treating clinician should be able to classify the type of coma into one of the following major categories:

1. Supratentorial mass lesion with brain herniation
2. Diffuse cortical damage
3. Bilateral diencephalic damage
4. Infratentorial mass lesion with brainstem compression
5. Brainstem structural lesion
6. Diffuse cerebral dysfunction.

Recognizing the type of coma on the basis of these simple categories narrows the differential diagnosis and has a direct impact on treatment and prognosis. Patients with a hemispheric mass causing impending herniation, a cerebellar lesion compressing the pons, or obstructive hydrocephalus must be urgently evaluated by a neurosurgeon. Meanwhile, patients with massive brainstem hemorrhages do not require any emergency treatment since all interventions will fail to improve their grim prognosis regardless of the cause of the hemorrhage. Prognosis is less uniform in cases of diffuse cortical damage, depending on the cause and extent of the injury. However, apart from preventing new or recurrent seizures and maintaining adequate cerebral perfusion and oxygenation, no therapy is likely to have a major impact on the outcome of these patients once laminar necrosis has occurred. Similar concepts may be applied to patients with bilateral diencephalic damage, with some notable exceptions. Patients with MRI signal changes in both thalami due to venous thrombosis may still achieve remarkable recovery after prompt anticoagulation (local thrombolysis may be necessary in some cases). Intravenous or intra-arterial thrombolysis or other endovascular interventions (e.g., clot retrieval or mechanical disruption of a proximal or mid-basilar clot) must be attempted in comatose patients with bilateral thalamic diffusion abnormalities on MRI secondary to basilar artery occlusion (typically involving the top of the vessel), since those changes may be reversible or compatible with meaningful functional recovery. However, interventions are going to be futile if evidence of widespread brainstem ischemia is already present.

It is those patients with diffuse cerebral dysfunction of unclear cause who pose the greatest challenge. In such patients the priority is to exclude conditions that may become rapidly fatal if not specifically addressed. Examples include carbon monoxide poisoning, cyanide poisoning, nonconvulsive status epilepticus, thrombotic thrombocytopenic purpura, herpes encephalitis, bacterial meningitis, and major endocrine crises. Most intoxications and drug overdoses have no specific antidotes and care concentrates on maintaining hemodynamic stability, equilibrating the acid–base

Table 20.3

Most common drug classes detected by comprehensive gas chromatography with mass spectrometry

Alkaloids (most of them)
Analgesics (acetaminophen/paracetamol, salicylates, NSAIDs, opiates)
Antiarrhythmics
Anticonvulsants
Antidepressants (tricyclics, SSRIs, trazodone, bupropion, venlafaxine)
Antihistamines
Beta-blockers
Calcium channel blockers
Designer recreational drugs
Dopaminergic agents (most of them)
Hallucinogens (PCP, LSD)
Local anesthetics
Neuroleptics (phenothiazines, butyrophenones, atypical agents)
Sedatives and hypnotics (barbiturates, chloral hydrate, zolpidem)
Solvents and atypical alcohols (including ethylene glycol, methanol, IPA)
Stimulants (xanthines, cocaine, amphetamines)
Tranquilizers (benzodiazepines and others)

IPA, isopropyl alcohol; LSD, lysergic acid diethylamide; NSAIDs, nonsteroidal anti-inflammatory drugs; PCP, phencyclidine; SSRIs, selective serotonin-reuptake inhibitors.
Source: modified from Wening, 2005.

status, and monitoring for complications such as cardiac arrhythmias. Care is also supportive in patients with postresuscitation coma. Sepsis and multiorgan dysfunction syndrome are perhaps the most common causes of coma in non-neurological intensive care units. Their management is often complex since it must address multiple factors at play.

Because of their frequency and importance, the last portion of this chapter will be devoted to discuss in greater detail the management of some specific treatable causes of coma.

20.3.1. Supratentorial mass lesions

Hemispheric mass lesions may require different treatments based on the specific nature of the lesion but also share one major similarity in that they generate pressure gradients or globally increased ICP that may result in brain herniation. Thus, therapy of raised ICP is at the core of the management of these patients.

Ensuring adequate ventilation and oxygenation, maintaining euvolemia, aggressively treating fever and hyperglycemia, preventing seizures (using prophylactic anticonvulsants when seizures are deemed likely), and perhaps adopting mild head elevation are general measures that apply to all patients with raised ICP (Rabinstein, 2006). Some patients with depressed level of consciousness may experience pain and this may trigger elevations in ICP that may be dangerous in patients with reduced compliance. Therefore clinicians must check patients for subtle signs of pain, such as tachycardia in relation to manipulations, and prescribe analgesics when appropriate.

ICP monitors are typically placed in patients with coma secondary to traumatic brain injury (Bullock et al., 1996). In patients with subarachnoid hemorrhage or intraparenchymal hematomas with intraventricular clots, ventriculostomy catheters inserted to drain the blood also serve as monitors of ICP. In most other cases, the use of an ICP monitor is decided based on individual circumstances. Specific therapies aimed at reducing ICP may be guided by measurements provided by a monitor or by clinical changes noted on serial examinations.

Hyperventilation is very effective in reducing ICP but does so by producing cerebral vasoconstriction, which may potentially precipitate ischemia (Carmona Suazo et al., 2000). Hence, deep and prolonged falls in P_{CO_2} should be avoided. Hyperventilation is best used for brief periods and targeting a P_{CO_2} goal between 30 and 34 mmHg (Diringer, 2002; Diringer et al., 2002). Its effect is noticeable within minutes but attenuation is maintained for several hours because efficient buffering systems work to reverse the alkalinization of the cerebrospinal fluid.

Osmotic therapies using mannitol (20% solution) or hypertonic saline (3–23.4% solution) are the mainstay of the medical treatment of intracranial hypertension (Rabinstein, 2006). Like hyperventilation, these two agents are effective regardless of the pathophysiology and distribution of brain edema. They are effective and fairly safe interventions when used appropriately but their precise indications and best protocol of administration remain matters of debate. Both intermittent boluses as needed and protocols with scheduled doses have proponents and detractors. When administering mannitol, it is essential to ensure that the patient does not become hypovolemic, since that status magnifies the risk of renal failure. In patients with renal insufficiency, hypertonic saline may be a safer option.

Corticosteroids are very effective in ameliorating vasogenic edema such as is associated with tumors and infections and after radiation (Kaal and Vecht, 2004). Dexamethasone is the drug most commonly prescribed because of its low mineralocorticoid activity. However, steroids have no role in the treatment of conditions with predominantly cytotoxic edema, e.g., infarctions and hemorrhages, or in trauma. In fact, they have been found to be deleterious in patients with ischemic stroke (Norris and Hachinski, 1986), intraparenchymal hematomas (Poungvarin et al., 1987), and traumatic brain injury (Edwards et al., 2005). The detrimental impact of hyperglycemia on the injured brain may help explain these negative results.

Barbiturates, neuromuscular paralysis and hypothermia may be used in refractory cases (Rabinstein, 2006). The rationale for these interventions is to reduce cerebral metabolic demand. While theoretically appealing, they have problematic disadvantages, including that their application is very labor-intensive and quite often associated with complications (Table 20.4). Additionally, they obscure the neurological examination, thus impairing the ability of the clinician to determine when the patient is undergoing clinical changes. Still, these options may be valuable and should be considered in patients with recalcitrant intracranial hypertension in whom surgery is not a viable option. Hypothermia appears particularly promising and greater experience with endovascular cooling catheters may provide a means of achieving rapid reduction of body temperature as well as controlled rewarming.

Table 20.4 offers a succinct summary of the specific medical therapies available for the treatment of intracranial hypertension and their most frequent complications.

Whenever possible, the increased pressure should be relieved surgically. In selected cases, evacuation of a brain hematoma may be compatible with favorable functional recovery even after clinical or radiological

Table 20.4

Specific medical therapies for raised intracranial pressure

Therapy	Application/dose	Most common complication
Hyperventilation	Increase minute ventilation to reach P_{CO_2} 30–34 mmHg	Cerebral ischemia
Mannitol	20% solution 1–1.5 g/kg IV bolus, then repeat as necessary or give 0.25–0.5 mg/kg IV every 4–6 h	Renal failure
Hypertonic saline	7.5% solution 2 ml/kg boluses*	Hypernatremia Chronic heart failure
Dexamethasone	10–100 mg bolus, then 4 mg every 6 h†	Hyperglycemia Hypertension/Infections
Pentobarbital	1–3 mg/kg/h	Pneumonia/sepsis Hypotension
Hypothermia	Target bladder temperature 32–34°C using external or endovascular cooling methods	Pneumonia/sepsis Arrhythmias Electrolyte imbalances

*3–23.4% hypertonic solutions and continuous infusions have been used.
†Doses up to 96 mg/d have been used.
IV, intravenous(ly).

signs of herniation are noted (Rabinstein et al., 2002). However, patients in coma failed to benefit from surgical evacuation in a recent large trial that assessed the value of surgery in intracerebral hemorrhage (Mendelow et al., 2005). Emergency ventriculostomy placement is life-saving in patients with obstructive hydrocephalus. Insertion of a drainage tube into a brain abscess and placement of a lumbar catheter in patients with communicating hydrocephalus are also essential interventions. Decompressive hemicraniectomies often prevent death and may preserve function in selected patients with massive hemispheric lesions, most notably large middle cerebral artery infarctions with malignant edema (Schwab et al., 1998). However, older age is a predictor of poor recovery (Gupta et al., 2004) and hemicraniectomy should be reserved for younger patients with good rehabilitation potential. Hemicraniectomies have been successfully used to treat patients with subarachnoid hemorrhages and large sylvian hematomas (Smith et al., 2002). Extended hemicraniectomies and bilateral craniectomies are also used to relieve ICP in patients with medically intractable traumatic edema. Although not always effective (Munch et al., 2000), these procedures may be followed by remarkable recovery, especially in children and young adults (Albanese et al., 2003).

20.3.2. Infratentorial mass lesions

These lesions are numerically less common but, because of their rapid progression and high rates of mortality, large cerebellar lesions imposing pressure on the brainstem demand emergent surgical evacuation. This is equally true for infarctions and hematomas (Jensen and St Louis, 2005), although the former may be occasionally amenable to timely treatment with osmotherapy. The decision on the timing of surgery should be based on the appearance of early signs of clinical worsening from mass effect. The first signs denoting deterioration are often subtle. Behavioral changes, either in the form of confusion or decreased activity and probably resulting from progressive obstructive hydrocephalus, may precede the development of unilateral facial paralysis (typically with a peripheral pattern) or abducens palsy. Once the patient becomes comatose, the chances of favorable functional recovery are slim even after successful surgical decompression (Kirollos et al., 2001; Salvati et al., 2001).

Surgical indications are often inappropriately based only on radiological findings. Nonetheless, the volume of cerebellar hematomas and infarctions on brain imaging correlates positively with the likelihood of poor outcome (Da Pian et al., 1984; van Loon et al., 1993). Furthermore, vermian location of the hematoma and acute obstructive hydrocephalus are highly predictive of subsequent neurological deterioration (St Louis et al., 1998) and early neurosurgery may be advisable when these findings are present. Preemptive surgery has also been advocated when there is total effacement of the quadrigeminal cistern or obliteration of the fourth ventricle (Taneda et al., 1987; Kirollos et al., 2001).

In patients with clinical or radiological evidence of massive brainstem ischemia, aggressive treatment will be futile and the irreversibility of the injury should be communicated to the family.

20.3.3. Bacterial meningitis

The degree of depression of consciousness is one of the strongest prognosticators of poor outcome in patients with bacterial meningitis (van de Beek et al., 2004). Nonetheless, meaningful recovery is possible for patients presenting to the emergency department in coma, especially if they are young and do not exhibit signs of sepsis. When bacterial meningitis is suspected in a comatose patient, antibiotics must be started without delay after obtaining blood cultures. Withholding antibiotics until the CT scan and lumbar puncture have been performed is a potentially fatal mistake (Aronin et al., 1998). Concomitant administration of dexamethasone (10 mg every 6 h for 4 days started minutes before or at the time of the first dose of antibiotics) is particularly beneficial in patients with meningitis who present with reduced level of consciousness (de Gans and van de Beek, 2002).

20.3.4. Viral encephalitis

Antiviral agents are only started when there is strong clinical suspicion of viral encephalitis (history of immunosuppression, coexistence of seizures and fever, temporal lobe or multiple subcortical enhancing lesions on brain imaging) or after cerebrospinal fluid analysis reveals abnormalities suggestive of this diagnosis (i.e., lymphocytic pleocytosis, moderate elevation of protein level, sometimes xanthochromia). Only a minority of viral encephalitides respond to antiviral treatment, namely herpes simplex and sometimes varicella zoster to acyclovir and cytomegalovirus to ganciclovir (Tattevin et al., 2001; Griffiths, 2004). The gold standard for the diagnosis of these agents is the detection of viral DNA using the PCR technique to study the cerebrospinal fluid (Markoulatos et al., 2001). The results are highly reliable and can be obtained rapidly. The outcome of comatose patients with viral encephalitis caused by treatable agents has not been formally studied but depressed consciousness predicts mortality or limited recovery in patients with encephalitis by arbovirus (Misra et al., 1998).

20.3.5. Status epilepticus

Early endotracheal intubation is necessary in most cases of status epilepticus. Even in those cases with preserved oxygenation, aspiration risk is very elevated. Hypoxic patients should be evaluated for the possibility of either bronchial obstruction, aspiration pneumonitis, or neurogenic pulmonary edema (Wijdicks and Hubmayr, 1994; Fountain, 2000). Patients should be closely monitored for the development of cardiac arrhythmias, hypotension, rhabdomyolysis, and metabolic acidosis (Guven et al., 1998; Fountain, 2000). Beta-blockers may be beneficial for patients with repolarization changes or extreme sinus tachycardia, since these abnormalities result from excessive sympathetic drive (Tigaran et al., 1997). First-line treatment with a benzodiazepine (the ideal agent is lorazepam at a dose of 0.1 mg/kg) should be started as soon as possible. In fact, out-of-hospital treatment administered by paramedics has been shown to improve the chances of early termination of status epilepticus (Alldredge et al., 2001). Phenytoin or fosphenytoin should be instituted in the emergency department (20 mg/kg at 50 mg/min for phenytoin or 150 mg/min for fosphenytoin). Fosphenytoin is preferable to phenytoin because of the lower incidence of hypotension and cardiac arrhythmias (afforded by avoiding the use of propylene glycol as a vehicle), which allows for a faster rate of infusion, and the elimination of serious infusion-site reactions. Still, continuous cardiac monitoring is mandatory during the infusion of either drug.

The best second-line treatment drug is a matter of debate. Traditionally, barbiturates have played this role but new options may be comparable or even better alternatives. Phenobarbital (20 mg/kg at 50–75 mg/min) is effective but associated risks include sedation, respiratory depression, and hypotension. The long half-life of barbiturates makes the problem of sedation particularly problematic. Midazolam, propofol, and valproic acid are available alternatives to barbiturates. Midazolam (0.2 mg/kg bolus, then 0.1–2 mg/kg/h continuous infusion) has a rapid onset of action and a short half-life. Its disadvantages include the risk of hypotension, rapid development of tachyphylaxis, and very high cost. Propofol (2–5 mg/kg bolus followed by a continuous infusion of 1–15 mg/kg/h) also becomes rapidly effective but prolonged infusions may induce metabolic acidosis (especially in children and young adults) and infections (Marik, 2004). Dietary caloric intake should be adjusted because of the high lipid content of the propofol infusion. Withdrawal myoclonus and seizures may occur after discontinuation of the drug, particularly if tapered fast or stopped suddenly (Finley et al., 1993). The role of intravenous valproic acid in the management of status epilepticus remains to be formally studied. It is used in some centers after phenytoin to treat hemodynamically unstable patients, since valproic acid is less likely than other second-line agents to provoke pronounced hypotension. Doses of 20–30 mg/kg may be infused rapidly (as fast as 200–500 mg/min) with minimal risk in both children and adults (Limdi and Faught, 2000).

Pentobarbital (10–15 mg bolus followed by a continuous infusion of 1–3 mg/kg/h) is reserved for refractory cases. It induces prolonged coma, the duration of which is very difficult to predict and depends on the amount of body fat and the metabolic efficiency of

the liver. The risks of hypotension during initial bolus and subsequent dose titration and later of pneumonia due to immunosuppression and ciliary dysfunction are elevated (Parviainen et al., 2002). Anesthesia with ketamine isoflurane may be successful in patients who fail to respond to pentobarbital.

The ideal EEG goal of therapy in patients with refractory status epilepticus is also a topic of persistent discussion. In a metaanalysis of available studies, titration of anticonvulsants to attain suppression of background activity (i.e., EEG displaying near-total electrical silence or a burst-suppression pattern) was associated with reduced likelihood of breakthrough seizures in comparison with drug titration to achieve seizure suppression (Claassen et al., 2002). Yet, more aggressive strategies may also augment the risk of systemic complications from adverse drug effects. Once seizures have been suppressed for 24 hours, slow tapering of the continuously infused anticonvulsant may commence (e.g., 25% every 12 h). It is important to ensure that phenytoin levels (as well as measurable levels of any other antiepileptic medication planned to be used as part of the maintenance regimen) are adequate while second-line agents are progressively withdrawn.

20.3.6. Specific treatment of some common poisonings, acute intoxications, and drug overdoses

20.3.6.1. Carbon monoxide

Patients should breathe 100% oxygen and use of a hyperbaric chamber should be considered, if available. When compared to 100% oxygen at ambient pressure, hyperbaric oxygen appears to lower the incidence of delayed sequelae (Thom et al., 1995), probably by hastening removal of CO and dissociation of CO from cytochrome oxydase. There are no clear guidelines as to when to use hyperbaric oxygen. However, it is reasonable to regard the presence of coma at the time of initial examination as an indication (Raphael et al., 1989), regardless of the carboxyhemoglobin concentration (levels of 25–40% have been used as cutoffs to treat with hyperbaric oxygen) (Hampson et al., 1995). Treatment should be initiated as soon as possible, ideally within the first 6 hours from exposure. One to three treatment sessions are typically prescribed, each session lasting less than 2 hours. The most common side effects are seizures (grand mal type) due to brain oxygen toxicity (Hampson et al., 1996), middle ear barotraumas, and transient visual disturbances due to transient changes in the lens.

20.3.6.2. Cyanide

Nitrites and thiosulfate are effective antidotes against cyanide toxicity (Way, 1984). Inhaled amyl nitrate and intravenous sodium nitrate promote conversion of ferrous hemoglobin (Fe^{2+}) to methemoglobin (Fe^{3+}). Since hydrogen cyanide has much higher affinity for Fe^{3+}, it dissociates from cytochrome oxydase to bind to methemoglobin. The resulting cyanmethemoglobin is subsequently reduced back to hemoglobin in a process that releases cyanide. Sodium thiosulfate markedly enhances the conversion of unbound hydrogen cyanide (including that released from cyanmethemoglobin) to thiocyanate, a much less toxic compound.

Initially, while intravenous access is being established, a pearl of amyl nitrate should be crushed and held in front of the patient's nose and mouth or facing the intake valve of the ventilation mask for 30 seconds of every minute. As soon as an intravenous access becomes available, 10 ml of 3% sodium nitrate (300 mg) must be administered. The rate of administration depends on the severity of the case, from 2 to several minutes. Hypotension complicates fast infusion. Anemic and very young patients require dose adjustments to prevent potentially lethal methemoglobinemia. After the administration of intravenous sodium nitrate is completed, the patient must receive 50 ml of 25% sodium thiosulfate over 5 minutes. Doses of sodium nitrate and sodium thiosulfate may be repeated if coma and metabolic acidosis persist or recur. Levels of methemoglobin should be monitored before administering a second dose of sodium nitrate.

Hydroxocobalamin (5–15 g intravenously over 30 min) and dicobalt edetate (300 mg intravenously over 1–5 min) effectively chelate unbounded cyanide (Riou et al., 1990). They are useful alternatives if administered early. Hydroxocobalamin is preferable because of the greater toxicity of dicobalt edetate (severe hypotension, arrhythmias, seizures, edema; side effects may be mitigated by the concurrent infusion of dextrose).

20.3.6.3. Ethylene glycol

Severe metabolic acidosis demands aggressive treatment. It results from the rapid accumulation of the toxic metabolites glycolic acid and oxalic acid. Intravenous drips of sodium bicarbonate are almost routinely used, but concurrent administration of alcohol dehydrogenase inhibitors is often needed to attain correction of the acidosis. Alcohol dehydrogenase is the enzyme that catalyzes the conversion of ethylene glycol to glycoaldehyde, which in turn is the precursor of glycolic and oxalic acid. Inhibition of alcohol dehydrogenase can be achieved using ethanol or fomepizole. Fomepizole offers the advantage of not inducing central nervous system depression while being easier to administer than ethanol. A loading dose of 15 mg/kg is followed by doses of 10 mg/kg every 12 hours for four doses, and

then 15 mg/kg every 12 hours until ethylene glycol serum level is <20 mg/dl. Each dose is infused slowly over 30 minutes. When promptly administered, fomepizole may prevent hemodialysis (Brent et al., 1999) but the exact pathophysiology of renal failure due to ethylene glycol intoxication has not yet been elucidated.

Hypocalcemia results from the precipitation of calcium in oxalate crystals and, when extreme, may produce seizures. Only when hypocalcemic seizures are present should intravenous calcium gluconate be used since its infusion may favor further precipitation of crystals and tissue damage.

20.3.6.4. Methanol

The toxicity of methanol results from the severe and refractory metabolic acidosis it induces. Aggressive treatment with sodium bicarbonate must be accompanied by the administration of ethanol or, ideally, fomepizole to prevent the acidosis from becoming resistant to bicarbonate (these two substances reduce the conversion of methanol to formaldehyde, a precursor of the neurotoxin formic acid) (Brent et al., 2001). Fomepizole doses are the same of those used to treat ethylene glycol poisoning. Ethanol is mixed in a 10% solution with dextrose and given as a bolus of 8 ml/kg (over 30 min) followed by an infusion of 1.5 ml/kg/h until reaching a therapeutic blood level of approximately 100 mg/dl. Hemodialysis should be instituted immediately in any patient with evidence of new visual impairment and when patients have persistent metabolic acidosis despite pharmacological treatment. More frequent doses of fomepizole and higher concentrations of ethanol are necessary to sustain a therapeutic level when the patient is receiving hemodialysis. Treatment should be continued until the patient becomes asymptomatic or level of methanol drops below 20 mg/dl (6 mmol/l).

20.3.6.5. Isopropyl alcohol

Hypoglycemia should be promptly diagnosed and fully corrected as an emergency (concomitant thiamine administration is advised). Crystalloids and sometimes vasopressor drugs are frequently necessary to reverse hypotension. Supportive therapy usually suffices since isopropyl alcohol is metabolized to acetone, which does not cause significant end-organ damage. Only cases with refractory hypotension with levels of isopropyl alcohol greater than 400 mg/dl merit hemodialysis (Church and Witting, 1997).

20.3.6.6. Benzodiazepines

Treatment is mostly supportive. Activated charcoal may be beneficial for patients who reach the emergency department within 1–2 hours of oral benzodiazepine ingestion. Flumazenil specifically antagonizes the sedative effects of benzodiazepines by binding to the $GABA_A$ receptor site and reducing chloride permeability. However, this antidote has short-lasting effects and carries the risk of precipitating withdrawal in chronic benzodiazepine users. Moreover, convulsions may occur, especially in patients who have also overdosed with other drugs that may lower the seizure threshold (most notably tricyclic antidepressants) (Gueye et al., 1996). Thus, the usefulness of flumazenil is limited to confirming the diagnosis of benzodiazepine toxicity and it should be administered only to patients with presumed low risk of withdrawal or seizures (e.g., patients who fail to awaken after conscious sedation). Given its high degree of protein binding, clearance of benzodiazepines is not markedly accelerated by hemodialysis.

20.3.6.7. Opioids

Treatment of ventilatory depression often requires intubation and mechanical assistance. Hypotension and less commonly bradycardia may demand specific therapy. Activated charcoal should be given to patients brought in after oral overdose. Naloxone, an opioid antagonist, must be used judiciously while monitoring for the emergence of signs of withdrawal. Doses as low as 0.05 mg intravenously are recommended for patients suspected of pre-existing opioid dependency. Otherwise, the starting dose may be 0.1–0.4 mg and escalating doses of up to 10 mg may be administered to maximize the response. After improvement, the patients should be carefully monitored for the possibility of recurrent sedation.

20.3.6.8. Tricyclic antidepressants

These patients are at high risk of complications from respiratory failure, hemodynamic collapse, cardiac arrhythmias, and seizures. Activated charcoal (1 g/kg), with or without gastric lavage, may effectively reduce drug absorption when promptly administered (Bosse et al., 1995). Mortality is closely related to cardiac toxicity caused by delayed depolarization, conduction abnormalities, and decreased myocardial contractility due to inhibition of voltage-gated sodium channels. Sodium channel blockade may be partially overcome by serum alkalinization (potential mechanisms are enhanced tricyclic drug protein binding, or reduced binding to the sodium channel) (Hoffman et al., 1993; McCabe et al., 1998). Sodium bicarbonate is the preferred method of alkalinization because it also augments the extracellular sodium concentration. Infusion of sodium bicarbonate is recommended for patients

with widened QRS complex >100 ms or ventricular arrhythmias. The target blood pH should not be higher than 7.50–7.55 to avoid iatrogenic complications. If the ventricular arrhythmia is frequent, severe, or persistent after administration of sodium bicarbonate, intravenous lidocaine or bretylium are prescribed. Torsade de pointes is treated with intravenous magnesium sulfate, isoproterenol, or overdrive pacing. Vasopressors (norepinephrine (noradrenaline), dopamine, epinephrine (adrenaline)) must be infused when hypotension cannot be controlled with intravenous fluids (Vernon et al., 1991). All means of hemodynamic support are justified when treating patients with tricyclic antidepressant overdose, since the cause of circulatory collapse is eminently reversible. Good outcome has been reported after temporary extracorporeal circulation (Williams et al., 1994).

Most seizures occur shortly after drug ingestion and are self-limited. Multiple recurrent seizures are seen in less than 10% of cases, although the risk of status epilepticus is elevated after amoxapine and maprotiline overdoses (Cassidy and Henry, 1987). When anticonvulsant therapy is needed, benzodiazepines are used first (Ellison and Pentel, 1989). In refractory cases, continuous infusion of barbiturates, propofol, or midazolam may be used.

20.3.6.9. Neuroleptics

After sufficient ventilation and circulation are ensured, activated charcoal should be administered. Since the anticholinergic effect of neuroleptics leads to paralysis of peristalsis, activated charcoal may be beneficial even hours after the overdose. Hypotension responds best to direct alpha-sympathetic agonists (e.g., norepinephrine (adrenaline), phenylephrine). Ventricular or wide-complex tachycardias are treated similarly to those caused by tricyclic antidepressant overdose, namely sodium bicarbonate and lidocaine. Benzodiazepines, barbiturates, and probably propofol may be used in cases of seizures. Anticholinergic signs, including agitation, may respond to physostigmine but this agent is contraindicated if conduction block is present on the ECG.

20.3.6.10. Organophosphates and other cholinesterase inhibitors

The mainstay of therapy for these patients is intravenous atropine, which should be administered as soon as possible as basic stabilizing and decontaminating measures (skin washing or gastric lavage) are being completed. Atropine doses should be titrated to control bronchorrhea and bronchospasm and large cumulative doses may be required. Diazepam is beneficial by ameliorating fasciculations and preventing or aborting seizures. Other antiepileptics may need to be added in severe cases. Oximes (such as pralidoxime 30 mg/kg followed by an infusion of 8–10 mg/kg/h) effectively reverse the inhibition of acetylcholinesterase caused by the toxin, thus leading to enzymatic reactivation (Willems et al., 1993). It should be administered to all severe cases (including all cases with depression of consciousness) for as long as atropine is required.

20.3.7. Endocrine emergencies

Nonketotic hyperosmolar state, diabetic ketoacidosis, hypoglycemia, thyroid storm, myxedema, addisonian crisis, and pituitary apoplexy are acute endocrine disorders that may result in coma. Prompt adequate treatment of these conditions is not only life-saving but also compatible with full neurological recovery. Among them, pituitary apoplexy offers the most dramatic and protean presentation; as a result, misdiagnosis is not uncommon. Emergency administration of corticosteroids is essential to the survival of the patient. Urgent surgical decompression may be indispensable in comatose patients with considerable mass effect. Also, ophthalmoplegia and visual field deficits are only reversible when pressure is promptly relieved by effective evacuation (Elsasser Imboden et al., 2005).

20.3.8. Hepatic encephalopathy

Lactulose is administered to reduce intestinal absorption of ammonia. Doses should be titrated until diarrhea is induced (30–60 ml each hour) and then continued to promote two to four loose stools each day (usually 15–30 ml every 6–8 h) (Riordan and Williams, 1997). The use of broad-spectrum antibiotics to reduce the intestinal load of ammonia-producing bacteria is debated (Bongaerts et al., 2005). Neomycin has fallen out of favor because its absorption leads to renal toxicity. Other less toxic agents, such as metronidazole, may be used but their effectiveness has not been proved. Some experts have advocated employing probiotic agents but this strategy remains to be studied (Bongaerts et al., 2005).

Flumazenil may produce transient awakening in patients with liver failure but has no impact on ultimate recovery and survival (Als-Nielsen et al., 2004). Astrocyte swelling and increased cerebral blood flow (cerebral hyperemia) are the mechanisms responsible for the development of brain edema and raised intracranial pressure in patients with fulminant hepatic failure (Vaquero et al., 2003). The resulting increase in apparent diffusion coefficient may be monitored using diffusion-weighted MRI (Lodi et al., 2004). Treatment with hypertonic

saline solution (Murphy et al., 2004) may have advantages over mannitol, and propofol infusion may be a valuable alternative (Wijdicks and Nyberg, 2002). Strategies aimed at maximizing cerebral perfusion pressure should be discouraged, since they will worsen brain hyperemia. Application of a molecular adsorbent recycling system may be helpful for some patients but experience with this technique is limited (Sorkine et al., 2001). Liver transplantation is the only hope for the most desperate cases (Kobayashi et al., 2003).

20.4. Conclusions

Neurological examination has to be supplemented with neuroimaging and specific laboratory tests to find the explanation for coma. Treatable causes may only be compatible with good recovery if diagnosed promptly. Attention to detail and a comprehensive evaluation may be the difference between severe impairment and full return to function.

Some patients awaken rapidly but others require prolonged periods of support and assistance. Supportive measures include prevention or treatment of airway tract or pulmonary infections, prevention of decubitus ulcers, eye and mouth care, and physical therapy to minimize the risk of contractures.

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Chapter 21

Ethical issues in the management of patients with impaired consciousness

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21.1. Introduction

Optimal management of patients with disorders that impair consciousness requires proper decision making about life-sustaining treatment. Decision making in critically ill neurological patients generally turns on two essential questions: 1) What is the prognosis for the patient's recovery? and 2) What ethical and medical procedural issues are relevant to the decision to treat? The prognosis for recovery is an obvious consideration because, in nearly all cases, the decision whether to treat aggressively will be made entirely differently depending on whether there is a reasonable chance for recovery with treatment (Bernat, 2004). Ethical and medical procedural issues become a fundamental consideration in patient management because physicians should strive to provide those treatments that critically ill patients wish to receive based on the patients' personal healthcare goals. How patients' values and treatment preferences should be identified and expressed through an authorized surrogate decision maker, and how they are optimally incorporated into medical decisions about their treatment, is the focus of this chapter.

In this chapter I explore the ethical issues underlying the care of patients with acute and chronic disorders that impair consciousness. I begin by discussing the ethical principles and concepts that form the foundation of medical practice. I then analyze the physician–patient relationship in the context of patient-centered medicine, explain the doctrine of shared decision making and emphasize the critical role of the surrogate. I briefly review the role of the hospital ethics committee and ethics consultant. I then discuss the application of these principles in the most common ethical problems arising in patients with impaired consciousness: refusal of life-sustaining treatment, refusal of artificial hydration and nutrition, and determining medical futility. I end with a brief summary discussion of ethical issues in specific syndromes of impaired consciousness. I have discussed these and other ethical issues in neurological practice more comprehensively elsewhere (Bernat, 2008).

21.2. Ethical principles

The practice of medicine is fundamentally a moral enterprise because physicians have a professional duty to care for their patients and always to do what is best for them. Medical ethics is the application of principles of moral philosophy to the context of medical care. Although some scholars make a distinction between the terms 'ethical' and 'moral' (usually attributing a religious meaning to 'moral'), because their similarities exceed their differences, I use them synonymously.

Moral philosophers have created theories to make explicit our most strongly felt moral intuitions. In general, the theories can be reduced to two types: utilitarian (or consequentialist) theories that grade the moral worth of acts by their consequences, and deontological theories that grade the worth of moral acts by the motives that drive them and the universality of their application. Most contemporary moral philosophers believe that neither utilitarian nor deontological factors alone are sufficient to account for the totality of our moral intuitions, and therefore a complete system of morality must embrace both considerations. Complete systems of morality can be constructed on purely secular grounds that, despite cultural differences, remain universally applicable to all rational persons (Gert, 2005).

The most popular account of the philosophical basis of medical ethics is that offered in the textbook *Principles of Biomedical Ethics* by Beauchamp and

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Childress (2001). Although not a rigorous, coherent, or complete account of morality like Gert's system, it has an instant accessibility to physicians that has made it the most popular account of medical ethics in the Western world (Gillon, 1994). The Beauchamp–Childress model is based upon four 'principles' of biomedical ethics: respect for autonomy, nonmaleficence, beneficence, and justice. Although critics have rightly pointed out that these four topics are not truly principles but rather are complex concepts that often conflict with each other (Clouser and Gert, 1990), the Beauchamp–Childress approach succeeds in distilling the essence of many clinical ethics situations and creates a useful means for physicians to conceptualize ethical issues in patient care.

Respect for autonomy has grown in importance markedly over the past generation in parallel with the growing acceptance throughout the world of the principle of respecting human rights and dignity. Respecting the autonomy and self-determination of persons and allowing them to make autonomous choices is intrinsic to the concept of human liberty and respect for persons. The ethical and legal doctrines of informed consent are based on respect of autonomy and dignity. A recent trend of medical practice worldwide is the growth of respect for autonomy and the consequent waning of medical paternalism. Although autonomy represents an important goal, it has limits because it is only one of several competing moral goods. Unfettered autonomy that is not tempered by other considerations could interfere with achieving justice if individuals selfishly pursued their personal goals without considering the wishes and legitimate needs of others. Unfettered autonomy also permits patients to make terrible mistakes without a process for beneficent physician intervention to stop them (Brock and Wartman, 1990). Overemphasis of the concept of individualistic autonomy also ignores the reality that most patients make medical decisions about themselves while seriously considering the impact on their family members and others (Breslin, 2005).

Nonmaleficence is the duty of physicians not to harm patients and to help them avoid harm. It is embodied in the ancient motto of medicine, *Primum non nocere* (Above all, do no harm). Of course, patients may experience much harm from the complications of modern medical and surgical therapies. But that harm may be justified by the greater anticipated benefits of treatment to the patient if the patient's valid consent is obtained. Beneficence is the related moral duty to promote good to patients. It is the moral basis for paternalistic acts designed for the patient's good. It is easy to see how beneficence and autonomy can come into conflict when a physician believes that a patient is making a very harmful decision and feels the duty to intervene to prevent unnecessary harm by overruling the patient's decision (Pellegrino and Thomasma, 1988). An overemphasis on beneficence, however, leads to unjustified medical paternalism, which can harmfully disenfranchise patients from making autonomous decisions in which they wish to participate (Wulff, 1995).

Justice in the medical context (distributive justice) concerns the distribution of finite societal resources and rewards based on concepts of fairness and desert. Justice in a medical ethics context further concerns the balance of the rights of the individual against those of others in society and the societal impact of medical decisions about a single patient. Concepts of justice ultimately stem from a political philosophy of what comprises the fairest and most deserving distribution of finite resources; thus there are multiple theories of justice that follow various political philosophies, including utilitarianism, egalitarianism, and libertarianism, among others (Solomon and Murphy, 1990).

Alternative conceptualizations of the process of ethical deliberation complement the moral philosophical theories. Virtue-based ethics holds that ideal moral acts would always take place if physicians cultivated and routinely practiced virtuous behaviors, a situation that would render formal systems of moral rules unnecessary (Pellegrino and Thomasma, 1993). Care-based ethics is based on the idea that medical decision making optimally is conducted through caring relationships within families so it de-emphasizes the concept of respecting individualistic autonomy (Carse and Nelson, 1995). Narrative ethics focuses on the story of the patient's illness and attempts to distill its personal meaning within the context of the patient's life (Charon, 2001). Feminist ethics conceptualizes the patient–physician relationship within the context of social power hierarchies and studies how gender inequalities that disempower women can harm all patients (Sherwin, 1992).

The world's organized religions contain powerful systems of morality that regulate human behavior. The sacred teachings of Judaism, Christianity, Islam, Hinduism, Buddhism, and Confucianism, for example, each contain powerful moral rules and ideals that believers are expected to follow and aspire to. These religion-based moral rules and ideals comprise a real and important element of the moral intuitions of many people. While acknowledging their importance in the medical decision making process of individual patients, because they pertain only to devout believers, religion-based rules cannot be universal. The discussion of morality in this chapter, while recognizing the relevance of religiously based moral rules as a

potentially important factor in a particular patient's treatment decision, focuses on an account of secular morality that can be universal because of its appeal to all rational persons (Gert, 2005).

21.3. Ethical practice

Physicians operationalize ethical principles at the bedside through the practices of valid consent, shared decision making, patient-centered medicine, and surrogate decision making. Respect for patients' autonomy requires that physicians obtain their free and informed consent prior to ordering testing and treatment, except in medical emergencies. In urgent conditions when consent is impossible or impractical, physicians are authorized to treat by the doctrine of implied consent. Implied consent means that the physician is authorized to treat without explicit consent because it is highly probable that the patient would have consented to the treatment if doing so had been possible. The doctrine of implied consent, however, permits physicians to prescribe only the generally accepted treatment for the emergency condition in question and not innovative or experimental treatments. The application of the rule of implied consent turns on the concept of 'accepted therapy' and its risk–benefit ratio. For example, it remains debatable if, under the doctrine of implied consent, physicians can prescribe intravenous tissue plasminogen activator for threatened stroke in the absence of a patient's or surrogate's explicit consent because of the significant risks of treatment and the fact that many patients and surrogates refuse it as a result (American Academy of Neurology, 1999).

A patient's consent becomes valid when three conditions are fulfilled: the patient has the capacity to make a decision; the patient has been given sufficient information to reach a decision; and the patient is not coerced into making a particular decision (Gert et al., 1997). Patients whose consciousness is impaired as a result of stupor, coma, vegetative state, or metabolic–toxic encephalopathy usually fail the first condition because they lack the capacity to make medical decisions. In those instances of mildly or intermittently impaired consciousness in which the patient's capacity is not obvious, standardized tests may be employed to assess decisional capacity (Freedman et al., 1991). Impaired patients do not surrender the right of consent as a result of their cognitive incapacity. Rather, a surrogate decision maker must be consulted to consent or refuse on behalf of the incapacitated patient. Surrogate consent requires the same conditions to become valid as patient consent.

The amount of information a physician must explain to a patient or surrogate is the amount that a reasonable person would need to make the decision in question (Meisel and Kuczewski, 1996). Generally, patients need to know their diagnosis, prognosis, treatment choices, and probable outcomes. Consent is a process and not an event. It is not a signature on a consent form. Rather, consent is a dialogue that evolves over time in which physicians educate patients or surrogates and agreement on treatment is reached. A patient's written consent is merely the evidence of the preceding consent conversation (Bernat and Peterson, 2006). Consent requires an absence of coercion to become valid. It is coercive to threaten patients or surrogates with abandonment or to exaggerate the benefits of following the recommended therapy or the risks of not doing so.

Surrogate decision makers can be identified through formal legal means or informally. All American jurisdictions and many other countries permit a person, while competent, to appoint another person as their healthcare agent (known also as healthcare proxy or durable power of attorney for healthcare) to make medical decisions for them if they become incapacitated. Most jurisdictions empower healthcare agents with the same full legal authority as the competent patient to consent to or refuse all offered therapies. In situations in which an incapacitated patient did not formally designate a healthcare agent, many jurisdictions, by statute, provide an automatic appointment of an agent from an ordered list of close relatives. In jurisdictions without such laws, no legally authorized surrogate exists. In practice and common law, by default, the nuclear family becomes a joint surrogate. But this informal surrogacy arrangement works only as long as the family members are in agreement about treatment decisions. In the face of intractable disagreement that cannot be resolved by intervention by the ethics committee or other mediation, it may become necessary for a judge to appoint a guardian who is legally authorized to speak for the patient (Bernat, 2008). It is highly desirable for patients, when competent, to execute a legal surrogate appointment, and neurologists should encourage them to do so (Goldblatt, 2001).

Surrogates should be instructed on the accepted standards for surrogate decision making. The highest standard is to follow the expressed wishes of the patient if the patient has made these wishes known through written or oral advance directives. Without knowing the patient's expressed wishes, the surrogate should attempt to reproduce the exact decision the patient would have made by applying the patient's known values and preferences to the present clinical situation and execute a substituted judgment. If the patient's values and preferences are unknown, the surrogate should attempt to balance the benefits to the patient of the proposed therapy against its burdens

and determine what course of action lies in the patient's best interest (Bernat, 2001a). Physicians should approach best interest judgments only as a last resort and always with caution and humility because of the tendency for healthy physicians and surrogates to unjustifiably devalue the quality of life of disabled patients (Drane and Coulehan, 1995).

Surrogate decision making is a lonely and anxiety-filled experience. Physicians need to establish a partnership with the surrogate analogous to that of the patient–physician relationship (Post et al., 1999). They can assist surrogates by providing relevant and current information about prognosis at each stage of the illness, and provide ongoing emotional support. They can help to mitigate a surrogate's guilt by explaining that the surrogate is not making an independent decision (which s/he later may regret or feel ambivalence over) but is merely communicating the decision the patient would have made in the clinical circumstance in question. Finally, physicians can reassure the surrogate that s/he has made the right decision because s/he has strived to accurately communicate the patient's treatment preference (Voltz et al., 2004).

21.4. The patient–physician relationship

The physician–patient relationship has elements of both a contract and a fiduciary trust. Patients and physicians enter an unwritten contract in which the physician promises to provide competent and conscientious medical care and to respect the dignity, privacy, confidentiality, and autonomy of the patient. The patient promises to cooperate with the mutually agreed-upon diagnostic and treatment plan and to tell the physician the truth. Within the patient–physician relationship, physicians, as learned professionals, have a fiduciary duty to protect the interests of and do what is best for their patients (Rodwin, 1995). This fiduciary duty provides the foundation for physicians' responsibility not to abandon patients, to communicate effectively with patients, to grant primacy to patients' interests in circumstances in which their interests may conflict with other interests (Bernat et al., 1998), to respect patient confidentiality and privacy, and to respect the dignity of patients and their medical decisions (American Academy of Neurology, 1993a).

Within the patient–physician relationship, obtaining valid consent at the bedside is best accomplished through the practice of shared decision making (Balint and Shelton, 1996). In the shared decision making model, the physician and patient (or surrogate for incapacitated patients) comprise a decisional dyad. The physician contributes specialized knowledge, training, and experience regarding medical diagnosis, prognosis, and treatment options and their outcomes; the patient contributes his/her unique knowledge of personal values, preferences, and healthcare goals through which to interpret and assign value to the medical facts. Together, they reach a mutually agreeable medical care plan that represents the best treatment for that patient (Brock, 1991). The shared decision making model does not abdicate complete control of healthcare decisions to patients. It merely acknowledges that only patients can define what treatment options ultimately are best for themselves by achieving their health goals (Quill and Brody, 1996). When patients lose the capacity to participate in shared decision making as a result of dementia, encephalopathy, or coma, the surrogate decision maker becomes the physician's decision making partner.

The shared decision making model is based on a concept of the patient–physician relationship known as patient-centered medicine. Patient-centered medicine is healthcare that is congruent with and responsive to the wants, needs, and preferences of patients (Laine and Davidoff, 1996). It replaces physician-centered medicine (still practiced in many societies) in which the prerogatives and preferences of physicians are afforded greater primacy than those of patients. Patient-centered medicine evolved in the context of the patients' rights movement, particularly the increased recognition of patients' ethical and legal rights to participate in all medical decision making that affects them. The growing emphasis on respecting the ethical and legal doctrine of informed consent is the most tangible sign of this evolution (Bernat, 2001a).

The wishes, values, and preferences for treatment of neurologically impaired patients are best communicated to their physicians before patients lose capacity. Advance care planning is the technique that enables patients to anticipate future incapacity and make their wishes for treatment known so their physicians can follow them (Gillick, 2004a). Advance directives are an important mechanism to accomplish that goal (Goldblatt, 2001). The written directive ('living will') is generally a less useful advance directive than the appointment of a healthcare agent because it can be activated only in terminal illness and is usually drafted in vague, ambiguous language. Appointment of a healthcare agent provides decisional authority as soon as a patient is incapacitated (whether terminally ill or not) and permits the flexible and timely application of the patient's general preferences for treatment and healthcare goals to each novel medical situation. The communication between patients and their physicians required for effective advance care planning is one of the most important elements of the physician–patient relationship (Virmani et al., 1994).

21.5. The hospital ethics committee

The hospital ethics committee is a multidisciplinary group of professionals within a hospital who are charged with advising physicians, patients, and families when bioethical issues arise in the course of patient care. They are most useful in clinical practice to analyze the elements of ethical conflicts, to identify the ethically acceptable choices, and to work with physicians, patients, and families to implement the optimal course of action (American Medical Association Judicial Council, 1985). An additional increasingly common role in large medical centers is for ethics committees to help mediate disputes over treatment that arises between families and the medical staff (Orr and deLeon, 2000). The clinical role of hospital ethics committees is purely advisory and they lack the authority to make clinical decisions (Ross et al., 1993). The decisional authority remains in the hands of patients or their authorized surrogates and the responsible physician.

Many hospitals have retained ethics consultants to perform ethics consultations and subsequently report back to the whole committee. The consultants are professionals with training and experience in clinical ethics who are knowledgeable in analyzing, understanding, and assisting with common ethical issues that arise in hospitalized patients (Aulisio et al., 2000). It is desirable for physicians to play a leading role in the ethics consultation process because knowledge of medicine is essential to understand a patient's diagnosis, prognosis, and treatment options. The ethics consultants review the medical record, interview the patient, family members, and staff, analyze the case, and set into motion a process to help resolve the conflict. Neurologist ethics consultants ('neuroethicists') play a special role in analyzing the common ethical issues that arise in patients with impairments of consciousness (Cranford, 1989).

The ethics committee and ethics consultant have a well defined role to play in the management of the patient with impaired consciousness. When their assistance is requested, they can help neurologists and neurosurgeons clarify the patient's diagnosis and prognosis and communicate it to family members, assist in determining the treatment preferences of the patient through studying advance directives and discussions with the family, and aid in maintaining clear channels of communication with families at each stage of the illness (Cranford, 1989). This role can be particularly helpful in cases of brain death or vegetative state in which surveys have shown widespread misunderstanding of the medical facts by patients and families, which may yield faulty decisions because they are based upon unrealistic expectations (Youngner et al., 1989). Clinical ethics intervention is unnecessary if the physicians and nurses caring for the patient can adequately accomplish each of these objectives independently.

One common situation in which ethics consultation is highly desirable, even in the presence of ideal communication, is when surrogates refuse life-sustaining treatment on behalf of a patient who is not terminally ill. An oversight review of the decision making process by the ethics committee helps protect both the patient and the physician. The patient is protected by assurance that proper due process has been followed and that the decision reached most probably represents what the patient would have wanted. The physician is protected by assurance that peers have validated that the process of decision making has followed accepted practice standards.

21.6. Refusal of life-sustaining treatment

Nothing in medicine is more satisfying than successfully rescuing a critically ill patient from dying by timely and skillful high-technology critical treatment performed in an intensive care unit (ICU). But some patients admitted to ICUs have illnesses that remain unsalvageable despite maximal intensive treatment. Once it becomes clear that a critically ill patient is terminally ill, the goal of medical care should change from life prolongation to palliation. Surveys have shown that most patients wish to receive high-technology ICU treatment only if such care can help them recover from their illness to regain their baseline functioning (Frankl et al., 1989). If life-sustaining treatment cannot help them regain acceptable functioning, most patients and surrogates ultimately refuse it. Such patients should receive optimum palliative care.

A seminal ethical and legal achievement of the last generation is the general acceptance that all patients have a right to refuse life-sustaining treatment even if they die as a result. The US Supreme Court in 1990 found a constitutional basis for this right in the 14th Amendment liberty rights clause (Meisel, 1992). Withdrawing or withholding life-sustaining treatment that has been refused by a patient or surrogate is now a common medical practice. And refusal of life-sustaining treatment represents a common cause of death in American ICUs. In several studies, 40–65% of all deaths in ICUs resulted from withholding or withdrawing life-sustaining treatment (Raffin, 1995). In a large survey reviewing the fate of 5910 patients in 136 ICUs, 74% of all patients who died had at least some forms of life-sustaining treatment withdrawn earlier (Prendergast et al., 1998).

The locus of the decision to withhold or withdraw life-sustaining treatment has changed with the evolution from physician-centered to patient-centered medicine. In the earlier context of physician-centered medicine, decisions to withhold or withdraw life-sustaining treatment were conceptualized as identifying those circumstances in which physicians were ethically and legally permitted to withdraw and withhold a patient's life-sustaining treatment. Based on prognosis and other factors, physicians unilaterally decided whether and when to 'terminate life-sustaining treatment' on such patients and then ordered continuation or termination of such treatment. The term 'passive euthanasia' was often applied when patients died from their underlying disease as a result of the physician's decision and action to terminate life-sustaining treatment (Hopkins, 1997).

By contrast, in today's environment of patient-centered medicine, the same phenomenon is conceptualized as the 'refusal' of life-sustaining treatment by a competent patient or by the surrogate of an incompetent patient. It is no longer the contemporary physician's role to decide unilaterally to maintain or withdraw life-sustaining treatment. Rather, the physician's role is to pronounce the correct diagnosis, communicate the prognosis with and without treatment as accurately as possible, determine the treatment preferences of the competent patient, make the most appropriate treatment recommendation, instruct the surrogates of incompetent patients how to consent or refuse on the patient's behalf, and then work with the patient and surrogate to implement the decision. If patient or surrogate refuses life-sustaining treatment, and the patient subsequently dies of the underlying illness, it is misleading to refer to such an act as 'passive euthanasia'. Patients have an ethical and legal right to refuse life-sustaining treatment and physicians usually cannot continue treatment once patients or their legally authorized surrogates have refused it.

Evidence-based reviews of physicians' practices of withdrawing life-sustaining treatment in the ICU (Prendergast and Puntillo, 2002) show that physicians' willingness to stop such treatment is more often a gradual process evolving over time than a discrete event (Faber-Langendoen and Bartels, 1992). Longitudinal ICU studies over the past 20 years show an increasing willingness of physicians to discontinue life-sustaining treatment (Koch et al., 1994; Prendergast and Luce, 1997). One ICU study found that physicians most often discontinued therapies in the following order: cardiopulmonary resuscitation, vasopressors, ventilators, supplemental oxygen, blood transfusions, antibiotics, antiarrhythmic drugs, dialysis, neurosurgery, intravenous fluids, and total parenteral nutrition (Smedira et al., 1990). Physicians preferred to withdraw therapies: 1) from organs that failed from natural, rather than from iatrogenic, causes; 2) that had been started recently, as opposed to those of longer duration; 3) that would result in the patient's immediate death rather than in delayed death; 4) that would result in delayed death in the presence of the physician's diagnostic uncertainty (Christakis and Asch, 1993); and 5) that were related to their own specialty rather than to other specialties (Christakis and Asch, 1995).

Several studies generated evidence-based recommendations for the technique of withdrawing life-sustaining treatment in the ICU, including the provision of palliative opioid and benzodiazepine drugs to minimize patient suffering (Wilson et al., 1992; Daily et al., 1996; Brody et al., 1997). Sudden extubation and prolonged terminal ventilator weaning have been found to be inferior to rapidly dialing down the ventilator volumes as a means of discontinuing ventilatory support (Gilligan and Raffin, 1996).

The largest and most comprehensive study of American physicians' practices of withdrawing life-sustaining treatment from critically ill and dying patients was the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT Principal Investigators, 1995). SUPPORT was a 4-year study of over 9000 hospitalized, seriously ill patients whose goals were to measure the quality of end-of-life decision making, to assess the frequency of unnecessarily painful or prolonged deaths in the hospital, and to attempt to improve the quality of terminal care. Phase I of SUPPORT disclosed serious deficiencies in the care of critically ill and dying patients: 1) many patients did not receive DNR orders until 2 days before death; 2) less than half of physicians knew their patients' resuscitation preferences; and 3) half of conscious patients suffered pain before they died. Phase II of SUPPORT showed that an intervention by nurses to communicate to physicians the patient's current prognosis failed to influence physicians' treatment behaviors.

SUPPORT showed that a common barrier to discontinuing life-sustaining treatment was ambivalence about treatment created by an intermediate prognosis for survival. Many SUPPORT patients were critically ill but not clearly terminally ill. In a typical SUPPORT patient, the prognostic model predicted a 50% chance of survival for 6 months. Many of these patients and their families wished them to have aggressive therapy until it was clearer that their prognosis was poor. Such a time-limited trial of therapy is frequently appropriate pending further clarification of the prognosis (Lo, 1995). SUPPORT made explicit the prognostic ambiguity in many critically ill patients and showed that whether a critically ill patient also is terminally ill is a determination often made more accurately in retrospect.

The process of withdrawal of life-sustaining treatment in a neurological–neurosurgical ICU on patients with disorders of consciousness has been studied. Excluding brain-dead patients, 43% of dying patients were terminally extubated with a mean duration of survival following extubation of 7.5 hours. Morphine or fentanyl was administered to combat labored breathing in two-thirds of patients. A subsequent survey of surrogate decision makers revealed that 88% were comfortable and satisfied with the process of withdrawing life-sustaining treatment (Mayer and Kossoff, 1999).

Cultural practices and local laws are highly relevant to patient and family decisions to withdraw life-sustaining treatment in different countries. For example, the cultural differences in the beliefs and practices of withdrawing life-sustaining treatment have been reported from France (Ferrand et al., 2001), the Netherlands (Pijenborg et al., 1995), Canada (Cook et al., 1995), and Israel (Glick, 1997). In an attempt to reach international consensus on a unifying set of principles underlying the withholding and withdrawing of life-sustaining treatment, representatives from 15 countries developed the Appleton International Guidelines in 1991 (Stanley, 1992). Although these principles have not been ratified by medical societies within the countries of origin, they do comprise a set of generally acceptable normative guidelines. American guidelines have been published by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1983) and the Hastings Center (1987). Mendelson and Jost (2003) recently reviewed the differences in practices and laws in different countries.

American neurologists are inappropriately concerned about legal sanctions and permissions when they are faced with actions to withdraw life-sustaining treatment. In a 1999 survey of practicing neurologist members of the American Academy of Neurology, 40% of respondents wrongly believed that they needed to consult legal counsel before withdrawing a patient's life-sustaining treatment and 38% were concerned, wrongly, that they might be charged with a crime for withdrawing life-sustaining treatment (Carver et al., 1999). Surveys of non-neurologist physicians have disclosed similar legal misconceptions (Meisel et al., 2000). In fact, there are few legal constraints on American physicians who withdraw or withhold life-sustaining treatment when it follows the valid refusal of life-sustaining treatment by competent patients or by the legally authorized surrogates of incompetent patients. Public prosecutors do not pursue physicians who discontinue life-sustaining treatment that has been validly refused, although they may pursue physicians who have committed euthanasia or physician-assisted suicide (Meisel et al., 1999).

21.7. Refusal of artificial hydration and nutrition

A lessening controversy surrounds the question of whether patients and surrogates should have a right to refuse artificial hydration and nutrition along with medical therapies. The controversy historically resulted both from the question of whether artificial hydration and nutrition was considered a medical therapy and from the physician-centered framing of the question as 'Should physicians be permitted to terminate artificial hydration and nutrition on a hopelessly ill patient?' Now that the issue has been reframed as the patient-centered concept of a competent patient's or surrogate's 'refusal of artificial hydration and nutrition', a practice that has been given medical guideline and legal support in the USA and Europe, it has lost much of its controversy.

Most authorities in clinical ethics accept that competent patients and the surrogates of incompetent patients have a right to refuse artificial hydration and nutrition along with all other therapies (Winter, 2000). Artificial hydration and nutrition can be considered a medical therapy because it requires: 1) a physician's order to receive it; 2) surgery to insert a permanent feeding tube; and 3) a nurse to carry out the precise nutrition and hydration orders. But opponents of classifying artificial hydration and nutrition as a medical therapy argue that it represents basic, humane care and, whereas some patients may survive without penicillin or a ventilator, no one can survive without hydration and nutrition. Therefore, they argue that stopping artificial hydration and nutrition in a patient who cannot swallow is tantamount to killing the patient and is therefore wrong under any circumstance (Rosner, 1993).

In the 1990 *Cruzan* decision, the US Supreme Court asserted a constitutional right for all American citizens to refuse all unwanted medical therapies including artificial hydration and nutrition. Legally authorized surrogates can consent or refuse medical therapies including artificial hydration and nutrition on behalf of incompetent patients, once the state's standards of evidence have been satisfied regarding the validity of the patient's prior treatment wishes (Meisel, 1992). In the USA, nearly all healthcare agent statutes permit surrogates to withhold or withdraw artificial hydration and nutrition, along with other medical therapies, but some statutes require the patient's prior specific written stipulation before artificial hydration and nutrition can be stopped. The *Bland* decision in the UK similarly permitted artificial hydration and nutrition to be stopped on a patient in a persistent vegetative state. Physicians need to be knowledgeable about the relevant laws that prevail where they practice.

Physicians have a responsibility to prescribe appropriate palliative care to patients once their artificial hydration and nutrition is stopped to prevent any potential suffering. The necessary degree of palliation with opioids and benzodiazepine drugs depends on the patient's level of consciousness and consequent capacity for suffering, according to established treatment guidelines (Society of Critical Care Medicine Ethics Committee, 2001).

21.8. Medical futility

In caring for patients with altered states of consciousness, the process of shared decision making may fail when the physician and surrogate cannot reach a mutually agreeable decision about treatment. Sometimes, physicians who believe that the patient is salvageable wish to use more aggressive life-sustaining treatments than the surrogate believes the patient would desire. At other times, physicians conclude that the patient is unsalvageable, that life-sustaining treatment should be stopped, and that only palliative care is appropriate but the surrogate demands further aggressive treatment. In the latter case, some physicians have decided to unilaterally stop life-sustaining treatment despite the objections of the surrogate or family members, citing the futility of further treatment. According to the medical futility rationale, because physicians have no ethical obligation to order futile treatment, they may therefore withhold or withdraw any treatment they deem futile. Some ethicists even argue that physicians have a justice-based ethical duty not to provide futile care because of the harms to others (Jecker and Schneiderman, 1993).

The topic of medical futility remains controversial for several reasons. First, there is disagreement on the definition of medical futility because 'futility' has been applied to two distinct phenomena: 1) a physician's prognostication that a particular therapy will produce no physiological effect; and 2) a physician's prognostication that the therapy may produce a physiological effect but the effect will provide no medical benefit to the patient (Truog et al., 1992). There also is disagreement on the statistical threshold for futility. One review showed that some physicians do not declare a therapy to be futile unless its success rate is 0% whereas others consider it futile even with success rates as high as 13% (Lantos et al., 1989). Further, there is a lack of concordance in futility determinations, as shown by a recent ICU study that found disagreement among physicians and nurses on at least one of the daily futility judgments in 63% of dying patients (Frick et al., 2003). More consensus has been achieved during the past decade, as evidenced by the publication of fewer scholarly articles about medical futility than during the previous decade (Helft et al., 2000). I have recently reviewed this topic in greater detail in an article from which this section is abstracted (Bernat, 2005).

Schneiderman et al. (1990, 1996) define a medical treatment as futile if, based on empirical data, the desired outcome is overwhelmingly improbable because the hoped-for benefit will not occur based upon the best available evidence. This definition generates two criteria that comprise independent variables: quantitative and qualitative futility. The quantitative component is the numerical probability that a treatment will produce the desired physiological effect. The qualitative component is the numerical probability that the physiological effect will benefit the patient. A futility calculation is the product of the quantitative and qualitative components. As either component approaches zero, the product approaches zero and the treatment becomes futile.

There are categorical limits to determining the quantitative component. Many treatment decisions lack valid outcome data from which to determine confidence intervals and other statistical measures of the certainty of outcomes. Some published outcome data are invalid because of faulty study design or because of the incorporation of systematic errors such as the fallacy of the 'self-fulfilling prophecy' (Becker et al., 2001). Even with valid and correctly applied outcome data, usually only a statistical prognosis can be given because outcome data predict the behavior of a group more accurately than that of individuals within the group. And most importantly, there is no consensus on the numerical threshold for an act to be labeled futile. For example, should we say a proposed therapy is futile if the probability of physiological effect is 0.001, 0.01, or 0.1? There is a continuum of outcome probabilities for every clinical intervention. The point on the outcome probability continuum at which futility occurs is inherently arbitrary and will be determined differently among physicians and patients (Prendergast, 1996).

The qualitative dimension of futility is limited even further because, by requiring a judgment of the quality of the treatment outcome, it becomes inherently subjective. Who should be authorized to judge and by what standards? What minimal quality of a patient's life an intervention must achieve not to be considered futile? What if the physicians and patient or family disagree? Consider, for example, an intervention that succeeded only in prolonging the life of a patient in a persistent vegetative state but did not improve the patient's chance of regaining awareness. Most physicians would judge it to be futile because they generally believe that merely maintaining a noncognitive state

confers no benefit to the patient. But what if the patient's family members disagreed, as in the celebrated Wanglie persistent vegetative state case (Miles, 1991), and believed that their loved one's continued life in a persistent vegetative state was beneficial to her even if she could never regain awareness? Whose opinion should prevail?

Physicians' specialized training confers upon them the authority to determine medical benefit. But in the case of a therapy that prolongs the life of a patient in a persistent vegetative state without which s/he will die, is declaring such a therapy futile a learned, technical assessment or simply a value judgment about the quality of the patient's life for which physicians can claim no special professional authority? The intersection of moral and medical judgments of clinical outcomes is a gray area over which some physicians assert professional prerogative (Brody, 1994) and over which some nonphysician ethicists deny that physicians deserve any professional prerogative (Veatch, 1994).

Futility disputes have been conceptualized using several models: 1) a power struggle between physicians and surrogates over medical decisional authority (Morreim, 1994); 2) a breakdown of the patient–physician relationship, particularly in communication (Lantos, 1994); 3) an assertion by physicians that their professional prerogative authorizes them to alone define the limits of their duties (Brody, 1994); and 4) an exercise of physicians' stewardship duty to allocate society's scarce medical resources (Jecker and Schniderman, 1992). Each of these models contains an important element of the futility concept but its essence is a breakdown in the relationship of trust and communication between patients and physicians.

The patient–physician relationship is based upon trust, honesty, fidelity, and good communication. Futility disputes arise most often in ICUs in situations in which there has been insufficient time to nurture a trusting relationship between the surrogate and the treating physician. A surrogate's mistrust in a physician may result from the absence of a previous professional relationship compounded by the surrogate's fears, ignorance, and unrealistic expectations of treatment. Some surrogates express a dogged determination to do 'everything possible' irrespective of outcome probabilities because of their fierce loyalty to what they consider the patient's best interests or because of their guilt from conceptualizing the alternative as abandoning the patient. Careful, compassionate explanations of diagnosis and prognosis, emotional support to address surrogates' feelings about making decisions, and fostering clear communication are necessary components of establishing trust. Explaining the principles of palliative medicine can reassure surrogates that there are active and effective treatments that can benefit the patient, such as those described by the Society of Critical Care Medicine Ethics Committee (2001) in their end-of-life ICU treatment guidelines.

Intractable futility disputes are fortunately uncommon. In a futility prevalence survey by Halevy et al. (1996), only 0.9% of ICU patients had predicted mortality rates exceeding 90%. In the multicenter study of Prendergast et al. (1998), 57% of patients and surrogates agreed immediately to physicians' recommendations to limit ICU treatment, 90% agreed within 5 days, and in only 4% of cases did patients or surrogates insist that all forms of treatment be continued. In an educational intervention carried out in over 225 hospitals, Fins and Solomon (2001) studied the elements of communication necessary to resolve futility disputes in the ICU. They found that good communication required not only the use of clear and understandable language but importantly also clinicians' awareness and recognition of the early stages of impending disputes, psychological insight into the cause of disputes, and an institutional culture that promoted good communication with families.

Futility disputes are easier to prevent than to resolve. The critical preventive step is to establish clear channels of communication between ICU physicians and surrogates and other family members from the point of admission. Communication can be difficult in a busy ICU where attending and house staff physicians rotate frequently, family members get mixed messages from different physicians and nurses, and family members may be unclear exactly who is in charge. Surrogates and family members require answers to questions and explanations that may be time-consuming. They may ask questions about prognosis to which confident answers cannot be given, creating physician anxiety that may lead to avoidance of the family. Family members also commonly harbor their own fears and anxieties, which color their perception of the reality of the situation, and require emotional support (Society of Critical Care Medicine Ethics Committee, 2001). In Table 21.1, Prendergast (1997) outlined the strategies to minimize conflicts and negotiate limits that can be employed to prevent futility disputes.

Futility disputes can best be resolved if hospitals draft and follow policies outlining fair procedures for their hearing and disposition. These policies should possess the following features: 1) they are disclosed in the public record; 2) they reflect moral values acceptable to the community; 3) they are not based exclusively on prognostic scoring systems; 4) they articulate appellate mechanisms; and 5) they be recognized by the courts

Table 21.1

Strategies to minimize conflicts and negotiate treatment limits in the intensive care unit

1. Keep patients and families informed
2. Identify other staff members to facilitate good patient relations
3. Promote realistic expectations
4. Strive for accuracy in prognosis
5. Maintain continuity of care
6. Be compassionate and flexible
7. Show firmness about limits
8. Beware of making decisions based on economic market forces

Source: modified from Prendergast, 1997.

(Society of Critical Care Medicine Ethics Committee, 1997). The American Medical Association Council on Ethical and Judicial Affairs (1999) proposed a procedural algorithm for physicians faced with resolving futility disputes that is shown in Table 21.2.

The 1997 US Supreme Court ruling that denied a constitutional right to physician-assisted suicide also affirmed the critical importance of providing palliative care to the dying patient (Capron, 1997). The ruling asserted the legal acceptability of physicians always providing relief of pain and suffering in palliative care, even at the risk of unintentionally hastening death when necessary to provide adequate palliation (McStay, 2003).

Table 21.2

An algorithm for physicians faced with futility disputes in the intensive care unit

1. Deliberate values with surrogates and transfer patients to the care of another physician if the values conflict
2. Conduct joint shared decision making using outcome data and value judgments
3. Involve consultants if disagreements about data arise
4. Involve the hospital ethics committee if disagreement continues
5. Attempt to transfer the patient to another physician within the institution if disagreement continues
6. Consider transfer to another hospital, if possible
7. Only if all these measures fail and disagreement continues can physicians unilaterally cease the futile intervention

Source: modified from the American Medical Association Council on Ethical and Judicial Affairs, 1999.

21.9. Other ethical controversies

Physician-assisted suicide and voluntary active euthanasia of dying patients remain among the most controversial topics in medical ethics. Scholars and physicians continue to actively debate the morality, social consequences, and public policy desirability of legalizing them (Foley and Hendin, 2002; Quill and Battin, 2004). But even the advocates of legalizing these activities all agree that they require the informed consent of the fully conscious and cognitively capable patient. In the USA, Oregon, the only state that has legalized physician-assisted suicide, requires that the patient be competent before receiving a lethal prescription (Hedberg et al., 2003). Similarly, in the Netherlands, where physician-assisted suicide and voluntary active euthanasia have been practiced since 1985, the patient requesting it must be fully competent (Hendin et al., 1997). Therefore, despite their ethical importance in other spheres of neurological practice, these subjects are not directly relevant to the consideration of patients with impaired consciousness. I have discussed physician-assisted suicide and voluntary active euthanasia in detail in my monograph (Bernat, 2008).

Similarly, the topic of palliative sedation in the imminently dying patient ('terminal sedation') remains ethically controversial but is not usually relevant in the patient with an impairment of consciousness because the issue is the ethical acceptability of rendering an alert patient unconscious to palliate pain, dyspnea, or agitation (Gillick, 2004b). I have also discussed this topic in detail in my monograph (Bernat, 2008).

21.10. Ethical issues in specific syndromes of impaired consciousness

The disorders of consciousness in which ethical questions commonly arise are brain death, coma, persistent vegetative state, minimally conscious state, dementia, and locked-in syndrome. The medical details of these conditions are described in chapters elsewhere in this volume. The American Academy of Neurology has published practice advisories addressing the medical and ethical issues in most of these conditions, including brain death (1995a), persistent vegetative state (1995b), dementia (1996), and states of paralysis with intact cognition such as locked-in syndrome (1993a). Guidelines on the medical and ethical aspects of managing patients in a persistent vegetative state also have been published by the American Medical Association Council on Scientific Affairs and Council on Ethical and Judicial Affairs (1990), the American Neurological Association Committee on Ethical Affairs (1993), and the British Medical Association (1996).

The principal ethical issue in the brain-dead patient arises when family members refuse to accept that the patient is dead and insist on further treatment. Family members may reject the diagnosis because the patient with intact circulation does not 'look dead'. They may cite cases of unexpected recovery in cases of allegedly irreversible coma that they hope will occur for their loved one. A family's rejection of brain death is usually an emotional reaction that stems from an inability to accept the finality of the tragic illness, not from a conceptual disagreement about the definition of death. Optimally handling this circumstance requires patience, tact, and compassionate understanding of the family's emotional state. Physicians need to explain the concept of brain death, the utter futility of any treatment, the legality of brain death, and the opportunity of organ donation because of the benefits to both the recipient and donor family. Although there is legal justification in the USA for discontinuing the ventilator despite the opposition of the family, the compassionate physician will continue ventilator treatment for a short time to permit the family to accommodate to the reality of the death of their loved one (Cranford, 1999). Additional ethical issues arising more rarely in brain death include opposition on religious grounds, the management of the brain-dead pregnant woman, and using brain-dead patients for teaching and research. I have discussed these problems elsewhere (Bernat, 2001b).

The two most common ethical problems encountered in patients in coma, persistent vegetative state, or minimally conscious state are the decision to continue or discontinue life-sustaining treatment, including artificial hydration and nutrition, and the determination of medical futility. As discussed previously, the optimal approach to decisions to continue or discontinue life-sustaining treatment involves following the sequential steps listed in the algorithm in Table 21.3. Futility disputes in persistent vegetative state patients, such as that depicted in the Wanglie case (Miles, 1991), should be prevented and resolved following the steps listed in the algorithms in Tables 21.1 and 21.2.

Patients with dementia face a series of ethical problems at each stage of their illness (Sachs and Cassel, 1989). Ethical issues relevant to impaired consciousness may arise in the final stages of illness that are analogous to those arising in persistent vegetative state and minimally conscious state, namely the decision to withhold or withdraw treatment, including artificial hydration and nutrition, and resolving disputes over medical futility. There now is a clear consensus that feeding tubes are not necessarily part of a palliative care plan for severely demented patients who are unable to eat (American Academy of Neurology, 1996), and may be harmful to them (Post, 2001). Mildly demented patients can be encouraged to complete advanced directives early in the course of their disease, stating their treatment wishes and naming a healthcare agent in anticipation of their progressive cognitive incapacity (Finucane et al., 1993).

Table 21.3

An algorithm for decision making about life-sustaining treatment

1. Clarify the diagnosis and prognosis
2. Identify the authorized surrogate decision maker
3. Instruct the surrogate decision maker about decision making standards
4. Have the surrogate identify the patient's preference for treatment
5. Request oversight by the hospital ethics committee if conflicts arise
6. Go to court for judicial review if the treatment conflicts remain intractable
7. Implement the treatment decision
8. Assure that the patient receives excellent palliative care

Source: modified from Bernat, 2008.

The locked-in syndrome is a state of profound paralysis with 'pseudocoma'. In its classic presentation resulting from an infarction or hemorrhage in the pontine base and tegmentum, affected patients are profoundly paralyzed ('de-efferented') but, once the acute stage has passed, they resume normal consciousness and cognition (Patterson and Grabois, 1986). Because of their profound paralysis, they may falsely appear unconscious to the careless observer, who fails to note that they can demonstrate their intact awareness by following commands to look up and down. Even vertical eye movements may be absent in patients in a locked-in syndrome resulting from end-stage amyotropic lateral sclerosis or severe Guillain–Barré syndrome.

Ethical issues in managing the locked-in syndrome patient include: 1) the need to establish a reliable means of communication with patients to permit them to participate in medical decisions, such as that which permitted the French journalist Jean-Dominique Bauby to write his personal poignant account of life in the locked-in syndrome before he died (Bauby, 1997); 2) the difficulty of knowing with confidence if locked-in syndrome patients can make a valid refusal of therapy when their ability to communicate is so marginal; and 3) the need to mitigate suffering, which can be enormous in locked-in syndrome because, despite the profound paralysis, sensory pathways often are preserved (Bernat, 1990).

The American Academy of Neurology (1993b) summarized the duties of neurologists who honor a competent, paralyzed patient's (such as those with locked-in syndrome) refusal of life-sustaining treatment. Patients have the right to refuse treatment but certain preconditions should be met before neurologists discontinue it. The patient should be competent, fully educated about treatment options, and reassured that the neurologist will continue to provide comfort care and will not abandon the patient. Communication should be optimized to permit the patient to fully participate in treatment decisions. The patient's decision to discontinue life-sustaining treatment should be stable over time and not impulsive. Depression should be considered and treated if present. Ideally, the patient's family should agree with and support the decision to discontinue life-sustaining treatment (Bernat et al., 1993).

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