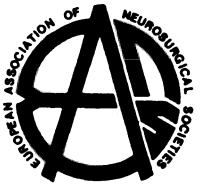


Sponsored by the
European Association of Neurosurgical Societies

Advances and Technical Standards in Neurosurgery

Edited by

L. Symon, London (Editor-in-Chief)
L. Calliauw, Gent
F. Cohadon, Bordeaux
J. Lobo Antunes, Lisbon
F. Loew, Homburg/Saar
H. Nornes, Oslo
E. Pásztor, Budapest
J. D. Pickard, Cambridge
A. J. Strong, London
M. G. Yaşargil, Zurich

Volume 21

Springer-Verlag
Wien New York 1994

With 69 partly coloured Figures

Library of Congress Catalog Card Number 74-10499

Typesetting: Thomson Press, New Delhi, India

by A. Holzhausens Nfg., A-1070 Wien

Printed on acid free and chlorine-free bleached paper

ISSN 0095-4829
ISBN-13: 978-3-7091-7369-5 e-ISBN-13: 978-3-7091-6648-2
DOI: 10.1007/978-3-7091-6648-2

Preface

As an addition to the European postgraduate training system for young neurosurgeons we began to publish in 1974 this series of Advances and Technical Standards in Neurosurgery which was later sponsored by the European Association of Neurosurgical Societies.

This series was first discussed in 1972 at a combined meeting of the Italian and German Neurosurgical Societies in Taormina, the founding fathers of the series being Jean Brihaye, Bernard Pertuiset, Fritz Loew and Hugo Krayenbühl. Thus were established the principles of European co-operation which have been born from the European spirit, flourished in the European Association, and have throughout been associated with this series.

The fact that the English language is well on the way to becoming the international medium at European scientific conferences is a great asset in terms of mutual understanding. Therefore we have decided to publish all contributions in English, regardless of the native language of the authors.

All contributions are submitted to the entire editorial board before publication of any volume.

Our series is not intended to compete with the publications of original scientific papers in other neurosurgical journals. Our intention is, rather, to present fields of neurosurgery and related areas in which important recent advances have been made. The contributions are written by specialists in the given fields and constitute the first part of each volume.

In the second part of each volume, we publish detailed descriptions of standard operative procedures, furnished by experienced clinicians; in these articles the authors describe the techniques they employ and explain the advantages, difficulties and risks involved in the various procedures. This part is intended primarily to assist young neurosurgeons in their post-graduate training. However, we are convinced that it will also be useful to experienced, fully trained neurosurgeons.

The descriptions of standard operative procedures are a novel feature of our series. We intend that this section should make available the findings of European neurosurgeons, published perhaps in less familiar languages, to neurosurgeons beyond the boundaries of the authors' countries and of Europe. We will however from time to time bring to the notice of our European colleagues, operative procedures from colleagues in the United

States and Japan, who have developed techniques which may now be regarded as standard. Our aim throughout is to promote contacts among neurosurgeons in Europe and throughout the world neurosurgical community in general.

We hope therefore that surgeons not only in Europe, but throughout the world will profit by this series of Advances and Technical Standards in Neurosurgery.

The Editors

Contents

A. Advances

B. Technical Standards

Listed in Index Medicus

List of Contributors

Caemaert, J., MD, University Hospital of Gent, Neurosurgeon, Ghent, Belgium.
Ceha, J., MD, Psychiatric Hospital "Ursula Kliniek", Psychiatrist, Wassenaar, The Netherlands.
Choux, M., MD, Professor, Service de Neurochirurgie Pediatrique, Centre Hospitalier Régional et Universitaire de Marseille, Hôpital des Enfants de la Timone, Bd Jean Moulin, F-13385 Marseille, Cedex 5, France.
Ciricillo, S. F., MD, Department of Neurological Surgery, The Editorial Office, 1360 Ninth Avenue, Suite 210, University of California, San Francisco, CA 94122, U.S.A.
Cohadon, F., MD, Professor. Clinique Universitaire de Neurochirurgie, Hôpital Pellegrin Tripode, F-33076 Bordeaux, France.
Cosyns, P., MD, Universitair Ziekenhaus Antwerpen, Wilrykstraat 10, B-2520 Edegem, Antwerp, Belgium.
Daumas-Duport, C., MD, Professor, Service de Neurochirurgie, Centre Hospitalier Sainte-Anne, 1 rue Cabanis, F-75674 Paris, Cedex 14, France.
Foroutan, M., MD, Service de Neurochirurgie Pediatrique, Centre Hospitalier Régional et Universitaire de Marseille, Hôpital des Enfants de la Timone, Bd Jean Moulin, F-13385 Marseille, Cedex 5, France.
Genitori, L., MD, Service de Neurochirurgie Pediatrique, Centre Hospitalier Régional et Universitaire de Marseille, Hôpital des Enfants de la Timone, Bd Jean Moulin, F-13385 Marseille, Cedex 5, France.
Gybels, J., MD, Catholic University of Leuven, Neurosurgeon, Louvain, Belgium.
Haaijman, W., MD, Hospital for Psychotherapy "Overwaal", Psychiatrist, Lent, The Netherlands.
Lantos, P. L., MD, DSc, FRCPath, Professor, Department of Neuropathology, Experimental Neuro-Oncology Group, Bethlem Royal Hospital, University of London, De Crespigny Park, Denmark Hill, London, SE5 8AF, U.K.
Lena, G., MD, Service de Neurochirurgie Pediatrique, Centre Hospitalier Régional et Universitaire de Marseille, Hôpital des Enfants de la Timone, Bd Jean Moulin, F-13385 Marseille, Cedex 5, France.
Van Manen, J., MD, Academic Medical Center, Amsterdam, and University Hospital of Groningen, Neurologist, Groningen, The Netherlands.
Pilkington, G. J., Ph.D., MIBiol, MRCPath, Department of Neuropathology, Experimental Neuro-Oncology Group, Bethlem Royal Hospital, University of London, De Crespigny Park, Denmark Hill, London, SE5 8AF, U.K.
Rosenblum, M. L., MD, Department of Neurological Surgery, The Editorial Office, 1360 Ninth Avenue, Suite 210, University of California, San Francisco, CA 94122, U.S.A.
Van Veelen, C., MD, University Hospital of Utrecht, Neurosurgeon, Utrecht, The Netherlands.

A. Advances

Biological Markers for Tumours of the Brain

G. J. PILKINGTON and P. L. LANTOS

Department of Neuropathology, Institute of Psychiatry, London, (U.K.)

With 10 Figures

Contents

Classification of Brain Tumours

Tumours of the central nervous system (CNS) represent a strikingly wide range of derivation, reflecting the histological complexity of the organ in which they arise. Neoplasms may originate from the four main types of neuroepithelium: neuronal, glial, pineal and retinal cells. The single most important and frequent group of neoplasms is the gliomas which can be subdivided, according to the three major cell types, into astrocytomas, oligodendrocytomas and ependymomas. The meninges ensheathing the CNS also give rise to a group of neoplasms, the meningiomas which appear to have an increasingly large number of subtypes. The associated cranial and spinal nerves are the sites of Schwannomas and neurofibromas. The blood vessels permeating neural tissues are hosts of both neoplasms and malformations. Haemopoietic and germ cell tumours may primarily affect the brain. Cysts and other tumour-like lesions often develop in the CNS and local extensions from regional tumours or secondary deposits from distant malignancies are not infrequent complications. In addition, the brain is associated with the pituitary gland and tumours may arise both from the endocrine and neural parts of this organ.

Considering this histological spectrum it is not surprising that the classification of these neoplasms has been fraught with considerable difficulties. The first classification was devised by Bailey and Cushing (1926) who distinguished, using metallic impregnation techniques, 14 main categories. These corresponded to those developmental stages through which the various neural cell types evolve during normal ontogenesis. Cox (1933), recognising the importance of anaplasia in histological diagnosis, simplified this classification and separated tumours of adult tissue from anaplastic and transitional forms. It was Kernohan *et al.* (1949) who introduced the concept of grading to neuroepithelial tumours. He distinguished astrocytomas, oligodendrogliomas, ependymomas, neuro-astrocytomas and medulloblastomas and graded all groups, with the exception of the last,

according to increasing malignancy from Grade I to IV. Of the more recent attempts, both Russell and Rubinstein (1977) and Zülch (1965) proposed tumour classification schemes: the former concentrated on neuroepithelial neoplasms, whilst the latter included other tumour types.

The World Health Organisation (WHO) attempted to devise a comprehensive classification (Zülch 1979) which has been revised recently (Kleihues *et al.* 1993). This classification eliminates or reclassifies some of the more controversial and confusing entities, and has recognised and included several new types. The classification is based on the histological assessment of cell types and tissue patterns, although progress, brought about by immunocytochemistry, has been fully acknowledged. The presence of several entities of unknown origin is the evidence that further investigations are necessary for a classification based on cytogenesis. However it is hoped that the new classification will be generally accepted by various groups of neuroscientists, including neurosurgeons, neuroradiologists, neuropathologists and neurologists. The following review is based on this classification.

General Features of Brain Tumours

Tumours of the CNS have several unique features. First, most originate and grow in a limited space: both the brain and the spinal cord are encased in an unyielding fibrous and bony structure, the skull and the spinal canal respectively. Thus there is a conflict between the increasing volume of the tumours and the fixed space available to accommodate them. This is particularly important in the case of brain tumours, since the consequences, the signs and symptoms of increased intracranial pressure are often life-threatening. Dislocation and herniation of structures, haemorrhages, hydrocephalus and cerebral oedema, may all occur as part of a chain of events initiated by tumour growth. These complications will not be considered here.

Second, the usual histological and cytological criteria of malignancy cannot be applied automatically to neuroepithelial tumours. The most important criterion of malignancy, the ability to give rise to secondary deposits in distant organs, clearly does not hold for even the highest grade of brain tumours: secondary growths from these tumours outside the skull are extremely rare.

Conversely, local invasive behaviour is, perhaps, the most significant biological feature of intrinsic brain tumours, irrespective of their histological grade of malignancy. Even low grade neuroepithelial tumours are poorly demarcated and hardly ever properly encapsulated; consequently

their complete surgical removal is difficult, if not impossible. Not surprisingly, they often recur and carry a poor prognosis. An histologically low grade astrocytoma, even a pilocytic astrocytoma, may behave biologically as a malignant tumour, if it invades and destroys important functional centres.

Third, neoplasms, particularly gliomas, often show striking cellular pleomorphism and contain mixed cell populations. Consequently the histological pattern of a given tumour may vary considerably from area to area. Cellular pleomorphism is the consequence of differentiation and anaplasia: neuroepithelial tumours are often composed of cells at various stages of differentiation, primitive precursors and anaplastic or bizarre forms. Glioblastoma multiforme is the best, but by no means the only example, of this cellular heterogeneity. In addition, there are genuinely mixed tumours: various glial cell types (e.g. mixed oligoastrocytoma), neuronal and glial cells (e.g. ganglioglioma) and gliomatous and sarcomatous components (e.g. gliosarcoma) may form a single neoplasm.

For this cellular complexity alone, various tumours types of the CNS require specialised, diagnostic investigations. These, in turn, are of considerable help in improving diagnostic accuracy.

Investigative and Diagnostic Neuro-Oncology Techniques

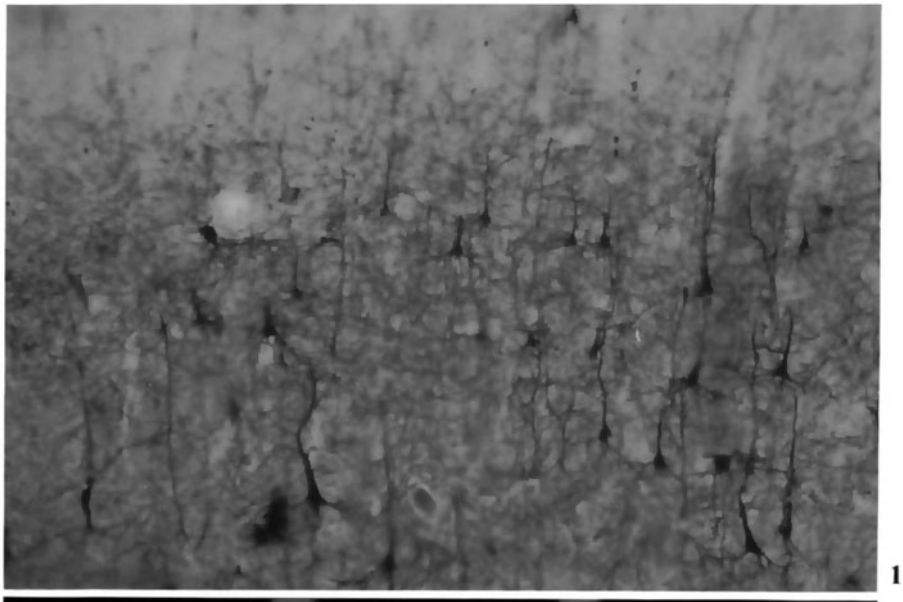
Early studies by Rudolph Virchow (1846) provided evidence for the existence of non-neuronal cells in the nervous system. These cells, which he called neuroglia or "nerve glue", constitute the major target for neoplastic transformation in the CNS. The recognition and classification of the neuroglia was given further impetus with the advent of the metallic impregnation techniques pioneered by Camillo Golgi, Santiago Ramon y Cajal and Pio del Rio Hortega (Fig. 1). The basis of these techniques was the treatment of potassium bichromate fixed tissue with silver nitrate, which resulted in the deposition of silver bichromate deposit on some, but not all, types of neural cell. Such "special" stains were used to complement conventional histological stains such as haematoxylin and eosin but, although commonplace in most neuropathology laboratories some 20 years ago, they have now been largely superseded by electron microscopy and immunohistochemistry for the demonstration of glial cells.

Because of the use of short wavelength image-forming radiation, transmission electron microscopy (EM) permits high resolution examination of the intracellular organelles and cell membranes and, although it is not generally necessary to use EM in diagnostic neuro-oncology, it does provide

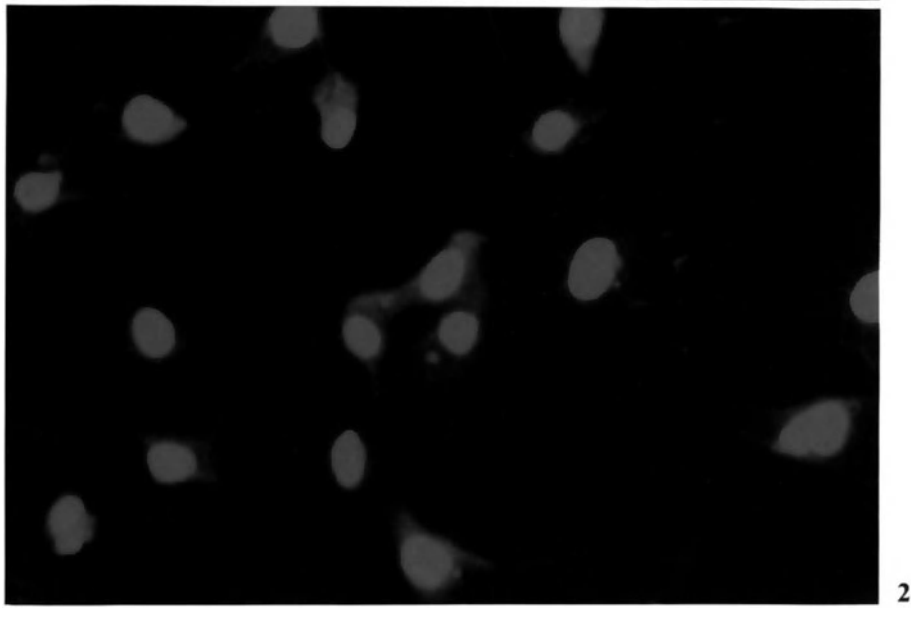
a powerful tool with which to secure a diagnosis in certain difficult cases. For example, the ultrastructural demonstration of neurosecretory granules may be needed to establish the nature of neuronal tumours.

The immunohistochemical and immunocytochemical techniques used today owe much to the work of Albert Coons who, more than four decades ago, succeeded in labelling an antibody with the fluorescence dye, fluorescein isocyanate, which he used subsequently to localize a specific antigen in tissue sections. There is now an ever-increasing range of fluorochromes available for fluorescence immunocytochemistry. Such methods are, however generally restricted to the localisation of antigenic sites on or in cultured cells or unfixed frozen sections since conventional paraffin wax processing and aldehyde fixation can lead to "background" fluorescence staining. Fixed, embedded sections are normally stained using immunoenzymic techniques in which antibody-linked enzyme complexes such as horseradish peroxidase and alkaline phosphatase can be rendered to insoluble chromogens by their respective substrates. In addition, the use of sophisticated modern methods, such as the biotin/streptavidin technique, provide signal amplification. Here, the small, water-soluble vitamin, biotin, is conjugated to a species-specific antibody to bridge the reaction between primary antibody and fluorochrome or enzyme/chromogen-linked streptavidin (a protein isolated from *Streptomycetes avinidii*) which has four, high affinity binding sites for avidin. The advent of monoclonal antibody technology (Kohler and Milstein 1975) has provided a wealth of reagents for the identification of cell surface molecules, proteins and lipids comprising the cell organelles, cytosol enzymes and nuclear epitopes of both normal and neoplastic tissues. It should be borne in mind, however, that the concept of a tumour-differentiation specific antibody is, perhaps, naive and immunohistological stains should be considered as "signposts" rather than definitive markers (Rubinstein 1986). The use of a multi-methodological approach and a battery of antibody stains, therefore, ensures an accurate picture of the tumours observed. Immunocytochemistry may also be carried out at ultrastructural level using intrinsically electron-dense, metallic (e.g. colloidal gold) particles of known, constant size, conjugated to specific antibodies. Such immuno-electron microscopical techniques provide highly specific antigen localisation. For example, the contents of neurosecretory granules or protein components of the cytoskeleton can be accurately demonstrated.

In recent years three antibody-mediated methods have been introduced which are aimed at gaining an insight into the proliferative activity of neoplasms and its prognostic significance. The first of these involves treating patients or biopsy-derived cultured cells with the thymidine analogue, bromodeoxyuridine (BUdR), which is incorporated into the nucleic acid of S-phase cells (Fig. 2). The labelled cells can then be detected by immunocyto-



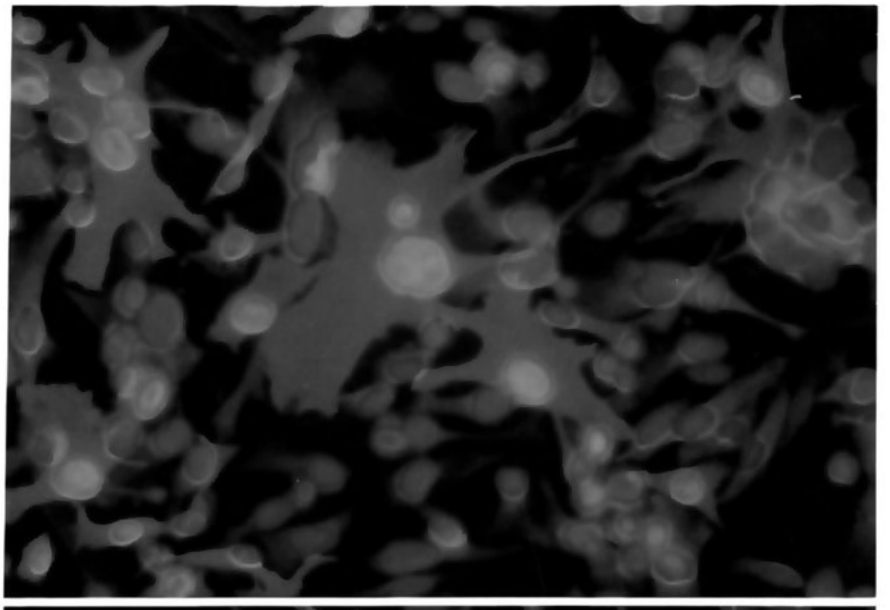
1



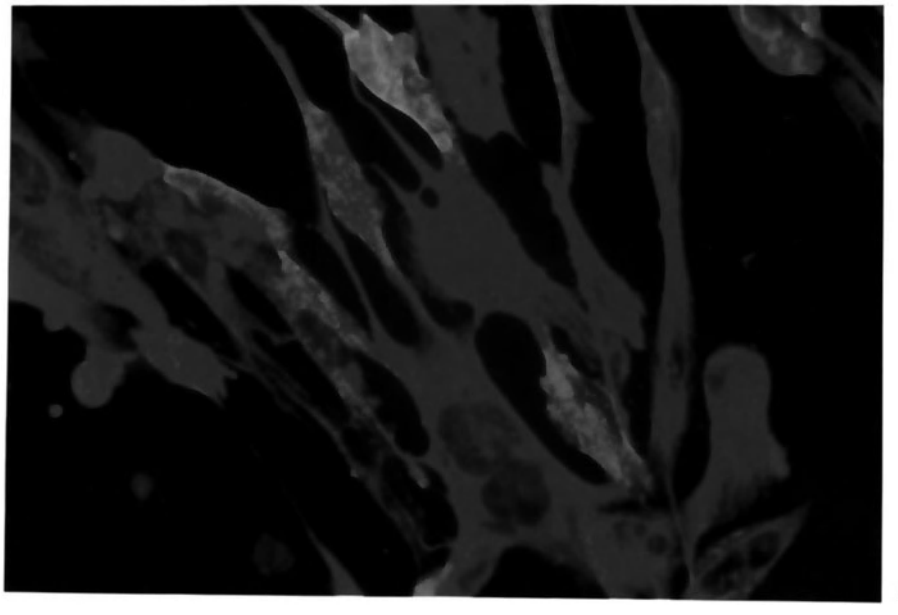
2

Fig. 1. Golgi metallic impregnation of neocortex demonstrating pyramidal neurones

Fig. 2. Bromodeoxyuridine-labelling (fluorescein isothiocyanate green fluorescence) demonstrates S-phase nuclei in glioma cells in vitro



3



4

Fig. 3. Astrocytoma cells in vitro are labelled with glial fibrillary acidic protein (green cytoplasmic fluorescence). Nuclei are counterstained red with propidium iodide

Fig. 4. Yellow surface immuno-labelling with fluorescein for the ganglioside-recognizing monoclonal antibody, A2B5, overlies cytoplasmic Texas red fluorescence staining for glial fibrillary acidic protein on human glioma cells

chemical staining of biopsied sections or cells with a monoclonal antibody directed against BUdR (Nagashima *et al.* 1985).

The growth fractions of neoplasms may also be assessed by use of monoclonal antibody Ki-67 which reacts with nuclear epitopes expressed during G1, S, G2, and M phases of the cell cycle (Gerdes *et al.* 1984). This antibody has the disadvantage, however, that staining must be carried out on unfixed, frozen sections, although a new Ki-67 antibody has been recently developed which will work on microwave-treated paraffin sections.

The third method, proliferating cell nuclear antigen (PCNA), does not suffer from the problems of pre-operative administration of antibodies to the patient or from the restriction of using frozen sections. PCNA (Takasaki *et al.* 1984) or cyclin (Celis and Celis 1985) is a cell cycle regulated protein (Tan *et al.* 1986) that appears to act as an auxiliary protein for polymerase that accumulates in the nucleus during S-phase (Landberg and Roos 1991). Monoclonal antibodies, such as PC-10, which recognise PCNA will mark either S-phase cells or all cycling cells according to the fixation regimen used.

An alternative approach to the study of cell proliferation in malignant tumours is selective silver staining of nucleolar organiser regions (AgNORs) (Crocker and Nar 1987) in which ribosomal gene activity is visualised. In neural neoplasms higher numbers of AgNORs have been observed in malignant brain tumours compared to low grade lesions (Plate *et al.* 1991). This method may, therefore, provide a valuable means by which malignancy can be monitored.

Although it has only attracted interest in the field of neuro-oncology in recent years, *in situ* hybridisation has, perhaps surprisingly, been employed for almost a quarter of a century (John *et al.* 1969; Pardue and Gail 1969) to detect messenger RNA in cultured cells as well as frozen or paraffin sections. This method is based on the assumption that a cell contains a given mRNA species if it is transcribing that gene and synthesising the encoded protein (Harrison and Pearson 1990). The technique is semi-quantitative in that, with the aid of densitometry, changes in levels of expression may be detected in response to drug treatment or in certain disease states (Emson 1993). The success or failure of this technique rests in the choice of a suitable probe, a single-stranded length of DNA which is complementary in sequence to the target message. Probes may be constructed using recombinant DNA technology or produced on a DNA synthesiser. Short oligonucleotides, 20 to 50 bases in length, have the advantages of being inexpensive to produce and they allow hybridisation conditions to be standardised. However, if the quantity of target message in the tissue is low, it may be necessary to resort to longer cDNA/cRNA probes which may be as many as 200 or more bases in length. These may be multiply labelled to amplify a weak signal, but their

preparation and use are complicated. Non-radioactive methods of labelling and visualisation, based on either biotin or enzymes such as alkaline phosphatase, are becoming increasingly favoured over isotopic methods. Not only do they offer advantages in terms of safety and cellular resolution, but they often yield results in hours rather than days or weeks.

Molecular and cytogenetic investigations have revealed a number of chromosomal abnormalities in neoplastic neuroepithelial cells, including deletions, translocations and rearrangements. Low grade glial neoplasms usually show karyotypic homogeneity, while high grade gliomas may exhibit extensive heterogeneity within neoplastic cell sub-populations, with variable chromosome numbers in distinct regions of the tumour (Shapiro *et al.* 1981). In addition, the identification of proto-oncogenes, oncogenes and anti-oncogenes (tumour-suppressor genes) may also yield important information in relation to the biological behaviour, etiology and prognosis of CNS neoplasms.

Progression and prognosis of neural neoplasms may be a function of the genetic configuration of component cells. Cytogenetic analysis may, therefore, provide markers which will indicate the biological behaviour of the tumours. The picture of genetic abnormalities is complex in brain tumours; gliomas variously exhibiting aberrations on chromosomes 7, 9, 10, 13, 17 and 22. The relevance of these chromosomal changes to development and malignant progression of brain tumours is not yet fully understood and is, therefore, the subject of intensive studies of oncogenes, regulatory sequences and gene products.

Tumour suppressor genes, the expression of which inhibits the cancer phenotype (Knudsen 1971; Commings 1973), have been a focus for interest in many branches of cancer research, including neuro-oncology. Evidence exists that certain tumours are produced by two genetic events in a single cell; the so-called "two-hit" hypothesis (Knudsen 1983). The best example of this is retinoblastoma where in familial cases a mutation to a tumour suppressor gene on chromosome 13 is inherited (Lee *et al.* 1987) and only if a second, somatic, mutation occurs in the stem cell (retinoblast) do the cells become unresponsive to normal differentiation controls and continue to divide, resulting in tumour formation. The somatic mutation occurs in 90% of carriers of the recessive gene (Friend *et al.* 1986). In sporadic cases of retinoblastoma both "hits" are somatic, occurring in the retinoblasts and resulting in loss of function of a tumour suppressor gene.

The wild type p53 gene, mapping to region p13 of chromosome 17, which is a transcriptional activator, may serve as a barrier to the progression of neoplastic processes (Steck and Saya 1991). p53 is lost or mutated in a number of malignancies, including those of the brain, and may, therefore, be a candidate tumour suppressor gene. Cells containing mutant p53 are

present in low grade gliomas but are more apparent in high grade tumours, particularly recurrences. It has also been suggested that the evolution of low grade brain tumours into more malignant neoplasms may be associated with clonal expansion of cells containing mutant p53 (Sidransky *et al.* 1992). Both p53 immunohistochemistry, using the monoclonal antibody PAb 1801, and single-strand conformational polymorphism with sequence analysis have been carried out on human astrocytomas and sub-sets of neoplasms have been proposed on the basis of these studies (Louis *et al.* 1993).

The response of brain tumours to various therapeutic regimens may be assessed at a cellular level. Assays for both chemo- and radio-sensitivity have been developed and are currently the subject of clinical evaluation. In addition, immunocytochemical staining may assist in appraising potential cellular response to drug and radiation therapy.

A major factor which contributes to the lack of response to cancer chemotherapy is the development of multidrug resistant tumour cells during malignant progression. The highly conserved membrane transport protein, P-glycoprotein, has been shown to be over-expressed in many multidrug resistant tumour cell lines including those derived from human brain tumours (Matsumoto *et al.* 1991). The expression of the MDR1 gene, which encodes for P-glycoprotein, has also been recently reported in human glial tumours (Becker *et al.* 1991) and may contribute to the non-responsiveness of some intracranial tumours to drug therapy.

Current microscopical, immunological, biochemical and molecular biological approaches can all, therefore, provide markers with applications to both the diagnosis of brain tumours and in the biological research which aims to provide improved therapeutic measures for this complex group of neoplasms. Such markers may yield information on: *cell type (of tumour origin), degree of malignancy, prognosis, invasive behaviour, cell kinetics, drug sensitivity and genetic aberrations.* The correlative examination of histological sections of tumours together with tumour-derived cell cultures may also contribute significantly to a knowledge of the dynamic mechanisms involved in tumourigenesis and malignancy of CNS neoplasms.

1. Tumours of Neuroepithelial Tissue

1.1. Astrocytic Tumours

Astroglial neoplasms constitute some 20% of neuroepithelial tumours, can occur at any age, but most commonly in the fourth and fifth decades and affect men more frequently than women, the ratio being 3 to 2. They may

develop anywhere along the neuroaxis, in the cerebellum of children, in the brainstem of young adults and in the white matter of the cerebral hemispheres in adults. In the spinal cord, they are the second most common form of intrinsic tumour after the ependymomas. With the exception of cerebellar astrocytomas which tend to be circumscribed, they are invasive growths with infiltration and subsequent destruction of neighbouring structures.

The most commonly used immunocytochemical marker in diagnostic neuropathology is the glial fibrillary acidic protein (GFAP) which shows specificity for cells of astrocytic lineage (Fig. 3). The 47 kD protein, GFAP, was first isolated from multiple sclerosis plaques, post leucotomy scars and the occipital and frontal horns of the lateral ventricles of old hydrocephalic patients (Eng *et al.* 1971). Its specificity for normal and reactive astrocytes has been extended to the study of astrocytic tumours (Deck *et al.* 1978; Duffy *et al.* 1977), where it has proved invaluable in both diagnosis and research. Although the intermediate filaments of well-differentiated astrocytes are comprised mainly of GFAP, a second protein, vimentin, with a molecular weight of 57 kD and a much wider distribution throughout eukaryotic cells, has been identified as the major cytoskeletal element of developing glia (Dahl *et al.* 1981). Thus a developmental relationship exists between vimentin and GFAP whereby vimentin is gradually replaced by GFAP as the cells mature towards astrocytic differentiation. A similar relationship exists between vimentin and desmin in muscle and between vimentin and cytokeratins in epithelium. Co-expression of GFAP and vimentin has also been reported in human astrocytomas (Herpers *et al.* 1986) and may reflect the proliferative propensity of the neoplastic astrocytes or suggest anaplasia. Alternatively, vimentin staining may indicate the presence of mesenchymal cells or reactive astrocytes in gliomas (Schiffer *et al.* 1986). Both GFAP and vimentin are expressed by glioma-derived cells in vitro. However, GFAP is rarely expressed at late passage (Knott *et al.* 1990), while vimentin is ubiquitous in cultured cells. The enzyme glutamine synthetase (GS), which plays an important role in the detoxification of ammonia and in the metabolism of glutamate, has been shown to be confined largely to astrocytes in the mammalian brain (Norenberg 1979). Antibodies produced against GS were proposed as a second marker of astrocytic differentiation in brain tumours (Pilkington and Lantos 1982), although subsequent studies have shown reactivity in metastases, meningiomas and oligodendrogliomas (McCormick *et al.* 1990).

The in vitro findings of Raff *et al.* (1983) indicate that, at least in 7 day rat optic nerve, there are two pathways of astrocytic differentiation resulting in the concept of type 1 and type 2 astrocytes on the basis of the binding propensity of their respective precursors for the ganglioside-recognising

monoclonal antibody A2B5. This work has lead to studies aimed at classifying astrocytic tumours according to their antigenic expression. A "dual lineage" for astrocytic brain tumours has been proposed (Bishop and de la Monte 1989) which suggests that neoplasms which express A2B5 (Fig. 4) carry a better prognosis than those where no staining is apparent. As the site of biological activity of gangliosides is the cell surface, such an interpretation of immunocytochemical staining patterns in histologcial sections may not be accurate, since the in vitro lineage studies are based on the expression of gangliosides on the cell surface of intact, unfixed glial cells. It should be noted that gangliosides can also be demonstrated at the sites of synthesis (rough surfaced endoplasmic reticulum), metabolism (Golgi apparatus) and degradation (lysosomes) respectively, in the cytoplasm of cells where the plasma membrane has been breached. Moreover, recent studies have shown that the expression of such surface gangliosides can be modulated in normal (Drago *et al.* 1989) and neoplastic (Pilkington *et al.* 1993b) glia by the application of exogenous growth factors. Levels of such growth factors, including basic fibroblast growth factor (bFGF) and platelet-derived growth factor (PDGF) are significantly different in glioma tissue compared to normal brain and thus A2B5 expression may not reflect lineage but may be dependent upon tumour microenvironment. In addition, the expression of gangliosides may be related to cell cycle phase (Pilkington 1992). Although cell surface gangliosides may not, therefore, give an accurate indication of the glial lineage of tumours, their presence has been linked with both glioma cell motility (Pilkington 1992) and invasiveness (Engebraaten *et al.* 1991). Gangliosides are, in fact, particularly numerous in the mammalian nervous system; structurally simple forms being characteristic of neoplastic neural tissue (Yates 1988).

Astrocytomas

Histologically, three subtypes can be distingished: fibrillary, protoplasmic and gemistocytic. There are no specific markers for these three variants of the neoplastic astrocyte. However a recent study has suggested that antibodies against metallothionen may mark protoplasmic astrocytes in brain tumours (Troost *et al.* 1993).

Fibrillary astrocytomas are the most common variety of astrocytomas. The cellular and nuclear profiles may vary, but the common feature of these gliomas is the fibrillary matrix, formed by the numerous cell processes. These, in turn, contain masses of 10 mm diameter astrocytic filaments which can be demonstrated by EM and specialised neurohistological stains, such

as phosphotungstic acid haematoxylin (PTAH) or Holzer, and immunocytochemistry using antibodies against GFAP and vimentin.

Increased number of Ki-67 labelled cells in primary astrocytic neoplasms of the brain has been reported to be proportional to the increasing histological degree of malignancy of the tumour; percentages of positive cells ranging from 1% in pilocytic astrocytoma to 40–50% in glioblastoma multiforme (Giangaspero *et al.* 1987).

From a more extensive study of 174 cases of astrocytic brain tumour, Hoshino *et al.* (1993) established that while the probability of survival is a function of both age and BUdR kinetic labelling index (LI), BUdR LI provides the single most accurate predictor of survival in low grade astrocytomas. Thus kinetic labelling, to assess proliferative potential in astrocytic brain tumours, provides a valuable marker of both survival time and effectiveness of different treatment modalities.

Monoclonal antibodies, such as M2, have been raised which are expressed less in juvenile astrocytomas than in malignant astrocytomas of adulthood (Sarawar *et al.* 1991). Such antibodies may be markers for oncogene products associated with increased malignancy.

Anaplastic (Malignant) Astrocytomas

These gliomas show focal or more generalised features of anaplasia, including cellular and nuclear pleomorphism, increased cellularity and mitotic activity. GFAP, a differentiated gene product, may not be apparent, or may be weakly demonstrated in this group of tumours.

Glioblastoma Multiforme

These are highly malignant tumours characterised by striking cellular pleomorphism, high mitotic rate, endothelial hyperplasia and necrosis. The neoplastic cells show considerable variation in shape and size: small, undifferentiated cells with hyperchromatic nuclei, pleomorphic astrocytes and giant, multinucleated forms may all be seen. Indeed, the histology may vary from area to area. Endothelial hyperplasia is often prominent and the mitotically active endothelial cells pile up to form glomeruloid structures. In extreme cases real mixed neoplasms, gliosarcomas, may arise. However, the blood supply may not match the rate of tumour growth and, as result, small, multiple areas of serpiginous necrosis may appear with pseudopalisading of neoplastic cells. Macroscopically, glioblastomas are large,

destructive lesions, most often arising in the deep white matter of the cerebral hemispheres and not infrequently they spread, through the corpus callosum into the contralateral hemisphere, forming the characteristic butterfly configuration. Although these tumours are now generally considered to be of astrocytic origin, GFAP is not always identifiable in the component cells due to their poor level of cellular differentiation.

Glioblastoma multiforme and anaplastic astrocytomas have formed the focus for many cell culture (Fig. 5) and molecular biological studies, the fruits of which are now becoming apparent. The morphological features on which successive generations of neuropathologists have based their diagnoses of glioblastoma multiforme may now be explained by growth factor mechanisms eliciting cellular change in neural tissues. For example, the marked endothelial hyperplasia which characterises glioblastoma multiforme, may arise as a result of platelet-derived growth factor (PDGF) activity. PDGF has been described as the dominant mitogenic factor for malignant gliomas (Pollack *et al.* 1991). Three isoforms of PDGF exist (AA, AB and BB) and there are two receptor types (A and B) (Heldin and Westermark 1989). The A type receptor exists on endothelial cells while the B type is found on neoplastic glia. Since the AA isoform of PDGF

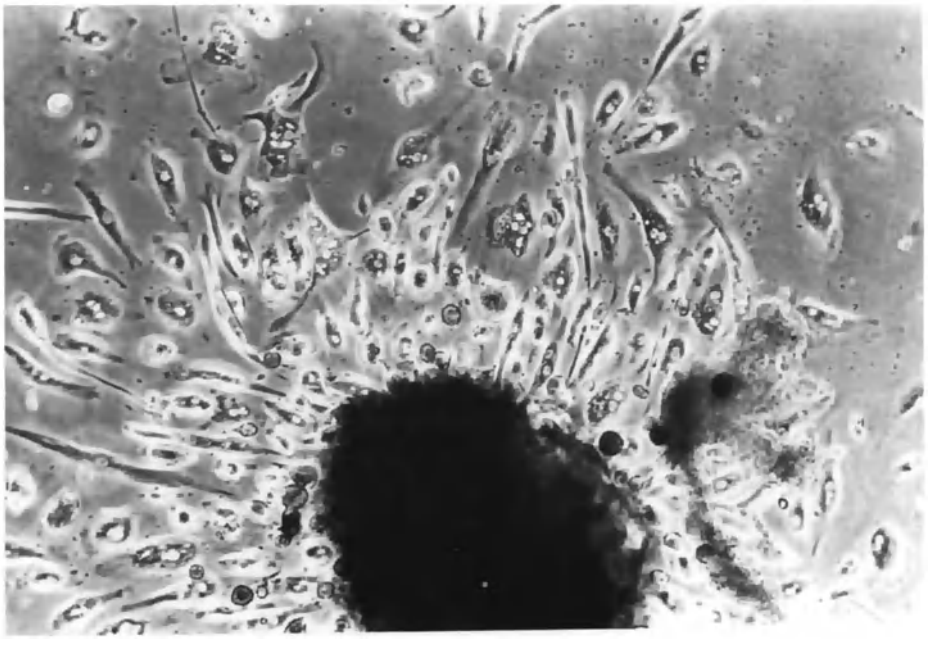


Fig. 5. Phase contrast micrograph of a primary explant culture derived from a glioblastoma multiforma. Cells migrate away from the explant mass to form a monolayer

interacts with the A type receptor, the high levels of PDGF AA reported in glioblastoma multiforme probably accounts for the endothelial hyperplasia in these tumours. A second receptor for a mitogenic growth factor associated with increasing malignancy of glial neoplasms is the epidermal growth factor receptor (EGFR) (Schmidek 1987). The EGFR gene is reported to be amplified in 40–60% of glioblastoma multiforme cases while immunocytochemistry has shown that high grade gliomas contain more tumour cells rich in EGFR than low grade gliomas (Torp *et al.* 1991). However, patients with EGFR amplification show shorter survival times irrespective of age, sex, treatment or histological features of the neoplasm (Hurtt *et al.* 1992).

Pilocytic Astrocytomas

These astrocytic tumours occur mainly in children and young adults. They often develop in the cerebellum, brainstem, third ventricle and optic nerves. The cerebral hemispheres, particularly the temporal lobe, and the basal ganglia are less frequently involved. In the cerebellum they are well circumscribed, cystic or solid lesions and when not demarcated they grow slowly and have a favourable prognosis. Juvenile pilocytic astrocytomas have been studied by BUdR kinetic labelling but there is no apparent correlation between the solid or cystic nature of the neoplasm or with outcome after original diagnosis. BUdR labelling does, however, suggest that these are generally slow growing tumours but, exceptionally, some show a high LI, indicating a high proliferative potential (Ito *et al.* 1992). These studies also indicate that the rate of tumour growth may change during development but generally becomes slower with increasing age of the patient up to approximately 20 years. Histologically they often show a biphasic pattern: areas composed of elongated cells with fusiform nuclei and long, tapering processes arranged in bundles alternate with microcystic areas of stellate, poorly fibrillated astrocytes. Elongated, carrot-like, eosinophilic structures (Rosenthal fibres) and eosinophilic protein droplets are common. Both of these entities are generally negative for GFAP and GS although GFAP may be present, particularly at the periphery of small Rosenthal fibres (Smith and Lantos 1985).

Pleomorphic Xanthoastrocytomas

This rare variant of astrocytoma is superficial, developing in children and young adults (Kepes *et al.* 1979). Although the cells are strikingly pleomorphic

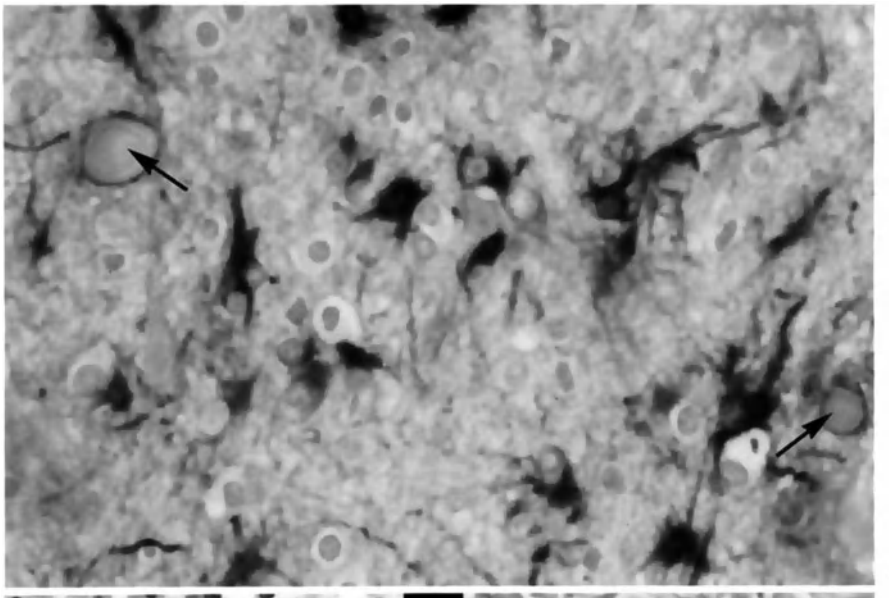
and range from fibrillary astrocytes to multinucleated, giant forms, these gliomas are confined and carry a favourable prognosis in most cases. The finding of GFAP positivity in these tumours and in the "heavily lipidized" malignant gliomas described by Kepes and Rubinstein (1981), which were thought previously to be fibrohistiocytic in origin, led to the concept of an astrocytic derivation. GFAP is, however, often restricted to spindle cells, with giant cells showing little or no reactivity. The tumour is rich in reticulin and many cells contain lipid droplets, hence the xanthomatous appearance. A subpial astrocyte origin has been suggested since basal laminae can be demonstrated at ultrastructural level.

Subependymal Giant Cell Astrocytomas

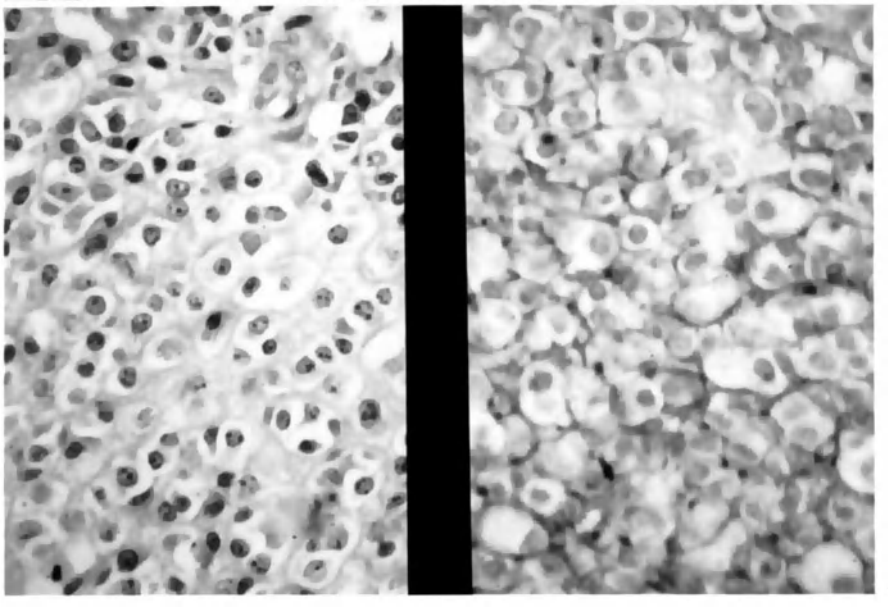
These lesions, associated with tuberous sclerosis, usually develop in the subependymal area, forming an intraventricular mass. The neoplastic cells are large, polygonal, pyramidal or fusiform and the fibrillary matrix is often calcified. The tumours may be multiple and occasionally occlude the foramen of Monro, causing hydrocephalus. In many of the component cells GFAP is restricted to a narrow peripheral zone (Duffy *et al.* 1980). The re-location of GFAP filaments under the plasmalemma in these large cells may result in their round shape. Neuronal, rather than astrocytic origin of some of the large cells has been suggested by the EM observation of neurosecretory granules as well as 10 nm diameter neurofilaments (Nakamura and Becker 1983).

1.2. Oligodendroglial Tumours

These constitute only 5 per cent of intracranial gliomas and their peak incidence is in the fourth and fifth decades of life. Most often they occur in the white matter of the cerebral hemispheres and, spreading through the cortex, they may reach the leptomeninges. The neoplasm is composed of a rather uniform population of cells: the round or oval nucleus is suspended in a clear cytoplasm demarcated by a well-defined cell membrane. This honeycomb structure is the most typical but not the only appearance of oligodendrogliomas. Calcification is common. A thin fibro-vascular stroma,



6



7

Fig. 6. Glial fibrillary acidic protein labelled reactive astrocytes at the periphery of an oligodendroglioma. Horseradish peroxidase label. Note negative oligodendrocytes surrounded by a "halo" of degenerate cytoplasm and large, calcium deposits (arrows)

Fig. 7. Haematoxylin and eosin staining of an oligodendroglioma (left) showing a characteristic "honeycombe" configuration. Brown Leu-7 immuno-staining (horseradish peroxidase) is restricted to cell membrane (right)

branching at acute angle, breaks up the tumour mass. Oligodendrogliomas usually grow slowly and are less likely to undergo malignant transformation than astrocytomas. However, anaplastic variants also exist with all the histological hallmarks of anaplasia.

A number of antibody "markers" of oligodendroglia have been used successfully in normal and pathological brain and in oligodendroglioma-derived cell cultures. Sections of oligodendroglial tumours, however, present an obstacle in that there is frequent degeneration of the cytoplasm resulting in a "halo" appearance around the nuclei of neoplastic oligodendrocytes. Since most oligodendrocyte markers are directed against cytoplasmic antigens their application to the diagnosis of this group of tumours is limited. Such cytoplasmic immuno-markers include carbonic anhydrase C (isoenzyme II) which is abundantly present in its high activity form in oligodendrocytes (Delaunoy *et al.* 1977) but has also been localised in the cytoplasm of reactive astrocytes. Two further cytoplasmic markers, cyclic nucleotide phosphodiesterase (CNPase) (Sprinkle 1989) and E14 (Newcombe *et al.* 1991) have also been applied but suffer from similar problems. Probes against the former, however, may be used more successfully in in situ hybridization. A recent study has also shown that, when used in concert with GFAP (Fig. 6), antibodies against transferrin can be used in double immunostaining for the demonstration of astrocytes and oligodendrocytes respectively (Martin *et al.* 1991). The application of this approach to the study of neural tumours, however, has still to be determined. Unfixed normal and neoplastic oligodendroglia in culture can be demonstrated by the use of antibodies which recognise cell surface epitopes such as galactocerebroside (Gal C) (Raff *et al.* 1978; Ranscht *et al.* 1982) and HNK-1 or Leu-7 (Abo and Balch 1981). In addition, monoclonal antibody 04 has been shown to detect oligodendrocyte precursor cells (Schachner *et al.* 1982). Of these markers the only one to have attracted any attention in the context of the diagnosis of oligodendrogliomas, using frozen and paraffin tissue sections is Leu-7 (Fig. 7) (Motoi *et al.* 1985). The Leu-7 antigen is not, however, exclusive to oligodendrocytes; in tumours, cells of both neuronal and astrocytic lineage may be positive (Perentes and Rubinstein 1986). Oligodendroglial tumours containing cells of oligodendroglial morphology which express GFAP have been described as "transitional" between astrocytic and oligodendrocytic lineage (Herpers and Budka 1984). This may parallel the events in normal oligodendroglial development, where transient GFAP expression is noted (Choi and Kim 1984). It has been suggested, from immunoelectron microscopical studies, that such gliofibrillary oligodendrocytes in oligodendrogliomas may convert to become minigemistocytic astrocytes (Kros *et al.* 1992).

Plant lectins have also been claimed to be reliable markers for oligo-

dendrogliomas and intensity of lectin binding may be related to the degree of differentiation (Cruz-Sanchez *et al.* 1990).

1.3. Ependymal Tumours

Ependymomas develop most frequently in children, adolescents and young adults. About 60% are subtentorial: they occur most commonly in the fourth ventricle, followed by the lateral and then the third ventricles. Ependymomas are also the commonest intrinsic tumours of the spinal cord. They tend to be relatively well circumscribed, slow growing and carry a good prognosis. Histologically, the neoplastic cells are regular and form rosettes, canals, perivascular pseudo-rosettes or groups of various sizes. In rosettes, the cells surround a central lumen, whilst in the perivascular pseudo-rosettes the cells, with their processes, are aligned towards a blood vessel. These structures, particularly the rosettes, are useful diagnostic features.

The recent WHO classification (Kleihues *et al.* 1993) distinguishes three subtypes: cellular, papillary and clear cell ependymomas. In the rare anaplastic variant high cellularity, increased mitotic activity, nuclear atypia and endothelial proliferation may all occur.

Reactive and neoplastic ependymal cells express abundant intermediate filaments, as shown by EM and immunocytochemistry (Deck *et al.* 1978, Duffy *et al.* 1979) suggestive of the notion that these cells are a variant of, or share a common precursor with, astrocytes. Normal, mature ependymal cells possess few intermediate filaments and may be negative for GFAP. However, transient expression of GFAP during normal development has been shown to be co-incident with the appearance of cilia (Roessmann *et al.* 1980). Moreover, fetal human tanycytes – cells of the ependymal layer whose processes extend into the underlying neuropil – also transiently express GFAP. It has been proposed, on the basis of EM studies (Fig. 8), that ependymomas originate either as a derivative of an ependymoglial progenitor or, in many cases, from tanycytes (Friede and Pollak 1978). Since tanycytes bear microvillus-like processes but not cilia, it is interesting to note the presence of these organelles and their basal bodies (blepharoplasts) in ependymomas by EM. Such features may, therefore, distinguish between neoplastic ependymal cells of different origin.

1.4. Choroid Plexus Tumours

Tumours arising from the choroid plexus are either benign papillomas or malignant carcinomas. Positive GFAP and cytokeratin immunostaining is

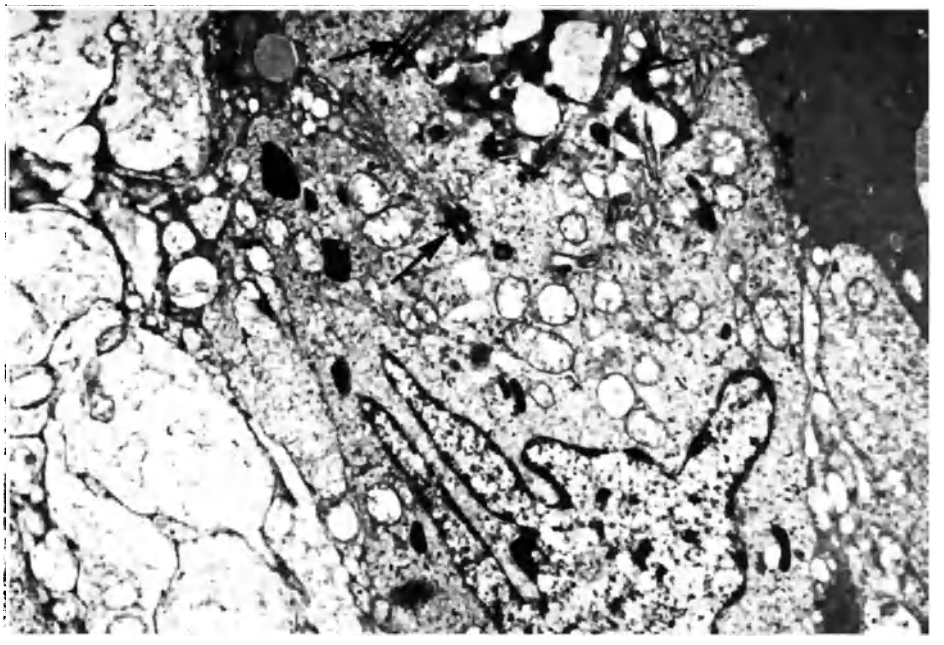


Fig. 8. Electron microscopy of a neoplastic ependymal cell reveals an irregular nuclear profile and numerous cilia (arrows)

indicative of the choroid plexus origin of these neoplasms and may discount the possibility of other forms of CNS-metastasising papillary tumours. Choroid plexus papillomas usually occur in adults, but a large proportion may develop in children. The tumours grow in the fourth, lateral and third ventricles in this order of frequency. They form lobulated, cauliflower-like, often heavily calcified masses which are liable to bleeding. Histologically they imitate the normal structure of the choroid plexus: papillae are formed by columnar or cuboidal cells covering the fibrovascular stroma. This is an important feature to distinguish these tumours from papillary ependymomas in which the stroma is chiefly neuroglial. Both are GFAP positive but focal reactivity of neoplastic cells characterises choroid plexus neoplasms. The presence of basal laminae, seen at EM level, and of laminin immunoreactivity are also features of choroid plexus tumours, rather than ependymomas. In the rare malignant form, choroid plexus carcinomas, there are features of anaplasia, including nuclear atypia, increased mitotic activity, loss of the regular papillary structures and invasion of the brain.

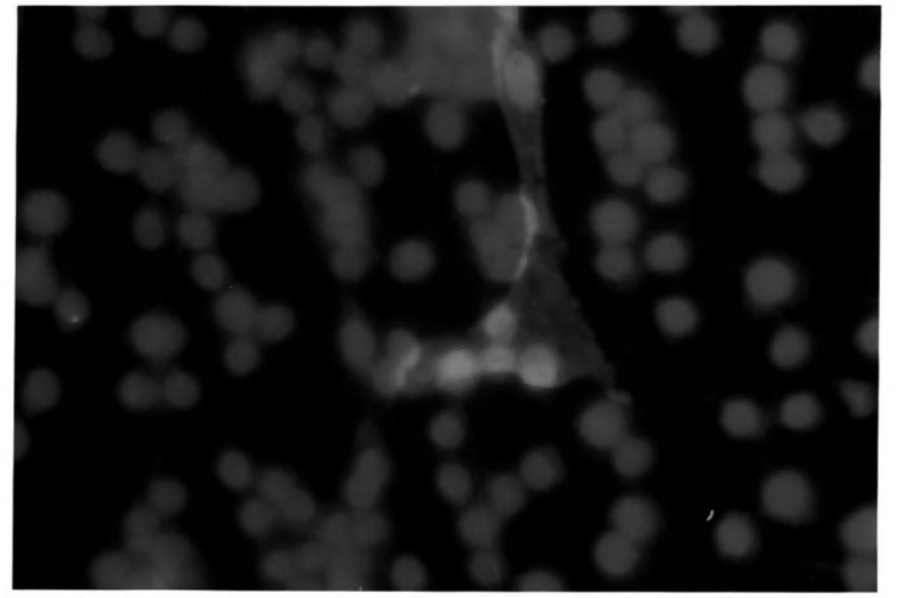
1.5. Neuronal and Mixed Neuronal-Glial Tumours

Neuronal differentiation in neoplasms may be confirmed by parallel EM and immunocytochemical studies. Features at EM level which are consistent with nerve cell origin include the presence of prominent nucleoli, neurosecretory granules and stacks of rough endoplasmic reticulum cisternae (Nissl substance).

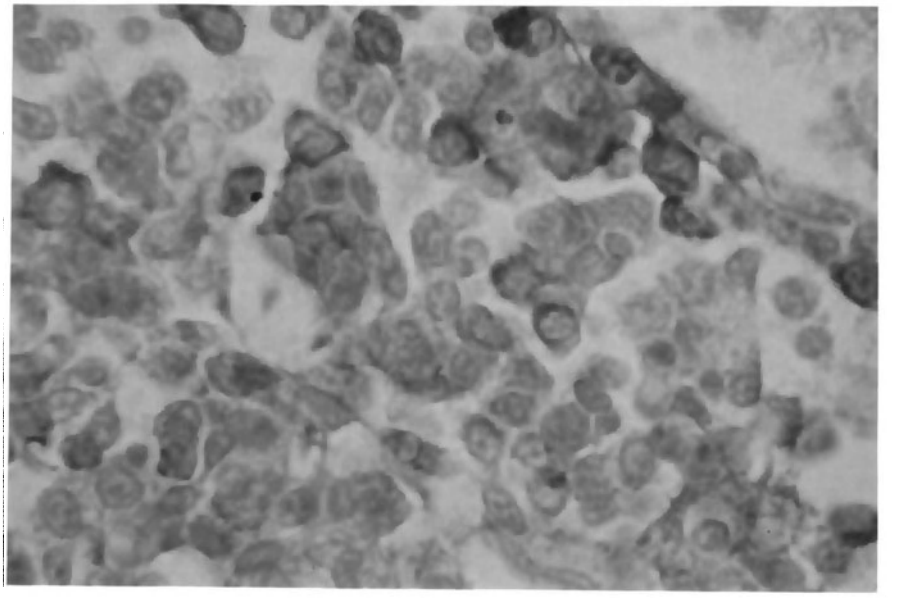
Immunocytochemical "markers" of neuronal differentiation include PGP 9.5 (Rode *et al.* 1985) and neurone-specific ($\gamma\gamma$) enolase (NSE). Since these epitopes may be present in non-neuronal cells, strong rather than diffuse positivity is usually the indicator of neuronal derivation. In fact, although NSE was originally thought to be a definitive marker for neuroendocrine cells, neoplasms including astrocytomas, oligodendrogliomas, ependymomas, choroid plexus papillomas, medulloblastomas, meningiomas and Schwannomas have all been seen to exhibit NSE reactivity. In addition, perhaps more significantly, NSE staining has been described in cells of carcinoma of the breast and lung (Ghobrial and Ross 1986; Cras *et al.* 1988). The neuronal intermediate filament system is comprised of a triplet of subunit proteins of 68, 150 and 200 kD respectively (Lee *et al.* 1982). Monoclonal antibodies directed against the 68 kD sub-unit, however, show a different pattern of reactivity from the higher molecular weight isoforms; recognising either axonal or perikaryal—but not both—intermediate filaments. It is prudent, therefore, to carry out staining with antibodies which recognise all three epitopes. In recent years synaptophysin (Gould *et al.* 1986) and chromogranin (Wilson and Lloyd 1984) antibodies have been developed which recognise pre-synaptic vesicles and dense core neurosecretory granules respectively in cells of neuronal origin. Astrocytic differentiation can be unequivocally confirmed by immunostaining for GFAP. The above immunocytochemical staining can be applied to the tumours below which have neuronal and mixed neuronal and glial populations.

Dysembryoplastic Neuroepithelial Tumour (DNT)

This entity has been defined recently as a tumour occurring usually in children and young adults and clinically associated with intractable epilepsy (Daumas-Duport *et al.* 1988). The lesions are multicentric with several nodules in the cortex and underlying white matter; most often involving the temporal lobes. Histologically they are composed of astrocytes, oligodendrocytes and neurons. They are slow growing, the prognosis is excellent and they do not recur after surgical removal. Although the DNT has been described as a well demarcated, surgically curable neuro-



9



10

Fig. 9. Green fluorescein isothiocyanate CD44 immuno-staining on the surface of isolated cells from a cultured ependymoma demonstrates the major receptor for hyaluronic acid. Red, propidium iodide nuclear counterstaining

Fig. 10. Cells of a B-cell lymphoma in an AIDS brain are immuno-positive for the B-cell monoclonal antibody marker, L26. Brown horseradish peroxidase immuno-staining. Haematoxylin nuclear counterstaining

epithelial neoplasm of mixed cellularity (Daumas-Duport *et al.* 1988), more recently diffuse, microscopically indistinct lesions, also diagnosed as DNETs, have also been described (Honavar *et al.* 1991). Antibodies directed against CD44 which recognise the receptor for hyaluronic acid, an extracellular matrix proteoglycan associated with invasive behaviour in non-neural neoplasms, have been reported recently to react with normal and neoplastic astrocytes (Fig. 9) both in sections and on cultured cells (Asher and Bignami 1992; Girgrah *et al.* 1991). A recent study of early passage cultured brain tumours has revealed differences in binding of this antibody on invasive and non-invasive tumours. This may prove to be a valuable predictor of outcome in tumours such as DNET (Pilkington *et al.* 1993a).

Ganglioglioma

These are slowly growing mixed tumours of neurons and glial cells—usually astrocytes. They develop most frequently in the temporal lobe, floor of the third ventricle or basal ganglia of children and young adults. The presence of the glial component which distinguishes gangliogliomas from gangliocytomas, composed of mature neurons, carries the potential of malignant transformation.

Desmoplastic Infantile Ganglioglioma

This neoplasm has been recognised recently as a superficial lesion in which the neuroepithelial cells, displaying both neuronal and astrocytic differentiation, demonstrated by immunohistochemistry, are embedded in a fibrous stroma. They occur in children usually under two years of age (Vandenberg *et al.* 1987).

Central Neurocytoma

These neoplasms develop in association with the ventricular system, typically in the region of the foramen of Monro or the septum pellucidum, of young adults. Despite their superficial resemblance to oligodendrocytomas they are composed of a uniform population of cells with neuronal differentiation, although a proportion of tumours also shows astrocytic

differentiation by virtue of GFAP positivity (von Deimling *et al.* 1990). The neuronal nature of these neoplasms is, however, usually confirmed by fine structural examination which reveals features including neurosecretory granules and microtubules (Kim *et al.* 1992). Immunocytochemistry has revealed NSE and synaptophysin reactivity in most cases and Western blotting confirms the presence of the synaptic vesicle protein, synapsin I. Concurrent molecular studies, however, have failed to identify the neuronal form of $pp60^{src}$ protein tyrosine kinase, an oncogene product expressed in neurones of the CNS, in these neoplasms. N-myc, however, which is frequently amplified in neuroblastomas, has been detected (von Deimling *et al.* 1991). The persistence of embryonic-type neural cell adhesion molecules (N-CAMs), as shown by immunoblotting, and the non-expression of neurofilament proteins (Figarella-Branger *et al.* 1992) are suggestive of a primitive neuronal cell origin. Such studies have shown that, although committed to neuronal differentiation, neurocytomas retain the potential for glial differentiation. It has been proposed, therefore, that they may originate from bipotential progenitor cells in the periventricular matrix (von Deimling *et al.* 1991).

1.6. Pineal Tumours

Neoplasms arising from the pineal tissue are pineocytomas and pineoblastomas. Pineocytomas most often occur in young adults and are relatively well demarcated. The tumour cells may form rosettes, perivascular pseudorosettes and linear palisades and the overall lobulated pattern is marked by a delicate fibrovascular stroma. The cells may show neuronal or astrocytic differentiation. Of the immunohistochemical markers for neuronal differentiation only NSE and synaptophysin appear to be consistently expressed, while astrocytic differentiation, determined by GFAP expression, is apparent in less than 15% of tumour cells (Coca *et al.* 1992). A complex ultrastructural appearance is associated with these tumours; clear and dense-core vesicles, intermediate filaments, microtubules, diverse configurations of smooth endoplasmic reticulum, vesicle-crowned rodlets, zonulae adherentes and microtubular sheaves have all been described (Hassoun *et al.* 1983). Pineoblastomas are malignant tumours similar to medulloblastomas: they are cellular, composed of primitive cells with high mitotic rate and a tendency to invade. They are less well defined than pineocytomas and also develop in a younger age group, usually in children. Photoreceptor cell differentiation, as defined by S-antigen expression, is occasionally noted in both pineocytomas and pineoblastomas (Perentes *et al.* 1986).

1.7. Embryonal Tumours

Primitive Neuroectodermal Tumours (PNETs)

The term primitive neuroectodermal tumour (PNET) was originally introduced by Rorke (1983) to denote all the embryonal tumours of the central nervous system. This view has not been universally accepted and PNET is now applied, as a generic name, to the medulloblastomas of the cerebellum and to the similar, but much rarer neoplasms of the cerebral hemispheres and the spinal cord.

Medulloblastomas of the cerebellum most often develop in children and young adults either in the midline or in the hemispheres. The tumour may grow into the fourth ventricle and, occluding the flow of the CSF, may cause obstructive hydrocephalus. They are diffusely invasive, and destroying the cerebellum and reaching the leptomeningeal surface or the ventricular cavity, may spread along the neuroaxis. The cellular tumour is composed of small, mitotically active primitive cells with hyperchromatic nuclei and sparse cytoplasm. The tumour cells are multipotential and differentiation along neuronal, astrocytic, ependymal or even melanocytic lines may occur. A special sub-type of medulloblastoma, derived from photoreceptor cells, has been proposed on the basis of S-antigen and rhodopsin immunopositivity of cells in about 30% of cases. This sub-type may be related to the retinoblastomas and pineal cell tumours. Although more extensive studies are required, survival times for photoreceptor marker-positive medulloblastomas appears to be considerably better than for cases where S-antigen and rhodopsin are absent (Czerwionka *et al.* 1989). GFAP immunostaining may reflect the presence of both reactive and neoplastic astrocytes and further criteria—such as nuclear morphology and position within the tumour—are necessary to distinguish between these two types of cell. In fact, a study of over 100 cases of medulloblastoma showed scanty GFAP-positive cells in only 8 of the cases. These were considered as reactive astrocytes and GFAP staining was, therefore, thought to be of no prognostic significance (Marsden *et al.* 1983). Medulloblastomas are highly malignant, although they initially respond to radiotherapy. The desmoplastic variant, characterised by a reticulin-rich stroma and superficial, lateral position carries a slightly more favourable prognosis. This desmoplastic variant fibrillated processes (Mannoji *et al.* 1981; Pilkington and Lantos 1982). In vitro, medulloblastomas frequently grow in suspension culture, characteristically as "grape-like bunches" or clusters. This propensity for suspension growth probably relates to the embryonic neural cell adhesion molecule

(N-CAM) configuration of medulloblastoma cells determining their cell-cell/cell-substrate adhesion properties. The non-floating cells, which adhere to the substrate, represent a diverse morphological picture which may be composed of reactive and connective tissue stromal cells as well as neoplastic elements.

Neuroblastomas

These highly malignant embryonal tumours usually occur in the peripheral nervous system, but may also involve the brain. They develop in children, usually in the cerebral hemispheres, although other sites may be involved. The neoplasm is composed of poorly differentiated neuronal cells which may form Homer-Wright-type rosettes. The desmoplastic variant may be associated with a prominent fibrous stroma. Immunostaining for NSE and PGP 9.5 is generally positive while in one study, S-100 protein staining was reported in only 43% of cases examined (Carter *et al.* 1990). Amplification of the oncogene, N-myc, has been reported in neuroblastoma and has been found to be associated with malignant progression (Brodeur *et al.* 1984; Schwab *et al.* 1984). However, in some diploid neuroblastomas N-myc amplification may be just one of a number of biological factors which determine the aggressiveness of these neoplasms (Cohn *et al.* 1990).

2. Tumours of Cranial and Spinal Nerves

2.1. Schwannomas

These tumours occur in the cranial nerves, spinal nerve roots and peripheral nerves. Intracranial Schwannomas constitute 8% of intracranial neoplasms, they are usually discovered in the middle decades of life and there is a female preponderance (Russell and Rubinstein 1989). Of the cranial nerves the vestibular nerves are most commonly involved, while the trigeminal, vagus and glossopharyngeal nerves are rarely affected. They tend to be single, whilst multiple lesions are often associated with von Recklinghausen's disease. The tumours are usually well circumscribed, encapsulated and firm. In the spinal nerve roots, they arise selectively in the posterior roots, most commonly in the lumbar segments. They may extend through the inter-vertebral foramen to form the so-called hour-glass tumour.

Schwannomas are benign and carry a good prognosis after surgical removal. Histology reveals a biphasic pattern of compact Antoni A- and B-type tissues. The former is composed of interweaving bundles of elongated Schwann cells with bipolar nuclei, whilst in the latter the more pleomorphic cells are haphazardly distributed in an eosinophilic matrix which lends itself to mucinous degeneration, microcyst formation and xanthomatous change. The tumour is rich in reticulin: individual neoplastic cells are surrounded by a basal lamina. Thick walled hyalinised blood vessels are often seen. Immunocytochemical staining for Leu-7 may be used to differentiate between Schwannomas and other nerve sheath neoplasms (Perentes and Rubinstein 1985). Antibodies against the S-100 protein (Moore 1965), which are reactive with most neuro-ectodermally-derived cells, are also of value in distinguishing Schwannomas from malignant nerve sheath tumours (Johnson *et al.* 1988).

2.2. Neurofibroma

Neurofibromas are benign, single or multiple, growths; these latter forms are associated with von Recklinghausen's disease. The affected nerves assume a fusiform, cylindrical or even spherical shape. Histologically they are composed of Schwann cells and fibroblasts without the typical biphasic architecture of Schwannomas.

3. Tumours of the Meninges

3.1. Meningiomas

These are common, benign neoplasms, which constitute 14% of all primary intracranial neoplasms and 12% of those arising in the spinal canal (Russell and Rubinstein 1989). Although they may occur at any age, they are discovered most often in the middle decades of life, and are more common in women than in men. The single most common site is over the convexity of the brain in relation to the sagittal sinus (parasagittal meningiomas), but they may develop in the Sylvian fissures, at the base of sphenoidal ridges, olfactory grooves and pituitary fossa and in the ventricular system. In the spinal canal the thoracic segments are most commonly involved. The new classification distinguishes 11 subtypes (Kleihues *et al.* 1993) of which the four commonest types are the meningotheliomatous or syncytial, fibrous or

fibroblastic, transitional and psammomatous. Quite often more than one histological type may occur within the same tumour. The rare papillary variant is cellular, and often aggressive with a less favourable prognosis. Atypical and anaplastic (malignant) meningiomas are also distinguished (Kleihues *et al.* 1993). Immunocytochemistry is generally not contributory to the diagnosis of meningioma, however, cytokeratin, epithelial membrane antigen (EMA), NSE, S-100 and vimentin may all show positive reaction. Perhaps the most significant of these is EMA, which may be of value in distinguishing between meningiomas and Schwannomas (Perentes and Rubinstein 1987). Conversely, Leu-7 is generally positive in Schwannomas but is absent from meningiomas. Ki-67 labelling studies of meningiomas have revealed a lack of homogeneity of proliferative cells throughout the tumour. Moreover, recurrence does not appear to correspond to a high LI (Siegers *et al.* 1989).

3.2. Mesenchymal, Non-Meningothelial Tumours

Haemangiopericytomas

These are mesenchymal, non-meningothelial, malignant neoplasms. The cellular tumour is composed of a rather uniform population of elongated or polygonal cells with oval nuclei and sparse cytoplasm. The mitotic rate is variable, but often quite high. The neoplasm is permeated by an extensive network of vascular channels lined by unremarkable endothelium. The tumour cells produce an amorphous basement membrane-like material which is responsible for the rich intercellular pattern of reticulin staining.

3.3. Tumours of Uncertain Histogenesis

Capillary Haemangioblastomas

These tumours have been recently classified as tumours of uncertain origin, indeed the origin and role of the principal, so-called stromal cells in the formation of the neoplasm are controversial. Capillary haemangioblastomas constitute between 1.1 and 2.4% of all intracranial tumours (Zülch 1986), they may occur at any age, but the peak incidence is in the fourth decade and develop most often in the cerebellum. Multiple lesions suggest Lindau's syndrome, a familial, inherited condition frequently associated

with angiomatosis of the retinae (von Hippel's disease). The association of erythrocytocaemia with capillary haemangioblastoma is well established. The tumours are well circumscribed, often cystic and may occasionally be found outside the CNS. The most striking histological feature is the presence of vascular channels, ranging from capillary structures to dilated sinusoidal vessels. The endothelial lining may be plump, but without cellular pleomorphism or crowding. The stromal cells of disputed origin are polygonal and often foamy.

4. Haemopoietic Neoplasms

Primary Malignant Lymphomas

These neoplasms are the most important of the lymphomatous proliferations affecting the nervous system. They commonly develop in the setting of immunosuppression and are a frequent consequence of HIV infection (Morgello *et al.* 1990). Previously the peak of incidence was in the fifth and sixth decades, but now they occur in a younger age group of AIDS patients. The neoplasm may be single, multiple or diffuse. Primary lymphomas are cellular, angiocentric and pleomorphic. The neoplastic cells infiltrate not only the perivascular space, but also the vascular walls and diffusely invade the surrounding brain. The dense basal lamina or "reticulin" which surrounds perivascular neoplastic lymphocytes is probably produced by pericytes or reactive astrocytes in an attempt to restrict the spread of these cells in the brain. Immunostaining for basal lamina components, such as laminin and type IV collagen, may clarify the perivascular pattern characteristic of these neoplasms (Kalimo *et al.* 1985). A plethora of antibodies recognising B-cell (Fig. 10) and T-cell differentiation are available and may be utilised to further classify the lymphomas. Indeed, these neoplasms—previously named microgliomas—were re-classified on the basis of immunocytochemical staining with such antibodies. The majority of lymphomas are B-cell derived (Kumanishi *et al.* 1986); T-cell derived lymphomas showing a predilection for leptomeningeal presentation (Grove and Vyberg 1993). A reactive, predominantly perivascular T-cell population is, however, characteristic of B-cell lymphomas (Murphy *et al.* 1989).

5. Germ Cell Tumours

Primary germ cell tumours occur in the midline, usually in the pineal and suprasellar regions. Children and young adults are most commonly affected.

The major types include germinomas, yolk sac tumours, chorio-carcinomas and teratomas. About 65% of germ cell tumours are germinomas; these occur most often during the second decade of life, with a male to female ratio of about 2:1. Histologically germinomas are composed of two cell types: large polygonal or spheroidal cells with large round or oval nuclei and well-defined cell borders are interspersed with lymphocytes. Immunocytochemistry shows that most large cells are positive, for placental alkaline phosphatase, but negative for cytokeratin and vimentin. The lymphocytes are a mixture of T- and B-cells with a predominance of the former. The comparison of intracranial germinomas with testicular seminomas reveals a similar immunocytochemical profile, supporting the hypothesis of a common derivation (Bentley *et al.* 1990).

6. Pituitary Adenomas

The true incidence of pituitary adenomas is difficult to assess, since so-called microadenomas may be discovered on histological examination of apparently normal glands. The figure given by Zülch (1986) of 8–10% of all intracranial tumours is realistic. Pituitary adenomas are usually detected between 30 and 50 years of age, although growth-hormone producing tumours present at an earlier age. Their original classification based on tinctorial properties of the secretory cells, distinguished chromophobe, acidophil and basophil types. It was the combination of immunocytochemistry, for demonstration of secretory products (Kovacs and Horvath 1986) and electron microscopy, permitting analysis of size and distribution of secretory granules (Farmer 1979), that transformed this descriptive system into a functional one. In the endocrinologically active group of adenomas the prolactin-secreting adenoma, or prolactinoma, is the most frequent but there are also somatotrophic and corticotrophic adenomas, the rare thyrotrophic and gonadotrophic adenomas and the mixed secretory tumours. This last type represents 10% of all pituitary adenomas. The endocrinologically inactive group constitutes less than 25% of pituitary adenomas, the most frequent type being the so-called null-cell adenoma (for review see Russell and Rubinstein 1989).

7. Local Extension from Regional Tumour

In this group, chordomas are often encountered. These tumours arising from the remnants of the notochord develop at the base of the skull and in the vertebral column, and occur usually in the third and fourth decades

of life. They are soft, often translucent, gelatinous masses composed of physaliphorus cells. These show a vacuolated cytoplasm with a relatively small, hyperchromatic nucleus. CAM 5.2 and S-100 immunostaining may be useful in excluding a diagnosis of metastatic carcinoma and low grade chondrosarcoma; chordomas generally showing positivity for these two immunomarkers.

8. Metastatic Tumours

Spread of malignant tumours to the CNS is common and cerebral metastasis occurs in 5% of all patients with fatal malignant disease (Willis 1973). Carcinomas are the commonest source of secondary deposits: bronchial carcinoma in men and breast cancer in women head the list in this country, but kidney, alimentary tract, uterus, thyroid gland, chorio-carcinomas, testicular tumours and malignant melanomas also spread to the CNS. These secondary deposits tend to be well defined and multiple. Lymphomas and leukaemias may also be source of secondary growths which are usually more diffuse, often involving the meninges. Carcinomas may be identified immunohistochemically by use of antibodies against cytokeratin intermediate filaments (Ramaekers *et al.* 1983) and epithelial membrane antigen (EMA) (Pinkus *et al.* 1986) while melanomas fail to express these antigens but show vimentin intermediate filaments, NSE and S-100 protein (Loffel *et al.* 1985). Additionally, chromogranin (Heitz 1987) and carcinoembryonic antigen (CEA) (Wachter *et al.* 1984) may be used to ascertain the precise nature of metastatic carcinomas.

As can be seen from the above, biological "markers" for brain tumours are most frequently related to morphological appearance and immunocytochemical staining profiles. We are, however, living in exciting times and the next decade promises to provide a rich supply of molecular markers which should greatly facilitate diagnostic and therapeutic practice based on a new, dynamic approach to the neuropathology of brain tumours.

References

1. Abo T, Balch CM (1981) A differentiation antigen of human NK and K cells identified by a monoclonal antibody (HNK-1). J Immunol 127: 1024–1029
2. Asher R, Bignami A (1992) Hyaluronate binding and CD44 expression in human glioblastoma cells and astrocytes. Exp Cell Res 203: 80–90
3. Bailey P, Cushing H (1926) A classification of the tumours of the glioma

groups on a histogenetic basis with a correlated study of prognosis. Lippincott, Philadelphia
4. Becker I, Becker K-F, Meyermann R, Hollt V (1991) The multidrug resistance gene MDR1 is expressed in human glial tumors. Acta Neuropathol (Berl) 82: 516–519
5. Bentley AJ, Parkinson MC, Harding BN, Bains RM, Lantos PL (1990) A comparative morphological and immunohistochemical study of testicular seminomas and intracranial germinomas. Histopathology 17: 443–449
6. Bishop M, de la Monte SM (1989) Dual lineage of astrocytomas. Am J Pathol 135: 517–527
7. Brodeur GM, Seeger RC, Schwab M, Varmus HE, Bishop JM (1984) Amplification of *N-myc* in untreated human neuroblastomas correlates with advanced disease stage. Science 224: 1121–1124
8. Carter RL, Al-Sam SZ, Corbett RP, Clinton S (1990) A comparative study of immunohistochemical staining for neuron-specific enolase, protein gene product 9.5 and S-100 protein in neuroblastoma, Ewing's sarcoma and other round cell tumours in children. Histopathology 16: 461–467
9. Celis JE, Celis A (1985) Cell cycle dependent variations in the distribution of the nuclear protein cyclin PCNA in cultured cells–subdivision of S-phase. Proc Natl Acad Sci (USA) 82: 3262–3266
10. Choi BH, Kim R (1984) Expression of glial fibrillary acidic protein in immature oligodendroglia. Science 223: 407–409
11. Coca S, Vaquero J, Escandon M, Moreno M, Peralba J, Rodriguez J (1992) Immunohistochemical characterization of pineocytomas. Clin Neuropathol 11: 298–303
12. Cohn SL, Rademaker AW, Salwen HR, Franklin WA, Gonzales-Crussi F, Rosen ST, Bauer KD (1990) Analysis of DNA ploidy and proliferative activity in relation to histology and *N-myc* amplification in neuroblastoma. Am J Pathol 136: 1043–1052
13. Commings DE (1973) A general theory of carcinogenesis. Proc Natl Acad Sci (USA) 70: 2324–2328
14. Cox LB (1933) The cytology of the glioma group; with special reference to the inclusion of cells derived from the invaded tissue. Am J Pathol 9: 839–898
15. Cras P, Martin JJ, Gheuens J (1988) γ-Enolase and glial fibrillary acidic protein in nervous system tumours. Acta Neuropathol (Berl) 75: 377–384
16. Crocker J, Nar P (1987) Nucleolar organizer regions in lymphomas. J Pathol 151: 111–118
17. Cruz-Sanchez F, Rossi ML, Finneron PW, Jones NR, Buller J (1990) Oligodendroglioma: an immunohistological and lectin binding study of 27 cases. Neuropath Appl Neurobiol 16: 534–535
18. Czerwionka M, Korf H-W, Hoffmann O, Busch H, Schachenmayr W (1989) Differentiation in medulloblastomas: correlation between the immunocytochemical demonstration of photoreceptor markers (S-antigen, rod-opsin) and the survival rate in 66 patients. Acta Neuropathol (Berl) 78: 629–636

19. Dahl D, Rueger DC, Bignami A, Weber K, Osborn M (1981) Vimentin, the 57,000 MW protein of fibroblast filaments, is the major cytoskeletal component in immature glia. Eur J Cell Biol 24: 191–196
20. Daumas-Duport C, Scheithauer BW, Chodkiewicz J-P, Laws Jr ER, Vedrenne C (1988) Dysembryoplastic neuroepithelial tumour: a surgically curable tumor of young patients with intractable partial seizures. Neurosurgery 23: 545–556
21. Deck JHN, Eng LF, Bigbee J, Woodcock SM (1978) The role of glial fibrillary acidic protein in the diagnosis of central nervous system tumors. Acta Neuropathol (Berl) 42: 183–190
22. Delaunoy J-P, Roussel G, Mandel P (1977) Localisation immunohistochimique de l'anhydrase carbonique forme C dans le systeme nerveux central du rat. Cr Hebd Seanc Acad Sci Paris 285: 801–803
23. Drago J, Reid KL, Bartlett PF (1989) Induction of the ganglioside marker A2B5 on cultured cerebellar neural cells by growth factors. Neurosci Lett 107: 245–250
24. Duffy PE, Graf L, Huang Y-Y, Rapport MM (1979) Glial fibrillary acidic protein in ependymomas and other brain tumors. J Neurol Sci 40: 133–146
25. Duffy PE, Graf L, Rapport MM (1977) Identification of glial fibrillary acidic protein by the immunoperoxidase method in human brain tumors. J Neuropath Exp Neurol 36: 645–652
26. Duffy PE, Huang Y-Y, Rapport MM, Graf L (1980) Glial fibrillary acidic protein in giant cell tumors of the brain and other gliomas. Acta Neuropathol (Berl) 52: 51–57
27. Emson PC (1993) In situ hybridization as a methodological tool for the neuroscientist. TINS 16: 9–16
28. Eng LF, Vanderhaeghen JJ, Bignami A, Gerstl B (1971) An acidic protein isolated from fibrous astrocytes. Brain Res 28: 351–354
29. Engebraaten O, Bjerkvig R, Morkve O, Laerum O-D, Fredman P, Svennerholm L, Bigner DD (1991) GM2 ganglioside and P53 expression is linked to glioblastoma cell invasiveness. Proceedings of the Ninth International Conference on Brain Tumor Research and Therapy. Asilomar, California, September 1991
30. Farmer PM (1979) Electron microscopy in the diagnosis of pituitary tumors. Ann Clin Lab Sci 9: 275–288
31. Figarella-Branger D, Pellissier JF, Daumas-Duport C, Delisle MB, Pasquier B, Parent M, Gambarelli D, Rougon G, Hassoun J (1992) Central neurocytomas. Critical evaluation of a small-cell neuronal tumor. Am J Surg Pathol 16: 97–109
32. Friede RL, Pollak A (1978) The cytogenetic basis for classifying ependymomas. J Neuropath Exp Neurol 37: 103–118
33. Friend SH, Bernards R, Rogelj S, Weinberg RA, Rapaport JM, Albert DM, Dryja TP (1986) A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. Nature 323: 643–649
34. Gerdes J, Lemke H, Baisch H, Wacker H-H, Schwab U, Stein H (1984) Cell cycle analysis of a cell proliferation-associated human nuclear antigen defined by the monoclonal antibody Ki-67. J Immunol 133: 1710–1715

35. Ghobrial M, Ross ER (1986) Immunocytochemistry of neurone-specific enolase: a re-evaluation. In: Zimmermann HM (ed) Progress in neuropathology, Vol 6. Raven, New York pp 199–221
36. Giangaspero F, Doglioni C, Rivano MT, Pileri S, Gerdes J, Stein H (1987) Growth fraction in human brain tumors defined by the monoclonal antibody Ki-67. Acta Neuropathol (Berl) 74: 179–182
37. Girgrah N, Ackerley CA, Moscarello MA (1991) Localization of CD44 (P80) on the external surface of a human astrocytoma cell. NeuroReport 2: 441–444
38. Gould VE, Lee I, Wiedemann B, Moll R, Chejfec G, Franke WW (1986) Synaptophysin: a novel marker for neurons, certain neuro-endocrine cells, and their neoplasms. Hum Pathol 17: 979–983
39. Grove A, Vyberg M (1993) Primary leptomeningeal T-cell lymphoma: a case and a review of primary T-cell lymphoma of the central nervous system. Clin Neuropathol 12: 7–12
40. Harrison PJ, Pearson RCA (1990) In situ hybridisation histochemistry and the study of gene expression in the human brain. Prog Neurobio 34: 271–312
41. Hassoun J, Gambarelli D, Peragut JC, Toga M (1983) Specific ultrastructural markers of human pinealomas. A study of four cases. Acta Neuropathol (Berl) 62: 31–40
42. Heitz PU (1987) Neuroendocrine tumor markers. In: Seifert G (ed) Morphological tumor markers. Curr Top Pathol 77: 279–306
43. Heldin C-H, Westermark B (1989) Platelet-derived growth factor: three isoforms and two receptor types. Trends Gen 5: 108–111
44. Herpers MJHM, Budka H (1984) Glial fibrillary acidic protein (GFAP) in oligodendroglial tumors. Gliofibrillary oligodendroglioma and transitional oligoastrocytoma as subtypes of oligodendroglioma. Acta Neuropathol (Berl) 64: 265–272
45. Herpers MJ HM, Ramaekers FCS, Aldeweireldt J, Moesker O, Sloof J (1986) Co-expression of glial fibrillary acidic protein- and vimentin-type intermediate filaments in human astrocytomas. Acta Neuropathol (Berl) 79: 333–339
46. Honavar M, Ansari S, Janota I, Polkey CE (1991) Dysembryoplastic neuro-epithelial tumour. Neuropath Appl Neurobiol 17: 242–243
47. Hoshino T, Ahn D, Prados MD, Lamborn K, Wilson CB (1993) Prognostic significance of the proliferative potential of intracranial gliomas measured by bromodeoxyuridine labelling. Int J Cancer 53: 550–555
48. Hurtt MR, Moossy J, Donovan-Peluso M, Locker J (1992) Amplification of epidermal growth factor receptor gene in gliomas: histopathology and prognosis. J Neuropath Exp Neurol 51: 84–90
49. Ito S, Hoshino T, Shibuya M, Prados MD, Edwards MSB, Davis RL (1992) Proliferative characteristics of juvenile pilocytic astrocytomas determined by bromodeoxyuridine labelling. Neurosurgery 31: 413–419
50. John H, Birnstiel M, Jones K (1969) RNA-DNA hybrids at the cytological level. Nature 223: 582–587
51. Johnson HD, Glick AD, Davis BW (1988) Immunohistochemical evaluation of Leu-7, myelin basic protein, S100 protein, glial fibrillary acidic protein and

LN3 immunoreactivity in nerve sheath tumors and sarcomas. Arch Path Lab Med 112: 155–160
52. Kalimo H, Lehto M, Nato-Salonen K, Jalkanen M, Risteli L, Risteli J, Narva EV (1985) Characterization of the perivascular reticulin network in a case of primary brain lymphoma. Acta Neuropathol (Berl) 66: 299–305
53. Kepes JJ, Rubinstein LJ (1981) Malignant gliomas with heavily lipidized (foamy) tumor cells. A report of three cases with immunoperoxidase study. Cancer 47: 2451–2459
54. Kepes JJ, Rubinstein LJ, Eng LF (1979) Pleomorphic xanthoastrocytoma: a distinctive meningocerebral glioma of young subjects with relatively favorable prognosis. Cancer 44: 1839–1852
55. Kernohan JW, Habon RF, Svien HJ, Adson AW (1949) A simplified classification of gliomas. Proc Mayo Clin 24: 71–75
56. Kim DG, Chi JG, Park SH, Chang KH, Lee SH, Jung H-W, Kim HJ, Cho B-K, Choi KS, Han DH (1992) Intraventricular neurocytoma: clinicopathological analysis of seven cases. J Neurosurg 76: 759–765
57. Kleihues P, Burger PC, Scheithauer BW (1993) Histological typing of tumours of the central nervous system. Springer, Berlin Heidelberg New York Tokyo
58. Knott JCA, Edwards AJ, Gullan RW, Clarke TM, Pilkington GJ (1990) A human glioma cell line retaining expression of GFAP and gangliosides, recognized by A2B5 and LB1 antibodies, after prolonged passage. Neuropath Appl Neurobiol 16: 489–500
59. Knudsen AG (1971) Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci (USA) 68: 820–823
60. Knudsen AG (1983) Hereditary cancers in man. Cancer Invest 1: 187–193
61. Kohler G, Milstein C (1975) Continuous cultures of fused cells secreting antibodies of predefined specificity. Nature 256: 495–497
62. Kovacs K, Horvath E (1986) Tumors of the pituitary gland. In: Atlas of tumor pathology, 2nd series, Fascicle 21. AFIP, Bethesda
63. Kros JM, De Jong AAW, Van der Kwast Th H (1992) Ultrastructural characterization of transitional cells in oligodendroglioma. J Neuropath Exp Neurol 51: 186–193
64. Kumanishi T, Washiyama K, Saito T, Nishiyama A, Abe S, Tanaka T, (1986) Primary malignant lymphoma of the brain: an immunohistochemical study of eight cases using a panel of monoclonal and heterologous antibodies. Acta Neuropathol (Berl) 71: 190–196
65. Landberg G, Roos G (1991) Antibodies to proliferating cell nuclear antigen as S-phase probes in flow cytometric cell cycle analysis. Cancer Res 51: 4570–4574
66. Lee V, Wu HL, Schlaepfer WW (1982) Monoclonal antibodies recognise individual neurofilament triplet proteins. Proc Natl Acad Sci (USA) 79: 6089–6092
67. Lee WH, Bookstein R, Hong F, Young LJ, Shew JY, Lee EY (1987) Human retinoblastoma susceptibility gene: cloning, identification and sequence. Science 235: 1394–1399
68. Loffel SC, Gillespie Y, Mirmiran SA, Miller EW, Golden P, Askin FP, Siegel

GP (1985) Cellular immunolocalization of S-100 protein within fixed tissue sections by monoclonal antibodies. Arch Pathol Med 109: 117–122
69. Louis DN, von Deimling A, Chung RY, Rubio M-P, Whaley JM, Eibl RH, Ohgaki H, Wiestler OD, Thor AD, Seizinger BR (1993) Comparative study of p53 gene and protein alterations in human astrocytic tumors. J Neuropath Exp Neurol 52: 31–38
70. Mannoji H, Takeshita I, Fukui M, Ohta M, Kitamura K (1981) Glial fibrillary acidic protein in medulloblastoma. Acta Neuropathol (Berl) 55: 63–69
71. Marsden HB, Kumar S, Kahn J, Anderton B (1983) A study of glial fibrillary acidic protein (GFAP) in chidhood brain tumours. Int J Cancer 31: 439–445
72. Martin SM, Landel HB, Lansing AJ, Vijayan VK (1991) Immunocytochemical double labelling of glial fibrillary acidic protein and transferrin permits the identification of astrocytes and oligodendrocytes in the rat brain. J Neuropath Exp Neurol 50: 161–170
73. Matsumoto T, Tani E, Kaba K Shindo H, Miyaji K (1991) Expression of P-glycoprotein in human glioma cell lines and surgical glioma specimens. J Neurosurg 74: 460–466
74. McCormick D, McQuaid S, McClusker C, Allen IV (1990) A study of glutamine synthetase in normal brain and intracranial tumours. Neuropath Appl Neurobiol 16: 205–211
75. Moore BW (1965) A soluble protein characteristic of the nervous system. Biochem Biophys Res Comm 19: 739–744
76. Morgello S, Petito CK, Mouradian JA (1990) Central nervous system lymphoma in the acquired immunodeficiency syndrome. Clin Neuropathol 9: 205–215
77. Motoi M, Yoshino T, Hayashi K, Nose S, Horie Y, Ogawa K (1985) Immunohistochemical studies on human brain tumors using anti-Leu 7 monoclonal antibody in paraffin-embedded sections. Acta Neuropathol (Berl) 66: 75–77
78. Murphy JK, O'Brien CJ, Ironside JW (1989) Morphologic and immunophenotypic characterization of primary brain lymphomas using paraffin-embedded tissue. Histopathology 15: 449–460
79. Nagashima T, De Armond SJ, Murovic J, Hoshino T (1985) Immunocytochemical demonstration of S-phase cells by anti-BrdU monoclonal antibody in human brain tumor tissues. Acta Neuropathol (Berl) 67: 155–159
80. Nakamura Y, Becker LE (1983) Subependymal giant cell tumor: astrocytic or neuronal? Acta Neuropathol (Berl) 60: 271–277
81. Newcombe J, Li LH, Cuzner ML (1991) 14E antigen expression in human normal and pathological glial cells. Neuropath Appl Neurobiol 17: 243–244
82. Norenberg MD (1979) The distribution of glutamine synthetase in the rat central nervous system. J Histochem Cytochem 27: 756–762
83. Pardue ML, Gail JG (1969) Molecular hybridization of radioacitve DNA to the DNA of cytological preparations. Proc Nat Acad Sci (USA) 64: 600–604
84. Perentes E, Rubinstein LJ (1985) Immunohistochemical recognition of human nerve sheath tumors by anti-Leu 7 (HNK-1) monoclonal antibody. Acta Neuropathol (Berl) 68: 319–324

85. Perentes E, Rubinstein LJ (1986) Immunohistochemical recognition of human neuroepithelial tumors by anti-Leu 7 (HNK-1) monoclonal antibody. Acta Neuropathol (Berl) 69: 227–233
86. Perentes E, Rubinstein LJ (1987) Recent application of immunoperoxidase histochemistry in human neuro-oncology. Acta Pathol Lab Med 111: 796–812
87. Perentes E, Rubinstein LJ, Herman MM, Donoso LA (1986) S-antigen immunoreactivity in human pineal glands and pineal parenchymal tumors. A monoclonal antibody study. Acta neuropathol (Berl) 71: 224–227
88. Pilkington GJ (1992) Glioma heterogeneity in vitro: the significance of growth factors and gangliosides. Neuropath Appl Neurobiol 18: 434–442
89. Pilkington GJ, Akinwunmi J, Ognjenovic N, Rogers JP (1993a) Differential binding of anti-CD44 on human gliomas in vitro. NeuroReport 4: 259–262
90. Pilkington GJ, Lantos PL (1982) The role of glutamine synthetase in the diagnosis of cerebral tumours. Neuropath Appl Neurobiol 8: 227–236
91. Pilkington GJ, Dunan JR, Rogers JP, Clarke TM, Knott JCA (1993b) Growth factor modulation of surface ganglioside expression in cloned neoplastic glia. Neurosci Lett 149: 1–5
92. Pinkus G, Etheridge CL, O'Connor EM (1986) Are keratin proteins a better tumor marker than epithelial membrane antigen? A comparative immunohistochemical study of various paraffin-embedded neoplasms using monoclonal polyclonal antibodies. Am J Clin Pathol 85: 269
93. Plate KH, Ruschoff J, Mennel HD (1991) Cell proliferation in intracranial tumours: selective silver staining of nucleolar organizer regions (AgNORs). Application of surgical and experimental neuro-oncology. Neuropath Appl Neurobiol 17: 121–132
94. Pollack IF, Randall MS, Kristofik MP, Kelly RH, Selker RG, Vertosick FT (1991) Response of low-passage human malignant gliomas in vitro to stimulation and selective inhibition of growth factor-mediated pathways. J Neurosurg 75: 284–293
95. Raff MC, Mirsky R, Fields KL, Lisak RP, Dorfman RP, Silberberg DH, Gregson NA, Liebowitz S, Kennedy M (1978) Galactocerebroside: a specific cell surface antigen marker for oligodendrocytes in culture. Nature 74: 813–816
96. Raff MC, Miller RH, Noble M (1983) A glial progenitor cell that develops in vitro into an astrocyte or an oligodendrocyte depending on culture medium. Nature 303: 390–396
97. Ramaekers FCS, Puts JJG, Moesker O, Kant A, Huysmans A, Haag D, Jap PHK, Herman CJ, Vooijs GP (1983) Antibodies to intermediate filament proteins in the immunohistochemical identification of human tumours: an overview. Histochem J 15: 691–713
98. Ranscht B, Clapshaw PA, Price J, Noble M, Seifert W (1982) Development of oligodendrocytes and Schwann cells studied with a monoclonal antibody against galactocerebroside. Proc Natl Acad Sci (USA) 79: 2709–2713
99. Rode J, Dhillon AP, Doran JF, Jackson P, Thompson RJ (1985) PGP 9.5, a new marker for human neuroendocrine tumours. Histopathology 9: 147–158
100. Roessmann U, Velasco ME, Sindely SD, Gambetti P (1980) Glial fibrillary

acidic protein (GFAP) in ependymal cells during development. An immunocytochemical study. Brain Res 200: 13–21
101. Rorke LB (1983). The cerebellar medulloblastoma and its relationship to primitive neuroectodermal tumors. J Neuropathol Exp Neurol 42: 1–15
102. Rubinstein LJ (1986) Immunohistochemical signposts—not markers—in neural tumour differentiation. Neuropath Appl Neurobiol 12: 523–537
103. Russell DS, Rubinstein LJ (1977) Pathology of tumours of the nervous system, 4th Ed. Edward Arnold, London
104. Russell DS, Rubinstein LJ (1989) Pathology of tumours of the nervous system, 5th Ed. Edward Arnold, London
105. Sarawar SR, Bonshek RE, Marsden HB, Yates PO, Kumar S (1991) A monoclonal antibody which discriminates between sub-types of astrocytoma. Anticancer Res 11: 1429–1432
106. Schachner M, Sommer I, Lagenaur C (1982) Monoclonal antibodies to antigens in the mammalian nervous system. In: Hammerling GJ, Hammerling U, Kearney JF (eds) Monoclonal antibodies and T-cell hybridomas. Elsevier/North Holland, Amsterdam, pp130–142
107. Schiffer D, Giordana MT, Mauro A, Migheli A, Germano I, Giaccone G (1986) Immunohistochemical demonstration of vimentin in human cerebral tumors. Acta Neuropathol (Berl) 70: 209–219
108. Schmidek HH (1987) The molecular genetics of nervous system tumors. J Neurosurg 67: 1–16
109. Schwab M, Ellison J, Busch M, Rosenau W, Varmus HE, Bishop JM (1984) Enhanced expression of the human gene *N-myc* consequent to amplification of DNA may contribute to malignant progression of neuroblastoma. Proc Natl Acad Sci (USA) 81: 4940–4944
110. Shapiro JR, Yung WKA, Shapiro WR (1981) Isolation, karyotype, and clonal growth of heterogeneous subpopulations of human malignant gliomas. Cancer Res 41: 2349–2359
111. Sidransky D, Milkkelsen T, Schwecheimer K, Rosenblum ML, Cavenee W, Vogelstein B (1992) Clonal expansion of p53 mutant cells is associated with brain tumour progression. Nature 355: 846–847
112. Siegers HP, Zuber P, Hamou M-F, Van Melle GD, De Tribolet N (1989) The implications of the heterogeneous distribution of Ki-67 labelled cells in meningiomas. Br J Neurosurg 3: 101–108
113. Smith DA, Lantos PL (1985) Immunocytochemistry of cerebellar astrocytomas: with a special note on Rosenthal fibres. Acta Neuropathol (Berl): 66: 155–159
114. Sprinkle TJ (1989) 2′,3′-cyclic nucleotide 3′-phosphodiesterase, an oligodendrocyte-Schwann cell and myelin-associated enzyme of the nervous system. Crit Rev Neurobiol 235–301
115. Steck PA, Saya H (1991) Pathways of oncogenesis in primary brain tumors. Curr Opin Oncol 3: 476–484
116. Takasaki Y, Fishwild D, Tan EM (1984) Characterisation of PCNA recognised by auto antibodies in Lupus sera. J Exp Med 159: 981–992

117. Tan CK, Castillo C, So AG, Downey KM (1986) An auxilliary protein for DNA polymerase alpha from fetal calf thymus. J Biol Chem 261: 1231–1236
118. Torp SH, Helseth E, Dalen A, Unsgaard G (1991) Epidermal growth factor receptor expression in human gliomas. Cancer Immunol Immunother 33: 61–64
119. Troost D, Blaauwgeers HGT, Leenstra S, Bosch DA (1993). Metallothionein: a marker for protoplasmic astrocytes in brain tumours. Br J Neurosurg 7: 113
120. Vandenberg SR, May EE, Rubinstein LJ, Herman MM, Perentes E, Vinores SA, Collins VP, Park TS (1987) Desmoplastic supratentorial neuropithelial tumors of infancy with divergent differentiation potential ("desmoplastic infantile gangliogliomas"). J Neurosurg 66: 58–71
121. Virchow R (1846) Ueber das granulierte Ansehen der Wandungen der Gerhirnventrikel. Allg Z Psychiat 3: 242
122. von Deimling A, Janzer R, Kleihues P, Wiestler OD (1990) Patterns of differentiation in central neurocytoma. Acta Neuropathol (Berl) 79: 473–479
123. von Deimling A, Kleihues P, Saremaslani P, Yasargil MG, Spoerri O, Sudhof TC, Wiestler OD (1991) Histogenesis and differentiation potential of central neurocytomas. Lab Invest 64: 585–591
124. Wachter R, Wittekind C, VonKleist S (1984) Localization of CEA, ß-HCG, SPI, and keratin in the tissue of lung carcinomas. An immunohistochemical study. Virchows Arch 402: 415–420
125. Willis RA (1973) The spread of tumours of the human body, 3rd Ed. Butterworths, London
126. Wilson BS, Lloyd RV (1984) Detection of chromogranin in neuroendocrine cells with a monoclonal antibody. Am J Pathol 115: 458–468
127. Yates AJ (1988) Glycolipids and gliomas. A review. Neurochem Pathol 8: 157–180
128. Zülch KJ (1965) Brain tumours. Their biology and pathology, 2nd Ed. Heinemann, London
129. Zülch KJ (1986) Brain tumors. Their biology and pathology, 3rd Ed. Springer, Berlin Heidelberg New York Tokyo
130. Zülch KJ (ed) (1979) Histological typing of tumours of the central nervous system. International histological classification of tumours, No 21. World Health Orgnanisation, Geneva

Histoprognosis of Gliomas

C. DAUMAS-DUPORT

Centre Hospitalier Sainte-Anne, Paris (France)

With 5 Figures

Contents

Introduction

The present paper focuses on the most common forms of glial neoplasms of astrocytic and oligodendrocytic lineage. The term of glioma will therefore be used, here, in a restrictive sense.

From a clinical point of view, the histological assessment of gliomas is expected: 1) to predict the life expectancy of individual patients, 2) to provide a rational basis on which to plan therapy, and 3) to define reproducible groups of patients with statistically homogeneous prognosis, in order that the results of various treatment options may be accurately evaluated and compared.

Current conventional histological classifications, based on the predominant cell type and degree of malignancy, are far from being satisfactory. In addition to the inherent complexity of glial neoplasms, multiple factors contribute to the confusion. As will be emphazised in this paper, most current problems have their origin in the amalgamation of divergent historical concepts, in a long tradition of blind histological interpretation without integration of clinical or radiological data and in the lack of reproducibility of the currently used grading systems. Neglect of the existence of two distinct patterns of tumour growth in glial neoplasms, i.e. of the structural type of gliomas, also contributes to inadequate histological typing and histoprognostic assessment of these tumours.

Pathologists are, no doubt, conscious that they answer imperfectly the demands of clinicians and therapists. During this last decade, their efforts have been directed mainly toward the introduction of more sophisticated histological techniques. Immunohistochemical markers however have not had significant impact on the classification of gliomas and, further, their introduction into daily laboratory practice has not proved to be useful in clinical terms.

The absence of significant progress in the histological assessment of gliomas has led to the opinion that current routine histology has severe limitations. Kinetic markers are now increasingly used by pathologists, and molecular biology is, also thought to offer a key solution in the field of neuro-oncology. In contrast, modern imaging techniques that could be used by pathologists as an equivalent of macroscopic examination, have had little impact on the histological interpretation of gliomas.

The main objective of this paper is to suggest that information that can be provided by simple histological techniques and integration of imaging and clinical data in the histological interpretation of gliomas has not yet been correctly and fully exploited.

Historical Considerations

The first attempts to classify gliomas were based on the observation that gliomas resemble the normal glia of mature brain tissue (Virchow 1864).

Accordingly, gliomas have been categorized subsequently as astrocytomas, oligodendrogliomas and ependymomas.

First attempts at the surgical treatment of brain tumours have later stimulated the idea of classification for prognostic information. In 1926, Bailey and Cushing (1926) developed a classification based on a histogenetic hypothesis, and thus introduced the concept of tumour differentiation. Histological categories were individualized according to the resemblance of a tumour with one of the successive stages of differentiation of glial cells during embryogenesis. In their classification, prognostic significance was attached to each histologic subtype according to its supposed situation in a scale of differentiation.

In 1948, following Broders (1926), who conceived a grading system for epithelial tumours, Kernohan introduced a numerical grading for gliomas (Kernohan *et al.* 1949, Kernohan *et al.* 1952). Adhering to the concept that gliomas may arise from pre-existing adult cell types still capable of proliferation by a process of anaplastic transformation or de-differentiation, Kernohan returned to a simplified classification of gliomas into astrocytoma, oligodendroglioma and ependymoma. Without distinction of histological sub-cell types, astrocytomas were subjectively graded 1 to 4, according to their apparent degree of de-differentiation. In addition, Kernohan described the presence and progressive increase of additional histological features of anaplasia that were observed in each of these four grades: pleomorphism, necrosis, mitosis, vascular proliferation, etc... including different degrees of macroscopic circumscription.

A year later, Ringertz (1950) proposed a grading system for astrocytomas based on histological criteria similar to those used by Kernohan, but which distinguished only 3 degrees of malignancy: astrocytomas, malignant astrocytomas and glioblastomas.

However, scepticism was soon expressed concerning the efficacy of grading gliomas in general. The objections have been, and are still, most often based on the following (Zülch *et al.* 1979): firstly, available sampling size: the tumour may display various degrees of histological malignancy in different areas; secondly, progressive evaluation over a period of months or years of an originally benign neoplasm to a more malignant one; thirdly, grading systems alone fail to take into account the topography of a tumour and age of the patient, factors which have been found consistently to affect clinical behaviour.

In 1979, in order to increase uniformity among pathologists, the WHO classification amalgamated these three fundamental types of brain tumour classification (Zülch *et al.* 1979). Gliomas were classed into four categories according to their predominant cell type: astrocytomas, oligodendro-

gliomas, oligoastrocytomas and ependymomas. The principle of assigning numerical grades of malignancy to a given cytologic type of glioma based on unspecific histologic features of malignancy (nuclear atypia, mitoses, etc...) was rejected.

Astrocytomas were subdivided into distinct sub-cell types, each having its own prognostic significance. A numerical grade was, however, arbitrarily attributed to each sub-cell type. Pilocytic astrocytomas were considered as grade 1, fibrillary protoplasmic and gemistocytic astrocytomas as grade 2, anaplastic astrocytomas as grade 3, and glioblastomas were considered as grade 4.

Oligodendrocytomas were separated into two categories: oligodendrogliomas (grade 2) and "anaplastic" oligodendrogliomas (grade 3). Oligoastrocytomas were indistinctly graded 2.

The ambiguities of such a classification are readily apparent: Firstly the WHO classification has rejected the principle of grading gliomas but "de facto" uses a scheme based upon "increasing grade of malignancy". Secondly the term 'anaplasia' by itself does not mean anything more than "bad thing". This, has generated a major problem in the current histological assessment of gliomas. In fact, individual pathologists have their own concept of anaplasia, either based on a subjective feeling of de-differentiation, or on variable basic histological features, thought to be associated with a poor prognosis. Thirdly, application of a grading system makes sense on condition that tumours included in a given histological category demonstrate variable behaviour, from less malignant to more malignant, and on condition that in tumours regrouped into a given histological category, histological criteria other than the cytologic type or sub-cell type have prognostic significance. The systematic attribution of a histological grade even to lesions which have distinct homogeneous behaviour creates confusion. For example, in studies describing "low-grade astrocytomas", pilocytic and microcystic cerebellar astrocytomas ("WHO grade 1") are often indiscriminately regrouped with fibrillary, protoplasmic or gemistocytic astrocytomas ("WHO grade 2").

Intra-tumoural Heterogeneity of Gliomas

Intra-tumoural heterogeneity is a characteristic feature of glial neoplasms (Scherer 1940). Regional variations in the distribution of morphological features of malignancy are evident especially in high-grade gliomas. In these neoplasms, foci of high cell density accompanied by neovascularity, endothelial proliferation and/or necrosis, often co-exist with areas of low

cell density resembling low-grade gliomas. Intra-tumoural heterogeneity can also be seen in low grade neoplasms where there are foci of increased cellularity and mitotic activity.

Regional heterogeneity of gliomas has traditionaly been considered to reflect a spatial heterogeneity in the potential of growth. Co-existence of low and high-grade components within a given neoplasm, is a widely accepted concept, and is regarded as a consequence of tumour progression. This concept has for a large part found its roots in the theory of fields (Willis 1960). According to this author, malignant transformation at first involves large fields of brain parenchyma. Following this early event, within these fields, the tumour may remain a low-grade glioma, or as an unpredictable event, certain areas may become more malignant.

Intra-tumoural Heterogeneity and Structure Type of Gliomas

The simple recognition of two distinct patterns of tumour growth: the solid "tumour tissue" proper versus "isolated tumour cells" offers another approach to the interpretation of the intra-tumoural heterogeneity of gliomas (Daumas-Duport *et al.* 1979, Daumas-Duport *et al.* 1982).

In the solid tumour tissue, tumour cells are crowded and are unaccompanied by intervening normal brain parenchyma. The tumour tissue proper possesses new formed microblood vessels (Fig. 1A). Isolated tumour cells (ITCs) reflect an arrangement wherein the tumour cells are not in contact with each other but permeate largely intact brain parenchyma. This pattern is not accompanied by neovascularity. However, the presence of ITCs is usually associated with edema (Fig. 1B).

In astrocytomas, the tumour tissue is composed of cells which possess visible cytoplasm and cell processes, whereas ITCs usually lack visible cytoplasm giving the appearence of "naked nuclei". Such individual tumour cells can be identified, because of distinct nuclear abnormalities. Their lack of visible cytoplasm permits their distinction from reactive astrocytes. In oligodendrogliomas, identification of ITCs at the advancing edge of the tumour depends entirely on the recognition of characteristic nuclear abnormalities (Daumas-Duport *et al.* 1987).

The two distinct growth patterns, singly or in combination, are the basis of the following structural classification of gliomas (Fig. 2): type I, solid tumour tissue only, no peripheral ITCs; type II, solid tumour with peripheral ITCs; type III, ITCs within intact brain parenchyma and no solid tumor tissue.

In patients explored by imaging-based stereotactic biopsies, routine

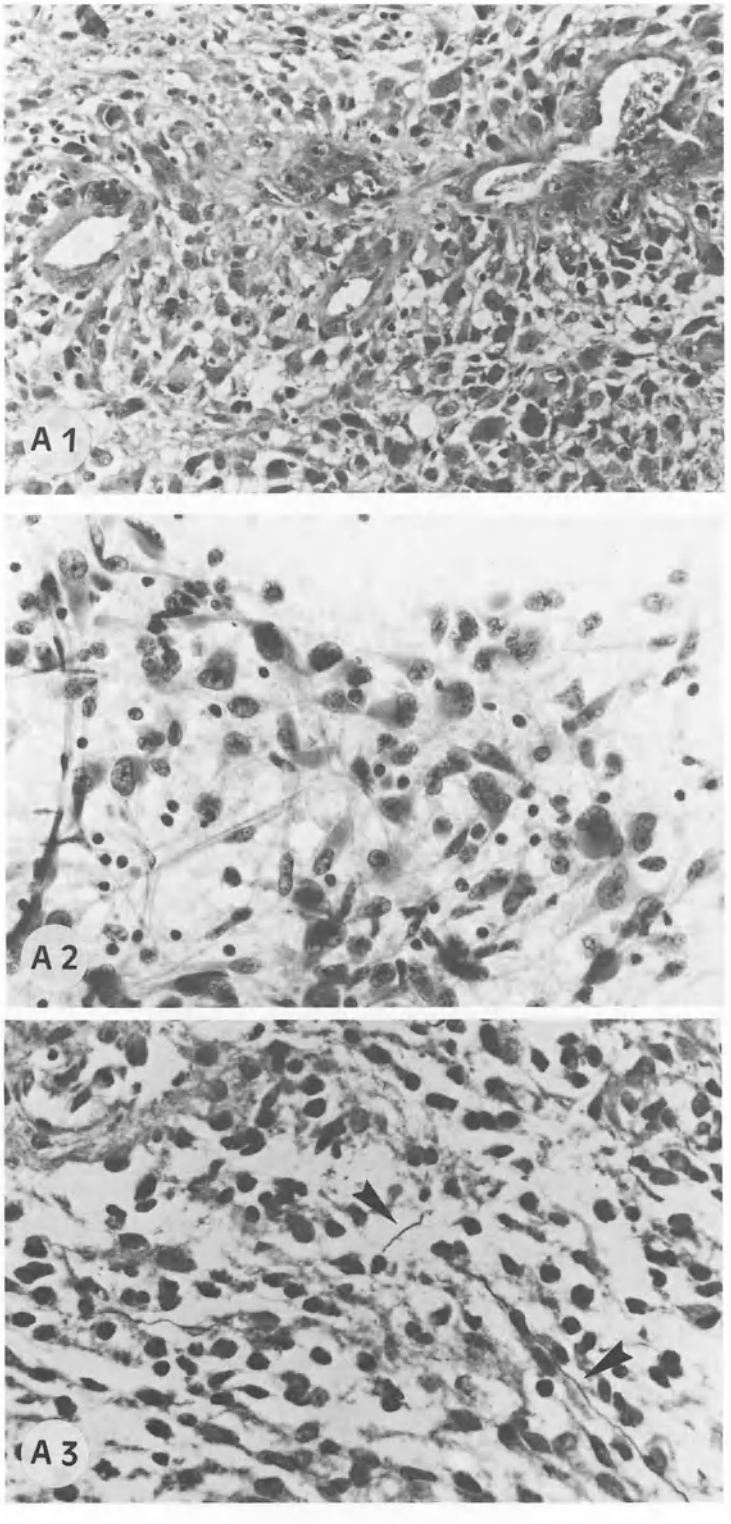


Fig. 1. (A1–A3) Caption see p. 50

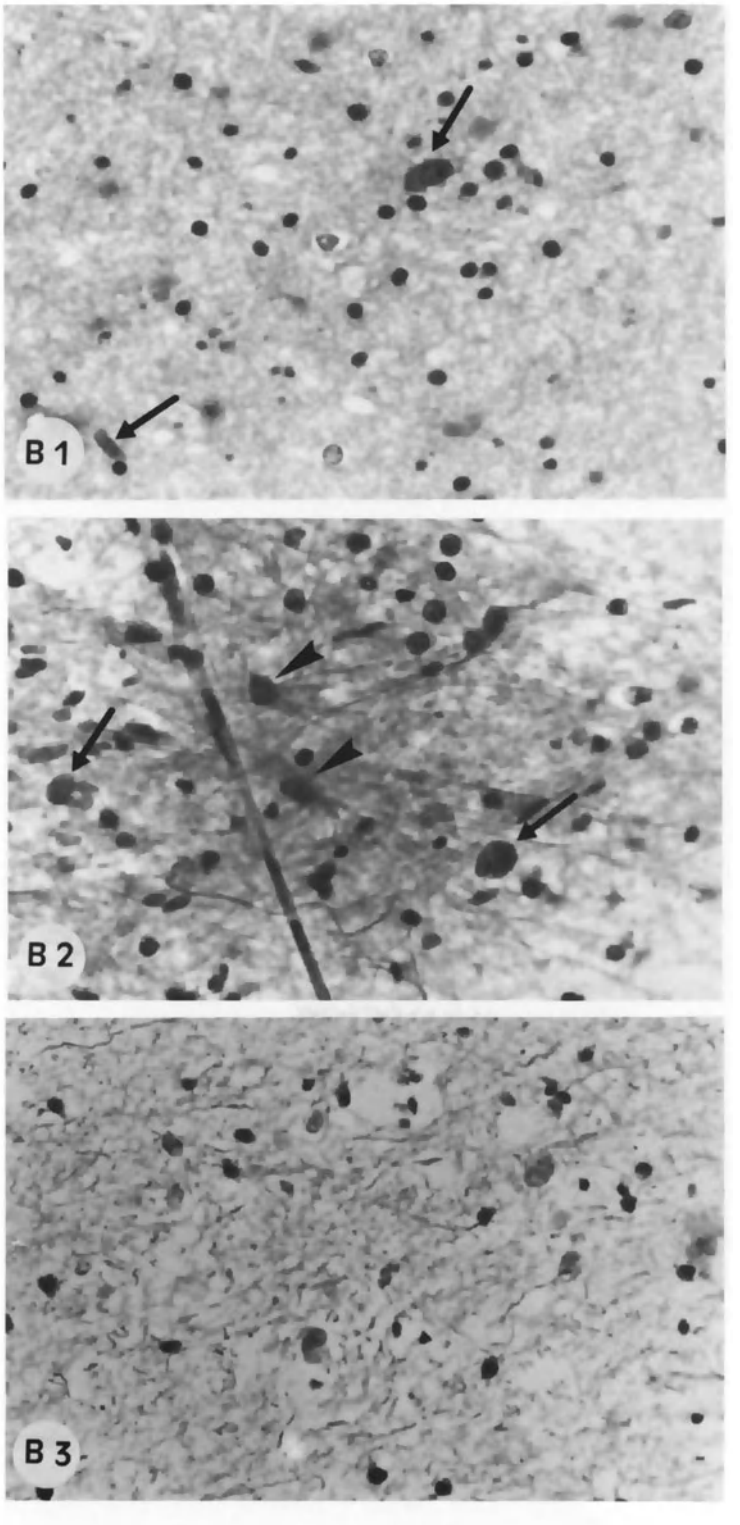


Fig. 1. (B1–B3)

Fig. 2. Structural types of gliomas. Type I (left) solid tumour tissue only; type II (middle) tumour tissue and peripheral isolated tumor cells; and type III (right) isolated tumour cells only

histological examination can provide information concerning both the histological type, grade of malignancy and structure type of glial neoplasms. For example, a given neoplasm can be diagnosed as an astrocytoma grade 4, structure type II, or as an oligodendroglioma grade 2, structure type III.

Studies of a series of patients, who underwent serial stereotactic biopsies at our institution, have shown that ordinary astrocytoma cell types (i.e. fibrillary, protoblastic, gemistocytic astrocytoma, and anaplastic astrocytomas and gliobastomas) are predominantly of structure type II. Pilocytic astrocytomas are of type I (100%); a large proportion of oligodendrogliomas adopt a structure type III (Daumas-Duport *et al.* 1989).

Definition of the structure type of glial neoplasms allows a better interpretation of imaging data, and can provide useful information for planning therapy. In addition, simple consideration given to the existence of two different tumour growth patterns could avoid current misconception regarding the spatial kinetics of gliomas.

Structure Type of Gliomas and Imaging

We have demonstrated that there is a strong correlation between the degree of tumour microvascularity and CT or MRI contrast enhancement (Daumas-Duport *et al.* 1986, Kelly *et al.* 1987). When present, contrast

---

Fig. 1. Pattern of tumour growth of a gemistocytic astrocytoma grade 4 structure type II (necrosis not shown). (A1) and (B1) HES staining (X 200, X 250), (A2) and (B2) smear preparations (X 250), (A3) and (B4): Bodian stain (X 250). (A) Solid tumour tissue: cells are crowded and are associated with neovascularity (A1 and A2). Bodian stain demonstrates only residual axons (A3, arrowheads). (B) Isolated tumour cells in white matter (ITCs): ITCs (arrows) show nuclear atypia and lack visible cytoplasm (B1 and B2) whereas reactive astrocytes possess stellate processes (B2 arrowheads). Parenchyma is architecturally intact as demonstrated by Bodian stain (B3)

enhancement corresponds to the solid tumour tissue itself but does not occur in areas containing ITCs which are devoid of neovascularity. Since the presence of ITCs is usually accompanied by oedema, parenchyma infiltrated by ITCs usually appears as an area of hypodensity on CT scan, or of hypersignal on MRI T2 weighted images.

As a consequence, a relationship is observed between the structure type of gliomas and the appearance of these tumours on imaging. Contrast enhancement on C.T. is constant in structure type I, but absent in structure type III gliomas. In a structure type II tumour, contrast enhancement is inconstant depending on the degree of neovascularity. However, contrast enhancement is constant in malignant structure type II gliomas. Necrotic foci are also usually well demonstrated on post-contrast enhancement (Daumas-Duport *et al.* 1986, Kelly *et al.* 1987).

Structure Type of Gliomas and Treatment Planning

Identification of the histological structure type of gliomas can provide important data for planning treatment (Daumas-Duport *et al.* 1982, Daumas-Duport *et al.* 1986, Kelly *et al.* 1987, Kelly *et al.* 1992). The solid tumour tissue contains little or no residual brain parenchyma (see Fig. 1A). This component can thus be destroyed without a resultant deficit. On the other hand, parenchyma infiltrated by ITCs is morphologically and functionally intact (Fig. 1B), thus ITCs components must not be damaged in an important brain structures if the patient's neurological function is to be maintained.

Nowadays, the structure type and tumour volume of gliomas can be determined by imaging-based serial stereotactic biopies (Daumas-Duport *et al.* 1979, Kelly *et al.* 1987).

In structure type I tumours, contrast enhancement is constant, and the tumour volume corresponds to the contrast enhancement volume defined by CT or MRI. The limits of the tumour can thus be precisely estimated. These tumours comprised solid circumscribed tissue can be entirely resected without resultant deficit. Deep-seated tumours can also be treated by interstitial irradiation which allows the destruction of a precise target volume.

In structure type II tumours, the extent of ITCs usually precludes complete removal. Excision, or selective radiosurgical destruction of the solid tumour tissue can theoretically be achieved in any location. Post-operative radio or chemotherapy are the only available methods for the

treatment of ITCs that infiltrate the surrounding parenchyma which can not be removed.

In structure type III tumours, the extent of ITCs infiltration also usually precludes complete surgical removal. Partial resection of these tumours which occupy intact brain parenchyma is of questionable benefit. Radiotherapy seems to be more appropriate treatment.

Structure Type and Spatial Kinetics of Gliomas

Structure type II tumours have an heterogeneous appearance. Since the tumour tissue possesses high cell density, increased vascularity and may contain necrotic changes, the tumour tissue is traditionally interpreted as high-grade components, whereas ITCs which appear as an area of lower cell density are often believed to be low-grade components. However, our ongoing studies based on organotypic cultures and on kinetic markers, suggest that the so-called "low grade areas" of structure type II gliomas are in fact areas of active tumour growth.

Organotypic cultures: we have suggested that ITCs of astrocytomas type II, having a "naked nuclei" appearance, are morphologically immature tumour cells capable of motility (Daumas-Duport *et al.* 1987). Our studies of gliomas maintained in organotypic cultures (unpublished data), seem to confirm this hypothesis. The so-called "organotypic cultures" simply consist of the deposition of tumour tissue samples on a gelfoam matrix. As illustrated in Fig. 3, as soon as the fourth day of tissue culture, the gelfoam matrix is invaded by isolated tumour cells which closely resemble those seen "in vivo" in structure type II astrocytomas.

This observation suggests that, contrary to the "centripetal" interpretation of Willis, tumour growth of gliomas does not differ from that of other solid tumours, but is the result of a progressive invasion of the surrounding normal brain parenchyma by new-born motile tumour cells.

Kinetics and pattern of tumour growth: We have studied the kinetics of ten astrocytomas grade 4 type II with MIB antiserum (Immunotech S.A.). This recently commercialised kinetic marker, an equivalent of Ki 67, labels compounds which are naturally expressed by cycling cells.

Comparable results were observed in these ten tumours. As illustrated in Fig. 4, in ITC components (the so-called low-grade areas) the MIB labelling index was, at least, equivalent or superior to that of the tumour tissue proper. It is however necessary to take account of the normal glial cell population incorporated within area of ITCs infiltration.

Given the increasing number of publications devoted to kinetic immuno-

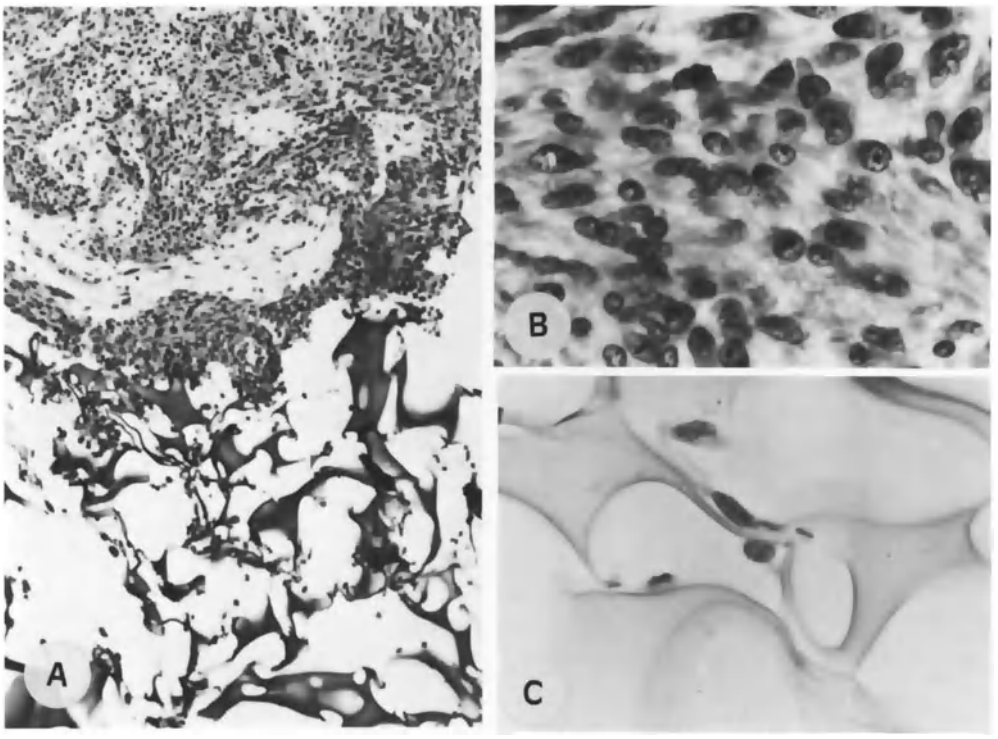


Fig. 3. Organotypic culture of a grade 4 astrocytoma after 10 days of culture. (HES staining X 50, X 300). From the tumour tissue implant (A), isolated tumour cells have migrated within the gelfoam matrix (B). These ITCs have a nacked nuclei appearance, comparable to that observed in vitro (C)

histochemical studies of glial neoplasms, it may appear surprising that such observations have not yet been mentioned. This can, however, be explained by the fact that, in order to encompass the intra-tumoural heterogeneity of glial neoplasms, the growth tumour fraction is currently evaluated in an area of apparently higher labelling index, and that no distinction is made between the solid tumour tissue and ITCs components, labelling indices being calculated as the proportion of nuclei which are labelled, compared to the total number of nuclei observed in a given field.

Since it is widely accepted that the prognosis of a tumour depends on its more malignant component, current misconceptions in the interpretation of heterogeneous structure type II high-grade gliomas would be of no consequence in the histoprognostic evaluation of gliomas. However, in the 1979 WHO classification (Zülch 1979), the presence and proportion of fields of tumour differentiation (i.e. of low-grade components) within a

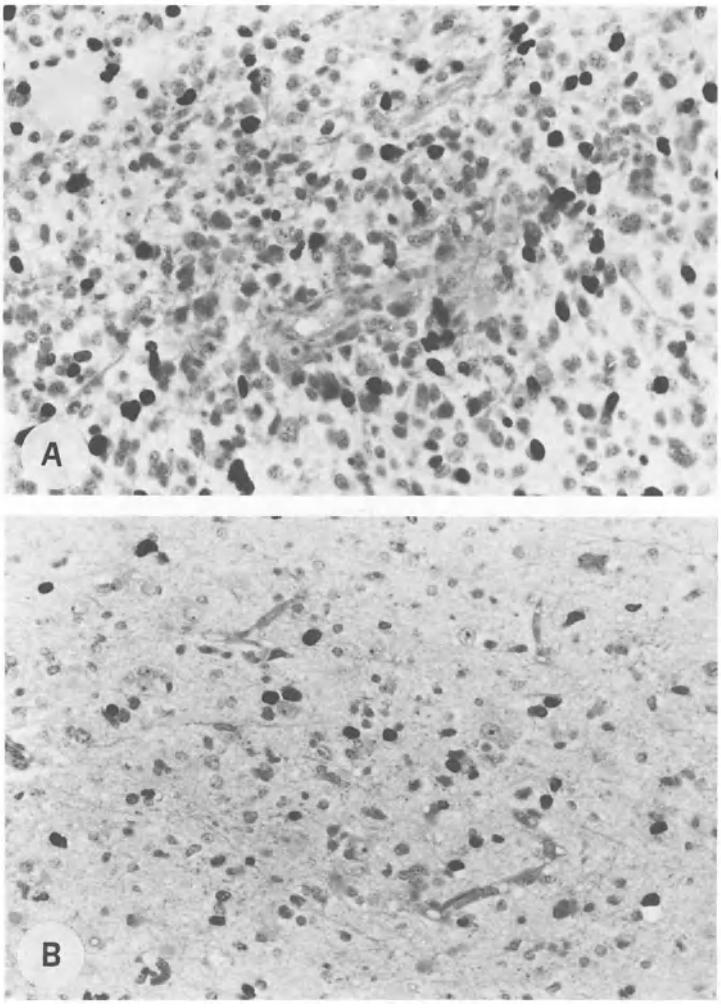


Fig. 4. Astrocytoma grade 4-structure type II: kinetic immunostaining with MIB1 antisera, Hemalun and Phloxin counter stain (X 200). (A) Tumour tissue, (B) isolated tumour cells in subcortical white matter. The tumour tissue contains only tumour cells (A), whereas ITCs are mixed with normal glial cells and neurons (B). Accordingly, the actual labelling index in the ITCs component (B) (the so called "low-grade components") is superior to that of the tumour tissue (A)

malignant astrocytoma, are designated as a key criterion for differentiating anaplastic astrocytomas (grade 3) from glioblastomas (grade 4).

Similarly, Brucher (1989) considers that "tumours with foci of pronounced hypercellularity, pronounced pleomorphism and even necrosis are anaplastic astrocytomas (rather than glioblastomas), if quiescent areas

outside of these foci demonstrate a lower malignancy of the whole tumour and a better resistance of the host".

Current pitfalls in interpreting peripheral ITCs areas of malignant gliomas as low grade components are apparent in the results of surgical resection. If this concept were correct, surgical resection of the higher grade part of the tumour would provide expectancy of life comparable with that of low-grade gliomas. However, the benefit of surgery in glioblastomas remains unclear in the literature (for review see Devaux *et al.*, 1993). In a recent study of a series of 196 patients with grade 4, structure type II, gliomas, comparison of survival of patients who underwent biopsy only, with that of patients who had surgical resection of the solid tumour part of the tumour, demonstrated that surgical removal of the "high-grade" part of the tumor offered only a modest prolongation of survival of about 4 months (Devaux *et al.*, 1993).

Intra-tumoural Heterogeneity and Tumour Progression: Recent Molecular Biology Data

Molecular characterization of human gliomas also tends to confirm that malignant gliomas are biologically less heterogeneous than traditionally considered. In a recent study, Leenstra *et al.* (1992) have characterized molecularly different areas within four malignant astrocytomas, histologically interpreted as composed of low- and high-grade components. In order to determine whether the coexistence of high- and low-grade foci could be explained by heterogeneity in DNA constitution, the tumours were examined for events not detected in "pure" low-grade astrocytomas: loss of heterozygozity on chromosomes 9P, 10 and 17P and also for amplification of the epidermal growth factor receptor gene. In all tumours, identical alterations were found in the "low-grade" and "high-grade" areas.

This study strongly argues for a common origin of tumour cells that compose phenotypically heterogeneous gliomas, and tends to demonstrate that the genetic alterations associated with tumour progression are, in fact, already present in the so-called low-grade part of malignant astrocytomas.

Recent data concerning gene mutation associated with tumour progression are in good concordance with the study of Leenstra. Using a sensitive sequencing assay Sidransky *et al.* (1992) have demonstrated that p53 gene mutation, found in a majority of tumour cells of malignant astrocytomas, are already present in a minority of cells of gliomas diagnosed as low-grade gliomas before they evolve into faster growing high-grade gliomas. This

study sustains Nowell's clonal evolution model of tumour progression who postulated that tumour progression is not the result of accidental mutation but is due to the selective growth advantage of cells that have previously acquired a genetic change (Nowell 1976).

Intra-tumoural Morphological Heterogeneity of Gliomas: Issue of Sampling

Heterogeneity in the spatial distribution of morphological features used for evaluating the prognosis of gliomas has been considered one of the major impediments to histological tumour grading. According to the opinion of Russell and Rubinstein (1977a) "grading if used at all should be restricted to autopsy material, when the whole tumour can be sampled".

Underestimation of the actual grade of malignant gliomas in biopsy samples is an old problem which has become even more accurate with the now common practice of stereotactic biopsy. Concern is still repeatedly expressed by pathologists about "small needle stereotactic biopsies" (Glantz *et al.* 1991, Paulus *et al.* 1989). However, the idea that big pieces of tissue offer better accuracy of tumour grading than small biopsies is based on a practice of surgical pathology dating back to the advent of modern imaging techniques and of stereotactic neurosurgical methods.

As illustrated in the paper of Paulus and Peiffer (1989), the potential input of imaging-guided stereotactic biopsies in the histological assessment of gliomas has not yet been well understood among the community of pathologists. In order to evaluate the potential accuracy of small biopsies in gliomas, the authors have randomly punched small and large samples from 50 unembedded tumours. They demonstrated that the mean grade for the small samples was lower than for the large one and calculated that a grade 2 stereotactic biopsy sample had an approximately 32% of chance to belong to a malignant glioma.

Nowadays however, stereotactic methods can provide tissue samples from areas with different appearance on CT-scan and/or MRI. A correct histological diagnosis depends less on the size than on correct orientation of biopsy sampling (Daumas-Duport *et al.* 1986, Kelly *et al.* 1987). As discussed above, correlations that exist between histology and appearance of gliomas on post-contrast CT or MRI imaging, allow the surgeon to provide significant samples to the pathologist. These correlations can also be exploited by the pathologist in order to evaluate the validity of sampling.

In our experience and that of other authors (Scerrati *et al.* 1984) serial

stereotactic biopsies from areas with different appearance on imaging techniques can reach a high diagnostic accuracy. In a series of 95 patients who underwent surgical removal following serial stereotactic biopsy, at our institutes, an average of six biopsies per patient allowed an accurate grading in 98% of the cases (Personal communication).

Technical considerations and tumour location may obviously impose limitation on sampling. However, knowledge of the appearance of a glioma on imaging techniques allows the pathologist to evaluate the validity of sampling. If no obvious neovascularity is apparent on histological examination, but contrast enhancement is present on-CT scan, it can be deduced that the neoplasm possesses a solid tumour tissue component which has not been sampled. In such cases, a tumour grade should not be disclosed. Morphological features present in the samples could, however, be considered in order to indicate a minimum grade.

On the other hand, necrosis being, used in most grading systems as a key criterion for the indentification of grade of astrocytomas (or glioblastomas) it is no more conceivable that pathologists diagnose a grade 3 (or anaplastic) astrocytoma when necrotic foci are obvious on imaging.

Current Problems in Histological Typing of Glial Neoplasms

Since histological criteria of malignancy have no intrinsic value, but have highly variable significance according to the histological type of the tumour in which they are encountered, the accuracy of histo-prognosis is, at first, dependent on a correct diagnosis (Alvord 1992). However, many problems still persist in the histological typing of glial neoplams. Factors that combine to create difficulties in the histological diagnosis of gliomas are the following: 1) high cytological plasticity of astroctytic and oligodendrocytic tumour cells; 2) the tendency of gliomas to reproduce cells of different lineages, a feature which is now well explained by the fact that astrocytes and oligodendrocytes have a common progenitor (Raff *et al.* 1983, French-Constant *et al.* 1986) and 3) the inclusion of normal and reactive glial cells within infiltrative gliomas.

The above considerations as well as the lack of suitable markers for the recognition of tumoural oligodendrocytes, make it apparent that current official classification scheme based on the predominant cell type are inaccurate for the characterization of a large proportion of glial neoplasms. This is especially true for tumour diagnosed in children. Specific problems in typing children's gliomas will be discussed separately.

Histological Typing of Astrocytomas

In contrast to what may be suggested by conventional classifications, the spectrum of astrocytic tumours is not made up of clearcut easily recognizable entities. The subdivision of astrocytomas based solely on cytologic criteria into fibrillary, protoplasmic, gemistocytic and pilocytic astrocytomas is in large part artificial. Best observed on smear preparations, astrocytoma cell types include a myriad of cytologic variants including many transitory aspects between these different conventional cell types. In addition, in most astrocytomas, either of low- or high-grade, a mixture of different cell types is frequently observed.

The histological typing of an astrocytomas as fibrillary protoplasmic or gemistocytic is, however, of no consequence for tumour grading since, in these different subcell types, the histological features of malignancy used for grading astrocytoma have identical histoprognostic significance. The distinction of pilocytic astrocytomas, and microcystic cerebellar astrocytomas from "ordinary" astrocytomas cell types is, however, of paramount importance in order to avoid overgrading and overtreatment.

Pilocytic Astrocytomas versus Ordinary Astrocytoma Cell Type

Pilocytic astrocytomas have distinct slow-growing behaviour, and morphological features used for grading "ordinary" astrocytoma cell types, such as nuclear atypia and endothelial proliferation, have no prognostic significance in these neoplasms (Rubinstein 1972).

Currently, the diagnosis of pilocytic astrocytomas is solely based on cytologic criteria. In the 1979 WHO classification (Zülch 1979), as well as in the revised WHO classification (Kleihues *et al.*, in press), pilocytic astrocytomas are defined as tumours predominantly composed of bipolar fusiform piloid fibrillary astrocytic cells. However, malignant ordinary astrocytomas often contain fusiform astrocytes. In addition, in certain structures such as the brain stem and the corpus callosum, tumour cells of ordinary infiltrative astrocytomas, which are intermingled with parallel axons, may adopt or mimic a bipolar pattern (Russell and Rubinstein 1977).

Cytologic criteria are, thus, insufficient to establish the diagnosis of pilocytic astrocytoma. The structure type is important to consider in order to avoid misinterpretation with ordinary astrocytomas. In fact, "true" pilocytic astrocytomas are of structure type I, i.e. they are made only of a solid tumour tissue component (Daumas-Duport 1989).

Accordingly, contrast enhancement is constant in these tumours, and the diagnosis of pilocytic astrocytoma should be reconsidered when no contrast enhancement is visible on imaging.

In addition to a diagnostic point of view, the structure type of pilocytic astrocytomas is also important to consider in planning treatment. The tumour volume exactly corresponds to the area of contrast enhancement on imaging, and those neoplasms which are made only of solid tumour tissue, can be totally removed without a resultant deficit (McGirr *et al.* 1987, Kelly 1991). When no residual contrast enhancement is seen on post-operative CT or MRI, adjuvant radio and/or chemotherapy are contraindicated.

Microcystic Cerebellar Astrocytomas versus Pilocytic Astrocytomas

Microcystic cerebellar astrocytomas are often predominantly composed of pilocytic astrocytes. Therefore, in the WHO classification of 1979 (Zülch 1979) as well as in the revised WHO classification (Kleihues *et al.*, 1993a) these tumour have been incorporated into the categories of pilocytic astrocytomas. In our opinion however, these tumours should be considered as a separate entity.

In contrast with pilocytic astrocytomas, which are slowly growing tumours, microcystic cerebellar astrocytomas are stable lesions. Survival curves of patient harbouring microcystic cerebellar astrocytomas are comparable with that of a normal population (Daumas-Duport *et al.* 1987). Normal lifespan in patients with incomplete removal have been repeatedly reported (Bucy *et al.* 1968, Gessinger *et al.* 1971, Gjerris *et al.* 1978, Davis 1981). However, the current inclusion within the category of microcystic cerebellar astrocytomas of "true" pilocytic astrocytomas of the cerebellum and of the so called "diffuse form of microcystic cerebellar astrocytomas" which, in fact, may correspond to "ordinary" astrocytomas of the cerebellum, creates confusion. This explains contradictory data about the actual behaviour of microcystic cerebellar astrocytomas. Histologically, these polymorphic tumours, often contain multiple astrocytic subcell types and oligodendrocytic components (Ilgren *et al.* 1987). Their complex structure also makes it impossible to class them in one of the three structure types encountered in astrocytomas.

In our opinion, two morphological features strongly argue for a dysembryoplastic origin of these tumours: first) a dysplastic disorganisation of the cerebellar cortex adjacent to the tumour is often observed (personal observation), second) the classical "local invasion" of the subarachnoid

space, which is well known to have no prognostic significance, may be non tumoural (for review see Ilgren *et al.* 1987). The so-called focal meningeal invasion, in fact, closely resembles glial bridge formation observed in a number of cerebellar malformations.

Histological Typing of Oligodendrogliomas

Misdiagnosis between oligodendrogliomas and astrocytomas is a major impediment in the validity of tumour grading. A large proportion of oligodendrogliomas are infiltrative structure type III gliomas, i.e. made of isolated oligodendrocytes that infiltrate intact brain parenchyma (Daumas-Duport *et al.* 1989). These infiltrative oligodendrogliomas are currently misinterpreted as fibrillary astrocytomas for two reasons (Daumas-Duport *et al.* 1987). Firstly in the white matter, these slow-growing tumours induce chronic reactive gliosis, in addition due to either artefactual distortion created by careless handling of fresh tissue or retraction induced by formalin fixation, entrapped axons easily mimic a fibrillary astrocytic background (see Fig. 5). Secondly, cytological criteria used for the identification of oligodendrogliomas emphasize the characteristic "fried egg" appearance of tumoural oligodendrocytes (Burger *et al.* 1976, Russell and Rubinstein 1989, Zülch *et al.* 1979, Bruner *et al.* 1987). This artefact is however inconstant, and is usually absent in the infiltrative structure type III oligodendrogliomas.

To avoid misclassification of glial neoplasms, the first step in histological examination should be the distinction of the solid tumour tissue from ITCs

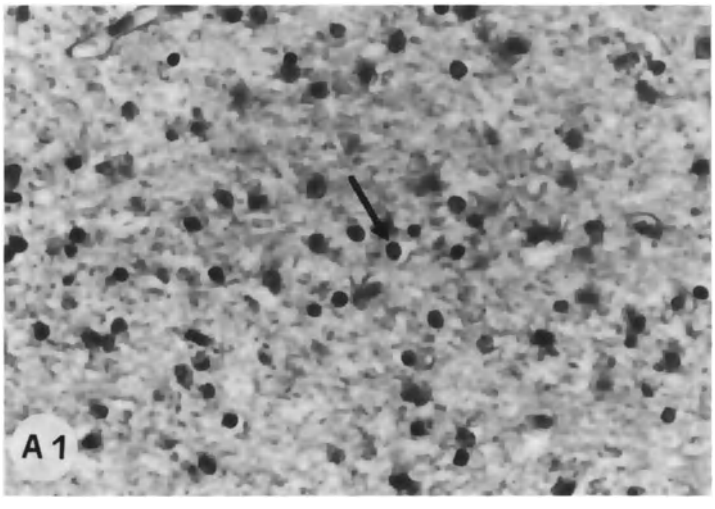


Fig. 5. (A1) Caption see p. 62

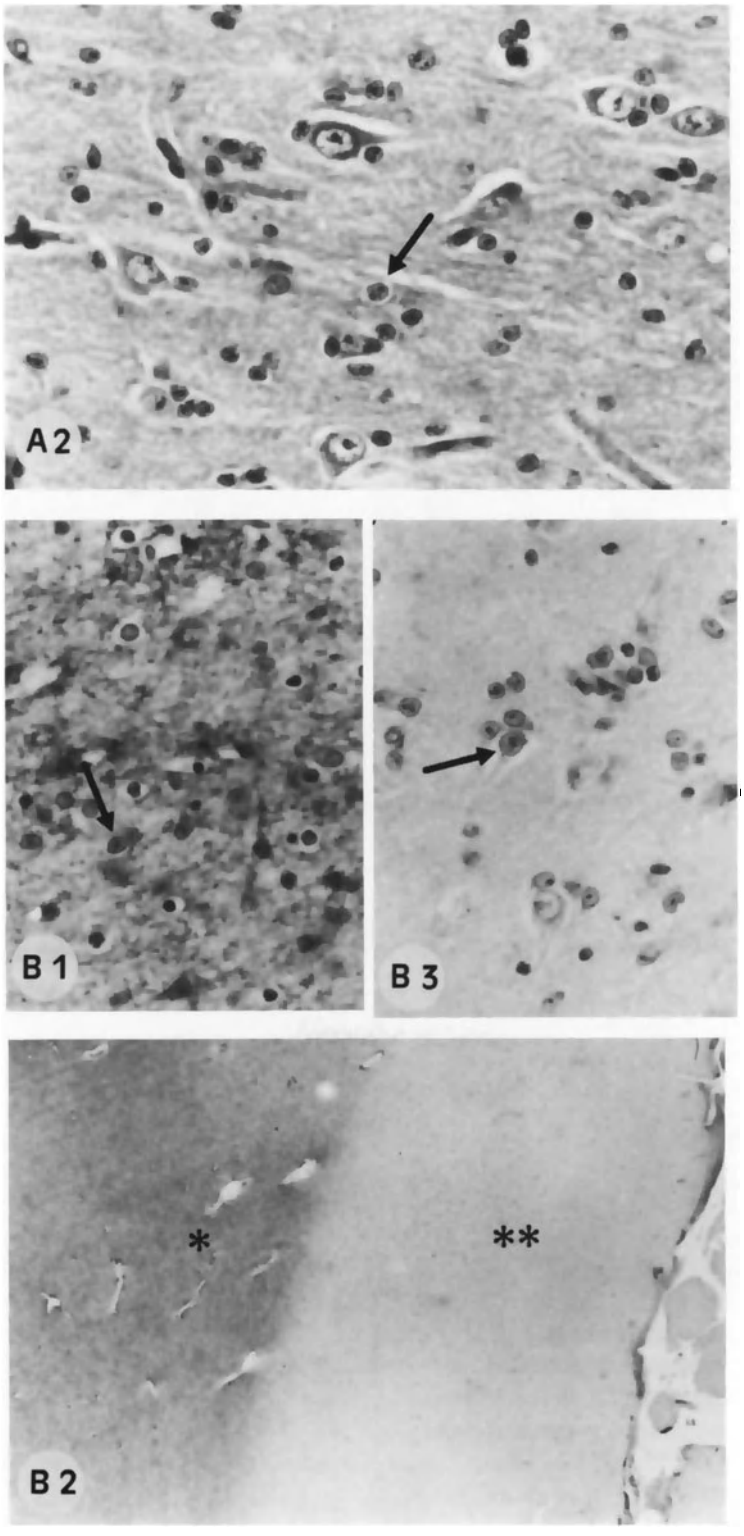


Fig. 5. (A2, B1–B3)

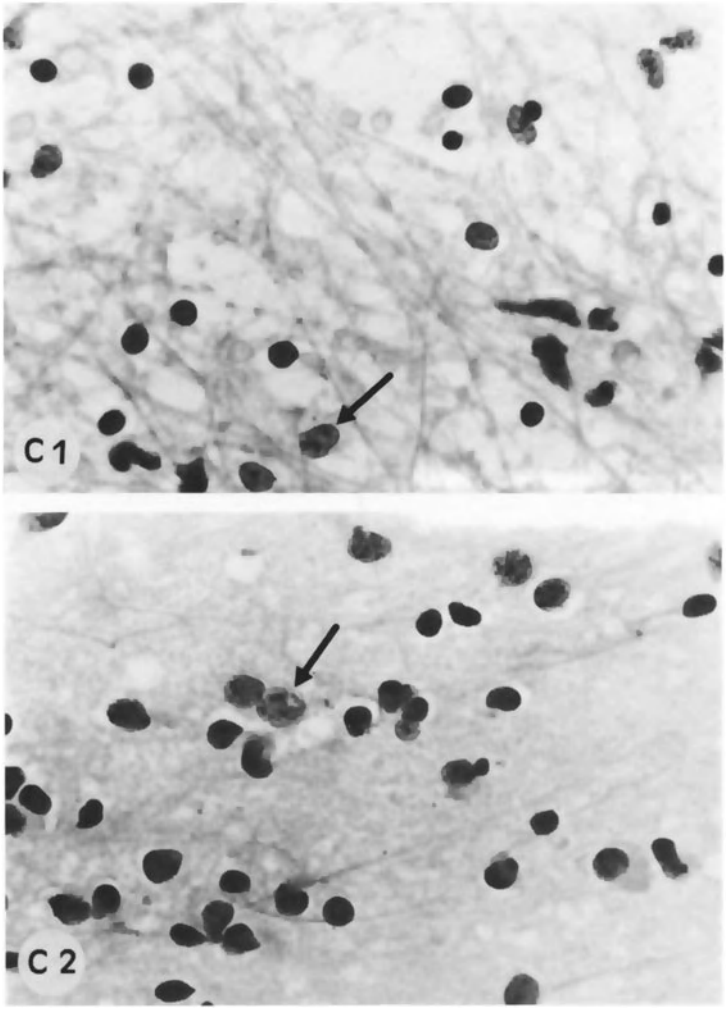


Fig. 5. Oligodendrocytoma grade 2 structure type III. (A1, A2) HPS stain (X 250), (B1–B3): GFAP immunostaining and Hemalun (X 200, X 30, X 200), (C1, C2): smear preparations (X 300). Isolated tumour cells in white matter mimick a fibrillary astrocytoma on routine staining (A1). As demonstrated by GFA immunostaining, the fibrillary background is in fact composed of chronic reactive gliosis (B1 and B2*) and of axons, this is as well apparent on smear preparation (C1). Isolated tumoural oligodendrocytes (arrows) have characteristic nuclei with conspicuous dots of chromatin and have no visible process as best demonstrated on smear preparations (C1, C2). In the cortex infiltrated by ITCs, no fibrillary background is apparent on routine preparation (A2) only few axones are present (C2) and GFAP negativity (B2** and B3) confirms that the fibrillary astrocytic frame seen in the white matter is due to reactive gliosis.

components. Thereafter, as illustrated in Fig. 5, both nuclear and cytoplasmic characteristics of tumoural oligodendrocytes (conspicuous dots of chromatin and a lack of visible cytoplasmic processes) permit distinction between infiltrative oligodendrocytes and tumoural fibrillary astrocytes, and, as well, isolated tumoural oligodendrocytes from reactive gliosis.

Figure 1 of the WHO "Blue Book" (Zülch 1979) which is given as an example of fibrillary astrocytoma is, in our opinion, an infiltrative oligodendroglioma. Current misdiagnosis between oligodendrogliomas and fibrillary astrocytomas has obvious consequences on tumour grading. For example, in our grading system of astrocytomas, tumours which show nuclear atypia and mitosis are diagnosed as grade 3, and median survival in patients harbouring grade 3 astrocytomas is about 2 years (Daumas-Duport *et al.* 1988a), whereas with the new grading system of oligodendrogliomas that we have recently described (see below), oligodendrogliomas with nuclear atypia or mitosis are diagnosed as grade 2 and median survival of patients with grade 2 oligodendrogliomas is about 8 years (unpublished data).

Current immunohistochemical methods are unfortunately of little help for differentiating oligodendrogliomas from astrocytomas. Suitable markers for tumoural oligodendrocytes are still awaited, and on the other hand, it is now well recognised that tumoural oligodendrocytes can express GFAP (Herpes *et al.* 1984, Nakagawa *et al.* 1986, De Armond *et al.* 1980, Bruner 1987). It is thus unfortunately obvious that GFAP immunostaining, which also labels reactive astrocytes, contributes to overdiagnosis of astrocytomas.

Histological Grading Systems of Astrocytomas

Although individual pathologists are still reluctant to use a grading system for the histological assessment of glial neoplasms in general, there is unequivocal evidence that fibrillary, protoplasmic and gemistocytic astrocytomas (including their more malignant variant) can be usefully graded, and that the same grading system can be applied to these different subcell types here regrouped under the terms of "ordinary astrocytomas".

As a prelimanary to the following analysis, it must be understood that histological grading systems of astrocytomas, as with histological tumour grading in general, are in essence arbitrary.

"Ordinary astrocytomas" as a group, are not made of separate tumour categories with clear-cut differing prognosis, but include a spectrum of tumours which show a continuum of variable growth potential, from the less aggressive to the more malignant behaviour. This is now well established by the multiple kinetic studies devoted to these neoplasms. Markers that

explore the tumour growth fraction, either BUDR (Hushino *et al.* 1984, Hoshino *et al.* 1982, Labrousse *et al.* 1991), KI 67 (Schroder *et al.* 1991) or PCNA (Allegranza 1991), all show a continuum in the value of the labelling index, from less than 1% to 38%.

The division of astrocytomas into distinct grades can thus be made in very different ways. From a strict histoprognostic point of view, all grading systems currently used work, i.e. they define histological groups which are statistically relevant with regard to patient survival. However, the true difficulty in establishing a grading system is to provide guidelines that allow all users to separate the continuum of malignancy at the same level, i.e. that define grades in a reproducible manner.

Unfortunately the reproducibility of the systems which are currently used, either that of Kernohan (1952), of the WHO classification (Zülch *et al.* 1979), or that proposed by Nelson *et al.* (1983) and Burger *et al.* (1985) have not been tested before their introduction. Their lack of reproducibility could be anticipated from the fact that all systems use criteria that involve subjectivity in their appreciation, such as cellular density or cell differentiation, and give weight to different degrees of atypia coded in a subjective manner, in terms of "moderate", "marked", "slight", etc. (For review of grading of astrocytomas see Davis, 1989).

In order to evaluate the trends in grading astrocytomas, we have recently analyzed 25 articals, published in four journals during the past year, concerning the results of various modes of treatment (Daumas-Duport 1992). The system used for evaluting prognosis was indicated in only ten reports (40%). The WHO "grades" were used in six studies, the Burger grading system was applied twice and those of Kernohan and Nelson once each.

This analysis indicated that the four-grade Kernohan system is falling into disuse and that most current approaches to grading have evolved into three-tiered systems. The Kernohan grading system has been found difficult to apply in its original discription, and in fact only separates two tumour groups (Daumas-Duport *et al.* 1988a). The apparent abandonment of the Kernohan grading system has, however, not yet clarified the situation. The large proportion of publications without indication of the system used, and the simultaneous use of three-tiered and four-tiered system render the situation even more confused. In addition, transposition from one system to another produces necessarily inaccurate results, since, the grading systems under consideration use quantitatively as well as qualitatively different histological criteria. At one extreme, Kernohan uses 11 criteria, each subjectively subdivided according to various degrees of atypia, whereas the WHO classification (Zülch *et al.* 1979) only considers "anaplasia" versus cell differentiation. Clusters of histological features used for determining grades

also vary from one system to another. For example, both the Burger and Nelson systems use necrosis as a key criterion for distinguishing glioblastoma from anaplastic gliomas whereas Kernohan (1952) and the WHO classification (Zülch *et al.*, 1979) respectively include in grade 3 or anaplastic astrocytomas tumours considered as glioblastomas in the Burger or Nelson classification.

Differences in grading astrocytomas obviously preclude accurate evaluation and comparison of the different therapeutic protocols used in different institutions. This, also leaves scope for subjective analysis of therapeutic results.

Bias introduced into the histoprognostic assessment of astrocytomas has, however, different implications in high-grade and low-grade astrocytomas. Currently, patients harbouring grade 3 or grade 4 astrocytomas (anaplastic astrocytomas and glioblastomas) are indiscriminately selected for radio or chemotherapy, thus differences in grading high-grade gliomas are of no consequence for therapeutic decisions. In most institutions, however, classification of an astrocytoma as grade 2 versus grade 3 (or astrocytoma versus anaplastic astrocytoma) is used as a landmark for inclusion of patients in aggressive adjuvant therapeutic protocols or their exclusion therefrom. Unfortunately in the grading system of the WHO (Zülch *et al.*, 1979) or that of Burger or Nelson, the distinction of astrocytoma from anaplastic astrocytoma is highly subjective. For example, according to Burger, tumours with only slight hypercellularity and pleomorphism are classified as astrocytomas, whereas tumours with moderate hypercellularity and pleomorphism are considered as anaplastic astrocytomas. Thus, it is obvious that the current distinction between "benign" and "malignant" astrocytomas, and therefore the selection of individual patient for aggressive therapy, remain, to a large extent, arbitrary.

In order to provide a system as reproducible as possible, we proposed a simple grading based on four histological criteria (Daumas-Duport *et al.*, 1982, 1988a): nuclear atypia, mitosis, necrosis and endothelial proliferation, both considered as present or absent. The system results in a summary score which is translated into grades as follows: 0 criterion = grade 1, 1 criterion = grade 2, 2 criteria = grade 3, 3 or 4 criteria = grade 4.

Among the multiple histological features used for grading gliomas, these four criteria were selected because they can be assessed as present or absent, and their recognition was found to be less subjective than that of other criteria. For example, mitosis was selected but not cell density because high cell density is usually accompanied by mitosis and whereas mitosis can be recognized as present or absent, boundaries between low or high cell density cannot be objectively defined. For the same reason, reference to cell differentiation has been avoided: necrosis and/or endothelial proliferation

are, by themselves, powerful criteria for the distinction of grade 4 (or glioblastomas) from grade 3 astrocytomas.

In its principle, this grading is different from most other systems in which certain variables, such as necrosis, are given special weight. This was prompted by the observation that the four histological criteria appear in a well-defined order corresponding to increasing malignancy: Grade 2 astrocytomas possesses nuclear atypia, grade 3 shows addition of mitosis, and grade 4 tumours further show endothelial proliferation and/or necrosis.

The reproducibility of this system as been found to reach 96% of interobserver agreement (Daumas-Duport 1988 a, Kim *et al.* 1991).

In addition to its efficiency and reproducibility, this grading system may avoids errors in histological typing. For example, when endothelial proliferation is present but mitosis and nuclear atypia are absent, the diagnosis of "ordinary astrocytoma" must be controlled in order to avoid misdiagnosis with a pilocytic astrocytoma. The diagnosis of astrocytoma must also be reconsidered when mitoses are not accompanied by nuclear atypia. In such instances, the tumour is rather likely to be an oligodendroglioma. Grade 1 astrocytoma in addition being a rare event, reactive gliosis must be considered when none of the four criteria are identified in the lesion.

Important changes in the histological grading of astrocytomas have been introduced in the revised WHO classification (Kleihues *et al.* 1993a). Apparently, the principle of attribution of a given grade to each astrocytoma subcell type has been maintained, but in fact, a grading system based on the presence or absence of nuclear atypia, mitosis, endothelial proliferation and/or necrosis, similar to the system we proposed for grading astrocytomas, has been introduced. In fibrillary astrocytoma (grade 2), only nuclear atypia can be present, in anaplastic astrocytomas (grade 3) nuclear atypia and mitosis only are present, whereas both necrosis and endothelial proliferation are used as key criteria for separating glioblastomas from anaplastic astrocytomas. Thus, this modification should, carry better uniformity among pathologists and better reproducibility in grading astrocytomas (Kleihues *et al.* 1993).

Histological Grading Systems of Oligodendrogliomas

Data in the literature, concerning the value of histological grading for predicting survival in patients with oligodendrogliomas have, for a long time, been contradictory (for review see Brunner, 1987 and Alvord 1992). More aggressive behaviour for histologically malignant tumours or no difference in behaviour between tumour with or without anaplasia have

been claimed in the past literature. This has obviously generated scepticism concerning the usefulness of histological grading of oligodendrogliomas.

Recently however, after Smith *et al.* (1983) proposed a new specific four-tiered grading system for oligodendrogliomas, there is a new trend considering that oligodendrogliomas can be usefully graded. Since this publication, several attempts have been made to identify individual or clusters of histological indices of prognostic significance (Burger *et al.* 1985, Mork *et al.* 1986).

Smith's system uses five histological features: endothelial proliferation, necrosis, nuclear cytoplasmic ratio, cell density and pleomorphism. The features are considered either as present/high or absent/low. Grades are determined as follows: grade A: all five features absent or low, grade B: pleomorphism present and/or high cell density and neclear ratio, grade C: pleomorphism and endothelial proliferation present plus high nuclear/cytoplasmic ratio and cell density, grade D: all five features present or high. Results of a statistical study in a series of 323 patients have indicated a significant relationship between grade and survival. However the authors themselves have indicated that of the five features, comprising grade, only pleomorphism was statistically correlated with survival by itself. In addition, no significant difference was found in survival curves between the patients with grade B or grade C neoplasms.

Based on a study of a series of 72 oligodendrogliomas, Kros *et al.* (1990) have confirmed that the grading system of Smith only distinguishes three groups of patients. In addition, these authors found that 24% of the tumours showed histological features that did not fit with the cluster of features used by Smith for determining grade. As proposed in its original form, the reproducibility of the grading system of Smith is thus questionable.

Following the publication of Smith *et al.* (1985), Burger *et al.* (1985) and Mork *et al.* (1986) have studied the influence of individual histologic variables in oligodendroglial neoplasms. Smith *et al.* and Mork *et al.* respectively included in their series mixed oligoastrocytomas composed of less than 50% or less than 25% of tumoural astrocytes. Burger *et al.* did not introduce the percentage of tumoural astrocytes as a criterion of selection, however, they found that 31% of the studied tumours included astrocytic components.

Among multiple criteria, these three studies have both considered mitosis, necrosis and cell density. Whereas for Smith *et al.* none of these criteria were correlated with survival, Mork *et al.* found that both necrosis and cell density were of prognostic significance, and for Burger *et al.* only necrosis was correlated with survival. However, the study of Burger *et al.* included a large proportion of oligodendrogliomas with necrosis (46%), a feature which, in our experience, is infrequent in pure oligodendrogliomas.

A subjective appreciation of cell density as well as differences in mitotic count may explain in part divergences concerning these two criteria. However necrosis is easily observed and was considered as present or absent in both studies.

Using recent data from the literature, Alvord transcribed the reported results concerning the follow-up of patients with astrocytomas, glioblastomas or oligodendrogliomas, into graphic representation. His analysis demonstrated well that necrosis carries a very bad prognosis in astrocytomas, whereas in oligodendrogliomas, necrosis does not necessarily imply a bad prognosis and does not separate the various grades of oligodendrogliomas from each other (Alvord 1992).

It is thus likely that difficulties in differentiating tumoural oligodendrocytes from small anaplastic cells, presumably of astrocytic origin (Alvord 1992) and asymetry in the classification of oligodendrogliomas, with inclusion of a variable proportion of astrocytic components, explain for a large part discordant results concerning the influence of individual features of malignancy, and divergent opinions regarding the usefulness of grading oligodendrogliomas.

In his pertinent editorial, Alvord (1992) also emphasized that the idea that mixed gliomas share the prognosis of their predominant cell type is extremely subjective. Since individual features of malignancy have no intrinsic significance, the actual behaviour of mixed oligoastrocytomas remains unknown. Actually, the literature data concerning mixed oligoastrocytomas are contradictory (for review see Alvord, 1992).

These considerations make it obvious that the study of series of oligodendrogliomas, as "pure" as possible, is an indispensable step if one wants to clarify the situation in the histoprognosis of gliomas.

Application of our grading system for astrocytomas in a series of 81 patients harbouring "pure" oligodendrogliomas, treated at the Mayo Clinic, has demonstrated that the system is unsuitable for grading oligodendrogliomas. Statistical analysis demonstrated that in these neoplasms necrosis is not correlated with survival but that endothelial hyperplasia as well as endothelial proliferation is a powerful prognostic factor in olidodendrogliomas (unpublished data).

In the recent paper of Shaw *et al.* (1992), the fact that our grading of astrocytomas is unsuitable for grading "pure" oligodendrogliomas was however not apparent, because a statistical significance was reached by regrouping low grades (1 and 2) with high grades (3 and 4) tumours.

Taking account of these data, we have conceived a specific grading system for oligodendrogliomas (Daumas-Duport 1992). The system is based on the recognition of nuclear atypia, mitosis, endothelial hyperplaisa and/or endothelial proliferation. The presence or absence of these three criteria

defines three grades as follows: all criteria absent = grade 1, one or two criteria present = grade 2, and three criteria present = grade 3.

In collaboration with the authors of the above mentioned paper, application of this specific system to the same series of 81 patients with "pure" oligodendrogliomas, treated at the Mayo Clinic, demonstrated that grades are highly correlated with patient survival (unpublished data). The reproducibility of the system is however still under study.

Further studies are required in order to evaluate the prognosis of mixed oligoastrocytomas. We beleive that the best way to solve the problem of grading mixed oligoastrocytomas would be to study a series of gliomas containing any proportion of both tumoural oligodendrocytes and astrocytes and to grade these tumours, on the one hand with the system for astrocytomas, and on the other hand with the system for oligodendrogliomas. Then, comparison of the resultant survival curves, with that of astrocytomas and that of pure oligodendrogliomas, would help in determining whether mixed oligoastrocytomas should be graded as astrocytomas or oligodendrocytomas or whether mixed oligoastrocytomas require the elaboration of a specific grading system.

Histological Typing and Grading in Childhood Gliomas

As with adults, children harbouring a "grade 3 or grade 4 glioma" are currently included in aggressive adjuvant therapeutic protocols. The central nervous system of children is however particularly vulnerable. The long term deleterious effects of brain irradiation in children are now well recognized which include mental retardation, hearing loss, nanism, and radiation induced brain tumours (for review see Duffner *et al.* 1991).

The sequelae of chemotherapy protocols used for the treatment of gliomas in children are not yet well documented. There is however, a priori, no reason why these sequelae, such as sterility, should be different from those observed after chemotharapy used for the treatment of other tumours of children. On the other hand, it is demonstrated that additional chemotherapy increases the risks of leucoencephalopathy observed after brain irradiation (Duffner *et al.* 1991). Accurate histoprognosis is thus of paramount importance in order to avoid overtreatment in children harbouring glial neoplasms.

However the spectrum of childhood gliomas differs markedly from that of adults (Becker 1985, Gilles 1985, Rorke *et al.* 1985). Current neglect of this fact creates a high potential for misdiagnosis and inappropriate therapeutic strategies.

Multiples factors combine to create confusion in the assessment of children's gliomas. Under the understandable pressure of clinicians and therapists who need "a grade" for a planning therapy, most of childhood gliomas are currently graded. In fact, only a small proportion of them can be graded: firstly, pilocytic astrocytomas and microcystic cerebellar are the most common types of "pure" astrocytomas encountered in children (Steven *et al.* 1991, Gilles *et al.* 1992) and, on the other hand "pure" oligodendrogliomas are rare among children (for review see Favier *et al.* 1985). Secondly, heterogeneity in cell composition is a characteristic feature of childhood gliomas (Gilles 1985). The real frequency of mixed oligoastrocytomas in children is however difficult to appreciate: current conventional classifications, based on the predominant cell type, and the lack of a suitable scheme for grading mixed gliomas both force mixed tumours into the category of "ordinary astrocytoma". This is very apparent in the literature. Most published series of childhood gliomas either include a small percentage of mixed oligoastrocytomas or do not individualise this histological category. For example, among the large series of 887 children with brain tumours identified in the SEER programme between 1973 and 1980, mixed oligoastrocytomas accounted only for 1% of the neoplasms (Duffner *et al.* 1986).

Invariably, in the literature, survival curves according to grade show better survival in childhood astrocytomas compared with that of adults. This observation has led to the widely admitted conclution that age is a more important prognostic factor than tumour grade (Cohadon *et al.* 1985). If better resistance of the host may play a role, it is highly probable that the bias introduced by misclassification of childhood gliomas, also accounts for the apparently better survival rate of children harbouring astrocytomas. In the series of "pure" ordinary astrocytomas, which we have studied in order to test the validity of our grading system, statistical analysis has demonstrated that grade was a major prognostic factor superseding the effect of age (Daumas-Duport *et al.* 1988).

In addition to the problem of typing ordinary forms of gliomas in children, there is increasing evidence that conventional classifications of gliomas, such as that of the WHO, which have emphasized tumours in adults, are inadequate in a substantial proportion of childhood tumours.

Since the publication of the WHO classification of 1979, new benign tumour entities have been recognized among tumours of children which superficially resemble ordinary gliomas.

"Transependymal benign dorsally exophytic brainstem gliomas", first recognized by Hoffman in 1980, represent a specific group of benign tumours which are still histologically interpreted as astrocytomas. In a further study of the same institution, these surgically curable neoplasms accounted for 22% of the childhood brainstem tumours treated between

1976 and 1985 (Stroink *et al.* 1987). Other topographic variants have been described as "focal midbrain astrocytomas" (Vandertrop *et al.* 1992) or as "intrinsic gliomas of the cervico-medullary junction" (Epstein *et al.* 1987). In a recent studies of 6 cases, May *et al.* (1991) have demonstrated that these tumours are in fact perfectly stable on imaging. Previous inclusion of these benign lesions among ordinary astrocytomas most probably explains the rapid fall in survival within 12 months followed by a plateau effect, that Cohen *et al.* (1986) have observed among their series of children with brain stem gliomas. According to the histological descriptions in data in the literature, we believe that these indolent lesions are likely to be ectopic microcystic cerebellar astrocytomas, and that they may be of dysembryoplastic origin.

Dysembryoplastic Neuroepithelial Tumours (DNETs) are similar to another group of indolent lesions which have been recently identified among supratentorial tumours superficially resembling ordinary astrocytomas or mixed oligoastrocytomas (Daumas-Duport *et al.* 1987). This new tumour entity has been introduced in the revised WHO classification (Kleihues *et al.* 1993a and b). Using the restrictive criteria described in our first publication, the WHO classification will however allow identification of only a small proportion of these highly polymorphic tumours. As a matter of fact, our further studies, have demonstrated that tumours which looks like astrocytomas, oligodendrogliomas or mixed oligo-astrocytomas, even with anaplastic appearance, are in fact a perfectly stable lesion, when the three following criteria are present: 1) cortical topography recognizable on MRI, 2) partial seizures with onset before age 20 years, and 3) no neurological deficit, or stable congenital deficit (such as quadrantanopsia) (Daumas-Duport 1993).

Ignored in the past, these stable lesions are now detected by modern imaging techniques. Their actual frequency is difficult to appreciate since most of these lesions are currently diagnosed as "ordinary gliomas". It is, however, our belief that DNETs are not uncommon among children, and that they may account, at least in part, for the recent increase of the relative frequency of supratentorial gliomas in children (Gills *et al.* 1992). Similar to the profile of survival curves of children with brain stem astrocytomas, the plateau effect observed in published series of supratentorial astrocytomas of children, for example, see the publication of Marchese *et al.* (1990), may be explained by current misdiagnosis of DNETs.

Diagnosis of DNETs and their histological distinction from other ordinary gliomas is of paramount importance in avoiding overtreatment in those children with normal life expectancy. DNETs often show apparent histological features of malignancies, such as nuclear monstrosities or vascular endothelial proliferation. Kinetic markers are of no help in distin-

guishing these lesions from "ordinary gliomas". Actually, we have observed that Ki 67, or MIB labelling index, may reach that observed in high grade astrocytomas. This may be explained by the fact that in these lesions, the coefficient of cell loss is equivalent to that of the tumour growth fraction (Daumas-Duport 1993).

Systematic, blind or subjective histoprognostic evaluation of gliomas in children is no longer defensible for two reasons. In case of doubt concerning the actual behaviour of a childhood glioma, the growth potential of the tumour can be estimated on successive post-operative, or post-biopsy CT or MR imaging. In addition in "ordinary gliomas", adjunctive radio or chemotherapy are only palliative, wheareas the long term deleterious effects of these aggressive treatments in children are well-documented. In individual children, the risks of delaying radio or chemotherapy are thus minor compared to the risks of overtreatment of young patients with, potentially a normal life expectancy.

New data concerning glial neoplasms in children again demonstrates that a correct histological diagnosis requires on the part of pathologists, knowledge of clinical and radiological data, and this information must be integrated into the histological interpretation of any brain tumours.

References

1. Alvord EC Jr (1992) Is necrosis helpful in the grading of gliomas? Editorial opinion. J Neuropathol Exp Neurol 51: 127–132
2. Allegranza A, Girlando S, Arrigoni GL, Veronese S, Mauri FA, Gambacorta M, Pollo B, Dalla Palma P, Barbareschi M (1991) Proliferating cell nuclear antigen expression in central nervous system neoplasms. Virchows Arch 419: 417–423
3. Bailey P, Cushing H (1926) A classification of the tumours of the glioma group on a histogenetic basis with a correlated study of prognosis. Lippincott, Philadelphia
4. Becker LE (1985) An appraisal of the World Health Organization classification of tumours of the central nervous system. Cancer 56: 1858–1864
5. Broders AC (1926) Carcinoma: grading and practical application. Arch Pathol Lab Med 2: 376–381
6. Brucher JM (1989) Grading of brain tumours according to the WHO classification: applicability to clinical medicine. In: Fields WS (ed) Primary brain tumours. A review of histological classification. Springer, Wien New York, pp 181–187
7. Bruner JM (1987) Oligodendroglioma: diagnosis and prognosis. Semin Diagn Pathol 4: 251–261
8. Burger PC, Vogel FS (1976) Surgical pathology of the nervous system and its coverings. Wiley, New York, pp 282–292

9. Burger PC, Vogel FS, Green SB, Strike TA (1985) Glioblastoma multiforme and anaplasic astrocytoma. Cancer 56: 1106–1111
10. Burger PC, Rawlings CE, Cox EB, McLendon RE, Schold SC, Bullard DE (1987) Clinicopathologic correlations in the oligodendroglioma. Cancer 59: 1345–1352
11. Cohadon F, Aouad N, Rougier A, Vital C, Rivel J, Dartigues JF (1985) Histologic and non-histologic factors correlated with survival time in supratentorial astrocytic tumors. J Neurooncol 3: 105–111
12. Cohan ME, Duffner PK, Heffner RR, Lacey DJ, Brecher M (1986) Prognostic factors in brainstem gliomas. Neurology 36: 602–605
13. Daumas-Duport C, Vedrenne C, Szikla G (1979) Contribution of stereotaxic biopsies to the 3D localization of brain tumours, gliomas in particular. In: Szikla G (ed) Stereotaxic cerebral irradiation. INSERM Symposium No 12. Elsevier, North-Holland Biomedical Press, pp 33–41
14. Daumas-Duport C, Monsaingeon V, Szenthe L, Szikla G (1982) Serial stereotaxic biopsies: a double histological code of gliomas according to malignancy and 3D configuration as an aid to therapeutic decision and assessment of results. Appl Neurophysiol 45: 431–437
15. Daumas-Duport C, Monsaingeon V, N'Guyen JP, Missir O, Szikla G (1984) Some correlations between histological and CT aspects of cerebral gliomas contributing to the choice of significant trajectories for stereotaxic biopsies. Acta Neurochir (Wien) 33: 185–194
16. Daumas-Duport C, Monsaingeon V, Blond S, Munari C, Musolino A, Chodkiewicz JP (1986) Serial stereotaxic biopsies and CT-scan in gliomas: correlative study in 100 astrocytomas, oligo-astrocytomas and oligodendrocytomas. J Neurooncol 4: 317–328
17. Daumas-Duport C, Scheithauer BW, Kelly PJ (1987) A histologic and cytologic method for the spatial definition of gliomas. Mayo Clin Proc 62: 545–556
18. Daumas-Duport C, Scheithauer B, O'Fallon J, Kelly P (1988a) Grading of Astrocytomas, a simple and reproducible method. Cancer 62: 2152–2165
19. Daumas-Duport C, Scheithauer BW, Chodkiewicz JP, Laws ER, Vedrenne C (1988b) Dysembryoplastic neuroepithelial tumour: a surgically curable tumour of young patients with intractable partial seizures. Report of thirty-nine cases. Neurosurgery 23: 545–556
20. Daumas-Duport C (1989) A new uniform grading system (using Mayo Clinic material). In: Fields WS (ed) Primary brain tumours. A review of histological classification. Springer, Wien New York, pp 159–170
21. Daumas-Duport C (1992) Histological grading of gliomas. Curr Opin Neurol Neurosurg 5: 924–931
22. Daumas-Duport C (1993) Dysembryoplastic neuroepithelial tumors. Brain Pathol 3: 283–295
23. Davis RL (1989) Grading of gliomas. In: Fields WS (ed) Primary brain tumours. A review of histologic classification. Springer, Wien New York, pp 150–158
24. De Armond SJ, Eng LF, Rubinstein LJ (1980) The application of glial fibrillary acidic protein immunohistochemistry in neurooncology. Pathol Res Pract 168: 374–394

25. Devaux B, O'Fallon JR, Kelly PJ (1993) Resection, biopsy and survival in malignant glial neoplasms: a retrospective study of clinical parameters, therapy and outcome. J Neurosurg 78: 767–775
26. Duffner PK, Cohen ME, Myers MH, Heise HW (1986) Survival of children with brain tumors: SEER program, 1973–1980. Neurology 36: 597–601
27. Duffner PK, Cohen ME (1991) The long-term effects of central nervous therapy on children with brain tumors. In: Brain tumors in children. Neurologic clinics, Vol 9, No 2, pp 480–494
28. Epstein F, McCleary EL (1986) Intrinsic brain-stem tumors of childhood. Surgical indications. J Neurosurg 64: 11–15
29. Favier J, Pizzolato GP, Berney J (1985) Oligodendroglial tumors in childhood. Childs Nerv Syst 1: 33–38
30. French-Constant C, Raff MC (1986) Proliferating bipotential glial progenitor cells in adult rat optic nerve. Nature 319: 499–502
31. Gilles FH (1985) Classification of childhood brain tumors. Cancer 56: 1850–1857
32. Gilles F, Sobel IL, Levitin A, Hedley-Whyte ET, Tavare CJ Adelman L, Sobel RA (1992) Temporal trends among childhood brain tumour biopsies. J Neurooncol 13: 137–149
33. Glantz MJ, Burger PC, Herndon JE, Friedman AH, Cairncross JV, Vick NA, Schold SC (1991) Influence of the type of surgery on the histologic diagnosis in patients with anaplastic gliomas. Neurology 41: 1741–1744
34. Herpers MJHM, Budka H (1984) Glial fibrillary acidic protein (GFAP) in oligodendroglial tumors: gliofibrillary oligodendroglioma and transitional oligoastrocytoma as subtypes of oligodendroglioma. Acta Neuropathol (Berl) 64: 265–272
35. Hirsch JF, Sainte Rose C, Pierre-Kahn A, Pfister A, Hoppe-Hirsch E (1989) Benign astrocytic and oligodendrocytic tumors of the cerebral hemispheres in children. J Neurosurg 70: 568–572
36. Hoffman HJ, Becker L, Craven MA (1980) A clinically and pathologically distinct group of benign brain stem gliomas. Neurosurgery 7: 243–248
37. Hoshino T, Prados M, Wilson CB, Cho KG, Lee KS, Davis RL (1989) Prognostic implications of the bromodeoxyuridine labeling index of human gliomas. J Neurosurg 71: 335–341
38. Hoshino T, Ito S, Asai A, Shibuya M, Prados MD, Dodson BA, Davis RL, Wilson CB (1992) Cell kinetic analysis of human brain tumours by in situ double labelling with Bromodeoxyuridine and Iododeoxyuridine. Int J Cancer 50: 1–5
39. Kelly PJ, Daumas-Duport C, Scheithauer BW, Kall BA, Kispert DB (1987) Stereotaxic histologic correlations of computed tomography and magnetic resonance imaging-defined abnormalities in patients with glial neoplasms. Mayo Clin Proc 62: 450–459
40. Kelly PJ (1991) Tumor stereotaxis. Saunders, Philadelphia, pp 333–338
41. Kernohan JW Mabon RF, Svien HJ, Adson AW (1949) Symposium on a new and simplified concept of gliomas (a simplified classification of gliomas). Mayo Clin Proc 24: 71–75
42. Kernohan JW, Sayre GP (1952) Atlas of tumor pathology: tumors of the

central nervous system. Armed Forces Institute of Pathology, Washington
43. Kim TS, Halliday AL, Hedley-Whyte ET, Convery K (1991) Correlates survival and the Daumas-Duport grading system for astrocytomas. J Neurosurg 74: 27–37
44. Kleihues P, Burger PC, Scheithauer BW (1993a) Histological typing of tumours of the central nervous system. World Health Organization, Geneva
45. Kleihues P, Burger PC, Scheithauer BW (1993) The new WHO classification of brain tumours. Brain Pathol 3: 255–268
46. Kross JM, Van Eden CG, Stefanko SZ, Waayer-Van Batenburg M, Van Der Kwast T (1990) Prognostic implications of glial fibrillary acidic protein containing cell types in oligodendrogliomas. Cancer 66: 1204–1212
47. Labrousse F, Daumas-Duport C, Batorski L, Hoshino T (1991) Histological grading and bromodeoxyuridine labelling index of astrocytomas. Comparative study in a series of 60 cases. J Neurosurg 75: 202–205
48. Leenstra S, Troost D, Westerveld A, Bosch DA, Hulsebos Tjm (1992) Molecular characterisation of areas with low grade tumor of satellitosis in human malignant astrocytomas. Cancer 52: 1568–1572
49. Marchese MJ, Chang CH (1990) Malignant astrocytic gliomas in children. Cancer 65: 2771–2778
50. May PL, Blaser SI, Hoffman HJ, Humphreys RP, Harwoodnash DC (1991) Benign intrinsic tectal "tumours" in children. J Neurosurg 74: 867–871
51. McGirr SJ, Kelly PJ, Scheithauer BW (1987) Stereotactic resection of juvenile pilocytic astrocytomas of the thalamus and basal ganglia. Neurosurgery 20: 447–452
52. Mork SJ, Halvorsen TB, Lindegaard KF, Eide GE (1986) Oligodedroglioma. Histologic evaluation and prognosis. J Neuropathol Exp Neurol 45: 65–78
53. Nakagawa Y, Parentes E, Rubinstein LJ (1986) Immunohistochemical characterization oligodendrogliomas: an analysis of multiple markers. Acta Neuropathol (Berl) 72: 15–22
54. Nelson SJ, Tsukada Y, Schoenfeld D, Fulling K, Lamarche J Peress N (1983) Necrosis as a prognostic criterion in malignant supratentorial, astrocytic gliomas. Cancer 52: 550–554
55. Nowell PC (1976) The clonal evolution of tumor cell populations. Science 194: 23–28
56. Paulus WP, Peiffer J (1989) Intratumoral heterogeneity of gliomas. A quantitative study. Cancer 64: 442–447
57. Raff MC, Miller RH, Noble M (1983) A glial progenitor cell that develops in vitro into an astrocyte or an oligodendrocyte depending on culture medium. Nature 303: 390–396
58. Ringertz J (1950) Grading of gliomas. Acta Pathol Microbiol Scand 27: 51–64
59. Rorke LB, Gilles F, Davis RL, Becker LE (1985) Revision of the World Health Organisation classification of brain tumours for childhood brain tumours. Cancer 56: 1869–1886
60. Roselli R, Iacoangeli M, Scerrati M, Rossi GF (1989) Natural history of neuroepithelial tumours: Contribution of stereotactic biopsy. Acta Neurochir Wien [Suppl] 46: 79–81

61. Rubinstein LJ (1972) Tumors of the central nervous system. In: Atlas of tumor pathology, Series 2, Fasc 6. Armed Forces Institute of Pathology, pp 35–36
62. Russell DS, Rubinstein LJ (1977a) Pathology of tumours of the nervous system, 4th Ed. Edward Arnold, London, pp 146–148
63. Russell DS, Rubinstein LJ (1977b) Pathology of tumours of the nervous system, 4th Ed. Edward Arnold, London, pp 156–163
64. Russell DS, Rubinstein LJ (1989) Pathology of tumours of the nervous system, 5th Ed. Edward Arnold, London, pp 173–177
65. Scerrati M, Rossi GF (1984) The reliability of stereotaxic biopsy. Acta Neurochir (Wien) [Suppl] 33: 210–205
66. Scherer HJ (1940) Cerebral astrocytomas and their derivatives. Am J Cancer 40: 159–197
67. Schröder R, Bien, K, Kott R, Meyers I, Vossing R (1991) The relationship between Ki-67 labelling and mitotic index in gliomas and meningiomas: demonstration of the variability of the intermitotic cycle time. Acta Neuropathol (Berl) 82: 389–394
68. Shaw EG, Sheithauer BW, O'Fallon JR, Tazelaar HD, Davis DH (1992) Oligodendrogliomas: the Mayo Clinic experience. J Neurosurg 76: 428–434
69. Sidransky D, Mikkelsen T, Schwechheimer K, Rosenblum ML, Cavanee W, Vogelstein B (1992) Clonal expansion of p53 mutant cells is associated with brain tumour progression. Nature 355: 846–847
70. Smith MT, Ludwig CL, Godfrey AD, Armbrustmacher VW (1983) Grading of oligodendrogliomas. Cancer 52: 2107–2114
71. Steven McG, Cameron AH, Muir KR, Parkes SE, Reid H, Whitwell H (1991) Descriptive epidemiology of primary central nervous system tumours in children: a population-based study. J Clin Oncol 3: 323–329
72. Stroink AR, Hoffman HJ, Hendrick EB, Humphreys RP, Davidson G (1987) Transependymal benign dorsally exophytic brain stem gliomas in childhood: diagnosis and treatment recommendations. Neurosurgery 20: 439–444
73. Vandertrop WP, Hoffman HJ, Drake JM, Humphreys RP, Rutka JT, Armstrong DC, Becker LE (1992) Focal midbrain tumors in children. Neurosurgery 31: 180–194
74. Virchow R (1864) Die krankhaften Geschwulste. Hirschwald, Berlin
75. Willis RA (1960) Pathology of tumors, 3rd Ed. Butterworth, London, pp 121–122
76. Zülch KJ (1979) Histological typing of tumours of the central nervous system. International histological classification of tumours. World Health Organization, Geneva, pp 21

Brain Protection

F. COHADON

Clinique Universitaire de Neurochirurgie Hôpital Pellegrin Tripode, Bordeaux (France)

With 11 Figures

Contents

I. Introduction: Historical Perspective

The concept of protection has a long history in medicine. The empirical use of cold for example, to attenuate the reactions to and consequences of injuries, particularly of brain injuries, has been acknowledged from the time of the Greeks (Frost 1981, Hoff 1986). The modern concept of brain protection however emerges in the fifties in the particular field of thoracic surgery. Resection of the aortic arch was attempted using temporary shunts and hypothermia (Cooley 1955) and later, circulatory arrest under extracorporeal circulation (De Bakey 1957) and deep hypothermia (Niazi and Lewis 1958). In these pioneering works as well as in subsequent developments in our own neurosurgical field (Rosomoff 1959, Drake 1964), protection means prevention and mitigation of a foreseeable ischemic insult (Fig. 1a) highly likely to occur in given circumstances. Brain protection associates on the one hand hemodynamic manipulations to avoid ischemia and, on the other hand, various pharmacological or physical methods aimed at reducing the metabolic demand to limit the consequences of ischemia if eventually it is in part unavoidable. In this first period of its development brain protection is based on hypometabolism, it is essentially an intraoperative procedure and it is inseparable from other anesthetic and resuscitation techniques. In fact it marks the beginning of modern neuroreanimation around hemodynamic and metabolic preoccupations (Campan 1981).

From this initial concept brain protection has been considerably extended both in its field of application and in its therapeutic aims. It has been applied to different types of ischemic or anoxic ischemic disorders occurring in a wide variety of conditions from stroke, the encephalopathy of near-drowning. It has been also appropriately extended to traumatic

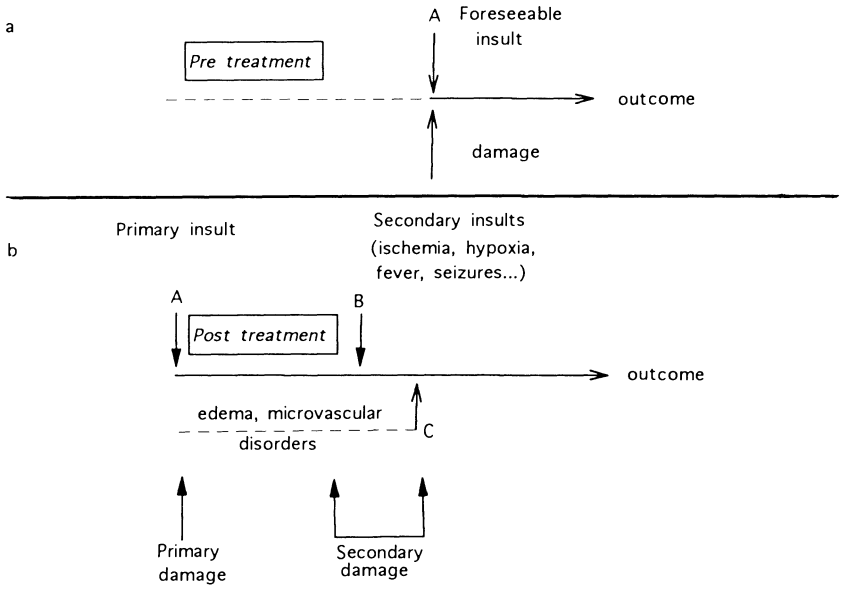


Fig. 1. Brain protection as a pretreatment of a forseeable insult by post treatment of primary insult/pretreatment of secondary insult an secondary damage

brain injuries because in most cases of severe trauma ischemia from various mechanisms plays a major role.

Moreover the concept of brain protection has shifted from its original etymological meaning which supposes measures taken before the insult (*pretreatment*) to a larger concept which comprises therapy given after the insult (*post treatment*) for prevention of secondary disorders (Fig. 1b). The notion that secondary disorders do occur following an initial brain insult and that they may cause secondary damage with a definite bearing on outcome was shaped in the seventies and is now largely accepted. A considerable amount of experimental research has been devoted to the understanding of pathophysiological events triggered by each type of brain insult and responsible for secondary damage. The unravelling of these complicated processes at the molecular level has allowed us to recognize that, despite differences in time course and sequences, all types of acute brain insult have in common a limited number of destructive biochemical cascade reactions (Siesjö 1981). Emphasis has been put on the fact that these reactions are progressive or at least that they may involve brain tissue progressively via vicious circle and feed-forward processes. The concept that brain tissue destruction is not a simple event entirely accomplished at the time of insult but rather an ongoing and gradual phenomenon has given a considerable thrust to therapeutic research. Each step of each pathophysiological chain

of events identified at the molecular level has been the target of pharmacological attempts. Many molecules have been tried with promising results in animal models. The current concept of brain protection is based on the assumption that part of the progressive tissue destruction following an insult would be preventable by drugs.

The literature devoted to brain protection in the last fifteen years is extensive with a number of books, meeting reports and many review articles, most of the time centered on one or another aspect of the problem. There is little excuse for contributing one more such review. Our aim has been to put together and articulate the many topics relevant to brain protection with the intention of giving to neurosurgeons a concise overview and a manageable list of references on each of them.

The first section summarises the basic features of ischemic/metabolic stress and outlines the main aspects of secondary damage in acute brain insults. The second section, based mainly on experimental research data, describes the basic physiopathological mechanisms leading to tissue alteration and disruption, together with the corresponding protective measures which have been proposed to counter them. The third section considers some clinical situations of acute brain insult and the actual results of protective strategies currently applied.

II. Pathophysiology of Brain Insults

This chapter does not intend to give an in depth description of the pathophysiology of brain insult. Our aim is only to identify some pathophysiological situations and recall a number of relevant notions in order to set the stage for a discussion of brain protection.

1. Aspects of Brain Ischemia

Energy Production in the Normal Brain (see Siesjö 1978 for a general study, also Astrup 1982)

The ultimate object of respiratory and circulatory function is to provide brain cells with the amount of O_2 and glucose which covers their energy requirements for both functional needs and structural maintenance. The O_2 availability at the cell level is the end point parameter of these processes. According to the simplified equation.

$$\text{Available oxygen} = \text{CBF} \times \text{Hb} \times \text{SO}_2/100.$$

The amount of available O_2 depends on: the cerebral blood flow (CBF), the haemoglobin concentration (Hb) and the O_2 saturation of the blood $SO_2/100$ which in turn is directly related to pO_2. The Oxygen-haemoglobin dissociation curve which links SO_2 and pO_2 is influenced by both temperature and pH. In normal conditions, SO_2 and Hb are stable and O_2 is supplied to the brain in excess of its needs. There is a tight coupling between CBF and the level of functional activity in a given area. This coupling is directly regulated by local metabolism. In cells with intact machinery, the available oxygen and/or glucose determines the amount of ATP produced by oxydative phosphorylation in the mitochondria and hence the level of functional activity.

$$1 \text{ glucose} + 6O_2 + 38ADP + 38Pi \rightarrow 6CO_2 + 6H_2O + 38ATP.$$

The cerebral mean rate of O_2 consumption (CMR O_2) deduced from blood flow and arteriovenous differences is rather independent of the usual functional activity. It is much increased in case of seizures and it is lowered by anaesthesia (Kety 1950). Moreover it is strictly dependent on temperature and considerably decreased in hypothermia (Hagerdal 1975). In the case of complete sudden ischemia the disappearance of substrates, glycogen or glucose, and high energy compounds, ATP and phosphocreatine is complete within 2 minutes (Lowry *et al.* 1964).

Thresholds and Duration of Ischemia

In ischemic hypoxic conditions available oxygen being reduced, alterations of function swiftly occurs and can be evidenced by electrophysiological recordings. The critical CBF threshold for electrical failure in the cerebral cortex is fairly constant in all studied species (Astrup *et al.* 1981) and in man around 16 → 18 ml/100 g/mn. At this level ATP concentration remain close to normal. With further reduction of flow, energy stores are progressively decreased. At a threshold of around 8–12 ml/100 g/mn, ions pumping is stopped, cells are depolarized and the destructive reactions leading to structural alterations are triggered (Astrup *et al.* 1981).

The identification of 2 distinct thresholds for functional impairment and for the initiation of structural damage has marked an essential progress in our thinking. However it soon appeared that not only the absolute level of flow but also the duration of low flow is important to determine the irreversibility of damage (Heiss and Rosner 1983, Kaplan *et al.* 1991). Heiss and Rosner established in cats that critical for the survival of neurons is residual flow below 5 ml/100 g/mn for more than 20 minutes, or below 8 ml/100 g/mn for more than 30 minutes, or below 14 ml/100 g/mn for more

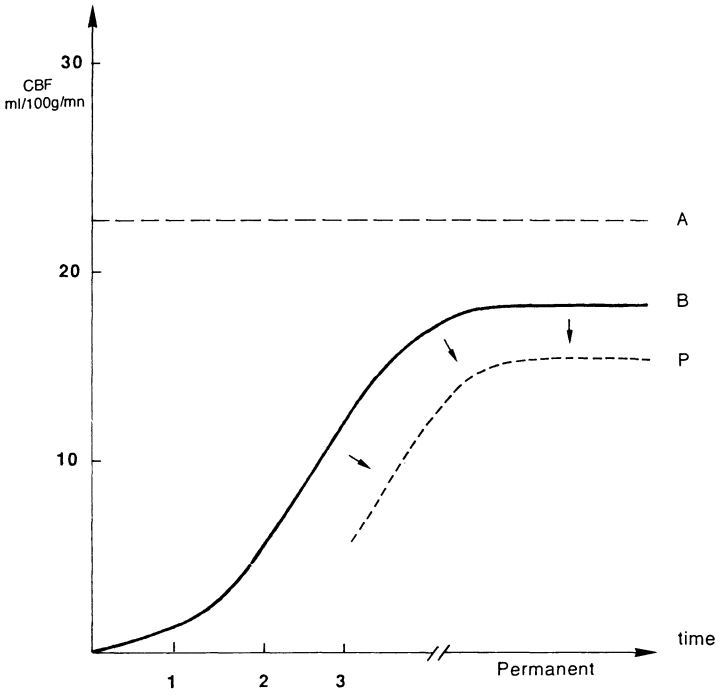


Fig. 2. Thresholds in brain ischemia: *A* threshold for functional impairment, *B* threshold for cell destruction: infarction Cafter Jones 1981), *P* possible effect of brain protection

than 45 minutes. A flow at around 18 ml/100 g/mn would be tolerated indefinitely (Heiss and Rosner 1983). Jones *et al.* assessed the brain tolerance to MCA occlusion in monkeys: even profound ischemia can be tolerated for a brief time. With a CBF around 8–12 ml/100 g/mn infarction follows within 2–3 hours. In permanent occlusion of the MCA infarction is associated with a residual flow below 18 ml/100 g/mn. Jones has proposed a diagrammatic representation of the notion of infarction threshold related to both intensity and duration of ischemia (Fig. 2) (Jones *et al.* 1981).

Global Ischemia and Delayed Neuronal Death

Global ischemia has been extensively studied in a number of animal models and corresponds to clinical situations like cardiac arrest or near drowning. The extent of damage depends only on the duration of CBF interruption. After some time gross complete infarction is constantly observed (Myers

and Yamaguchi 1977). However even in cases in which rapid restoration of flow has been obtained, that is after a brief transient period of ischemia, some damage to neurons does occur with 2 characteristic features: first the distribution of damage is non-vascular, neurons are damaged according to their so-called *selective vulnerability* (review in Collins *et al.*). Vulnerability is related to the connection pattern and membrane arrangement of particular neurons located in specific regions like the CA_1 area in the hippocampus (Simon 1984, review in Schmidt-Kastner *et al.* 1991). Second, histological evidence of damage is observed only after hours or days (Pulsinelli *et al.* 1982). Ito described this phenomenon as *maturation of ischemic injury* and describe a direct relationship between the intensity and duration of ischemia and the rate of maturation of corresponding damage (Ito *et al.* 1975, update in Ito *et al.* 1990). The essential feature of maturation is the fact that the death of vulnerable neurons is delayed (Kirino 1982, Araki 1989) which may suggest that for some time these cells are perhaps salvageable. "Maturation phenomena should be considered as a bidirectional process leading either to cell death or recovery" (Ito and Klatzo in Ito *et al.* 1990).

Focal Isçhemia and the "Penumbra" Zone

Focal ischemia has been mainly studied using the MCA occlusion model in a large variety of species and mimics a common type of stroke in man (review in Siesjö 1992 a and b). In the case of complete occlusion the extent and type of alteration depends on the collateral circulation. Around a densely ischemic center with flow under 10 ml/100 g/mn a ring of tissue with flow between 18 ml/100 g/mn and 10 ml/100 g/mn has been defined as the "penumbra" (Astrup *et al.* 1981). In the penumbra cells are functionally silent but alive. According to local flow changes this ring of tissue would either be included in the infarcted central core or recover normal function. This rather unstable condition may persist for a prolonged period of time (Symon *et al.* 1975).

Many experimental studies have confirmed the reality of penumbral phenomena around ischemic lesions. In cats the ischemic penumbra can be defined functionally by suppression of EEG amplitude and maintenance of steady state extracellular K^+ activity, that is a normal ions homeostasis, there is no edema and no major histopathological change (Strong *et al.* 1983a, b). In man PET scan studies in stroke have detected around an area of dense ischemia a region of *misery perfusion* (Baron 1981) with blood flow inadequate relative to the metabolic demand. A large number of PET scan observations (Baron 1987, review in Heiss 1992) confirms the existence in most cases of viable tissue with low perfusion in the border zone of ischemia,

this condition may persist for several days (Baron 1987). This rim of tissue should be potentially salvageable. However until now we have to admit that in the most available data, this area eventually becomes necrotic. Only border areas with from the outset, normal or hyper-perfusion are able to recover (Heiss *et al.* 1992).

2. *Secondary Brain Damage*

The concept of *secondary damage* (update in Baethmann *et al.* 1993) means that, following primary damage caused by an initial insult, secondary processes may arise and be responsible for further destruction of tissue and worsening of outcome. Secondary damage being delayed would be potentially preventable and it would be possible to provide a pretreatment during the *time window* that takes place between the primary insult and the development of further disorders. Assuredly the related notions of "secondary damage" and "time window for treatment" have opened great hopes in the, as yet, rather unrewarding domain of stroke and trauma therapy and is central to our present understanding of brain protection. The concept of the time window is self-explanatory. The concept of secondary damage is more complex, it includes 2 distinct sets of disorders: first a worsening of primary lesions may take place from local and also systemic causes, second the brain may suffer secondary insults (Fig. 3).

Evolution of the Primary Insult

The concepts of maturation and delayed neuronal death are derived from global ischemia studies and are time related. The concept of flow threshold

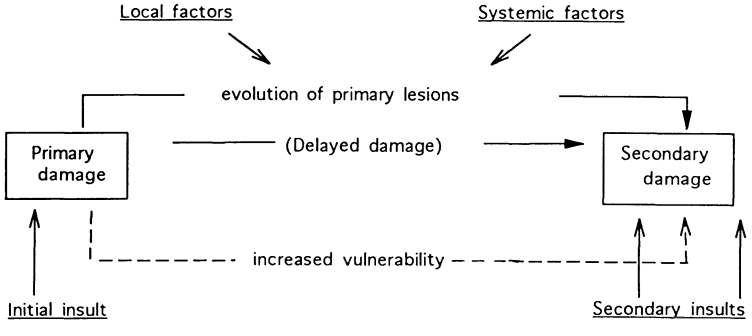


Fig. 3. Primary versus secondary damage

and penumbral zone are derived from focal ischemia studies and are space related. These concepts, though distinct, are closely linked and complementary. Originally associated with the pathophysiology of ischemia they can be applied to the pathophysiology of trauma as well (Stratham *et al.* 1989). The delayed type of neuronal lesion has been identified in an experimental model of axonal injury (Povlishock 1992). The area of unstable hemodynamic conditions around traumatic lesions can be described as a "traumatic penumbra". This implies that whatever the type of ischemic or traumatic injury following the initial insult, with possibly its immediate irreversible consequences, there is a portion of brain tissue in which cells are sick, silent, but not dead. This portion of brain tissue is at risk and it has been a constant aim of physiopathological research to identify the mechanisms which can precipitate its complete destruction (update in Bazan *et al.* 1992). These mechanisms are triggered locally and may be considerably worsened by systemic disorders. Locally the initial breakdown of energy or the mechanical disruption of tissue sets off a number of biochemical chain reactions destroying molecular structures and liberating toxic mediators. Globally these reactions are responsible for brain edema and disorders of microcirculation. Some of these mechanisms are diagrammatically represented in Fig. 4. The main fact is the vicious circle closed between microcirculatory disorders and edema with generation of local tissue pressure gradients, this being much aggravated in the case of recirculation. Systemic disturbances on the other hand may considerably increase local metabolic stress. Even slight variations in blood pressure, intrathoracic pressures, pO_2,

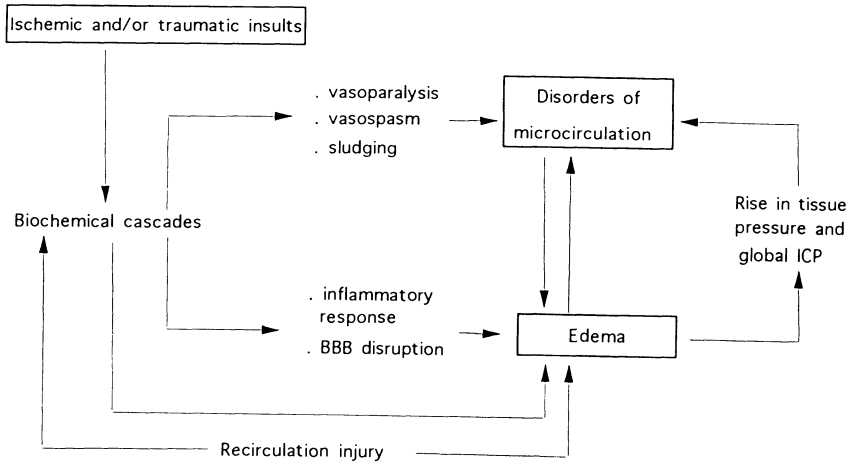


Fig. 4. Some mechanisms involved in the pathophysiology of secondary damage

pCO_2 or, serum osmolarity have a direct impact on metabolic conditions at the level of injured tissue.

Secondary Insults

Any circumstances that impose on the already damaged tissue, a new metabolic stress may be defined as secondary insult. In the circumstances of brain trauma, early anoxic-ischemic episodes are very common. In hours and days following all type of brain insult, hyperthermia from various mechanisms is frequent, seizures may be observed. Secondary insults are all the more dangerous as, following an initial blow, there is an *increased vulnerability* of tissue to similar or other types of aggression. Experimental protocols designed to mimic the succession of two major brain insults have consistently shown that a first insult increases the vulnerability of brain tissue towards a secondary insult. As a model for the frequently observed situation in trauma, Jenkins *et al.* produce a mild mechanical injury followed one hour later by forebrain ischemia. Ischemic lesions are much enhanced as compared to the same model without previous trauma (Jenkins *et al.* 1989). In order to model subarachnoid haemorrhage (SAH) events, Valtysson *et al.* create in rats a sudden transient elevation of ICP (to mimic the effect of initial outburst of blood in SAH) followed 2.5 hours later by an occlusion of MCA (to mimic the vasospasm in SAH). The area of infarction thus produced is larger that the standard one after MCA occlusion without previous ICP elevation (Valtysson *et al.* 1992). The mechanisms of increased vulnerability are not clear. Vascular events affecting autoregulation and microvascular perfusion may be involved in some circumstances. In the common case of a combination of mechanical and ischemic-hypoxic insults it has been shown that trauma induces long lasting disturbances of energy metabolism which simply lower the threshold of energy failure. Pathological agonist-receptor interactions might be another mechanism of damage which could act in addition in successive injuries (Nilsson *et al.* 1990).

3. Ischemic and Traumatic Brain Insults: Common Mechanisms

One important notion in physiopathological research over the last 20 years is that the main mechanisms of damage are basically the same in ischemic and in traumatic injuries. First, ischemia itself is widely recognized as the main cause of secondary aggravation of all types of severe head injuries (Graham *et al.* 1978, Graham *et al.* 1989). The global type of ischemic hypoxic condition is very often observed in trauma due to systemic associated

injuries and/or respiratory disorders inherent in comatose states. The global type of brain ischemia can also result from elevated intracranial pressure. The focal type of ischemia is common around expansive lesions creating local tissues pressure gradients. Second, the penumbral conditions in ischemia and in focal trauma are similar. In ischemia the failure of energy triggers biochemical reactions that produce, around the central core, edema formation and alterations of microcirculation which secondarily extend the lesion. In trauma the disruption of tissue directly produces biochemical disorders resulting in similar edema and similar microcirculatory disturbances leading to secondary perifocal ischemia and further enlargement of lesion.

In fact at the molecular level, the mechanisms of destruction are basically the same even though they may operate in different sequences and with different time course and intensity in various situations of ischemia and/or trauma. Since these mechanisms are the very target of brain protection, they will be considered in some detail in the next chapter.

III. Mechanisms of Damage and Related Protection

A general scheme of the pathophysiology of brain insult is given in Fig. 5. In ischemia the first essential and primary mechanism of damage is the *failure of energy*. As already seen at a threshold of 8–12 ml/100 g/mm, as a direct effect of ATP depletion, ion pumping stops. There is a massive efflux of K^+ from the cell and membranes are depolarised (review in Astrup 1982).

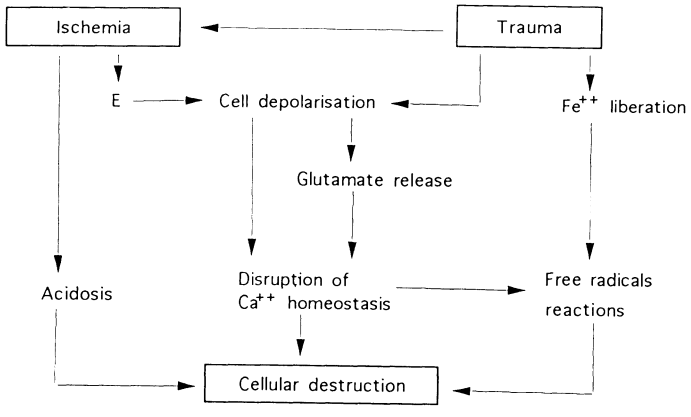


Fig. 5. Common mechanisms of cellular destruction in ischemia and trauma

The rise of extracellular K^+ concentration is accompanied by an increase in extracellular glutamate which has been shown to originate in part from the transmitter pools in glutamatergic neurons (Drejer *et al.* 1985, Benveniste *et al.* 1984). Very similar sequence of events has been described in trauma. A number of trauma models produce a compressive type of ischemia. However even in the absence of compression, cell depolarisation, massive efflux of K^+ and of glutamate are well documented following mechanical disruption of tissue (Takahashi *et al.* 1981, Katayama *et al.* 1990, Baethman *et al.* 1989, Nilsson *et al.* 1990, Persson 1992). A sudden intense neuronal discharge at the time of trauma is likely to be the initial event liberating K^+ and initiating a positive feed back loop between K^+ and glutamate liberation (Katayama *et al.* 1990). The role of immediate or rapidly occurring disturbances of local blood flow with energy disorders is seemingly also important (Nilsson *et al.* 1990).

Thus energy failure, membrane depolarisation, K^+ efflux and glutamate release appear as the first set of events triggered by brain insult. The next step is a *disruption of* Ca^{++} *homeostasis* which immediately follows energy failure. A sudden rise of intracellular Ca^{++} occurs, either directly caused by depolarisation or indirectly, by glutamate mediated mechanisms. Ca^{++} in excess activates a number of enzymatic reactions which eventually destroy cell structures. This seems to be the first major mechanism which mediates cellular damage.

The outburst of highly destructive *free radical mediated peroxydation* is the second major mechanism of damage. Peroxydative stress appears in ischemia as a downstream consequence of Ca^{++} disorders. In trauma the same reactions can also be directly activated by the presence of ferrous iron. In ischemic conditions if some glucose is still available the cells shift to the anaerobic glycolytic pathway. This reaction with a poor yield of ATP produces lactic acid and consequently leads to acidosis. *Acidosis* stands as the 3rd major mechanism of tissular disruption. This chapter will consider the physiopathological mechanisms and corresponding protective measures concerning first the failure of energy, second the three successive mechanisms of cellular destruction namely Ca^{++} disorders, free radicals reactions and acidosis.

1. Energy Failure and Metabolic Protection

The physiology of energy production and physiopathology of ischemia has been dealt with in the preceding section. Against energy failure we have 2 lines of protection which aim at maintaining a sufficient level of available O_2 and energy production at the cellular level: hemodynamic and metabolic.

Hemodynamic protection comprises shunting procedures during surgery and, in a number of clinical circumstances attempts at restoring circulation or at improving its efficiency via manipulations of blood pressure, vasoreactivity and blood rhelogy. Quite arbitrary, hemodynamic manipulations and treatments are not traditionally included in the domain of brain protection and will not be covered in the present review. The alternative strategy is to reduce the needs by lowering $CMRO_2$. The only way to reduce functional requirements is to depress the function itself. This is metabolic protection which includes manipulations of brain temperature and the use of CNS depressants, barbiturates and similar drugs.

Barbiturates and Similar Drugs

Barbiturates provoke a dose dependent depression of neuronal function and hence a parallel reduction of O_2 and glucose requirements. Increasing doses of thiopental or pentobarbital progressively reduce brain activity down to an isoelectric electroencephalogram at which level $CMRO_2$ is lowered by 50%. Cerebral blood flow is also considerably reduced, however this does not lead to ischemia since the decrease in $CMRO_2$ is more profound than the decrease in CBF. The reduction of CBF is accompanied by a concomitant reduction in CBV and consequently one of the major beneficial effect of barbiturates is a reduction of ICP level (Shapiro 1973). The vasoconstriction induced by barbiturates concerns the normal brain capillary bed and not the microvasculature more or less altered by acidosis in ischemic brain areas, thus an inverse steal phenomenon occurs which could improve the overall circulatory condition (Kofke 1979). Another beneficial side effect of barbiturates is the reduction in the formation of brain edema of vasogenic (Clasen 1974) as well as ischemic type (Simeone *et al.* 1979, Lawner *et al.* 1979). The protective effect of barbiturates seem to be either directly related to the reduction of metabolic demand or indirectly to the vascular consequences of this reduction. However another mechanism of protection has been postulated: in vitro studies (Demopoulos *et al.* 1977, Flamm *et al.* 1980, Smith *et al.* 1980) have shown that barbiturates particularly thiopental (Smith *et al.* 1974–1980) are potent free radical scavengers.

In the middle seventies a large number of experimental studies considering a protective effect of barbiturates on various models of brain ischemia were published with mostly positive results. For example, in focal ischemia following MCA occlusion in monkey, dogs, cats, barbiturates were shown to reduce neurological morbidity as well as infarct size (Hoff 1975, Smith *et al.* 1974, Selman *et al.* 1981). Similar results were obtained in various models of global ischemia (Wright *et al.* 1964, Yatsu *et al.* 1972, Bleyaert *et al.*

1978). Though some of these studies can be and have been criticized, at that time the overall impression from laboratory investigations was clearly encouraging and many clinical applications, using various modalities of barbiturate treatment, were proposed in the early eighties. First reports were positive and sometimes enthusiastic. In aneurysm surgery (Hoff *et al.* 1977, Rockoff *et al.* 1979), cardiopulmonary bypass (Nussmeier *et al.* 1986), in survivors from cardiac arrest (Breivik *et al.* 1979), near-drowning syndrome (Conn *et al.* 1980), Reye's syndrome (Marshall 1978) and severe brain trauma (Rockoff 1979; Marshall *et al.* 1979). However it soon became clear that the use of barbiturates in the clinical setting, even by experienced doctors with appropriate monitoring facilities, is a high risk therapy owing mainly to the hemodynamic effects of these drugs. Several well done clinical trials were undertaken and failed to demonstrate a protective action or any beneficial effect of barbiturate treatment in prevention of cerebral complications of cardiac surgery (Scheller 1992), encephalopathy following cardiac arrest (Nesour 1986) and severe brain trauma (Schwartz *et al.* 1984, Ward *et al.* 1985).

If the protective action of barbiturates is related to the reduction of metabolic rate and blood flow, other anesthetic drugs with similar effects should have comparable protective action. Gammahydroxybutyric acid has been in used for many years as a central neuronal depressant (Laborit *et al.* 1961, Bralet *et al.* 1979, Escuret *et al.* 1977), very few studies have been published either experimental (Baumann *et al.* 1982) or clinical (Strong 1984). Etomidate is a carboxylated imidazol which depresses cerebral metabolism in the same proportion as barbiturates but is devoid of cardiovascular toxicity (review in Batjer 1993). Extensive experimental studies in dogs have shown that Etomidate mediates independently a reduction of CBF and a progressive metabolic suppression, $CMRO_2$ falling to 48% of baseline values. During induced hypotension Etomidate entirely protects the fall of ATP (Milde *et al.* 1985–1986). Studies in a model of incomplete forebrain ischemia in rats suggest that Etomidate protection might be effective in cases of CBF reduction of intermediate severity (Watson *et al.* 1992). Clinical experience with Etomidate extends over some time (Renou 1978); its use as a brain protective agent in aneurysm surgery has been advocated (Tulleken 1982), its value and its safety recently re-emphasized (Batjer 1993).

Hypothermia

Anecdotal observations on the beneficial effect of cold on pain and injuries date back for many years. As early as 1939 Fay, a neurosurgeon and a great

believer in cold, tried cooling to treat severe head injuries (Fay 1943), and cancer patients as well. Laborit and Huguenard explored the possibilities of "artificial hibernation" a procedure in which a pharmacological blockade of the autonomic system is supposed to potentiate hypothermia and at the same time prevent adverse reactions to cold like shivering or vasoconstriction (Laborit and Huguenard 1951).

At that time, a number of experimental studies by Rosomoff *et al.* clearly established that hypothermia induces a reduction of CBF and $CMRO_2$. CBF decreases by 6.7% per degree between 35° and 25°, brain volume and intracranial pressure are similarly reduced. The protective value of hypothermia was assessed by the same group in permanent MCA occlusion and in experimental trauma in dogs (Rosomoff *et al.* 1954–1959). These very positive experimental findings prompted various clinical applications and deep hypothermia (24°–30 °C) was used particularly in the surgery of intracranial aneurysms (Drake *et al.* 1964), the treatment of severe head injuries (Lazorthes and Campan 1958) and cardiac arrest (Benson 1959). However the development of deep hypothermia as a routine intensive care procedure was hampered by the high incidence and severity of complications.

More recently interest has focused on the potential protective value of mild hypothermia in the range 32°–35°. The protective effect of a small decrease in brain temperature has been investigated in a number of experimental studies. Busto *et al.* using a 4 vessel occlusion model in the rat convincingly shown that the degree of brain damage strictly paralleled the brain temperature during ischemia and that a decrease of 2 °C is sufficient to provide marked protection (Busto *et al.* 1987, 1989a, 1989b, review in Ginsberg *et al.* 1992). Minamisawa *et al.* in a 2 vessel occlusion model producing forebrain ischemia for various periods of time in rats demonstrates that lowering the brain temperature to 35 °C is sufficient to protect forebrain regions which are constantly affected at 37 °C (Minamisawa *et al.* 1990a, b). Recently similar protection has been obtained in dogs following prolonged cardiac arrest (Sterz *et al.* 1991, Leonov *et al.* 1990). As we will see later clinical studies on mild hypothermia are just beginning and look promising in brain trauma (Marion *et al.* 1993, Shiozaki *et al.* 1993).

The mechanisms of the beneficial effect of hypothermia are incompletely elucidated. Besides the lowering of ICP which is clearly related to CBF changes, the protective action in ischemic conditions is probably multifactorial. Hypothermia may delay ATP depletion, reduce acidosis and help recovery of energy charge at recirculation. A global inhibition of neurotransmitter traffic is observed and it has been shown that the release of glutamate and Dopamine is markedly reduced (review in Ginsberg *et al.* 1992). These changes could reflect subtle modification induced by hypo-

thermia in the physical structure of cellular membranes (Williams *et al.* 1984).

Hypothermia may well have a future in brain protection. At all events the direct influence of brain temperature on $CMRO_2$ should always be kept in mind: clearly hyperthermia potentializes metabolic stress and is additive to ischemic injury (Dietrich *et al.* 1990), metabolic protection begins with measures against hyperthermia.

2. *Ca^{++} Damage, Excitotoxic Mechanisms and Related Therapies*

A persistent increase in cytosolic concentration of free Ca^{++} initiates a series of metabolic processes which globally have a lethal effect on the cell. This effect was recognized as early as 1967 in the myocardial cell and later in the hepatocyte. In the central nervous system such mechanism was considered a final common pathway for cell death in many physiopathological situations and a full theory of calcium damage, or *calcitoxicity* has been progressively developed (Farber 1981, Hass 1981, Siesjö 1981, Raichle 1983, Siesjö and Wieloch 1985, Cheung *et al.* 1986).

Ca^{++} can enter the cell via two types of specific channels: those opened by membrane depolarisation (voltage operated channels: VOCs) (review in Campbell *et al.* 1985) and those opened by the action of a specific ligand on a receptor coupled to the canal itself (Receptor Operated Channels: ROCs) (review in Tsumoto 1990). Initially calcitoxic theory proposed that in case of energy failure (anoxia, ischemia and/or trauma...), the cellular membrane being depolarized, Ca^{++} in excess enters the cytosol via VOCs (Siesjö 1981). Later on in the same pathological field, emphasis was placed on the role of excitatory aminoacid (EAA) particularly glutamate: the receptors that operate Ca^{++} channels (ROCs) are bound by glutamate (and/or aspartate) and in case of trauma or ischemia, an excess of glutamate would be responsible for abnormal Ca^{++} entry. This new hypothesis met the concept of *excitotoxicity* – toxic effect of an excess of excitation – proposed by Olney some years before (Olney *et al.* 1971). A new "excitotoxic theory" was thus developed (Chöi 1987, 1988a, Siesjö and Bengstrom 1989). There is no contradiction between calcitoxic and excitotoxic theories of brain damage. In both Ca^{++} overload is ultimately responsible for cell damage and that is the pivotal concept. However calcitoxicity may concern all cells, excitotoxicity only concerns cells equipped with EAA. ROCs, that is essentially neurons. In the early eighties experimental research and thinking was centred on the consequences of Ca^{++} overload and the biochemical cascades of destruction triggered by Ca^{++} entry. Since 1988 however speculations and efforts are centred rather on one, allegedly the main, cause

of Ca^{++} overload, namely the excess of extracellular EAA concentration and the interaction between EAA and their specific receptors.

Mechanism of Ca^{++} Increased Cytosolic Concentrations

Comprehensive reviews of the role of calcium in cell biology are available (Borle 1981, Carafoli 1987). Ca^{++} is an essential intracellular second messenger and that function requires a strict control of its cytosolic concentration at a very low level. When channels are open, Ca^{++} enters the cell down a steep concentration gradient and, after binding specific cytosolic proteins, particularly Calmoduline, it can activate a number of enzymes within the cytosol. Afterwards it should disappear immediately, otherwise enzymatic activation would persist. For that purpose, Ca^{++} is either stored in intracellular organelles, mainly mitochondria and endoplasmic reticulum, or is extruded through an ATP dependent Ca^{++} pump or through a Ca^{++}/Na^{+} exchanger. Ca^{++} becomes toxic whenever the cytosolic concentration is elevated beyond the capacity of control of the cell. This may happen either from massive entry or from impairment of storing and/or extrusion mechanisms. In pathological circumstances, excess of entry and deficiency of control mechanisms are probably always associated: all those mechanisms are directly (mitochondria, Ca^{++} pump) or indirectly (Ca^{++}/Na^{+} exchanger) ATP dependent and run out of energy in case of ischemia or similar situations (Siesjö 1981).

According to the excitotoxic concept (review in Meldrum *et al.* 1985, Olney 1989, Rothman and Olney 1986, Schwarcz 1989) a rise in the EAA concentration is the main cause of Ca^{++} entry via specific Glutamate operated Ca^{++} channels. Indeed extracellular glutamate concentration is elevated in pathological situations (Meldrum *et al.* 1985, Meyer 1989, Rothman 1992). Glutamate is multiplied by a factor of 8 in the hippocampus of the rat after 10 mn of vascular arrest (Benveniste *et al.* 1984) and by a factor of 100 in the rabbit after 30 mn (Hagberg *et al.* 1985). There are 2 main causes for this rise in extracellular glutamate concentration in such conditions: first the depolarisation and the rise of extracellular K^{+} enhance the liberation of glutamate from pre synaptic neurons, second the normal reuptake of glutamate by glial cells along a high affinity transport system is impaired and may even be reversed (Nichols and Attwell 1990) in the absence of energy (Benveniste *et al.* 1984, Drejer *et al.* 1985).

Glutamate receptors: The immediate consequence of extracellular glutamate elevation is an enhanced stimulation of post synaptic receptors. Considerable efforts have been devoted to the pharmacological identification and functional characterisation of these receptors. Different types are

currently described (review in Monaghan *et al.* 1989) and for each of them molecular cloning has revealed several isoforms (Shaw 1993, Nakanishi 1992). We have to look at these receptors in some detail (Figs. 6, 7, and 8). One complex includes ionotropic receptors: the N-methyl-D-aspartate receptor (NMDA), the quisqualate or alpha-amino-3-hydroxy-3-methyl-4-isoxasol (AMPA) receptor and the Kainate receptor. The NMDA receptor complex comprises a number of modulatory sites. Another glutamate receptor, the metabotrophic receptor has a completely different mode of action: it activates phospholipase C and this enzyme splits particular membranal phospholipids into diacylglycerol (DAG) and inositol triphosphate (IP3). IP3 behaves as an intracellular messenger liberating Ca^{++} stored in the endoplasmic reticulum, which directly enters the cytosol (Berridge 1984).

Mechanism of excitotoxicity: In pathological conditions with an abnormally high extracellular glutamate concentration, the ionic fluxes triggered by the abnormal activation of these receptors associate 2 components (Rothman and Olney 1986, Choi 1987, Choi 1988a) one is an immediate entry of Na^+ via the Quisqualate Kainate receptor associated channel, accompanied by Cl^- and water, which creates sudden intracellular edema and can kill neurons very rapidly (after 30 mm of exposure to toxic glutamate doses). This Na^+ influx depolarises the cell membrane, can open VOCs and probably reverse the Na^+/Ca^{++} transport (Choi 1988b). The second component is an entry of Ca^{++} via the NMDA receptor associated channel which is a slower process (Choi 1987, Olney 1989), and would be responsible for a delayed type of neuronal death.

According to this scheme, in the presence of an excess of glutamate many sources may contribute to Ca^{++} entry: VOCs, NMDA and non-NMDA receptor associated channels, metabotrophic receptor activation and reversal of Na^{++}/Ca^{++} transport. However the intricacies of these mechanisms are not completely unravelled. For example the influx of Ca^{++} via NMDA associated channel has been shown to mobilize high amount of Ca^{++} from intracellular stores, thus opening a feed-forward mechanism (Frandsen and Shousboe 1992, Lei *et al.* 1992). Inversely in some experiments the activation of the metabotropic receptor has led to an attenuation of NMDA mediated neurotoxic effects (Koh *et al.* 1991).

Moreover the respective part played by Ca^{++} regulatory systems is presumably different in various pathological situations according to a number of local parameters, particularly membrane polarisation and pH. For example it has been speculated that membrane depolarisation triggered by brain insult could relieve the Mg^{++} block of the NMDA gated channel. Other metabolic factors may contribute to enhance excitotoxic mechanisms. The metabolism of Polyamines is greatly exaggerated in ischemia via an

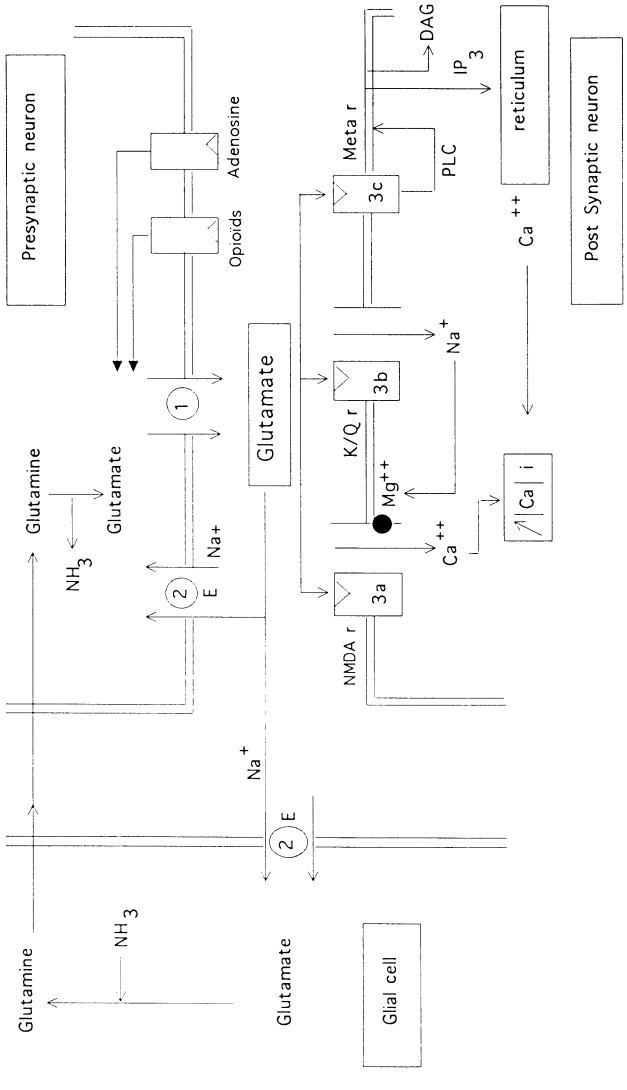


Fig. 6. Glutamatergic synapse. *1* glutamate release, *2* flutamate reuptake, *3* glutamate receptors

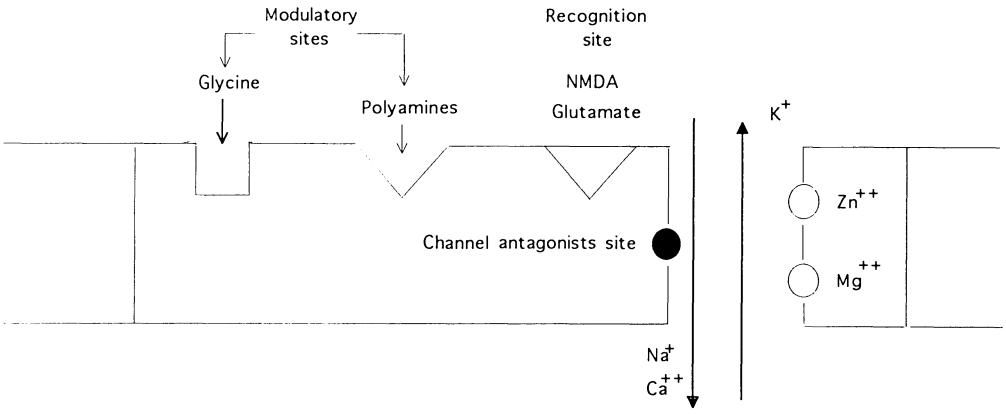


Fig. 7. NMDA receptor and associated ionic channel

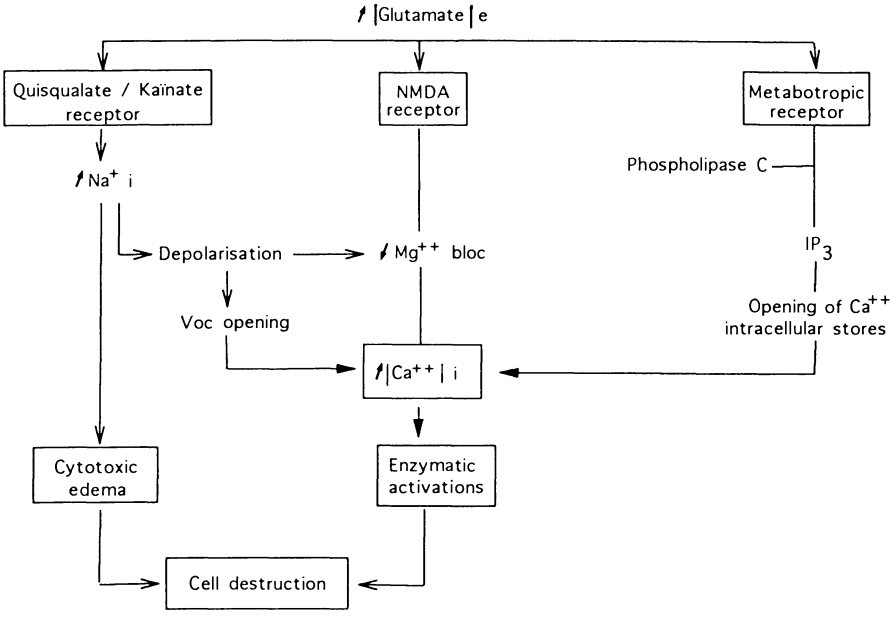


Fig. 8. Mechanisms of excitotoxic Ca^{++} overload

increased activity of ornithine decarboxylase (Dempsey 1988, review in Hossmann and Paschen 1992). Polyamines acting on one modulatory site strongly potentiate the stimulation of NMDA receptors (review in Scatton 1991). Finally we should insist on the fact that EAA damage namely "excitotoxicity" only concerns neurons and particularly those postsynaptic

neurons with high Ca^{++} conductances due to a rich array of glutamate receptors which are involved in excitatory processes. Though it has been recently recognized that glia express non-NMDA and metabotropic glutamate receptors, their potential role in pathological conditions, is not explored (Teichberg 1991).

Consequences of Increased Cytosolic Ca^{++} Concentration

Many physiological functions of cells depend on the transitory activation of a given class of enzymes by Ca^{++} signals. If the signal is abnormally high or persistent the ensuing enzymatic activations may result in direct or indirect deleterious consequences. Highly abnormal activation of the following enzymes has been successively identified in conditions of brain insult, particularly in ischemia; phospholipases, non-lysosomal proteases, protein kinases and phosphatases, endonucleases and recently NO synthetase (Fig. 9).

The activation of phospholipases leads to destruction of membrane phospholipids which has long been recognized in trauma and in ischemia (Bazan 1970, Edgar *et al.* 1982, review in Kogure 1992). The activation of

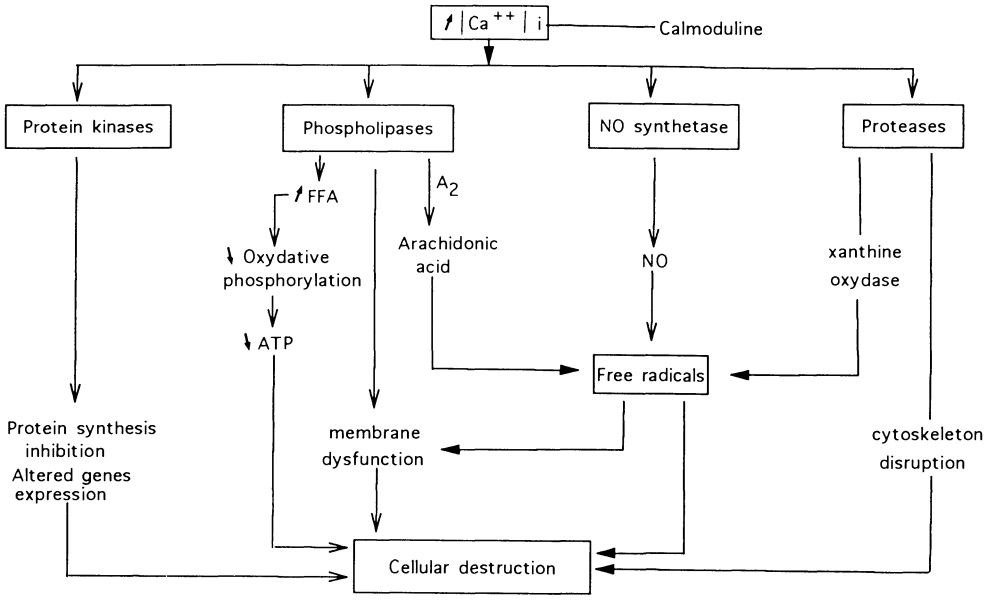


Fig. 9. Activation of some Ca^{++} dependent enzymes mediating Ca^{++} damage

phospholipases releases free fatty acids (FFA) (Rehncrona *et al.* 1982) which, if present in excess, modify the permeability of the mitochondrial membrane to protons and uncouple the oxidative phosphorysation process. The activation of phospholipase A2 releases arachidonic acid (AA). The large amounts of AA produced in ischemia (Abe *et al.* 1987, Dumuis *et al.* 1988), directly provoke an increase in capillary permeability and enhance disorders of BBB function (Ohnishi *et al.* 1992). Moreover the oxidation of arachidonic acid, along the cyclooxygenase pathway produces prostanoids and along the lipooxygenase pathway produces leucotrienes, these "*arachidonic cascades*" (Fig. 10) bring about excessive and unbalanced amounts of a number of derivatives, the "*lipidic mediators*" which mediate various deleterious actions. The over production of eicosanoids has been well documented in ischemia (review Kempski *et al.* 1987). Some of these by-products have free radical properties and participate in the overall outburst of peroxidation. Others interfere with microcirculation: the production of thromboxane A2 (vasoconstricting and aggregating) and prostacycline (vasodilating and antiaggregating) are unbalanced leading to vasomotor disorders and micro-thrombosis (Moreland *et al.* 1989, Pettigrew *et al.* 1989, Wei *et al.* 1980). Recently the role of platelet aggregating factor (PAF) another derivative of structural phospholipid hydrolysis has been stressed (Spinnewyn *et al.*

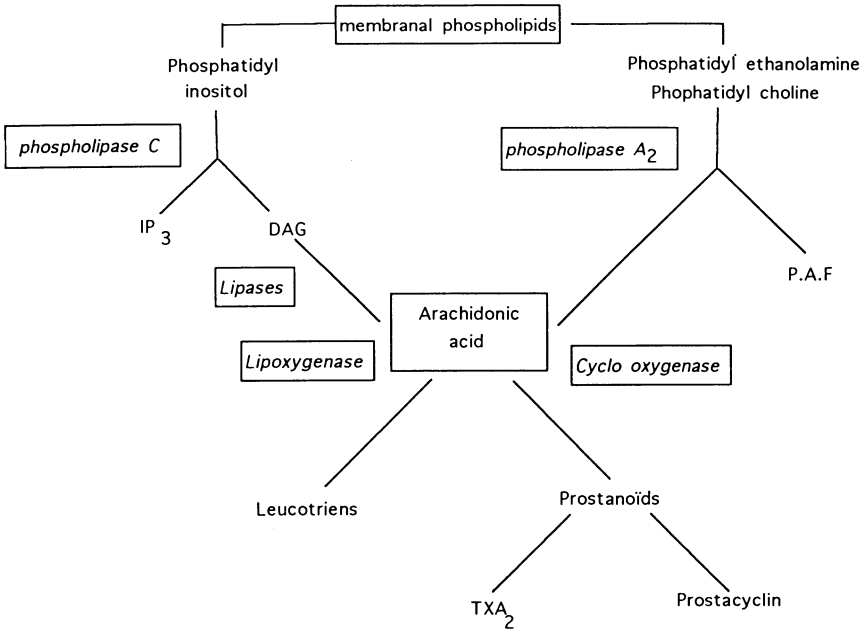


Fig. 10. Enzymatic attack on membranal phospholipids and arachidonic cascade

1987). When liberated in excess, it mediates local intravascular inflammatory response with BBB disruption and edema (Kumar *et al.* 1988, Kochanek *et al.* 1988a, b, Frerichs *et al.* 1990, Lindsberg *et al.* 1990). The activation of phospholipase C (Ikeda *et al.* 1986) attacks the functional inositol phospholipids. This produces a second messenger IP3 which opens Ca^{++} intracellular stores as already seen, but also diacylglycerol DAG which activates protein Kinase C (review in Nishizuka 1989). Further degradation of DAG by lipases produces further arachidonic acid.

The activation of proteases by Ca^{++} leads to another set of structural lesions and functional impairment: depolymerization of microtubules (Zimmerman and Schlaepfer 1982) causes disorders of axonal transport. Degradation of the cytoskeleton due to neurofilament injury, changes the number and functional characteristics of receptors and finally the membrane conductance to Ca^{++} (Seubert *et al.* 1989). A Ca^{++} dependent degradation of spectrin has been demonstrated in ischemia. Using a traumatic model Arrigoni in our laboratory was able to demonstrate neutral proteases (Calpaïn) activation in synaptosomal membranes following traumatic lesions (Arrigoni *et al.* 1991). Recently it has been suggested that nodal blebs, an early secondary axonal injury observed in trauma, are caused by local cytoskeleteral alterations due to Ca^{++} activation of Calpaïns (Gennarelli *et al.* 1993). Moreover, proteases are able to activate a number of enzymes through proteolytic splitting: one of these activations could have serious deleterious consequences: the transformation of xanthine dehydrogenase (an enzyme involved in the catabolism of AMP to urates) into xanthine oxidase induces a massive production of free radicals. Since AMP derivatives accumulate during ischemia, this reaction could lead to a massive production of free radicals (Kinuta *et al.* 1989a, b).

Ca^{++} regulates the activity of 2 important protein kinases, Ca^{++}/calmoduline dependent protein kinase II and protein kinase C. These enzymes control multiple cellular processes. Their activity is severely decreased after ischemia (Wieloch *et al.* 1991, Aronowski 1992–1993). PKC normally activates certain membrane proteins particularly Ca^{++} ATPase and Na/Ca^{++} exchanger, therefore – the inhibition of PKC in ischemia could contribute to aggravate intra cellular Ca^{++} retention. PKC also influences protein synthesis and its inhibition could be one important mechanism of delayed death of vulnerable neurons (Zivin *et al.* 1990), this inhibition would be caused by a Ca^{++} mediated block at the step of mRNA translation (Hossmann *et al.* 1992).

Nitric oxide (NO) synthetase is a neuronal and endothelial Ca^{++}-calmoduline activated enzyme molecularly cloned from brain. Its activation is specifically dependent on NMDA receptor stimulation (Marin *et al.* 1992). NO normally acts as a retrograde transmitter (review in Dawson *et al.* 1992)

but produced in excess it functions as a powerful neurotoxin. NO combines with superoxide anion O_2^- produced by xanthine oxidase activation, to yield the peroxynitrite anion $ONOO^-$ which is an extremely potent free radical. It has been speculated that liberation of NO could account in part for glutamate mediated neurotoxicity (Dawson 1991). Inhibition of NO synthetase has a potent neuroprotective action on ischemic damage following MCA occlusion (Nowicki *et al.* 1992).

Evidence of Ca^{++} Damage in CNS Injuries

Speculations on the role of Ca^{++} in brain injuries began with the eighties (Siesjö 1981, Hass 1981). Since that time a large body of experimental work has been accumulated and we have now considerable evidence that first, Ca^{++} mediated damage is one of the key mechanisms involved in tissue alterations and second, that in many circumstances an excess of EAA activity is responsible for the Ca^{++} entry within neurons.

Following the induction of ischemia, it is well established that Ca^{++} invades the cell when cerebral blood flow falls below 6–9 ml/100 g/mn. The rise of intracellular Ca^{++} concentration at a definite level of CBF is well documented (Harris *et al.* 1981, Dienel 1984). At a CBF around 6–9 ml/100 g/mn the extracellular Ca^{++} concentration falls from 1.31 to 0.28 mM giving a mirror image of the intracellular Ca^{++} loading (Harris *et al.* 1981). Intracellular concentration of Ca^{++} has been directly measured (Uematzu *et al.* 1988) and is correlated with histopathological alterations. Ca^{++} damage can also be assessed by measuring the products of Ca^{++} dependent enzymatic activation: free fatty acid liberation rises within 5 mn of ischemic induction (Bazan 1970, Huang and Sun 1987).

In the case of complete and permanent ischemia following MCA occlusion, Ca^{++} invasion should be massive, the cell membrane being completely depolarized and all the mechanisms of Ca^{++} control being inefficient. In these models, infarction occurs within 6 to 24 hours in the core of the ischemic area. In such rapidly complete structural destruction the respective role of Ca^{++} damage and of other types of disorder such as failure of all anabolic processes or acidosis, is difficult to assess. In cases of incomplete and/or transient ischemia, the responsibility of Ca^{++} itself is more clearly established. In these cases, Ca^{++} damage seems to be mainly dependent on excitotoxic mechanisms (Benveniste *et al.* 1984). The direct role of glutamate is well documented in various models. In transient global ischemia, the destruction of glutamatergic afferents prevents ischemic damage in vulnerable areas (Johansen 1986, Benveniste *et al.* 1989). Glutamate concentration rises in the rat striatum in episodes of ischemia (Ueda

et al. 1992). In the penumbra region, extracellular glutamate may rise as soon as CBF falls under 20 ml/100 g/mn (Shimada *et al.* 1989). As we will see later, various types of competitive and non competitive antagonists of NMDA receptors have a protective role and in focal ischemia can reduce the size of infarct (Albers *et al.* 1989). However, conflicting results have also been published (Buchan and Pulsinelli 1991).

In brain trauma, similar mechanisms are at work. The deleterious role of glutamate is well established (Baethman 1980). Acute subdural hematoma in rats creates a situation of compressive ischemia after 30 mn CBF falls under 25 ml/100 g/mn. In such condition, extracellular glutamate raises to 750% of control value (Bullock *et al.* 1991). In non ischemic models of brain trauma, around a cryogenic lesion, classically comparable to a non-compressive brain contusion (Baethmann *et al.* 1989, Arrigoni 1987) or following fluid percussion injury (Katayama *et al.* 1990, Faden *et al.* 1989), a rise in glutamate concentration is also observed. Microdialysis around traumatic lesions in man has shown similar findings (Persson *et al.* 1992). In these traumatic models, the classical effects of Ca^{++} dependent enzymatic activation, are well documented (Chan *et al.* 1983, Arrigoni *et al.* 1987–1991).

In spinal cord trauma, the toxic role of Ca^{++} is clearly established (review in Young 1985). The simple application of Ca^{++} solution or Ca^{++} ionophore on the cord creates histopathological lesions comparable to those of mechanical trauma (Balentine 1983–1984). A protective effect of NMDA antagonists has also been reported (Faden and Simon 1988).

Pharmacological Protection Against Ca^{++} Overload

In the last 10 years many efforts have been made to develop first molecules acting at the level of VOCs known as "calcium entry blockers" and, more recently, molecules interacting at various level with glutamate associated processes. There is little doubt that Ca^{++} overload is not only a side consequence of ischemia but a major cause of ischemic damage. What we do not know precisely, is the exact balance of various mechanisms involved in Ca^{++} entry, and in particular the respective responsibility of VOCs and ROCs in various pathological circumstances is difficult to assess. Both types are probably concerned: This is suggested by experiments in which Ca^{++} is directly measured within the cytosol. Following MCA occlusion, a considerable size in intracellular Ca^{++} signal occurs which can be reduced both by Ca^{++} entry blockers and by NMDA antagonists and moreover, completely abolished by an association of both drugs (Uematsu *et al.* 1989, Greenberg *et al.* 1991).

Calcium entry blockers: The drugs inhibiting Ca^{++} intake through VOCs belong to different chemical families. Those developed in brain protection, are mainly dihydropyridines, and among them nimodipine has gained a recognized place in clinical practice. The experimental literature on the action of these drugs in brain injuries is extensive and confusing: doses, modes of administration, animal models, outcome measures are many. Most of the time, the drug appears clearly active, if the experimental endpoint is an elementary phenomenon (energy production, acidosis, brain edema). However, experiments assessing brain protection through either morphological criteria (infarct size in focal, or percentage of dead neurones in global ischemia) or clinical criteria (survival time or functional outcome) have yielded conflicting results from very positive (Steen *et al.* 1985, Bartkowski *et al.* 1988, Uematsu *et al.* 1989), to negative (Van Reempt *et al.* 1986, Vibulsreth *et al.* 1987). Most of clinical studies of Ca^{++} entry blockers concern the action of nimodipine. They will be considered later. In brief there is a striking contrast between clearly positive results in SAH patients and rather negative or uncertain results in stroke and trauma patients.

Excitatory aminoacid antagonists: Strategies to oppose excitotoxic mechanisms have been the object of intense research and a host of experimental drug trials has been collected. A simple classification is given in Table 1. In order to reduce the level of extracellular glutamate it would be possible either to limit glutamate synthesis, to reduce glutamate release or to enhance glutamate re-uptake in neurons and glia. To oppose the over stimulation of postsynaptic receptors, various antagonists or modulators have been studied. A competitive NMDA antagonist acts at the level of NMDA recognition sites. Indirect non-competitive NMDA antagonists may block the associated ionic channel or bind modulatory sites of the NMDA receptors. Other compounds are active on the non-NMDA receptors.

The protective effects of competitive and non-competitive NMDA direct antagonists have been investigated in a variety of animal models in ischemia brain and spinal cord trauma (review Meldrum 1990, Meldrum 1992, Gotti *et al.* 1990, Scatton 1991, MacCulloch 1992). In models of global ischemia when delayed cell death in the Hippocampus is considered, the reported results are conflicting and in large animals rather negative (Swan and Meldrum 1990, Diemer *et al.* 1990). In MCA occlusion models in most cases with some species differences, relative protection is generally provided (for example Bullock *et al.* 1990, Dirnagz *et al.* 1990). As summarized by Meldrum, sparing of 40 to 50% of the infarcted volume is commonly reported concerning the neocortex with on the contrary a little sparing of the striatum, this presumably being explained by the fact that the striatum has a terminal type of vascularisation in contrast to the collateral type in the cortex. Few studies have been carried on in spinal cord or brain

Table 1. *Classification of Substances Acting on Glutamate Processes*

I. Pre synaptic synthesis of glutamate	
II. Pre synaptic release of glutamate	
– Adenosin, adenosin receptor agonists A1	
– Kappa opioids	
III. Glutamate reuptake	
IV. Post synaptic receptors	
– NMDA receptor complex	
Recognition site antagonists (competitive)	CPP
	D. CPP ene
	APV
	APH
Channel blockers	Dextrorphan
	Ketamine
	MK 801
	Phencyclidine
Glycine site antagonists	Kynurenate
Polyamines site antagonists	Ifenprodil
	SL 820715
– Non-NMDA receptors	Quinoxaline diones (CNQX, DNQX)

After Scatton *et al.* 1991, Meldrum 1992, Mc Culloch 1992.

trauma; they report positive results (Faden and Simon 1988). Despite these encouraging experimental results, many of these NMDA antagonists are unsuitable for clinical use. Apart from the fact that some do not pass the blood brain barrier, many also have important psychological and neurotoxic effects. It is of interest that an endogenous substance has been found to have NMDA receptor antagonist action namely kynurenic acid, a metabolite of tryptophan. Its pharmacological manipulation could have neuroprotective effects (Nozaki and Beal 1992). Interestingly also older drugs used in other fields of pathology have been found to be NMDA antagonists and have displayed a neuroprotective action including memantine an anti-Parkinsonian drug (Chen *et al.* 1992) and nitroglycerine (Lei *et al.* 1992). Drugs that act indirectly on glutamate transmission by affecting modulator sites of the NMDA complex are of particular interest. Ifenprodil and SL820715, antagonists of the polyamine modulator site are examples of such drugs with well documented protective effects in animal models (Carter *et al.* 1988, Gotti *et al.* 1990), the latter is presently under clinical investigation.

Substances interfering with ionotropic non-NMDA receptors and with the metabotropic receptor have been tried and a protective effect has most of the time been demonstrated (Nellgard and Wieloch 1992) an association of NMDA and non-NMDA receptor antagonists should yield an optimal protection (Mosinger *et al.* 1991, Kaku *et al.* 1991).

Different strategies have more recently been explored to reduce the extracellular level of glutamate. One is, logically, to inhibit the release from presynaptic terminals (Graham *et al.* 1993). Adenosine, a purine base is able to reduce the presynaptic release of glutamate and to stabilize the membrane potential of neurons and astrocytes. Adenosine would also have a favourable action on microcirculation and local CBF. Adenosine receptor antagonists aggravate ischemic damage. Adenosine as an endogenous protecting agent could probably be useful in cases of limited insult in penumbral areas. Drugs that could reinforce the action of adenosine might be developed (review in Rudolphi *et al.* 1992, Schubert and Kreutzeberg 1993). Agonists of the kappa opioid receptor have been shown to have a neuroprotective effect on focal ischemic models in rats and cats (Hall *et al.* 1987, Kusumoto 1992). This beneficial action could again result from an inhibition of glutamate release. However kappa agonists also modulate vasopressin release, induce diuresis and increase plasma osmolarity, and part of their beneficial effect could be due to a reduction of brain edema (MacKay *et al.* 1992). Some years ago the opioid receptor antagonist naloxone was found to have a neuroprotective effect in spinal trauma models (Faden *et al.* 1981) possibly by improving blood flow (Young *et al.* 1981). A controlled trial in human spinal injury failed to confirm a positive action (Bracken *et al.* 1990–1992). In fact there are in the literature some contradictory results and speculations concerning the possible role of opioids in neuroprotection (review in Faden and Salzman 1992).

3. Peroxidative Damage and Antioxidant Therapy

Free radicals are considered to be involved in a large variety of pathophysiological processes from inflammatory-immune diseases to cancer, ischemia, toxic injuries and normal aging. Free radical damage to cellular membranes was discussed as a likely mechanism of brain edema as early as 1972 (Demopoulos 1972). Since that time a large number of research papers and many speculative and/or teaching reviews have been published on free radicals as mediators of CNS injuries (Mc Cord 1985, Kontos and Povlishock 1986, Asano *et al.* 1987, Siesjö *et al.* 1989, Ikeda and Long 1990, Chan *et al.* 1990, Hall 1989, Schmidley 1990). However, perhaps because

free radicals are an extremely elusive species, unequivocal proof that they play a major role in brain lesions, remain equally elusive.

Free Radical Reactions

For the last 20 years, the biology of free radicals has been under intense study (review in Fridovich 1978, Halliwell and Gutteridge 1989). Free radicals are extremely aggressive molecules, due to the presence of one or more solitary (unpaired) electrons in outer orbits. Free radicals may react with most non-radical species producing new free radicals in chain reactions. The best known target of these reactions in the CNS are membrane phospholipids in which polyunsaturated fatty acids (PUFA) are attacked at the level of their double bonds and destroyed in a self propagating process (Freeman and Crapo 1982, Slater *et al.* 1984). The main steps of free radical generations are outlined in Fig. 11.

Free radical reactions occur in small amounts in normal cells in which they are well controlled by a full array of natural scavengers. Normally, within the mitochondria, 1 to 5% of molecular oxygen escape total reduction ($O_2 + 4e^- + 4H = 2H_2O$) along the respiratory chain and forms the superoxide anion O_2^- ($O_2 + 1^- \rightarrow O_2^-$). This superoxide anion is converted by superoxide dismutase into hydrogen peroxide H_2O_2 which in turn is quenched by glutathione peroxidases (requiring Selenium) and Catalases. Beside these enzymatic detoxication processes, the cell contains non-

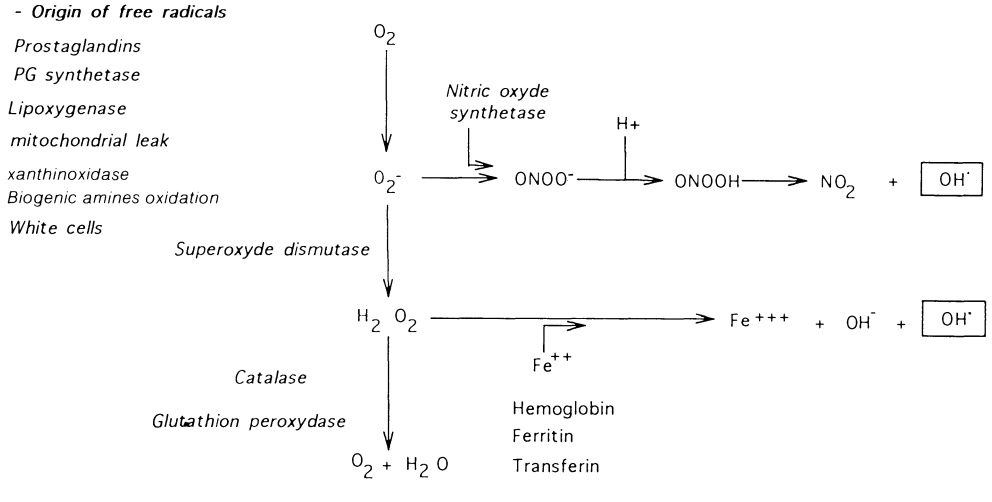


Fig. 11. Formation of free radicals (courtesy of E.D. Hall 1994)

enzymatic antioxidants: within the membrane, the hydrophobic alpha-tocopherol (vitamin E) quenches free radicals protecting PUFAS from ongoing chain peroxidation. Water soluble ascorbic acid (vitamin C) has a comparable role.

O_2^- and H_2O_2 are moderately toxic species and are normally completely controlled by enzymatic processing and natural anti-oxidants. However, in pathological conditions, the same radicals and other comparable species, are produced in enormous quantities, and some of them may be transformed in more toxic molecules: O_2 and H_2O_2 in the presence of iron or copper ions, are transformed into the hydroxyl radical OH^- a notable killer of everything around (the active agent in ionizing radiation).

Origin of Free Radicals in CNS Injury

The CNS seems to be particularly exposed to oxidative damage for several reasons: cellular PUFA in cell membranes are rich in side chains, antioxidant defences are rather poor, intracellular iron is common in many areas, the CSF is poor in transferrin which could bind liberated iron. Biochemical processes leading to enhanced free radical production, are likely to be the same in brain ischemia and in non-ischemic brain trauma. Free radical reactions appear as a down stream mechanism of Ca^{++} damage. Free radical production is the consequence of the arachidonic acid cascade triggered by Ca^{++} activated phospholipase A2 (Kinuta 1989a). In brain slices arachidonic acid and other PUFAS induce the production of superoxide anion, and provoke a parallel swelling of the tissue (Chan and Fishman 1980); similar results are reported in astrocyte culture (Chan *et al.* 1988). The role of Ca^{++} activated proteases splitting xanthine dehydrogenase into xanthine oxidase may be even more important (Patt *et al.* 1988). In ischemic conditions the excess of AMP greatly enhances the metabolic rate of xanthine degradation to urate production (Uemura *et al.* 1991) and that pathway has been considered as the major source of free radicals in ischemia. In a model of continuous partial ischemia, treatment with Allopurinol, a well known inhibitor of xanthine oxidase activity, reduces the infarct size by 35% (Martz *et al.* 1989). The activation of NO synthetase is another possible Ca^{++} dependent mechanism of free radical production (Beckman *et al.* 1990).

Not only free radical damage appears dependent on Ca^{++} activated enzymes but also several pharmacological manipulations on elementary models support the hypothesis that EAA stimulation triggers free radical reactions and that conversely these reactions increase EAA release, thus forming a vicious circle of deleterious reactions (Monyer *et al.* 1990,

Pellegrini-Giampietro *et al.* 1988–1990). Interaction between EAA and free radicals have again been discussed in the formation of ischemic brain edema (OH *et al.* 1991). However the production of free radicals does not appear as a simple proportional consequence of Ca^{++} overload. The importance of such a free radical outburst triggered by Ca^{++} disturbances depends a great deal upon other factors and particularly upon the degree of acidosis (Siesjö *et al.* 1992). In vitro experiments on brain slices have shown that moderate to marked acidosis of a degree encountered in brain ischemia (pH 6,5–6) greatly enhances the formation of free radicals (Siesjö 1985). One of the mechanisms would be that acidosis liberates iron from its binding proteins and iron in turn very potently enhances free radical formation (Siesjö 1985, Rehncrona *et al.* 1989). The role of iron is not limited to the condition of ischemic acidosis, it has been observed in many models. Direct injection of iron chloride into the cortex produces severe peroxidative damage (Singh *et al.* 1990). In brain trauma iron provided by haemorrhages has been considered to play a major role. Iron chelating agents like Deferoxamine are able to reduce cold induced edema in cata (Ikeda *et al.* 1989b).

Evidence of Free Radical Injury in CNS Insult

We may reasonably consider that free radical reactions do occur in CNS injuries at least in the experimental setting and may be responsible at least in part for cell destruction, endothelial disorders, brain edema (review in Ikeda *et al.* 1989a, Siesjö *et al.* 1989). However due to the transient nature of free radicals, it is always difficult to get direct evidence of their involvement in a given pathological process in vivo. Many facts referred to as proofs of free radical reactions are in vitro observations. In vivo reactions of superoxide anions may be detected by a coloured reaction, the reduction of nitroblue tetrazolium, NBT (Kontos and Wei 1986). Evidence of peroxidative damage to PUFAS is gained by measuring the final products of this reaction, Malondialdehyde (Chan 1980, Averet *et al.* 1990) or diene conjugates (Goldberg *et al.* 1984, Yoshida *et al.* 1985). Direct measure of free PUFAS is also possible (Rehncrona *et al.* 1982). Another set of arguments may come from the measure of abnormally high consumption of natural antioxidants (Demopoulos *et al.* 1982, Pietronigro *et al.* 1983), or from the favourable action of drugs with established antioxidant properties.

Free radicals are probably active from the onset of ischemia, particularly if residual blood flow is maintained, or following transient episodes of low flow (Bromont *et al.* 1989, Watson *et al.* 1984). In a model of MCA occlusion, the production of superoxide anions increased by 222, 420 and 614% at 1, 4 and 24 hours post ischemic onset respectively. The topical application of

superoxide dismutase (SOD) suppressed this reaction and reduced the amount of ischemic edema (Chan *et al.* 1987). Free radical generation is likely to be considerably enhanced at the time of recirculation when O_2 is again fully available. Peroxidative damage would be a major mechanism of recirculation injury (review in Bulkley 1987, Downey 1988, Ernster 1988, Ikeda and Long 1990). Damage could affect most severely the capillary endothelium (Halliwell 1989b).

Free radical reactions have also been described in models of brain trauma (Kontos and Povlischock 1986). After fluid percussion injury in cats, the reduction of NBT has been observed through a cranial window. This production of superoxide anion seems to be responsible for vascular disorders and endothelial lesions (Kontos and Wei 86). Averet in our laboratory has detected a highly significant increase of MDA production as soon as 30 seconds after the onset of a cryolesion in the rabbit. This MDA production lasted for 24 hours and was parallel to the edema formation (Averet *et al.* 1990). Destruction of the structure of membrane lipids was shown in the same model (Mitamura *et al.* 1981).

Therapies Against Free Radicals

Many drugs with antioxidant properties of various nature have been used in experimental protocols. If they are able to counteract a given pathological process, to reduce a given lesion, assuming that the drug has a specific and unequivocal type of action, this result is considered as a good proof that free radicals were indeed involved. Some of these drugs have been or are presently under clinical trial.

Direct antioxidants: Superoxide dismutase (SOD), the specific scavenger of superoxide anion could raise reasonable hopes since its effects on reperfusion injury in the heart, gastrointestinal tract and lung have already been documented (McCord 1985). SOD manipulations have been used in a number of experiments on ischemic models: SOD does not pass the blood brain barrier, but treatment with liposome entrapped SOD (Turrens et al. 1984, Chan *et al.* 1987) as well as polyethyleneglycol conjugated SOD (Liu *et al.* 1989) reduces the infarct size after MCA occlusion. SOD may also reduce neuronal alterations and delayed neuronal death, present after 5 minutes of total ischemia in the gerbil (Kitagawa *et al.* 1990). Similar results have been obtained using human recombinant SOD (Uyama *et al.* 1992). Chan has developed transgenic mice overexpressing human Cu, Zn, SOD. After a standard cryolesion, these animals, as compared to normal, develop a reduced water content, BBB alterations are less pronounced and the infarcted lesion is smaller (Chan 1991). In the clinical setting, vitamin E

(alpha-tocopherol) is the oldest recognized biological antioxidant. It has been used to prevent or reduce retrolental fibroplasia in premature infants or other diseases caused by peroxydative processes. Vitamin E acts as a true "scavenger" by donating a phenolic hydrogen atom to a free radical, thereby resolving the unpaired electron of the radical, and terminating the chain reaction. Its protective effect is attested on many experimental models (Yoshida *et al.* 1983–1985, Yamamoto *et al.* 1983, Busto 1984). No clinical trial is as yet available. Vitamin E is one of the components of the so-called "Sendai cocktail" (Susuki 1981).

Allopurinol, the inhibitor of xanthine oxidase, has a safe history of use in humans with gout as well as Deferoxamine, the iron chelator used in thalassemic patients. Both these drugs displayed protective action in animal models (Mink *et al.* 1991), but we are not aware of any trial in CNS injuries in man. A number of chemicals with various type of antioxidant properties have been found "protective" in experimental protocols with as yet no clinical development (Lysko *et al.* 1992, Clemens *et al.* 1993).

High dose corticoids and lazaroids: New seemingly justified hopes are founded in recent advances in the field of corticoids. Studies with methylprednisolone showed that large doses could be beneficial in spinal cord trauma (Hall and Braughler 1982, Hall *et al.* 1984, Anderson *et al.* 1985, Braughler *et al.* 1987) and in brain ischemia (Braughler and Lainer 1986). It was hypothesized that these beneficial effects were not related to gluco corticoid receptor mediated effects of the drug but rather to an inhibition of lipid peroxidation. This hypothesis led to the development of methylprednisolone analogues which were screened for their ability to inhibit CNS lipid peroxidation. A new family of compounds later known as lazaroids has been produced (review in Hall 1992). These compounds have no classical gluco or minerallocorticoid effects but an antioxidant action mechanistically similar to vitamin E. In fact, these drugs seem to spare vitamin E slowing its inactivation and enhancing its quenching capacity for free radicals. A number of animal models demonstrate a protective effect of 21 aminosterods and sparing of vitamin E (Hall *et al.* 1989).

Different compounds have been tried, the one selected for clinical development, a 21-aminosteroid, U 74006 F, tirilazad mesylate, is 100 times more potent than methylprednisolone in the inhibition of lipid peroxidation. It has been examined in several models of spinal cord and brain trauma and in ischemic conditions, including stroke and SAH models. To mention only a few results, this drug completely prevents post traumatic hypoperfusion following spinal cord trauma (Hall *et al.* 1988), it improves early neurological recovery and survival in head injured mice (Hall *et al.* 1988), it reduces ion shifts and edema in the ischemic area after MCA occlusion in rats (Young *et al.* 1988). A prophylactic effect on chronic vasospasm after

SAH has been demonstrated in primates in 2 differents studies (Steinke *et al.* 1989, Kanamaru *et al.* 1990–1991). Preliminary results of the curent clinical trial concerning post SAH mortality and morbidity have been presented recently and look promising.

4. Acidotic Damage and Antiacidotic Therapies

When O_2 is not available the metabolism of glucose is blocked at the level of pyruvate. Instead of being oxidised in the Krebs cycle, pyruvate is reduced to lactate. This reaction yields only 2 mol of ATP per mol of glucose and is accompanied by the liberation of H^+ according to the simplified equation.

$$1 \text{ glucose} \rightarrow 2 \text{ pyruvates} \rightarrow 2 \text{ lactactes} + 2 \text{ ATP} + 2 H^+.$$

Therefore in anaerobic conditions not only is there a breakdown of ATP production but also the cell is acidified.

The role of acidosis as an independant mechanism of tissue damage has been thoroughly investigated in a number of experimental studies (Rehncrona *et al.* 1981, Siesjö *et al.* 1985, review in Siesjö 1988). It was shown that incomplete ischemia is a worse insult than complete ischemia because the glucose provided by the residual flow allows the production of a higher level of cellular acidosis (Salford *et al.* 1974, Nordström *et al.* 1978a, b).

At the same time it has become clear that in the case of ischemia, the plasma glucose concentration influences the extent and degree of tissue damage because it determines the level of resulting acidosis (Siemkonicz and Hansen 1978, Myers and Yamaguchi 1976). The detrimental effect of hyperglycemia in ischemic conditions has been confirmed in various models of cerebral ischemia (Nedergard 1987, Venables *et al.* 1985, Chopp *et al.* 1987–1988, Bolas *et al.* 1988, Plum 1983). Insulin has been shown to have a neuroprotective effect (Strong *et al.* 1990) and some observations in man are in keeping with these experimental findings (Plum 1983, Lam *et al.* 1991).

The main neuropathological features of acidosis related brain damage include edema, widespread neuronal necrosis and complete tissue destruction (Myers and Yamaguchi 1976–1977, Kalimo *et al.* 1981). Not only neurons are concerned but glial and endothelial cells as well. The specific responsibility of acidosis is evidenced when one compares tissue alterations caused by hypoglycemia and by ischemia (Siesjö 1988). In the case of hypoglycemic coma, a condition with complete energy failure but no acidosis, and extensive neuronal necrosis is observed. In the case of ischemia with a comparable breakdown of energy and lactate accumulation, there is complete destruction of the tissue with blood brain barrier destruction, edema and infarction. In fact the level of acidosis and the severity of tissue damage, depends on the interaction between 3 factors, the residual blood flow, the

plasma glucose concentration and the duration of ischemia (Siesjö 1988). In vitro studies suggest that the cellular damage is induced by acidosis per se and not by the accumulation of lactate anion (Norenberg *et al.* 1987) or other correlative changes. It is likely that the main mechanism of cell damage is related to cell swelling induced by acidosis. In the anaerobic condition it seems that the cell sacrifices its volume to save its pH. The accumulation of H^+ activates a Na^+/H^+ transporter. H^+ is extruded but Na^+ accumulates in exchange. The sodium pump being out of energy cannot evacuate this excess of Na^+ and the cell swells with osmotically attracted water (Siesjö 1988). This would be the main mechanism of ischemic cytotoxic brain edema.

Acidosis is inevitably linked to ischemia and it is not possible to prevent acidosis if ischemia itself cannot be avoided. However given the fact that CO_2 diffuses freely across cell membranes, acidosis can be opposed by measures acting on blood pCO_2 and pH. Some years ago, hyperventilation, which causes a systemic respiratory alkalosis, was thought to reduce brain acidosis (Rossanda 1973). However it may worsen the oxygen supply to brain cells because it reduces CBF and shifts the oxyhaemoglobin dissociation curve unfavourably (Yoshida and Marmarou 1991). Though it is routinely used in the management of ICP in brain trauma, hyperventilation in fact enhances lactate production (Yoshida and Marmarou 1991). The use of sodium bicarbonate is limited because it may enhance metabolic acidosis (Graff *et al.* 1985) and lead to hypernatremia and hyperosmolarity (Bishop and Weisfeldt 1976). However it has been recently advocated in total cerebral ischemia following cardiac arrest (Kohama *et al.* 1991).

Another way to reduce brain acidosis could be to provide sufficient amount of bases. Tromethamine (THAM) a weak base which crosses the plasma membrane and acts directly on intracellular acidosis has been used with success in models of experimental head injury (Rosner *et al.* 1984, Gaab *et al.* 1980, Yoshida and Marmarou 1991). THAM effectively reduces lactate production and protects energy depletion (Yoshida and Marmarou 1991). THAM has been used in head injuries in man with favourable effects on brain edema and intracranial pressure (Wolf *et al.* 1993).

5. *Miscellaneous Mediators of Brain Damage and Neuroprotective Agents*

Many different substances have been identified in the experimental literature which are able either to create or to worsen brain damage and/or neuronal loss in CNS injuries. Among neurotransmitters acetylcholine, noradrenaline, dopamine, serotonin and opioids may have a place in this pathophysiological field (review in Wieloch 1990, Pappius 1991, Lipton 1993). Acetylcholine,

presumably entering the CNS via BBB disturbances, could enhance Ca^{++} loading via muscarinic receptors (Hayes *et al.* 1992). The antagonist scopolamine has been credited with a neuroprotective action in a fluid percussion model in the rat (Lyeth *et al.* 1992).

Disorders of microcirculation are an important aspect of secondary damage in traumatic and ischemic conditions. Several independent mechanisms are involved and may be opposed by specific therapies. The activation of the kallikrein-Kinin system and the role of bradykinin in BBB alterations and the spread of vasogenic edema has been recognized in traumatic (Wahl *et al.* 1980) and ischemic models (Kamiya *et al.* 1993). Histamine also might contribute to Ca^{++} damage in endothelials cells (Joo *et al.* 1992). It has long been known that granulocyte and platelet adhesion and local accumulation plays a major part in secondary microthrombosis and BBB disorders affecting ischemic tissue. Several studies using anti-leucocyte adhesion antibodies in spinal cord injury models have demonstrated clearly positive results (Kochanek and Hallenbeck 1992). Similarly, protection against reperfusion injury in brain ischemia was obtained with a PAF antagonist (Panetta *et al.* 1987).

In fact it would be difficult to give a complete list of all the compounds which have been shown to have neuroprotective effects in the recent literature including hormones like TRH (Faden and Salzman 1992) agonists of inhibitory transmission (Lyden *et al.* 1992) potentiators of energy metabolism like acetyl carnitine (Rosenthal *et al.* 1992) and inhibitors of anion transport (Kohut *et al.* 1992).

Among these miscellaneous "neuroprotective agents" gangliosides deserve a special mention. These compounds were thoroughly studied a few years ago (review in Mahadik 1992). An action via modulation of protein Kinase activity was hypothesised (Vaccarino *et al.* 1987). The effects on animal models of ischemia and trauma were encouraging despite notable negative findings (Mayer and Pulsinelli 1992). The pooled result of a number of clinical trials in stroke were positive. However some cases of immunologic disease have been attributed to such treatment (Raschetti *et al.* 1992) and the drug is no longer available. Further studies of this type of compound are necessary.

IV. Acute Brain Insults and Attempts at Protection

In this section we would like to look at some clinical conditions in which brain protection is usually considered a major goal of treatment. For each situation we will briefly review pathophysiological specificities and the results of brain protection, mainly in the clinical setting.

1. Intraoperative Brain Protection

Cardiovascular Surgery

Cardiovascular surgeons have a considerable experience in brain protection (Guilmet *et al.* 1986, Cooley *et al.* 1981, Coselli *et al.* 1988). They use essentially two techniques, profound hypothermia with circulatory arrest and moderate hypothermia with selective carotid perfusion (Frist *et al.* 1986, review in Le Mee 1993).

Profound hypothermia (18°) provides good brain and myocardial protection. The duration of circulatory arrest according to experimental (Treasure *et al.* 1983) or clinical studies (Mahfoud *et al.* 1984) should remain under 40–45 mn. At more than 60 minutes there is a high risk of neurological problems. Complications of deep hypothermia are well known, hypocoagulability with severe thrombopenia and fibrinolysis is invariable, aggravated by the duration of cardiopulmonary bypass and by hemodilution. Pulmonary disorders and infection are also common problems encountered.

Moderate hypothermia (23°–25°) (Livesay *et al.* 1983, Sweeney *et al.* 1985) allows only 30 minutes of circulatory arrest which is not enough time for many surgical procedures on the aortic arch. This prompted the development of moderate hypothermia (25°–28°) with selective perfusion of cooled blood (6°–8°) into the carotid arteries (Crawford *et al.* 1979, Bachet *et al.* 1991). A large experience is now available (review in Le Mée 1993). Experimental (Tanaka *et al.* 1988) and clinical studies (Greeley *et al.* 1989) show that autoregulation of CBF is maintained provided that perfusion pressure is kept above 50 mm Hg. Using monitoring of $CMRO_2$ it has been found that for a temperature at 25° and a perfusion pressure at 40–60 mm Hg, a blood flow at around 500 ml/mn is sufficient (Kuwabara 1992).

Another method of brain protection recently developed by UEDA consists in retrograde perfusion of oxygenated blood through the jugular veins. This perfusion can be used after a period of circulatory arrest under deep hypothermia judged too long, in order to wash out from the brain accumulated waste products and potentially toxic metabolites. Following experimental studies (Ueda *et al.* 1989a, b) clinical application confirms the feasibility and safety of this technique (Ueda et al. (1992).

Carotid Surgery

It is generally agreed that the main cause of ischemic damage during carotid endarterectomy is the formation and migration of emboli from the plaque. Careful handling of the vessel is the only possible prevention. A decrease in

cerebral perfusion during clamping can also lead to brain ischemia. However, this risk should be lowered in the case of severe stenosis (> 70%) for which endarterectomy is presently of proven value.

In fact the risk of intraoperative hemodynamic ischemia is difficult to evaluate. Intraoperative measurement of common carotid stump pressure, monitoring of somatosensory evoked potentials or homolateral CBF have been widely used most of the time to guide the decision for shunting. Indeed the simplest way to maintain adequate CBF during clamping is to use a temporary in-lying bypass shunt. However this clearly complicates the surgical procedure and carries its own risks. Authoritative voices have advocated routine use of shunt (Javid *et al.* 1979), elective shunting based on monitoring (Sundt *et al.* 1975), and no shunting at all (Ferguson 1982). This old question is still unanswered despite recent discussions (Halsey 1992, Jansen *et al.* 1993).

Pharmacological protection is provided only by using barbiturates and etomidate as hypnotic agents. Inotropic drugs are also used to maintain systemic pressure at a preanesthetic level. One should bear in mind that one major cause of serious morbility and death in patients undergoing carotid endarterectomy is myocardial infarction.

Aneurysm Surgery

There is always an impending threat of distal ischemia following aneurysm rupture though this risk is relatively lower, at the time generally elected for surgery, before or after the period of arterial spasm. This risk is considerably increased intraoperatively by anesthesia, by vascular manipulations and above all by temporary clipping. Monitoring of somatosensory potentials is currently used and thought to provide useful warning (Symon *et al.* 1984, Symon *et al.* 1986, Lazorthes *et al.* 1992). Brain protection in aneurysm surgery (review in Castel *et al.* 1994) begins with a careful control of normotension and normovolaemia. The use of hypotension, once very common (Lazorthes 1978) is now generally abandoned. Metabolic protection is insured by using thiopental (Selman *et al.* 1987), MacDernott *et al.* 1989) or etomidate (Batjer *et al.* 1988, MacDernott *et al.* 1989) as hypnotic drugs. Deep hypothermia is reserved for very special cases (Spetzler *et al.* 1988, Silverberg *et al.* 1989, Chyatte *et al.* 1989). Pharmacological protection with various drugs has been attempted many times but with no proper evaluation. The so-called "Sendai cocktail" which associates 20% mannitol vitamin E, phenytoin and dexamethasone (Suzuki 1981) is popular in some groups. In fact a number of neurosurgeons have tried and given up various methods of pharmacological protection and believe that careful retraction, a reason-

ably rapid dissection and temporary clipping under electrophysiological monitoring, with needless to say, adequate placement of the final clip, assure by far the best guarantees against ischemic sequellae of aneurysm surgery.

2. *Subarachnoid Haemorrage*

The mechanisms of delayed brain ischemia following subarachnoid haemorrage (SAH) are many. CBF is reduced from the onset and remains reduced in poor grade patients (Fazl *et al.* 1991). However the most conspicuous cause of ischemia is secondary "vasospasm". The pathophysiology of arterial narrowing is not completely understood. Subarachnoid blood plays a determining role (Harada *et al.* 1990), a sustained smooth muscle contraction being triggered by oxyhaemoglobin derivatives via protein kinase Ca^{++} dependent activation (Minami 1992, Takanashi *et al.* 1992). An imbalance between vasoactive substances from the endothelium, endothelin a vasoconstrictor, and the vasodilatator nitric oxide, could have an additional effect (Susuki *et al.* 1992, Edwards *et al.* 1992). However spasm per se is not the only mechanism: a proliferative response of the arterial wall (Findlay *et al.* 1989) has been well documented and may involve inflammatory-like local reactions (Peterson *et al.* 1990). In addition to vasospasm a number of factors contribute to the ischemic threat. Disorders of microcirculation may be important, particularly, disturbances of autoregulation (Dernbach *et al.* 1988) and of blood brain barrier permeability (Doczi *et al.* 1986). Following SAH there is a particular brain tissue susceptibility to ischemia (Nagai *et al.* 1988, Nilsson 1991). Moreover systemic factors including hyponatremia (Wijdicks *et al.* 1991) and hypovolaemia are also to be considered. The medical management of SAH has been extensively reviewed in this series (Castel 1991). Brain protection includes, first the correction of hypovolaemia. Monitoring, or frequent measurement of central venous pressure is often considered mandatory and volume expansion with colloids is routinely used. Induced hypervolaemia has also been proposed as having rheologic and hemodynamic favourable effects on brain circulation (Tanabe *et al.* 1988).

The first class of drugs for which a favourable effect in SAH patients has been demonstrated are the Ca^{++} blockers. Nimodipine has a well documented action on experimental arterial spasm and is usually presented as a vessel targeted drug (Krueger *et al.* 1985, Nosko *et al.* 1985–1986, Alborch *et al.* 1987). However direct protection at the cellular level should also be considered since in several clinical studies the clinically evident beneficial effect appears to be independent of any effect on vessels as studied by angiography and CBF measurements. After a number of uncontrolled prospective studies, a large controlled British multicentre trial in 554

patients suffering SAH with all grades of severity showed that with Nimodipine as compared to placebo, the risk of cerebral infarction was reduced by 34% and the incidence of poor outcome by 40% (Pickard *et al.* 1989). Since that study Nimodipine has been widely accepted as a standard treatment in SAH patients in the acute stage. Another Ca^{++} antagonist AT 877 with a different mode of action from Nimodipine has been studied in Japan in a large multicentre controlled trial, with similar positive results and also a favourable effect on angiographycally demonstrable vasospasm (Shibuya *et al.* 1992).

The interest in antioxidant drugs is more recent, based on the purported role of peroxidative processes in mediating the arterial response (Asano *et al.* 1980). 21-aminosteroids have been shown to decrease the arterial narrowing in rabbits (Zucarello *et al.* 1989) and primates (Kanamaru *et al.* 1991, Steinke *et al.* 1989) models of SAH. Other more potent inhibitors of lipid peroxidation have also been successfully tried in animals (Takahashi *et al.* 1993). A large controlled trial on the effect of tirilazad mesylate in SAH patients has recently been completed in which the drug was associated with Nimodipine as a standard treatment. Preliminary results seem positive with beneficial effects on both mortality and morbidity.

3. Stroke

Physiopathology of focal cerebral ischemia has been already dealt with. The typical lesion at the acute stage is characterized by a densely ischemic core surrounded by a rim of ischemic penumbra. Animal models with MCA occlusion have been thoroughly investigated in many species and MCA occlusion in the baboon yields a situation similar to the commonest form of stroke in man (Symon 1974), even though we must keep in mind that at least 1/2 of stroke in man involves embolic rather than haemodynamic mechanisms. The ultimate extent of the lesion depends first on whether or not early recirculation can occur in the ischemic core and second on whether or not a penumbral zone actually exists. Accordingly the first goal of acute treatment of stroke is to improve the overall circulatory conditions in and around the focus, the second is to oppose destructive chain reactions in suboptimal flow areas. The nature and intensity of biochemical processes in the penumbral area are probably different in different cases and at different time. The respective role of glutamate toxicity (Butcher *et al.* 1990) and free radical mediated inflammatory response, with microvascular injury and edema, is difficult to assess. Peroxidative damage is probably limited in areas with very low available oxygen but should be enhanced at recirculation.

Recirculation on the other hand carries the risk of increased vasogenic edema in view of BBB disturbances.

The success of primary prevention of stroke is in striking contrast with the failure of all treatment regimens tried thus far in the acute condition. We have as yet no treatment of proven efficacy after the onset of lesions (review in Harrison 1992). Antithrombotic therapy which yields clear clinical benefit in cardiac disease does not give comparable results in stroke (review in Sandercock *et al.* 1993). Despite encouraging animal studies (Sakaki *et al.* 1990, Cole *et al.* 1990) haemodilution has shown no appreciable benefit (Asplund 1991, Thomas 1993).

Ca^{++} channel blockers particularly Nimodipine have been extensively tested. Animal data though inhomogeneous and sometimes contradictory was encouraging (Hadley 1991). A large clinical trial enrolling 1215 acute stroke patient led to negative results (Trust study group 1990). Meta-analysis concerning 3714 cases is also disappointing (Mohr 1992). However there is a strong suspicion that these negative results may reflect a too late onset of treatment. In the largest trial (Trust study group 1990) 50% of the patients were recruited between 24 an 48 hours after their stroke. The meta-analysis revealed an orderly effect of time of drug administration on outcome. For the group of patients recruited within 12 hours the pooled odds ratio clearly favoured Nimodipine (Mohr 1992).

A large number of compounds purported to interfere with excitotoxic mechanisms have been used in animal models of focal ischemia with rather impressive results but clinical trials of these drugs are not yet available.

Protection against free radical reactions in focal ischemia has also obtained interesting results in animal models (Young *et al.* 1988, Xue *et al.* 1992, Wilson *et al.* 1992), however not so impressive as those of drugs targeted at the glutamate system. Clinical trials in stroke are envisioned.

4. Brain Trauma

At the time of injury immediate primary focal and diffuse type of tissue alterations are produced. Focal damage includes direct "coup" lesions under a local blow and/or indirect, often multifocal, "contre-coup" lesions resulting from brain motion in relation to the skull and dural positions. Diffuse damage consists of lesions described as "diffuse axonal injuries" produced by acceleration stress and scattered in the central white matter down to the upper brainstem. Secondary damage to the brain first results from the evolution of primary lesions. Around focal contusions biochemical cascades are triggered leading to vasomotor disorders, cytotoxic and vasogenic edema and further destruction of tissue (Wahl *et al.* 1988). The role of ferrous

ions from haemorrhagic foci which activate peroxidation seems particularly important in mediating this local expansion of lesions (review in Kontos and Povlishock 1986, Ikeda and Long 1990). Diffuse axonal injury on the other hand is not complete at the time of the accident as already seen, it has been recently recognized in experimental animals submitted to elongation injuries that axon rupture may be progressive (Povlishock 1992, Gennarelli *et al.* 1993).

Ischemia is by far the most common type of secondary insult observed in head injuries (Graham *et al.* 1978, Graham *et al.* 1989) a decrease in CBF has been documented during the first 6 hours following head trauma and was found to be highly correlated with outcome (Bouma *et al.* 1991). Ischemic stress may result from many systemic and intracranial mechanisms as listed after (Miller 1993).

Systemic	*Intracranial*
Immediate	High ICP
Hypotension	Hematomas
Hypoxemia	Edema
Anemia	Swelling
	Brain shift
Delayed	Vasospasm
Coagulopathies	Epileptic seizures
Hyperthermia	

Most of these situations create a global type of ischemia but the reduction of flow may be unevenly distributed according to local or generalised vasomotor paralysis, local or generalized pressure gradients. A penumbral type situation is likely to exist in widespread regions under extracerebral hematomas and around focal contusions. The secondary aggravation of such lesions in brain trauma has been clearly evidenced in patients in whom 2 successive CT scan have been obtained within 72 hours of admission. These comparisons demonstrate an increase in lesions. There was a highly significant correlation between the severity of the initial injury and the evidence of worsening lesion on CT. In the same study it was shown that secondary damage is highly associated with higher mortality, lower recovery and poorer outcome. Particularly secondary injury is an independent contributor to outcome for patients in whom the initial injury is of mild to moderate severity (Stein *et al.* 1993).

Protection of the brain in head injuries should first consist in prevention of secondary ischemic/hypoxic insults from systemic causes. This implies the maintenance of a clear airway, normal blood pressure and normalvolaemia. Attention must also be paid to the occurrence of hyperthermia and epileptic seizures. Adequate diagnosis and treatment of intracranial masses and

specific therapies to reduce ICP according to its likely mechanism are mandatory. This basic management of head injuries is or should be standard practice in intensive care units receiving these patients. It requires appropriate monitoring of relevant parameters particularly ICP and CPP.

Pharmacological protection against ongoing secondary damage has been attempted along several lines. We have previously reported experimental results with anesthetic drugs particularly barbiturates, mild hypothermia, Ca^{++} blockers, various agents acting upstream and downstream, EAA accumulation and drugs with antioxidant properties. As yet only few of these approaches have been applied to man. Though barbiturate trials failed to support a beneficial effect, (Swartz *et al.* 1984, Ward *et al.* 1985) these drugs are still used with the aim of immediate reduction of ICP, particularly if high ICP is likely to be caused by vascular engorgement. Favourable results could be obtained in patients with preserved vasoreactivity (Nordström *et al.* 1988). Metabolic protection using cold has been again recently investigated. A randomised trial in a consecutive series of 40 patients with severe head injury established that lowering the brain temperature to 32–33 °C with cooling blankets and cold saline gastric perfusion is feasible and safe. This study demonstrated that such a small difference in brain temperature produced a 26% reduction of CBF with a 40% drop in ICP. A trend is observed towards better outcome in the treated group (Marion *et al.* 1993). Another randomised trial concerns 33 patients with severe head injuries and elevated ICP (above 20 mm Hg) resisting conventional treatment including thiopental. Lowering of CBF, CM RO_2 and ICP was constantly obtained in the hypothermia group with ultimately a significant improvement in outcome (Shiozaki *et al.* 1993). The Ca^{++} blocker Nimodipine has been studied in two large European trials with somewhat equivocal results, though not entirely negative (Braakman 1994). Nimodipine treatment was found beneficial in patients with subarachnoid haemorrhage diagnosed on the first CT, particularly in the younger patients (Kakarieka *et al.* 1993). The mechanism of protection could be similar to the one provided in aneurysm SAH, comparable vasospasm being observed in a large number of severe head injuries (Weber *et al.* 1990). Several competitive or non competitive NMDA antagonists are now ready for clinical use or are already being tested in controlled trials. Considering the presumably important place of peroxidative damage in trauma the advent of efficient antioxidants is of interest. The controlled trial of high doses methylprednisolone in brain trauma (Giannotta *et al.* 1984) has been criticized. The results of the tirilasad mysilate trial are not yet known. Interestingly, a recent report from Muizelaar *et al.* 1993, described a phase II trial of polyethylene glycol-conjugated SOD in severe head injuries. The drug appears "well tolerated" and "promising in improving outcome" in this indication (Muizelaar *et al.* 1993).

5. *Spinal Trauma*

The importance of secondary versus primary damage is probably more obvious and more constant in spinal cord trauma than it is in most other CNS insults. Blunt injuries very rarely result in a complete transection of the cord but rather in a compression and partial laceration by bone dislocation. Following that, severe alterations of the microcirculation and a major reduction of blood flow constantly occurs and has been consistently documented in experimental models (review in Tator and Fehlings 1991). Post-traumatic ischemia worsens over the first few hours and persists at least 24 hours in all species studied. The likely cause is a combination of local autoregulation disorders (Senter and Venes 1979) and systemic hypotension due to sympathetic tone decrease (Rawe and Perot 1979). The role of Ca^{++} (Young 1985), excitotoxic mechanisms (Faden and Simon 1988) and of free radical reactions (Hall and Wolf 1986, Francel *et al.* 1993) has been thoroughly investigated and corresponding drugs have been tried in experimental models. The efficacy of the opiate antagonist Naloxone (Young *et al.* 1981, Flamm *et al.* 1982), the protective effect of high doses of methylprednisolone (Hall *et al.* 1984, Young *et al.* 1982), and later on of 21-aminosteroid have been recognized. In spinal trauma laboratory results have been quite readily transferred into clinical trials. The National Acute Spinal Cord Injury Study (NASCIS I and II) was among the first large multicentre clinical trials in CNS pathology with a successful organisation and useable results (Young 1992). These trials concerned Methylprednisolone and Naloxone. The main conclusion was that in patients treated within 8 hours of injury with highdoses of methylprednisolone (30 mg/kg bolus and 5,4 mg/kg/h for 23 following hours) a certain degree of increased recovery of neurological function was seen at 6 weeks and 6 months (Bracken *et al.* 1990) and confirmed at 1 year followup (Bracken *et al.* 1992). Following these results the use of high doses of methylprednisolone has become standard practice in North America and in some other countries for patients suffering acute spinal cord trauma. However reservations have been expressed (Johnston 1993) and this treatment is not completely established.

V. Concluding Remarks

As outlined in the introduction there are 2 periods and correspondingly 2 domains in brain protection: metabolic and pharmacological. Following the relative failure of barbiturates and given the lack of new concepts in brain depressants, the possibilities and limits of *metabolic brain protection* seemed to have been fixed for the last ten years. However recent investigations in

mild hypothermia might be of great practical importance. Cold backs on a large empiric tradition, mild cold seems a rather non invasive technique, it may come anew particularly in severe trauma patients. At least, a larger clinical experience is worth a trial.

The balance of hopes and actual achievements in *pharmacological brain protection* is not satisfactory. Nearly all the compounds of "proven" efficacy in animal models of ischemia and trauma have failed to demonstrate consistent usefulness in clinical trials. As adequately said by Molinari we are repeating "a familiar and recurrent sequence..." to renew hopes through animal modelling, only to be disappointed by the results of large scale statistically valid clinical trials"...(Molinari 1986). As concluding remarks we would like to briefly comment on some of the reason which might explain this situation. We will consider three classes of problems concerning (1) the relevance of experimental research, (2) the methodology of clinical trials and finally our overall philosophy of brain protection.

1. Relevance of Experimental Research

The clinical relevance of experimental research in brain insult has been questioned many time (Rosner *et al.* 1982, Molinari 1986, 1988, Wiebers *et al.* 1990, Pulsinelli and Buchan 1989, Hsu 1993). A large number of ingenious preparations have been designed in animals to mimic human brain pathology in ischemia (review in Garcia 1990) and trauma (review in Gennarelli 1983, Stälhammer 1990) all these models share some common flaws: models set simple, pure and relatively reproducible situations, pathology is always complex intricated and heterogeneous. Animals are young and healthy, men, particularly those affected by stroke, are aged, with a number of associated risk factors. Experiments in animals are always done under some type of anesthesia. In the large majority of laboratory studies protective drugs have been provided as a pretreatment or at least at very short time interval following the insult. It is difficult in man to begin a treatment within 6 hours of any insult.

Other difficulties arise with the interpretation and extrapolation of experimental results. Much research work published even in peer reviewed journals is poor and over interpreted. The results of different groups using the same drugs in the same model in the same or in different animals species are often different or contradictory. However, only "promising results" are retained, repeated and advertised. The experimental conditions and the chosen endpoints in a large number of drug studies, though interesting in themselves are simply not transposable. The fact that a given drug reduces Ca^{++} shift or PUFA liberation in vitro, the fact that it enhances CBF or

reduces brain edema or even reduces the infarct size in animals, simply does not predict useful clinical results. In fact the definition of relevant measures of therapeutic efficacy in animals has yet to be done (Hsu 1993). The proposal that measures of clinical outcome may be the only valid measure of treatment success may be difficult to apply to animal research (Wiebers *et al.* 1989).

2. *Methodology of Clinical Trials*

Given the limitation of experimental modelling as listed in the preceding section, one could tentatively conclude that preclinical research is unable to screen drugs useful for clinical application and that this is a straightforward explanation of our persistent lack of success in clinical trials. However we should also consider the possibility that the methodology of clinical trials developed thus far is unable to prove the efficacy of any compound in the particular field of brain protection and will simply miss potentially important drugs. The present methodology of clinical trials is well established and it seems unlikely that it could be substantially improved in the coming years (see review in Adams 1993 for Stroke, Clifton 1992, Braakman 1993 for Trauma). However several constraints inherent in clinical trials may hamper their overall pertinence. One is the considerable heterogeneity of the patient population gathered according to entry criteria. For example, in severe trauma entry criteria are essentially limited to a given interval in the Glasgow Coma Scale (GCS) or to a general statement like "not obeying commands at admission". In European countries, 80% of severe head injuries are under neurosedation at the time of admission and to make a therapeutic window for assessment delays the start of treatment and creates other sources of errors. The assessment of GCS, or similar clinically based criteria, is simply not very reliable. Moreover such clinical definition covers a wide spectrum of lesions with very different pathophysiological mechanisms from focal contusion to diffuse acceleration injury with possibly very different responses to treatment. In stroke also the pathophysiological mechanisms might vary considerably. Reducing patient variability using CT scan data or prognostic factors to stratify randomisation may be of use in future trials. One fact strongly demonstrated in the experimental literature is that the efficacy of any drug is inversely associated with the delay of administration. The sooner the better, and the usual 6 hours of delay accepted for practical reasons may be simply to late. But, to shorten the delay of admission would considerably limit the number of patients eligible.

The generally accepted outcome measure in brain trauma is the Glasgow outcome scale (GOS) with its 5 categories of outcome (death, vegetative

state, severe disability, moderate disability, good recovery) often reduced to 3 (death, unfavourable or dependent, favourable or independent). One strength of the GOS is the fact that it is widely used and that more subtle tests to assess neuropsychological disabilities, though more sensitive, are difficult to use and do not seem to be suitable as primary outcome measures (Clifton *et al.* 1993). Another apparent strength of the GOS is that it is supposed to distinguish between clinically meaningful categories of outcome. Dependent versus independent is clinically meaningful indeed. However for a relatively large number of patients, the best among severely disabled and the worst among moderately disabled, final categorization may appear arbitrary. It is our feeling that the future of phase III trials in trauma depends on the development of a set of inclusion criteria selecting relatively homogeneous groups of patients, and of sensitive outcome measures assessing long term motor functions, neuropsychological disturbances, personality changes and social adjustment. The difficulties and costs involved may be considerable, however, the frustrations and costs of false negative conclusions are also very great.

3. Overall Philosophy of Brain Protection

Protection etymologically refers to one who holds a shield in front of his chest to guard against arrows and spears. In medicine protection should refer to a pretreatment prescribed in order to avoid a possible insult. In that sense hemodynamic and metabolic measures routinely taken in cardioaortic surgery for example, are brain protection. Beyond that original sense, to extend the concept of brain protection to encompass pretreatment of secondary damage is questionable. It is based on 2 implicit assumptions: one, that secondary damage does occur and has a sizeable influence on outcome, second that it is preventable in principle and that the type of drug that we are currently developing can contribute to this prevention. Let us briefly reconsider these assumptions.

In many cases of brain insult of a certain severity the occurrence of secondary damage in man is well documented. The major impact of secondary insult of ischemic hypoxic type from systemic disorders in trauma patients has been clearly demonstrated. Our possibilities of protection against these secondary insults by peventive measures are presumably very efficient though, even under medical care, hypoxic episodes are still common. In the absence of systemic problems, in most cases, proven secondary damage with clear bearing on outcome is caused by ICP elevation. That is evident in trauma as well as in stroke. In most cases of trauma high ICP is caused either by haematoma or by swelling and diffuse

edema. In most cases of stroke it is caused by rapidly worsening ischemic edema (Silver *et al.* 1984). In such situations even though the initial mechanisms of edema involve biochemical toxic mediators producing cell disordes and BBB alterations, the real threat comes from the bulk of edema and is related to vascular factors and mainly to an increase in hydrostatic pressures (Todd *et al.* 1986). Our treatments aimed at preventing or lowering high ICP have well known limitations. With no major changes in ICP, the ongoing cascade of biochemical events in the penumbral zone around a common type of stroke or a common type of traumatic contusion assuredly creates an area of secondary damage. Whether that type of secondary lesion has a decisive influence on outcome is likely in some cases but not clearly documented in general. Indeed it is that later type of secondary damage that could be the main target of pharmacological brain protection. The concept that tissue in this penumbral type of situation is salvageable (Memezawa *et al.* 1992), that maturation phenomena can end up in recovery (Ito and Klatzo 1992) is very popular. It seems to be warranted by a large collection of physiopathological and biochemical data accumulated in recent years. Certainly the many molecular mechanisms so often described by authoritative voices form a very consistent body of physiopathological explanations. Our concern is rather with the overall pertinence of these biochemical stories for the practicalities of brain protection. What is the exact time course of biochemical destruction? Does it occur in such time and space conditions that it is plausible that our drugs might usefully oppose is? A protective agent would be one which could lower and shift to the right the schematic curve given in Fig. 1, meaning that a larger part of the penumbral area could sustain a more severe reduction of flow for a longer time. For that to occur 2 conditions are required. One that the agent reach this particular area and be present in adequate concentration despite CBF disturbances. Second that the time course of the treatment be not far behind the time course of destruction, that it pretends to oppose. Relatively few solid facts suggest that this is possible in man. Most animals models produce a situation of *pre-* or *early post-treatment* of a *primary type* of insult, in which the time conditions are widely different. We have some indications in animals that following MCA occlusion, hypoperfused areas can regain normal function but PET scan studies in man have rather shown that hypoperfused area eventually turn to infarction.

The present concept of brain protection brings together in a unique piece of mechanistic thinking, facts, hypothesis and hopes. The investigation of biochemical cascades allows a scientific description of *facts*; the assumption that specifically these biochemical events are a major aspect of the secondary evolution of brain insults is for a large part *hypothesis*; the proposal that appropriate drugs could oppose this evolution in a clinically meaningful manner is as yet only a *hope*. Such a mixture of solid data, nice ideas and

dreams for a better world is typical of ideological thinking, and to some extent Brain Protection is a medical ideology. Ideologies are very common in medicine, they function as holistic and reassuring explanations within a given field of clinical experience and therapeutic expectancy. In whatever domain, ideological thinking always appears when we have to confront great challenges. Given the epidemiological data and our nearly complete lack of therapeutic effectiveness in brain trauma and stroke, brain protection is indeed a major challenge for medicine. Moreover the treatment of stroke and trauma is also a major challenge for pharmaceutical companies. These companies largely share, encourage and propagate the ideology of brain protection. A growing liaison is established between them and doctors involved as basic scientists or clinicians in brain protection research. This liaison, for many reasons, functions with a positive mutual reinforcement and is in itself a very clear determinant of the present vogue of brain protection.

The future of brain protection is not a sombre one. A major breakthrough in the therapy of acute brain insult is implausible. However more modest progress in selected subgroups of patients, perhaps in the medium range of severity, with one or another drug, or with a combination of drugs, or with drugs associated with hypothermia are, one may hope, quite possible. A major problem will remain how to assess modest beneficial effects of any treatment in such clinical circumstances. If as doctors in charge of patients with stroke or trauma we feel at the present time rather frustrated by the actual achievements of brain protection, we may wish to shift to the next ideology. One is already well at hand: namely Repair and/or Restoration in the CNS. There is a new set of concepts and hopes in our minds for more than ten years (Nottebohn 1985). And there are already links between destruction and repair: the proto-oncogenes of the fos and jun families are immediately expressed following ischemia (An *et al.* 1993) this expression seems to be induced by Ca^{++} overload and it is suggested that the target genes will include those that participate in protective and regenerative responses of the cell (Sagar 1993). We could smoothly pass from an ideology of protection to an ideology of repair.

Brain protection in itself as an important medical metaphor may be of great promise in the large field of chronic disorders, degenerative diseases and aging of the CNS (see Taylor *et al.* 1991, Olanow 1992, Beal 1992). As we already know calcium damage, excitotoxicity, and free radicals can also well explain degeneration and aging.

Acknowledgement

It is a pleasure to acknowledge the expert secreterial assistance of Ms. Isabelle Sese.

References

1. Abe K, Kogure K, Yamamoto H, *et al* (1987) Mechanism of arachidonic acid liberation during ischemia in gerbil cerebral cortex. J Neurochem 48: 503–509
2. Adams HP (1993) Trials of trials in acute ischemic stroke. Stroke 24: 1410–1415
3. Aitkenhead A, (1986) Cerebral protection. Br J Hosp Med 35(5): 290–298
4. Albers GW, Goldber MP, Choi DW (1989) N-methyl-D-aspartate antagonists: ready for clinical trial in brain ischemia? Ann Neurol 25: 398–403
5. Alborch E, Torregrosa G, Terrasa JC, Salom JB, Miranda FJ (1987) Effects of calcium entry blockers on experimental cerebral vasoconstriction. In: Cervos-Navarro J, Ferszt R (eds) Stroke and microcirculation. Raven, New York, pp 437–442
6. An G, Lin TN, Liu JS, et al (1993) Expression of c-fos and c-jun family genes after focal cerebral ischemia. Ann Neurol 33: 457–464
7. Anderson DK, Saunders RD, Demediuk P, Dugan LL, Braughler JM, Hall ED, Means ED, Horrocks LA (1985) Lipid hydrolysis and peroxidation in injured spinal cord: partial protection with methylprednisolone or vitamin E and selenium. CNS Trauma 12: 257–267
8. Araki J, Kato H, Kogure K (1989) Selective neuronal vulnerability following transient cerebral ischemia in the gerbil: distribution and time course. Acta Neurol Scand 80: 548–553
9. Aronowski J, Grotta JC, Waxham MN (1992) Ischemia-induced translocation of $Ca2^{+}$/calmodulin-dependent protein kinase II: potential role in neuronal degeneration. J Neurochem 58: 1743–1753
10. Aronowski J, Waxham MN, Grotta JC (1993) Neuronal protection and preservation of calcium/calmodulin-dependent protein kinase 11 and protein kinase C activity by destrorphan treatment in global ischemia. J Cereb Blood Flow Metab 13: 550–557
11. Arrigoni E, Avéret N, Loiseau H, Cohadon F (1987) Relationship between epileptic activity and edema formation in the acute phase of cryogenic lesion. Neurochem Pathol 7: 207–220
12. Arrigoni E, Cohadon F (1991) Calcium-activated neutral protease activities in brain trauma. Neurochem Res 16: 483–487
13. Asano T, Shigeno T, Johshita H, Usui M, Hanamura T (1987) A novel concept on the pathogenetic mechanism underlying ischaemic brain oedema: relevance of free radicals and eicosanoids. Acta Neurochir (Wien) [Suppl] 41: 85–94
14. Asano T, Tanishima T, Sasaki T, Sano K (1980) Possible participation of free radical reactions initiated by clot lysis in the pathogenesis of vasospasm after subarachnoid hemorrhage. In: Wilkins RH (ed) Cerebral arterial spasm. Williams and Wilkins, Baltimore, pp 190–201
15. Asplund K (1991) Hemodilution in acute stroke. Cerebrovasc Dis 1: 129–138
16. Astrup J (1982) Energy-requiring cell functions in the ischemic brain. J Neurosurg 56: 482–497
17. Astrup J, Siesjö BK, Symon L (1981) Thresholds in cerebral ischemia. The ischemic penumbra. Stroke 12(6): 723–725

18. Averet N, Coussemacq M, Cohadon F (1990) Thiobarbituric acid reaction material content and enzymatic protection against per-oxidative damage during the course of cryogenic rabbit brain edema. Neurochem Res 15: 791–795
19. Bachet J, Guilmet D, Goudot B, Termignon JL, Teodori G, Dreyfus G, Brodaty D, Dubois C, Delentdecker P (1991) Cold cerebroplegia: a new technique of cerebral protection during operations on the transverse aortic arch. J Thorac Cardiovasc Surg 102: 85–94
20. Baethmann A, Kempski O, Schürer L (1993) Mechanisms of secondary brain damage. Current state. Acta Neurochir (Wien) [Suppl] 57
21. Baethmann A, Maier-Hauff K, Schürer L, Lange M, Guggenbichler C, Vogt W, Jacob K, Kempski O (1989) Release of glutamate and of free fatty acids in vasogenic brain edema. J Neurosurg 70: 578–591
22. Baethmann A, Oettinger W, Rothenfusser W, *et al* (1980) Brain edema factors: current state with particular reference to plasma constituents and glutamate. Adv Neurol 28: 171–195
23. Balentine JD (1983) Calcium toxicity as a factor in spinal cord injury. Surv Synth Pathol Res 2: 184–193
24. Balentine JD, Greene WB (1984) Ultrastructural pathology of nerve fibers in calcium-induced myelopathy. J Neuropathol Exp Neurol 43: 500–510
25. Baron JC (1987) Ischemic stroke studied by 150-labeled compounds: misery perfusion and luxury perfusion. In: Heiss WD, Pawlik G, Herholz K, Wienhard K (eds) Clinical efficacy of positron emission tomography. Nijhoff, Dordrecht, pp 15–23
26. Baron JC, Bousser MG, Rey A, Guillard A, Comar D, Castaigne P (1981) Reversal of focal "misery-perfusion syndrome" by extra-intracranial arterial bypass in hemodynamic cerebral ischemia. Stroke 12: 454–459
27. Bartkowski HM, Brakel A, Mondora RA, Kutan R (1988) Therapeutic value of a constant intravenous infusion of nimodipine for 24 hours after acute cerebral infarction. Stroke 19: 147
28. Batjer HH (1993) Cerebral protective effects of etomidate experimental and clinical aspects. Cerebrovasc Brain Metab Rev 5: 17–32
29. Batjer HH, Frankfurt Al, Purdy PD, Smith SS, Samson DS (1988) Use of etomidate, temporary arterial occlusion and intraoperative angiography in surgical treatment of large and giant cerebral aneurysms. J Neurosurg 68: 234–240
30. Baumann KW, Kassell NF, Olin J, Yamada T (1982) The effects of gamma-hydroxybutyric acid on canine cerebral blood flow and metabolism. J Neurosurg 57: 197–202
31. Bazan NG (1970) Effects of ischemia and electroconvulsive shock on free fatty acid pool in the brain. Biochim Biophys Acta 218: 1–10
32. Bazan NG, Braquet P, Ginsberg MD (eds) (1992) Neurochemical correlates of cerebral ischemia. In: Advances in neurochemistry, Vol 7. Plenum, New York
33. Beal MF (1992) Does impairment of energy metabolism result in excitotoxic neuronal death in neurodegenerative illnesses? Ann Neurol 31: 119–130

34. Beckman J, Beckman T, Chen J, Marshall P, Freeman B (1990) Apparent hydroxyl radical production by peroxynitrite: implications for endothelical injury from nitric oxide and superoxide. Proc Natl Acad Sci 87: 1620–1624
35. Benson DW, Williams GR Jr, Spencer FC, Yates AJ (1959) The use of hypothermia after cardiac arrest. Anesth Analg 38: 423–428
36. Benveniste H, Drejer J, Schousboe A and Diemer NH (1984) Elevation of the extracellular concentrations of glutamate and aspartate in rat hippocampus during transient cerebral ischemia monitored by intracerebral microdialysis. J Neurochem 43: 1369–1374
37. Benveniste H, Jòrgensen B, Sandberg M, Christensen T, Hagberg H, Diemer NH (1989) Ischaemic damage in hippocampus CA1 is dependent on glutamate release and intact innervation from CA3. J Cereb Blood Flow Metab 9: 629–639
38. Berridge MJ (1984) Inositol trisphosphate and diacylglycerol as second messengers. Biochem J 220: 345–360
39. Bishop RL, Weisfeldt ML (1976) Sodium bicarbonate administration during cardiac arrest, effect on arterial pH, pCO_2 and osmolality. JAMA 235: 506–509
40. Bleyaert AL, Nemoto EM, Safar P, *et al* (1978) Thiopental amelioration of brain damage after global ischemia in monkeys. Anesthesiology 49: 390
41. Bolas N, Rajgopalan B, Mitsumori F, *et al* (1988) Metabolic changes during experimental cerebral ischemia in hyperglycemic rats, observed by ^{31}P and ^{1}H magnetic resonance spectroscopy. Stroke 19: 608–614
42. Borle AB (1981) Control, modulation and regulation of cell calcium. Rev Physiol Biochem Pharmacol 90: 13–164
43. Bouma GJ, Muizelaar JP, Choi SC, Newlon PG, Young HF (1991) Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischemia. J Neurosurg 75: 685–693
44. Braakman R (1993) Clinical trials in neurotrauma. Possibilities and pitfalls. Communication at the second International symposium on brain trauma. Glasgow, 1993
45. Braakman R (1994) Multicentre trials on the efficacy of nimodipine on outcome after severe head injury. European Study Group. J Neurosurg (in press)
46. Bracken MB, Shepard MJ, Collins WF, *et al* (1990) A randomized controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury: results of the second national acute spinal cord injury study. N Engl J Med 322: 1405–1411
47. Bracken MB, Shepard MJ, Collins WF, *et al* (1992) Methylprednisolone or naloxone treatment after acute spinal cord injury: 1-year follow-up data. J Neurosurg 76: 23–31
48. Bralet J, Beley P, Bralet AM, *et al* (1979) Influence of various agents on the development of brain edema in the rat following microembolism. Protective effect of gammabutyrolactone. Stroke 10: 653–656
49. Braughler JM, Hall ED, Means ED, *et al* (1987) Evaluation of an intensive methylprednisolone sodium succinate dosing regimen in experimental spinal cord injury. J Neurosurg 67: 102–105

50. Braughler JM, Lainer MJ (1986) The effects of large doses of methylprednisolone on neurologic recovery and survival in the Mongolian gerbil following three hours of unilateral carotid occlusion. Cent Nerv Syst Trauma 3: 153–162
51. Breivik H, Safar P, Sands P (1978) Clinical feasibility trials of barbiturate therapy after cardiac arrest. Crit Care Med 6: 228
52. Bromont C, Marie C, Bralet J (1989) Increased lipid peroxydation in vulnerable brain regions after transient forebrain ischemia in rats. Stroke 20: 918–924
53. Buchan A, Li H, Pulsinelli W (1991) The N-methyl-D-aspartate antagonist, MK-801, fails to protect against neuronal damage caused by transient, severe forebrain ischemia in adult rats. J Neurosci 11: 1049–1056
54. Bulkley GB (1987) Free radical-mediated reperfusion injury: a selective review. Br J Cancer [Suppl] 55: 66–73
55. Bullock R, Butcher SP, Chen MH, Kendall L, McCulloch J (1991) Correlation of the extracellular glutamate concentration with extent of blood flow reduction after subdural hematoma in the rat. J Neurosurg 74: 794–802
56. Bullock R, Graham DI, Chen MH, Lowe D, McCulloch J (1990) Focal cerebral ischemia in the cat: pretreatment with a competitive NMDA receptor antagonist D-CPP-ene. J Cereb Blood Flow Metab 10: 668–674
57. Busto R, Dletrich WD, Globus MY-T, Valdes I, Scheinberg P, Ginsberg MD (1987) Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. J Cereb Blood Flow Metab 7: 729–738
58. Busto R, Dietrich WD, Globus MY-T, Ginsberg MD (1989a) The importance of brain temperature in cerebral ischemic injury. Stroke 20: 1113–1114
59. Busto R, Globus MY-T, Dietrich WD, Martinez E, Valdes I, Ginsberg MD (1989b) Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. Stroke 20: 904–910
60. Busto R, Yoshida S, Ginsberg MD, Alsonso O, Smith DW, Goldberg WJ (1984) Regional blood flow in compression-induced brain edema in rats: effect of dietary vitamin E. Ann Neurol 15: 441–448
61. Butcher SP, Bullock R, Graham DI, McCulloch J (1990) Correlation between aminoacid release and neuropathological outcome in rat brain following middle cerebral artery occlusion. Stroke 21: 1727–1733
62. Campan L (1981) De la réanimation à la mort cérébrale. Agressologie 22: 89–100
63. Campbell KP, Leung AT, Sharp AH (1988) The biochemistry and molecular biology of the dihydropyridine-sensitive calcium channel. TINS 11: 425–430
64. Carafoli E (1987) Intracellular calcium homeostasis. Ann Rev Biochem 56: 395–433
65. Carter C, Benavides J, Legendre P, Vincent JD, Noel F, Thuret F, Lloyd KG, Arbilla S, Zivkovic B, MacKenzie ET, Scatton B, Langer SZ (1988) Ifenprodil and SL 820715 as cerebral anti-ischemic agents. II. Evidence for N-methyl-D-aspartate receptor antagonist properties. Pharmacol Exp Ther 247: 1222–1232
66. Castel JP (1991) Aspects of the medical management in aneurysmal sub-

arachnoid hemorrhage. In: Symon L, Calliauw L, Cohadon F, *et al* (eds) Advances and technical standards in neurosurgery, Vol 18. Springer, Wien New York, pp 47–110
67. Castel JP, Frerebeau P, Lagarrigue J, Moreau JJ (1994) Traitement neurochirurgical des anévrysmes intracraniens. Cours de la Société de Neurochirurgie de Langue Française, Paris, Décembre 1992. Neurochirurgie (in press)
68. Chan PH, Chen SF, Yu ACH (1988) Induction of intracellular superoxide radical formation by arachidonic acid and by polyunsaturated fatty acids in primary astrocytic cultures. J Neurochem 50: 1185–1193
69. Chan PH, Fishman RA (1980) Transient formation of superoxide radicals in polyunsaturated fatty acid-induced brain swelling. J Neurochem 35: 1004–1007
70. Chan PH, Fishman RA, Wesley MA, Longar S (1990) Pathogenesis of vasogenic edema in focal cerebral ischemia: role of superoxide radicals. Adv Neurol 52: 177–183
71. Chan PH, Longar S, Fishman RA (1983) Phospholipid degradation and edema development in cold-injured rat brain. Brain Res 277: 329–337
72. Chan PH, Longar S and Fishman RA (1987) Protective effects of liposome-entrapped superoxide dismutase on post-traumatic brain edema. Ann Neurol 21: 540–547
73. Chan PH, Yang GY, Chen SF, Carlson E, Epstein CJ (1991) Cold-induced brain edema and infarction are reduced in transgenic mice overexpressing Cuzn superoxide dismutase. Ann Neurol 29: 482–486
74. Chen HSV, Pellegrini JW, Aggarwal SK, Lei SZ, Warach S, Jensen FE, Lipton SA (1992) Open-channel block of NMDA responses by memantine therapeutic advantage against NMDA receptor-mediated neurotoxicity. J Neurosci 12: 4427–4436
75. Cheung JY, Bonventre JV, Malis CD, Leaf A (1986) Calcium and ischemic injury. N Engl J Med 314: 1670–1676
76. Choi DW (1987) Ionic dependence of glutamate neurotoxicity. Neuroscience 7(2): 369–379
77. Choi DW (1988a) Calcium mediated neurotoxicity: relationship to specific channel types and role in ischemic damage. Trends Neurosci 11: 465–469
78. Choi DW, Koh JY, Peters S (1988b) Pharmacology of glutamate neurotoxicity in cortical cell culture: attenuation by NMDA antagonists. Neuroscience 8: 185–196
79. Chopp M, Frinak S, Walton DR, *et al* (1987) Intracellular acidosis during and after cerebral ischemia in vivo nuclear magnetic resonance study of hyperglycemia in cats. Stroke 18: 919–923
80. Chopp M, Welgh KMA, Tidwell CD, *et al* (1988) Global cerebral ischemia and intracellular pH during hyperglycemia and hypoglycemia in cats. Stroke 19: 1383–1387
81. Chyatte D, Elefteriades J, Kim B (1989) Profound hypothermia and circulatory arrest for aneurysm surgery. J Neurosurg 70: 489–491
82. Clasen RA, Pandolfii S, Casey D (1974) Furosemide and phenobarbital in cryogenic cerebral injury and edema. Neurology 24: 642

83. Clemens JA, Saunders RD, Ho PP, Phebus LA, Panetta JA (1993) The antioxidant LY231617 reduces global ischemic neuronal injury in rats. Stroke 24: 716–723
84. Clifton GL (1992) Outcome measures for clinical trials involving traumatically brain-injured patients: report of a conference. Neurosurgery 31: 975–978
85. Clifton GL, Kreutzer JS, *et al* (1993) Relationship between Glasgow outcome scale and neuropsychological measures after brain injury. Neurosurgery 33: 34–39
86. Cole DJ, Drummond JC, Ruta TS, Peckham NH (1990) Hemodilution and hypertension effects on cerebral hemorrhage in cerebral ischemia in rats. Stroke 21: 1333–1339
87. Collins RC, Dobkin BH, Choi DW Selective vulnerability of the brain: new insights into the pathophysiology of stroke. Annals Intern Med 110: 992–1000
88. Conn AW, Montes JE, Barker GA, Edmonds JF (1980) Cerebral salvage in near drowning following neurological classification by triage. Can Anaesth Soc J 27: 201
89. Cooley DA, Mahaffey DE, De Bakey ME (1955) Total excision of the aortic arch for aneurysm. Surg Gynecol Obset 101: 667–672
90. Cooley DA, Ott DA, Frazier OH, Walker WE (1981) Surgical treatment of aneurysm of the transverse aortic arch: experience with 25 patients using hypothermic techniques. Ann Thorac Surg 32: 260–272
91. Corbett D, Evans S, Thomas C, Wang D, Jonas RA (1990) MK-801 reduced cerebral ischemic injury by inducing hypothermia. Brain Res 514: 300–304
92. Coselli JS, Crawford ES, Beall AC, Mizrahi EM, Hess KR, Patel VM (1988) Determination of brain temperatures for safe circulatory arrest during cardiovascular operation. Ann Thorac Surg 45: 638–642
93. Crawford ES, Saleh SA, Schessler J (1979) Treatment of aneurysm of transverse aortic arch. J Thorac Cardiovasc Surg 78: 383–393
94. Dawson TM, Dawson VL, Snyder SH (1992) A novel neuronal messenger molecule in brain: the free radical, nitric oxide. Ann Neurol 32: 297–311
95. Dawson VL, Dawson T, London ED, Bredt DS, Snyder SH (1991) Nitric oxide mediates glutamate neurotoxicity in primary cortical cultures. Proc Natl Acad Sci USA 88: 6368–6371
96. De Bakey ME, Crawford ES, Cooley DA, Morris GC (1957) Successful resection of fusiform aneurysm of aortic arch with replacement by homograft. Surg Gynecol Obstetric 105: 657–664
97. Demopoulos HB, Flamm ES, Seligman ML, *et al* (1977) Antioxidant effects of barbiturates in model membranes undergoing free radical damage. Acta Neurol Scand 56: 7
98. Demopoulos HB, Flamm E, Seligman M, Pietronigro DD (1982) Oxygen free radicals in central nervous system ischemia and trauma. In: Autor AP (ed) Pathology of oxygen. Academic Press, New York, pp 127–155
99. Demopoulos HB, Milvy P, Kakari S, Ransohoff J (1972) Molecular aspects of membrane structure in cerebral edema. In: Reulen HJ, Schürmann K (eds) Steroids and brain edema. Springer, Berlin Heidelberg New York, pp 29–39

100. Dempsey RJ, Maley BE, Cowen D, Olson JW (1988) Ornithine decarboxylase activity and immunohistochemical location in postischemic brain. J Cereb Blood Flow Metab 8: 843–847
101. Dernbach PD, Little JR, Jones SC, Ebrahim ZY (1988) Altered autoregulation an CO2 reactivity after aneurysmal subarachnoid hemorrhage. Neurosurgery 22: 822–826
102. Diemer NH, Johansen FF, Jorgensen MB (1990) N-methyl-D-aspartate and non-N-methyl-D-aspartate antagonists in global cerebral ischemia. Stroke 21 [Suppl III]: 39–42
103. Dienel GA (1984) Regional accumulation of calcium in postischemic rat brain. J Neurochem 43: 913–925
104. Dietrich WD, Busto R, Valdes I, Loor Y (1990) Effects of normothermic versus mild hyperthermic forebrain ischemia in rats. Stroke 21: 1318–1325
105. Dirnagl U, Tanabe J, Pulsinelli W (1990) Pre- and posttreatment with MK-801 but not pretreatment alone reduces neocortical damage after focal cerebral ischemia in the rat. Brain Res 527: 62–68
106. Doczi T, Joo F, Sonkodi S, *et al* (1986) Increased vulnerability of the BBB to experimental SAH in hypotensive rats. Stroke 17: 498–500
107. Downey JM (1988) Ischaemia-reperfusion injury: current research status. Free Rad Res Commun 5: 185–208
108. Drake CG, Barr HWK, Coles JC, Gergely NF (1964) The use of extracorporeal circulation and profound hypothermia in the treatment of ruptured intracranial aneurysm. J Neurosurg 21: 575–581
109. Drejer J, Beneviste H, Diemer NH, Schousboe A (1985) Cellular origin of ischemia induced glutamate release from brain tissue in vivo and in vitro. J Neurochem 45: 145–151
110. Dumuis A, Sebben M, Haynes L, Pin JP, Bockaert J (1988) NMDA receptors activate the arachidonic acid cascade system in striatal neurons. Nature 336: 68–73
111. Edgar AD, Strosznajder J, Horrocks LA (1982) Activation of ethanolamine phospholipase A2 in brain during ischemia. J Neurochem 39: 1111–1116
112. Edwards DH, Byrne JV, Griffith TM (1992) The effect of chronic subarachnoid hemorrhage on basal endothelium-derived relaxing factor activity in intrathecal cerebral arteries. J Neurosurg 76: 830–837
113. Ernster L (1988) Biochemistry of reoxygenation injury. Crit Care Med 16: 947–953
114. Escuret E, Roquefeuil B, Frerebeau P, *et al* (1977) Effect of hyperventilation associated with administration of central nervous depressants in brain injuries. Acta Neurol Scand 56 [Suppl 64]: 154–155
115. Faden Al, Demediuk P, Panter SS, Vink R (1989) The role of excitatory amino acids and NMDA receptors in traumatic brain injury. Science 244: 798–800
116. Faden AI, Jacobs TP, Mougey E, *et al* (1981) Endorphins in experimental spinal cord injury: therapeutic effect of naloxone. Ann Neurol 10: 326–332
117. Faden Al, Salzman S (1992) Pharmacological strategies in CNS trauma. Trends Pharmacol Sci 13: 29–35

118. Faden AI, and Simon RP (1988) A potential role for excitotoxins in the pathophysiology of spinal cord injury. Ann Neurol 23: 623–626
119. Farber JL (1981) The role of calcium in cell death. Life Sci 29: 1289–1295
120. Fay T (1943) Observations on generalized refrigeration in cases of severe cerebral trauma. Assoc Res Nerv Ment Dis Proc. 24: 611–619
121. Fazl M, Houlden DA, Weaver K (1991) Correlation between cerebral blood flow, somatosensory evoked potentials, CT scan grade, and neurologic grade in patients with subarachnoid hemorrhage. Can J Neurol Sci 18: 453–457
122. Ferguson GG (1982) Intra-operative monitoring and internal shunts: are they necessary in carotid endarterectomy? Stroke 13: 287
123. Findlay JM, Weir BKA, Kanamaru K, Espinosa F (1989) Arterial wall change in cerebral vasospasm. Neurosurgery 25: 736–746
124. Flamm ES, Seligman ML, Demopoulos HB (1980) Barbiturate protection of the ischemic brain. In: Cotterell JE, Turndorf H (eds) Anaesthesia and neurosurgery. Mosby, Saint Louis, pp 248–260
125. Flamm ES, Young W, Demopoulos HB, *et al* (1982) Experimental spinal cord injury: treatment with naloxone. Neurosurgery 10: 227–231
126. Francel PC, Long BA, Malik JM, Tribble C, Jane JA, Kron IL (1993) Limiting ischemic spinal cord injury using a free radical scavenger 21-aminosteroid and/or cerebrospinal fluid drainage. J Neurosurg 79: 742–751
127. Frandsen A, Schousboe A (1992) Mobilization of Dantrolene-sensitive intracellular calcium pools is involved in the cytotoxicity induced by quisqualate and N-methyl-D-aspartate but not by 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionate and kainate in cultured cerebral cortical neurons. Proc Natl Acad Sci USA 89: 2590–2594
128. Freeman BA, Crapo JD (1982) Biology of disease: free radicals and tissue injury. Lab Invest 47: 412–426
129. Frerichs KU, Lindsberg PJ, Hallenbeck JM, Feuerstein GZ (1990) Platelet-activating factor and progressive brain damage following focal brain injury. J Neurosurg 73: 223–233
130. Fridovich I (1978) The biology of oxygen radicals. The superoxide radical is an agent of oxygen toxicity: superoxide dismutases provide an important defense. Science 201: 875–880
131. Frist WH, Baldwin JC, Starnes VA, Stinson EB, Oyer PE, Crig Miller D, Jamieson SW, Scott Mitchell R (1986) A reconsideration of cerebral perfusion in aortic arch replacement. Ann Thorac Surg 42: 273–281
132. Frost EAM (1981) Brain preservation. Anesth Analg 60: 821–832
133. Gaab M, Knoblich OE, Spohr A, *et al* (1980) Effect of THAM on ICP, EEG and tissue edema. In: Shulman K, Marmarou A, Meller JD, *et al* (eds) Intracranial pressure, Vol I. Springer, Wien New York, pp 664–668
134. Garcia JH (1990) Relevance of experimental models to clinical stroke. In: Weinstein PR, Faden AI (eds) Protection of the brain from ischemia, pp 75–79
135. Gennarelli TA (1983) Head injury in man and experimental animals: clinical aspects. Acta Neurochir (Wien) [Suppl] 32: 1–13
136. Gennarelli TA, Tipperman R, Maxwell WL, Graham DI, Adams JH, Irvine A

(1993) Traumatic damage to the nodal axolemma: an early, secondary injury. Acta Neurochir (Wien) [Suppl] 57: 49–52
137. Giannotta SL, Weiss MH, Apuzzo MLJ, *et al* (1984) High dose glucocorticoids in the management of severe head injury. Neurosurgery 15: 497–501
138. Ginsberg MD, Sternau LL, Globus MYT, Dietrich WD, Busto R (1992) Therapeutic modulation of brain temperature: relevance to ischemic brain injury. Cerebrovasc. Brain Metab Rev 4: 189–225
139. Goldberg WJ, Watson BD, Busto R, Kurchner H, Santiso M, Ginsberg MD (1984) Concurrent measurement of (Na^{++} K^{+})-ATPase activity and lipid peroxides in rat brain following reversible global ischemia. Neurochem Res 9: 1737–1747
140. Gotti B, Benavides J, MacKenzie ET, Scatton B (1990) The pharmacotherapy of focal cortical ischaemia in the mouse. Brain Res 522: 290–307
141. Gotti B, Duverger D, Bertin J, Carter C, Dupont R, Frost J, Gaudilliere B, MacKenzie ET, Rousseau J, Scatton B, Wick A (1988) Ifenprodil and SL 82.0715 as cerebral anti-ischemic agents. I. Evidence for efficacy in models of focal cerebral ischemia. J Pharmacol Exp Ther 247: 1211–1221
142. Graff HW, Leach W, Arieff AI (1985) Evidence for a detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. Science 227: 754–757
143. Graham DI, Adams JH, Doyle D (1978) Ischaemic brain damage in fatal non-missile head injuries.
144. Graham DI, Ford I, Adams JH, Doyle D, Teasdale GM, Lawrence AE, McLellan DR (1989) Ischaemic brain damage is still common in fatal non-missile head injury. J Neurosurg Psychiatry 52: 346–350
145. Graham SH, Chen J, Sharp FR, Simon RP (1993) Limiting ischemic injury by inhibition of excitatory amino acid release. J Cereb Blood Flow Metab 13: 88–97
146. Greeley WWJ, Ungerleider RM, Smith LR, Reves JG (1989) The effects of deep hypothermic cardiopulmonary bypass and total circulatory arrest on cerebral blood flow in infants and children. J Thorac Cardiovasc Surg 97: 737–745
147. Greenberg JH, Uematsu D, Araki NI, Reivich M (1991) Changes in intracellular free calcium during cerebral ischemia and the effects of nimodipine on calcium and histological damage. In: Scriabine A, Teasdale GM, Tettenborn D, Young W (eds) Nimodipine: pharmacological clinical results in cerebral ischemia. Springer, Berlin Heidelberg New York Tokyo, pp 9–24
148. Guilmet D, Roux PM, Bachet J, Goudot B, Tawil N, Diaz F (1986) Nouvelle technique de protection cérébrale; chirurgie de la crosse aortique. Presse Med 15: 1096–1098
149. Hadley MN (1991) Experimental models of focal ischemia: results with Nimodipine. In: Scriabine A, Teasdale GM, Tettenborn D, Young W (eds) Nimodipine: pharmacological clinical results in cerebral ischemia. Springer, Berlin Heidelberg New York Tokyo, pp 29–32
150. Hagberg H, Lehmann A, Sandberg M, Nyström B, Jacobson I, Hamberger A (1985) Ischemia-induced shift of inhibitory and excitatory amino acids from intra- to extracellular compartments. J Cereb Blood Flow Metab 5: 413–419
151. Hagerdal M, Harp J, Milsson L, Siesjö BK (1975) The effect of induced

hypothermia upon oxygen consumption in the rat brain. J Neurochem 24: 311–316
152. Hall ED (1992) The neuroprotective pharmacology of methylprednisolone. J Neurosurg 76: 13–22
153. Hall ED (1988) Effects of the 21-aminosteroid U74006F on posttraumatic spinal cord ischemia in cats. J Neurosurg 68: 462–465
154. Hall ED (1989) Free radicals and CNS injury. Crit Care Clin 5: 793–805
155. Hall ED, Braughler JM (1982) Glucocorticoid mechanisms in acute spinal cord injury: a review and therapeutic rationale. Surg Neurol 18: 320–327
156. Hall ED, Wolf DL, Braughler JM (1984) Effects of a single large dose of methylprednisolone sodium succinate on experimental posttraumatic spinal cord ischemia. Dose-response and time-action analysis. J Neurosurg 61: 124–130
157. Hall ED, Wolf DL (1986) A pharmacological analysis of the pathophysiological mechanisms of posttraumatic spinal cord ischemia. J Neurosurg 64: 951–961
158. Hall ED, Wolf DL, Althaus JS, von Voigtlander PF (1987) Beneficial effects of the kappa opioid receptor agonist U-50488H in experimental acute brain and spinal cord injury. Brain Res 435: 174–180
159. Hall ED, Yonkers PA, Horan KL, Braughler JM (1989) Correlation between attenuation of posttraumatic spinal cord ischemia and preservation of tissue vitamin 21-aminosteroid U74006 F: Evidence for an in vivo antioxidant mechanism. J Neurotrauma 6(3): 169–176
160. Halliwell B (1989) Oxidants and the central nervous system: some fundamental questions. Acta Neurol Scand 126: 23–33
161. Halliwell B (1989b) Superoxide, iron, vascular endothelium and reperfusion injury. Free Rad Res Commun 5: 315–318
162. Halliwell B, Gutteridge JMC (1989) Free radicals in biology and medicine, 2nd Ed. Clarendon Press, Oxford
163. Halsey JH (1992) Risks and benefits of shunting in carotid endarterectomy. Stroke 23: 1583–1587
164. Harada T, Suzuki Y, Satoh S, Ikegaki I, Asano T, Shibuya M, Sugita K (1990) Blood component induction of cerebral vasospasm. Neurosurgery 27: 252–256
165. Harris RJ, Symon L, Branston NM, Bayhan M (1981) Changes in extracellular calcium activity in cerebral ischemia. J Cereb Blood Flow Metab 1: 203–209
166. Harrison MJG (1992) Protection against ischaemia: the basis of acute stroke therapy. Current Opin Neurol Neurosurg 5: 33–38
167. Hass WK (1981) Beyond cerebral blood flow, metabolism and ischemic thresholds: an examination of the role of calcium in the initiation of cerebral infarction. In: Meyer JS, Lechner H, Reivich M, Ott EO, Arabinar A (eds) Cerebral vascular disease, Vol 3. Proceedings of the 10th Salzburg Conference on Cerebral Vascular Disease. Excerpta Medica, Amsterdam, pp 3–17
168. Hayes RL, Jenkins LW, Lyeth BG (1992) Neurotransmitter-mediated mechanisms of traumatic brain injury: acetylcholine and excitatory amino acids. J Neurotrauma 9 [Suppl 1]: S173–S187
169. Heiss WD (1992) Experimental evidence of ischemic thresholds and functional recovery. Stroke 23: 1668–1672

170. Heiss WD, Fink GR, Pietrzyk U, Huber M, Herholz K (1992) Do PET data support a therapeutic window in ischemic stroke? In: Krieglstein J, Oberpichler-Schwenk H (eds) Pharmacology of cerebral ischemia. Wissenschaftliche Verlagssellschaft, Stuttgart, pp 529–536
171. Heiss WD, Rosner G (1983) Functional recovery of cortical neurons as related to degree and duration of ischemia. Ann Neurol 14: 294–301
172. Hoff JT (1986) Cerebral protection. J Neurosurg 65: 579–591
173. Hoff JT, Pitts LH, Spetzler R, *et al* (1977) Barbiturates from protection from cerebral ischemia in aneurysm surgery. In: Ingvar DH, Lassen N (eds) Cerebral function, metabolism and circulation. Acta Neurol Scand 56: 158
174. Hoff JT, Smith AL, Hankinson HL (1975) Barbiturate protection from cerebral infarction in primates. Stroke 6: 28
175. Hossmann KA (1982) Treatment of experimental cerebral ischemia. J Cereb Blood Flow Metab 2: 275–297
176. Hossmann KA, Paschen W (1992) Disturbances of protein and polyamine metabolism after reversible cerebral ischemia. In: Bazan NG, Braquet P, Ginsberg MD (eds) Neurochemical correlates of cerebral ischemia. Advances in neurochemistry, Vol 7. Plenum, New York, pp 59–83
177. Hossmann KA, Widmann R, Wiessner Ch, Dux E, Djuricic B, Röhn G (1992) Protein synthesis after global ischemia and selective vulnerability. In: Krieglstein J, Oberpichler-Schwenk H (eds) Pharmacology of cerebral ischemia. Wissenschaftliche Verlagsgesellschaft, Stuttgart, pp 289–299
178. Hsu CY (1993) Criteria for valid preclinical trials using animal stroke models. Stroke 24: 633–663
179. Huang SFL, Sun GY (1987) Acidic phospholipids, diacylglycerols, and free fatty acids in gerbil brain: a comparison of ischemic changes resulting from carotid ligation and decapitation. J Neurosci Res 177: 162–167
180. Ikeda Y, Anderson JH, Long DM (1989a) Oxygen free radicals in the genesis of traumatic and peritumoral brain edema. Neurosurgery 24: 769–685
181. Ikeda Y, Ikeda K, Long DM (1989b) Comparative study of different iron-chelating agents in cold-induced brain edema. Neurosurgery 24: 820–824
182. Ikeda Y, Long DM (1990) The molecular basis of brain injury and brain edema: the role of oxygen free radicals. Neurosurgery 27: 1–11
183. Ikeda M, Yoshida S, Busto R, *et al* (1986) Polyphosphoinositides as a probable source of brain free fatty acids accumulated at the onset of ischemia. J Neurochem 47: 123–132
184. Ito U, Kirino T, Kuroiwa T, Klatzo I (eds) (1990) Maturation phenomenon in cerebral ischemia. Proceedings of the satellite symposium of the XIth International Congress of Neuropathology, Tokyo. Springer, Berlin Heidelberg New York Tokyo, pp 11–12
185. Ito U, Spatz M, Walker JT Jr, Klatzo I (1975) Experimental cerebral ischemia in Mongolian gerbils. I. Light microscopic observations. Acta Neuropathol (Berl) 32: 209–223
186. Jansen C, Vriens EM, Eikelboom BC, Vermeulen FEE, Van Gijn J, Ackerstaff FGA (1993) Carotid endarterectomy with transcranial Doppler and electro-

encephalographic monitoring: a prospective study in 130 operations. Stroke 24: 665–669
187. Javid H, Julian OC, Dye WS, *et al* (1979) Seventeen-year experience with routine shunting in carotid artery surgery. Stroke 3: 167
188. Jenkins LW, Moszynski K, Lyeth BG, Lewelt W, DeWitt DS, Allen A, Dixon CE, Povlishock JT, Majewski TJ, Clifton GL, Young HF, Becker DP, Hayes RL (1989) Increased vulnerability of the mildly traumatized rat brain to cerebral ischemia: the use of controlled secondary ischemia as a research tool to identify common or different mechanisms contributing to mechanical and ischemic brain injury. Brain Res 477: 211–224
189. Johansen FF, Jorgensen MB, Ekstrom von Lubitz KJ, Diemer NH (1986) Selective dendrite damage in hippocampal CA1 stratum radiatum with unchanged axon ultrastructure and glutamate uptake after transient cerebral ischaemia in the rat. Brain Res 291: 373–377
190. Johnston RA (1993) The management of acute spinal cord compression. J Neurol Neurosurg Psychiatry 56: 1046–1054
191. Jones TJ, Morawetz RB, Crowell RM, Marcoux FW, Fitzgibbon SJ, Degirolami U, Ojemann RG (1981) Thresholds of focal cerebral ischemia in awake monkeys. J Neurosurg 54: 773–782
192. Joo F, Kovàcs J, Szerdahelyi P, Temersvàri P, Tosaki A (1992) Treatment with histamine receptor antagonists of ischemic brain edema. In: Krieglstein J, Oberpichler-Schwenk H (eds). Pharmacology of cerebral ischemia. Wissenschaftliche Verlagsgesellschaft, Stuttgart, pp 217–225
193. Kakarieka, Braakman R, Schakel EH (1993) Traumatic subarachnoid hemorrhage. Importance and treatment perspective with nimodipine. Communication 2nd International Neurotrauma Symposium, Glasgow (in press)
194. Kaku DA, Goldberg MP, Choi DW (1991) Antagonism of non-NMDA receptors augments the neuroprotective effect of NMDA receptor blockade in cortical cultures subjected to prolonged deprivation of oxygen and glucose. Brain Res 554: 344–347
195. Kalimo K, Rehncrona S, Söderfeldt B, Olsson Y, Siesjö BK (1981) Brain lactic acidosis and ischemic cell damage, Vol 1. Histopathology. J Cereb Blood Flow Metab 1: 313–327
196. Kamiya T, Katayama Y, Kashinagi F, Terashi A (1993) The role of bradykinin in mediating ischemic brain edema in rats. Stroke 24: 571–576
197. Kanamaru K., Weir BKA, Findlay JM, Grace M, MacDonald RL (1990) A dosage study of the effect of the 21-aminosteroid U74006 F on chronic cerebral vasospasm in a primate model. Neurosurgery 27: 29–38
198. Kanamaru K, Weir BKA, Simpson I, Witbeck T, Grace M (1991) Effect of 21-aminosteroid U-74006F on lipid peroxidation in subarachnoid clot. J Neurosurg 74: 454–459
199. Kaplan B, Brint S, Tanabe J, Jacewicz M, Wang XJ, and Pulsinelli W (1991) Temporal thresholds for neocortical infarction in rats subjected to reversible focal cerebral ischemia. Stroke 22: 1032–1039
200. Katayama Y, Becker DP, Tamura T, *et al* (1990) Increase in extracellular

glutamate and associated massive ionic fluxes following concussive brain injury. J Neurosurg 73: 889–900
201. Kempski O, Shohami E, von Lubitz D, *et al* (1987) Postischemic production of eicosanoids in gerbil brain. Stroke 18: 111–119
202. Kety SS (1950) Circulation and metabolism of the human brain in health and disease. Am J Med 8: 205–217
203. Kinuta Y, Kimura M, Itokawa Y, Ishikawa M, Kikuchi H (1989a) Changes in xanthine oxidase in ischemic rat brain. J Neurosurg 1: 417–420
204. Kinuta Y, Kikuchi H, Ishikawa M, Kimura M, Itokawa Y (1989b) Lipid peroxydation in focal cerebral ischemia. J Neurosurg 71: 421–429
205. Kirino T (1982) Delayed neuronal death in the gerbil hippocampus following ischemia. Brain Res 239: 57–69
206. Kitagawa K, Matsumoto M, Oda T, Niinobe M, Hata R, Handa N, Fukunaga R, Isaka Y, Kimura K, Maeda H, Mikoshiba K, Kamada T (1990) Free radical generation during brief period of cerebral ischemia may trigger delayed neuronal death. Neuroscience 35: 551–558
207. Kochanek PM, Hallenbeck JM (1992) Polymorphonuclear leukocytes and monocytes/macrophages in the pathogenesis of cerebral ischemia and stroke. Stroke 23: 1367–1379
208. Kochanek PM, Dutka AJ, Kumaroo KK, *et al* (1988a) Effects of prostacyclin, indomethacin, and heparin on cerebral blood flow and platelet adhesion after multifocal ischemia of canine brain. Stroke 19: 693–699
209. Kochanek PM, Nemoto EM, Melick JA, *et al* (1988b) Cerebrovascular and cerebrometabolic effects of intracarotid infusion of platelet-activating factor in rats. J Cereb Blood Flow Metab 8: 546–551
210. Kofke WA, Nemoto EM, Hossman KA, *et al* (1979) Brain blood flow and metabolism after global ischemia and post-insult thiopental therapy in monkeys. Stroke 10: 554
211. Kogure K and Nakano S (1992) Dysmetabolism in lipid brain ischemia. In: Bazan NG, Braquet P, Ginsberg MD (eds) Neurochemical correlates of cerebral ischemia. Advances in neurochemistry, Vol 7. Plenum, New York, pp 103–116
212. Koh JY, Palmer E, Cotman CW (1991) Activation of the metabotropic glutamate receptor attenuates N-methyl-D-aspartate neurotoxicity in cortical cultures. Proc Natl Acad Sci USA 88: 9431–9435
213. Kohama A, Takasu N, Ishimatsu S, Maenosono A, Suzuki K (1991) The effects of sodium bicarbonate on cerebrospinal fluid acid-base disturbances in total cerebral ischemia. In: Takeshita H, Siesjö BK, Miller JD (eds) Advances in brain resuscitation. Springer, Berlin Heidelberg New York Tokyo, pp 151–163
214. Kohut JJ, Bednar MM, Kimelberg HK, McAuliffe TL, Gross CE (1992) Reduction in ischemic brain injury in rabbits by the anion transport inhibitor L-644,711. Stroke 23: 93–97
215. Kontos HA, Povilshock JT (1986) Oxygen radicals in brain injury. CNS Trauma 3: 257–263
216. Kontos HA, Wei EP (1986) Superoxide production in experimental brain injury. J Neurosurg 64: 803–807

217. Krueger C, Weir B, Nosko M, *et al* (1985) Nimodipine and chronic vasospasm in monkeys. Part 2: pharmacological studies of vessels in spasm. Neurosurgery 16: 137–140
218. Kumar R, Harvey SAK, Kester M, *et al* (1988) Production and effects of platelet-activating factor in the rat brain. Biochim Biophys Acta 963: 375–383
219. Kusumoto K, Mackay KB, McCulloch J (1992) The effect of the kappa-opioid receptor agonist CI-977 in a rat model of focal cerebral ischaemia. Brain Res 576: 147–151
220. Kuwabara M (1992) Continuous monitoring of blood oxygen of internal jugular vein as a useful indicator for selective cerebral perfusion during aortic arch replacement. J Thorac Cardiovasc Surg 103: 355–362
221. Laborit G, Kind A, DeLeon RC (1961) 220 Cases of anesthesia in neurosurgery with sodium 4-hydroxybutyrate. Presse Med 69: 1216–1217 (Fre)
222. Laborit H, Huguenard P (1951) L'hibernation artificielle par moyens pharmacodynamiques et physiques en chirurgie. J Chir 67: 631–641
223. Lam AM, Winn HR, Cullen BF, Sundling (1991) Hyperglycemia and neurological outcome in patients with head injury. J Neurosurg 75: 545–551
224. Lawner P, Lourent J, Simeone F, *et al* (1979) Attenuation of ischemic brain edema by pentobarbital after carotid ligation in the gerbil. Stroke 10: 644
225. Lazorthes G (1978) L'hypotension artérielle contfolée en neurochirurgie. Neurochirurgie 24: 143–196
226. Lazorthes G, Campan L (1958) Hypothermia in the treatment of craniocerebral traumatism. J Neurosurg 15: 162–167
227. Lazorthes Y, Sonilhac FR, Lagarrigue J, Scavazza R (1992) La surveillance des potentiels évoqués somesthésiques dans la chirurgie des anévrysmes sylviens. Neurochirurgie 38: 333–346
228. Le Mée F (1993) Protection cérébrale par perfusion cérébrale sélective dans la chirurgie de la crosse aortique. Université de Bordeaux II, année 1993. Thèse no 3013
229. Lei SZ, Pan ZH, Aggarwal SK, Chen HS, Hartman J, Sucher NJ, Lipton SA (1992) Effect of nitric oxide production on the redox modulatory site of the NMDA receptor-channel complex. Neuron 8: 1087–1099
230. Lei SZ, Zhang D, Abele AE, Lipton SA (1992) Blockade of NMDA receptor-mediated mobilization of intracellular Ca^{++} prevents neurotoxicity. Brain Res 598: 196–202
231. Leonov Y, Sterz F, Safar P, *et al* (1990) Mild cerebral hypothermia during and after cardiac arrest improves neurologic outcome in dogs. J Cereb Blood Flow Metab 10: 57–70
232. Lindsberg PJ, Yue TL, Frerichs KU, Hallenbeck JM, Feuerstein G (1990) Evidence for platelet-activating factor as a novel mediator in experimental stroke in rabbits. Stroke 21: 1452–1457
233. Lipton SA (1993) Molecular mechanisms of trauma-induced neuronal degeneration. Curr Opin Neurol Neurosurg 6: 588–596
234. Liu TH, Beckman JS, Freeman BA, Hogan EL, Hsu CY (1989) Polyethylene glycol-conjugated superoxide dismutase and catalase reduce ischemic brain injury. Am J Physiol 56: H589–H593

235. Livesay JJ, Cooleu DA, Real GJ, Walker WE, Frazier OH, Duncan JM, Ott DA (1983) Resection of aortic arch aneurysms: a comparison of hypothermic techniques in 60 patients. Ann Thorac Surg 36: 19–28
236. Lowry OF, Passonneau JV, Hasselberger FX, Schultz PM (1964) Effect of ischemia on known substrates and cofactors of the glycocytic pathway in brain. J Biol Chem 239: 18–30
237. Lyden PD, Hedges B (1992) Protective effect of synaptic inhibition during cerebral ischemia in rats and rabbits. Stroke 23: 1463–1470
238. Lyeth BG, Ray M, Hamm RJ, Schnable J, Sandy JJ, Poklis A, Jenkins LW, Gudeman SK, Hayes RL (1992) Postinjury scopolamin administration in experimental traumatic brain injury. Brain Res 569: 281–286
239. Lysko PG, Lysko KA, Yue TL, Webb CL, Gu JL, Feuerstein G (1992) Neuroprotective effects of carvedilal, a new antihypertensive agent, in cultured rat cerebellar neurons and in gerbil global brain ischemia. Stroke 23: 1630–1636
240. Mackay KB, Kusumoto K, Graham DI, McCulloch J (1992) The effects of a kappa opioid agonist in experimental focal cerebral ischemia. In: Krieglstein J, Oberpichler-Schwenk H (eds) Pharmacology of cerebral ischemia. Wissenschaftliche Verlagsgesellschaft, Stuttgart, pp 207–215
241. Mahadik S (1992) Gangliosides: new generation of neuroprotective agents. In: Marangos P (ed) Emerging strategies in neuroprotection. Birkhauser, Boston, pp 196–200
242. Mahfood S, Qazi A, Garcia J, Mispiret A, Corso P, Smyth N (1984) Management of aortic arch aneurysm using profound hypothermia and circulatory arrest. Ann Thorac Surg 39: 412–417
243. Marin P, Lafon-Cazal M, Bockaert J (1992) A nitric-oxide synthase activity selectively stimulated by NMDA receptors depends on protein kinase C activation in mouse striatal neurons. Eur J Neurosci 4: 425–432
244. Marion DW, Obrist WD, Carlier PM, Penrod LE, Darby JM (1993) The use of moderate therapeutic hypothermia for patients with severe head injuries: a preliminary report. J Neurosurg 79: 354–362
245. Maroon JC, Nelson PB (1979) Hypovolemia in patients with subarachnoid hemorrhage: therapeutic implications. Neurosurgery 4: 223–226
246. Marshall LF, Shapiro HM, Ranscher A, Kaufman NM (1978) Pentobarbital therapy for intracranial hypertension in metabolic coma: Reye's syndrome. Crit Care Med 6: 1
247. Marshall LF, Smith RW, Shapiro HM (1979) The outcome with aggressive treatment in severe head injuries. Part II: acute and chronic barbiturate administration in the management of head injury. J Neurosurg 50: 26–30
248. Martz D, Rayos G, Schielke GP, Betz AL (1989) Allopurinol and dimethylthiourea reduce brain infarction following middle cerebral artery occlusion in rats. Stroke 20: 488–494
249. Mayer S, Pulsinelli W (1992) Failure of GM1 ganglioside to influence outcome in experimental focal ischemia. Stroke 23: 242–246
250. McDernott MW, Durity FA, Borozny M, Mountain MA (1989) Temporary

vessel occlusion and barbiturate protection in cerebral aneurysm surgery. Surgery 25: 54–62
251. McCord JM (1985) Oxygen-derived free radicals in postischemic tissue injury. N Engl J Med 312: 159–163
252. McCulloch J (1992) Excitatory amino acid antagonists and their potential for the treatment of ischaemic brain damage in man. Br J Clin Pharmac 34: 106–114
253. Meldrum B (1990) Protection against ischaemic neuronal damage by drugs acting on excitatory neurotransmission. Cerebrovasc Brain Metab Rev 2: 21–57
254. Meldrum B (1992) Protection against ischemic brain damage by excitatory amino acid antagonists. In: Bazan NG, Braquet P, Ginsberg MD (eds) Neurochemical correlates of cerebral ischemia. Advances in neurochemistry, Vol 7. Plenum, New York, pp 245–264
255. Meldrum B, Evans M, Griffiths T, Simon R (1985) Ischemic brain damage: the role of excitatory activity and of calcium entry. Br J Anaesth 57: 44–46
256. Memezawa H, Smith ML, Siesjö BK (1992) Penumbral tissues salvaged by reperfusion following middle cerebral artery occlusion in rats. Stroke 23: 552–559
257. Meyer FB (1989) Calcium, neuronal hyperexcitability and ischemic injury. Research Reviews 14: 227–243
258. Milde LM, Milde JH, Michenfelder JD (1985) Cerebral functional, metabolic, and hemodynamic effects of etomidate in dogs. Anesthesiology 63: 371–377
259. Milde LM, Milde JH (1986) Preservation of cerebral metabolites by etomidate during incomplete cerebral ischemia in dogs. Anesthesiology 65: 272–277
260. Miller JD (1993) Head injury. J Neurol Neurosurg Psychiatry 56: 440–447
261. Minami N, Tani E, Maeda Y, *et al* (1992) Effects of inhibitors of protein kinase C and calpain in experimental delayed cerebral vasospasm. J Neurosurg 76: 111–118
262. Minamisawa H, Nordström CH, Smith ML, Siesjö BK (1990) The influence of mild body and brain hypothermia on ischemic brain damage. J Cereb Blood Flow Metab 10: 365–374
263. Minamisawa H, Smith ML, Siesjö BK (1990) The effect of mild hyperthermia and hypothermia on brain damage following 5, 10, and 15 minutes of forebrain ischemia. Ann Neurol 28: 26–33
264. Mink RB, Dutka AJ, Hallenbeck JM (1991) Allopurinol pretreatment improves evoked response recovery following global cerebral ischemia in dogs. Stroke 22: 660–665
265. Mitamura JA, Seligman ML, Solomon JJ, Flamm ES, Demopoulos HB, Ransohoff J (1981) Loss of essential membrane lipids and ascorbic acid from rat brain following cryogenic injury and protection by methylprednisolone. Neurol Res 3: 329–344
266. Mohr JP (1992) Calcium antagonists in acute ischemic stroke. In: Krieglstein J, Oberpichler-Schwenk H (eds) Pharmacology of cerebral ischemia. Wissenschaftliche Verlagsgesellschaft, Stuttgart, pp 553–558

267. Molinari GF (1986) Experimental models of ischemic stroke. In: Barnett HJM, Mohr JP, Stein BM, Yatsu FM (eds) Stroke pathophysiology, diagnosis, and management. Churchill Livingstone, New York, pp 57–73
268. Molinari GF (1988) Why model strokes? Stroke 19: 1195–1197
269. Monaghan DT, Bridges RJ, Cotman CW (1989) The excitatory amino acid receptors: their classes, pharmacology, and distinct properties in the function of the central nervous system. Ann Rev Pharmacol Toxicol 29: 365–402
270. Monyer H, Harley DM, Choi DW (1990) 21-Aminosteroids attenuate excitotoxic neuronal injury in cortical cell cultures. Neuron 5: 121–126
271. Moreland DB, Soloniuk DS, Feldman MJ (1989) Leukotrienes in experimental spinal cord injury. Surg Neurol 31: 277–280
272. Mosinger JL, Price MT, Bai HY, Xiao H, Olney JW (1991) Blockade of both NMDA and non-NMDA receptors is required for optimal protection against ischemic neuronal degeneration in the vivo adult mammalian retina. Exp Neurol 113:10–17
273. Muizelaar JP, Marmarou A, Young HF, Choi SC, Wolf A, Schneider RL, Kontos HA (1993) Improving the outcome of severe head injury with the oxygen radical scavenger polyethylene glycol-conjugated superoxide dismutase: a phase II trial. J Neurosurg 78: 375–382
274. Myers RE, Yamaguchi M (1976) Effects of serum glucose concentration on brain response to circulatory arrest. J Neuropathol Exp Neurol 35: 301
275. Myers RE, Yamaguchi M (1977) Nervous system effects of cardiac arrest in monkeys. Arch Neurol 34: 65–74
276. Nagai H, Kamiya K, Sugiyama N, Ueda Y (1988) Change of ischemic threshold after subarachnoid hemorrhage. In: Wilkins RH (ed) Cerebral vasospasm. Raven, New York, pp 57–78
277. Nakanishi S (1992) Molecular diversity of glutamate receptors and implications for brain function. Nature 258: 597–603
278. Nedergaard M (1987) Transient focal ischemia in hyperglycemic rats is associated with increased cerebral infarction. Brain Res 408: 79–85
279. Nellgard B, Wieloch T (1992) Postischemic blockade of AMPA but no NMDA receptors litigates neuronal damage in the rat brain following transient severe cerebral ischemia. J Cereb Blood Flow Metab 12: 2–11
280. Niazi SA, Lewis FJ (1958) Profound hypothermia in man. Ann Surg 147: 264
281. Nicholls D, Attwell D (1990) The release and uptake of excitatory amino acids. Trends Pharmac Sci 11: 462–468
282. Nilsson P, Hillered L, Pontén U, Ungerstedt U (1990) Changes in cortical extracellular levels of energy-related metabolites and amino acids following concussive brain injury in rats. J Cereb Blood Flow Metab 10: 631–637
283. Nishizuka T (1989) The family of protein kinase C for signal transduction. JAMA 262: 1826–1833
284. Nordström CH, Messeter K, Sundbärg G, Schalén W, Werner M, Ryding E (1988) Cerebral blood flow, vasoreactivity, and oxygen consumption during barbiturate therapy in severe traumatic brain lesions. J Neurosurg 68: 424–431
285. Nordström CH, Rehncrona S, Siesjö BK (1978a) Restitution of cerebral energy state, as well as of glycolytic metabolites, citric acid cycle intermediates

and associated amino acids after 30 minutes of complete ischemia in rats anaesthetized with nitrous oxide or phenobarbital. J Neurochem 30: 479–486
286. Nordström CH, Siesjö BK (1978b) Effects of phenobarbital in cerebral ischemia. Part I: cerebral energy metabolism during pronounced incomplete ischemia. Stroke 9: 327–335
287. Norenberg MD, Mozes LW, Gregorios JB, Norenberg LOB (1987) Effects of lactic acid on astrocytes in primary culture. J Neuropathol Exp Neurol 46: 154–166
288. Nosko M, Krueger CA, Weir BKA, Cook DA (1986) Effects of nimodipine on in vitro contractility of cerebral arteries of dog, monkey, and man. J Neurosurg 65: 376–381
289. Nosko M, Weir B, Krueger C, *et al* (1985) Nimodipine and chronic vasospasm in monkeys Part I: clinical and radiological findings. Neurosurgery 16: 129–136
290. Nottebohm F (ed) (1985) Hope for a new neurology. Annals of the New York Academy of Sciences, Vol 457, pp 1–238
291. Nowicki JP, Carreau A, Duval D, Poignet H, Vigé X, Scatton B (1992) Blockade of nitric oxide synthesis: a new pharmacological approach for the treatment of cerebral infarction? In: Krieglstein J, Oberpichler-Schwenk H (eds) Pharmocology of cerebral ischemia. Wissenschaftliche Verlagssellschaft, Stuttgart, pp 409–416
292. Nozaki K, Beal MF (1992) Neuroprotective effects of L-Kynurenine on hypoxia-ischemia and NMDA lesions in neonatal rats. J Cereb Blood Flow Metab 12: 400–407
293. Nussmeier NA, Arlund C, Slogoff S (1986) Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. Anesthesiology 64: 165–170
294. Oh SM, Betz AL (1991) Interaction between free radicals and excitatory amino acids in the formation of ischemic brain edema in rats. Stroke 22: 915–921
295. Ohnishi T, Posner JB, Shapiro WR (1992) Vasogenic brain edema induced by arachidonic acid: role of extracellular arachidonic acid in blood-brain barrier dysfunction. Neurosurgery 30: 545–551
296. Olanow CW (1992) An introduction to the free radical hypothesis in Parkinson's disease. Ann Neurol 32: S2–S9
297. Olney JW (1989) Excitatory amino acids and neuropsychiatric disorders. Biol Psychiatry 6: 505–525
298. Olney JW, Ho OC, Rhee V (1971) Cytotoxic effects of acidic and sulphur containing amino acids on the infant mouse central nervous system. Exp Brain Res 14: 61–76
299. Panetta T, Marcheselli VL, Braquet P, *et al* (1987) Effects of a platelet activating factor antagonist (BN 52051) on free fatty acids, diacylglycerols, polyphosphoinositides and blood flow in the gerbil brain: inhibition of ischemia reperfusion induced cerebral injury. Biochem Biophys Res Commun 149: 580–587
300. Pappius HM (1991) Brain injury new insights into neurotransmitter and receptor mechanisms. Neurochem Res 16: 941–949
301. Patt A, Harken AH, Burton LK, *et al* (1988) Xanthine oxidase-derived

hydrogen peroxide contributes to ischemia reperfusion-induced edema in gerbil brains. J Clin Invest 81: 1556–1562
302. Pelligrini-Giampietro DE, Cherici G, Alesiani M, Carla V, Moroni F (1988) Excitatory amino acid release from rat hippocampal slices as a consequence of free-radical formation. J Neurochem 51: 1960–1963
303. Pellegrini-Giampietro DE, Cherici G, Alesiani M, Carla V, Moroni F (1990) Excitatory amino acid release and free radical formation may cooperate in the genesis of ischemia-induced neuronal damage. J Neurosci 10: 1035–1041
304. Persson L, Hillered L (1992) Chemical monitoring of neurosurgical intensive care patients using intracerebral microdialysis. J Neurosurg 76: 72–80
305. Peterson JW, Kwun BD, Hackett JD, Zervas NT (1990) The role of inflammation in experimental cerebral vasospasm. J Neurosurg 72: 767–774
306. Pettigrew LC, Grotta JC, Rhoades HM, *et al* (1989) Effect of thromboxane synthase inhibition on eicosanoid levels and blood flow in ischemic rat brain. Stroke 20: 627–632
307. Pickard JD, Murray GD, Illingworth R, *et al* (1989) Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid hemorrhage: British aneurysm nimodipine trial. B M J 298: 636–642
308. Pietronigro DD, Hovsepian M, Demopoulos HB, Flamm ES (1983) Loss of ascorbic acid from injured feline spinal cord. J Neurochem 41: 1072–1076
309. Plum F (1983) What causes infarction in ischemic brain? The Robert Wartenberg lecture. Neurology 33: 222–233
310. Povlishock JT (1992) Traumatically induced axonal injury pathogenesis and pathobiological implications. Brain Pathol 2: 1–12
311. Pulsinelli WA, Brierly JB, Plum G (1982) Temporal profile of neuronal damage in a model of transient forebrain ischemia. Ann Neurol 11: 154–159
312. Pulsinelli WA, Buchan A (1989) The utility of animal ischemia models in predicting pharmacotherapeutic response in the clinical setting. In: Ginsberg MD, Dietrich WD (eds) Cerebrovascular diseases. Raven, New York, pp 87–91
313. Raichle ME (1983) The pathophysiology of brain ischemia. Ann Neurol 13: 2–10
314. Raschetti R, Maggini M, Popoli P (1992) Guillain-Barré syndrome and ganglioside therapy in Italy. Lancet 340: 60
315. Rawe SE, Perot PL (1979) Pressor response resulting from experimental contusion injury to the spinal cord. Neurosurgery 50: 58–63
316. Rehncrona S, Hauge HN, Siesjö BK (1981) Brain lactic acidosis and ischemic cell damage 1, biochemistry and neurophysiology. J Cereb Blood Flow Metab 1: 297–311
317. Rehncrona S, Hauge HN, Siesjö BK (1989) Enhancement of iron-catalyzed free radical formation by acidosis in brain homogenates: differences in effect by lactic acid and CO_2. J Cereb Blood Flow Metab 9: 65–70
318. Rehncrona S, Westerberg E, Akesson B, Siesjö BK (1982) Brain cortical fatty acids and phospholipids during and following complete and severe incomplete ischemia. J Neurochem 38: 84–93
319. Renou AM, Vernhier J, Macrez P, *et al* (1978) Cerebral blood flow and metabolism during etomidate anesthesia in man. Br J Anaesth 50: 1047–1051

320. Rockoff MA, Marshall LF, Shapiro HM (1979) High-dose barbiturate therapy in humans: a clinical review of 60 patients. Ann Neurol 6: 194
321. Rosenthal RE, Williams R, Bogaert YE, Getson PR, Fiskum G (1992) Prevention of postischemic canine neurological injury through potentiation of brain energy metabolism by acetyl-L-carnitine. Stroke 23: 1312–1318
322. Rosner MJ, Becker DP (1984) Experimental brain injury: successful therapy with the weak base, tromethamine. With an overview of CNS acidosis. J Neurosurg 60: 961–971
323. Rosner MJ Bennett MD, Becker DP (1982) The clinical relevance of laboratory head injury models: prerequisites of therapeutic testing. In: Grossman RG, Gildenberg PL (eds) Head injury; basic and clinical aspects. Raven, New York
324. Rosomoff HL (1957) Hypothermia and cerebral vascular lesions. II. Experimental middle cerebral artery interruption followed by induction of hypothermia. AMA Arch Neurol Psychiatry 78: 454–464
325. Rosomoff HL (1959) Experimental brain injury during hypothermia. J Neurosurg 16: 177–187
326. Rosomoff HL (1959) Hypothermia and cerebral vascular lesions. I. Experimental interruption of the middle cerebral artery during hypothermia. J Neurosurg 13: 332–343
327. Rosomoff HL, Holaday DA (1954) Cerebral blood flow and cerebral oxygen consumption during hypothermia. Am J Physiol 179: 85–88
328. Rossanda M, Selenativ VL (1973) Role of automatic ventilation in treatment of severe head injuries. J Neurosurg Sci 17: 265–270
329. Rothman SM (1992) Excitotoxins: possible mechanisms of action. Ann N Y Acad Sci 11: 132–139
330. Rothman SM, Olney JN (1986) Glutamate and the pathophysiology of hypoxic ischemic brain damage. Ann Neurol 19: 105–111
331. Rudolphi KA, Schubert P, Parkinson FE, Fredholm BB (1992) Adenosine and brain ischemia. Cerebrovasc Brain Metab Rev 4: 346–369
332. Sagar SM (1993) The molecular biology of brain ischemia: trendy genes in sick neurons. Ann Neurol 33: 437–438
333. Sakaki T, Tsunoda S, Utsumi S (1990) The influence of volume expansion with induced hypertension on vessel reactivities, the blood-brain barrier and cerebral infarction in cats, with one hour occlusion of the middle cerebral artery. Neurosurgery 27: 268–274
334. Salford LG, Siesjö BK (1974) The influence of arterial hypoxia and unilateral carotid artery occlusion upon regional blood flow and metabolism in the rat brain. Acta Physiol Scand 92: 130–141
335. Sandercock PAG, Van Den Belt AGM, Lindley RI, Slattery J (1993) Antithrombotic therapy in acute ischaemic stroke: an overview of the completed randomised trials. J Neurol Neurosurg Psychiatry 56: 17–25
336. Scatton B, Carter C, Benavides J, Giroux C (1991) N-methyl-D-aspartate receptor antagonists: a novel therapeutic perspective for the treatment of ischemic brain injury. Cerebrovasc Dis 1: 121–135
337. Scheller MS (1992) Routine barbiturate brain protection during cardio-

pulmonary bypass cannot be recommended. J Neurosurg Anesthesiol 4(1): 60–63
338. Schmidley JW (1990) Free radicals in central nervous system ischaemia. Stroke 21: 1086–1090
339. Schmidt-Kastner R, Freund TF (1991) Selective vulnerability of the hippocampus in brain ischemia. Neuroscience 40: 599–636
340. Schubert P, Kreutzberg GW (1990) Neuroprotective mechanisms of endogenous adenosine action and pharmacological implications. In: Krieglstein J, Oberpichler H (eds) Pharmacology of cerebral ischemia. Wissenschaftliche Verlagsgesellschaft, Stuttgart, pp 417–426
341. Schwarcz R (1989) Excitotoxic and anti-excitotoxic mechanisms in neurological disease. Curr Opn Neurol Neurosurg 2: 504–508
342. Schwartz ML, Tator CH, Rowed DW, *et al* (1984) The University of Toronto head injury treatment study: a prospective randomized comparison of phenobarbital and mannitol. Can J Neurol Sci 11: 434–440
343. Selman WR, Spetzler RF, Roessmann UR, Rosenblatt JI, Crumrine RC (1981) Barbiturate-induced coma therapy for focal cerebral ischemia. J Neurosurg 55: 220–226
344. Senter HJ, Venes JL (1979) Loss of autoregulation and post-traumatic ischemia following experimental spinal cord trauma. J Neurosurg 50: 198–206
345. Seubert P, Lee K, Lynch G (1989) Ischemia triggers NMDA receptor linked cytoskeletal proteolysis in hippocampus. Brain Res 492: 366–370
346. Shapiro HM, Galindo A, Wyte SR, Harris AB (1973) Rapid intraoperative reduction of intracranial pressure with thiopentone. Br J Anaesth 45: 1057
347. Shaw PJ (1993) Excitatory amino acid receptors, excitotoxicity and the human nervous system. Curr Opin Neurol Neurosurg 6: 414–422
348. Shibuya M, Suzuki Y, Sugita K, Saito I, Sasaki T, Takakura K, Nagata I, Kikuchi H, Takemae T, Hidaka H, Nakashima M (1992) Effect of AT877 on cerebral vasospasm after aneurysmal subarachnoid hemorrhage. J Neurosurg 76: 571–577
349. Shimada N, Graf R, Rosner G, Wakayama A, George CP, Heiss WD (1989) Ischemic flow threshold for extracellular glutamate increase in cat cortex. J Cereb Blood Flow Metab 9: 603–606
350. Shiozaki F, Sugimoto H, Taneda M, Yoshida H, Iwai A, Yoshioka T, Sugimoto T (1993) Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. J Neurosurg 79: 363–368
351. Siemkonicz E, and Hansen J (1978) Clinical restitution following cerebral ischemia in hypo-, normo-, and hyperglycemic rats. Acta Neurol Scand 58: 1–8
352. Siesjö BK (1978) Brain energy metabolism. Wiley, New York
353. Siesjö BK (1981) Cell damage in the brain: a speculative synthesis. J Cereb Blood Flow Metab 1: 155–185
354. Siesjö BK (1988) Acidosis and ischemic brain damage. Neurochem Pathol 9: 31–88
355. Siesjö BK (1992a) Pathophysiology and treatment of focal cerebral ischemia. Part I: pathophysiology. J Neurosurg 77: 169–184

356. Siesjö BK (1992b) Pathophysiology and treatment of focal cerebral ischemia. Part II: mechanisms of damage and treatment. J Neurosurg 77: 337–354
357. Siesjö BK, Agardh CD, Bengtsson F (1989) Free radicals and brain damage. Cerebrovasc Brain Metab Rev 1: 165–211
358. Siesjö BK, Bendek G, Koide T, *et al* (1985) Influence of acidosis on lipid peroxidation in brain tissues in vitro. J Cereb Blood Flow Metab 5: 253–258
359. Siesjö BK, Bengtsson F (1989) Calcium fluxes calcium antagonists, and calcium-related pathology in brain ischemia, hypoglycemia, and spreading depression: a unifying hypothesis. J Cereb Blood Flow Metab 9: 127–140
360. Siesjö BK, Katsura K, Pahlmark K, Smith ML (1992) The multiple causes of ischemic brain damage: a speculative synthesis. In: Krieglstein J, Oberpichler-Schwenk H (eds) Pharmacology of cerebral ischemia. Wissenschaftliche Verlagsgesellschaft, Stuttgart, pp 511–525
361. Siesjö BK, Wieloch T (1985) Cerebral metabolism in ischemia: neuchemical basis for therapy. Br J Anaesth 57: 47–62
362. Silver FL, Norris JW, Lewis AJ, *et al* (1984) Early mortality following stroke: a prospective view. Stroke 15: 492–496
363. Silverberg GD, Reitz BA, Ream AK (1981) Hypothermia and cardiac arrest in the treatment of giant aneurysms of the cerebral circulation and hemangioblastoma of the medulla. J Neurosurg 55: 337–346
364. Simeone FA, Frazer G, Lawner P (1979) Ischemic brain edema: comparative effects of barbiturates and hypothermia. Stroke 10: 8–12
365. Simon RP, Griffiths T, Evans MC, Swan BS, Meldrum BS (1984) Calcium overload in selectively vulnerable neurons of the hippocampus during and after ischemia: an electron microscopy study in the rat. J Cereb Blood Flow Metab 4: 350–361
366. Singh R, Pathak DN (1990) Lipid peroxidation and glutathione peroxidase, glutathione reductase, superoxide dismutase, catalase, and glucose-6-phosphate dehydrogenase activities in FeC13-induced epileptogenic foci in the rat brain. Epilepsia 31: 15–26
367. Slater TF (1984) Free-radical mechanisms in tissue injury. Biochem J 222: 1–15
368. Smith AL, Hoff JT, Nielsen SL, Larson CP (1974) Barbiturate protection in acute focal cerebral ischemia. Stroke 5: 1–7
369. Smith DS, Rehncrona S, Siesjö BK (1980) Inhibitory effects of different barbiturates on lipid peroxidation in brain tissue in vitro: comparison with the effects of promethazine and chlorpromazine. Anesthesiology 53: 186
370. Spetzler RF, Hadley MN, Rigamonti D, *et al* (1988) Aneurysms of the basilar artery treated with circulatory arrest, hypothermia, and barbiturate cerebral protection. J Neurosurg 68: 868–879
371. Spinnewyn B, Blavet N, Clostre F, *et al* (1987) Involvement of platelet-activating factor (PAF) in cerebral post-ischemic phase in monygolian gerbils. Prostaglandins 34: 337–349
372. Stälhammar D (1986) Experimental models of head injury. Acta Neurochir (Wien) [Suppl] 36: 33–46
373. Steen PA, Gisvold SE, Milde JH, Newberg LA, Scheithauer BW, Lanier WL,

Michenfelder JD (1985) Nimodipine improves outcome when given after complete cerebral ischemia in primates. Anesthesiology 62: 406–414
374. Stein SC, Spettell C, Young G, Ross SE (1993) Delayed and progressive brain injury in closed-head trauma: radiological demonstration. Neurosurgery 32: 25–31
375. Steinke DE, Weir BKA, Findlay JM, Tanabe T, Grace M, Krushelnycky BW (1989) A trial of the 21-aminosteroid U74006F in a primate model of chronic cerebral vasospasm. Neurosurgery 24: 179–186
376. Sterz F, Safar P, Tisherman S, *et al* (1991) Mild hypothermia cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. Crit Care Med 19: 379–389
377. Stratham PF, Johnston RA, Macpherson P (1989) Delayed deterioration in patients with traumatic frontal contusions. J Neurol Neurosurg Psychiatry 52: 351–354
378. Strong AJ (1984) γ-Hydroxybutyric acid and intracranial pressure. Lancet 1304
379. Strong AJ, Fairfield JE, Montero E, Kirby M, Hogg AR, Snape M, Ross-Field L (1990) Insulin protects cognitive function in experimental stroke. J Neurol Neurosurg Psychiatry 53: 847–853
380. Strong AJ, Venables GS and Gibson G (1983) The cortical ischaemic penumbra associated with occlusion of the middle cerebral artery in the cat: 1. Topography of changes in blood flow, potassium ion activity, and EEG. J Cereb Blood Flow Metab 3: 86–96
381. Strong AJ, Tomlinson BE, Venables GS, Gibson G, Hardy JA (1983) The cortical ischaemic penumbra associated with occlusion of the middle cerebral artery in the cat: 2. Studies of histopathology, water content, and in vitro neurotransmitter uptake. J Cereb Blood Flow Metab 3: 97–108
382. Sundt TM Jr, Sharbrough FW, Trautmann JC, *et al* (1975) Monitoring techniques for carotid endarterectomy. Clin Neurosurg 22: 199
383. Suzuki J, Yoshimoto T, Mizoi K (1981) Preservation of the olfactory tract in bifrontal craniotomy for anterior communicating artery aneurysms, and functional prognosis. J Neurosurg 54: 342–345
384. Suzuki R, Masaoka H, Hirata Y, *et al* (1992) The role of endothelin-1 in the origin of cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg 76: 96–100
385. Swan JH, Meldrum BS (1990) Protection by NMDA antagonists against selective cell loss following transient ischaemia. J Cereb Blood Flow Metab 10: 343–351
386. Sweeney MS, Cooley DA, Reul RG (1985) Hypothermic circulatory arrest for cardiovascular lesions: technical considerations and results. Ann Thorac Surg 40: 498
387. Symon L, Crockard HA, Dorsch NWC, *et al* (1975) Local cerebral blood flow and vascular reactivity in a chronic stable stroke in baboons. Stroke 6: 482–492
388. Symon L, Momma F, Schwerdtfeger K, Bentivoglio P, Costa e Silva IE, Wang A (1986) Evoked potential monitoring in neurosurgical practice. In: Symon L

et al (eds) Advances and technical standard in neurosurgery, Vol 14. Springer, Wien New York, pp 26–70
389. Symon L, Pasztor E, Branston NM (1974) The distribution and density of reduced cerebral blood flow following acute middle cerebral artery occlusion: an experimental study by the technique of hydrogen clearance in baboons. Stroke 5: 355–364
390. Symon L, Wang AD, Costa e Silva IE, Gentili F (1984) Perioperative use of somatosensory evoked responses in aneurysm surgery. J Neurosurg 60: 269–275
391. Takahashi H, Manaka S, Sano K (1981) Changes in extracellular potassium concentration in cortex and brain stem during the acute phase of experimental closed head injury. J Neurosurg 55: 708–717
392. Takahashi S, Kassell NF, Toshima M, Dougherty DA, Foley PL, Lee KS (1993) Effect of U88999E on experimental cerebral vasospasm in rabbits. Neurosurgery 32: 281–288
393. Takanashi Y, Weir BKA, Vollrath B, *et al* (1992) Time course of changes in concentration of intracellular free calcium in cultured cerebrovascular smooth muscle cells exposed to oxyhemoglobin. Neurosurgery 30: 346–350
394. Tanabe T, Lewis PJ, Itoh H, *et al* (1988) Hypervolemic therapy without induced hypertension in patients with severe subarachnoid hemorrhage. In: Wilkins RH (ed) Cerebral vasospasm. Raven, New York, pp 421–424
395. Tanaka J, Shiki K, Asou T, Yasui H, Tokunaga K (1988) Cerebral autoregulation during deep hypothermic non pulsatile cardiopulmonary bypass with selective cerebral perfusion in dogs. J Thorac Cardiovasc Surg 95: 124–132
396. Tator Ch, Fehlings MG (1991) Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. J Neurosurg 75: 15–26
397. Taylor R (1991) A lot of "excitement" about neurodegeneration. Science 252: 1380–1381
398. Teichberg VI (1991) Glial glutamate receptors: likely actors in brain signalling. Faseb J 5: 3086–3091
399. Thomas DJ (1992) Rheology and stroke. Curr Opin Neurol Neurosurgery 5: 44–48
400. Todd NV, Picozzi MD, Crockard HA, *et al* (1986) Reperfusion after cerebral ischemia: influence of duration of ischemia. Stroke 17: 460–466
401. Treasure T, Naftel DC, Conger KA, Garcia JH, Kirklin JW, Blackstone EH (1983) The effect of hypothermic circulatory arrest time on cerebral function, morphology and biochemistry. J Thorac Cardiovasc Surg 86: 761–770
402. Trust Study Group (1990) Randomised, double-blind placebo controlled trial of Nimodipine in acute stroke. Lancet 336: 1205–1209
403. Tsumoto T (1990) Excitatory amino acid transmitters and their receptors in neural circuits of the cerebral neocortex. Neurosci Res 9: 79–102
404. Tulleken CAF, Van Dieren A, Jonkman J, *et al* (1982) Clinical and experimental

experience with etomidate as a brain protective agent. J Cereb Blood Flow Metab 2 [Suppl 1]: S92–S97
405. Turrens JF, Crapo JD, Freeman BA (1984) Protection against oxygen toxicity by intravenous injection of liposome-entrapped catalase and superoxide dismutase. J Clin Invest 73: 87–95
406. Ueda T, Yamamoto YL, Diksic M (1989a) Transvenous perfusion of the brain with verapamil during focal cerebral ischemia in rats. Stroke 20: 501–506
407. Ueda T, Yamamoto YL, Takara E, Diksic M (1989b) Tolerance of the cerebral venous system to retrograde perfusion pressure in focal cerebral ischemia in rats. Stroke 20: 378–385
408. Ueda Y, Obrenovitch TP, Lok SY, Sarna GS, Symon L (1992) Changes in extracellular glutamate concentration produced in the rat striatum by repeated ischemia. Stroke 23: 1125–1131
409. Ueda Y, Miki S, Kusuhara K, Okita Y, Tahata T, Yamanaka K (1992) Deep hypothermia systemic circulatory arrest and continuous retrograde cerebral perfusion for surgery of aortic arch aneurysm. Eur J Cardiothorac Surg 6: 36–41
410. Ueda Y, Obrenovitch TP, Lok SY, Sarna GS, Symon L (1992) Efflux of glutamate produced by short ischemia of varied severity in rat striatum. Stroke 23: 253–259
411. Uematsu D, Greenberg JH, Reivich M, Karp A (1988) In vivo measurement of cytosolic free calcium during cerebral ischemia and reperfusion. Ann Neurol 24: 420–428
412. Uematsu D, Greenberg JH, Hickey WF, Relvich M (1989) Nimodipine attenuate both increase in cytosolic free calcium and histologic damage following focal cerebral ischemia and reperfusion in cats. Stroke 20: 1531–1537
413. Uemura Y, Miller JM, Matson WR, Beal MF (1991) Neurochemical analysis of focal ischemia in rats. Stroke 22: 1548–1553
414. Uyama O, Matsuyama T, Michishita H, Nakamura H, Sugita M (1992) Protective effects of human recombinant superoxide dismutase on transient ischemic injury of CA1 neurons in gerbils. Stroke 23: 75–81
415. Vaccarino F, Guidotti A, Costa E (1987) Ganglioside inhibition of glutamate-mediated protein kinase C translocation in primary cultures of cerebellar neurons. Proc Natl Acad Sci USA 84: 8707–8711
416. Valtysson J, Jiang M, Persson L (1992) Transient elevation of the intracranial pressure increases the infarct size and perifocal edema after subsequent middle cerebral artery occlusion in the rat. Neurosurgery 30: 887–890
417. Van Reempts J, Haseldonckx M, Van Deuren B, Wouters L, Borgers M (1986) Structural damage of the ischemic brain: involvement of calcium and effects of postischemic treatment with calcium entry blockers. Drug Develop Res 8: 387–395
418. Venables GS, Miller SA, Gibson G, *et al* (1985) The effects of hyperglycemia on changes during reperfusion following focal cerebral ischemia in the cat. J Neurol Neurosurg Psychiatry 48: 663–669
419. Vibulsresth S, Dietrich WD, Busto R, Ginsberg MD (1987) Failure of nimodipine to prevent ischemic neuronal damage in rats. Stroke 18: 210–216

420. Wahl M, Unterberg A, Baethmann A, Schilling L (1988) Mediators of blood brain barrier dysfunction and formation of vasogenic brain edema. J Cereb Blood Flow Metab 8: 621–634
421. Ward JD, Becker DP, Miller JD, *et al* (1985) Failure of prophylactic barbiturate coma in the treatment of severe head injury. J Neurosurg 62: 383–388
422. Watson BD, Busto R, Goldberg WJ, Santiso M, Yoshida S, Ginsberg MD (1984) Lipid peroxidation in vivo induced by reversible global ischemia in rat brain. J Neurochem 42: 268–274
423. Watson JC, Drummond JC, Patel PM, *et al* (992) An assessment of the cerebral protective effects of etomidate in a model of incomplete forebrain ischemia in the rat. Neurosurgery 30: 540–544
424. Weber M, Grolimund P, Seiler RW (1990) Evaluation of posttraumatic cerebral blood flow velocities by transcranial doppler ultrasonography. Neurosurgery 27: 106–112
425. Wei EP, Dietrich WD, Povlishock JT, Navari RM, Kontos HA (1980) Functional morphological and metabolic abnormalities of the cerebral microcirculation after concussive brain injury in cats. Circ Res 46: 37–47
426. White BC, Grossman LI, Krause GS (1993) Brain injury by global ischemia and reperfusion: a theoretical perspective on membrane damage and repair. Neurology 43: 1656–1665
427. Wiebers DO, Adams HP, Whisnant JP (1990) Animal models of stroke: are they relevant to human disease (editorial). Stroke 21: 1–3
428. Wiedemann K, Hoyer S (eds) (1983) Brain protection: morphological, pathophysiological and clinical aspects. Springer, Berlin Heidelberg New York Tokyo
429. Wieloch T (1990) Neuronal injury and cerebrovascular disorders. Curr Opin Neurol Neurosurg 3: 944–950
430. Wieloch T, Cardell M, Bingren H, Zivin J, Saitoh T (1991) Changes in the activity of protein kinase C and the differential subcellular redistribution of its isozymes in the rat striatum during and following transient forebrain ischemia. J Neurochem 56: 1227–1235
431. Wijdicks EFM, Ropper AH, Hunnicutt EJ, *et al* (1991) Atrial natriuretic factor and salt wasting after aneurysmal subarachnoid hemorrhage. Stroke 22: 1519–1524
432. Williams WM, Lu ST, Delcerro M, *et al* (1984) Effect of 2450 MHz microwave energy on the blood-brain barrier to hydrophilic molecules. D. Brain temperature and blood-brain barrier permeability to hydrophilic tracers. Brain Res 319: 191–212
433. Wilson JT, Bednar MM, McAuliffe TL, *et al* (1992) The effect of 21-aminosteroid U74006F in a rabbit model of thromboembolic stroke. Neurosurgery 31: 929–934
434. Wolf AL, Levi L, Marmarou A, Ward JD, Muizelaar PJ, Choi S, Yong H, Riagmonti D, Robinson WL (1993) Effect of THAM upon outcome in severe head injury: a randomized prospective clinical trial. J Neurosurg 78: 54–59
435. Wright RL, Ames A (1964) Measurement of maximal permissible cerebral

ischemia and a study of its pharmacologic prolongation. J Neurosurg 21: 567–574
436. Xue D, Slivka A, Buchan AM (1992) Tirilazad reduces cortical infarction after transient but not permanent focal cerebral ischemia in rats. Stroke 23: 894–899
437. Yamamoto M, Shima T, Uozumi T, Sogabe T, Yamada K, Kawasaki T (1983) A possible role of lipid peroxidation in cellular damages caused by cerebral ischemia and the protective effect of α-tocopherol administration. Stroke 14: 977–982
438. Yatsu FM, Diamond I, Graziano C, Lindquist P (1972) Experimental brain ischemia. Protection from irreversible damage with a rapid-acting barbiturate (methohexital). Stroke 43: 726
439. Yoshida S, Busto R, Ginsberg MD, Abe K, Martinez E, Watson BD, Scheinberg P (1983) Compression-induced brain edema: modification by prior depletion and supplementation of vitamin E. Stroke 33: 166–172
440. Yoshida S, Busto R, Watson BD, Santiso MK, Ginsberg MD (1985) Post-ischemic cerebral lipid peroxidation in vitro: modification by dietary vitamin E. J Neurochem 44: 1593–1601
441. Yoshida S, Inoh S, Asano T, Sano K, Kubota J, Shimazaki H, Meta N (1980) Effect of transient ischemia on free fatty acids and phospholipids in the gerbil brain. J Neurosurg 53: 323–331
442. Yoshida K, Marmarou A (1991) Effects of tromethamine and hyperventilation on brain injury in the cat. J Neurosurg 74: 87–96
443. Young W (1985) The role of calcium in spinal cord injury. Neurotrauma 2: 109–114
444. Young W (1992) Medical treatments of acute spinal cord injury. J Neurol Neurosurg Psychiatry 55: 635–639
445. Young W, Flamm ES, Demopoulos HB (1981) Effect of naxolone on posttraumatic ischemia in experimental spinal contusion. J Neurosurg 55: 209–219
446. Young W, Flamm ES (1982) Effect of high-dose corticosteroid therapy on blood flow, evoked potentials, and extracellular calcium in experimental spinal injury. J Neurosurg 57: 667–673
447. Young W, Wojak JC, DeCrescito V (1988) 21-aminosteroid reduces ion shifts and edema in the rat middle cerebral artery occlusion model of regional ischemia. Stroke 19: 1013–1019
448. Zimmerman VJP, Schlaepfer WW (1982) Characterization of a brain calcium activated protease that degrades neurofilaments proteins. Biochemistry 21: 3977–3983
449. Zivin JA, Kochhar A, Saitoh T (1990) Protein phosphorylation during ischemia. Stroke 21 [Suppl III]: 117–121
450. Zuccarello M, Marsch JT, Schmitt G, Woodward J, Anderson DK (1989) Effect of the 21-aminosteroid U-74006F on cerebral vasospasm following subarachnoid hemorrhage. J Neurosurg 71: 98–104

B. Technical Standards

AIDS and the Neurosurgeon—an Update

S. F. CIRICILLO and M. L. ROSENBLUM

Department of Neurological Surgery, School of Medicine, University of California, San Francisco, CA, and Department of Neurological Surgery, Henry Ford Medical Center, Detroit, MI (U.S.A.)

With 7 Figures

Contents

Summary

Over the past decade, acquired immunodeficiency syndrome (AIDS) has become the leading public health crisis in the United States, Western Europe,

and Africa. Despite improvements in the diagnosis and treatment of AIDS-related disorders, the number of people infected with the human immunodeficiency virus (HIV-1) continues to grow, requiring a greater proportion of limited financial, medical, and human resources. Since nearly one half of symptomatic AIDS patients have neuropathologic disease, clinicians must be aware of the myriad neurologic manifestations of AIDS and use the most effective methods to diagnose and treat them. The work-up of the AIDS patient with neurologic symptoms includes a careful history and physical examination, laboratory studies, and radiographic imaging. Gadolinium-enhanced magnetic resonance (MR) imaging has become the radiographic screening study of choice. MR imaging can be used to predict which patients should undergo stereotactic biopsy before an empirical trial of anti-toxoplasmosis therapy. Any patient with a mass lesion that does not respond to empirical therapy for toxoplasmosis should also undergo biopsy to exclude another treatable disorder. While the number of patients with neurological complications can be expected to increase in the near future, better imaging techniques may obviate the need for biopsy in many of these patients. The increasing threat of HIV-1 infection in the workplace requires meticulous care both in and out of the operating room to minimize accidental exposure of health-care workers.

Key words: Acquired immunodeficiency syndrome; AIDS; neurological manifestations; diagnosis, treatment strategies.

Introduction

Since the initial reports of the acquired immunodeficiency syndrome (AIDS) appeared a decade ago, AIDS has become the leading public health crisis in the United States, Western Europe, and Africa (Piot *et al.* 1988). More than 1.5 million people in the United States, and 10 million people worldwide, are estimated to be infected with HIV-1 (Curran *et al.* 1988, Morgan and Curran 1986, Taylor 1989, Wiley and Samuel 1989). As of June 1992, 230,179 cases of AIDS and 152, 153 AIDS-related deaths in the United States had been reported to the Centers for Disease Control and Prevention (CDC); more than 500,000 cases have been reported to the World Health Organization. These numbers correspond well to the 230,000–270,000 cases of AIDS projected earlier in the epidemic using statistical models (Curran *et al.* 1988, Morgan and Curran 1986, Taylor 1989, Wiley and Samuel 1989). In the 1990's, a 10-fold increase is expected in the number of adults (10 million) and children (5 million) developing AIDS (Mann 1992).

Neurologic diseases remain a major source of AIDS-related morbidity and mortality (Rosenblum *et al.* 1988c). Neurologic complications arise either from primary infection of the nervous system with human immunodeficiency virus (HIV-1) or from opportunistic infections and neoplasms and their treatment (De La Paz and Enzmann 1988, Rosenblum *et al.* 1988b). Neurologic involvement occurs in almost 40% of AIDS patients at some time during their illness and may become more frequent as treatment of pulmonary complications improves and life expectancy increases. In 10% of AIDS patients, a neurologic disorder is the initial manifestation of AIDS (Koppel *et al.* 1985; Levy *et al.* 1985). Because of the large number of infected patients and the frequency of neurologic disorders, all physicians must be familiar with the neurologic manifestations of HIV-1 disease, especially as improved diagnostic and treatment modalities have become available in the past few years.

Incidence and Epidemiology

Neurologic complications occur in nearly 40% of patients with AIDS (Koppel *et al.* 1985, Levy *et al.* 1985, Rosenblum *et al.* 1988b, Snider *et al.* 1983). This percentage appears to be increasing as prophylaxis for the pulmonary complications of AIDS has greatly improved survival. Autopsy studies show that central nervous system (CNS) abnormalities occur in at least 75% of patients infected with HIV-1 (Moskowitz *et al.* 1984, Rosenblum *et al.* 1988b).

Much of the early AIDS literature focused on groups at higher risk of infection (Table 1). Risk of AIDS-related neurologic disease varies by risk groups and by geographic location (Cornblath *et al.* 1987). For example, toxoplasmosis is most commonly seen in Florida, with its warmer climate and its large number of Haitian AIDS patients, who for some reason have neurologic complications more frequently than other groups (Rosenblum *et al.* 1988b). Recent reports have focused on the risks of HIV-1 infection in health-care workers (Schiff 1990). Surgeons are at especially high risk because they perform invasive diagnostic and therapeutic procedures on patients infected with HIV-1. The estimated cumulative risk to surgeons over a 30-year career ranges from 1 in 100 to 1 in 5, depending on the prevalence of HIV-1 infection in the surgical population and the number of operations performed (Schiff 1990). Thus, the potential risk of seroconversion remains an important issue to neurosurgeons who treat AIDS patients and patients at high risk for HIV-1 infection.

Table 1. *Groups at Risk for the Acquired Immunodeficiency Syndrome*

Risk group[a]	Percentage of AIDS patients	
	December 1985	July 1992
Homosexual/bisexual males[b]	72.2	63
Intravenous drug abusers[b]	16.8	22
Immigrants[c]	2.5	—
Blood transfusion recipients	1.9	2
Heterosexual contact with persons with AIDS or at risk for AIDS	1.0	6
Children of mothers with AIDS	1.2	1.4
Hemophiliacs	0.8	0.8
No known risk	3.6	4

Reproduced in part, with permission, from Rosenblum ML, Levy RM, Bredesen DE (1988b) Neurosurgical implications of the acquired immunodeficiency syndrome (AIDS). Clin Neurosurg 34: 419–445. December 1985 data from Centers for Disease Control: Update (1986) Acquired immunodeficiency syndrome—United States. JAMA 256: 20–25. July 1992 data from: Centers for Disease Control and Prevention: HIV/AIDS surveillance. Atlanta.

[a]Hierarchical ordering of risk groups. Patients with two risk factors are listed according to the more common one.

[b]In 1985, 7.9%, and in 1992, 6% of all AIDS patients were both homosexual or bisexual and intravenous drug abusers; this dual risk group is included in the former category.

[c]Includes primarily immigrants from Haiti and Central Africa, in whom transmission of HIV infection is thought to be through heterosexual contact. Recent epidemiological surveys combine these patients with others who got AIDS through heterosexual contact.

Neurologic Manifestations

Primary HIV-1 infections occur in four phases (Price *et al.* 1988). As early as 2 weeks after the initial exposure to the virus, an acute retroviral syndrome consisting of fever, myalgias, pharyngitis, diarrhea, weight loss, and lymphadenopathy occurs; the symptoms are self-limiting and may be so mild as to be overlooked. Seroconversion is most likely to occur during the first 6–12 weeks, but may not occur for up to 3 years after exposure (Imagawa *et al.* 1989). The vast majority (95%) of infected patients undergo seroconversion during the first 6 months after exposure (Hessol *et al.* 1990).

After seroconversion, the retrovirus enters a latent phase that lasts months to years, and the patient becomes an asymptomatic carrier of HIV-1. During this period, the host's immune defenses are slowly destroyed, allowing "minor" opportunistic infections characteristic of AIDS-related complex (ARC) to develop. During the final phase of HIV-1 infection, the immune system is profoundly impaired and the more serious opportunistic infections and tumors, the hallmarks of AIDS, develop (Price *et al.* 1988).

CNS involvement after HIV-1 infection parallels the phases of systemic infection. During the acute retroviral syndrome, HIV-1 may be recovered from the cerebrospinal fluid (CSF) (Levy 1989). Patients become asymptomatic, but CSF studies may continue to demonstrate a pleocytosis and elevated protein, immunoglobulin, and viral antigen levels (Ho *et al.* 1985). A weakening immune system allows chronic meningitis to develop. The later stages of CNS involvement are characterized by opportunistic infection, HIV-1 encephalopathy, and HIV-1 myelopathy. The delayed development of HIV-1 encephalopathy despite early CNS exposure to HIV-1 and chronic leptomeningeal infection suggests that although the AIDS virus is neurotropic, it is relatively nonpathogenic for the CNS in the absence of immunosuppression (Price *et al.* 1988).

The CNS disorders associated with HIV-1 infection may be classified as primary HIV-1 syndromes, opportunistic viral diseases, nonviral infections, neoplasms, and cerebrovascular diseases (Table 2). The clinical manifestations of these disorders may be attributed to diffuse or focal involvement of brain parenchyma or to hydrocephalus resulting from the obstruction of normal CSF pathways or CSF absorption. The initial symptoms (e.g., headache, diminished level of consciousness, cognitive impairment, focal motor or sensory impairment, seizures, ataxia, and visual disturbances) are nonspecific and make the accurate diagnosis of particular CNS diseases impossible on clinical grounds alone. Moreover, up to 30% of AIDS patients with neurologic symptoms have multiple CNS diseases, which further complicates the diagnosis, treatment, and follow-up.

Serologic tests and CSF analysis can provide supportive evidence of CNS involvement, but are often unreliable in the diagnosis of AIDS-related CNS disorders. Radiologic studies are more useful in clinical practice. Computerized tomographic (CT) scans show diffuse cerebral atrophy in 33% of patients and focal abnormalities in 38%, but these findings are not specific enough to establish a diagnosis (De La Paz and Enzmann 1988). Magnetic resonance (MR) imaging is more sensitive than CT and is therefore the radiographic study of choice in AIDS patients with neurologic complications. While MR studies cannot establish pathological diagnoses with the same degree of security as histopathologic evaluations, preliminary results indicate that MR images obtained with good-quality, high-field-

Table 2. *Diseases Affecting the Central Nervous System in Patients with AIDS*

Type	Disease
Primary viral (HIV-1) syndromes	HIV encephalopathy
	atypical aseptic meningitis
	vacuolar myelopathy
Secondary viral syndromes (encephalitis, myelitis, retinitis, vasculitis)	cytomegalovirus
	herpes simplex virus types I and II
	herpes varicella-zoster virus
	papovavirus (PML)
Nonviral infections (encephalitis, meningitis, abscess)	*Toxoplasma gondii*
	Cryptococcus neoformans
	Candida albicans
	Mycobacterium species
	other fungal species
Neoplasms	primary CNS lymphoma
	metastatic systemic lymphoma
	metastatic Kaposi's sarcoma
Cerebrovascular	infarction
	hemorrhage
	vasculitis
Complications of systemic therapy for AIDS	

Adapted, with permission, from Levy RM, Bredesen DE (1988) Central nervous system dysfunction in acquired immunodeficiency syndrome. In: Rosenblum ML, Levy RM, Bredesen DE (eds) AIDS and the nervous system. Raven, New York, pp 29–63.

AIDS acquired immunodeficiency syndrome; *HIV* human immunodeficiency virus; *PML* progressive multifocal leukoencephalopathy; *CNS* central nervous system.

strength magnets can be used to guide treatment in patients with CNS mass lesions (unreported data).

Because clinical, laboratory, and radiologic studies are often not specific enough to establish a diagnosis of AIDS-related intracranial masses, histologic evaluation is frequently necessary. Operative confirmation may also be necessary as HIV-infected patients may also have neurologic diseases unrelated to AIDS, such as malignant gliomas, benign neoplasms, hemorrhages, and herniated lumbar discs (Rosenblum *et al.* 1988b). The signs and symptoms, radiologic and CSF findings, and options for treatment of specific CNS diseases are summarized in Table 3.

The prevalence of neurologic diseases in AIDS patients was characterized in a review of 1,286 cases of AIDS treated at the hospitals of the University

Table 3. *Diseases of the Central Nervous System Associated with the Acquired Immunodeficiency Syndrome*

Diagnosis	Pathogen	Signs/Symptoms	Radiologic findings	Cerebrospinal fluid	Treatment	Prognosis
Aseptic meningitis	HIV-1	headache, fever, meningismus	CT normal	increased protein, increased OCB, pleocytosis	none	good
HIV-1 encephalopathy	HIV-1	cognitive impairment, psychomotor slowing, dementia	CT atrophy	± HIV	none	poor
Vacuolar myelopathy	HIV-1	leg weakness, bowel/ bladder dysfunction	CT normal	± HIV	none	poor
PML	JC papovavirus	dementia, focal deficits	CT low density; MR white matter lesions, occasional mass effect or enhancement	normal	none	poor
Herpes virus	HSV, CMV, HVZ	meningitis, encephalitis, myelitis	CT atrophy, occasional mass effect and enhancement	increased protein, pleocytosis	ganciclovir, acyclovir	fair
Toxoplasmosis	*Toxoplasma gondii*	intellectual slowness, seizures, focal deficit	CT single or multiple mass lesions; MR multiple lesions	increased protein, pleocytosis	pyrimethamine, sulfadiazine	good
Cryptococcosis	*Cryptococcus neoformans*	fever, meningitis, focal deficits	CT focal mass in 10%	antigen and increased protein	amphotericin B, flucytosine	good
Primary CNS lymphoma	—	headache, focal deficit, AMS	CT ring or homogeneously enhancing mass (multiple in 50%)	normal	steroids, radiation	good
Kaposi's sarcoma	—	focal deficit, AMS, seizures	CT enhancing mass lesions	normal	radiation, interleukin	fair
Vascular disease	—	sudden onset of focal deficit	CT low-density lesion	normal	none	fair

Reproduced, with permission, from Ciricillo SF, Rosenblum ML (in press) Acquired immunodeficiency syndrome (AIDS). In: Kassell NF, Vollmer DG (eds) Advances in neurosurgery (Contemporary neurology series). Davis, Philadelphia.

HIV human immunodeficiency virus; *CT* computerized tomography; *OCB* oligoclonal bands; *PML* progressive multifocal leukoencephalopathy; *MR* magnetic resonance; *HSV* herpes simplex virus; *CMV* cytomegalovirus; *HVZ* varicella zoster virus; *CNS* central nervous system; *AMS* altered mental status.

Table 4. *Central Nervous System Diseases Identified by a Review of 1286 Patients with the Acquired Immunodeficiency Syndrome*

Disease	No. of cases	CNS masses
Nonviral infections		
Cryptococcus	68	8
Toxoplasma	53	47
Candida	3	3
Mycobacterium	3	3
Viral infections		
HIV encephalopathy	100	0
PML	8	0
Other viral	28	5
Tumors		
Primary CNS lymphoma	25	22
Kaposi's sarcoma	2	2
Unknown		
Treated for toxoplasmosis	31	22
No treatment	156	19
Total	477	130

Reproduced, with permission, from Rosenblum ML, Levy RM, Bredesen DE (1988) Neurosurgical implications of the acquired immunodeficiency syndrome (AIDS). Clin Neurosurg 34: 419–445.

CNS central nervous system; *HIV* human immunodeficiency virus; *PML* progressive multifocal leukoencephalopathy.

of California, San Francisco (UCSF), from 1981 to 1986 (Rosenblum *et al.* 1988b). Four hundred eighty-two patients (37%) had a total of 556 neurologic diseases, 477 (86%) involving the CNS (Table 4) and 79 (14%) involving the peripheral nervous system; 65 patients (13%) had more than one disease. The most common CNS disorders included HIV-1 encephalopathy, cryptococcal meningitis, *Toxoplasma* abscess, non-HIV viral encephalitis, and primary CNS lymphoma. Progressive multifocal leukoencephalopathy (PML), candidal abscesses, mycobacterial meningitis or abscess, and metastatic Kaposi's sarcoma occurred much less frequently. In 187 patients with CNS symptoms, a definitive diagnosis was not made.

Intracranial Mass Lesions

Intracranial mass lesions are found in approximately 10% of AIDS patients with CNS symptoms (Table 4). Toxoplasmosis and primary CNS lymphoma

are the most common; lesions from all other causes occur much less frequently. Since more than 90% of patients with intracranial mass lesions may respond, at least temporarily, to treatment, early and accurate diagnosis is imperative.

Nonviral Infections

Cryptococcal Infection

Meningitis caused by *Cryptococcus neoformans*, a ubiquitous soil fungus, is the most common intracranial nonviral infection in patients with AIDS. Studies suggest that approximately 5% of all AIDS patients have cryptococcal infection, but the risk appears to be as high as 10% in AIDS patients from New Jersey who are black and who use intravenous drugs (Rosenblum *et al.* 1988b).

The initial symptoms include decreasing mental status, headache, and signs of meningeal irritation. CT scans are usually normal. The diagnosis is made by CSF analysis and cultures, cryptococcal antigen titers, or microscopic examination of CSF stained with India ink. The CSF cell count may not be markedly elevated.

Cryptococcal meningitis results in a granulomatous meningitis; additional granulomas and cysts form in the cerebral cortex and deep white matter (Rosenblum *et al.* 1988b). While cryptococcal abscesses are rare in immunocompetent hosts, they are found in 10% of AIDS patients with cryptococcal meningitis; the lesions are usually small and located in the thalamus or hypothalamus.

Standard therapy consists of amphotericin B with or without flucytosine during the acute phase of the illness, followed by long-term suppressive therapy. The acute illness frequently responds to treatment with amphotericin B or azole compounds such as fluconazole (Bozzette *et al.* 1991); however, recurrent cryptococcal meningitis and toxicity reactions to antibiotics, especially flucytosine, are significant problems, and mortality rates as high as 50% have been reported (Rosenblum *et al.* 1988b). Neurosurgical consultation may be requested for placement of an Ommaya reservoir to facilitate CSF analysis and intrathecal drug administration or for biopsy of an intracranial mass lesion in a patient with cryptococcal meningitis.

Toxoplasmosis

Toxoplasmosis is the most frequent cause of intracranial mass lesions in patients with AIDS, accounting for 50–70% of all mass lesions in this

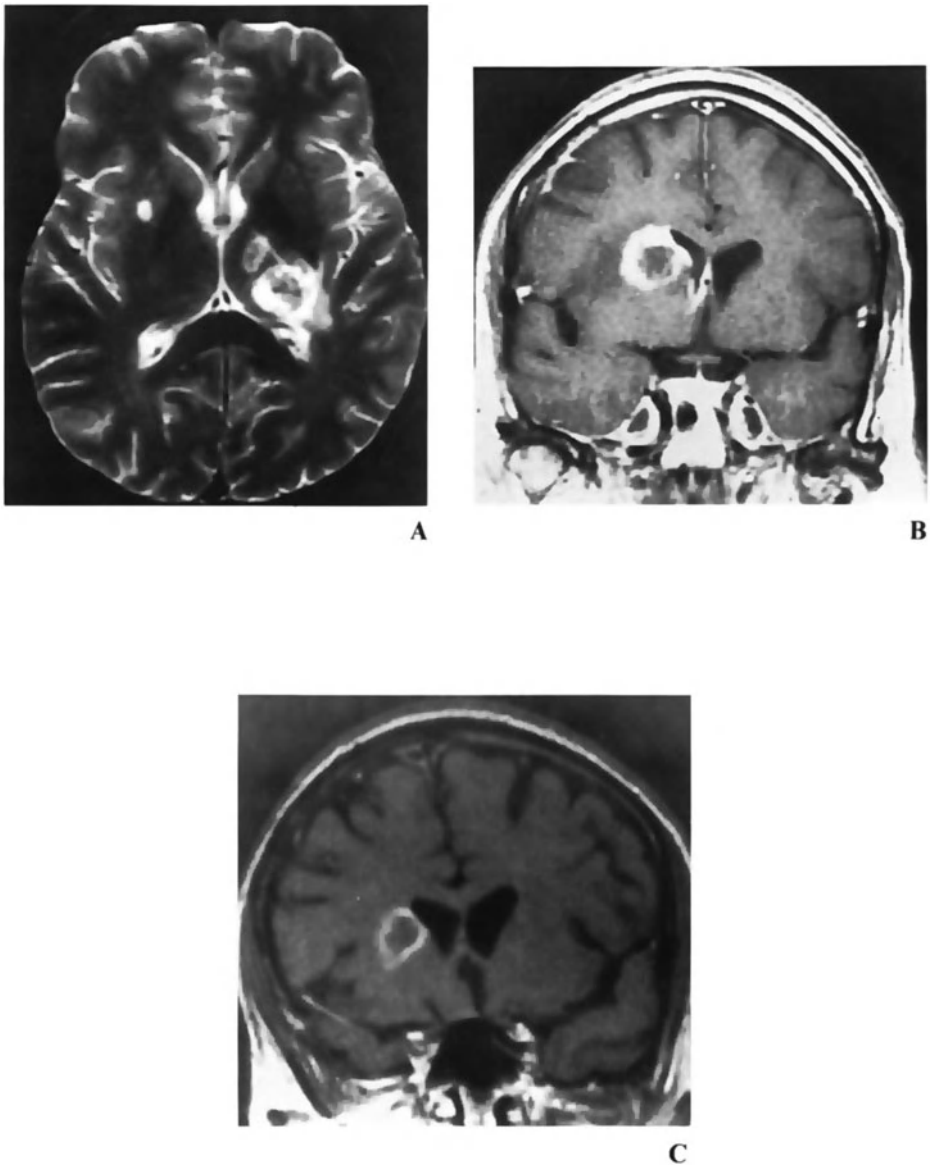


Fig. 1. Toxoplasmosis. (A) Axial T_2-weighted MR image in a 46-year-old gay man with AIDS shows high-signal lesions in the right putamen and left thalamus, common sites for *Toxoplasma* infection (TR = 2800, TE = 80). (B) Coronal T_1-weighted gadolinium-enhanced MR image from another AIDS patient shows a solitary ring-enhancing lesion in the right periventricular white matter (TR = 600, TE = 20). (C) The same lesion after 2 weeks of empirical anti-*Toxoplasma* therapy shows decreases in the size of the lesion, surrounding edema, and mass effect (TR = 500, TE = 30)

population. *Toxoplasma gondii* infection of the CNS produces acute focal or diffuse meningitis and encephalitis, tissue destruction, and signs of inflammation; both intracellular and extracellular organisms may be present. The incidence of cerebral toxoplasmosis is 2–13%, depending on the risk group and geographic location (Rosenblum *et al.* 1988b).

The usual clinical findings include lethargy, cognitive impairment, seizures, weakness, and other focal neurologic deficits. Certain radiographic findings may be highly suggestive of *Toxoplasma* infection; multiple small, uniformly ring-enhancing lesions with moderate to marked surrounding edema in the basal ganglia and subcortical regions suggests the diagnosis (Ciricillo and Rosenblum 1990, Levy *et al.* 1985, Levy *et al.* 1986). However, a solitary lesion on CT scans or MR images may also be a *Toxoplasma* abscess (Fig. 1).

The vast majority of patients with toxoplasmosis respond clinically and radiographically to an empirical trial of pyrimethamine and sulfadiazine and thus are never seen by a neurosurgeon. Systemic administration of corticosteroids must be avoided whenever possible during empirical antibiotic treatment because it decreases contrast enhancement on follow-up scans and may give the appearance of improvement when, in fact, none has occurred. If any mass lesion enlarges or remains unchanged in size despite adequate anti-toxoplasmosis therapy, a biopsy should be performed to rule out another disease. After treatment of the acute infection, life-long suppressive therapy with pyrimethamine and sulfadiazine is required to prevent reinfection.

Other Fungal Infections

Candida albicans is a rare CNS pathogen that may cause a localized abscess. Surgical excision of the abscess followed by systemic administration of amphotericin B appears to be the only effective therapy. *Aspergillus fumigatus* has caused focal abscesses, meningitis, and encephalitis in a few AIDS patients. Infections by *Coccidioides immitis*, *Rhizopus* species, *Histoplasma capsulatum*, *Acremonium alabamensis*, and other fungi appear to be quite rare (Rosenblum *et al.* 1988b).

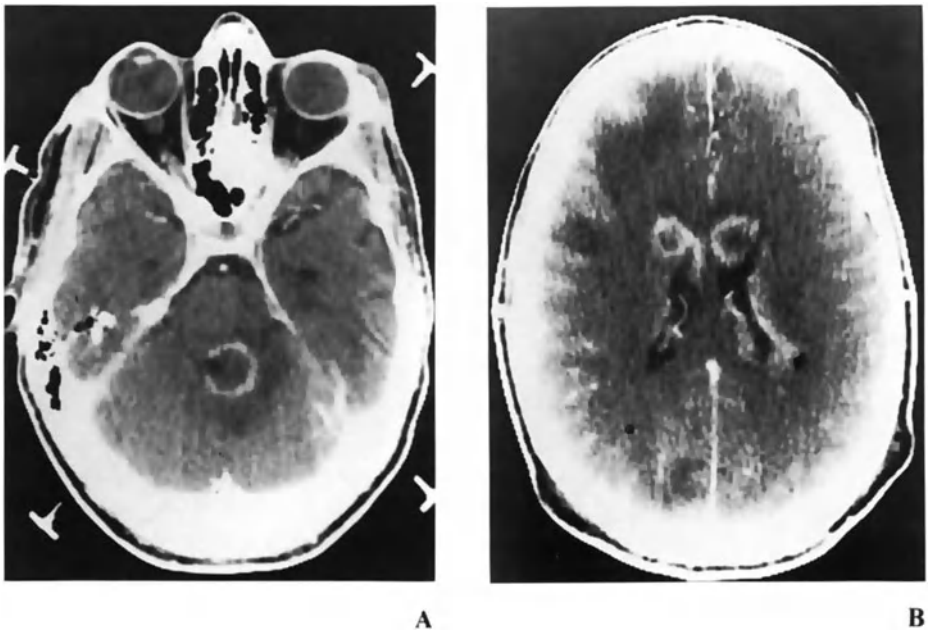
Neoplasms

Primary CNS Lymphoma

Primary malignant lymphomas of the CNS were once considered rare lesions, accounting for 0.5–1.5% of primary brain tumors. The risk of

primary CNS lymphoma in the general population has been estimated to be 0.0001% (Rosenblum *et al.* 1988b). That risk increases to 0.2–0.5% among immunosuppressed patients without AIDS, such as renal and cardiac transplant recipients, and soars to an estimated 2% in AIDS patients (Moskowitz *et al.* 1984, Rosenblum *et al.* 1988b). Before 1980, the annual incidence of primary CNS lymphoma in the United States was approximately 225 cases. Since then, primary CNS lymphoma has become predominantly an AIDS-related disease. It is the second most common cause of intracranial mass lesions in patients with AIDS, accounting for 10–25% of all intracranial mass lesions (Ciricillo and Rosenblum 1990, Rosenblum *et al.* 1988b). It has been estimated that more than 1,800 cases of AIDS-related primary CNS lymphoma occurred during 1991 (Rosenblum *et al.* 1988b); however, no published data are available to confirm this estimate.

The clinical and radiographic appearance of lymphoma in AIDS patients is different from that in patients without AIDS. Non-AIDS-related primary CNS lymphoma typically causes a slowly progressive decline in mental status, headaches, and, less frequently, focal neurologic findings.



A B

Fig. 2. Primary CNS lymphoma (A, B) CT scans from a 53-year-old gay man with AIDS shows multiple enhancing lesions in the cerebrum and brain stem. Note the subependymal tumor spread (arrow), which helps differentiate the lesions from *Toxoplasma* abscesses

CT scans may reveal a homogeneously enhancing mass or lesions with mild mass effect and surrounding edema. In AIDS patients, however, the lesions frequently show ring-enhancement on CT scans and may easily be confused with a CNS infection (Fig. 2). On MR images, the finding of a solitary mass lesion that enhances after administration of gadolinium and that shows a central area of T_2-shortening and surrounding edema on T_2-weighted images is twice as likely to be a lymphoma as it is to be CNS toxoplasmosis, despite the greater prevalence of toxoplasmosis in the AIDS population (Ciricillo and Rosenblum 1990, Ciricillo and Rosenblum 1991). However, a definitive diagnosis can only be established by prompt biopsy of the lesion (Fig. 3).

Until recently, the prognosis for patients with primary CNS lymphoma was dismal; few patients survived more than 2 months, none lived beyond 6 months, and most patients died from their tumors. However, a recent study has demonstrated the remarkable sensitivity of these lesions to radiation (Baumgartner *et al.* 1990). Aggressive early radiation therapy

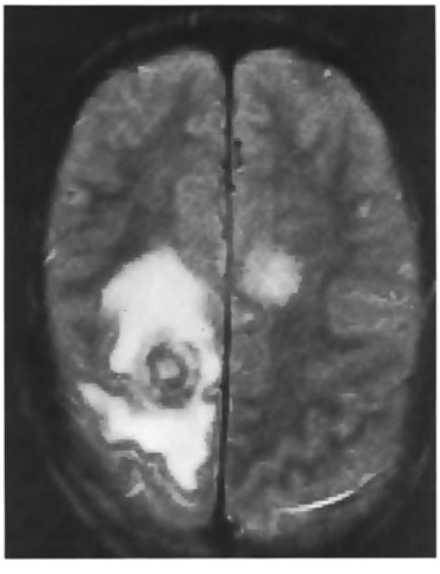


Fig. 3. Primary CNS lymphoma. T_2-weighted axial MR image in this AIDS patient shows two lesions with markedly different signal characteristics. The right hemispheric mass has a target-like appearance; the central area of T_2-shortening is thought to be due to the high nuclear to cytoplasmic ratio of the tumor cells. Also note the marked peritumoral edema (TR = 2000, TE = 80)

(4000 cGy over 3 weeks) resulted in clinical and radiographic improvement or stabilization in 85% of patients. With early radiation therapy, the mean survival time more than quadrupled, and only 10% of patients died of their tumors; many had no evidence of CNS tumor at the time of death. Thus, primary CNS lymphoma may now be considered a curable illness. As treatments for the systemic complications of AIDS improve, we can expect these patients to survive even longer.

Metastatic Neoplasms

Systemic (usually non-Hodgkin's) lymphoma may occasionally cause neurologic symptoms in AIDS patients. Symptoms result from invasion of the meninges or skull base, giving rise to cranial neuropathies, or from epidural compression of the spinal cord or cauda equina. Intraparenchymal metastasis is very uncommon (Rosenblum *et al.* 1988b). The diagnosis is made by cytologic examination of CSF, which demonstrates malignant cells in about 70% of cases. Chemotherapy, usually with intrathecal methotrexate, cytarabine, or both, may bring about temporary improvement, but most patients soon die from metastatic systemic lymphoma. Emergent radiation therapy and corticosteroids may be beneficial in cases of compressive myelopathy.

AIDS-related Kaposi's sarcoma is characteristically more aggressive than the classic form of the disease. The tumor progresses rapidly, causing widespread visceral involvement, but seldom metastasizes intracranially. The lesions are usually sensitive to radiation, but most patients die from the effects of diffuse systemic involvement.

Cerebrovascular Diseases

Symptomatic cerebrovascular complications occurred in only 20 patients (1.6%) in the UCSF series, but neuropathological studies indicate that the true incidence of cerebrovascular involvement is much higher, ranging from 12–19% (Levy *et al.* 1985, Rosenblum *et al.* 1988b, Snider *et al.* 1983). Infarcts may vary from small, multiple lesions to large bland or hemorrhagic infarcts. Hemorrhages are frequently associated with an underlying CNS tumor. The exact cause of these infarcts in unknown; cerebral vasculitis and circulating coagulation inhibitors have been identified in some patients (Cohen *et al.* 1986, Yanker *et al.* 1986).

Viral Infections

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is the third most common cause of focal lesions in AIDS patients, accounting for 10–22% of intracranial lesions in this population (Ciricillo and Rosenblum, 1990; Rosenblum *et al.* 1988b). The disease results from infection of oligodendroglial cells by the JC virus, a papovavirus that causes focal demyelination of the CNS. The initial symptoms (dementia, blindness, aphasia, hemiparesis, ataxia, and other focal deficits) reflect the involvement of white matter tracts in one or both hemispheres. CT scans usually show multiple areas of low attenuation in the white matter without significant mass effect; these areas do not enhance after administration of contrast material (Jarvik *et al.* 1988, Olsen *et al.* 1988). MR imaging, however, is much more sensitive than CT and will reveal many lesions not visible on CT scans (Fig. 4). The diagnosis can usually be established from the clinical and radiologic findings. Atypical cases in which only one lesion is seen, or in which the gray matter is involved (Fig. 5), may require biopsy to confirm the diagnosis (Ciricillo and Rosenblum 1990). Patients with PML rarely survive more than a few months. Autopsy findings include focal loss of myelin, axon sparing, and bizarre astrocytes and enlarged oligodendrocytes containing eosinophilic intranuclear inclusions. No effective therapy has been found.

Multiple CNS Diseases

Nearly 30% of AIDS patients with neurologic symptoms harbor more than one neurologic disease (Table 5). This fact greatly confounds the evaluation and treatment of patients in whom routine clinical, serologic, and radiologic studies are often nonspecific or relatively insensitive. Concomitant viral and nonviral opportunistic infections are the most common association. Of the treatable disorders, toxoplasmosis and primary CNS lymphoma are most often found together, either sequentially or simultaneously in different lesions or very rarely in the same radiographic lesion (Rosenblum *et al.* 1988b). Toxoplasmosis may also be associated with cytomegaloviral encephalitis. Treatment may be initiated based upon radiologic and serologic studies or histopathologic examination of one of multiple intracranial lesions, but patients who fail to respond completely to antibiotic therapy for presumed toxoplasmosis must be promptly reevaluated to rule out another CNS disease.

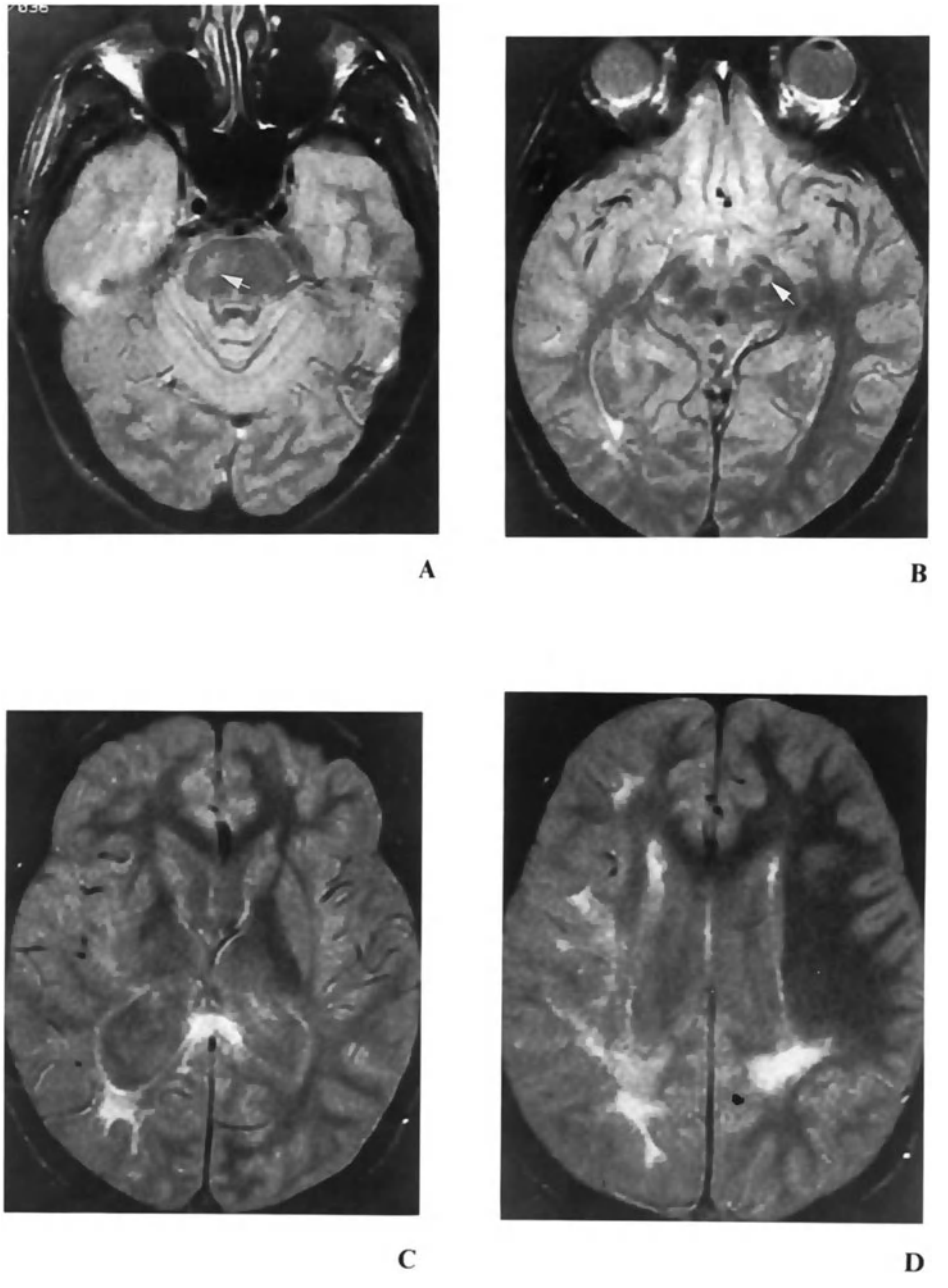


Fig. 4. Progressive multifocal leukoencephalopathy. (A–D) T_2-weighted MR images from a 34-year-old AIDS patient show multiple areas of high signal intensity in the right pons (arrow), left cerebral peduncle (arrowhead), right frontal and bilateral parietal lobes, and the corpus callosum without associated mass effect. Only the right parietal lesion was visible on CT scans (not shown). (TR = 2800, TE = 30)

Table 5. *Multiple Lesions Identified by CT Scans in 17 Patients with AIDS*

Lesions	No. of patients
Toxoplasmosis and lymphoma	6
Toxoplasmosis and cytomegalovirus encephalitis	4
Toxoplasmosis and cryptococcal meningitis	1
Toxoplasmosis and tuberculous abscess	1
Toxoplasmosis and cysticercosis	1
Lymphoma and cryptococcal meningitis	1
Cryptococcal meningitis and herpes varicella zoster encephalitis	1
Cryptococcal meningitis and cytomegalovirus encephalitis	1
Herpes simplex virus type I and cytomegalovirus encephalitis	1

Reproduced, with permission, from Rosenblum ML, Levy RM, Bredesen DE (1988) Neurosurgical implications of the acquired immunodeficiency syndrome (AIDS). Clin Neurosurg 34: 419–445.

CT computerized tomography; *AIDS* acquired immunodeficiency syndrome.

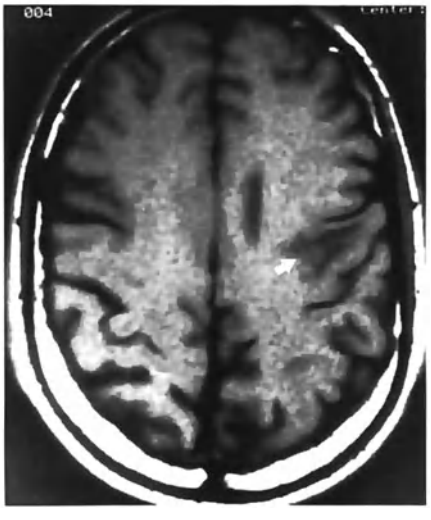


Fig. 5. Progressive multifocal leukoencephalopathy. T_1-weighted MR image shows a solitary lesion at the gray-white junction of the left precentral gyrus without surrounding edema or mass effect. The lesion appeared as a solitary area of hypodensity on contrast-enhanced CT scans (not shown) (TR = 600, TE = 30)

Peripheral Neuropathic Syndromes

Disorders of the peripheral nervous system, resulting either from direct HIV-1 infection or from toxic therapies used to treat other opportunistic infections or neoplasms, occur frequently in AIDS patients. Four syndromes have been identified: distal symmetric peripheral neuropathy, inflammatory demyelinating polyradiculoneuropathy, mononeuropathy multiplex, and progressive polyradiculopathy (Table 6) (Bredesen *et al.* 1989, Cornblath *et al.* 1987, Craddock *et al.* 1987, Eidelberg *et al.* 1986, Lipkin *et al.* 1985, Miller and Semple 1987, Miller *et al.* 1985 and 1988, Mishra *et al.* 1985, Tucker *et al.* 1985, Yarchoan *et al.* 1987). While these disorders are usually diagnosed and treated by neurologists, a neurosurgeon may rarely be consulted to perform a peripheral nerve biopsy in equivocal cases.

Evaluation of the Symptomatic Patient

The possibility of multiple, simultaneous neurologic illnesses, each with different therapies, makes the accurate diagnosis and treatment of the AIDS patient with neurologic symptoms both difficult and essential. The history and physical examination may provide clues to the diagnosis, based on the rapidity of onset of the symptoms and their progression. For example, the predominance of cognitive impairment over focal deficits may suggest global dysfunction due to HIV-1 encephalopathy. Usually, however, the symptoms are so nonspecific that they merely serve to identify patients who need further evaluation.

Serologic and CSF studies are invaluable in the laboratory evaluation of HIV-positive patients with neurologic symptoms. The CSF findings are often diagnostic, as in cases of cryptococcal meningitis, or further support a strong clinical suspicion, as in patients with multiple ring-enhancing lesions on MR images and positive *Toxoplasma* titers in blood or CSF. While *Toxoplasma* titers may be elevated in patients without active CNS toxoplasmosis, normal or negative *Toxoplasma* titers in a patient with known intracranial mass lesions strongly suggest a different diagnosis. In such cases, routine chemistry, cytology, and culture studies are indicated, as well as India ink preparations and special cultures for fungi, mycobacteria, and viruses. If no diagnosis is made, close neurologic follow-up evaluations at regular intervals are required.

A thorough neuropsychiatric assessment may help uncover a subtle dementia before gross signs of systemic or neurologic illness become apparent. Tests for HIV-1 infection (HIV antibody assays, p24 core antigen,

Table 6. *Peripheral Neuropathic Syndromes in HIV-Infected Patients*

Criteria	Distal symmetric peripheral neuropathy	Inflammatory demyelinating polyradiculoneuropathy	Mononeuropathy multiplex	Progressive polyradiculopathy
Type of patients	mostly AIDS	mostly non-AIDS	mostly non-AIDS	mostly AIDS
Symptoms	sensory function affected more than motor function	motor function affected more than sensory function	motor and/or sensory function affected	motor function affected more than sensory function
Symmetry	yes	yes	no	with progression
Cranial neuropathy	rare	common	very common	late, if at all
Urinary retention	no	no	no	yes
Chronicity	chronic	acute to chronic	usually subacute	usually subacute
Cerebrospinal fluid	usually normal	mononuclear pleocytosis, increased IgG level	mononuclear pleocytosis, increased IgG level	hypoglycorrhachia, mononuclear and polymorphonuclear pleocytosis
EMG	axonal loss	demyelination	axonal loss and demyelination	↓amplitude, ↓recruitment
Treatment	zidovudine, NSAID, anti-depressants, antibiotics	plasmapheresis, spontaneous remission	plasmapheresis	none

Adapted, with permission, from Bredesen DE, Levy RM, Rosenblum ML (1989) Human immunodeficiency virus-related neurological dysfunction. In: Aminoff MJ (ed) Neurology and general medicine. Churchill Livingstone, New York, pp 673–689.

HIV human immunodeficiency virus; *AIDS* acquired immunodeficiency syndrome; *IgG* immunoglobulin G; *EMG* electromyogram; *NSAID* nonsteroidal antiinflammatory drugs.

or HIV-1 virus culture) only indicate prior exposure to the virus and are not markers for active neurologic dysfunction in these patients (Rosenblum *et al.* 1988b).

Most early studies used CT for the initial evaluation and follow-up of AIDS patients with neurologic complaints (De La Paz and Enzmann 1988, Levy *et al.* 1986). Diffuse cerebral atrophy alone, thought to represent the effects of HIV-1 infection on the CNS, is seen in approximately 35% of these patients who undergo CT evaluation, while focal mass lesions are found in 25%. The presence of diffuse cerebral atrophy is purported to be of some prognostic value, as patients with atrophy are three times more likely than those with normal CT scans to develop progressive neurologic dysfunction and demonstrable CNS pathologic findings (Levy *et al.* 1986). In patients with evidence of CNS disease and normal CT scans, the most frequent diagnoses are HIV encephalopathy and cryptococcal meningitis (Post *et al.* 1988).

Patients whose CT scans show nonenhancing, low-density lesions often have PML (Jarvik *et al.* 1988, Olsen *et al.* 1988). Administration of a double-dose of contrast material improves the sensitivity of CT scans and may identify the rare primary lymphoma that does not enhance well. Ring-enhancing lesions are usually either toxoplasmosis or primary CNS lymphoma, but the rarer fungal or bacterial causes of brain abscess must also be considered. The diagnosis cannot be made with any certainty from CT scans alone (Ciricillo and Rosenblum 1990).

Table 7. *Comparison of CT and MRI Findings in 98 AIDS Patients*

Findings on brain scan	Percentage of patients
MRI positive, CT negative	22
MRI, more lesions than CT	22
MRI, same lesions as CT	16
CT positive, MRI negative	1
CT, more lesions than MRI	2
MRI and CT show atrophy	16
MRI and CT normal	21

Adapted, with permission from, De La Paz R, Enzmann D (1988) Neuroradiology of acquired immunodeficiency syndrome. In: Rosenblum ML, Levy RM, Bredesen DE (eds) AIDS and the nervous system. Raven, New York, pp 121–153.

CT computerized tomography; *MRI* magnetic resonance imaging; *AIDS* acquired immunodeficiency syndrome.

MR imaging has become the screening study of choice in AIDS patients with neurologic symptoms because it is more sensitive than CT (Table 7) and because the results correlate better with pathologic CNS findings at autopsy (Gill *et al.* 1986, Post *et al.* 1986, Ramsey and Geremia 1988). Administration of gadolinium increases the sensitivity of MR imaging and should be used routinely. CT scanning is now reserved for guiding stereotaxic procedures in these patients.

Although radiographic images can only suggest the pathologic diagnosis, radiographic techniques can sometimes help the neurosurgeon decide which patients should be biopsied (Table 8). If only the number of lesions is considered, a single lesion on CT scans or multiple lesions on CT or MR images does not help predict the CNS diagnosis (Ciricillo and Rosenblum 1991). However, a solitary mass lesion on MR images is twice as likely to be a primary lymphoma as it is to be toxoplasmosis. Thus, while MR images cannot yield an exact histopathologic diagnosis, they may sometimes help to select the initial treatment plan (Ciricillo and Rosenblum 1990).

Table 8. *Probability of Various Neurological Disorders in 274 AIDS Patients, Given a Particular Radiographic Finding*

Radiographic findings	Toxoplasmosis	PCNSL	PML
CT			
Solitary lesion	0.36	0.40	0.24
Multiple lesions	0.63	0.23	0.14
MRI			
Solitary lesion[a]	0.34	0.56	0.08
Multiple lesions	0.60	0.19	0.21

Adapted, with permission, from Ciricillo SF, Rosenblum ML (1990) Use of CT and MR imaging to distinguish intracranial lesions and to define the need for biopsy in AIDS patients. J Neurosurg 73: 720–724.

[a]Significantly different from expected frequency of disease in the AIDS population ($p < 0.001$, chi-square test).

AIDS acquired immunodeficiency syndrome; *PCNSL* primary central nervous system lymphoma; *PML* progressive multifocal leukoencephalopathy; *CT* computerized tomography; *MRI* magnetic resonance imaging.

Algorithms to Evaluate the AIDS Patient with Neurologic Symptoms

Algorithms to assist the clinician in evaluating the AIDS patient with neurologic symptoms have been established and widely published (Figs. 6 and 7) (Rosenblum *et al.* 1988a). We cannot overemphasize the importance of careful neurologic examination and follow-up observation in all cases.

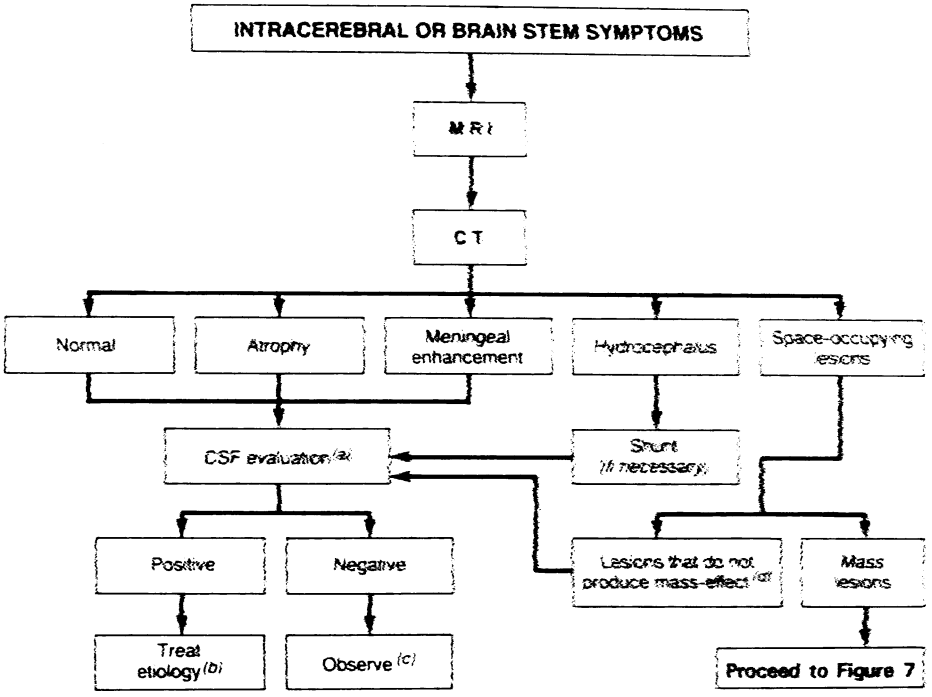


Fig. 6. Algorithm for the evaluation and treatment of intracerebral or brain stem symptoms in patients infected with human immunodeficiency virus (HIV-1). (*a*) CSF should be analyzed for cells, glucose, bacteria, tuberculous organisms and viruses. (*b*) See Table 3. (*c*) If neurologic symptoms persist, MR imaging or CT studies and the CSF evaluation are repeated monthly. If significant neurologic deterioration occurs or if new symptoms or signs develop, immediate MR or CT studies are warranted. (*d*) Space-occupying lesions that do not produce mass effect are usually seen on CT scans as areas of low density that do *not enhance* after the administration of contrast material. On T_2-weighted MR images, these lesions are seen as areas of high signal intensity. The majority are due to HIV-1, cytomegalovirus, progressive multifocal leukoencephalopathy, and strokes. (Reproduced, with permission, from Rosenblum ML, Bredesen DE, Levy RM (1988) Algorithms for the treatment of AIDS patients with neurologic disease. In: Rosenblum ML, Levy RM, Bredesen DE (eds) AIDS and the nervous system. Raven, New York, p 393)

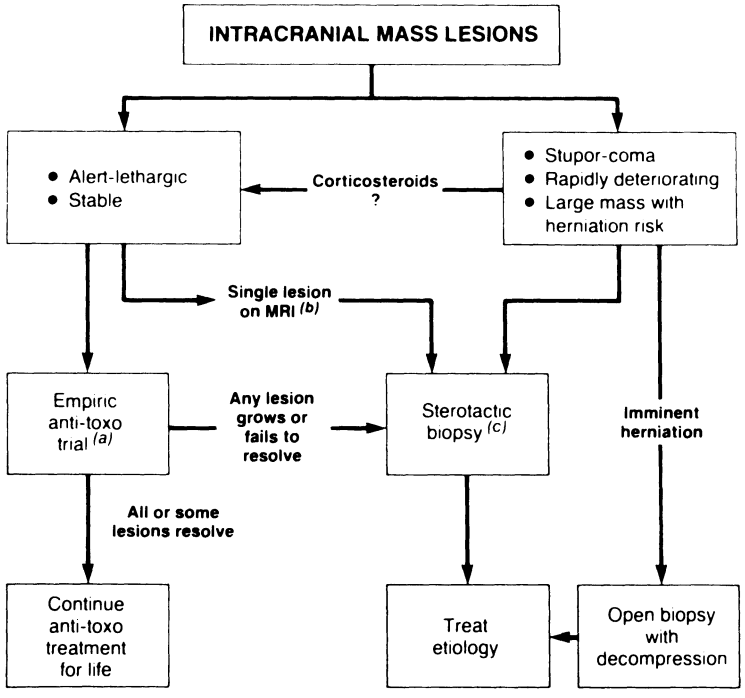


Fig. 7. Algorithm for the evaluation and treatment of intracranial mass lesions in patients infected with human immunodeficiency virus-1. (a) Three-week empirical trial of sulfadiazine and pyrimethamine for presumed toxoplasmosis. (b) Because the majority of single mass lesions shown by MR imaging are not caused by *Toxoplasma gondii*, a biopsy is recommended. (c) Stereotactic biopsies are guided by CT, MR imaging, or real-time ultrasonography. The only absolute contraindication to stereotactic biopsy is an uncorrectable bleeding diathesis. (Reproduced, with permission, from Rosenblum ML, Bredesen DE, Levy RM (1988) Algorithms for the treatment of AIDS patients with neurological disease. In: Rosenblum ML, Levy RM, Bredesen DE (eds) AIDS and the nervous system. Raven, New York, p 394)

Patients with evidence of a peripheral nervous system disorder usually undergo electrophysiologic studies, including both electromyography and nerve conduction studies. Occasionally, these studies are inconclusive, and the neurosurgeon may be asked to perform a nerve biopsy to establish a diagnosis. Inflammatory peripheral neuropathies with evidence of demyelination and axonal preservation may improve with plasmapheresis (Table 6), but treatment is largely supportive or palliative.

Patients with stable or slowly progressive neurologic deficits in whom CT or MR images show multiple focal mass lesions should be treated for presumed toxoplasmosis with pyrimethamine (25–50 mg/day) and sulfa-

diazine (2–4 g initially, followed by 1–1.5 g every 6 hours). Leucovorin (5–25 mg/day) is given to reduce bone marrow toxicity. Abscesses will resolve within 2–3 weeks in more that 75% of cases. If clinical and radiologic improvement occurs, full-dose treatment should be continued for life. If the patient deteriorates or fails to show improvement during empirical therapy, or if radiographic studies show enlargement of any lesion, a different diagnosis is likely, and a stereotactic biopsy guided by CT, MR, or ultrasound is indicated, except in patients with end-stage systemic illness.

Early biopsy is indicated to evaluate a solitary lesion on MR images, as lymphoma is twice as likely as toxoplasmosis in such cases (Ciricillo and Rosenblum 1990 and 1991, Rosenblum *et al.* 1988b). If there is rapid neurologic deterioration or a severely depressed level of consciousness, a stereotactic biopsy is reasonable before an empirical trial of anti-*Toxoplasma* therapy is undertaken; however, steroids can frequently improve the neurologic status sufficiently to permit an empirical trial. Before toxoplasmosis can be presumptively diagnosed, steroid therapy must be discontinued and both clinical and radiographic improvement must persist. Open craniotomy is rarely indicated and should be reserved for patients with infratentorial lesions or large mass lesions causing incipient or progressing uncal or tonsillar herniation that cannot be alleviated with corticosteroid therapy. The outcome of operative intervention in the latter group of patients is uniformly poor.

Impact of AIDS on Neurosurgical Practice

The AIDS epidemic has had a profound impact on every medical subspecialty, including neurosurgery. Using a polynomial mathematical model, the CDC had forecast that 74,000 new cases of AIDS would be diagnosed in the United States in 1991, bringing the cumulative total to 270,000 cases (Curran *et al.* 1988, Morgan and Curran 1986). While the actual number of reported cases of AIDS has begun to lag behind estimates predicted when very few cases were available, recent improvements in the treatment of the pulmonary and other systemic complications of AIDS has extended the life expectancy of these patients, allowing more time for neurologic complications to develop. As the population at risk for AIDS-related neurologic disease continues to increase at an alarming rate, steps must be taken to ensure that adequate financial, medical, and human resources are available to care for these patients (Bloom and Carlinier 1988).

The AIDS epidemic has dramatically increased the incidence of certain neurologic diseases which were once considered uncommon. Cryptococcal

meningitis, PML, and toxoplasmosis now constitute a regular part of the medical education for internists, neurologists, and neurosurgeons at most major medical centers. The number of cases of primary CNS lymphoma seen annually is approaching the number of meningiomas treated annually in the United States (Rosenblum *et al.* 1988b).

The constant threat of HIV-1 exposure has drastically changed the procedures and equipment used in most operative suites and medical offices throughout the United States. It is our policy to assume that all patients are potential carriers of HIV-1, regardless of their antibody status. Eye protection, impermeable barriers, double gloving, and occasionally knee-high "boot" covers are now used routinely at our institution. Disposable bone perforators and stereotactic needles are frequently used to avoid possible contamination of uninfected patients. Gloves are worn during the preoperative and postoperative handling and care of all patients, including shaving and positioning, to avoid possible exposure to infectious body fluids. Sharp instruments are placed on a special sterile Mayo stand and are handled by only one person at a time to avoid accidental skin puncture. Needles are not resheathed. Universal precautions can be augmented with special care when the patient is known to be HIV positive or to have AIDS.

References

1. Baumgartner JE, Rachlin JR, Beckstead JH, Meeker TC, Levy RM, Wara WM, Rosenblum ML (1990) Primary central nervous system lymphomas: natural history and response to radiation therapy in 55 patients with acquired immunodeficiency syndrome. J Neurosurg 73: 206–211
2. Bloom DE, Carlinier G (1988) The economic impact of AIDS in the United States. Science 239: 604–609
3. Bozzette SA, Larsen RA, Chiu J, Leal MA, Jacobsen J, Rothman P, Robinson P, Gilbert G, McCutchan JA, Tilles J (1991) A placebo-controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in the acquired immunodeficiency syndrome. N Engl J Med 324: 580–584
4. Bredesen DE, Levy RM, Rosenblum ML (1989) Human immunodeficiency virus-related neurological dysfunction. In: Aminoff MJ (ed) Neurology and general medicine. Churchill Livingstone, New York, pp 673–689
5. Ciricillo SF, Rosenblum ML (1990) Use of CT and MR imaging to distinguish intracranial lesions and to define the need for biopsy in AIDS patients. J Neurosurg 73: 720–724
6. Ciricillo SF, Rosenblum ML (1991) Imaging of solitary lesions in AIDS. J Neurosurg 74: 1029 (Letter)

7. Cohen AJ, Phillips T, Keffler C (1986) Circulating coagulation inhibitors in the acquired immune deficiency syndrome. Ann Intern Med 104: 175–180
8. Cornblath DR, McArthur JC, Kennedy PG, Witte AS, Griffin JW (1987) Inflammatory demyelinating peripheral neuropathies associated with human T-cell lymphotrophic virus type III infection. Ann Neurol 21: 32–40
9. Craddock C, Pasvol G, Bull R, Protheroe A, Hopkin J (1987) Cardiorespiratory arrest and autonomic neuropathy in AIDS. Lancet 2: 16–18
10. Curran JW, Jaffe HW, Hardy AM, Morgan WM, Selik RM, Dondero TJ (1988) Epidemiology of HIV infection and AIDS in the United States. Science 239: 610–616
11. De La Paz R, Enzmann D (1988) Neuroradiology of acquired immunodeficiency syndrome. In: Rosenblum ML, Levy RM, Bredesen DE (eds) AIDS and the nervous system. Raven, New York, p 121
12. Eidelberg D, Sotrel A, Vogel H, Walker P, Kleefield J, Crumpacker CS 3rd (1986) Progressive polyradiculopathy in acquired immune deficiency syndrome. Neurology 36: 912–916
13. Gill PS, Graham RA, Boswell W, Meyer P, Krailo M, Levine AM (1986) A comparison of imaging, clinical, and pathologic aspects of space-occupying lesions within the brain in patients with acquired immune deficiency syndrome. Am J Physiol Imaging 1: 124–141
14. Hessol NA, Byers RH, Lifson AR, O'Malley PM, Cannon L, Barnham JL, Harrison JS, Rutherford GW (1990) Relationship between AIDS latency period and AIDS survival time in homosexual and bisexual men. J Acquir Immune Defic Syndr 3: 1078–1085
15. Ho DD, Rota TR, Schooley RT, Kaplan JC, Allan JD, Groopman JE, Resnick L, Felsenstein D, Andrews CA, Hirsch MS (1985) Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neurologic syndromes related to the acquired immunodeficiency syndrome. N Engl J Med 313: 1493–1497
16. Imagawa DT, Lee MH, Wolinsky SM, Sano K, Morales F, Kwok S, Sninsky JH, Nishanian PG, Giorgi J, Fahey JL (1989) Human immunodeficiency virus type 1 infection in homosexual men who remain seronegative for prolonged periods. N Engl J Med 320: 1458–1462
17. Jarvik JG, Hesselink JR, Kennedy C, Teschke R, Wiley C, Spector S, Richman D, McCutchan JA (1988) Acquired immunodeficiency syndrome. Magnetic resonance patterns of brain involvement with pathologic correlation. Arch Neurol 45: 731–736
18. Koppel BS, Wormser GP, Tuchma AJ, Maayan S, Hewlett D Jr, Daras M (1985) Central nervous system involvement in patients with acquired immune deficiency syndrome (AIDS). Acta Neurol Scand 71: 337–351
19. Levy JA (1989) Human immunodeficiency virus and the pathogenesis of AIDS. JAMA 261: 2997–3006
20. Levy RM, Bredesen DE, Rosenblum ML (1985) Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): experience at UCSF and review of the literature. J Neurosurg 62: 475–495

21. Levy RM, Rosenbloom S, Perrett LV (1986) Neuroradiologic findings in AIDS: a review of 200 cases. AJR 147: 977–983
22. Lipkin WI, Parry G, Kiprov D, Abrams D (1985) Inflammatory neuropathy in homosexual men with lymphadenopathy. Neurology 35: 1479–1483
23. Mann J (1992) AIDS. The second decade: a global perspective. J Infect Dis 165: 245–250
24. Miller RF, Semple SJ (1987) Autonomic neuropathy in AIDS. Lancet 2: 343–344 (Letter)
25. Miller RG, Kiprov DD, Parry G, Bredesen DE (1988) Peripheral nervous system dysfunction in acquired immunodeficiency syndrome. In: Rosenblum ML, Levy RM, Bredesen DE (eds) AIDS and the nervous system. Raven, New York, pp 65–78
26. Miller RG, Parry G, Lang W, Lippert R, Kiprov DD (1985) AIDS-related inflammatory polyradiculopathy: prediction of response to plasma exchange with electrophysiologic testing. Muscle Nerve 8: 626
27. Mishra BB, Sommers W, Koski CK, Greenstein JI (1985) Acute inflammatory demyelinating polyneuropathy in the acquired immune deficiency syndrome. Ann Neurol 18: 131
28. Morgan WM, Curran JW (1986) Acquired immunodeficiency syndrome: current and future trends. Public Health Rep 101: 459–465
29. Moskowitz LB, Hensley GT, Chan JC, Gregorios J, Conley FK (1984) The neuropathology of acquired immune deficiency syndrome. Arch Pathol Lab Med 108: 867–872
30. Olsen WL, Longo FM, Mills CM, Norman D (1988) White matter disease in AIDS: findings at MR imaging. Radiology 169: 445–448
31. Piot P, Plummer FA, Mhalu FS, Lamboray J-L, Chin J, Mann JM (1988) AIDS: an international perspective. Science 239: 573–579
32. Post MJD, Sheldon JJ, Hensley GT, Soila K, Tabias JA, Chan JC, Quencer RM, Moskowitz LB (1986) Central nervous system disease in acquired immunodeficiency syndrome: prospective correlation using CT, MR imaging, and pathologic studies. Radiology 158: 141–148
33. Post MJD, Tate LG, Quencer RM, Hensley GT, Berter JR, Sheremata WA, Maul G (1988) CT, MR, and pathology in HIV encephalitis and meningitis. AJR 151: 373–380
34. Price RW, Brew B, Sidtis J, Rosenblum M, Scheck AC, Cleary P (1988) The brain in AIDS: central nervous system HIV-1 infection and AIDS dementia complex. Science 239: 586–592
35. Ramsey RG, Geremia GK (1988) CNS complications of AIDS: CT and MR findings. AJR 141: 448–454
36. Rosenblum ML, Levy RM, Bredesen DE (1988a) Algorithms for the treatment of AIDS patients with neurological diseases. In: Rosenblum ML, Levy RM, Bredesen DE (eds) AIDS and the nervous system. Raven, New York, pp 389–395
37. Rosenblum ML, Levy RM, Bredesen DE (1988b) Neurosurgical implications of the acquired immunodeficiency syndrome (AIDS). Clin Neurosurg 34: 419–445

38. Rosenblum ML, Levy RM, Bredesen DE (1988c) Overview of AIDS and the nervous system. In: Rosenblum ML, Levy RM, Bredesen DE (eds) AIDS and the nervous system. Raven, New York, pp 1–12
39. Schiff SJ (1990) A surgeon's risk of AIDS. J Neurosurg 73: 631–660
40. Snider WD, Simpson DM, Nielson S, Gold JWM, Metroka CE, Posner JB (1983) Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. Ann Neurol 14: 403–418
41. Taylor JMG (1989) Models for the HIV infection and AIDS epidemic in the United States. Stat Med 8: 45–58
42. Tucker T, Dix RD, Katzen C, Davis RL, Schmidley JW (1985) Cytomegalovirus and herpes simplex virus ascending myelitis in a patient with acquired immune deficiency syndrome. Ann Neurol 18: 74–79
43. Wiley JA, Samuel MC (1989) Prevalence of HIV infection in the USA. AIDS 3[Suppl]: S71–S78
44. Yanker BY, Skolnick P, Shoukimas GM, Gabuzda DH, Sobel RA, Ho DD (1986) Cerebral granulomatous angiitis associated with acute HTLV-III infection of the central nervous system. Ann Neurol 20: 362–364
45. Yarchoan R, Berg G, Brouwers P, Fischl MA, Spitzer AR, Wickman A, Grafman J, Thomas RV, Safai B, Brunetti A, Perno CF, Schmidt PJ, Larson SM, Myers CE, Broder S (1987) Response of human-immunodeficiency-virus-associated neurological disease to 3'azido-3'-deoxythymidine. Lancet 1: 132–135

The Surgery of Occult Spinal Dysraphism

M. Choux, G. Lena, L. Genitori, and M. Foroutan

Department of Pediatric Neurosurgery, Hopital des Enfants, La Timone, Marseille (France)

With 24 Figures

Contents

Introduction

The spinal dysraphism state includes all lesions which are the consequence of incomplete formation of the midline structures of the dorsum. It is there-

fore related to all forms of spina bifida (spina bifida aperta or cystica) as well as occult spinal dysraphism. The basic differences of both malformations result from the nature of their origin. Spina bifida cystica is an intrinsic failure of development of the spinal cord tissues, with added destructive processes in utero and cellular dysplasia, together with brain anomalies. By contrast, in spina bifida occulta there may be some dysplasia of the spinal cord but none of the other destructive processes. Chiari malformation is very unusual in spina bifida occulta. The term occulta means that the malformation is covered by skin, with no cutaneous abnormalities. Occult spinal dysraphism and spina bifida occulta are generally synonymous. We prefer the term occult spinal dysraphism to spina bifida occulta. The common pathological finding is a tethered spinal cord even if lesions such as dermal sinus or neurenteric cysts (typically considered as occult spinal dysraphic lesions) are not generally associated with tethering of the spinal cord.

In cystic spinal anomalies clinical manifestations are present at birth due to the absence of normal nervous neural elements. In contrast in occult forms the clinical manifestations usually develop later. Both anomalies rarely exist as pure anatomical entities and in most of the cases different anomalies coexist in the same patient. Consequently a clear and understandable classification of anomalies of the dysraphic state remains difficult. In this chapter we will consider exclusively occult spinal dysraphic lesions. Widely different lesions may be included: lipomas, diastematomyelia, dermal sinus, anterior meningocele, neurenteric cysts, short thick filum or tethering bands. Moreover some combination of different lesions may be present in the same patient. Does embryology clarify our knowledge of anomalies of the dysraphic state?

Embryology and Foetal Development of the Spinal Cord. Pathogenesis of Malformations

We will follow the description of McLone and Naidich (1985) and Raybaud (1992). At stage VI of Streeter or by day 17, the two layer primitive pit becomes a three layer plate with migration of ectodermal cells into the center of the primitive pit. These migrated cells form the notochordal process which extends from the prochordal plate to Hensen's node caudally. The compact mass of cells called the notochordal process becomes a hollow canal when the primitive pit invaginates into it. The notochordal canal fuses ventrally first with the entoderm and secondly communicates with the yolk sac. The transient communication between the amnion and the yolk sac is called the neurenteric canal. Rapidly the notochordal process is

reformed and the communication with the yolk sac disappears. The notochord will induce the formation of the neural plate and the vertebrae. The neuro ectoderm forms the spinal cord. The cranial and caudal portions of the spinal cord are formed by two different processes. The main part, from the cephalic portion of the spinal cord to the conus, is formed by development of the neural canal (neurulation process). The caudal part, including the tip of the conus and the filum, is formed by a less-well-organized mechanism (canalization and retrogressive differentiation of the caudal cell mass). Consequently most of the spinal and vertebral malformations are located in the lower part of the spine.

IA. Neurulation

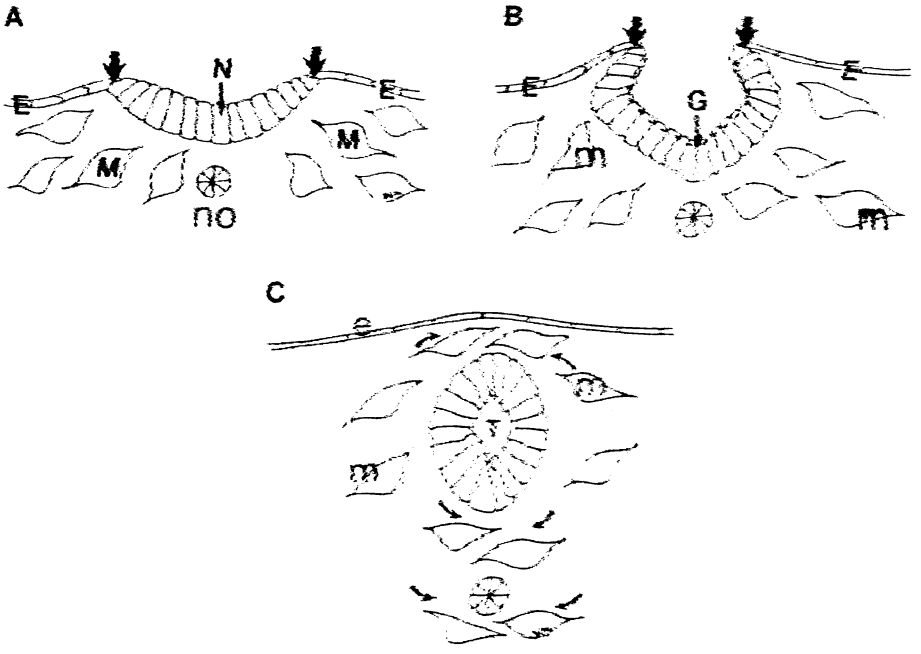
At the beginning of the third week (1.4 mm embryo), in the midline of the ectoderm layer, cephalad to Hensen's node, some ectodermal cells differentiate to form the neural plate. The lateral portions of the neural plate elevate to form the neural folds. Progressively the neural folds join and fuse in the midline to form neural tube (Table 1). This fusion starts at the level of the cervical region and extends cranially and caudally. The anterior neuropore represents the closure of the cephalic end of the neural canal at 23 days and the posterior neuropore the closure of the caudal end at 25 days. When the neural tube complete the two portions of the ectodermal layer join. It is the future skin of the back. Normally mesenchyme migrates between the neural tube and the ectoderm to form the meninges, the neural arches and the spinal muscles.

IB. Deranged Neurulation

Deranged Neurulation will produce in the main myelomeningoceles. In this malformation usually the distal portion of the spinal cord is open as a flat plate, without skin recovering. Since the superficial ectoderm does not separate from the neural tube, the ectoderm remains in a lateral position. The defect in embryogenesis which leads to myelomeningocele may be either nonclosure of the neural placode (3–5 mm embryo) or a secondary reopening of a closed and distended neural canal. Experimental work suggest that both mechanisms may participate in the formation of myelomeningocele.

Normally, around the fourth week of foetal development, the superficial ectoderm separates from the neurectoderm. When this mechanism fails,

Table 1. *Development of the Neural Tube Neurulation (from McLone)*



(A) *The ectoderm (E) junction (arrows) with the neural plate (N). The mesenchyme (M) is below and around the notochord (nO).*

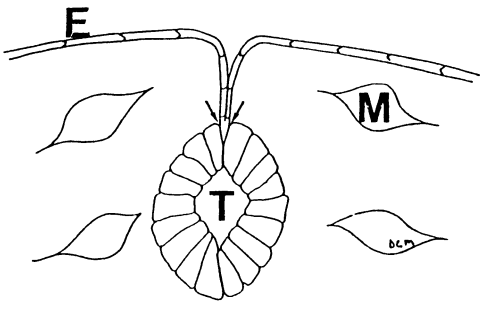
(B) *Process of closure of the neural canal. The junction of the superficial ectoderm (E) with the neuroectoderm represents the neural folds (arrows). The mesenchyme (m) is below and lateral to the neural tube (G).*

(C) *Complete closure of the neural tube (T). The superficial ectoderm is separated from the neural tube by the mesenchyme (m).*

focal adhesions may occur between the neural tube and the skin, explaining the occurrence of *dermal sinus, dermoid* or *epidermoid cysts*, depending on the extent of the adhesions (Table 2). Dermal sinuses are generally in the midline of the distal portion of the spinal canal. Since the growth of the spinal cord and the spinal column are different, the ascent of the spinal cord will explain why a focal dermal sinus will become finally an elongated epithelial tube extending from the skin to an upper segment of the spinal cord.

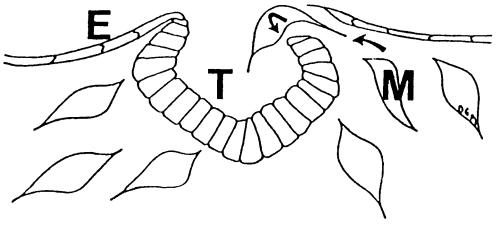
Many theories have been proposed to explain the presence of fat and fatty tumours in dysraphic spinal states connected with the spinal cord in the back. McLone, in 1982, suggested that *spinal lipomas* are the result of

Table 2. *Formation of Dermal Sinus (from McLone)*



Delayed disjunction of the neural tube from superficial ectoderm which result in a dermal sinus.

Table 3. *Formation of Spinal Lipoma (from McLone)*



Premature disjunction of the neural tube from superficial ectoderm and incomplete closure of the neural tube.
Mesenchyma (lipoma) may invade the neural groove and the dorsal portion of the neural canal.

premature failure of separation of the ectoderm and the neural canal, associated with an incomplete closure of the neural tube (Table 3). This event appears just before the closure of the neural canal (25–26 days). The mesenchyme which normally develops around the closed neural canal has access to the dorsal open neural canal and prevent its closure. Related to the date of this abnormality we will have all the degrees of association

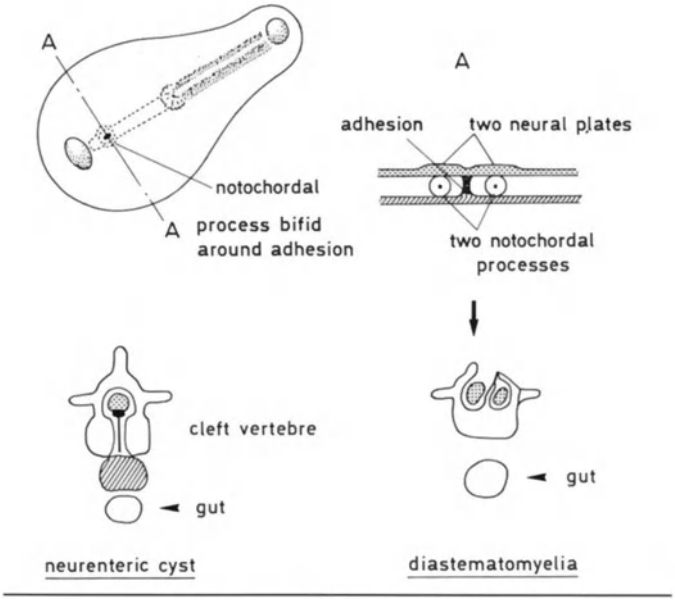
between spinal lipomas and myeloschisis. Fat tissue may be found independently or associated in the subcutaneous layer (fat mass), in the epidural space, in the dural sac or into the spinal cord.

The ventral portion of the neural tube, which remains normal in its structure, will induce, from mesenchyme, normal dura and normal arachnoid. Only the dorsal portion of the neural tube may induce the formation of fat from the mesenchyme. The open neural tube will be in continuity with the mesenchyme (fat tissue) and the lipoma will be bounded laterally by arachnoid and dura.

Diastematomyelia represents a more complex malformation with a sagittal splitting of the spinal cord and the dura, associated with abnormalities of the vertebrae (spina bifida, bony spurs, vertebral agenesis, hemivertebrae, butterfly vertebrae), and skin anomalies (hair or cutaneous naevi). There are several theories to explain diastematomyelia.

One theory is based on the existence of a primary anomaly of the neural tissue inducing changes in mesenchyme. In spite in having a single neural tube too rapid curling of the lateral edges of the neural plate will produce two neural tubes. The mesenchyme may develop between them, giving only pia in case of close by adjacent tubes (diastematomyelia with two spinal

Table 4. *Diastematomyelia and Neurenteric Formation*



cords in a single arachnoid and dura canal), or arachnoid, dura and bone in the case of more distant tubes (diastematomyelia with two separates spinal cords, two dural canals and bony spur).

Another theory supports the idea that the primary anomaly is extra-neural, from the notochordal process (Table 4). Bremer considers that the persistence of the neurenteric canal (canal of Kovalevsky), leads to a cleft of the neural plate. Accessory neurenteric canals may traverse the notochord and the neural plate explaining associated vertebral anomalies with twin spinal cords. The pathogenesis of diastematomyelia is not so different from that of neurenteric cysts and we know that both lesions may be present at the same time.

Recently Pang (1991) has proposed a unified theory of embryogenesis for double spinal cord malformations. The basic abnormality consists of an abnormal accessory neurenteric canal which is invested with mesenchyme to form an endomesenchymal tract that splits the notochord and the neural plate.

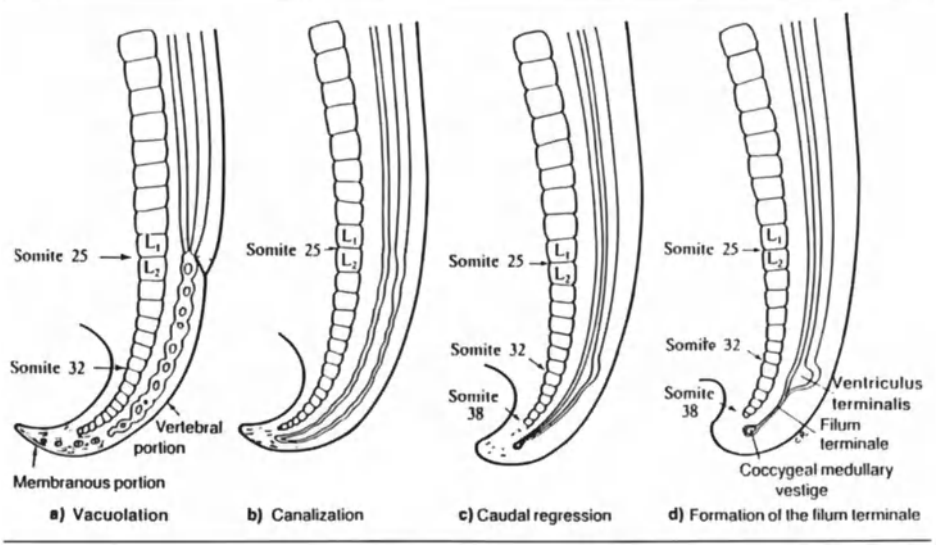
Neurenteric cyst is a manifestation of what Bentley and Smith have called the "split notochord syndrome". Local endo-ectodermal adhesion causes a splitting of the notochord. During growth at the level of this adherence an enteric diverticulum may be pushed into the neural tissue.

IIA. Canalization and Retrogressive Differentiation (Table 5)

Neurulation ends at day 25th. It leads to the formation of all the spinal cord from the foramen magnum. The distal portion of the spinal cord (the tip of the conus and the filum) will be formed now by the mechanism of canalization and retrogressive differentiation, from an aggregate of undifferentiated group of cells called the caudal cell mass. These cells develop at the level of the tail fold and will form not only neural structures but also genitourinary and notochordal structures. Consequently a neural congenital anomaly at this level is frequently associated with anorectal, renal, urinary or genital anomalies. The caudal cell mass includes undifferentiated cells and vacuoles which coalesce to form a canal. This canal will join to the central canal of the spinal cord formed by neurulation. The distal part of the spinal cord will form the tip of the conus medullaris and, after involution, the filum terminale. This involution is called retrogressive differentiation.

As McLone and Naidich have written: "At this point, it is sufficient to understand that the caudal spinal column also forms by a less-well-organized process than that responsible for the more cephalic portions of the spine above."

Table 5. *Canalization and Retrogressive Differentiation (from Ch. Raybaud)*



IIB. Deranged Canalization and Retrogressive Differentiation

Most of the malformations related to deranged neurulation arise during this period. Lipomas are generally explained by an anomaly starting during neurulation (*myelolipoma*). Others have their origin during the retrogressive differentiation (*lipoma of the filum*). Other anomalies have their origin exclusively at this period, as for example *terminal myelocystocele* where the distal end of the spinal cord is ballooned into a terminal cyst. This malformation is covered by normal skin, accompanied by spina bifida and frequently associated with exstrophy of the bladder. This terminal cyst of the cord originates from the caudal mass.

Failure of involution of the terminal cord may result in the *tight filum terminale syndrome*. In this anomaly the spinal cord is tethered by a thick and short filum terminale. This anomaly must be distinguished from a lipomatous filum. In the situation the conus is not routinely in a very low position.

Classification

In the literature the terms occult spinal dysraphism and tethered cord may be used as synonymous. We do not agree with this tradition since tethered

cord is a physical mechanism which explains the symptomatology observed in some anomalies such as lipomas, thick filum or intrasacral meningocele. In these anomalies the conus is in low position and fixed by a lipoma, by a short and thick filum, or attached to the dura by adhesions or bands. In some other anomalies, such as dermal sinus or neurenteric cyst which are part of occult spinal dysraphism, the conus may be in normal position and untethered. In the past the term "tethered spinal cord" was synonymous with "tight filum terminale". Such tethering of the cord may be seen also in cases of repaired myelomeningocele – this is called secondary tethering. In patients with tethered cord, intermittent stretching of the cord may occur with normal sitting or standing, with any body motion, and moreover with growth or with sports activities. As Reigel (1983) has mentioned: "Any process leading to lengthening or stretching of the cord such as pelvic flexion, cervical flexion, growth and development, and change in curvature of the vertebral column may lead to intermittent but chronic, repetitive ischemia or to progressive ischemia with resulting spinal cord dysfunction." A vascular factor as a cause of secondary spinal dysfunction must also be considered. During surgery a thin appearance of the spinal cord vessels is commonly observed. This finding may reverse immediately after untethering the cord. Yamada (1981) experimentally has shown that under constant or intermittent cord stretching an impairment of mitochondrial oxidative metabolism exists. The conclusion of the author is: "Untethering proved to be an effective means of improving oxidative metabolism, which corresponds to neurological improvement in human."

Within the literature many different anatomical entities are included in occult dysraphic category (Table 6). James and Lassman (1972) describe the following lesions in their monograph on spinal dysraphism: Diastematomyelia, dermoid cyst, traction lesion, pressure lesion, tight or lipomatous filum terminale and meningocele manqué. Traction lesions represent 71% of the anomalies and include lumbosacral lipoma, some diastematomyelias, bands, tight filum, dermal sinus and meningocele manqué. Till (1975) distinguishes diastematomyelia, intradural lipoma, extradural tethering band, dermoid cyst and neurenteric cyst. Pang (1982) in an adult series of 23 patients found a tight filum in 78% of the cases, the other lesions being lipoma (34.7%), bands (21.7%) and diastematomyelia (8.7%). Raimondi (1987) describes two main lesions, diastematomyelia and dysraphic hamartomas including lipomatous hamartoma, dermoid hamartomas and endodermal hamartoma. For this author the tethered cord with a thick filum does not appear in the group of dysraphic lesions. Scatliff (1989) in a pediatric series of 104 cases found a tethered cord in 14 cases, lipoma in 26, diastematomyelia in 25, meningocele in 5 and dermal sinus in 2. In the 14 cases of tethered cord an abnormally low position of the conus was mentioned, with thickening of the filum in 9 cases.

Table 6. *Classification of Occult Spinal Dysraphism in 6 Series*

	James (1972) 100 cases, children & adults	Till (1975) 160 cases, children	Anderson (1975) 73 cases, children	Pang (1982) 23 cases, adults	Scatliff (1989) 104 cases, children	Choux (1993) 169 cases, children
Tight filum	5	–	18	18	14	9
Diastematomyelia	42	73	1	2	25	14
Lipoma	19	67	21	8	26	99
Bands	3	35	18	3	–	–
Dermal sinus	6	14	25	0	2	33
Neurenteric cyst	–	3	–	–	–	4
Intraspinal meningocele	15	–	–	–	5	10

Table 7. *Occult Spinal Dysraphism: Lesions in 169 Pediatric Cases (Personal Series)*

Lipoma	98
Dermal sinus	33
Diastematomyelia	14
Anterior meningocele	10
Thick filum	9
Neurenteric cyst	4
Lipomyelocystocele	1

Some authors separate a category of lesions under the term "tethered spinal cord," with a low conus and a thickened filum measuring less than 2 mm in diameter. Hoffman (1976) makes the same distinction. Personally we consider the tethering as a mechanism to explain the main clinical manifestations and not an individualized lesion. Tethering is the end result of many different anatomical lesions.

The lesions we include in the group of occult spinal dysraphism are (Table 7):

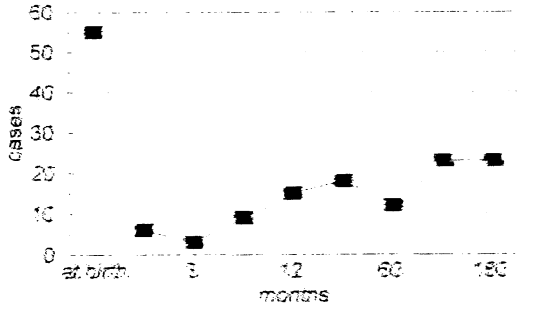
1) lipomas,
2) anomalies of spinal cord and roots including adhesions, bands, thick filum, diastematomyelia,
3) intra spinal or anterior meningoceles,
4) dermal sinus, dermoid cysts, and
5) neurenteric cysts.

Age and Sex Distribution

Improved knowledge of this pathology by pediatricians, urologists and orthopedic surgeons and earlier diagnosis, possible now in the neonatal period, explains the high rate of infants reported with spinal dysraphism, in recent literature series. In our personal series of 169 patients (Table 8) it appears that in 38% of the cases were diagnosed.

The tethered cord syndrome presents later in childhood in most of cases. Since the tolerance of stretching may be excellent this syndrome has been described in adults and even in elderly patients (Pang 1982). In adult age precipitating factors are generally present. Pang in a series of 23 cases

Table 8. Age Distribution, 169 Cases (Personal Series)



mentions definite events were present in 61% of the cases (*trauma, heavy* lifting, childbirth, sports, traffic accident).

The patients are predominantly female in all the series in the literature with a sex ratio of 1:2. It is well known that in spina bifida aperta there is a slight male predominance.

In contrast to myelomeningocele, familial cases of occult spinal dysraphism are extremely rare. Two cases of anterior sacral meningocele in the same family have been published (Klenerman 1973).

Clinical Presentation

The initial clinical manifestations may be grouped in 5 different categories: mainly cutaneous lesions; orthopedic abnormalities, either in the lower limbs or in the spine; *urological symptoms; neurological manifestations;* pain and other more rare symptoms (Tables 9 and 10). Presenting manifestations vary with the age. In neonates or small infants, skin lesions will be the most frequent and isolated initial symptom, while in older children or in adults the orthopedic or urological manifestations will be the main symptoms.

1. *Skin lesions* (Fig. 1) are present in most cases especially in infancy, allowing early diagnosis. They are visible at birth in more than 70% of cases. Sometimes they are less obvious and the diagnosis will be delayed in the absence of orthopedic or urinary symptoms. A subcutaneous lipomatous mass, skin dimple, dermal sinus, capillary naevus, hyperpigmented area, scar or hair patch are the most common cutaneous anomalies. An appendage as described by Humphreys (1991) is rare. The post-anal dimple is a common

Table 9. *Clinical Presentation in 169 Pediatric Cases with Occult Spinal Dysraphism (Personal Series)*

Cutaneous signs		158 (93%)
Mass	81	
Dimple	29	
Angioma	17	
Hair tuff	14	
Mass + dimple	9	
Mass + angioma	8	
Urinary signs		84 (50%)
Orthopedic signs		97 (51%)
Foot deformity	53	
Scoliosis	49	
Cyphosis	30	
Mal perforans	5	
Neurologic signs		67 (40%)
Motor deficit	32	
Amyotrophy	21	
Gait disturbance	9	

Table 10. *Clinical Presentation in Different Series of Occult Spinal Dysraphism*

	Cutaneous	Orthopedic	Urologic	Neurological
Till (1971) 160 cases	92%	72%	23%	4%
James and Lassman (1972) 100 cases	73%	59%	10%	10%
Lapras (1985) 58 cases	96%	31%	48%	45%
Our series (1993) 169 cases	93%	51%	50%	40%

finding but it does not always imply dysraphic state. Some anomalies are more specific to certain of anatomical entities. Abnormal hirsutism of the back generally represents the cutaneous stigmata of diastematomyelia. It is a very rare occurrence in lipomas (Pierre-Kahn 1986). A lumbar or sacral mass represents the superficial extension of a spinal lipoma and must be distinguished from a posterior meningocele.

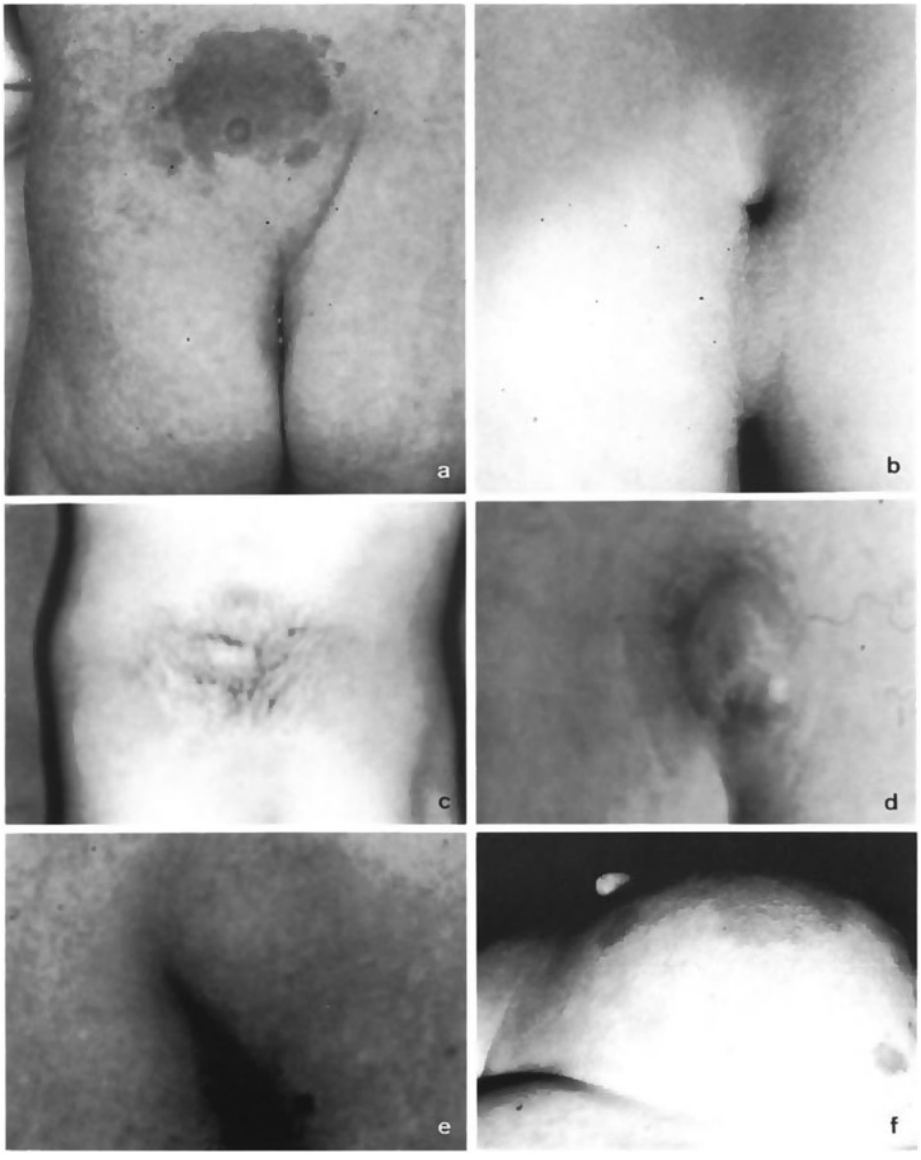


Fig. 1. Skin anomalies. (a) Cutaneous angioma with a fat mass (lipoma). (b) Dimple (tight filum). (c) Hair patch (diastematomyelia). (d) Dimple and cutaneous abcess (dermal sinus). (e) Asymmetrical fat mass (lipoma). (f) Large sacral mass with angioma and skin appendage (lipoma)

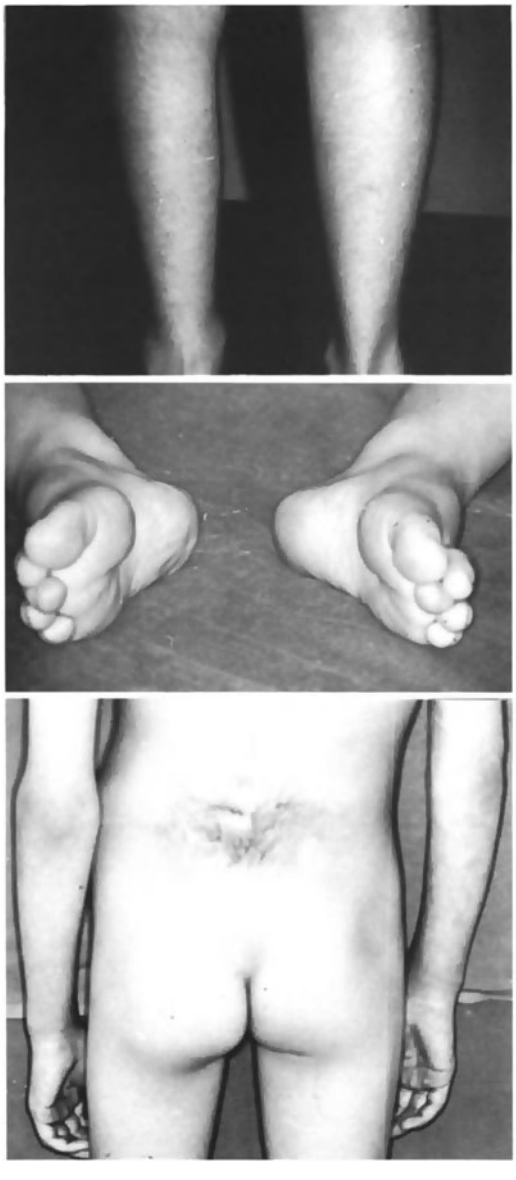


Fig. 2. Neurological and orthopedic manifestations. (a) Asymmetrical lower limbs (lipoma). (b) Club foot (low conus and tight filum). (c) Scoliosis and hypertrichosis (diastematomyelia)

II. *Orthopedic manifestations* (Fig. 2) are rarely present in the neonatal period. Few cases of children born with asymmetrical lower limbs have been described. The orthopedic anomalies are conditioned by the length of evolution and thus observed in older patients. Club foot, hollow foot, valgus, equino-varus, valgus knee, dislocation of the hip, asymmetrical feet or lower limbs, limb shortening or deformation of the gluteal fold may be noted. Most of these anomalies are asymmetrical and may be associated. Spinal deformities are not a rare occurrence, especially in diastematomyelia or in lipomas. Scoliosis is frequently mentioned in any type of tethered cord but more specifically in diastematomyelia. Isolated foot or limb anomaly, and isolated scoliosis are not always related to spinal dysraphism and consequently the diagnosis will be delayed. When associated with a skin anomaly, spinal dysraphism should be suspected and sought.

III. *Sphincter manifestations.* Autonomic sphincter disturbance is a frequent manifestation, especially in older patients. They represent 23% to 45% of initial manifestations in the literature. In our series urological symptoms were a first manifestation in 18.3% of the cases. Urinary infection is frequently associated. Constipation is more frequent than incontinence of faeces (3% of the cases in Tills series). It is interesting to note that patients with sacral agenesis develop secondary urinary problems in more than 50% of the cases.

It is suggested that early treatment in cases of spinal dysraphism is mandatory to prevent secondary sphincter disturbance. Till has pointed out: "Because improvement in bladder and sphincter function is unusual after surgical treatment of the spinal condition, it is clearly important to diagnose and treat the dysraphism as soon as possible"—that is before they become irreversible.

IV. *Neurological deficits* are surprisingly more rare. The neurological manifestations may be areflexia or an asymmetrical motor deficit. Rarely paraplegia or severe sensory deficit may occur. In our series only 16 children (19%) developed a neurological deficit. In the Lapras' series (1985) neurological symptoms were present in 26 cases (45%) and even in 6 cases they were present at birth. Minor neurological deficits may progress suddenly following minor traumatic events. Compliant of motor deficit may be absent but detailed muscle testing could reveal objective anomalies. Muscular testing is considered a fundamental element of the preoperative investigation.

V. *Other symptoms.* Pain is rarely an initial symptom in children. Backache is generally associated with other more significant symptoms of spinal dysraphism. Its frequency is around 3 to 5% in the literature. Lapras reported pain in 19% of the cases, either in the low-back or in a limb (sciatica or crural). Pain may appear suddenly after a fall in the sitting position or

following a knock on the back. In adults pain is the most common presenting feature (78% for Pang 1982).

Trophic ulcer or mal perforans have been described in very few cases. In two of our cases trophic ulceration was the first symptom one case of a spinal lipoma and one of a tight filum (Fig. 3).

Bacterial meningitis may be the first manifestation of a dermal sinus or a neurenteric cyst. In our series meningitis allowed the diagnosis of a dermal sinus in three cases and a neurenteric cyst in a fourth case.

Associated visceral anomalies with occult spinal dysraphism are present in a significant number of cases. In a series presented in 1981 by Carcassonne *et al.*, spinal anomalies were present in 106 cases of anorectal malformations (18%). In a series of 73 cases of spinal lipomas Pierre-Kahn (1986) found 3 genitoanal malformations. In 1991, Davidoff in a study of 87 patients with anal agenesis found a spinal cord anomaly in 8 and minor abnormalities in 6. This represents a reported minimal incidence of 9%. Consequently the authors recommend screening by MR imaging of the spine for all patients with anal agenesis. In our series we have found 6 cases of associated imperforate anus and lipoma.

Urogenital anomalies associated with spinal malformations are more frequent. In a series of 165 urogenital malformations, spinal anomalies were found in 14.8% of the cases (Carcassonne 1981). Pierre-Kahn (1986) found 3 urinary tract anomalies in a series of 73 cases of lipomas.

More recently Warf (1993) has reviewed 26 patients with anorectal or urogenital malformations. The author found a lipomeningocele in 7, a myelocystocele in 7 and a thick filum in 9. In 76 patients seen for cloacal related anomalies a spinal cord tethering was detected in 40.

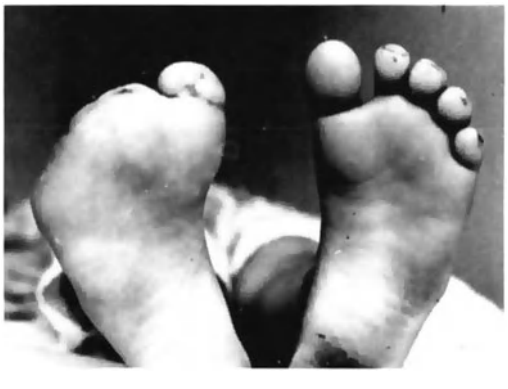
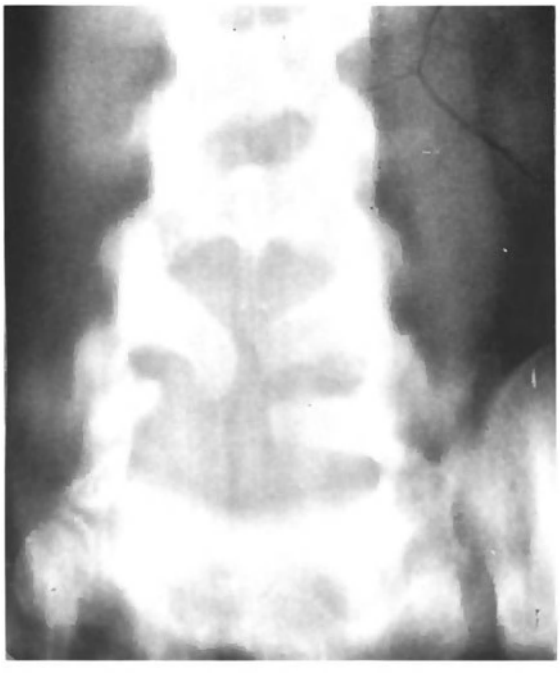
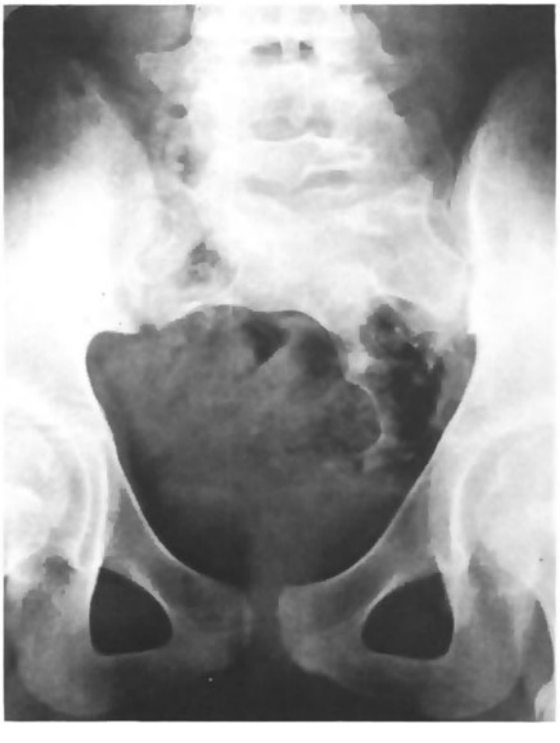


Fig. 3. Unilateral mal perforans in case of lipoma



a

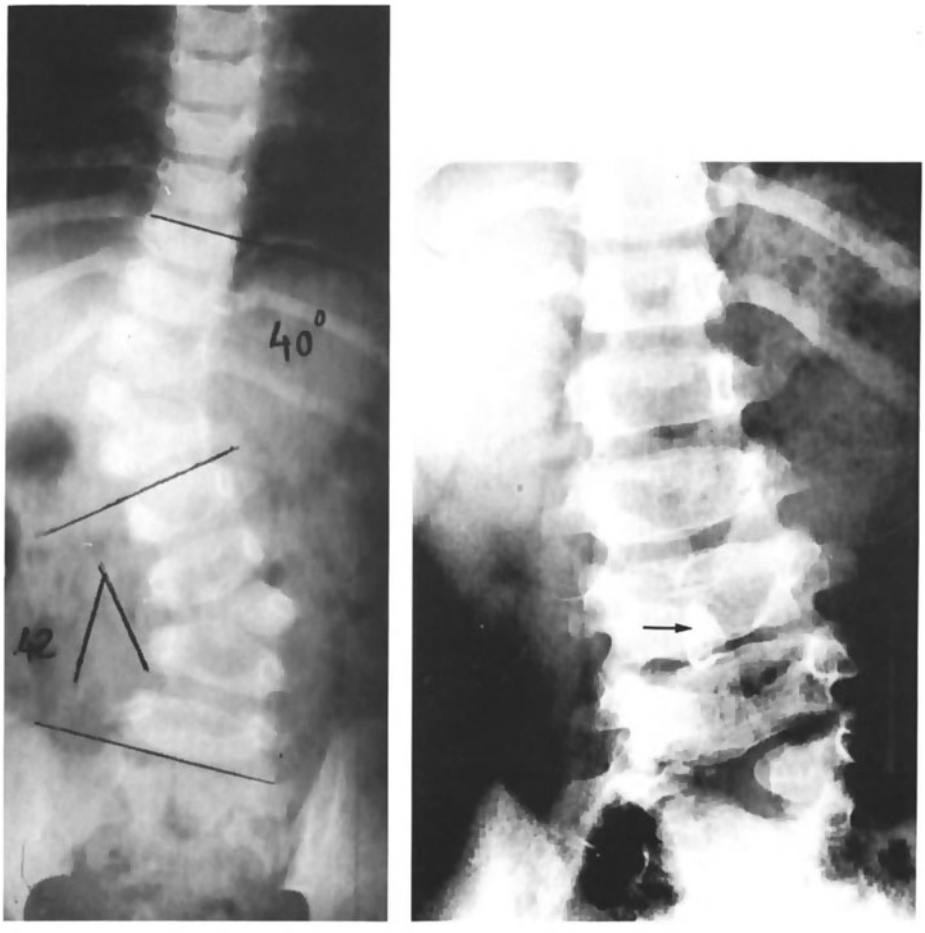


b

Indications for Investigations

The need for investigation in case of suspected spinal dysraphism differs in the neonatal period, in infancy or in older patients.

A neonate presenting with a subcutaneous mass, a sinus or an apendage must be thoroughly investigated in all cases. When a neonate has minimal skin anomalies such, as a capillary naevus or small superficial post-anal



c d

Fig. 4(a–d). Radiological findings. (a) Spina bifida oculta (tight filum). (b) Sacral agenesis (lipoma). (c) Multiple hemivertebrae with scoliosis in an infant (lipoma). (d) Hemivertebra with bonyspur (diastematomyelia)

dimple, no orthopedic or urinary symptoms, the decision of whether to investigate is more difficult. In the case of skeletal anomalies on X-ray, complementary investigations are mandatory.

In infancy or in older patients, the presence of skin anomalies such as deteriorating neurological deficit or the development of urinary incontinence suggests spinal dysraphism and thorough investigation.

In the cases of a suspected spinal dysraphic lesion we recommend a thorough examination and evaluation of all patients, whatever the lesion type.

I. Spine radiographs (Fig. 4), illustrate skeletal anomalies; a wide spinal canal, extensive or limited spina bifida, fused and malformed laminae, partial or total sacral agenesis, hemivertebrae, abnormal curvatures or midline bony spur. Spina bifida of the last lumbar or sacral lamina is the most common finding but may be difficult to visualize in neonates or small infants.

II. An orthopedic evaluation will include clinical examination by an orthopedic surgeon, detailed muscle testing, and eventually electromyography. The radiological examination of the hips is important, especially in small children. Recurrent hip dislocation or rotational changes of the lower extremities are present in a significant number of cases.

III. Urinary investigations, include intravenous pyelography, cystomanometry and retrograde cystography. They are necessary to evaluate a possible diagnosis of a neurogenic bladder. The urinary investigation may be normal, especially in the neonatal period or in young infants. Later tests may demonstrate decreasing compliance and a decreasing capacity of the bladder. The final result of a neurogenic bladder will be the destruction of detrusor.

IV. Neuroradiological evaluation

a) *B-mode sonography or more recently real-time spinal sonography* may be easily obtained in neonates or young children. In older children the spinal canal may be explored through open laminae or through the interlaminar spaces. The level of the conus, the presence of a mass, oscillations of the cord and roots may be determined. Detection of spinal cord movement and oscillations are useful in cases of tethered spinal cord. In the case of an asymptomatic infant with a minimal lumbosacral skin anomaly, normal spinal sonography will be reassuring. As Venes (1988) has pointed out. "Asymptomatic, neurologically intact children with minimal cutaneous markers have had no further studies if the sonogram adequately shows a normally positioned conus, good cord and root oscillation and no evident intraspinal mass." For McLone, investigating infants, a diagnosis of lipoma, tight filum terminale, dermal sinus, or myelocystocele is possible by ultrasonography.

b) *Air myelography* or *pantopaque myelography* have been used for many years. More recently, metrizamide CT-myelography enables study of the multiple features of spinal dysraphism. Despite the advent of MRI, there are still a few indications for CT-myelography. In our series two dermoid cysts were better visualized by this technique.

Reigel (1983) has summarized the main abnormal findings of myelography, in cases of tethered spinal cord: 1) the conus medullaris is below the level of L2, 2) posterior tethering of the cord, occurs as the anterior subarachnoid space remains free, 3) a greater caudal angle formed by the nerve roots with the lateral margin of the cord (greater than 90°), 4) progressive narrowing of the caudal spinal cord indicating tethering and traction, 5) a bulbous termination of the cord (thermometer sign) indicating the presence of an intramedullary mass, 6) a widened spinal cord to the point of termination indicating the probably presence of hydromyelia.

c) With MRI of this type of spinal dysraphic lesions associated anomalies, the level of the conus, the presence of a thick filum, the localization of fat tissue the integrity of the skin and the direction of the roots are nicely detected. MRI has taken first place in the exploration of occult spinal dysraphism (Han (1985), Barnes (1986), Wippold (1987)).

Sagittal and axial views are helpful for lipomas and dermoid cysts. Coronal planes are necessary for diastematomyelia. A further advantage of MRI is to obtain excellent tissue differentiation without bone scatter. A tethered cord is easily seen in from the CSF. Limitation between the lipoma and the cord is well shown with T1 weighted images (Fig. 5). MRI is better than CT in the detection of associated lesions such as hydromyelia, frequently encountered with spinal lipomas. Moreover, MRI allows regular, safe, non-invasive follow-up of the postoperative course of the patient and the early diagnosis retethering of the cord.

V. Somatosensory evoked potentials

The utility of spinal and scalp recorded somatosensory evoked potentials has been demonstrated in children and adults with a tethered spinal cord. Posterior tibial nerve somatosensory evoked potential predicts the level and the extent of the lesion. It is useful too in evaluating postoperative recovery. Roy (1986) has evaluated this technique in 22 patients (aged 18 months to 22 years), with tethered spinal cord syndrome. His conclusion is: "It appears to be a sensitive indicator of dysfunction, which, although not highly specific for severity, can be used as a guide for further evaluation." As his technique does not stimulate the S2–S4 (involved in sphincter function) directly responsible for sphinters anomalies, other authors such as Neuwirth (1988) have proposed the use of the pudendal nerve in monitoring lower sacral roots. The study of the bulbocavernous reflex plays a very significant role to evaluate the sacral centers.

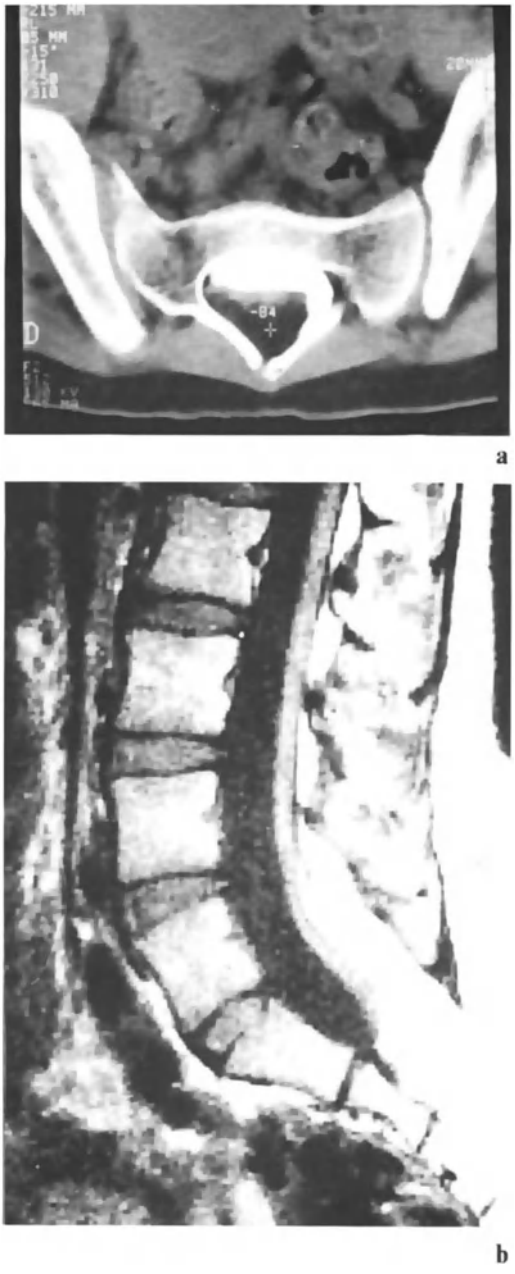


Fig. 5. CT scan and MRI in a case of lipoma. (a) CT Scan shows a dilated sacral spinal cavity with open laminae. An hypodense (−84) lipoma is attached posteriorly to the cord. (b) On MRI we see a tethered spinal cord going down at the level of S2 and attached to an extra and intradural lipoma. The interface cord-lipoma is well shown

The Lesions

I. Spinal Lipomas

These are the most common type of spinal dysraphic lesion and the main cause of a tethered cord (near 50% in all the series of literature). Table 11 shows the clinical manifestations of lipomas in different series in the literature. The diagnosis may be made early with the presence of a fat mass in the back. A dimple, an angioma or an appendage may be associated. Presence of a hair tuft is very rare (Pierre-Kahn 1986). In one-third of the cases such foot deformities as clubfoot or cavovarus are present. Neurogenic bladder is found in almost 50% of the cases and various anal abnormalities observed in more than 20% of the cases. Other dysraphic lesions are associated with lipomas such as diastematomyelia (7%), meningocele (4,5%) or dermal sinus (3%).

The radiological aspects of lipoma are not specific with the exception of a wide spinal canal. Segmentation anomalies or sacral anomalies are present in 65% of our cases. Ultrasonography especially in neonates and small infants may show the extent and the tethering of the lesion. McLone (1985) points out that he makes the diagnosis and operates upon an infant solely on the basis of an ultrasound study. CT and MRI both show spinal

Table 11. *Clinical Presentation of Spinal Lipomas in Different Series of the Literature*

	Cutaneous	Orthopedic	Urologic	Neurological
McLone (1983) 42 cases	81%	50%	33%	41%
Sato (1985) 24 cases	80%	12%	38%	30%
Hoffman (1985) 97 cases	100%	9%	24%	7%
Pierre-Kahn (1986) 73 cases	95%	14%	43%	47%
Harrison (1990) 20 cases	95%	—	100%	60%
Kosnick (1990) 94 cases	100%	12%	25%	18%
Our series 98 cases	94%	34%	70%	20%

lipomas satisfactorily (Fig. 5). Axial studies with CT and sagittal MRI shows the lesion well. MRI will show nicely the presence of fat tissue with high signal intensity on T1-weighted images. It displays the clear boundaries between lipoma and spinal cord.

The risk of deterioration in cases of spinal lipoma is high at all ages and increases with time. Pierre-Kahn (1986) estimates this risk as 56%. It is interesting to note that in infants the diagnosis is normally made on skin anomalies and in adults on neurological or urinary manifestations. The clinical deterioration is generally slowly progressive except in cases where trauma may precipitate acute symptomatology, as may significant weight gain. Histologically the fat tissue of a spinal lipoma must be considered as normal adipose tissue. It has been demonstrated in some cases that diet may prevent postoperative recurrence of neurological signs.

Considering *indications for surgery* there are four possibilities:

1) In neonates or infants presenting exclusively with skin anomalies, and no orthopedic, neurological or sphincter abnormalities, we strongly support the principle of routine operation as early as possible. This opinion is advocated by Anderson (1975), Villarejo (1976), Bruce-Schut (1979), Chapman (1983), McLone (1983), Hoffman (1985), Pierre-Kahn (1986), Kosnik (1990). According to the literature, collected by Pierre-Kahn (1986) on 387 operations, the operative mortality remains very low (0.3%). The risk of postoperative deterioration is 0.8% and there is a late deterioration of 6.3%. Clinical improvement is found in 64% of the cases. Other authors are not in favour of "prophylactic surgery" (Raimondi 1987). This author prefers to observe asymptomatic children and to operate on only those who develop clinical signs or symptoms.

2) In adolescents or in adults, with a cutaneous anomaly we prefer to wait and to operate only in cases of sphincter or neurological worsening. At this age the risk of secondary deterioration is lower and surgical procedures may be more hazardous.

3) In infants or children, with urinary or neurological anomalies, surgery is mandatory. In the cases of progressive orthopedic signs surgery is also preferable, bearing in mind that the possibilities of improvement are poor. Urinary or orthopedic anomalies rarely regress after surgery. In some cases failure of recovery could be explained by associated nerve root malformations. The main reason for untethering the spinal cord at this time, will be to stabilize the clinical condition of the patient.

4) In adolescents or in adults presenting new clinical symptoms surgery will be advocated in relation to the severity of the symptoms and signs. For us in cases of mild urinary or neurological anomalies, an expectant attitude will be preferred.

Table 12. *Anatomical Classification of Spinal Lipomas in the Literature*

Emery and Lenden (1969)	1) Fibrolipoma 2) Dural fibrolipoma 3) Leptomyelolipoma
Chapman (1982)	1) Dorsal lipoma 2) Caudal lipoma 3) Transitional lipoma
Sato (1985)	1) Dorsal type a) with direct b) with indirect insertion of the extrathecal lipoma 2) Caudal type 3) Combined type 4) Filar lipoma
Hoffman (1985)	1) Intradural lipoma 2) Lipomyelomeningocele
McLone (1985)	1) Spinal lipoma with intact dura (Subpial lipoma) 2) Spinal lipoma with deficient dura a) Lipomyelocele b) Lipomyelomeningocele 3) Lipoma of the filum
Pierre-Kahn (1986)	1) Lipoma with excluded ventral roots 2) Lipoma with included roots
Raimondi (1987) speaks on lipomatous hamartomas and subclassified them as:	1) Lipoma 2) Leptomyelolipoma 3) Dural fibrolipoma 4) Lipomeningocele
Scatliff (1989)	1) Lipoma 2) Lipomyelomeningocele
Choux (1993)	1) Extradural lipoma 2) Intradural lipoma a) Lipoma of the filum b) Intramedullary lipoma 3) Extra and intradural lipoma a) Dorsal lipoma b) Caudal lipoma

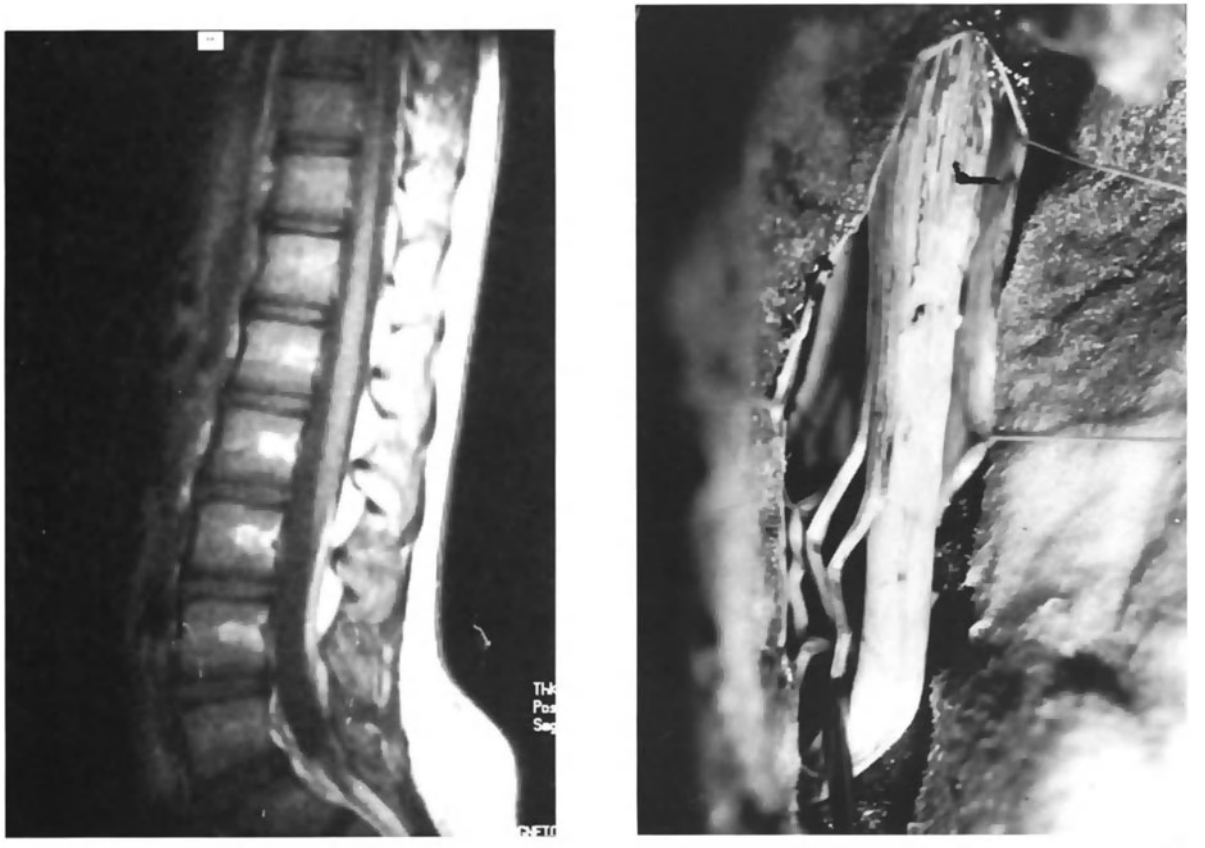


Fig. 6. Fibrolipoma (lipoma of the filum). (a) MRI. The conus is at the L3 level and attached to an intradural lipoma. (b) Operative view. The conus continues with a thick and lipomatous filum fixed to the dura. The roots have a normal direction

Different *anatomical classifications* have been described in the literature (Table 12). They have their importance considering surgical indications and techniques.

Surgically we may distinguish three types of lumbosacral lipomas. In the first two, lipoma of the filum and caudal lipoma, surgical untethering is easy or at least possible. It is much more hazardous in the third, the myelolipoma.

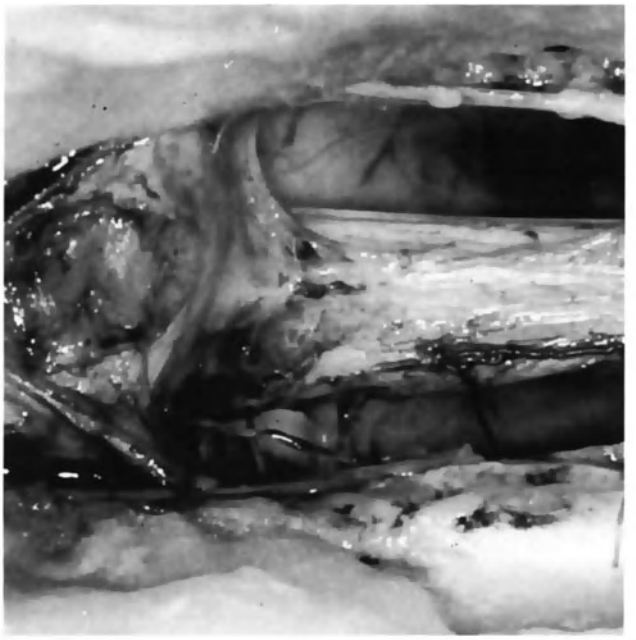
a) *In lipoma of the filum terminale* (filar lipoma, fibrolipoma), the conus medullaris is in low position, supported in this position by a thick filum. Incidentally a lipoma of the filum may be found in 5% of normal adults. In this case the dura is normal. The caudal part of the filum goes through the end of the dural sac to be extrathecal, ending in a dimple in the sacral region. Nevertheless, none of the roots run in an abnormal direction.

The surgery in case of filar lipoma is easy and consists, after a one or two level laminotomy, in opening the dura to visualize the junction between conus and thick filum (Fig. 6). Then the caudal part of the lipomatous filum is removed for some 2 cm. Occasionally the limit of the conus and the filum may be difficult to find and it will be better to cut the filum beneath the emergence of the last root. Sometimes, especially in young children, at the end of the procedure the conus may ascend for a few mm. This mobilization of the spinal cord after section of the filum is not usually seen in older patients.

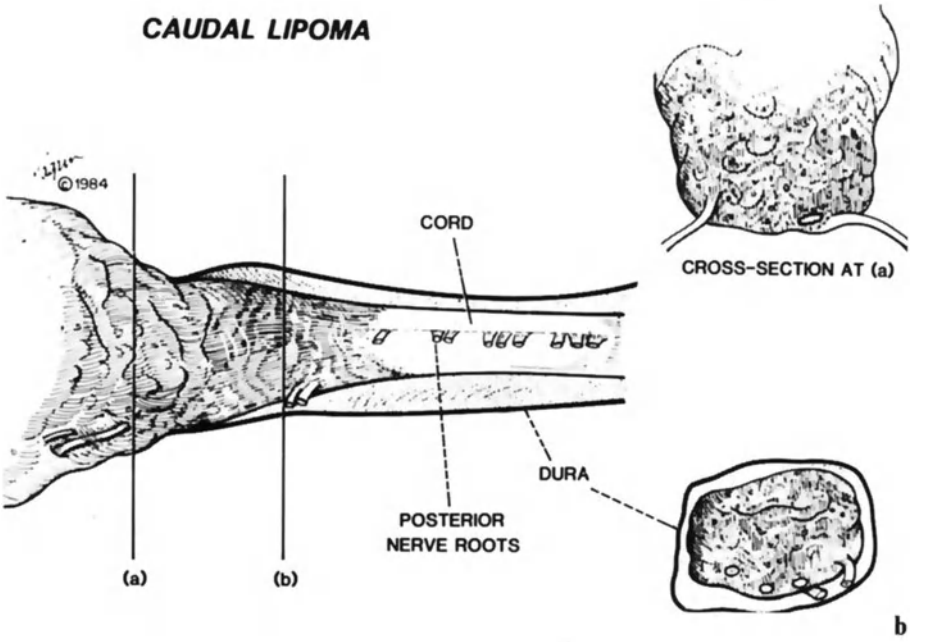
b) *In caudal lipoma* (caudal variant, caudal type) (Fig. 7), the lipomatous mass is attached to the caudal part of the conus medullaris and extends caudally into the subarachnoid space to penetrate the distal end of the cul-de-sac in the sacrococcygeal region. A subcutaneous component of the lipoma is not always present in this type, nor is a skin lesion.

The surgical technique for this type of lipoma is relatively simple, and untethering is achieved by dividing the lipoma below the transitional zone, which is identified between the conus and the lipoma, to avoid the neural elements. Frequently, after the division of the lipoma the cord shows a remarkable ascent.

c) *In lipomyelomeningocele*, the interface between the lipoma and the conus can be situated on the dorsal part of the conus or straddle the caudal and dorsal part of the conus. In this situation, there is always a defect of the dura in the dorsal midline which corresponds to the external aspect of the lipoma-cord interface. In this type, the surgical technique is different and much more difficult. It is necessary to control continuously the position of the conus and the posterior nerve roots. The roots emerge on both sides, ventrally to the lipoma-cord interface (Fig. 8). The most important point is to begin the surgical procedure over normal spine and dura. The surgical approach starts by an incision in the midline or surrounding one side of the



a



b

Fig. 7. Caudal lipoma. (a) Operative view. The lipoma has been almost completely removed. It is in continuity with the spinal cord. Some roots run horizontally (arrow). (b) Drawing of a caudal lipoma (from Chapman). The roots are involved in the lipomatous mass

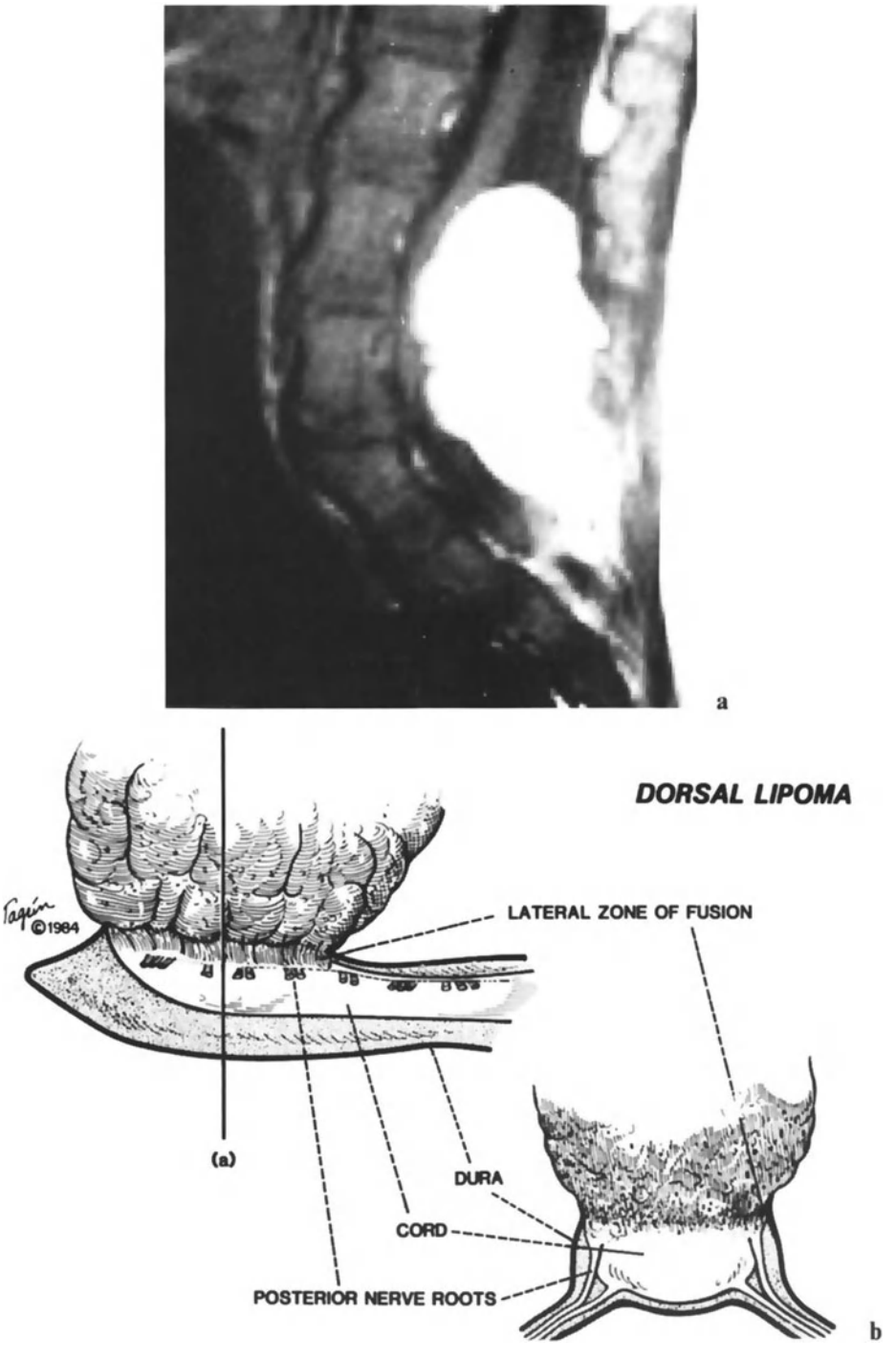
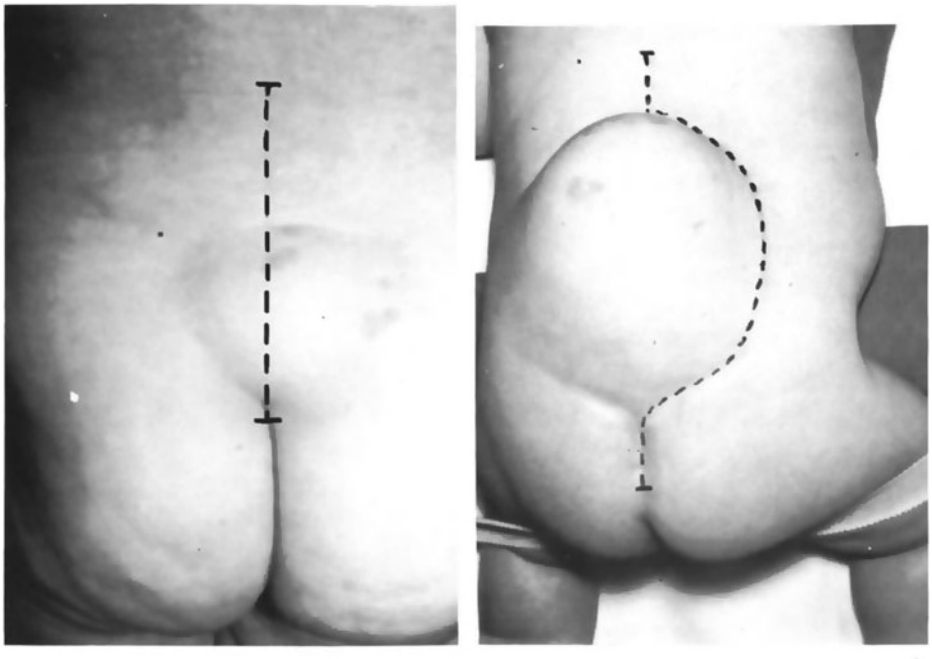


Fig. 8. Dorsal lipoma. (a) On MRI the lipoma is fixed dorsally to the spinal cord at L4 and L5 levels. The spinal canal is enlarged. (b) Diagram of surgical anatomy of a dorsal lipoma (from Chapman). The roots emerge from the cord anteriorly

lipomatous mass to find the normal tissue first (Fig. 9). Then the dura is exposed cranially after a limited laminotomy (two levels) and opened in a craniocaudal direction. Progressively the dura must be divided at the fusion zone between lipoma, conus and dura after identifying the posterior roots which run horizontally or upward towards their foramen. The dissection is carried around the caudal extremity (Fig. 10). The procedure is conducted under magnification using either a microscope or loupes. Removal of the lipoma may be achieved using scissors, ultrasonic aspiration (Hoffman 1985), CO_2 laser (James, McLone 1986) or combination. The main advantage of the laser is to reduce blood loss, particularly in infants, and to eliminate traction on the spinal cord and roots. To preserve neural elements during dissection, monitoring of the bladder and lower extremity motor responses to nerve stimulation are useful. Some authors use also somatosensory-evoked responses and rectal electromyography (Chapman 1982).

In our opinion, it is not necessary to pursue the residual lipoma into the cord, since the residual lipoma does not increase in size. An associated



a b

Fig. 9. Operative approach to spinal lipomas. (a) Midline skin incision in case of small subcutaneous lesion. (b) Incision around one side of the mass in case of large lipoma

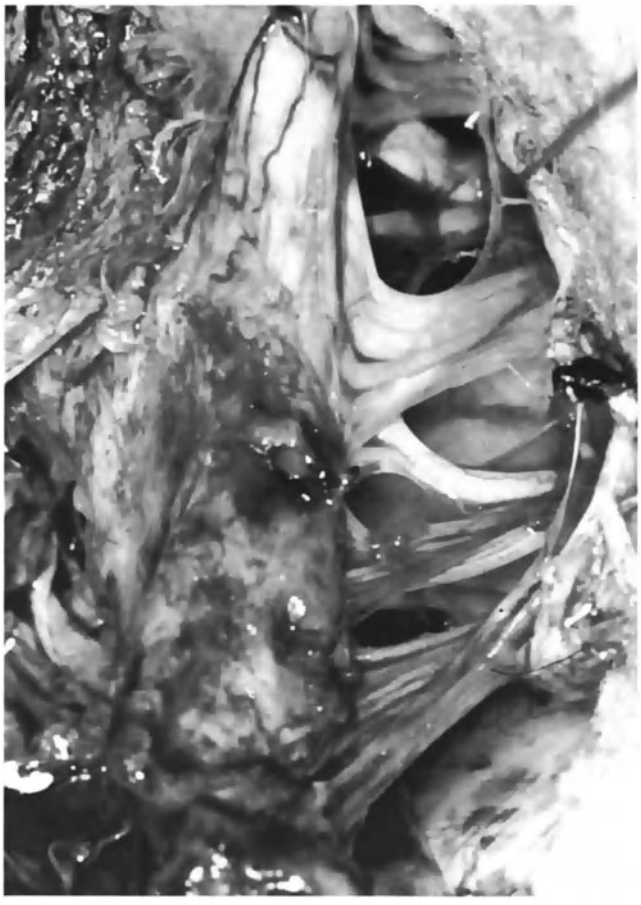


Fig. 10. Operative view in case of lipomyelomeningocele. The lipoma which was straddling the dorsal and caudal parts of the conus has been removed. Roots run horizontally and upwardly. The emergence of the posterior nerve roots at the lipoma–cord interface is visible

thick filum must be divided. In some spinal lipomas hydromyelic dilatation of the terminal ventricle may be observed (Fig. 11). In the case of large dilatation a small myelotomy must be made and the opening of the spinal cavity maintained by a small catheter.

A large duroplasty is performed before the closure using "vicryl collagen", fascia or silastic (Boop 1991). At the level of the lipomatous mass the dura may be difficult to recognize laterally and consequently the duroplasty may be fixed directly to the fascia. Application of tissue glue will allow a tight closure of the dural graft. This duroplasty creates a pseudomeningocele

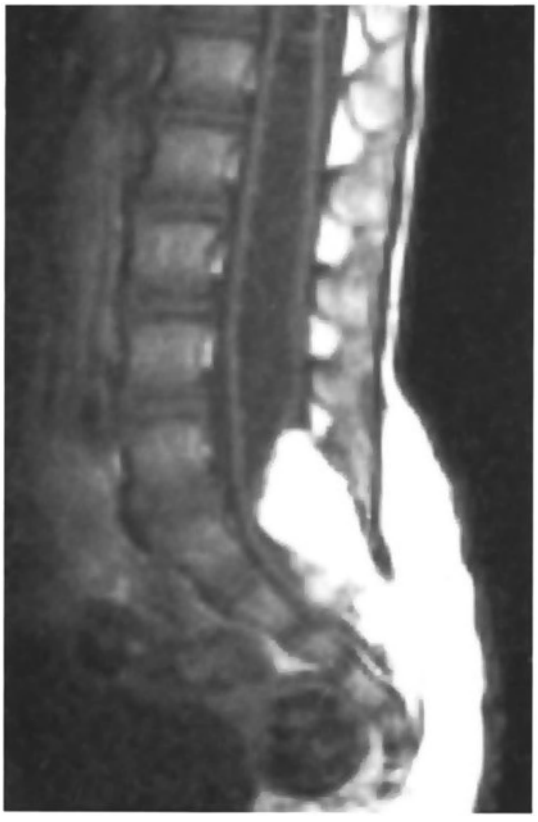


Fig. 11. MRI of a lipomyelomeningocele with a large hydromyelic cavity, extending close to a spinal lipoma

where the conus and the cauda equina are surrounded by CSF, it may prevent secondary retethering of the spinal cord. The skin closure must be carefully done to avoid a wound reopening in cases of subcutaneous accumulation of CSF. Large removal of subcutaneous fat tissue must be avoided to prevent problems of scarring.

A subcutaneous fluid collection may develop in some cases. Pierre-Kahn (1986) found this postoperative complication in 35% of his cases. We have seen such a complication in only few cases. To prevent it occurring position the patient head down for three or four days postoperatively.

d) *Results* (Fig. 12). The late postoperative outcome in 6 pediatric series are shown in Table 13. On average a late improvement is found in more than 60% of the cases and a secondary worsening in 6.3% of the cases.

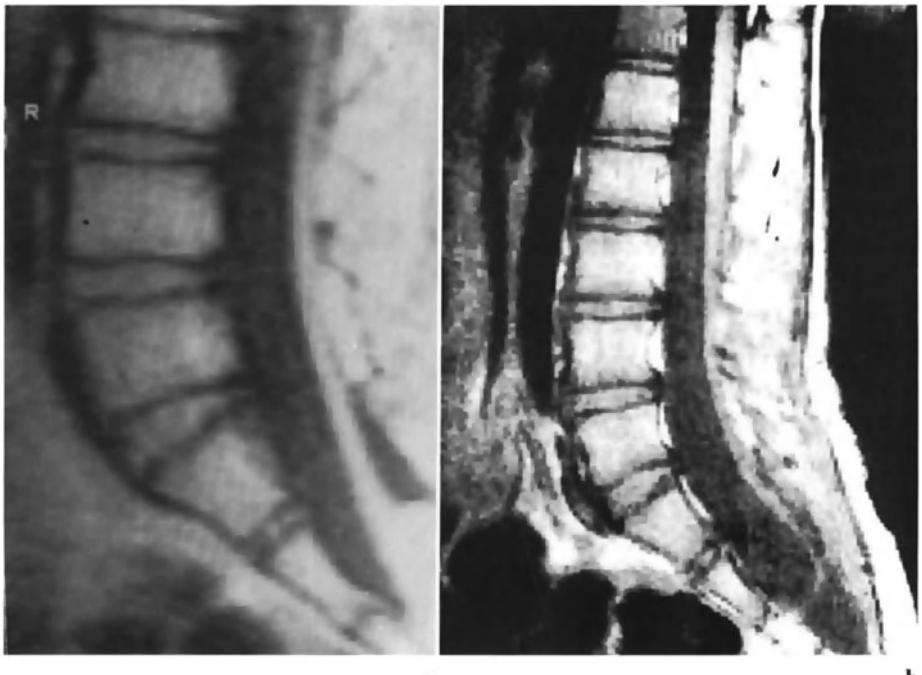


Fig. 12. Preoperative and postoperative MRI of a spinal lipoma. (a) The spinal cord is fixed anteriorly to a lipoma located in S2 and S3. (b) After surgery the lipoma has disappeared and the spinal cord is detethered but will remain at the same level

Table 13. *Late Results in Operated Patients in 6 Pediatric Series*

Authors	Number of cases	Clinical results (96)	
		Improvement	Deterioration
Bruce and Schut (1979)	40	35	5.5
James and Lasman (1981)	60	17	10
McLone *et al.* (1983)	42	0	14
Hoffman *et al.* (1985)	97	9.5	2.5
Pierre-Kahn *et al.* (1986)	64	42.5	3
Our series (1993)	48	17	4

II. Anomalies of the Spinal Cord and Roots

A. Adhesions and Bands

The spinal cord and roots may adhere directly to the dura, generally posteriorly. Fibrous bands may tether the conus or the roots. They may continue through the dura and end at the superficial tissues. Lassman and James, in 1972, first used the term "meningocele manqué" (Fig. 13). The anomalies consist of "fibrous bands, aberrant nerve roots and adhesions tethering the spinal cord, nerve roots and filum terminale within the meninges. Many of these bands continue through the dura matar either to the fibrous tissue substituting for defective laminae, or to the skin but many cases do not have cutaneous stigmata." Histologic findings, at the level of the skin or deeper tissues, indicated that during fetal life there had been a meningocele which had atrophied. Meningoecele manqué demonstrates a clear relation between spina bifida cystica and spina bifida occulta, the difference being a timing in embryonic development. Association with other anomalies such as diastematomyelia or lipomas are not rare. It is interesting to note that a low conus medullaris is present in 41% of the 45 cases presented by Lassman and James.

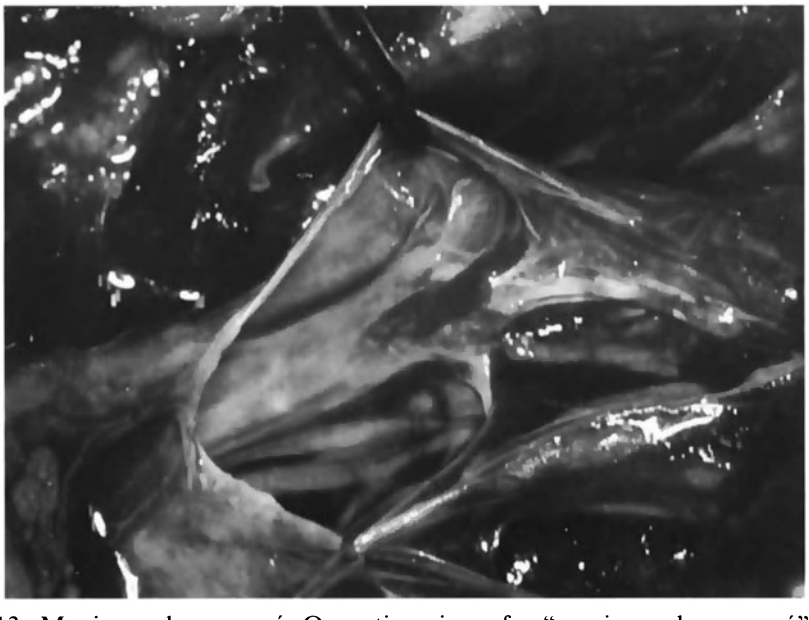


Fig. 13. Meningocele manqué. Operative view of a "meningocele manqué". The roots and the conus are adherent directly to the posterior part of the dura

Treatment is surgical to free the neural structures from these bands and adhesions. Since skin anomalies are not always present and the diagnosis of meningocoele manqué may be late and neurological deterioration permanent.

B. Tight Filum terminale

In this anomaly the spinal cord is tethered by an abnormal short and thick filum (Fig. 14). We have seen that failure of involution of the terminal cord (during the retrogressive differentiation) and failure of lengthening of the nerve fibres results in the tight filum. The "filum terminale syndrome" has been described by Garceau in 1953, in three patients, presenting with progressive neurological deficit with bladder dysfunction who improved after

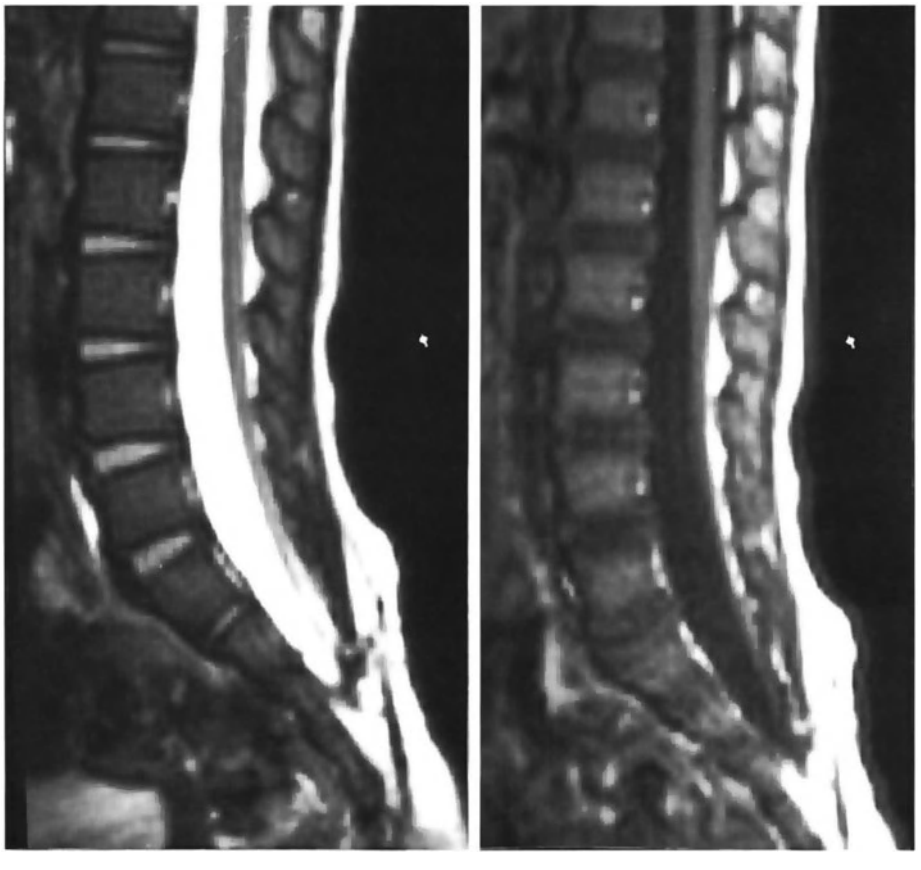


Fig. 14. Thick filum terminale. MRI aspects of tethered cord with a thick filum. T1 and T2 weighted images

section of a thick filum. Hoffman in 1976 published a series of 31 children designated as having a tethered spinal cord with a low conus and a thickened filum, measuring 2 mm or more in diameter. In patients presenting with skin lesions, neurological, orthopedic or bladder abnormalities in relation with a low conus fixed by a thick filum, it may be acceptable to cut it surgically. More controversial are the cases where there is urinary incontinence associated with a spina bifida occulta, with otherwise normal neurological examination and normal imaging studies. Suspected of having a tethered cord they are treated by transection of the filum (Khoury 1990).

C. Diastematomyelia and Diplomyelia

These two traditional terms introduced by Ollivier d'Angers (1937) to describe the main feature of these rare malformations, have been recently reclassified after the work of Pang (1992) who distinguished, on the basis of a unified theory of embryogenesis, two types of double spinal cord malformations. He recommends the terms of Split Cord Malformation (SCM) for all double spinal cords and distinguishes two types: a Type I SCM with two hemicords, within their own dural tube and separated by a rigid osteocartilaginous median septum and, a Type II SCM whith two hemicords located in a single dural tube and separated by a nonrigid fibrous median septum.

a) *Clinical manifestations.* Bollini in 1989 presented a large review of the literature collecting 361 cases, including 14 of his personal series. A large female predominance was observed (77%) and only one case was familial (Kapsalakis 1964). The clinical signs and symptoms are well known and a variable combination of cutaneous anomalies, orthopedic syndromes and neurological signs are generally observed.

1) Cutaneous anomalies are present in 69% of the cases. Bollini described hypertrichosis as the most frequent sign (47%). Pang recently, in his series of 39 SCM observed this skin anomaly in 56% of the cases. This is in agreement with other reported series with an incidence varing from 20 to 55% (Dale 1969, Guthkelch 1985, Humphreys 1982, James and Lassman 1960). Naevi and capillary hemangioma are the second most common skin anomalies: 33% for Pang (1992) and 18% for Bollini (1989). Subcutaneous lipomas, dermal sinus opening or meningoceles are more rarely observed.

2) The orthopedic syndrome, introduced by James and Lassman in 1960, associates morphologic deformities of the spine and of the lower limbs. The incidence of congenital kyphoscoliosis varies between 5 and 50% of the cases (Bret 1989, Bollini 1989, MacMaster 1984). A hypoplastic limb and a wide variety of foot deformities such as pes planus, vertical

talus, pes equinovarus and calcaneovalgus are present in nearly 50% of the cases (Bollini 1989). In Bret's series the most frequent anomaly is a reducible or fixed club-foot deformity. Recently, Scatliff (1975) noted that 23 of 25 patients had lower extremity signs.

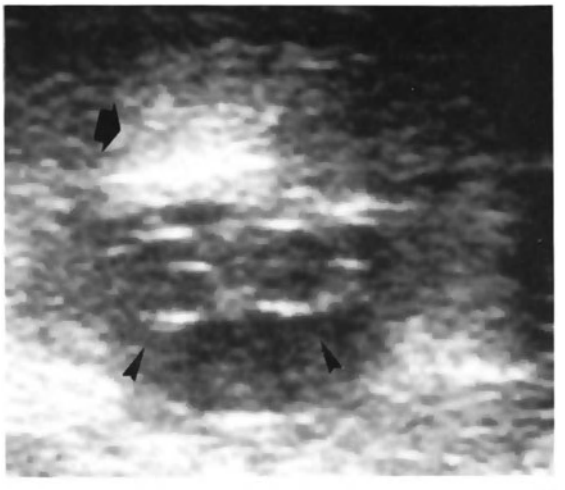
3) Neurological manifestations are inconsistent and frequently there is no functional difficulty (Bret 1989). Among the symptomatic patients, the neurological features differ considerably between children and adults (Pang 1992). While pain is the main sign in adults, particularly in the lower limbs or in the perineal region, in children this sign is more rare (Pang 1992). Clinical examination shows frequently an absence of tendon reflexes or anal reflex and sensory abnormalities in the perineal region, supplied by lumbar and sacral roots (Bret 1989). Acute paraplegia has been reported as a complication of the surgical correction of kyphoscoliosis (Faithful 1961, McEwen 1975) when this anomaly co-exists.

b) *Radiological investigations* (Figs. 15 and 16). Plain X-rays and tomograms show the bony spur and the morpho-logical deformities of the spine (Hilal 1974), but MRI and especially CT myelography (Pang 1992) are the most accurate radiological studies. The advantage of CT myelography over MRI is the demonstration of the bony spur or the fibrous septum, whereas MRI enables improved visualization of associated syrinx.

c) *Surgical indications and treatment.* The indications for surgery are controversial. Matson (1950) who described the surgical technique to remove the bone spur regarded this as "a prophylactic rather than a curative surgery." Some agree with this opinion, (James and Lassman 1964, Guthkelch 1974, Frerebeau 1983, Bret 1989, Pang 1992) especially in patients with both scoliosis and SCM (Goldberg 1984, Chapman and Beyel 1986) when the indication for surgery for the scoliosis is primary. This is also our opinion.

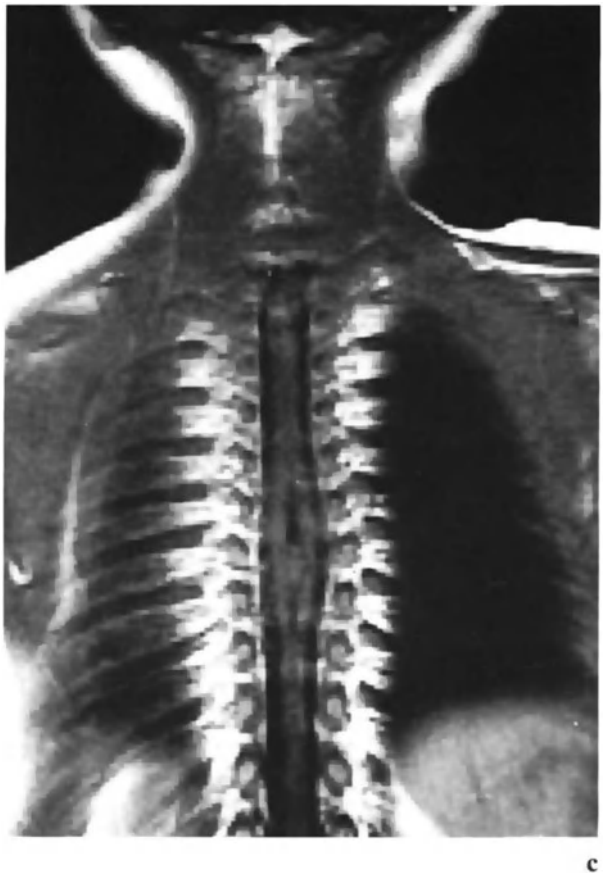
The aim of treatment is to release the cord, removing the median septum. The surgical technique varies with the two types of SCM.

In Type I, the osteocartilaginous spur must be removed, taking care of tight adhesions between cord and dura. The patient is in the prone position and the median incision is extended below and above the lesion. Laminae are exposed, starting where the spinous processes are normal. A minimal laminectomy is begun in a normal area to avoid the risk of producing or aggravating kyphoscoliosis. Progressively, the bony spur is exposed and removed after subperiosteal dissection of the septum avoiding lateral movements which can injure the adjacent hemicords. In this way, the two dural sacs are progressively exposed. At this point, opening of the posterior dura is necessary, by an incision encircling the dural cleft and extending towards each extremity.



a

b



c

Fig. 15 (a–c). Diastematomyelia. Radiological findings. (a) Spinal sonography shows the vertebral body (large arrow), and the two hemicords (small arrows). (b) Myelography shows the two cords separated by a bony spur. There is a severe deformation of the spinal column and the spinal canal is enlarged. (c) MRI aspect of a thoracic diastematomyelia in an infant.

Severe adhesions with fibrous bands on the medial part of the two hemicords between the cord and the dural sleeves are observed (Fig. 17). These adhesions must be progressively severed, as well as some paramedian dorsal nerve roots which are nonfunctional (Pang) but must be preserved (Bret). The two hemicords are now freed. Finally a posterior duroplasty is performed to close the posterior dural defect converting the initial double dural tube into a single one. When the bony spur is located in the conus or the cauda equina, the cord is frequently tethered by a short thick filum or a lipoma (Fig. 18). In these cases, it is necessary to extend the laminectomy in a caudal direction to detether the cord completely.

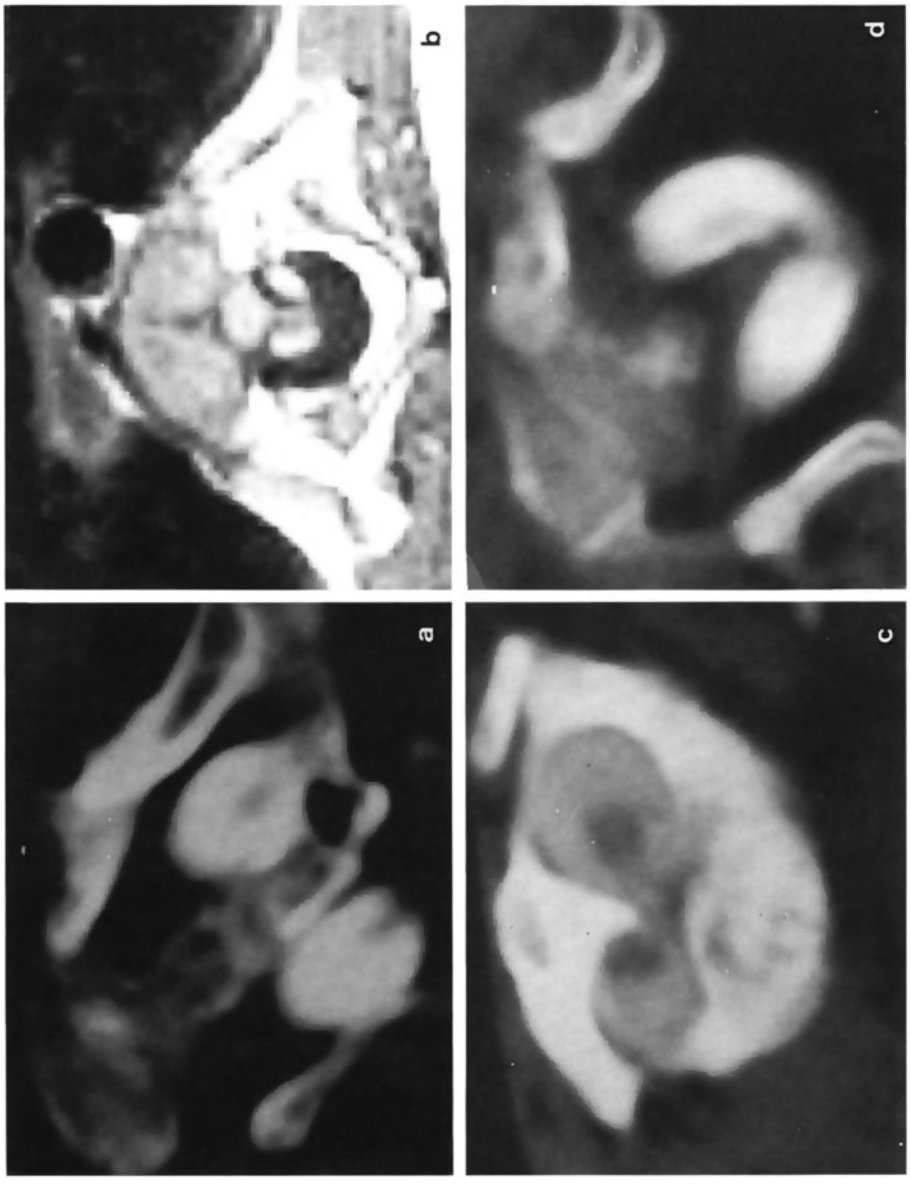


Fig. 16. CT Metrizamide studies in four cases of diastematomyelia. (a) The two hemicords are totally separated by a large bony spur totally crossing the spinal canal. (b) The bony spur is thin and completely separates the two cords. (c) The hemicords are joined anteriorly. (d) The two hemicords are in one dural sac

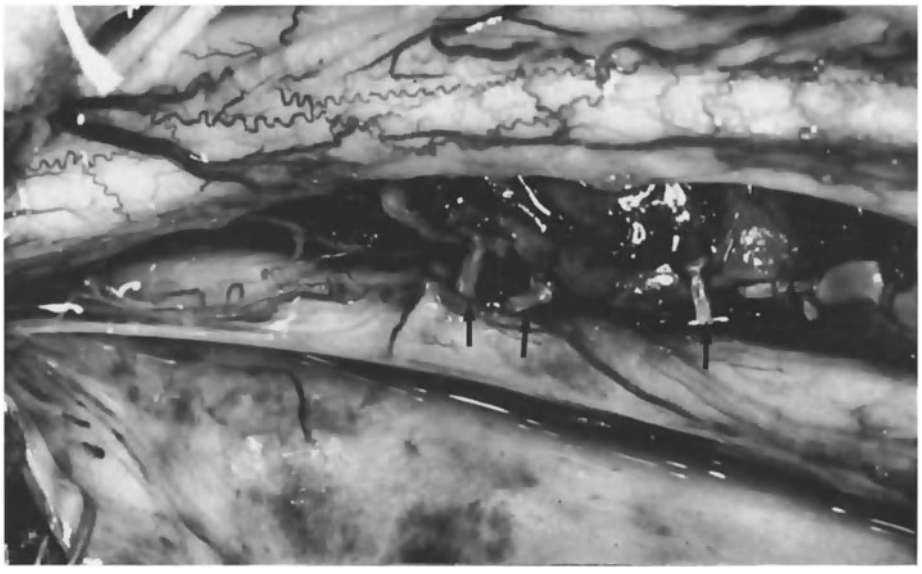


Fig. 17. Operative view in thoracic diastematomyelia. The bony spur has been removed. Note the presence of paramedian dorsal nerve roots (arrows) which emerge from the medial part of the two hemicords

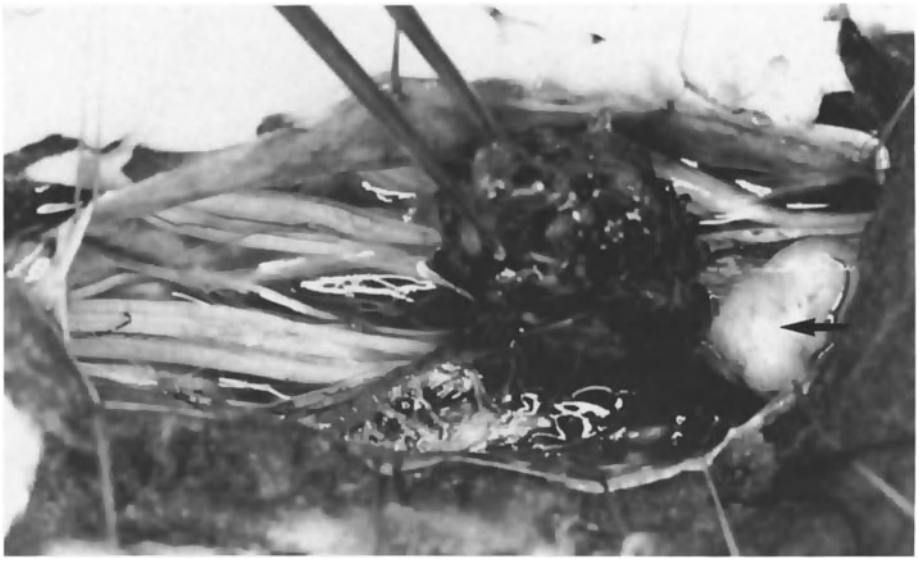


Fig. 18. Operative view in lumbar diastematomyelia. A wide spur is still in place and some roots are adherent to the bone. Note the presence of a dermoid close to the bony spur

In type II, the procedure is more simple. There is a single dural tube with two hemicords and the fibrous septum may have three different positions (Pang 1992). In the first type, a complete fibrous septum transfixes the hemicords and is fixed on the dorsal and ventral surfaces of the dura. In a second type, the septum is only ventral fixing the ventromedial aspects of the hemicords to the dura. More frequently, the septum is dorsal fixing the dorsomedial aspects of the hemicords to the dorsal dura. Severe spine anomalies which are always present in type I are very rare in this type, and the surgical procedure is much more simple. After opening the dura, a dorsal or complete septum, is easily identified and severed. In the presence of a ventral septum, it is also necessary to gently rotate the hemicords to sever this to detether the hemicords. Next the dura and the other planes are closed in the usual way.

d) *Results.* When neurological symptoms are present, surgical outcome remains uncertain (Bret 1989). In the series of 40 cases published by James and Lassman (1964), 25 were unchanged after surgery, 6 were improved and 2 were worsened. In Hood's (1980) series of 51 patients 39% showed some improvement and 61% were unchanged. However, Pang (1992) mentions among 39 patients, 16 cases improved, 19 stable and only 4 worsened.

III. Anterior Meningoceles

a) *Anterior sacral meningoceles* (Fig. 19) are the most frequent anterior meningoceles. The first description of an anterior sacral meningocele was by Bryant in 1837. It is a rare anomaly since only 160 cases have been reported in the literature. In our series we have diagnosed three cases. In one of our cases (Fig. 20) a 15 year old girl presented with a painful mass in the pelvis, associated with transitory urinary incontinence and constipation. Spine X-rays demonstrate a scimitar shaped defect of the sacrum and CT myelography showed a 10 × 12 cm large cyst, filled by contrast medium, passing through the anterior sacral defects located in the pelvis. The patient was operated on by an abdominal route and the cyst removed, after ligature of a small communication between it and the sacral dural sac. Inside the meningeal sac and close to the sacral communication a dermal cyst was found.

In the literature the majority of anterior meningoceles are diagnosed in the second or the third decade of life. In a series of 148 cases of the literature, Villarejo (1983) found a majority of females (80%).

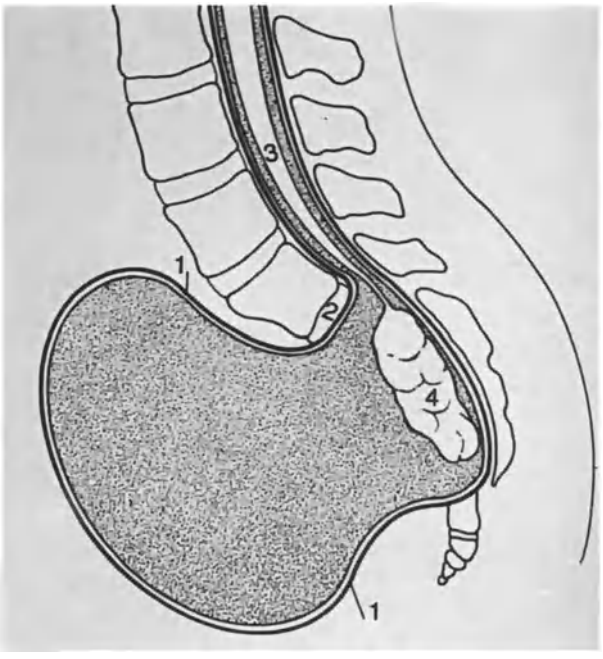
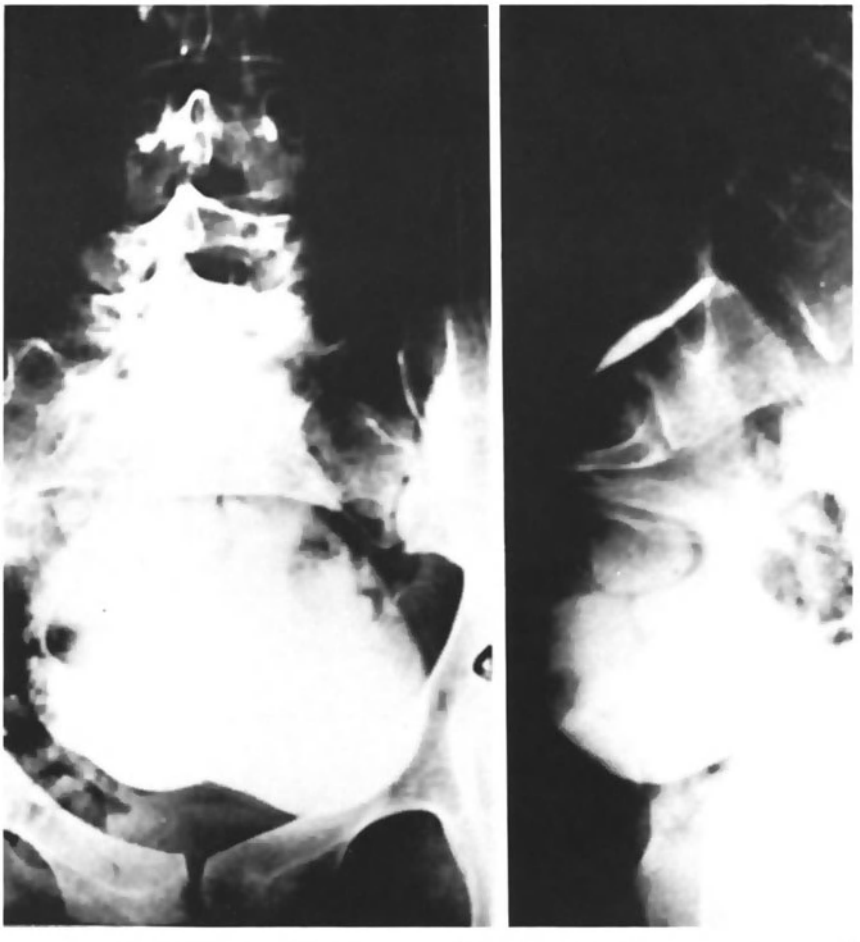


Fig. 19. Anterior meningocele (from Raimondi). *1* Ventral meningocele, *2* bony sacral defect, *3* neural tissue, *4* hamartomatous component

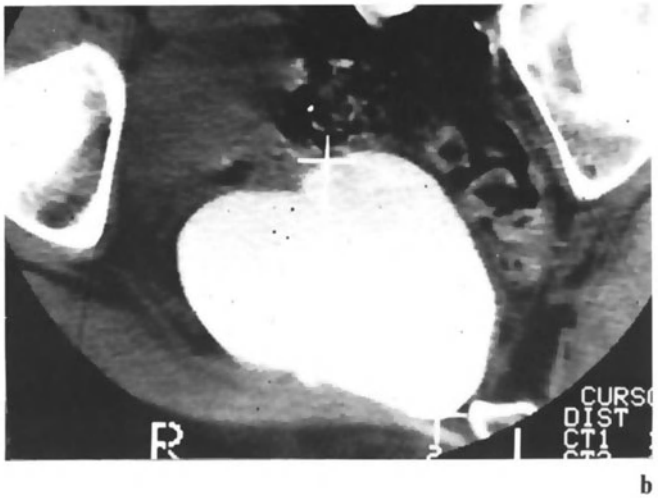
Surgery is required as very few cases of spontaneous disappearance of the cyst have been described. Amacher (1968) quoted a 30% mortality rate in non-operated patients, due to meningitis, destruction of the sacrum, or problems during labour. The two main surgical approaches are the posterior one, with a sacral laminectomy and ligature of the stalk, or the abdominal route allowing a better control of the cyst and the stalk. In cases with a large communication an abdominal route must be associated. Due to the number of associated lesions with presacral meningocele we strongly recommend a combination of anterior and posterior approaches for safe excision of the mass.

b) *Anterior lumbar meningoceles.* These are relatively more rare. The diagnosis is made in infancy or early childhood. Back pain, an abdominal or lateral lumbar mass are the most common symptoms. Generally the vertebral anomalies are localized on one or two levels. Anatomically lateral forms are more frequent and generally in the right side. Surgically a posterior approach is generally sufficient to close the stalk.

c) *Anterior thoracic meningoceles.* They are more frequent in female than in male (sex ratio F/M 6 to 4), frequently associated with neurofibromatosis (in 85% of the cases), in contrast to the sacral lesions. The main



a



b

symptoms are kyphoscoliosis (the main sign), back pain, dyspnea or cough. Vertebral anomalies are frequent. The midline variety is more rare than the lateral, right sided form.

IV. Dermal Sinus

A dermal sinus must be differentiated from a pilonidal sinus originating immediately above the anus. Typically the dermal sinus extends from the

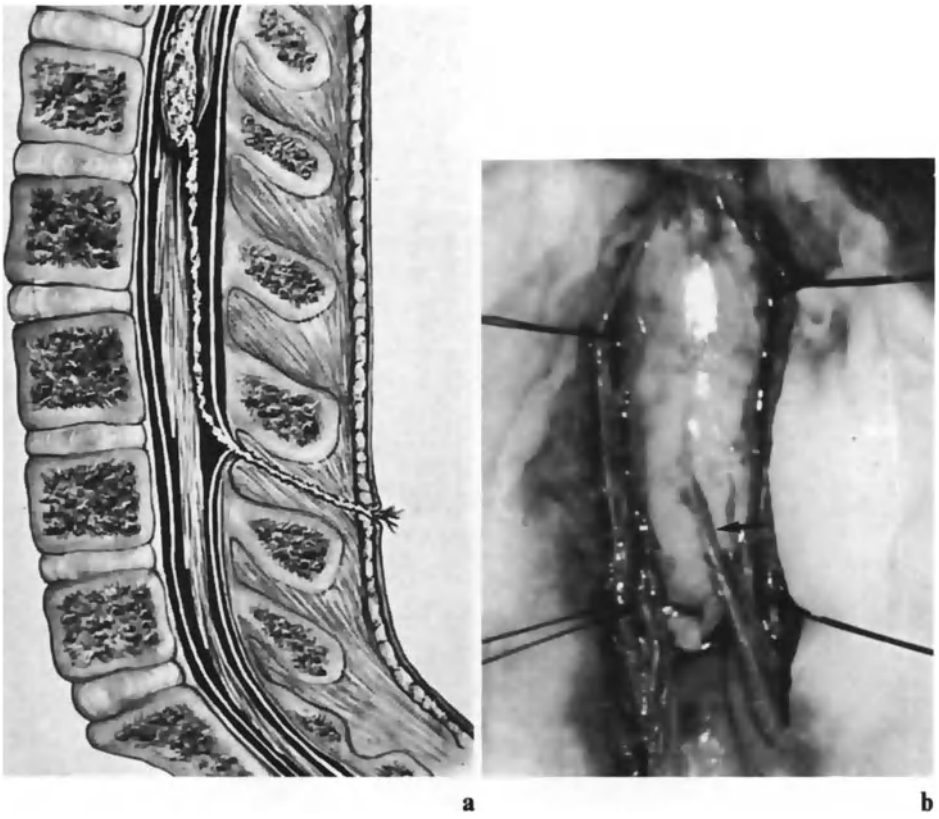


Fig. 21. Dermal sinus. (a) Diagram of a tubular tract extended from the skin to a dermoid inside the conus (from Matson). (b) Operative view of an intradural dermoid with a tract (arrow)

Fig. 20. (a, b). Sacral anterior meningocele in a 15 yr old girl. (a) Myelography shows a large pelvic cyst filled by contrast medium. In the lateral view, we see the communication between the dural sac and the meningocele through a sacral agenesis. (b) On CT-myelography we see a large liquid mass in the pelvis

skin to a variable depth (Fig. 21). It passes through the subcutaneous layer, through the bifid laminae toward the dura. It may end at the dura or penetrate the dura and end in the subarachnoid space. It may also end in a dermoid or epidermoid tumor situated among the roots of the cauda equina. The three main consequences of a dermal sinus are tethering of the conus mass effect when associated with a huge epidermoid or dermoid tumor and the risk of bacterial meningitis in the case of ruptured dermal cyst.

Locally a skin dimple is the most constant feature. Local signs of infection may be observed. Cutaneous hemangioma or hypertrichosis may also be present.

Anomalies of the lower limbs are rare (Eisenbrey 1982). In our series of 33 cases we have observed 4 cases of foot deformity and one case of hip luxation. In four cases a scoliosis was present.

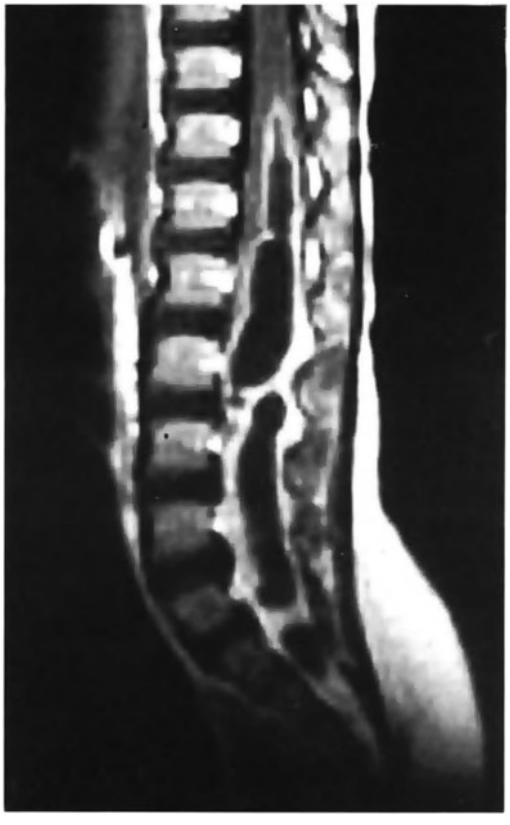


Fig. 22. Dermal sinus. MRI aspect of multiple intradural dermoids. The lesion extends from the extradural space of the conus

Bacterial meningitis may be the initial manifestation of a dermal sinus. The organism is usually Escherichia coli or Staphylococcus aureus. In cases of meningitis severe neurological manifestations such, as paraplegia or sphincter dysfunction may complicate the clinical presentation.

On CT the dermal tract appears as a dense line extending from the skin to the dura. The intradural course of the sinus may be well seen by CT-myelography. MRI (Fig. 22) will show the extraspinal tract of the sinus as a low signal tract that traverses the high signal subcutaneous fat. MRI not always may visualize the intradural course of the dermal sinus tract.

Surgery is mandatory in any cases of dermal sinus. The full extent of the tract must be excised. Injection of the tract or probing must be avoided. In the simplest circumstance, there is a tubular tract that extend from the cutaneous dermal sinus (Fig. 23) through the integument, to the central canal of the spinal cord. In this instance, untethering is achieved by dividing the stalk in the intradural space and then the sinus tract must be totally removed.

When there is a dermoid or an epidermoid tumor which continues the tract into the intradural space and sometimes inside the conus of the cord, an extensive laminotomy may be necessary to pursue the tumor which must be totally removed. If infection has already occurred, surgical irradication will be more difficult and permanent neurological deficit may be observed.

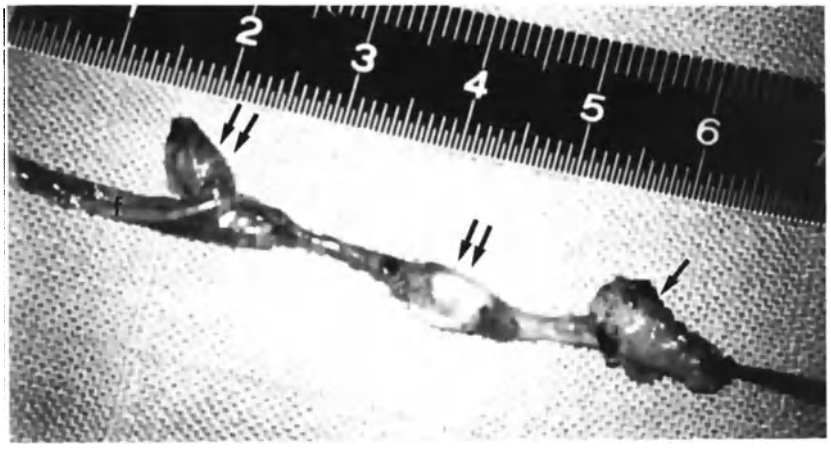


Fig. 23. Dermal sinus. Surgical specimen of a dermoid of the filum. The cutaneous dermal sinus (single arrow), the dermoid (double arrows), and the filum (*f*) are shown

V. Neurenteric Cysts

The first description of a neurenteric cyst was by Puusepp in 1934 in a 27-year-old patient presenting with paraplegia due to a cervical intestinoma, which he called a variety of teratoma. This very rare lesion may be defined as a cyst lined by gastrointestinal muccosa in contact with the central nervous system, usually at the level of the spinal cord. In the literature many other names have been used such as enterogenous cysts, foregut cysts or gastrocystomas. In our opinion bronchiogenic cysts in connection with the CNS must also be considered as neurenteric cysts.

In 1989 Hirsch collected only 26 cases in the literature: (male to female 3:1). Despite their congenital origin these cysts are rarely discovered in infancy. In our series of 169 cases of occult spinal dysraphism, four were neurenteric cysts, three of them in infants (2.4%). In the Till's series of 160 cases of spinal dysraphism, neurenteric cysts represent three cases (1.8%). Reigel (1983) find only one neurenteric cyst (1.6%) in a series of 62 lesions associated with tethered spinal cord.

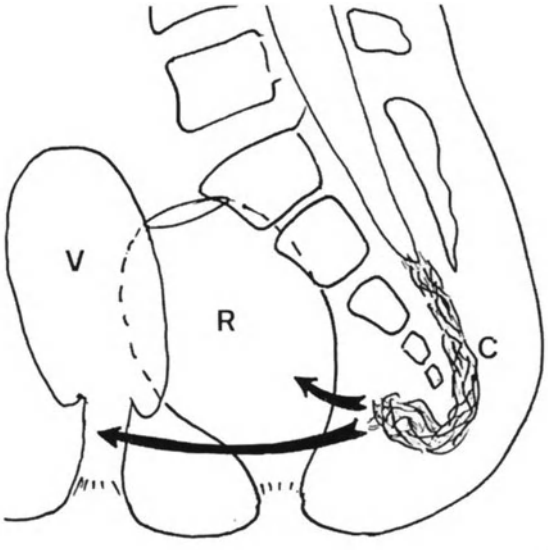
Anatomically the cysts are mostly anterior to the spinal cord (85%). The distribution along the spinal column in the 26 cases of the literature collected by Hirsch shows that 35% are cervical, 15% are cervico-thoracic, 35 are thoracic and 15% are thoraco-lumbar. In our series three were in the lumbar region and one in the cervical region.

Clinically the symptoms may be severe and acute. Paraplegia or a tetraplegia has been described. In our series meningitis was the initial clinical manifestation in a five-month old girl, associated with a discharge of pus through the vagina (Fig. 24). Spinal deformities are frequent in the literature while cutaneous signs are relatively rare. Associated vertebral anomalies, as anterior or posterior spina bifida, hemivertebrae, diastematomyelia, enlarged spinal canal or fused vertebrae, are generally present.

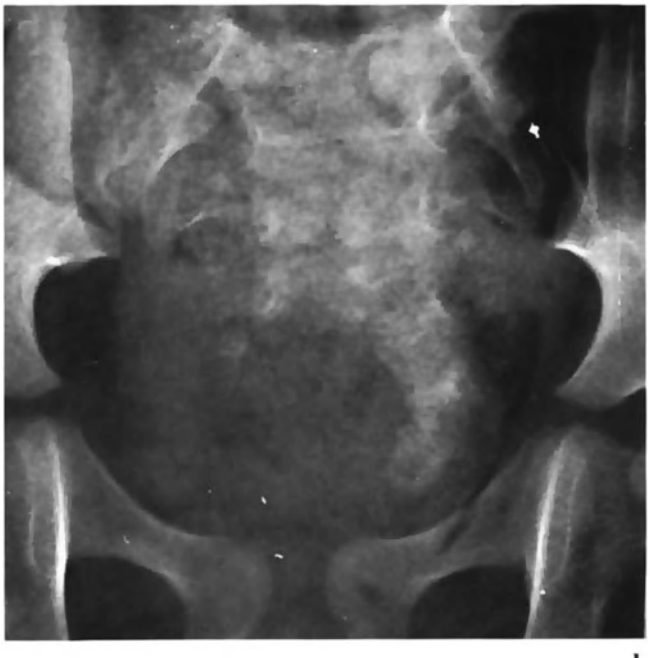
Spinal neurenteric cysts must be excised radically including the intraspinal connections; to the anterior compartment of the spinal column. In one of our cases the cyst was connected with the rectum and the vagina. In another case the cyst passed anterior to the spinal column through a vertebral defect.

VI. Sacral Agenesis

Sacral or lumbosacral agenesis are conditions where total or partial absence of the sacrum is present. Sacral agenesis is not only a radiological finding, it is often associated with many of the lesions we have already described.



a



b

Fig. 24. Neurenteric cyst. (a) Drawing of a neurenteric cyst in an infant, with communication between the dural sac and the rectum and the vagina V, C, R, (b) through a large sacral agenesis

Table 14. *Dysraphic Lesions Associated with Sacral Agenesis in 48 Cases (Personal Series)*

Lipoma	29	60.3%
Tight filum	9	19 %
Diastematomyelia	6	12.5%
Neurenteric cyst	2	4.1%
Anterior meningocele	2	4.1%

The malformation was first described by Hohl in 1852 in a newborn girl. Different types may be distinguished in relation to bone abnormalities and spinal cord involvement. Stanley, in 1979, described three groups of sacral agenesis:

Group I, with true agenesis of vertebral bone, corresponding to the caudal regression syndrome of Duhamel.

Group II, with sacral dysgenesis, hemivertebrae and butterfly vertebrae in the thoraco-lumbar spine. In this group, visceral anomalies are frequent and neurological deficit is minimal.

Group III is a dysraphic state with anomalies of the cord and tethering.

In our series of 169 cases of occult spinal dysraphism, we found 48 cases (28.4%) of sacral agenesis (Table 14).

Sacral agenesis is frequent in cases of neurenteric cyst (50%), in diastematomyelia (43%) and in Lipoma (29%). The clinical presentation of different dysraphic lesions shows a prevalence of urinary signs in cases of sacral agenesis. In our series, 73% of dysraphic lesions with sacral agenesis had a neurogenic bladder, compared to 50% of urinary disorders in the total group of patients with occult spinal dysraphism.

Pierre-Kahn (1986) in the analysis of prognostic factors in his series of lipomas found that sacral agenesis is the only negative factor, probably due to associated damage of the terminal sacral roots in such cases.

Consequently the presence of sacral agenesis on the spine X-Rays in a patient suffering urinary disorders suggest in most of the cases an underlying spinal cord lesion and an appropriate imaging studies must be undertaken.

Conclusion

The anomalies described in this chapter represent a group of lesions which appear very different from one another. For example what could be the connection between a neurenteric cyst and a thick filum or between a child

presenting a fat mass in the lesion region and a infant with a meningitis related to a dermal sinus? Nevertheless lesions such lipoma, diastematomyelia, dermal sinus, neurenteric cysts, thick filum may be included in the same pathological group, Occult Spinal Dysraphism, since their embyology, their pathophysiology, their clinical manifestations are similar and their consequences may be the same. The common factor in most of these lesions is the existence of a tethering of the spinal cord, leading to secondary clinical deterioration. All the lesions included in Occult Spinal Dysraphism potentially have a prior functional prognosis.

Consequently a good knowledge of this pathology is mandatory for pediatricians, urologists, orthopedics, neurologists, radiologists and neurosurgeons. The ignorance of this pathology may lead to imprevisible clinical consequences and a severe definitive handicap.

References

1. Amacher A, Drake CG, McLachine AD (1968) Anterior sacral meningocele. Surg Gynecol Obstet 126: 986–994
2. Anderson EM (1975) Occult spinal dysraphism: a series of 73 cases. Pediatrics 55: 826–835
3. Assaad A, Mansy A, Kotb M, Hafez M (1989) Spinal dysraphism: experience with 250 cases operated upon. Childs Nerv Syst 5(5): 324–329
4. Barnes PD, Lester PD, Yamanashi WS, Prince JR (1986) Magnetic resonance imaging in infants and children with spinal dysraphism. AJNR 7: 465
5. Bentley JFR, Smith JR (1960) Developmental posterior enteric remnants and spinal malformations. Arch Dis Child 35: 76–86
6. Bollini G (1989) Sacral and lumbar agenesis. In: Raimondi A, Choux M, Di Rocco C, Principles of pediatric neurosurgery. The pediatric spine, Vol II. Springer, Berlin Heidelberg New York Tokyo, pp 144–166
7. Bollini G (1989) Dysraphisme spinal fermé. Cahiers d'enseignement de la SOFCOT. Conférences d'enseignement. Masson, Paris, pp 11–34
8. Boop FA, Chadduck WM (1991) Silastic duraplasty in pediatric patients. Neurosurgery 29(5): 785–787 (discussion 788)
9. Borne G, Cristino G, Bedou G, Schaefer JP, Pinaudea M (1990) Dysembryome pluritissulaire mature medullaire lombaire avec spina bifida occulta sacre'. Neurochirurgie 36(3): 180–184
10. Bremer JL (1952) Dorsal intestinal fistula occupying vertebral canal: diastematomyelia. Arch Pathol Lab Med 54: 132–138
11. Bret P, Patet JP, Lapras C (1989) Diastematomyelia and diploymelia. In: Raimondi A, Choux M, Di Rocco C (eds) The principles of pediatric neurosurgery. The pediatric spine, Vol II
12. Bruce DA, Shut L (1982) Spinal lipomas in infancy and childhood. Childs Brain 5: 192–203

13. Bryant T (1837) Case of deficiency of the anterior part of the sacrum with a thecal sac in the pelvis; similar to the tumour of the spina bifida. Lancet: 358–360
14. Byrd SE, Darling CF, McLone DG (1991) Developmental disorders of the pediatric spine. Radiol Clin North Am 29(4): 711–752
15. Carcassonne M, Bergoin M, Choux M, Monfort G, Gregoire A, Morisson-Lacombe G, Bollini G (1981) Les malformations de la colonne lombo-sacrée et leurs implications viscérales. (Myéloméningocele exceptée). Chir Ped 22 (2–3): 1–223
16. Carvajal L, Uraga E, Tama, F, Martinez G (1989) Mal perforans and spinal dysraphia and lumbar stenosis syndromes. Med Cutan Ibero Lat Am 17(6): 360–364
17. Chapman PH (1982) Congential intraspinal lipomas. Anatomic considerations and surgical treatment. Childs Brain 9: 37–47
18. Chapman PH, Beyerl B (1986) The tethered spinal cord with particular reference to spinal lipoma and diastematomyelia. In: Hoffman HJ, Epstein F (eds) Disorders of the developing nervous system. Diagnosis and treatment. Blackwell , Boston, pp 109–132
19. Choux M (1981) Les Malformations de la colonne lombo-sacrée et leurs implications viscérales. (Myéloméningocele exeptée). Chir Ped 22(2–3): 136–159
20. Cohen AR (1991) The mermaid malformation: cloacal extrophy and occult spinal dysraphism. Neurosurgery 28(6): 834–843
21. Davidoff AM, Thompson CV, Grimm JM, Shorter NA, Filston HC, Oakes WJ (1991) Occult spinal dysraphism in patients with anal agenesis. J Pediatr Surg 26(8): 1001–1005
22. De-Bakker HM, Roos RA, Voormolen JH, Vielvoye GJ (1990) Lumbar disk degeneration in spinal dysraphism. AJNR 11(2): 415
23. Di Pietro MA, Venes JL (1988) Real time sonography of the pediatric spinal cord: horizons and limits. In: Concepts in pediatric neurosurgery, Vol 8. Karger, Basel, pp 120–132
24. Di Rocco C, Ceddia A, Colosimo C (1989) Spinal meningeal malformations. In: Raimondi A, Choux M, DiRocco C (eds) Principles in pediatric neurosurgery. The pediatric spine, Vol II. Springer, Berlin, Heidelberg, New York, Tokyo, pp 1–16
25. Eisenbrey A (1982) Dermal sinus. In: Pediatric neurosurgery. Surgery of the developing nervous system. Grune and Stratton, New York, pp 91–94
26. Erkulvrawatr S (1979) Intrathoracic meningoceles and neurofibromatosis. Arch Neurol 36: 557–559
27. French BN (1983) The embryology of spinal dysraphism. Clin Neurosurg 30: 295–340
28. Frerebeau Ph, Dimeglio A, Gras M, Harbi H (1983) Diastematomyelia report of 21 cases surgically treated by a neurosurgical and orthopedic team. Childs Brain 10: 328–339
29. Garceau GJ (1953) The filum terminale syndrome. J Bone Joint Surg 35A: 711–716

30. Guthkelch AN (1974) Diastematomyelia with median septum. Brain 4: 729–742
31. Guthkelch AN (1985) Diastematomyelia. In: Wilkins RH, Rengachary SS (eds) Neurosurgery, Vol III. McGraw-Hill, New York pp 2058–2061
32. Han JS, Benson JE, Kaufman B, Rekate HL, Alfidi RJ, Bohlman HH (1985) Demonstration of diastematomyelia and associated abnormalities with MR imaging. AJNR 6: 215
33. Harrison MJ, Mitnich RJ, Rosenblum BR, Rothman AS (1990) Leptomyelolipoma: analysis of 20 cases. J Neurosurg 73(3): 360–367
34. Hawnaur JM, Hughes D, Jenkins JP, Bannister CM, Isherwood I (1991) Investigation of children with suspected spinal dysraphism by magnetic resonance imaging. Eur J Pediatr Surg 1 [Suppl 1]: 18–9
35. Hilal SK, Marton D, Pollack E (1974) Diastematomyelia in children. Radiology 112: 609–621
36. Hirsch JF, Hirsch E (1989) Neurenteric cysts. In: Raimondi A, Choux M, DiRocco C (eds) Principles of pediatric neurosurgery. The pediatric spine, Vol II. Springer, Berlin Heidelberg New York Tokyo, pp 134–143
37. Hoffman HJ (1987) Spinal dysraphism. Am Fam Physician 36(6): 129–136
38. Hoffman HJ, Hendrick EB, Humphrey RP (1976) The tethered spinal cord: its manifestations, diagnosis and surgical correction. Childs Brain 2: 145–155
39. Hoffman HJ, Taecholarn C, Hendrick BE, Humphreys RP (1985) Lipomyelomeningoceles and their management. In: Concepts in pediatric neurosurgery, Vol 5. Karger, Basel, pp 107–117
40. Hoffman HJ (1989) The Tethered spinal cord. In: Raimondi A, Choux M, Di Rocco C (eds) Principles of pediatric neurosurgery. The pediatric spine, Vol II. Springer, Berlin Heidelberg New York Tokyo, pp 177–188
41. Hohl AF (1852) Zur Pathologie des Beckens. I. Das schräg-ovale-Becken. Engelmann, Leipzig, p 61
42. Hood RW, Risenborough EJ, Nehme AM, Micheli LJ, Strand RD, Neuhauser EB (1980) Diastematomyelia and structural spinal deformities. J Bone Joint Surg 62A: 520–528
43. Humphreys RP (1991) Current trends in spinal dysraphism. Paraplegia 29(2): 79–83
44. Humphreys RP, Manwaring KH, Carroll NC (1991) Accessory arm, dysraphism or disparity? Case report. J Neurosurg 74(2): 297–300
45. James CCM, Lassman LP (1960) Spinal dysraphism. Arch Dis Child 35: 315–327
46. James CCM, Lassman LP (1962) Spinal dysraphism. J Bone Joint Surg (Br) 44: 828–840
47. James CCM, Lassman LP (1972) Spinal dysraphism. Spina bifida occulta. Butterworths, London
48. James HE, Williams J, Brock W, Kaplan GW, U HS (1984) Radical removal of lipomas of the conus and the cauda equina with laser microneurosurgery. Neurosurgery 15: 340–343
49. Kapsalakis Z (1964) Diastematomyelia in two sisters. J Neurosurgery 21: 66–67

50. Khoury AE, Hendrick EB, McLorie GA, Kulkarni A, Churchill BM (1990) Occult spinal dysraphism: clinical and urodynamic outcome after division of the filum terminale. J Urol 144: 426–8; Discussion 428–429 and 443–444
51. Kosnic EJ (1990) A review of the treatment of children with a lipomyelomeningocele at the Columbus Children's Hospital. In: Concepts pediatric neurosurg, Vol 10. Karger, Basel, pp 15–21
52. Lapras C, Patet JD, Huppert J, Bret Ph (1985) Syndrome de traction du cone terminal ou syndrome de la moelle attachée; Lipomes lombo-sacrée. Rev Neurol 141: 207–215
53. Lapras C, Patet JD, Hupert J, Bret Ph, Mottolese C (1985) Tethered cord syndrome, experience of 58 cases. J Neuroped Sci 1(1): 39–50
54. Lapras C (1988) Spina bifida. Neurochirurgie 34 [Suppl 1]: 1–103
55. Lassman LP, James CCM (1977) Meningocele manquée. Childs Brain 3: 1–11
56. Leibowitz E, Barton W, Sadighi P, Ross JS (1984) Anterior sacral meningocele contiguous with a pelvic hamartoma, case report. J Neurosurgery 61: 188–190
57. Mac Master MJ (1984) Occult intraspinal anomalies and congenital scoliosis. J Bone Joint Surg 66A: 588–601
58. Matson DD, Ingraham FA (1969) Neurosurgery of infancy and childhood. Thomas, Springfield
59. Matson DD, Woods RP, Campbell JB, Ingraham FD (1950) Diastematomyelia (congenital clefts of the spinal cord). Diagnosis and surgical treatment. Pediatrics 6: 98–112
60. McComb JG (1985) Congenital dermal sinus. In: Wilkins RH, Rengachary SS (eds) Neurosurgery, Vol III. McGraw-Hill, New York, pp 2081–2083
61. McCullough DC, Levy LM, DiChiro G, Johnson DL (1990–91) Toward the prediction of neurological injury from tethered spinal cord: investigation of cord motion with magnetic resonance. Pediatr Neurosurg 16(1): 3–7, Discussion 7
62. McEwen GD, Bunnel WP, Sriram K (1975) Acute neurological complication in the treatment of scoliosis. A report of the Scoliosis Research Society. J Bone Joint Surg 57A: 404
63. McLone DG, Mutlur S, Naidich TP (1983) Lipomyelomeningoceles of the conus medullaris. In: Concepts in pediatric neurosurgery, Vol 3. Karger, Basel, pp 170–177
64. McLone DG, Naidich TP (1985) The tethered cord syndrome. In: Holtzman RN, Stein BM (eds) Spinal dysraphism experimental and clinical. Thieme-Stratton, New York, pp 14–28
65. McLone DG, Naidich TP (1986) Laser resection of fifty spinal lipomas. Neurosurgery 18: 611–615
66. Monfort G (1989) Diagnostic and management of urinary problems in neurogenic vesico-sphincteric dysfunction. In: Raimondi A, Choux M, DiRocco C (eds) Principles of pediatric neurosurgery. The pediatric spine, Vol III. Springer, Berlin Heidelberg New York Tokyo, pp 187–208
67. Neuwirth MG, Nainzadeh NK, Bernstein RL (1988) The use of pudendal nerve in monitoring lower sacral roots (S2-4) during anterior and/or posterior

spinal stabilization. A report of the Scoliosis Research Society, September/October 1988, Baltimore
68. Ollivier d'Angers (1937) Traité des maladies de la moëlle épinière, 3rd Ed, Vol 1. Mequignon-Marvis, Paris, pp 189–199
69. O'Neill P, Stack JP (1990–91) Magnetic resonance imaging in the preoperative assessment of closed spinal dysraphism in children. Pediatr Neurosurg 16: 240–246
70. O'Neill P, Singh J (1991) Occult spinal dysraphism in children: need for early neurosurgical referral. Childs Nerv Syst 7(6): 309–311
71. Page LK (1985) Occult spinal dysraphisms and related disorders. In: Wilkins RH, Rengachery SS (eds) Neurosurgery, Vol III. McGraw-Hill, New York, pp 2053–2058
72. Pang D, Wilberger JE (1982) Tethered cord syndrome in adults. J Neurosurg 57: 32–47
73. Pang D (1985) Sacral agenesis. In: Wilkins RH, Rengachery SS (eds) Neurosurgery, Vol III. McGraw-Hill, New York, pp 2075–2077
74. Pang D (1992) Split cord malformation (Part I): a unified theory of embryogenesis for double spinal cord malformation. Neurosurgery 3: 451–480
75. Pang D (1992) Split cord malformation (Part II): clinical syndrome. Neurosurgery 3: 481–500
76. Parkinson D (1991) Accessory limbs and spinal dysraphism. Letter. J Neurosurg 75(3): 498–499
77. Peter JC (1992) Occult dysraphism of the spine. A retrospective analysis of 88 operative cases, 1979–1989. S Afr Med J 81(7): 351–354
78. Pierre-Kahn A, Renier D, Sainte-Rose C, Hirsch JF (1983) Les lipomes lombo-sacrées avec spina bifida. Corrélations anatomo-cliniques. Résultats thérapeutiques. Neurochirurgie 29: 359–363
79. Pierre-Kahn A (1986) Intraspinal lipoma with spina bifida. Prognosis and treatment. J Neurosurg 65: 756–761
80. Puussepp M (1934) Variété rare de tératome sous-dural de la région cervicale (intestinome). Quadriplégie, extirpation. Guérison complète. Rev Neurol (Paris) 41: 876–886
81. Raimondi AJ (1987) Vertebrospinal congenital anomalies. In: Raimondi AJ (ed) Pediatric neurosurgery. Theoretical principles, art of surgical techniques. Springer, Berlin Heidelberg New York Tokyo, pp 423–452
82. Rasool MN, Govender S, Naidoo KS, Moodley M (1992) Foot deformities and occult spinal abnormalities in children: a review of 16 cases. J Pediatr Orthop 12(1): 94–9
83. Raybaud CA, Naidich TP, McLone DG (1992) Development of the spine and spinal cord. In: Manelfe C (ed) Imagerie of the spine and spinal cord. Raven, New York
84. Reigel DH (1983) Tethered spinal cord. Concepts in pediatric neurosurgery, Vol 4. Karger, Basel, pp 142–164
85. Roy MW, Gilmore R, Walsh JW (1986) Evaluation of children and young adults with tethered spinal cord syndrome. Utility of spinal and scalp recorded somatosensory-evoked potentials. Surg. Neurol 26: 241–248

86. Sato K, Shimoji T, Sumie H, Yaguachi K, Yagishita A, Kuru Y, Shozo S (1985) Surgically confirmed myelografic classification of the intraspinal lipoma in the lumbosacral region. Childs Nerv Syst 1: 3–11
87. Sauter R, Klemm T (1988) Spinal sonography of a newborn infant with postpartal paraplegia. Klin Padiatr 200(1): 70–73
88. Scatliff JH, Till K, Hoare RD (1975) Incomplete, false and true diastematomyelia. Radiological revaluation by air myelography and tomography. Neuroradiology 166: 349–354
89. Scatliff JH, Kendall BE, Kingsley DP, Britton J, Grant DN, Hayward RD (1989) Closed spinal dysraphism: analysis of clinical, radiological, and surgical findings in 104 consecutive patients. AJR 152(5): 1049–1057
90. Steinbok P, Cochrane DD (1991) The nature of congenital posterior cervical or cervicothoracic midline cutaneous mass lesions. Report of eight cases. J Neurosurg 75(2): 206–212
91. Till K (1969) Spinal dysraphism: a study of congenital malformations of lower back. J Bone Joint Surg 51: 415–422
92. Villarejo FJ, Blazquez MG, Gutierrez-Diaz JA (1976) Intraspinal lipomas in children. Childs Brain 2: 361–370
93 Villarejo F, Slavone C, Blazquez ME, Pascual-Castro-Viejo I, Perez-Higueras A, Fernandez-Sanchez A, Garcia Bertrand C (1983) Anterior sacral meningocele: review of the literature. Surg Neurol 19: 57–71
94. Walsh J, Markesbery W (1980) Histological features of congenital lipoma of the lower spinal canal. J Neurosurg 52: 564-569
95. Warf BC, Scott RM, Barnes PD, Hendren WH (1993) Tethered spinal cord in patients with anorectal and urogenital malformations. Pediatr Neurosurg 19: 25–30
96. Wilkins RH (1985) Intraspinal cysts. In: Wilkins RH, Rengachary SS (eds) Neurosurgery, Vol III. McGraw-Hill, New York, pp 2061–2070
97. Wilkins RH (1985) Lateral and anterior spinal meningoceles. In: Wilkins RH, Rengachary SS (eds) Neurosurgery, Vol III. McGraw-Hill, New York, pp 2070–2075
98. Wyspold F, Citrin C, Bakovich A, Sherman J (1987) Evaluation of MR in spinal dysraphism with lipoma, comparison with metrizamide computed tomography. Pediatr Radiol 17: 184–188
99. Yamane T, Shinoto A, Kamegaya M, Shinada Y (1991) Spinal dysraphism. A study of patients over the age of 10 years. Spine 16(11): 1295–1297
100 Yamada S, Zinke DE, Sandres D (1981) Pathophysiology of "tethered cord syndrome". J Neurosurg 54: 494–503
101. Zumkeller M, Seifert V, Stolke D (1989) Spinal dysraphia and disordered ascension of the spinal cord in adults. Z Orthop 127(3): 336–342

Functional Stereotactic Neurosurgery for Psychiatric Disorders: an Experience in Belgium and The Netherlands

We are pleased to publish the following commentary by Mr. John Bartlett of the Brook Hospital, London, who has Britain's greatest experience in the management of such cases.

The Editors

This chapter addresses the difficult and often contentious subject of psychosurgery which has been defined as "a neurosurgical intervention to sever fibres connecting one part of the brain with another, or to remove or destroy brain tissue with the intent of modifying or altering severe disturbance of behaviour, thought content or mood". The authors have traced the historical development of psychosurgery and brought out the fact that it is those patients suffering from anxiety, depression and obsessive compulsive illness who throughout this history of psychosurgery have benefited most. They also refer to the "taming effects" of the old leucotomy (obsolete since the mid-1950's) which had proved useful in the management of certain behaviour disorders of schizophrenia. This latter effect often left patients with severe blunting of personality, but the operation, judged in the context of the alternatives available at the time was better than nothing for this unfortunate group. It allowed 20% to return to life in the community. However, as the authors emphasize this became history with the discovery in the 1950's of the major tranquilizers and effective pharmacological agents for the treatment of depression and anxiety which has transformed psychiatry. Nonetheless, some patients remain resistant to the newer treatments and it is this which keeps an interest in psychosurgery alive. The introduction of stereotactic techniques, increasingly accurate imaging techniques for target identification and precise lesions have all contributed to a very low morbidity of modern procedures. It is now well recognised that Psychiatrists and Neurosurgeons must work in close partnership to ensure the cases are appropriately selected.

In the years between 1971 and 1991 all the cases offered psychosurgery in Belgium and the Netherlands have been considered by a Committee

which was initially set up by a group of Psychiatrists and Neurosurgeons in the Netherlands to form a review board. One hundred and eleven cases were considered and eighty-four accepted. The majority of patients were suffering from obsessive disorders (which has been particularly well defined) and anxiety, but there were twenty-eight patients treated for aggressive conduct disorder. Eleven of the eighty-four patients considered suitable by the Committee, mainly in the obsessive compulsive disorder and anxiety groups refused operation and these form a "control" group. Fifty-one patients in the obsessive and compulsive anxiety group were treated; eleven by progressive leuco-coagulation, a complex and lengthy procedure requiring the implanation of a sheath of electrodes stereotactically in the brain; thirty-three by subcaudate tractotomy and seven by anterior capsulotomy. The numbers in each group were small but the pattern of results showed that they did produce some significant and useful effect. However, the results of progressive leuco-coagulation were not superior to subcaudate tractotomy or anterior capsulotomy so leuco-coagulation has been abandoned on the basis of its complexity. When the obsessive compulsive patients, a group notoriously difficult to treat, were compared with the patients who refused operation the treated patients were significantly improved. Twenty-eight patients with aggressive conduct disorder were treated, twelve with amygdalotomy, sixteen with thalamotomy. The authors conclude that the outcome for patients with aggressive conduct disorder is unpredictable and although no patient was made worse with the surgical treatment its use remains an open question and therefore the utmost reservedness should be maintained when offering this type of surgery, a conclusion which is in keeping with the view of a wider international body politic.

The surgical techniques and the location of the lesions is described in sufficient detail that leaves the reader in no doubt as to what is done and is therefore an excellent reference for others working in this small field.

The authors describe the ethical issues, the setting up of their Committee which has seen all patients since 1971 and its operation. When a patient is accepted by the Committee the following criteria must be satisfied. That the diagnosis is correct and appropriate; all other relevant treatments have been tried and shown to fail; the correct operation is chosen and the site of the lesion is appropriate; the operation will be carried out by a surgeon trained in the technique; that there will be adequate follow-up and rehabilitation; the relatives are supportive of the procedure and adequate information has been given to the patient and the family and, finally, most important the consent of the patient is informed. The Dutch Health Council considered that the existence and operation of this Committee on psychosurgery in Belgium and the Netherlands was a good example of self-regulation. However, they recommended that the Committee should include a member

with a special knowledge of ethics. In many respects this Committee has a similar remit to the Commissioners who regulate psychosurgery in the United Kingdom, though without the same legal status or separation of those who treat the patient from those who give permission for the procedure to go ahead. The authors should be congratulated on producing their clear and informative chapter on a difficult subject.

J. Bartlett

P. COSYNS[1], J. CAEMAERT[2], W. HAAIJMAN[3], C. VAN VEELEN[4], J. GYBELS[5], J. VAN MANEN[6], and J. CEHA[7]

[1] University of Antwerpen, Psychiatrist, Antwerp (Belgium)
[2] University Hospital of Gent, Neurosurgeon, Ghent (Belgium)
[3] Hospital for Psychotherapy "Overwaal", Psychiatrist, Lent (The Netherlands)
[4] University Hospital of Utrecht, Neurosurgeon, Utrecht (The Netherlands)
[5] Catholic University of Leuven, Neurosurgeon, Louvain (Belgium)
[6] Academic Medical Center, Amsterdam, and University Hospital of Groningen, Neurologist, Groningen (The Netherlands)
[7] Psychiatric Hospital "Ursula Kliniek", Psychiatrist, Wassenaar (The Netherlands)

With 10 Figures

Contents

Preface

Psychiatric disorders are definitely, among other things, linked with the functioning of the central nervous system. Psychosurgery offers the opportunity to increase our knowledge about the interaction between brain and behaviour in human beings.

Storm van Leeuwen[48] founded a multidisciplinary committee on this subject in 1971 in Utrecht (The Netherlands). This monograph reflects the accumulated clinical and scientific data of this committee. Other European centers – mainly in Sweden, United Kingdom and Spain – work on the same topic, but this chapter will be limited to the experience of this committee.

Psychosurgery involves by definition a close collaboration between nurosurgeons and psychiatrists. Van Manen and van Veelen operated on patients in The Netherlands, while Belgian patients were operated on by Gybels and Caemaert. The review of "Stereotactic techniques" was coordinated by Caemaert. The psychiatrists Haaijman and Ceha (The Netherlands) together with Cosyns (Belgium) were involved in decisions for surgery, psychiatric treatment and follow-up.

1. Principles of Psychosurgery

1.1. Introduction

Operations on the brain for psychiatric disorders are the most controversial form of biological treatment in psychiatry. Physicians familiar with these treatments are convinced, from their clinical experience, that highly targeted stereotactic operations can benefit carefully selected chronically ill psychia-

tric patients with a low rate of unwanted side effects. Psychosurgery has a role as a treatment in psychiatry, albeit a limited one. In opposition are lay people and professionals who protest against both the alleged "political motives" of psychosurgeons and the "brain-disabling psychiatric model" that is carried to its extreme in psychosurgery[5]. Opponents argue also that, on the individual level, it blunts the intellectual and emotional functions, and removes freedom and autonomy.

In the Western world the debate became inflamed during the seventies; politics intruded into the decision process of this therapeutic approach. The medical world as such was left aside and many critical and uncritical ideas have been espoused, and debated in public arenas. The debate culminated in the report with recommendations of May 23, 1977 of the (US) National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research[42]. Although the National Commission issued a surprisingly favourable report, the imposition of a complex bureaucratic or legislative procedure de facto kills a medical practice. The psychosurgery problem subsided during the 1980's, and an opportunity thus arises to discuss and evaluate the actual state of the art objectively and without bias.

Scientific data concerning psychosurgery remain scarce in the medical literature. A computer search for the years 1985–1990 provided 41 publications with only 9 concerning recent patient material. Obviously we still need "hard" clinical data to evaluate the effectiveness and the occurrence of unwanted side effects of psychosurgical operations.

According to the American Psychiatric Association[1] psychosurgery may be defined as "a neurosurgical intervention to sever fibers connecting one part of the brain with another or to remove or to destroy brain tissue with the intent of modifying or altering severe disturbances of behaviour, thought content or mood". Such surgery may also be undertaken for the relief of intractable pain, but this indication will not be considered here. Psychosurgery is a well-established term in the medical literature, but in essence it is not an appropriate one. The surgeon is operating on the brain and not at all on the psyche of the patient. This remains a fact even if the aim of the operation is to alleviate severe psychic suffering. Other terms have been proposed but without lasting success: psychiatric surgery, limbic (system) surgery, behavioural surgery or neurosurgery for a psychiatric indication or purpose. In spite of this inaccuracy we will use the term psychosurgery or, referring to the actual neurosurgical procedures, stereotactic neurosurgery for psychiatric disorders.

Since 1971 a group of neurosurgeons, neurologists and psychiatrists interested in the therapeutic possibilities and limitations of psychosurgery has met on a regular basis in Utrecht (The Netherlands). They constitute a review board, named the "Committee on Psychosurgery", and give advice

on individual cases submitted for psychosurgery. More details about this Committee will be given later on, but the aim of this publication is to present the 20 years of expertise and clinical experience of this multidisciplinary review board.

1.2. Historical Overview

Some historical background is essential to understand the current state of affairs. The modern era of psychosurgery started in Lisbon on November 12, 1935 with an operation on a 63 year old woman suffering from involutional melancholia.

Egas Moniz, professor of Neurology, and his colleague Almeida Lima, neurosurgeon, used alcohol injections to destroy bilaterally parts of the frontal lobes. After the seven such operations, they switched to a new technique: cutting nerve fibers with a "cerebral leucotome". Moniz published the results of the first 20 operated psychiatric patients in 1936[40]. Seven schizophrenic or paraphrenic patients and 13 mainly mood or anxiety disordered patients were reported. Seven patients were regarded as cured, 7 as improved and 6 as unchanged. Surgery proved to be more beneficial for anxiety and mood disorders (7 cured, 5 improved, 1 unchanged) than for schizophrenia or paraphrenia (0 cured, 2 improved and 5 unchanged).

Neurosurgeons and neuropsychiatrists were encouraged to use this new and promising treatment method on the basis of these rather favourable results plus the relative absence of effective treatments for major psychiatric disorders. Walter Freeman, neuropsychiatrist, and James Watts, neurosurgeon, improved the technique that was eagerly adopted worldwide[14]. Moniz was awarded the Nobel prize for his work in 1949 and this increased the scientific credibility of psychosurgery even though the scientific quality of the publications in the early years was very uneven. Psychosurgery was increasingly used as therapy for large groups of patients with a wide variety of disorders. In 1951 and 1952 there were approximately 300 publications a year. In the second half of the 1950's and the 1960's there was a sharp decline in the use of psychosurgery.

Several factors precipitated this decline. It became obvious to clinicians that the early reports of therapeutic successes had been unduly optimistic and uncritical. Adverse physical, emotional, intellectual and behavioural consequences of psychosurgery were reported. The most common physical sequelae included epileptic seizures, weight gain, urinary incontinence and impairment of motor coordination. Emotional blunting or instability and a decrease of intellectual efficiency were noted. Intelligence, as measured by intelligence tests, was not impaired, but performance was reduced due to

emotional and motivational deficits. Cognitive defects in the areas of planning and anticipating likely personal and social consequences of behaviour were described. On the behavioural level disinhibited conduct and impaired social decorum were reported. These alterations of personality and behaviour are known in the psychiatric nosology as "Organic personality disorder"; 310.10 DSMIII-R[12] or F07.0 ICD10[18].

The standard surgical procedure was improved and the cerebral target areas more precisely located to avoid unwanted side effects. Neurosurgeons agreed to limit surgical brain destruction to the medial and basal or inferior orbital parts of the frontal lobe[4,7], while other parts of the limbic system such as the cingulum were also explored[2,3].

The emphasis on the "taming" or "quietening" effects of surgery in early reports posed an ethical problem to psychiatrists in charge of patients. The accent put on the improvement of troublesome behaviour suggests that problems of patient management played too important a role in patient selection and the evaluation of the results. Who benefits from psychosurgery, is it the patient with an improvement in the quality of his life, or the environment? The publication in 1970 of "Violence and the brain", by Vernon Mark and Frank Ervin, enhanced this controversy on surgery for behavioural control of disturbed or disturbing human beings[31].

Another major factor in the decline of psychosurgery has been the very successful development since the 1950's of new and very effective psychiatric treatment methods. Potential candidates for psychosurgery were diverted away from surgical therapies towards less radical ones. Discoveries of neuroleptics (chlorpromazine 1952, haloperidol 1958), benzodiazepines (1957) and tricyclic antidepressants (1958) played a key role in this development. The introduction of the psychotherapeutic community ideology in traditional psychiatric asylums initiated a new therapeutic approach in which psychosurgery no longer had a place[32]. Existing psychotherapeutic methods such as psychoanalysis were not useful for severe psychiatric cases where psychosurgery was considered, but the developing behaviour therapy in the 1960's appeared to be very effective in the treatment of anxiety, phobic and obsessive compulsive disorders. All these factors have contributed to reduce referrals for psychosurgery.

One might expect that psychosurgery would disappear from the psychiatric therapeutic armamentarium, as has been the case for malaria therapy, insulin treatments, hydrotherapy and many others. This is more or less the case in countries such as USA, Japan and Germany, but not for many European countries such as Sweden, The United Kingdom, Spain, Belgium and The Netherlands. Psychosurgery is still practised by a small number of well known surgical teams, usually in university hospitals. Two separate factors play an important role in this renewed interest in psychosurgery.

Firstly the development of stereotactic surgical techniques. These proved to be safer for the patient and more accurate, permitting smaller lesions at selected brain targets also, eventually in deeper parts of the brain. Secondly, the newer psychiatric therapies also have their limitations; psychiatrists are confronted with a small residual number of highly disturbed patients for which psychopharmological and psychotherapeutic treatments prove to be of very limited use.

1.3. Patient Data

During a period of 20 years (1971–1991) 79 psychiatric patients have been operated on in The Netherlands and Flanders (the northern part of Belgium). In a total population of 20 million inhabitants, this figure represents 4 patients a year or a rate of 0.2/million inhabitants. The comparison of the first period (1971–1981) with the second one (1982–1991) gives the same rate of 0.2/million and shows no decline. The figures are also known for the United Kingdom, 0.3/million (1985–1989), and Australia and New-Zealand, 0.2/million (1986–1989) (adapted from[16]). Psychosurgery is clearly being practised on a very limited, selective and restrictive basis. Extrapolated for the US, this rate of 0.2/million would amount now to around 43 cases a year.

Valenstein[50] estimates from surveys that approximately 35,000 psychosurgical operations were performed in the US from 1936 through 1978. The figures for the year 1971–1973 are approximately 400 per year[10], i.e. 1.8/million inhabitants and obviously higher than in The Netherlands and Belgium for the same period. In the US, such strict legal conditions have been imposed that the practice of psychosurgery is virtually banned.

In the UK a mean of 144 operations has been performed per year between 1974 and 1976, i.e. 2.6/million, and 41 operations for the period 1980–1984, i.e. 0.7/million. This figure dropped to 19 per year for the period 1985–1989, giving a base rate of 0.3/million inhabitants. Legal requirements make it more difficult for patients to have access to this form of treatment. Section 57 of the England Mental Act 1983 refers to "any surgical operation for destroying brain tissue or destroying the functioning of brain tissue" and empowers a Mental Health Act Commission including non-medical people to regulate psychosurgery[33,45].

In Australia and New-Zealand the mean estimated yearly number of operations performed between 1980 and 1989 was nine, i.e. 0.5/million inhabitants[16]. There was a sharp drop from 0.8/million for the period 1980–1984 to 0.2/million for the period 1985–1989. As already mentioned this decline is not observed in The Netherlands and Belgium, but the

frequency of psychosurgical operations has always been lower, even in the 1970's in these countries.

Psychosurgery has been prohibited in the former USSR by a special order of the Ministry of Health dated 09.12.1950. The (political) alleged reason was that "the use of prefrontal leucotomy in the treatment of neuropsychiatric disorders contradicts the basic principles of Pavlov's physiologic theory"[28]. The same author[28] mentions a Russian publication of 1991 on stereotactic cingulotomy in obsessive compulsive disorder. Psychosurgery has been resumed in Russia but more precise information is lacking.

1.4. Ethical and Legal Issues

The Committee on Psychosurgery defined over the years its position on ethical problems associated with this procedure. An agreement was reached on the following rules: (1) psychosurgery must be therapeutic and not experimental, (2) it is a treatment of last resort and (3) special attention must be given to the problem of consent.

The Committee is basically concerned with the treatment of apparently intractable psychiatric disorders and not with the development of new experimental methods. Research is not the main issue; the Committee has to distinguish between acceptable treatment and experimental procedures. The therapeutic purpose is indeed the ultimate legal basis to justify any act by which a surgeon invades the bodily integrity of a patient[45]. On the other hand we consider it our duty to gather medical information about the treated patients to enhance our knowledge in this field. Research on new surgical methods (for instance, intracerebral stimulation instead of destruction), new cerebral targets or new psychiatric indications must follow the specific rules of medical experiments on patients. That means, among other things, a research protocol approved by an official committee on medical ethics.

The irreversibility of psychosurgery is another matter of major concern. All intracerebral surgical procedures destroy brain tissue. Psychosurgery is therefore a therapy of last resort. All available therapeutic alternatives must have been utilized, without lasting or adequate results. The general principle is that reversible therapies must have failed before using irreversible ones. These include appropriate psychotherapy and biological therapies, such as drug and, if indicated, electroconvulsive therapy. Psychosurgery is never an emergency procedure. We take time to decide, and the requirements are such that all patients under consideration for psychosurgery have a long history of many years of distress on account of their psychopathology and as many years of therapeutic failures.

The patient's proper consent is obviously an absolute condition for psychosurgery. This issue receives a lot of attention; we require also the consent and explicit formal agreement of the nearest relative as well as that of the therapist in charge of the patient. Indeed, some patients have requested psychosurgery without the backing of their therapist. We ask for consensus among all persons, professional and lay, involved in the post-surgical treatment of the patient. The aim is to ensure a positive attitude and avoid dissenting opinions. Some patients could not give their consent for psychosurgery because of their psychopathology: some being too anxious to make such a decision, others too fixed in their doubts and indecision. Whenever a patient declines our advice for psychosurgery or when the patient's consent was only questionably positive, we always accepted and respected their choices, regardless of the motivation – healthy or pathological. Prisoners and involuntarily committed patients cannot be considered as they are not in a position to make free choices. For incompetent patients, the legally appointed guardian and therapist in charge must give their consent, after consultation. Even in these cases the patient's consent is requested as far as possible. Thus, psychosurgical treatment requires the consent of the patient, of his nearest relative, of his therapist and a positive recommendation from the Committee on psychosurgery.

In The Netherlands and Belgium no official regulations or restrictions are specifically applicable to this form of treatment. The Dutch Health Council, at the request of political authorities, and after extensive enquiries and repeated hearings, issued in 1990 a paper on psychosurgery (Neurosurgical treatment of patients with severe psychic disorders,[13]). They considered the existing Committee on psychosurgery as a good example of successful selfregulation of a delicate problem by professionals. They recommended giving official and formal status to the Committee and extending its membership with an ethicist, a lawyer and a member of the health commissioner's office. The Belgian Biomedical Ethical Committee of the National Institute for Scientific Research issued a similar statement in 1991[4]. However it did not demand the presence of non-medical people in the review board. As a result of the above mentioned developments and official recommendations no psychosurgical treatment occurs unless these Committees approve the procedure.

1.5. Committee on Psychosurgery

In the early 1970's Dutch and Belgian psychiatrists felt the need to pool their experiences in the treatment of patients with obsessive compulsive disorder (OCD) resistant to therapy; neurosurgeons with experience in stereotactic

methods were consulted. It was agreed that an individual psychiatrist could not – single handedly – develop sufficient experience to establish accurate indications for psychosurgery; neurosurgeons should not operate on psychiatric patients without adequate psychiatric expert advice and adequate psychiatric follow-up care. As a result the above-mentioned Committee on Psychosurgery was established, starting with the difficult problem of therapy-resistant chronic obsessive compulsive patients.

The Committee is an independent group of individual medical experts, neurosurgeons, psychiatrists and clinical neurophysiologists. It functions as a third opinion for the patient and his therapist, submitting the case for review. The following aspects are considered in each case: (1) that psychosurgery is an acceptable treatment for the actual psychiatric condition of the patient (accuracy of diagnosis and intensity of patient's suffering), (2) that all adequate therapeutic measures have been applied and proved to be ineffective, (3) the proposed target area in the brain is appropriate, (4) the proposed neurosurgeon and surgical unit is competent to perform the planned stereotactic intervention, (5) the availability of adequate pre- and post-operative psychiatric evaluation and treatment, (6) that the patient, his nearest relative and therapist will consent to the treatment after adequate information is given.

Only a formal stereotactic surgical method is used for this indication. All the previous more crude surgical methods are now part of the history of medicine. The same holds true for most of the medical literature related to these now-abandoned surgical methods.

For each submitted case a positive or negative advice as to psychosurgery is given. The decision of the Committee is advisory and not in itself mandatory. It may nevertheless be considered as binding advice. A positive recommendation means that psychosurgery may be performed in the submitted case but this is not obligatory, while negative advice means that surgery should not be performed. This decision is thus made when consensus is reached; we are of the opinion that approval by the majority of the Committee members may also be acceptable.

1.6. Committee on Psychosurgery: Patient Material

The authors reviewed all referred cases (N = 111) to the committee on psychosurgery between 1971 and 1991. For 84 of these psychosurgery was recommended, and was not advised in 27 cases. Of these 84 patients, 73 agreed to surgery and were subsequently operated upon. Eleven patients refused psychosurgery for various reasons and they constitute a tentative

control group, allowing comparisons – to some extent – between these two groups (Table 1).

One author (J.C.) operated on 6 OCD patients – all anterior capsulotomy – and joined the Committee later on. The total of operated patients is thus 79 (73 from the Committee and 6 from J.C.).

Table 2 shows the different types of operations performed for the two main psychiatric categories. All the data of this monograph originate from this patient material.

Table 1

	Committee on psychosurgery		
	Positive advice	No positive advice	Total
Surgery performed	73	0	73
Surgery not performed	11	27	38
Total	84	27	111

Table 2

Operated psychiatric patients (N = 79)			
OCD and anxiety. disorders	N	Aggressive conduct disorders	N
Progressive leucocoagulation	11	thalamotomy	16
Subcaudate tractotomy	33	amygdalotomy	12
Anterior capsulotomy	7		
Total	51		28

2. Stereotactic Techniques

2.1. Psychosurgery in Obsessive Compulsive Disorder

2.1.1. Introduction

For obsessive compulsive disorder many targets and types of operations have been used, out of which only four are accepted nowadays as effective. These are the cingulotomy, the subcaudate tractotomy, the limbic leucotomy and the anterior capsulotomy. Knight[21] described his technique (1964) in which the lesion is placed in the medio-postero-basal part of the frontal lobes. This has often been called the substantia innominata but more recent neuro-anatomical research[43] has shown that the lesion is still anterior to the actual substantia innominata. Therefore the term subcaudate tractotomy is more appropriate. Later Kelly[20] described the so called limbic leucotomy which adds to the former target a second one bilaterally in the anterior cingulum. In the United States cingulate bundle lesions were described by Meyer[34] and Ballantine[2,3].

It has been seen and demonstrated by Meyer and Beck[35] on autopsy cases that the best results in frontal lobotomy were encountered when the fronto-thalamic projections were interrupted. Therefore Talairach[49] performed limited electrocoagulations of the thalamo-frontal fibers at their sprouting from the anterior limb of the internal capsule. This led Leksell in 1952 to the so called stereotactic bilateral anterior capsulotomy. The first series with long term follow-up was published by Herner[17]. He demonstrated that the best indication for anterior capsulotomy is anxiety and obsessive compulsive disorder. The most recent analysis of the results of anterior capsulotomy is to be found in the thesis of Per Mindus[39].

2.1.2. Anterior Capsulotomy (AC): the Operative Technique Followed by Caemaert

Psychosurgical interventions for obsessive compulsive disorder are nearly always carried out under local anesthesia. Usually the patients were very co-operative and added the risk of general anesthesia was not necessary. More important is that intra-operative stimulation and control over the progressive extension of the lesion require a conscious patient. Depending upon the stereotactic instrument used, the patient is positioned on the operation table or simply in his bed. In the past the targeting was done on air-ventriculography as described by Meyerson[36]. His target was then on the anterior extension of the ACPC line 13 mm anterior to the AC and

18–20 mm lateral to the midline. He stresses however that air-encephalography may displace the internal capsule laterally. Nowadays CT-scan makes a visible target from the anterior internal capsule, so that it can easily be used for the determination of the coordinates[37]. The fibres form a horizontally orientated tract connecting the frontobasal cortex with the anterior thalamus, by way of the anterior limb of the internal capsule. The anterior limb of the internal capsule is found on an axial section of the brain between the head of the nucleus caudatus and the nucleus lentiformis (consisting of putamen and globus pallidus) (Fig. 1). It is a relatively narrow strip of white matter containing mainly the reciprocal fronto-thalamic pathways and the efferent frontopontine pathways running towards the precerebellar pontine nuclei. In its basal parts the connections of the basolateral amygdaloid nuclei with the prefrontal cortex[19], and the pyriform cortex[7] are also present.

An axial CT examination is made with 4 mm thickness slices. The targeting is carried out on the slice at the level of the foramina of Monro, connecting the frontal horns of the lateral ventricles and the third ventricle. It is always carried out bilaterally. The target is the funnel-like area between the head of the caudate nucleus and the putamen. When the contrast between grey and white matter is insufficient it may be difficult to localize

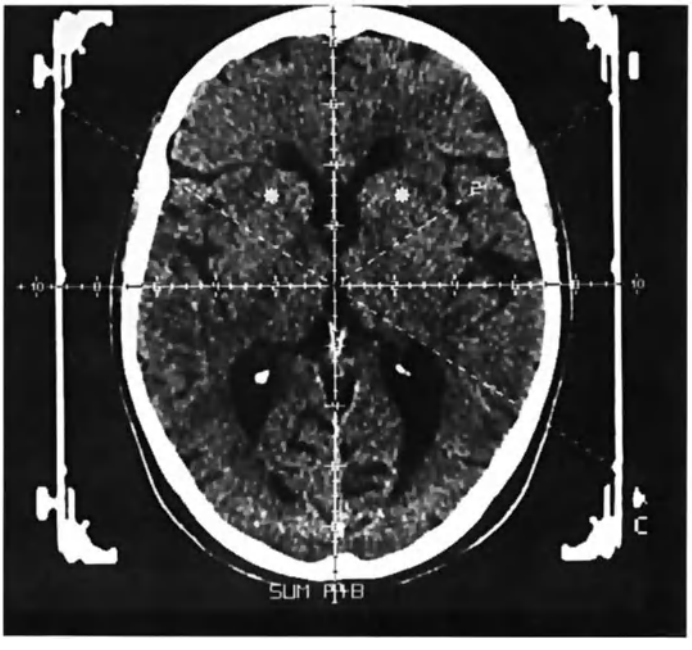


Fig. 1. Stereotactic targeting of the anterior capsule

the target. It may be helpful in such cases to make exactly the same CT slice twice and to superimpose these two images by help of the CT-software. The result is usually better than when only the contrast (center and window) is changed. When available, MRI gives additional information on the angle in the coronal plane. This will be about 20° to the sagittal plane. The determination of this angle can also be made on a frontal (coronal) reconstruction of the stereotactic CT scan, but this is less clear than on MRI.

The inferior extent of the planned lesion is easily determined by measuring the point where the Nc. caudatus and the putamen merge in the fundus striati (Nc. accumbens). From the target the measured distance should be added (usually target +8 to 10 mm).

It is wise to mark the burr holes on the skin through the stereotactic guidance under this angle in order to stay far enough from the midline.

The patient is then returned to the operation room. A limited area is shaved bilateraly, just in front of the coronal suture. The incision is always within the limits of the hairy scalp and becomes invisible after a few weeks. The hair and skin are thoroughly prepared with alcohol and the skin at the level of the incisions is additionally prepared. Draping is arranged in such a way that only the limited bare skin areas are free. The angle of the stereotactic arc in the sagittal plane will be about 90° from this pre-coronal burr hole towards the target. Two burr holes are drilled under local anesthesia. The dura mater is coagulated and then incised in a cruciform way after which the four flaps are coagulated additionally to prevent the coagulating electrode from touching the dura, or it may be excised completely.

The coordinates, pre-determined on the CT-scan, are adjusted on the frame. It is very important to communicate with the patient during the operation and even to explain a little bit the different steps and progress in the intervention. The coagulating probe is connected to the lesion generator and introduced in the cerebral cortex through the appropriate stereotactic guidance. Recording of the impedance is used to check the patency of the current circuit. The probe is now advanced to target. Stimulation at low and high frequency produces no effect at all, in and around this target but can be performed as a safety control.

Coagulation is then carried out by heating to 80° C for 60 s. The number of coagulations depends upon the type of electrode used but a lesion should be created of 20 mm length (supero-inferiorly) and 8 mm width (latero-laterally). The same procedure is carried out at the other side in exactly the same way. During the different steps one should ask the patient various questions and allow him to relate his experiences. We prefer the presence of a member of the psychiatric team, involved in pre- and post-operative treatment. Usually the patient does not feel anything special but in many cases very soon after the second coagulation the patient becomes to a

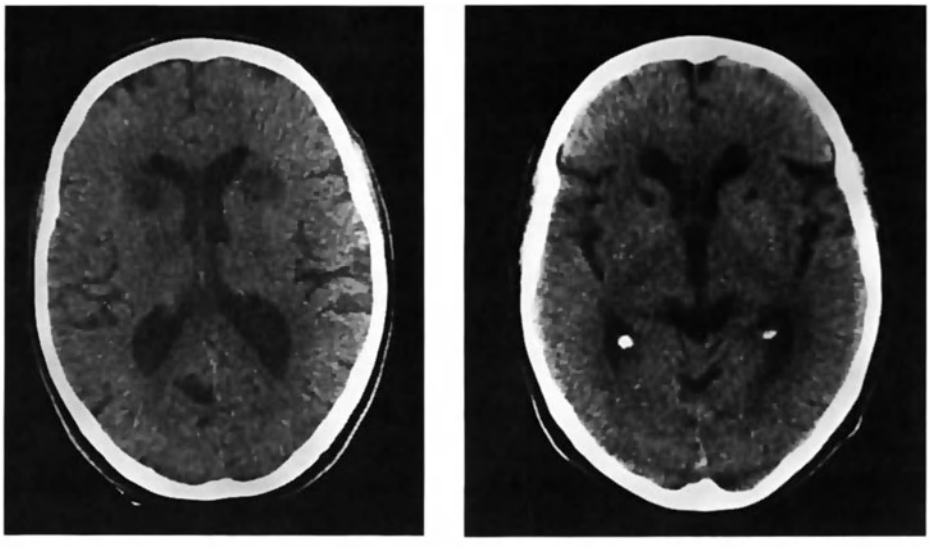
varying extent confused, most often mildly. This confusion is nearly always transitory, and some surgeons believe that it indeed predicts good outcome. The patient is then returned to the recovery room for 1 hour and subsequently to his room. Caemaert prefers to give antibiotic prophylaxis (amoxicilline/clavulanic acid during 24 hours) because the small area of brain necrosis after electrocoagulation might be more susceptible to infection.

Complications. There are very few complications associated with anterior capsulotomy. No mortality has been reported in the literature and none has occurred in our patients. Meyerson[38] reports 2 subcortical haemorrhages with transient slight hemiparesis and somnolence. In one of his cases a hematoma developed in the anterior internal capsule requiring temporary ventricular drainage. An interesting review of the vascularisation of this region is given by Marino[30]. Full recovery was seen in all cases. He describes one case of late epilepsy attributed to the intervention. In our limited series of eight operations there was no morbidity.

Postoperative care. The psycho-emotional stress of the intervention for the patients is easily under-estimated; in the first few days post-operatively the patients need rest. The confusion seen in some patients always subsides in a couple of days. In successful cases, a decrease of the anxiety level is often seen very soon after the operation, and although obsessions and compulsions can continue, they are experienced by the patient as much less threatening and anxiogenic. Depending upon the individual case, the patient is transferred to the psychiatric department after a couple of days to one week. From now the importance of continuing psychotherapy cannot be overemphasized. Postoperative CT and MRI controls show a much larger lesion after 1 week than after 6 months (Fig. 2). This is due to perilesional oedema in the first period. This might be the explanation in some cases why, after an initial improvement, a recurrence of symptoms is seen, followed by a secondary slower and progressive improvement.

Often a period of decreased initiative is observed starting two to four weeks after the intervention. The role of the psychiatrist to "fill the gap" should start now and continue for a long period. Sometimes, however, we have observed a lasting decrease in "drive" and initiative.

Meyerson[36] states that there is no tendency to relapse over time. Any recurrences are within one year from operation. A second intervention with extension of the first lesion may in some patients relieve symptoms, as reported by Burzaco[6]. In a series of 85 cases a reintervention was necessary in 17 cases out of which 52% improved significantly after this second operation.



a b

Fig. 2. Internal capsule lesion after radiofrequency electrocoagulation visualized by CT-scan. (a) Early (one week after operation), (b) late (one year after operation)

2.1.3. Subcaudate Tractotomy (STC)

2.1.3.1. Technique followed by Gybels

After fixation of the head in the stereotactic frame, bony landmarks were identified as reference structures for determination of the coordinates. The target is localized 1 cm above the skull base plane (orbital roof and planum sphenoidale). This lies 5 mm anterior to the anterior border of the sella turcica (Fig. 3). Initially the target was situated at 3 mm anterior to the sellar border, but since the time that the CT-scan showed the very near proximity of the anterior cerebral arteries the target was moved 2 mm more anteriorly. Originally Knight[21,22] described the use of radio-active yttrium 90 rods. A necrotic dose of beta-irradiation up to 2 mm from the seeds surface was delivered.

The lesion can also be produced by the formation of a series of small coagulations at multiple points. This method was followed in the present series. A minimal width of the lesion is necessary to isolate a sufficient zone of cortex. Three trajectories are followed at 12, 15 and 18 mm from the midline. This creates a lesion between 10 mm and 20 mm laterally. Coagulations are done at target, -6, -12 and -18 so that the rostro-caudal extent

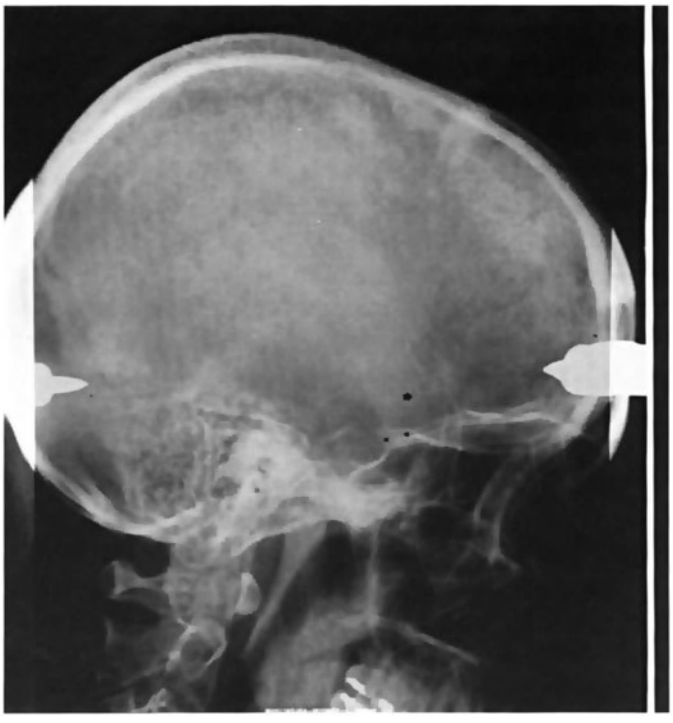


Fig. 3. Bony landmarks for subcaudate tractotomy of Knight

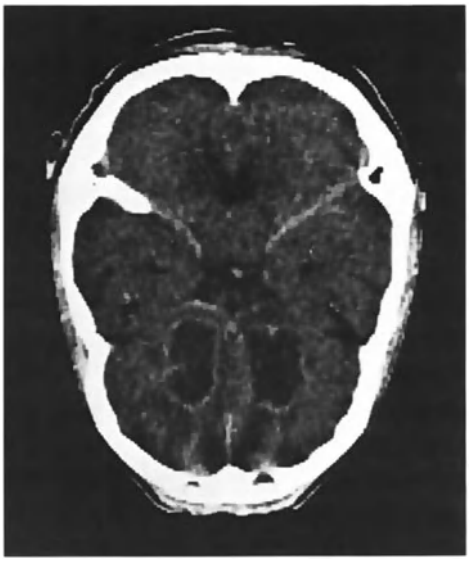


Fig. 4. Subcaudate tractotomy of Knight on axial CT-scan after extension of the lesion

of the lesion is 2 cm. If necessary a second operation to enlarge the lesion is carried out on two additional trajectories on 10 and 22 mm lateral to the midline, and 10 mm more anterior from the first target. Coagulations are then carried out at target −6, −12 and −18 on the medial trajectory, and on target −4, −8 and −12 on the lateral trajectory (Fig. 4). The importance of a low approach is stressed by Knight in order to prevent damage to the caudate nucleus itself. He described a case with fatal outcome from a lesion that entered the striatum[24].

Stimulation. Stimulation (pulse width 1 ms, frequency 3 and 100 Hz and amplitude 0.1–2 mA) in different target points prior to coagulation does not elicit any psychic or emotional effects in subcaudate tractotomy. Respiratory and cardiac accelerations have been observed with stimulation (2 mA 100 Hz) at T-5 in two cases.

2.1.3.2. Technique followed by van Manen and van Veelen

In the majority of the cases air-encephalography was used to localize the target point. The lesions were made by means of temperature-controlled diathermy. The diameter of the electrodes was 2 mm, the tip-length amounted 2–3 mm. Sometimes bipolar lesions were made using two parallel electrodes, electrode distance 6–8 mm. The lesions were almost spherical with a diameter of 6–7 mm at 70° C, ±8 mm at 80° C and 9–10 mm at 90° C.

The operations were performed under general anaesthesia. The burr holes were made through the electrode holder after target localisation. The skull was shaved only in the direct vicinity of the intended hole and only a very short incision was made. The frontal holes could always be made above the frontal sinuses in van Manen's series.

During the procedures electrical stimulation was never used. Post-operatively antibiotics and steroïds were not used.

Subcortical lesions in the orbitofrontal area were localized according to the description of Knight[22] or Newcombe[44].

First the van Manen stereotactic frame was used (van Manen 1967) and later the BRW (Brown Robert Wells) apparatus.

Proceeding from a line starting at the tuberculum sellae along the orbital roof on a lateral radiograph a point was chosen 5–7 mm in front of the tuberculum sellae and 10 mm perpendicular above this line (Fig. 5).

Knight supposed this point to be localized in the substantia innominata, but this is fortunately not the case because that area is localized above the anterior perforated substance, a highly vascularized area, lying more posteriorly, and thus somewhat deeper along this approach.

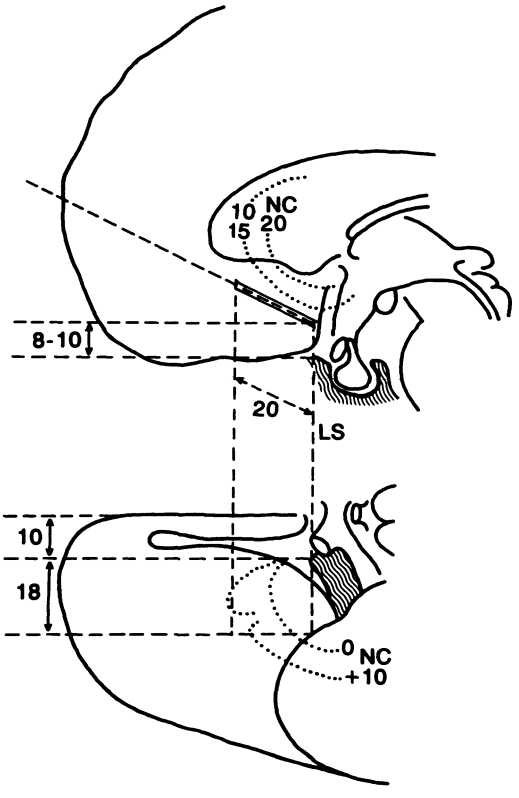


Fig. 5. Localization of Knight's subcaudate tractotomy as performed by van Manen

The zone starting from 5 mm in front of the tuberculum and extending from 10 to 28 mm from the midline and up to 20 mm in the frontal direction, parallel to the orbital roof is situated under cortical area 13 and part of area 14, as Knight mentions. Newcombe described a slightly different target point, namely 9–10 mm above the planum sphenoidale (PS) and perpendicular above the limbus sphenoidale (LS). This point appears to be localized approximately 5 mm in front of the target of Knight and is probably somewhat safer.

In this zone a double row of lesions was made, 6–8 mm apart and consecutively 3 mm behind each other, the deepest lesions at 70° C and the more frontally lying ones at 80°–90° C.

In determining the desired site of the lesion, the inferior border of the frontal horn was of assistance in the choice of the position of height and angle of the target line above the orbital roof in order to spare the head of

the caudate nucleus as well as the orbital cortex. In the latero-posterior extension of the lesion the uncinate fascicle can be damaged but this could be a favourable circumstance for the effect of the operation. An insufficient lateral extension of the lesion seems to lead to less favourable results. The main purpose of this rather deeply localized lesion is to interrupt the connections between the dorsomedial (MD), intralaminar (i.La.) and reticular thalamic nuclei on the one hand and the orbito-frontal cortex on the other hand. Bilateral operations were always performed in one session.

2.1.4. Surgical Complications of Subcaudate Tractotomy

The "leucotomy-syndrome" formerly seen after open surgery is not as a rule encountered after subcaudate tractotomy. In Gybels' series case 18 was complicated by an intracerebral hematoma in the upper frontal region paramedially at the right side. The patient had an epileptic attack after drilling of the burrholes. The patient recovered but showed a marked apathy, indifference, frontal ataxia, nystagmus by lateral gaze direction and a very pronounced snout reflex. Because of this complication no subcaudate tractotomy was performed in this patient but it is remarkable that his obsessive compulsive disorder resolved permanently after this intrafrontal hemorraghic complication.

In van Manen's series there was no mortality and no major morbidity. During the first days up to two weeks postoperatively the following side effects were seen: somnolence in 1 patient, confusion in 1 patient, excitation in 3 patients.

2.1.5. Technique of Progressive Leucocoagulation Followed by van Veelen and Haaijman

Methods. The psychosurgical technique of Crow, Cooper and Phillips[9] and Crow[8] has been used in 9 patients. By means of specially designed intracerebral depth electrodes lesions were made by electrocoagulation (5 mA 1 min, 10 mA 3 min, 20 mA 3 min) in white matter only. The lesions are gradually extended according to clinical effects. The electrodes are left in situ for about 7 months. Before coagulation is performed, records of the spontaneous electrical activity of the brain obtained from the depth electrodes indicate whether an electrode is situated in white or grey matter. This is further evaluated by means of electrical stimulation of the electrodes with 40 HZ (4 to 10 volts) current for 10 to 15 seconds. Stimulation of grey

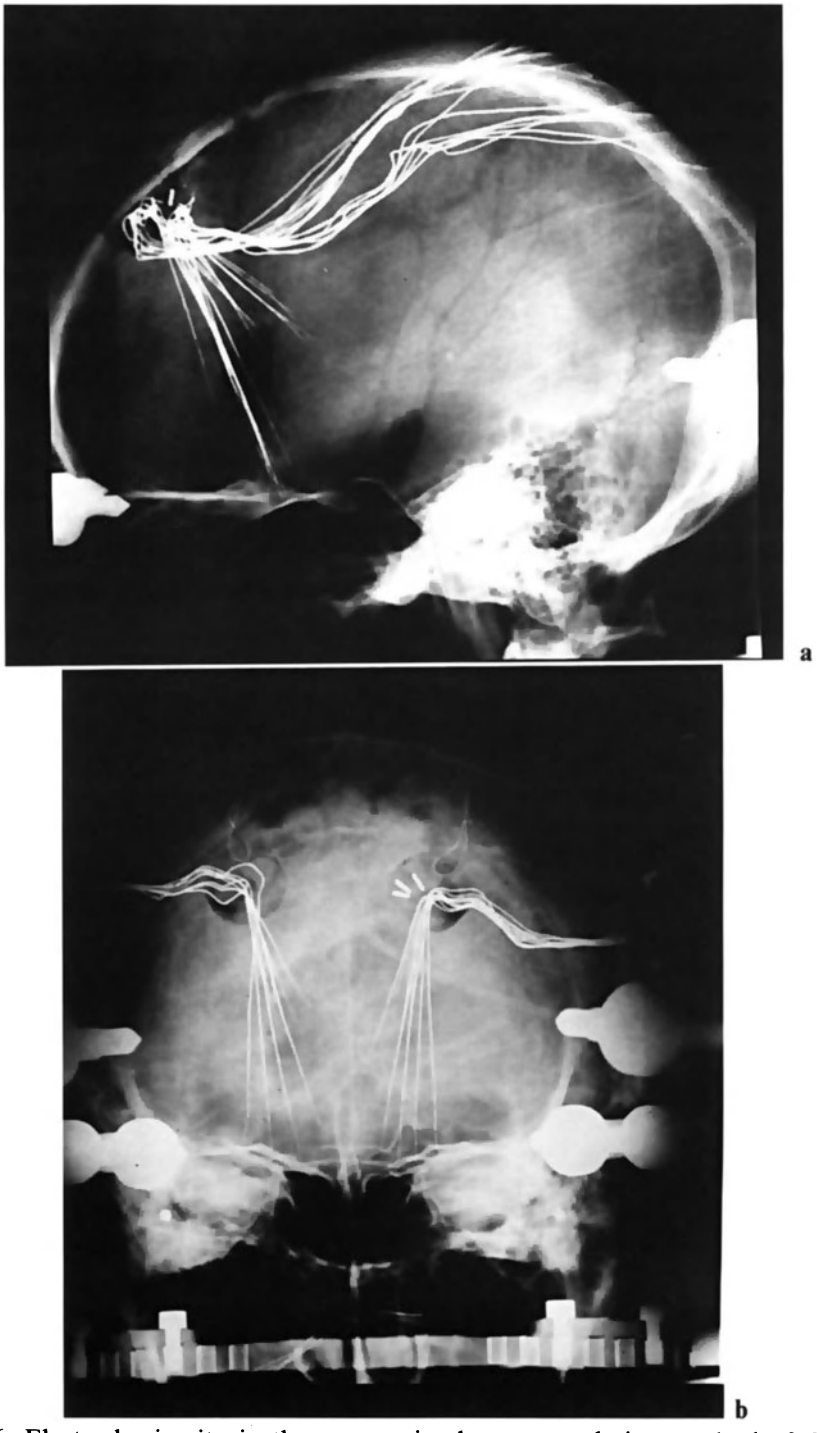


Fig. 6. Electrodes in situ in the progressive leuco-coagulation method of Crow. (a) Sagittal, (b) antero-posterior view

matter results in after-discharges. At the same time possible psychological and behavioural changes are investigated.

Figures 6a and b show the electrode bundles situated in the brain. The electrodes, each 4 mm in length, run in bundles and are placed 4 mm apart. Within the bundles the electrodes are intertwined and separated by insulating material. Based on data derived from Ballantine *et al.*[2] and Meyer *et al.*[34] an extra bundle of 4 electrodes was added and aimed at the region of the anterior cingulate area. Thirty-eight electrodes were placed in each hemisphere, the large number being necessary because of imprecise knowledge of the exact anatomical points at which coagulations should be directed.

Four areas are established as sites of lesions (Fig. 7). Area 1 comprises electrodes (4 to 6 lesion sites) in the radiations of the corpus callosum. Area 2 comprises electrodes (6 to 8 lesion sites) in the paracingulate white matter. They also lie in the radiation of the corpus callosum. Area 3 comprises electrodes (3 to 5 lesion sites) in the orbitofrontal white matter. Area 4 comprises electrodes (2 lesion sites) in the cingulum. The bundle passes through the posterior part of the rostral third of the corpus callosum. The electrodes are implanted with a specially designed stereotactic frame. The lesions are made with a special apparatus of own design. The average size of each lesion is $7 \times 4 \times 4$ mm.

Results. There were no direct complications of the implanted electrodes. One patient died of CO-intoxication when taking a shower at home during the

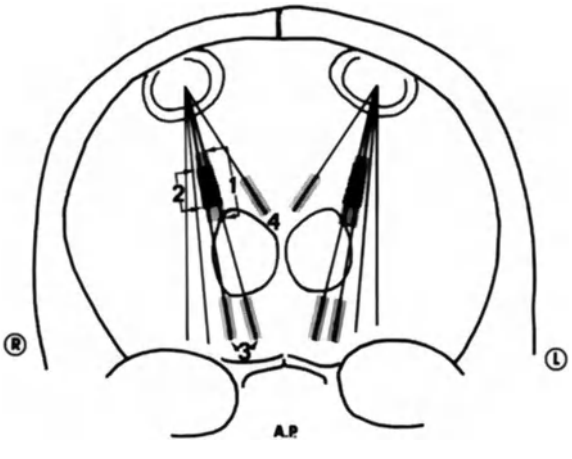


Fig. 7. Localization of the coagulation areas in Crow's progressive leucocoagulation. AP view

course of her psychosurgical treatment. At post mortem investigation the coagulation lesions were investigated. The size of the biggest individual lesion in the slices was 7 × 4 mm. In the walls of some veins lymphocytic infiltrations were found. They were evenly scattered through the white matter of the brain. These findings could not be adequately explained.

2.2. Psychosurgery in Aggressive Conduct Disorder

Among several targets for the stereotactic treatment of aggressive conduct disorders, only two types of operation are used in our group (Table 2).

2.2.1. Intralaminar (i. La.) and Dorsomedial (MD) Thalamotomy

The lamella medialis containing the intralaminar nuclei, is situated as a rather thin mantle around the dorsomedial nucleus. The most extended part is the anterior bulge at the lower anterior pole of the dorsomedial nucleus. This bulge proceeds forward along the medial border of the mammillothalamic tract of Vicq d'Azyr in the direction of the inferior thalamic peduncle, as is clearly visible on the horizontal myelin sheet series (plate 52) in the atlas of Schaltenbrand and Wahren[46].

Antero-laterally the lamella borders the nucleus ventralis oralis internus (v.o.i.) and ventrally the hypothalamic area. Because of this localisation and the narrow diameter, it is very difficult to make a lesion confined to this nucleus. Extension of the lesion into the mammillothalamic tract should be avoided in our opinion. Irreversible memory disturbances and disorientation can ensue. Extension of the lesion into the v.o.i. nucleus is advocated by Hassler[15] in cases of motor compulsions like tics, cries and coprolalia (Gilles de la Tourette syndrome). Lesioning of the dorsomedial nucleus in its mediolateral part is essential to obtain the desired effect.

2.2.1.1. Technique followed by van Manen

For hyperaggression, mostly in oligophrenic patients, the operation should be carried out under general anesthesia. Air encephalography was always used for localisation of the target.

The lesions were always made bilaterally in one session. Electrodes and lesion diameters in relation to applied temperatures were as mentioned in the paragraph on subcaudate tractotomy.

Three targets and approaches were chosen.

a) A frontal approach (Fig. 8) with an angle of 60–70° to the foramen of Monro-commissura posterior (FM-CP) line and with an angle of 10–15° to the mediosagittal plane. Two parallel electrodes were directed to a target 7 mm behind FM, 1 mm above FM-CP and 2,5 mm from the wall of the 3rd ventricle and a second target 14 mm behind FM, 4 mm above FM-CP and 4 mm from the ventricular wall laterally. These targets are located anteriorly respectively posteriorly to the mammillothalamic tract, the first one in the lamella medialis, the second in the dorsomedial nucleus. Only a small lesion (70° C at the target and 2 mm. above and below) can be made at the first and a larger lesion, encroaching also upon the lamella medialis at the second point (85° C at the target and 3 mm above, and 70° C 2 mm below).

b) A second approach (Fig. 8) reached a target point 10,5 mm behind FM, 1 mm below FM-CP and 4 mm lateral from the third ventricular wall, at an angle of 70° from posterior to the FM-CP line. Along this electrode-track coagulations were made at 70° C at the target point and 2 mm dorsally and 80° C at 4, 6 and 8 mm dorsally. This lesion was considered to start at the lamella medialis, a short distance behind the mammillothalamic tract and to include the dorsomedial nucleus as well as the lamella medialis in its dorsal extension.

c) Finally a row of lesions (Fig. 8) was made along one electrode track at 2 mm relative distances at 70°, 80°, 80°, 80° and 80°. This track leads

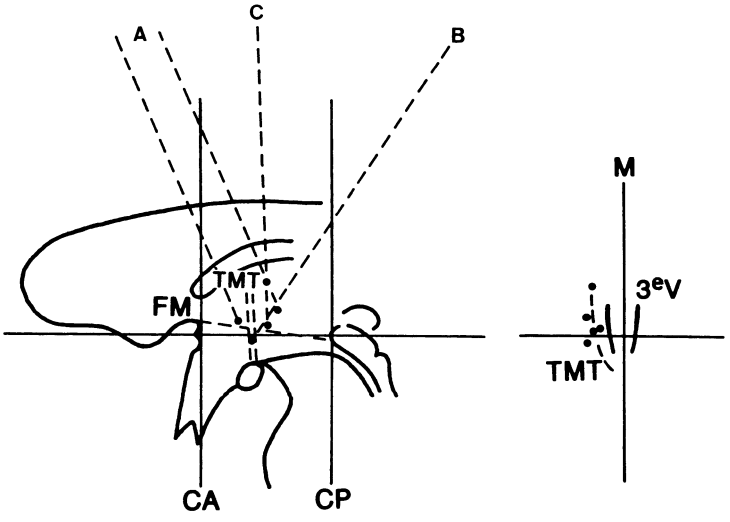


Fig. 8. Schematic diagram of the medio-dorsal and intralaminar thalamotomy as performed by van Manen

from a point 13 mm behind FM, 1 mm above FM-CP and 2 mm laterally from the third ventricular wall to a second point with coordinates respectively 10.5, 10 amd 4 mm.

Because of the unpredictable outcome of these operations and the small number of interventions undertaken, it was impossible to decide which of the three approaches is the most advisable. Anatomic controls are missing since none of the patients died. Although deterioration was fortunately never seen, as a consequence of these uncertainties the utmost reservedness concerning the use of this operation should be maintained.

2.2.1.2. Technique followed by Gybels

Peroperative ventriculography was performed with a combination of air and positive contrast medium (initially Lipiodol R, later Metrizamide).

An electrode with a 5 mm bare tip was used for coagulation at 70° C during 60 seconds creating a lesion of 2,5 to 5 mm. A parieto-occipital burr hole was made so that the trajectory was angulated about 55° to the AC-PC line (Fig. 9).

The target was situated 1 mm superior to the midpoint of the AC-PC line and two trajectories were made. On a laterality of 4 mm from the midline serial coagulations were made at target + 5 mm, target, and target − 5 mm. On a laterality of 6 mm from the midline coagulations were made at target, target − 2 and target − 5 mm. The lateral trajectory started more dorsally to avoid destruction of the tractus mammillothalamicus of Vicq d'Azyr.

2.2.1.3. Complications

Van Manen's and van Veelen's series: In 10 operations somnolence and dysarthria were seen in 3 patients, somnolence and hemiparesis in 1 patient. This hemiparesis persisted to a mild degree.

Gybels' series: In 6 patients 10 operations were performed, 4 bilaterally, 2 unilaterally. In one case transient confusion, memory disturbance and unilateral tremor were seen in the immediate post-operative period. In another case a pronounced supratentorial hydrocephalus developed two months after the second operation. The patient was admitted in a subcomatose state. Ventriculography showed an aqueduct occlusion and after insertion of a ventriculo-subcutaneous drain the patient recovered; a definitive shunt of the ventriculo-peritoneal type (Hakim medium pressure valve) was subsequently placed.

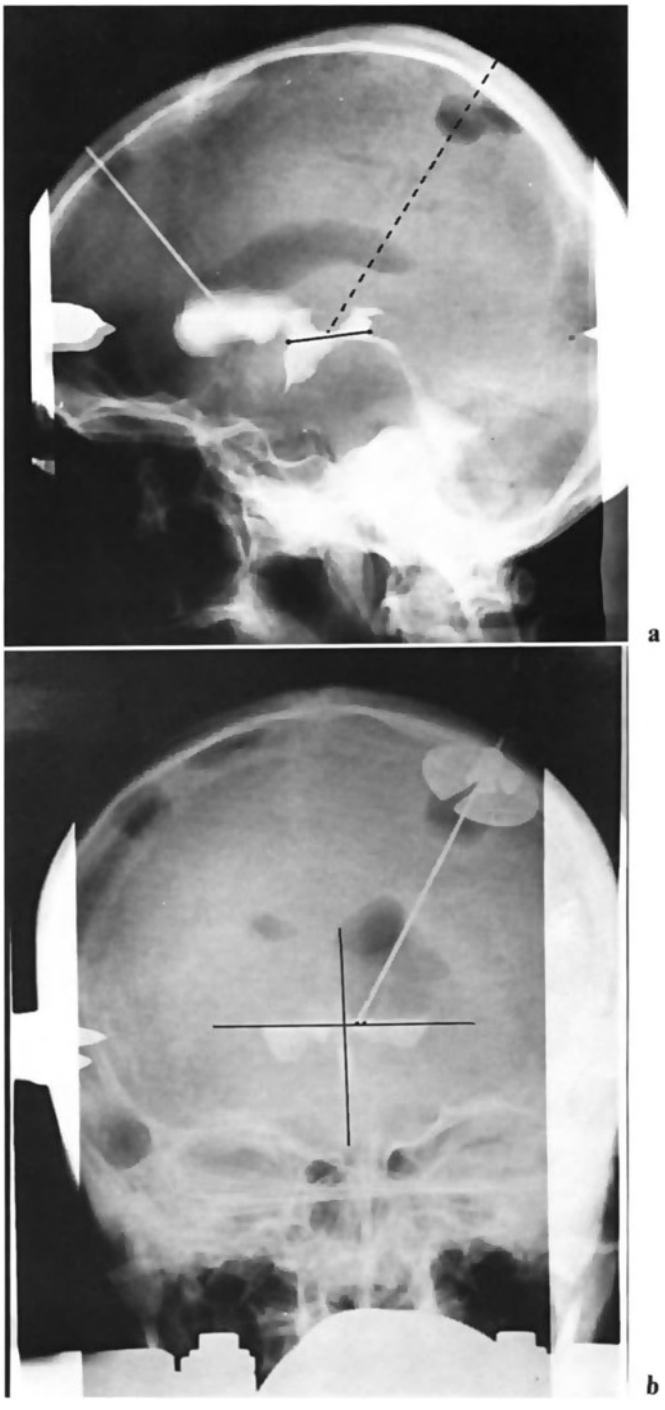


Fig. 9. Ventriculography. (a) Lateral view. (b) AP view for medio-dorsal and intralaminar thalamotomy as performed by Gybels

In a third case on the fifth postoperative day the patient had to be operated for a bleeding from a pre-existing gastric ulcer.

2.2.2. Amygdalotomy

2.2.2.1. Introduction

The anatomical division and physiology of the amygdala is still being studied very extensively and appears to vary greatly among animal species. The oldest, most commonly accepted subdivision describes a cortico-medial nuclear group and a basolateral nuclear group. The lateral part of the cortico-medial nuclear mass is the effective area for treatment of hyper-aggression, according to Narabayashi[41]. This area seems to be very close to or to involve the stria terminalis, which projects into the hypothalamus. Involvement of the basal nucleus remains possible. Narabayashi's surgical technique was based on air-encephalography; the border between the lateral and medial nuclei groups was assumed to be 20 mm. from the midline in an adult Japanese brain. The index of the lateral distance of the lateral extreme of the brain to the midline divided by the adult mean value was used in children for correction of the position of this border. The target was approached from a frontal burr-hole in a slightly postero-medial direction. Neurophysiologic checking of the position of the electrode was performed by recording injury discharges, spontaneous spikes, and olfactory evoked discharges. The medial nucleus receives direct input from the olfactory system through the lateral olfactory tract. The potentials evoked in this nucleus are described as "sharp" and of large amplitude. In the lateral nuclear group these potentials are blunt and of lower amplitude. A thorough investigation of 47 cases showed that amygdalotomy is most effective when the lesion is made in an area 17,5 to 20 mm lateral from the midline. Lesions placed more medially or more laterally were less successful. The calming effects and the effects on the epileptic paroxysmal symptoms were similar in most of the cases. The effective area seems to be related to the elimination of that part of the medial nuclear group that gives rise to part of the stria terminalis which is itself characterized by a prominent projection to the hypothalamus.

2.2.2.2. Technique followed by van Manen

On the A.P. pneumencephalography of the temporal horn the cornu ammonis bulges from the medial side into the horn. The lateral border of

this bulge coincides approximately with the lateral border of the amygdaloid nucleus. A medial and anterior border cannot be established on the pneumencephalography. The medio-lateral dimension of the nucleus measures 13–17 mm. The mean distance of the centre of the nucleus to the mid-plane is 23 mm (21.5–28.5 mm), the mean distance of the lateral border to the mid-plane 30 mm (27–33 mm). The dorso-ventral dimension of the nucleus is 15–20 mm, the ventral border is estimated 2 mm above the most ventral extension of the temporal tip along an axis drawn 2,5 mm in front of the tip of the temporal horn. On this line the deepest target point is chosen 3 mm more dorsally.

In the literature, distinction is made between lesions in the medial and the lateral parts of the nucleus. However as the medial border of the nucleus cannot be delineated on ventriculography van Manen only tried to make lesions more or less centrally placed. Unipolar and bipolar lesions (with two parallel electrodes) were made. The electrode track was chosen at an angle of 10–15° frontal to the main axis of the nucleus, in order to pass the cortex anterior to the motor area and penetrating through the putamen, avoiding the insula with its arborization of the middle cerebral artery. If a single electrode was used, it was directed to the presumed centre. The distance of this centre from the median plane was the X coordinate (latero-laterally). In the case of two parallel electrodes they were introduced at 3 mm distance on both sides of the centre.

3–5 coagulations were made along a maximum trajectory of 15 mm from the target upward with 3 mm intervals; on the deepest location at 70–80°C and at 80–90° on the remaining locations.

2.2.2.3. Technique followed by Gybels

Different techniques were followed during the past 20 years. Originally targeting was performed on ventriculography but nowadays MRI is preferred and only the latter is here described.

MRI targeting for amygdalatomy (Fig. 10a and 10b). The amygdala is quite far from the midline and only the lateral border can be outlined on ventriculography. Therefore it is now preferable to calculate the target positions on MRI. The angle of the axial slices is determined on a mid sagittal slice, according to the line trough the commissura anterior and the commissura posterior. More lateral parasagittal slices and mainly coronal slices allow a first determination of the superior-inferior Z coordinate. The axial slice corresponding to this Z co-ordinate allows us then to measure the X (latero-lateral) and Y (antero-posterior) coordinates.

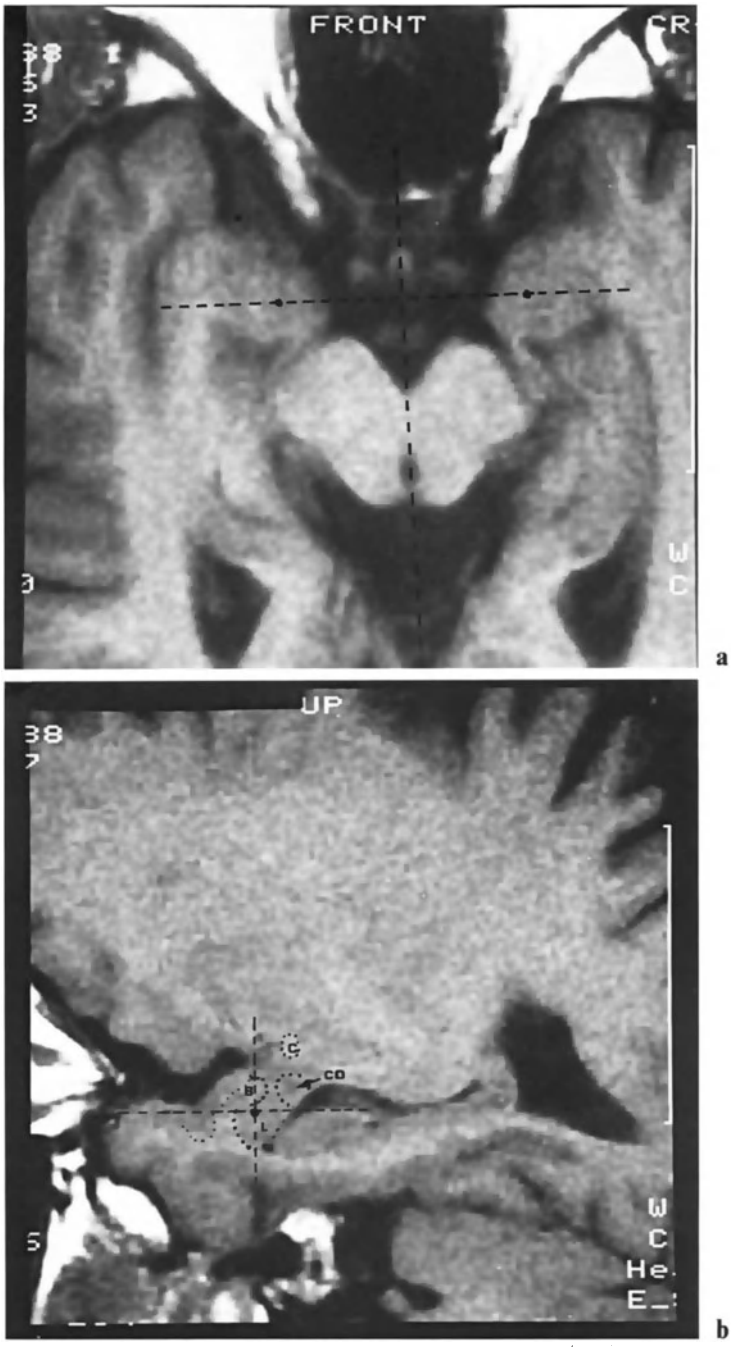


Fig. 10. MRI targeting for amygdalotomy. (a) Axial incidence; (b) MRI localization – a parasagittal view, *C* commissura anterior, *CD* cauda nuclei caudati, *B* basal nucleus, *L* lateral nucleus

3. Patients with Obsessive Compulsive Disorder (OCD)

3.1. Patient Data

71 cases were considered by the Committee on Psychosurgery in the first 11 years and 36 were OCD patients according to the DSM-III (300.30) criteria. We will focus on this patient group because long term follow-up data are available.

General criteria for eligibility have already been discussed and included at least for OCD patients:
- persistent obsessions and/or compulsions during 4 years or more,
- symptoms constituting a significant source of severe personal distress and suffering for the patient and gross interference with his/her normal daily routines,
- failure to achieve significant and lasting positive effects of the usual treatment procedures during sufficient periods of time. These include various forms of psychotherapy, and always intensive behaviour therapy, and psychopharmacotherapy, including the use of clomipramine, at a dose of 100–300 mg/day during a period of at least three months. A majority of patients received also one or more courses of electro-convulsive therapy. All patients had been hospitalised at least during a part of the preceding 4 years, mainly for intensive behaviour therapy as in-patient,
- during the course of OCD depressive episodes may appear; this constitutes no contra-indication for psychosurgery. The diagnosis of OCD implies that the core symptomatology should be present also in the absence of any significant mood changes,
- comorbidity with DSM-III schizophrenic or other psychotic disorders constitutes a contra-indication for psychosurgery. Comorbidity with personality disorders of cluster B – mainly the histrionic, borderline and antisocial personality disorder – needs a very close evaluation,
- the availability of intensive psychotherapeutic treatment following psychosurgery is also a prerequisite for a positive recommendation.

28 patients of the 36 were felt to fulfil the criteria for surgery and 21 were actually operated on: 12 by frontal stereotactic subcaudate tractotomy[23] and 9 by progressive leucocoagulation[9] in paracingular and orbito-frontal areas. 16 patients had adequate follow-up data, 9 following subcaudate tractotomy and 7 following leucocoagulation.

The group of 21 operated OCD patients – mean age of 43 years (27–65 years) – comprises 12 females and 9 males, of whom 10 are married and 4 divorced or widowed. Three patients deceased during the follow-up period: one by suicide and two died of natural causes. Follow-up results were obtained on the average of 7 years (2–9 years) after psychosurgery.

The second group of 7 patients, who refused psychosurgery after a positive advice from the Committee, is comparable with the group of 21 operated patients: mean age of 43 years (27–63 years), one male and 6 females, and follow-up results obtained after an average of 6 years (3–9 years). Only the marital status is very different: no one is married, 6 are divorced or single and one is widowed. One patient of this group committed suicide during follow-up. These two groups will be compared.

3.2. Post-Operative Psychiatric Evaluation

A letter questionnaire was used and the patients asked for permission to approach their therapists. A 6-point scoring scale was offered to them (patient and therapist) covering condition now as compared to pre-operative target symptoms, obsessions, compulsions, anxieties, depressive symptoms, scale covering "the problem is over" (1) to "worse" (6). Open ended questions were added in regards to positive or negative changes as a result of the psychosurgical intervention. Family members were asked to comment on patients overall functioning. The questions addressed the use of psychiatric support, psychotropic drugs, marital and social relationships and participation in daily life.

Table 3. *Follow-up Questionnaire Results of the Study Group of Operated OCD Patients*

Results of operated OCD[b] patients						
Responses from	Patients			Therapists		
Target symptom	Z[a]	P	N	Z	P	N
Compulsions	−1.9	ns	11	−2.5	0.01	10
Obsessions	−2.0	0.04	9	−2.7	0.008	11
Anxiety	−2.0	0.04	8	−2.5	0.01	9
Depression	−1.3	ns	7	−2.4	0.02	7

[a] *Z* Wilcoxon matched-pair signed ranks test; $P \leq .5$ significant; the exact probability is then given or "*ns*" (non significant).

[b] Obsessive compulsive disorder.

Table 4. *Follow-up Questionnaire Results of OCD Patients who Refused Psychosurgery*

Results of OCD patients who refused psychosurgery						
Responses from	Patients			Therapists		
Target symptoms	Z[a]	P	N	Z	P	N
Compulsions	−0.9	ns	5	−1.3	ns	5
Obsessions	−0.5	ns	4	−1.0	ns	2
Anxiety	−0.5	ns	3	–	–	1
Depression	−0.0	ns	4	−0.4	ns	4

[a] *Z* Wilcoxon matched-pairs signed rank test; $P \leq .5$ significant; the exact probability is then given or "*ns*" (non significant).

There were favourable results as far as the target symptoms were concerned. Overall obsessive-compulsive symptomatology fell from 5/6 to 3.5/6 at follow-up according to the patients, and the therapists evaluated the improvement even more, the score dropping from 5.5/6 to 3/6 at follow-up. Table 3 shows the results for the several target symptoms according to the operated OCD patients and their therapists. Generally these results are encouraging in the face of a chronic problem with grossly debilitating effects on the patient's life. None of the patients were in worse condition after psychosurgery.

The seven eligible patients who refused psychosurgery, showed no such improvement (Table 4).

3.3. Comparison of the Results of the Two Stereotactic Techniques (SCT and PL)

Subcaudate tractotomy (SCT) yielded better results than progressive leucocoagulation (PL) (Table 5). The significance of this is doubtful considering the small number of patients, but because the PL technique is more complex and treatment-intensive it has currently been abandoned. For treatment of OCD the group now exclusively use subcaudate tractotomy and anterior capsulotomy.

Table 5. *Comparison of the Results of the Subcaudate Tractotomy (SCT) with These of the Progressive Leucocoagulation (PL)*

Comparison of the results of two neurosurgical techniques							
Responses from	Target symptoms	Subcaudate Tractotomy N = 9 patients			Progressive Leucocoagulation N = 7		
		Z[a]	P	N	Z[a]	P	N
Patient' evaluations	Compulsions	2.02	0.04	5	0.94	ns	6
	Obsessions	1.6	ns	5	1.3	ns	4
	Anxiety	1.6	ns	4	1.3	ns	4
	Depression	0.5	ns	4	1.6	ns	3
Therapist's evaluation	Compulsions	2.02	0.04	6	1.6	ns	4
	Obsessions	2.2	0.03	8	1.6	ns	3
	Anxiety	2.2	0.03	7	1.3	ns	2
	Depression	2.4	0.02	7	–	–	–

[a] *t* Wilcoxon matched-pairs signed rank test; $P \leq .5$ significant; the exact probability is then given or "*ns*" (non significant).

3.4. Post-Operative Psychiatric Evaluation: Particular Clinical Observations

Anxiety and mood improvements precede improvements in obsessional or compulsive symptoms. And change in the latter is generally delayed in time and a direct influence of stereotactic surgery on this performative aspect of behaviour is generally not observed. In only one case could the OCD symptomatology be elicited by electric stimulation in the frontal part of the cingulate gyrus, and lesions in this area resulted in disappearence of the symptoms.

After surgery many patients show an increased sensitivity to anxiolytics and antidepressants and in 7 out of 21 operated cases either no or low doses of psychotropic drugs were reported to have been used. In the non-operated group only 2 out of 15 were without drugs at a year. Does psychosurgery influence the sensitivity of the CNS to drugs? Similar observations have been made in bipolar affective disorder after stereotactic subcaudate tractotomy[29].

Psychotherapeutic treatments previously ineffective became effective after surgery, as for example behaviour therapy. Anxiety level improvement may play a key role here.

Not all patients felt happier despite documented improvement, and personal relationships or family problems sometimes became more difficult. Some patients had difficulties in filling the time previously spent in obsessional or compulsive behaviours. Some undesirable transient changes in personality, greater impulsiveness, excessive extroversion or decreased reactivity and apathy have been reported. The authors therefore are cautious in recommending operation in patients with a personality disorder with a low threshold of "acting out". The organic personality disorder or postleucotomy syndrome do not occur after current stereotactic techniques.

Behavioural "disinhibition" was difficult to evaluate, though some patients reported increased assertiveness or vitality and an easier reporting of emotions and expression of feelings. Lovett[29] reports that even in bipolar affective disorders, hypomanic episodes have been more sensitive to SCT than depressive episodes, in that they have either stopped or occurred in a very attenuated form.

A transient confusional state may develop after surgery and is most probably linked to local cerebral oedema. Patients and relatives should be warned about it, but it lasts no more than a couple of days or weeks. Transient ataxia, oral dyskinesia and transient urinary incontinence were occasional complications. Three of our 21 cases developed delayed grand-mal seizures, although in 2 this was only once, after alcohol abuse.

Detailed psychological testing by W.A.I.S., M.M.P.I., modified word learning test, Grassi, Hooper and Bourdon Wiersma tests failed to show

deterioration. In some patients there was actual improvement in IQ, probably as a result of decreased anxiety and/or diminished intrusion of obsessive compulsive hindrance during test procedures. Test psychological evidence of changes in personality as well as neuropsychological deficits could not be recorded.

4. Aggressive Conduct Disorder in Patients with Mental Retardation (IQ 50)

4.1. Patient Data

In the first eleven years of the Committee on Psychosurgery a total of 18 case histories often with video-tapes were submitted for review in patients with an IQ below 50, often irritable and hyperexcitable with repetitive and persistent patterns of aggressive behaviour against themselves and/or other persons. Loss of control with aggression sometimes resulted in serious assaults out of proportion to any precipitating psychosocial stressor.

These cases have been followed-up long term. As before all appropriate therapeutic procedures have been attempted and indeed seclusion and/or restraint had often been necessary for prolonged periods or continuously.

The patients could not give valid or informed consent but after the approval by the Committee all necessary information was supplied to the referring team and the patient's relatives whose written consent for psychosurgery was requested.

15 out of 18 submitted were accepted because of their protracted severe therapy-resistant auto and/or hetero-aggressive behaviour, and 13 patients were operated on.

The mean age of this study group was 23 years (10–37 years): 9 were male and 4 female all single and institutionalized. Procedures used were thalamothomy and amygdalotomy. No results were evident from single-sided operations and as a result the surgery was usually performed in two separate sessions.

Follow-up results were available for 11 patients. Amygdalotomy appeared the procedure of choice when definite electro-encephalographic abnormalities in the temporal areas were present in addition to the behaviour disturbances.

Follow-up assessment was from the institutional therapists on the usual 1 (much better) – 6 (much worse) scale and questions dealing with changes in target symptoms were included. The mean follow-up period was 4–11 years after surgery (average 7).

Table 6. *Follow-up Results According to Therapists in 11 Patients with Aggressive Conduct Disorder and Mental Retardation (IQ < 50)*

		Mean score (1–6)	SD
Violent behaviour	before surgery	5.83	0.17
Hetero-aggression	at follow-up	2.83	1.37
Automutilation	before surgery	5.33	0.67
Auto-aggression	at follow-up	2.17	0.57

4.2. Post-Operative Psychiatric Follow-up

Table 6 summarizes the results. There was a general improvement in hetero-aggressive behaviour, score dropping from 5.83/6 to 2.83/6 and automutilation improved from 5.33/6 to 2.17/6. Side effects reported in 3 cases were rigid locomotion, slurring of speech, extrapyramidal movements well-controlled by anti-Parkinsonian drugs and one hemiparesis. Continued psychopharmacological therapy was necessary except in one case.

It is difficult to make general comments about these cases but the results on the whole appeared an improvement.

References

1. APA (1989) American psychiatric glossary. In: Stone EM (ed) American Psychiatric Press, Washington
2. Ballantine HT Jr, Cassidy WL, Flanagan NB, Marino R (1967) Stereotactic anterior cingulotomy for neuropsychiatric illness and intractable pain. J Neurosurg 26: 488–495
3. Ballantine HT, Levy BS, Dagi TF (1977) Cingulotomy for psychiatric illness. Report of 13 years' experience. In: Sweet WH, Obrador S, Martin-Rodriguez JG (eds) Neurosurgical treatment in psychiatry, pain and epilepsy. University Park Press, Baltimore, 333–353
4. Belgian Biomedical Ethical Committee (1991) Statement. National Fund for Scientific Research, Brussels, November
5. Bregging P (1980) Brain-Disabling therapies. In: Valenstein E (ed) The psychosurgery debate. Freeman, San Francisco, pp 467–492

6. Burzaco J (1981) Stereotactic surgery in the treatment of obsessive-compulsive neurosis. In: Perris C, Struwe G, Jansson B (eds) Biological psychiatry 1981. Proceedings of the Third World Congress on Biological Psychiatry. Elsevier, Amsterdam, pp 1103–1109
7. Crosby EC, Humphrey T (1944) Studies of the vertebrate telecephalon. III. The amygdaloid complex in the shrew (blarina brevicauda). J Comp Neurol 81: 285–305
8. Crow H (1977) The treatment of anxiety and obsessionality with chronically implanted electrodes. In: Smith JS, Kiloh LG (eds) Psychosurgery and society. Pergamon, Oxford, pp 67–74
9. Crow HJ, Cooper R, Philips DG (1961) Controlled multifocal frontal leucotomy for psychiatric illness. Neurol Neurosurg Psychiatry 24: 353–360
10. Culliton B (1976) Psychosurgery: National Commission issues surprisingly favorable report. Science 194: 299–301
11. Department of Health, Education, and Welfare (1977) Protection of human subjects, use of psychosurgery in practice and research: report and recommendations for public comment. Federal Register, May 23, 26318–26332
12. American Psychiatric Association (1987) Diagnostic and statistical manual of mental disorders, 3rd rev Ed. Washington, DC
13. Dutch Health Council (1990) Neurochirurgische behandeling van patiënten met zeer ernstige psychische aandoeningen. Gezondheidsraad, Publicatie 90/21, Den Haag
14. Freeman W, Watts JW (1950) Psychosurgery in the treatment of mental disorders and intractable pain, 2nd Ed. Thomas, Springfield, Ill
15. Hassler R (1982) Stereotaxic surgery for psychiatric disturbances. In: Schaltenbrand, Walker (eds) Stereotaxy of the human brain. Thieme, Stuttgart, pp 570–590
16. Hay P, Sachdev (1992) The present status of psychosurgery in Australia and New-Zealand. Med J Aust 157: 17–19
17. Herner T (1961) Treatment of mental disorders with frontal stereotactic thermolesions. Acta Psychiatr Neurol Scand [Suppl 36]
18. World Health Organisation (1992) ICD-10 Classification of mental and behavioural disorders. Geneva
19. Jacobson S, Trojanowski JQ (1975) Amygdaloid projections to prefrontal granular cortex in rhesus monkey demonstrated with horseradish peroxidase. Brain Res 100: 132–139
20. Kelly D (1973) Psychosurgery and the limbic system. Postgrad Med J 49: 825–833
21. Knight G (1964) The orbital cortex as an objective in the surgical treatment of mental illness. The results of 450 cases of open operation and the development of the stereotactic approach. Br J Surg 51(2): 114–124
22. Knight G (1965) Stereotactic tractotomy in the surgical treatment of mental illness. J Neurol Neurosurg Psychiatry 28: 304–310
23. Knight G (1972) Bifrontal stereotaxic tractotomy in the substantia innominata. An experience of 450 cases. In: Hitchcock E, Laitinen L, Vaernet K (eds) Psychosurgery. Thomas, Springfield, Ill, pp 267–277

24. Knight G (1973) Further observations from an experience of 660 cases of stereotactic tractotomy. Postgrad Med J 49: 845–854
25. Leksell L, Larsson B, Andersson B, Rexed B, Sourander P, Mair W (1960) Lesions in the depth of the brain produced by a beam of high energy protons. Acta Radiol (Stockh) 54: 251–264
26. Leksell L (1971) Stereotaxis and radiosurgery. An operative system. Thomas, Springfield, Ill, pp 1–69
27. Leksell L, Backlund E-O (1979) Stereotactic gamma capsulotomy. In: Hitchcock ER, Ballantine HR Jr, Meyerson BA (eds) Modern concepts in psychiatric surgery. Elsevier Biomedical Press, Amsterdam, pp 213–216
28. Lichterman B (1992) On the history of psychosurgery in Russia. Personal written communication of 5 pages
29. Lovett L, Shaw D (1987) Outcome in bipolar affective disorder after stereotactic tractotomy. Br J Psychiatry 151: 113–116
30. Marino R (1977) Stereotactic anatomy and vascularization of cingulate gyrus and adjacent areas. In: Sweet WH (ed) Obrador neurosurgical treatment of psychiatry pain and epilepsy. University Park Press, Congress 75, pp 321–332
31. Mark V, Ervin F (1970) Violence and the brain. Harper and Row, New York
32. Maxwell-Jones (1968) Beyond the therapeutic community. Yale University Press, New Haven
33. Merskey H (1991) Ethical aspects of the physical manipulation of the brain. In: Bloch S, Chodoff P (eds) Psychiatric ethics, 2nd Ed. Oxford Medical Publications, Oxford, pp 185–214
34. Meyer A, Beck E, McLardy T (1947) Prefrontal leukotomy. A neuro-anatomical report. Brain 70: 18–49
35. Meyer A, Beck E (1954) Prefrontal leucotomy and related operations. Anatomic aspects of success and failure. Churchill Livingstone, Thomas, Edinburgh
36. Meyerson BA (1977) Stereotactic anterior capsulotomy in the treatment of obsessive-compulsive neurosis. In: Carrea R (ed) Neurological surgery. International Congress Series No. 433. Exerpta Medica, Amsterdam, pp 307–312
37. Meyerson BA, Bergström M, Greitz T (1979) Target localization with the aid of computed tomography. In: Hitchcock E, Ballantine HT Jr, Meyerson BA (eds) Modern concepts in psychiatric surgery. Elsevier Biomedical Press, Amsterdam, pp 217–224
38. Meyerson BA (1988) The role of anterior internal capsulotomy in psychiatric surgery. In: Lundsford LD (ed) Modern stereotactic neurosurgery. Martinus Nijhoff, Boston, pp 353–364
39. Mindus P (1991) Thesis: capsulotomy in anxiety disorders. A multidisciplinary study. Karolinska Institute, Stockholm, Sweden
40. Moniz E (1936) Tentatives opératoires dans le traitement de certaines psychoses. Masson, Paris
41. Narabayashi H, Shima F (1973) Which is the better amygdala target, the medial or lateral nuclei (For behaviour problems and paroxysm in epileptics). In: Laitinen LV, Livingston KE (eds) Surgical approaches in psychiatry. Medical and Technical Publishing Co, Lancaster, pp 129–134

42. National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research (1977) Use of psychosurgery in practice and research: report and recommendation for public comment. Department of HEW, Federal Register May 23, 26318–26332
43. Newcombe RL (1972) Landmarks for lesions in the substantia innominata. In: Hitchcock E, Laitinen L, Vaernet K (eds) Psychosurgery. Thomas, Springfield, Ill, pp 289–290
44. Newcombe RL (1973) Anatomical placement of lesions in the ventromedial segment of the frontal lobe. In: Laitinen LV, Livingston KE (eds) Surgical approaches in psychiatry. Medical and Technical Publishing Co, Lancaster, pp 83–89
45. Nys H (1988) Psychosurgery and personality – some legal considerations. In: Brihaye J, Calliauw L, Loew P, van den Bergh R (eds) Personality and neurosurgery. Acta Neurochir (Wien) [Suppl] 44: 170–172
46. Schaltenbrand G, Wahren W (1977) Atlas for sterotaxy of the human brain. Thieme, Stuttgart
47. Scoville WB (1972) Psychosurgery and other lesions of the brain affecting human behaviour. In: Hitchcock E, Laitinen L, Vaernet K (eds) Psychosurgery. Thomas, Springfield, Ill, pp 5–21
48. Storm van Leeuwen W (1982) Neuro-physio-surgery in the Netherlands since 1971. Acta Neurochir (Wien) 61: 249–256
49. Talairach J, Hecaen H, David M (1949) Lobotomie préfrontale limitée par électrocoagulation des fibres thalamofrontales à leur émergence du bras anterieur de la capsule interne. In: VI Congress Neurologique International. Masson, Paris, p 141
50. Valenstein E (1980) The psychosurgery debate. Scientific, legal and ethical perspectives. Freeman, San Francisco

Background

1. Aggleton JP (1992) The functional effects of amygdala lesions in humans: a comparison with findings from monkeys. In: Aggleton JP (ed) The amygdala: neurobiological aspects of emotion, memory and mental dysfunction. Wiley-Liss, New York, pp 485–503
2. Alexander GE, Crutcher MD (1990) Functional architecture of basal ganglia circuits: neural substrates of parallel processing. TINS 13(7): 266–271
3. Alexander GE, Crutcher MD, DeLong MR (1990) Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. In: Uylings HBM, van Eden CG, de Bruin JPC, Corner MA, Feenstra MGP (eds) Progress in brain research, Vol 85. Elsevier, Berlin, pp 119–146
4. Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Ann Rev Neurosci 9: 357–381
5. Amaral DG, Price JL, Pitkänen A, Carmichael ST (1992) Anatomical organiz-

ation of the primate amygdaloid complex: In: Aggleton JP (ed) The amygdala: neurobiological aspects of emotion, memory and mental dysfunction. Wiley-Liss, New York, XII, pp 1–66
6. Bartlett JR, Bridges PK (1977) The extended subcaudate tractotomy lesion. In: Sweet WH, Obrador S, Martin-Rodriguez JG (eds) Neurosurgical treatment in psychiatry, pain and epilepsy. University Park Press, Baltimore, pp 387–398
7. Baxter L, Schwartz J, Mazziotta J, Phelps ME, Pahl JJ, Buze BE, Fairbanks L (1988) Cerebral glucose metabolic rates in nondepressed patients with obsessive-compulsive disorder. Am J Psychiatry 145: 1560–1563
8. Baxter LR Jr, Schwartz JM, Bergman KS, Szuba MP, Guze BH, Mazziotta JC, Alazraki A, Selin CE, Ferng HK, Munford P, Phelps ME (1992) Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. Arch Gen Psychiatry 49: 681–689
9. Bingley T, Leksell L, Meyerson BA, Rylander G (1977) Long term results of stereotactic capsulotomy in chronic obsessive-compulsive neurosis. In: Sweet WH, Obrador S, Martin-Rodriguez JG (eds) Neurosurgical treatment in Psychiatry. University Park Press, Baltimore, pp 287–289
10. Cosyns P, Gybels J (1979) Psychiatric process analysis of obsessive compulsive behavior modification by psychiatric surgery. In: Hitchcock E, Ballantine HT, Meyerson BA (eds) Modern concepts in psychiatric surgery. Elsevier Biomedical Press, Amsterdam, pp 225–233
11. Groenewegen HJ, Berendse HW, Wolters JG, Lohman AHM (1990) The anatomical relationship of the prefrontal cortex with the striatopallidal system, the thalamus and the amygdala: evidence for a parallel organization. In: Uylings HBM, van Eden CG, de Bruin JPC, Corner MA, Feenstra MFP (eds) Progress in brain research. Elsevier Science Publishers, Amsterdam, pp 95–118
12. Insel TR (1992) Toward a neuroanatomy of obsessive-compulsive disorder. Arch Gen Psychiatry 49: 739–744
13. Laitinen LV (1979) Emotional responses to subcortical electrical stimulation in psychiatric patients. Clin Neurol Neurosurg 81–83: 148–157
14. Ledoux JE (1992) Emotion and the amygdala. In: Aggleton JP (ed) The amygdala: neurobiological aspects of emotion, memory and mental dysfunction. Wiley-Liss, New York, pp 339–351
15. Le Gros Clark W (1948) The connexions of the frontal lobe of the brain. Lancet 1: 353–356
16. Le Gros Clark (1950) Anatomical relationships between the cerebral cortex and the hypothalamus. Br Med Bull 6(4): 341–345
17. Mindus P, Bergström K, Levander SE, Norén G, Hindmarsh T, Thuomas K-A (1987) Magnetic resonance images related to clinical outcome after psychosurgical intervention in severe anxiety disorder. J Neurol Neurosurg Psychiatry 50: 1288–1293
18. Nauta WJH (1971) The problem of the frontal lobe: a reinterpretation. J Psychiat Res 8: 167–87
19. Papez JW (1937) A proposed mechanism of emotion. Chicago. Arch Neurol Psychiatry 38: 725–743

Subject Index

Advances and Technical Standards in Neurosurgery

Volume 20

1993. 96 figures. XIII, 308 pages.
Cloth DM 240,–, öS 1680,–, approx. US $ 160.00
ISBN 3-211-82383-2

Advances:

R.D. Lobato: Post-traumatic Brain Swelling.
K.-F. Lindegaard, W. Sorteberg, and H. Nornes: Transcranial Doppler in Neurosurgery.
A.E. Harding: Clinical and Molecular Neurogenetics in Neurosurgery.

Technical Standards:

B. Williams: Surgery for Hindbrain Related Syringomyelia.
J.-F. Hirsch and E. Hoppe-Hirsch: Medulloblastoma.
F. Resche, J.P. Moisan, J. Mantoura, A.de Kersaint-Gilly, M.J. Andre, I. Perrin-Resche, D. Menegalli-Boggelli, Y. Lajat, and S. Richard: Haemangioblastoma, Haemangioblastomatosis, and von Hippel-Lindau Disease.

Prices are subject to change without notice

Springer-Verlag Wien New York

Sachsenplatz 4–6, P.O.Box 89, A-1201 Wien · 175 Fifth Avenue, New York, NY 10010, USA
Heidelberger Platz 3, D-14197 Berlin · 3-13, Hongo 3-chome, Bunkyo-ku, Tokyo 113, Japan

Advances and Technical Standards in Neurosurgery

Volume 19

1992. 44 partly colored figures. XIV, 224 pages.
Cloth DM 186,–, öS 1300,–, approx. US $ 129.00
ISBN 3-211-82287-9

Advances:

J.W. Berkelbach van der Sprenkel, N.M.J.Knufman, P.C. van Rijen, P.R. Luyten, J. A. den Hollander, and C.A.F. Tulleken: Proton Spectroscopic Imaging in Cerebral Ischemia, Where we Stand and what Can Be Expected.

L. Steiner, C. Lindquist, and M. Steiner: Radiosurgery.

F. Iannotti: Functional Imaging of Blood Brain Barrier Permeability by Single Photon Emission Computerised Tomography and Positron Emission Tomography.

Technical Standards:

B. Jennett and J. Pickard: Economic Aspects of Neurosurgery.

F. Gjerris and S.E. Børgesen: Current Concepts of Measurement of Cerebrospinal Fluid Absorption and Biomechanics of Hydrocephalus.

F. Gentili, M. Schwartz, K. TerBrugge, M.C. Wallace, R. Willinsky, and C. Young: A Multidisciplinary Approach to the Treatment of Brain Vascular Malformations.

Prices are subject to change without notice

Springer-Verlag Wien New York

Sachsenplatz 4–6, P.O.Box 89, A-1201 Wien · 175 Fifth Avenue, New York, NY 10010, USA
Heidelberger Platz 3, D-14197 Berlin · 3-13, Hongo 3-chome, Bunkyo-ku, Tokyo 113, Japan