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
V. V. Dolenc, Ljubljana
J. Lobo Antunes, Lisboa
H. Nornes, Oslo
J. D. Pickard, Cambridge
H.-J. Reulen, Munich
A. J. Strong, London
N. de Tribolet, Lausanne

Volume 22

Springer-Verlag
Wien New York 1995

With 149 partly coloured Figures

Softcover reprint of the hardcover 1st edition 1995

Library of Congress Catalogue Card Number 74-10499

Printing: A. Holzhausens Nfg., A-1070 Wien

Printed on acid-free and chlorine-free bleached paper

ISSN 0095-4829

ISBN-13:978-3-7091-7428-9 e-ISBN-13:978-3-7091-6898-1

DOI: 10.1007/978-3-7091-6898-1

Valedictory Note

It has been both an honour and a privilege to serve as Chief Editor of Advances and Technical Standards in Neurosurgery for the past ten years. During that time it has been a pleasure to work with distinguished colleagues from all over Europe and the yearly Editorial Board Meetings in London have enabled us to continue the tasks set by the founding members of the Board under Hugo Krayenbühl's direction. The increasing integration of Europe has seen the aims of those founding members and of their successors of increasing standards of education throughout Europe more readily realizable, and this progress will clearly continue.

The excellence of our publishers, Springer-Verlag of Vienna has maintained an impeccable standard of production and has been of inestimable value to us throughout.

With my retirement from active practice in 1995 it is a great pleasure to hand over the Chief Editorship to Professeur François Cohadon knowing that with the support of a distinguished group of co-editors from all over Europe, his task will prove as successful and as pleasurable as has been my own.

Lindsay Symon
CBE, TD, FRCS, FRCS (Ed), FACS (Hon)
Editor-in-Chief

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 postgraduate 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

The Surgery of Cavernomas Both Supra-Tentorial and Infra-Tentorial. By J. P. HOUTTEVILLE, Department of Neurosurgery, C.H.U. Caen (France)

Listed in Index Medicus

List of Contributors

Bricolo, A., MD, Professor, Department of Neurosurgery, University Hospital of Verona, Piazzele Stefani 1, I-37126 Verona, Italy.

Chazal, J., MD, Department of Anatomy, Auvergne University, Clermont-Ferrand, France.

Chirossel, J. P., MD, Professor, Service de Neurochirurgie, Hôpital A. Michallon, B. P. 217X, F-38043 Grenoble Cedex, France.

Coillard, Ch., MD, Department of Anatomy, Auvergne University, Clermont-Ferrand, France.

Ebeling, U., MD, Department of Neurosurgery, University of Berne, Berne, Switzerland.

Favre, J. J., MD, Service de Neurochirurgie, Hôpital A. Michallon, B. P. 217X, F-38043 Grenoble Cedex, France.

Garcier, J. M., MD, Department of Anatomy, Auvergne University, Clermont-Ferrand, France.

Guillot, M., MD, Department of Anatomy, Auvergne University, Clermont-Ferrand, France.

Houtteville, J. P., MD, Professor, Department of Neurosurgery, C. H. U., Avenue de la Côte de Nacre, Niveau 12, Caen 14033, France.

Kovacs, K., MD, Department of Pathology, St. Michael's Hospital, University of Toronto, 30 Bond Street, Toronto, Ontario M5B IW8, Canada.

Laws, E. R., MD, Department of Neurological Surgery, University of Virginia, Charlottesville, Virginia, U.S.A.

Matthies, C., MD, Department of Neurosurgery, Nordstadt Hospital, Haltenhoffstrasse 41, D-30167 Hannover, Federal Republic of Germany.

Passagia, J. G., MD, Service de Neurochirurgie, Hôpital A. Michallon, B. P. 217X, F-38043 Grenoble Cedex, France.

Reulen, H.-J., MD, Professor, Department of Neurosurgery, Ludwig Maximilians University, Marchioninistrasse 15, D-81377 Munich, Federal Republic of Germany.

Samii, M., MD, Professor, Department of Neurosurgery, Nordstadt Hospital, Haltenhoffstrasse 41, D-30167 Hannover, Federal Republic of Germany.

Thapar, K., MD, Department of Neurosurgery, St. Michael's Hospital, University of Toronto, 30 Bond Street, Toronto, Ontario M5B IW8, Canada.

Tonetti, J., MD, Service de Neurochirurgie, Hôpital A. Michallon, B. P. 217X, F-38043 Grenoble Cedex, France.

Turazzi, S., MD, Department of Neurosurgery, University Hospital, Piazzele Stefani 1, I-37126 Verona, Italy.

Vanneuville, G., MD, Department of Anatomy, Auvergne University, Clermont-Ferrand, France.

A. Advances

The Classification and Molecular Biology of Pituitary Adenomas

K. THAPAR[1], K. KOVACS[2], and E. R. LAWS[3]

Department of [1] Neurosurgery and [2] Pathology, St. Michael's Hospital, University of Toronto, Toronto (Canada), and [3] Department of Neurological Surgery, University of Virginia, Charlottesville, VA (U.S.A.)

With 1 Figure

Contents

Introduction

As illustrated throughout this volume, the contemporary management of pituitary tumors has been the collective product of decades of multidisciplinary contribution. Innovation has been especially brisk during the past two decades in which the introduction of highly sensitive hormone assays, superior resolution imaging technology, trans-sphenoidal microsurgery, receptor-mediated pharmacotherapy, and focused beam radiotherapy have ushered in a promising new era in the diagnosis and therapy of pituitary tumors. Collectively, these contributions from many disciplines have rendered pituitary tumors eminently treatable, with many patients enjoying long term survival or cure.

In parallel with such encouraging advances in the clinical sphere, has been the equally impressive and complimentary progress occurring in the basic science arena. Such research efforts have led to a number of conceptual advances, all of which serve to sharpen our understanding of the neoplastic process in the pituitary. An important first step was the introduction of electron microscopy as a means of classifying pituitary adenomas. Not only did electron microscopy definitively eclipse all other strategies in reliably and precisely classifying pituitary adenomas, it further demonstrated that these lesions, despite their seemingly uniform histologic appearance, were, in fact, morphologically heterogeneous. Subsequent clinical correlation demonstrated that differences in tumor ultrastructure were accompanied by clinically important differences in biological behavior. The recent application of immunohistochemical methods in the diagnosis of pituitary adenomas, by distinguishing adenomas on the basis of cellular hormonal content, has further refined ultrastructural diagnosis, permitting meaningful correlations between tumor ultrastructure and endocrine function (Kovacs and Horvath 1986).

Methodological advances continue to be made the most recent being the integration of conventional pathologic methods with the powerful applications of molecular science (reviewed in Thapar *et al.* 1993a). Such strategies have revealed new insights into some of the most fundamental questions concerning the pathogenesis, cellular origins, and overall biology of pituitary adenomas. Particularly informative from a conceptual standpoint have been reports concerning the clonal origins of pituitary adenomas. Such studies, by establishing a monoclonal composition for pituitary adenomas, emphasize the importance of somatic mutations involving a single adenohypophyseal

cell as a necessary event in pituitary tumorigenesis. This being the case, attention has now been directed at identifying the nature of genomic mutations necessary to accomplish the process. Of the structural genomic alterations identified, some have assumed the form of activating mutations of oncogenes whereas in a much smaller proportion of cases, deletion of genetic information or tumor suppressor gene loss appears to be the dominant tumorigenic mechanism. In that specific genomic alterations have been cataloged in only a minority of pituitary adenomas, the search for additional components of the tumorigenic process has been actively pursued. To this end, various growth factors as well as other trophic and transcriptional regulators, given their capacity for autocrine and paracrine stimulation, have emerged as potentially important mediators of the neoplastic process in the pituitary. Finally, increasing interest in cell cycle regulation has led to the identification of certain cell cycle-specific regulatory proteins whose immunochemical presence in pituitary tumors provides some estimate of their proliferative potential.

In this chapter we review current knowledge of the pathology, pathogenesis, and molecular biology of pituitary adenomas. Given the inseparable relationship which exists between tumor pathology and the overall biology of pituitary adenomas, this discussion necessarily begins with an overview of the current functional classification of pituitary adenomas. This is followed by a detailed review of current understanding of the molecular biology of pituitary adenomas. Included are discussions of the clonal origins of pituitary adenomas and the roles of oncogenes, tumor suppressor genes, growth factors, and other subcellular aberrations currently believed to contribute to neoplastic transformation and/or progression in the pituitary.

The Functional Classification of Pituitary Adenomas
(Kovacs and Horvath 1986)

The pituitary gland is a common substrate for neoplastic transformation, giving origin to approximately 15 per cent of all intracranial tumors. Arising from hormone secreting cells of the anterior lobe, the overwhelming majority of these are histologically benign adenomas. Although many pituitary adenomas exhibit varying degrees of local invasiveness, exceptionally few demonstrate the necessary metastasing capacity to merit a diagnosis of *pituitary carcinoma*. Even so, the "benign" histology of pituitary adenomas is an all too beguiling feature of their biology; the regularity with which they encroach upon critical neural structures, coupled with the distressing endocrinopathies they frequently induce, legitimize pituitary adenomas as both a frequent and significant source of morbidity, and occasionally, mortality.

Pituitary adenomas have, by convention, been classified pathologically on the basis of cytoplasmic staining affinities – a largely noninformative prac-

tice which attempted to confine a clinically and morphologically heterogeneous group of tumors into the elementary categories of acidophilic, basophilic, and chromophobic. Under such a scheme, acidophilic tumors were assumed to be exclusively growth hormone (GH) secreting adenomas, whereas basophil tumors were assumed the sole cause of adrenocorticotropin (ACTH) overproduction. Tumors which failed to stain were collectively designated as chromophobic and therefore believed to be hormonally inactive. In that the simplicity and convenience of this three-tiered classification were appealing, it persisted for many years. With the emergence of new methodologies it later became apparent that tinctorial characteristics of the cell cytoplasm correlate poorly with reliable cell type recognition, secretory activity, or cytogenesis. Thus, not all acidophilic tumors produce GH; some basophilic tumors do not cause Cushing's disease, and more than half of chromophobe tumors are endocrinologically active. Accordingly, the need for a comprehensive classification of pituitary adenomas, one permitting reliable correlation of morphologic characteristics with endocrine activity, cytogenesis, biological behavior, and response to various therapeutic modalities was clearly established. Electron microscopy and immunohistochemistry, by providing the means to address this challenge, have since led to the development of a new classification of pituitary adenomas, one correlating structure with function, cytogen-

Table 1. *Functional Classification of Pituitary Adenomas Based on Electron Microscopy and Immunohistochemistry*. The relative frequency of each tumor subtype in the authors' series of over 3000 surgically removed pituitary adenomas is given

Cell type	Incidence (%)
Sparsely granulated PRL cell adenoma	26.6
Densely granulated PRL cell adenoma	0.6
Sparsely granulated GH cell adenoma	7.3
Densely granulated GH cell adenoma	6.7
Mixed GH-PRL cell adenoma	4.8
Mammosomatotroph adenoma	1.4
Acidophil stem cell adenoma	2.2
Functioning corticotroph cell adenoma	8.0
Silent "corticotroph" cell adenomas	6.0
Gonadotroph adenoma	6.4
Thyrotroph adenoma	1.0
Null cell adenoma	16.3
Oncocytoma	8.9
Unclassified plurihormonal adenomas	3.7

esis with biology, and basic science with clinical applicability (Kovacs and Horvath 1986).

As outlined in Table 1, the functional classification of pituitary adenomas recognizes 14 principal pituitary adenoma subtypes, each having its own morphologic, immunohistochemical, and to some extent, biological profile. Pituitary adenomas are first stratified on the basis of their cellular origin and hormonal product(s), and secondarily subtyped on the basis of their ultrastructure. Comprising the normal adenohypophysis are five different cell types known as lactotrophs, somatotrophs, corticotrophs, thyrotrophs, and gonadotrophs, each functional, distinguished by their capacity to secrete prolactin (PRL), growth hormone (GH), adrenocorticotropin (ACTH), thyroid stimulating hormone (TSH), and gonadotrophins ((luteinizing hormone (LH), and follicle stimulating hormone (FSH)), respectively. Although susceptibilities vary, neoplastic transformation can, in a multistep and multicausal fashion, occur in each of these five cell types. Correspondingly, the resulting adenoma generally retains the secretory capability, morphologic characteristics, and nomenclature of the cell of origin. With this scheme in mind, an overview of the current functional classification of pituitary adenoma is provided. The emphasis of the discussion is clinical in nature, focusing on those clinico-pathologic correlates of broader relevance to the practising clinician. For a more detailed morphological treatment of pituitary tumor pathology, the reader is referred to a number of recent and comprehensive reviews (Scheithauer 1984a, b, Kovacs and Horvath 1986, Horvath and Kovacs 1991, Thapar *et al.* 1992).

Prolactin Producing Adenomas "Prolactinomas"

Prolactin producing pituitary tumors are the most commonly occurring tumors of adenohypophyseal origin. In addition to being the most common pituitary type encountered in clinical practice, prolactinomas account for almost one half of all subclinical pituitary adenomas discovered incidentally at autopsy (Burrows *et al.* 1981, McComb *et al.* 1983). Prolactinomas once represented approximately 30 per cent of all surgically removed pituitary adenomas. During recent years, however, the emergence of dopamine agonists as an effective non-surgical therapeutic option for many prolactinomas has led to a substantial decline in their frequency among recent surgical series.

The principal endocrinologic consequence of hyperprolactinemia is hypogonadism. That the clinical expression of the latter is so heavily gender and age dependent provides some insight into some of the epidemiologic and gross pathologic differences between prolactinomas occurring in men and women. Firstly, women, particularly those of reproductive age, are four times more likely to develop a prolactinoma than men. It is of interest that this

marked female preponderance seen clinically is not evident in unselected autopsy series wherein prolactinomas are identified with equal frequency in both sexes (McComb *et al.* 1983). Prolactinomas in men tend to be larger, have a higher incidence of dural invasion, and have usually transgressed the confines of the sellae at diagnosis. These differences may, in large measure, be due to the differences in which hyperprolactinemia manifests in men and women. In women of reproductive age, the resultant hypogonadism manifests itself conspicuously as menstrual dysfunction and infertility, thus promoting early evaluation. In men, however, corresponding symptoms of hypogonadism (decreased libido, relative infertility), are initially often subtle and frequently dismissed as "functional". Thus, tumors in men tend not to be recognized at an early stage, becoming apparent only after progressive tumor growth causes symptoms of mass effect. Whether delayed recognition alone is sufficient to account for large tumors seen in men is unclear, particularly in view of a number of longitudinal studies which suggest that prolactinomas are relatively stable from a growth standpoint, and that evolution of microadenomas to macroadenomas occurs in only a minority of cases (reviewed in Cooper 1990).

Gender related differences in clinical presentation and gross tumor features aside, prolactinomas in men and women are immunohistochemically and ultrastructurally indistinguishable. Pure prolactin secreting adenomas are of two types: the sparsely and densely granulated PRL cell adenomas. Although the former is chromophobic and common, and the latter is acidophilic and very rare, no clinical, biological, or prognostic differences exist between the two. When presenting as microadenomas, these tumors can typically be found in the lateral wing of the gland. Whereas 60 per cent of prolactinomas in women are detected in the microadenoma stage, prolactinomas of similar size are only rarely detected in men (Melmed *et al.* 1986). When presenting as macroadenomas, prolactinomas exhibit varying degrees of aggressiveness; some tumors simply cause sellar enlargement, whereas others relentlessly erode the skull base. Overall, more than half of all prolactinomas will be grossly invasive (Scheithauer *et al.* 1986a). Such tumors have a particular tendency for downward growth; involvement of the sphenoid sinus and destruction of the skull base can be striking. Psammatomous calcification is present in 10 per cent of prolactinomas. It typically occurs in microscopic form (calcospherites), but on occasion is so densely coalescent that macroscopic concretions or "pituitary stones" develop.

The *sparsely granulated PRL cell adenoma,* given the relative scarcity of free PRL secretory within its cytoplasm, appears chromophobic on hematoxylin and eosin (H&E) stain. Histologically indistinguishable from other chromophobic adenomas, the nature of this tumor is apparent only after immunostaining. Prolactin immunoreactivity generally assumes a globular, perinuclear distribution, one corresponding to the location of the Golgi

apparatus. Upon ultrastructural study, tumor cells are of intermediate size and polyhedral shape and have the following characteristic features: (i) an extensive and well developed endoplasmic reticulum which often assumes a range of distinctive configurations (concentric whorls, pleated parallel arrays); (ii) a prominent Golgi apparatus containing varying numbers of 150–300 nm PRL granules; and (iii) misplaced exocytosis. The latter phenomenon refers to extrusions of PRL granules from the lateral margins of the cell, margins devoid of capillary access. This contrast with the normal secretory process of endocrine cells wherein secretory granules are preferentially discharged at the cell's vascular pole, a zone adjacent to capillary access.

The rare *densely granulated PRL cell adenoma,* contains abundant free PRL granules within its cytoplasm, thus assuming an acidophilic appearance. Accordingly, diffuse PRL immunoreactivity is homogeneously present throughout the cytoplasm. Whereas the endoplasmic reticulum and Golgi complex are less prominent than in the sparsely granulated variant, secretory granules are much more numerous and considerably larger (600 nm).

Growth Hormone Producing Adenomas

The pituitary adenomas underlying acromegaly and gigantism are a heterogeneous group, one unified by pathologic hypersecretion of GH, but distinguished by their relative incidence, immunohistochemical profiles, ultrastructural morphology, and differences in biological behavior (Asa and Kovacs 1992b). Of the six GH secreting adenomas subtypes, only two are pure GH secreting tumors: the densely and sparsely GH cell adenomas. The remainder are bihormonal and plurihormonal tumors which co-secrete GH, PRL and sometimes additional hormonal products, respectively. Only pure GH cell adenomas are discussed here, the remainder being discussed in their respective sections.

The *densely granulated GH cell adenoma* represents the classical "acidophilic adenoma of acromegaly" and accounts for approximately 8 per cent of all pituitary adenomas. As relatively slow growing lesions with limited invasiveness, they frequently cause a gradual ballooning of the sella. An abundance of GH secretory granules renders them strongly acidophilic on H&E staining and diffusely immunoreactive for GH on immunostain. Indicative of its well differentiated nature, the ultrastructure of this tumor is reminiscent of normal somatotrophs. Cells are polyhedral in shape and harbor uniform, regular nuclei with prominent nucleoli. Their abundant cytoplasm contains well developed organelles; rough endoplasmic reticulum is arranged in parallel stacks and the Golgi complex contains maturing secretory granules. The most prominent ultrastructural feature is the abundance of large (300–600 nm), spherical GH containing secretory granules generously distributed throughout the cytoplasm.

The *sparsely granulated GH cell adenoma,* occurring with similar frequency as the densely granulated variant, has long been regarded as the more aggressive of the two. Although the sparsely granulated variant has the same capacity for GH secretion as the densely granulated adenoma, its cytoplasm contains few secretory granules, thus accounting for its chromophobic appearance on H&E staining. Varying degrees of cellular and nuclear pleomorphism may be observed, although they are without prognostic significance. Immunopositivity for GH is generally scant, often discernible only in the perinuclear region occupied by the Golgi complex. The ultrastructural appearance of sparsely granulated variant is a clear departure from either the normal somatotroph or the densely granulated GH cell adenoma. Tumors cells are irregular, varying considerably both in size and shape; their eccentric nuclei are frequently pleomorphic, multilobed, or concave. Rough endoplasmic reticulum is dispersed throughout the cytoplasm, being adequate in some and scant in others. Virtually diagnostic of this tumor is the 'fibrous body', a conspicuous aggregate of filaments immunoreactive for keratin and ubiquitin, and located in a paranuclear location. Whereas their function remains unknown, fibrous bodies do serve as a useful diagnostic marker, particularly at the histologic level where they are seen as acidophilic paranuclear bodies indenting nuclei. As such, they provide reliable evidence of somatotroph differentiation in an otherwise nondescript chromophobic adenoma. Finally, a scant population of small (100–250 nm) secretory granules are seen distributed throughout the cytoplasm. In all, the ultrastructure of the sparsely granulated variant is that of a less well differentiated tumor.

Despite similarities in incidence, endocrinologic presentation, and biochemical alterations between the sparsely and densely granulated variants, the former are distinguished by their notoriously aggressive biological behavior. Whereas 40 per cent of densely granulated GH adenomas are detected while still microadenomas, sparsely granulated variants are virtually always macroadenomas at the time of detection. In addition to faster growth, sparsely granulated tumors are three times more likely to be invasive, have a greater tendency for postoperative recurrence, and generally occur in younger individuals (Scheithauer *et al.* 1986a, Kovacs 1988).

Pituitary Adenomas Producing GH and PRL

Hyperprolactinemia is demonstrated in approximately 40 per cent of patients with acromegaly (Thorner *et al.* 1992). In some instances, only modest elevations (< 150 ng/ml) of PRL are present, being within the range attributable to the "stalk section effect". In a significant proportion, however, PRL levels exceed 150 ng/ml, a level which only tumoral PRL production can explain. In fact, three distinct pituitary tumors have been identified with dual secretion of both GH and PRL. These include the mixed GH cell-PRL

cell adenoma, mammosomatotroph adenomas, and the acidophil stem cell adenoma.

The *mixed somatotroph-lactotroph adenoma* is a bimorphous tumor composed of two distinct adenomatous elements, one producing GH and the other producing PRL. Clinically, these patients are acromegalic and have hyperprolactinemia of varying degree. Depending on the granularity of constituent cells, these tumors may appear acidophilic or chromophobic. In that densely granulated GH cells interspersed with sparsely granulated PRL cells is the most common combination, most tumors appear predominantly acidophilic but are interspersed with chromophobic cells. With immunohistochemistry, acidophilic cells are found to be immunoreactive for GH whereas chromophobic cells exhibit PRL immunoreactivity. The chimeric nature of this tumor is especially evident with electron microscopy wherein GH producing cells are clearly distinguished from those secreting PRL. Once considered to be a relatively indolent neoplasm, they appear from recent evidence to be more aggressive than previously thought. Gross invasion is identified intraoperatively in almost 30 per cent of cases (Scheithauer *et al.* 1986a). Moreover, in one recent surgical series, these tumors were less likely to experience postoperative endocrine "cure" than were pure GH secreting tumors (Nyquist *et al.* 1994).

Representing fewer that 2 per cent of all pituitary adenomas, the *mammosomatotroph adenoma* is one of the least common types of acromegaly associated tumor. The presumed cell of origin is the mammosomatotroph, a cellular element thought to be distributed in the normal pituitary and believed to share common lineage with somatotrophs and lactotrophs. Although the function of the normal somatotroph is uncertain, recent evidence suggests it to be a transitional cell type, one with a capacity for two way interconversion between lactotroph and somatotroph phenotypes. Despite these physiologic uncertainties, mammosomatotroph adenomas are discrete pathological entities. Most are small, well differentiated, biologically indolent lesions with minimal invasive potential.

Again, the clinical picture is one of acromegaly in association with modest hyperprolactinemia. Histologically, these tumors are strongly acidophilic and, upon immunostaining, exhibit strong GH and variable PRL immunopositivity. Ultrastructurally, the tumor consists of a uniform cell population which resembles densely granulated GH adenoma cells with the additional hallmark of PRL secretion, misplaced exocytosis. The secretory granules are, however, distinctive. They tend to be surprisingly pleomorphic, varying considerably in shape, electron density and size; some are often 1000 nm in diameter. Immunoelectron microscopy demonstrates the presence of GH and PRL within the same secretory granule.

The *acidophil stem cell adenoma* is a monomorphous bihormonal tumor characterized by an accelerated cell proliferation rate and relentless invasive-

ness. As inferred from their name, these tumors are thought to originate from primitive acidophil precursor cells of the normal pituitary, ones eventually differentiating into somatotrophs and lactotrophs. Fortunately, they are rare, and represent only 1–2 per cent of all pituitary adenomas. Whereas these tumors co-secrete both PRL and GH, the dominant endocrinologic effect is hyprolactinemia; acromegaly is an uncommon feature. Endocrine disturbances are sometimes overshadowed by the overt neurologic manifestations of a rapidly enlarging sellar mass. In that the growth of this tumor is typically brisk, the clinical history is correspondingly short, often measured in weeks. At diagnosis, these tumors have virtually always extending beyond the confines of the sella to involve adjacent structures. They exhibit a particular tendency to downward growth, as evidence by their frequent involvement of the sphenoid sinus and extensive erosion of the skull base. Histologically, most acidophil stem cell adenomas are chromophobic; only minor degrees of acidophilia are sometimes present. The tumors immunohistochemical profile closely parallels it secretory activity; strong PRL and scant GH immunoreactivities are the rule. The definitive diagnosis of this tumor requires ultrastructural study. Apparent at this level are a number of cytoplasmic aberrations compatible with the tumor's presumed primitive origins. Cellular and nuclear pleomorphism are often prominent, as reflected by cells of irregular size and shape, poorly organized rough endoplasmic reticulum, and primitive Golgi apparatus. Other abnormalities include giant, swollen mitochondria and oncocytic transformation. Misplaced exocytoses and fibrous bodies, features of PRL cell and sparsely granulated GH cell adenomas, respectively, are generally identifiable. A sparse population of small (150–200 nm) secretory is scattered throughout the cytoplasm.

ACTH Producing Adenomas

Neoplastic transformation of pituitary corticotrophs is the basis for four distinct adenoma types, which collectively account for 15 per cent of all pituitary adenomas. It is convenient to classify these on a functional basis, distinguishing hormonally active from endocrinologically "silent" tumors. The hormonally active, or functioning corticotroph adenomas secrete ACTH and other endorphin-related peptides in excess, causing Cushing's disease and Nelson's syndrome. The endocrinologically inactive or silent corticotroph adenomas, despite morphologic features of a corticotrophic lineage, are unaccompanied by measurable ACTH production. Such tumors present with the neurologic sequelae of a sellar mass.

Functioning Corticotroph Adenomas

The corticotroph adenomas underlying Cushing's disease and Nelson's syndrome are of two pathologic types: the *densely granulated* and *sparsely*

granulated corticotroph adenomas. The former are by far the most common, being the well differentiated and classical basophilic adenomas associated with Cushing's disease and Nelson's syndrome. The sparsely granulated tumors are rare, chromophobic in appearance, less well differentiated, and notorious for a more aggressive clinical profile. Immunoreactivity for ACTH, endorphins, and related pro-opiomelanocortin (POMC) peptides is present in both tumor types, although strong and diffuse in the densely granulated variant, and generally quite scant in the sparsely granulated adenoma. Morphologic differences between these two corticotroph adenomas are clearly evident upon ultrastructural study, as are differences in their differentiation. Densely granulated tumors are composed of intermediate sized angular cells having oval nuclei, well developed secretory organelles, and abundant tear-drop shaped, variably electron dense secretory granules (450 nm) that preferentially accumulate beneath the cell membrane. Another reliable diagnostic feature is the perinuclear accumulation of bundles of type 1 microfilaments. By contrast, the sparsely granulated variant is composed of smaller cells having poorly developed membranous organelles, a sparse distribution of small nondescript secretory granules, and only occasional tumors exhibit accumulation of type 1 microfilaments.

In Cushing's disease or other states of cortisol excess, nontumorous corticotrophs are subject to a conspicuous morphologic alteration known as "Crooke's hyalinization". The phenomenon refers to massive cytoplasmic accumulation of keratin microfilaments which encircle the nucleus and displace secretory granules and organelles to the periphery. Beyond providing evidence of sustained cortisol excess and being a marker of a functionally suppressed corticotroph, the pathophysiologic significance of Crooke's change is unknown.

It is important to acknowledge that more than 80 per cent of adenomas responsible for Cushing's disease are microadenomas, and many are only a few millimeters in diameter. Most arise in the mid-portion of the gland within its so-called "mucoid-wedge", a zone where corticotrophs are most numerous. Whereas only 10–15 per cent of microadenomas demonstrate local invasion, fully 60 per cent of macroadenomas are grossly invasive (Scheithauer *et al.* 1986a). The rare, but aggressive sparsely granulated variants are virtually always macroadenomas at presentation.

Despite the well established fact that corticotroph adenomas occurring in the context of Nelson's syndrome tend to be predictably more aggressive than those associated with Cushing's disease, differences in tumor morphology between the two are surprisingly subtle. Nevertheless, the majority of "Nelson's adenomas" are invasive macroadenomas, and as many as 20 per cent of patients harboring such lesions can be expected to succumb to uncontrollable local tumor growth. The aggressive behavior of these tumors has been ascribed to the loss of negative glucocorticoid feedback on account

of the bilateral adrenalectomy. That being the case, it suggests that corticotroph adenomas as a whole are not fully autonomous; instead, their secretory activity and growth rate appear subject to feedback and modulation by glucocorticoid hormones.

"Silent" Corticotroph Adenomas

During the past decade, a new class of pituitary adenomas have emerged as distinct clinicopathologic entities (Horvath *et al.* 1980, 1988). Termed "silent" corticotroph adenomas, they bear strong morphologic and immunohistochemical resemblance to hormonally active corticotroph adenomas, however, they are unaccompanied by clinical or biochemical evidence of ACTH excess. Why these tumors should be rendered functionally inert, despite an adequately developed secretory apparatus is unclear. One explanations relates to a failure of processing and post-translational cleavage of the POMC prohormone. Alternatively, the POMC molecule may be adequately cleaved but nascent ACTH is biologically inactive or subject to rapid degradation. The latter possibility has been supported by the finding of increased lysosomal activity in some silent corticotroph adenomas.

Two distinct silent corticotroph adenomas have been identified, each having a unique clinicopathologic profile. A third, no longer considered corticotrophic in nature, is discussed here for the sake of convenience.

Silent corticotroph adenoma subtype 1 is histologically and ultrastructurally identical to the densely granulated ACTH cell adenoma of Cushing's disease. Given their endocrinologic silence, these tumors remain concealed until progressive growth cause symptoms of mass effect. Accordingly, they are always macroadenomas at the time of diagnosis. An unusually large number of silent subtype 1 adenomas undergo apoplectic hemorrhage and infarction. In our experience, more than 40 per cent of subtype 1 adenomas presented in this fashion.

Silent corticotroph adenoma subtype 2 is morphologically and immunohistochemically similar to subtype 1 tumors and the densely granulated corticotroph adenoma. There are, however, subtle differences in their ultrastructure. Most subtype 2 tumors occur in men, usually as a large sellar mass accompanied by moderate elevations of PRL. In that the degree of hyperprolactinemia sometimes exceeds that attributable to simple stalk compression, it has been suggested that these tumors may be engaged in low level PRL secretion.

Silent subtype 3 adenoma is an unusual lesion with such peculiar clinical and morphologic features that precise classification of this tumor has been problematic. Once considered an odd variant of silent corticotroph adenoma subtypes, further study has excluded silent subtype three as having common origins as the corticotrophic subtypes. Histologically, these tumors may be

either acidophilic or chromophobic. Their immunohistochemical profile is even more variable as some tumors exhibit only faint focal ACTH immunoreactivity whereas others exhibit variable immunopositivity for a full spectrum of anterior pituitary hormones. The most common immunochemical profile involves co-expression of GH, PRL, ACTH, and alpha subunit. The ultrastructure of this tumor is complex but diagnostic. It more closely resembles well differentiated glycoprotein hormone producing adenomas than ones of corticotrophic type. The clinical presentation of these tumors is equally puzzling. Occurring with equal frequency in both sexes, tumors arising in men present during middle-age whereas those of women present during the second and third decades. In women, moderate elevations of PRL are the rule, producing a clinical picture suggestive of prolactinoma. In men, the typical presentation is that of a nonfunctioning adenoma, although sometimes a prolactinoma may be mimicked. Totally unexplained are acromegalic presentations which have, on rare occasions, been reported to accompany this tumor type (Horvath and Kovacs 1991).

Glycoprotein Hormone Producing Pituitary Adenomas

Pituitary adenomas engaged in glycoprotein hormone (FSH, LH, TSH) production are of two types: gonadotroph adenomas and thyrotroph adenomas. A third class, the plurihormonal adenomas, may also co-secrete glycoprotein hormones along with other secretory products; these are discussed separately below. Whereas thyrotroph adenomas may be associated with thyrotoxicosis, gonadotroph adenomas are unassociated with a recognizable hypersecretory endocrine state, and therefore present as "nonfunctioning" sellar masses.

The recent accumulation of data concerning glycoprotein hormone biosynthesis has significantly advanced understanding of the prevalence and secretory capabilities of glycoprotein hormone producing adenomas. Structurally, all members of the glycoprotein hormone family share a similar heterodimeric configuration, consisting of an "alpha" subunit common to all members of the class and a "beta" subunit which lends biochemical, immunological, and functional specificity (Gharib *et al.* 1990). Gonadotrophs and thyrotrophs, the glycoprotein hormone producing cells of the pituitary, normally synthesize equimolar concentrations of alpha subunit and their respective beta subunits, conjugating each to produce an intact, bioactive molecule prior to secretion. In the case of some gonadotroph and thyrotroph adenomas, faulty hormone synthesis results in excess production of the alpha subunit. Although without clinical consequence, such measurable excess of alpha subunit serves as a useful diagnostic marker for glycoprotein hormone producing adenomas, both in their initial diagnosis and during the postoperative surveillance of residual or recurrent disease ((Klibanski and Zervas 1991).

Gonadotroph Adenomas

Gonadotroph adenomas represent between 7 and 15 per cent of all pituitary adenomas. Since these tumors primarily affect the elderly, it has been suggested that gonadal failure may play a role in the genesis of gonadotroph adenomas, presumably by way of feedback inhibitory loss and the induction of gonadotroph hyperplasia. Whereas this notion does have some clinical and experimental merit, it is likely applicable only to tumors arising in postmenopausal women; elderly males generally have an intact pituitary-gonadal axis. It appears that gonadotroph adenomas occur more commonly in males, yet it is unclear if this apparent male predilection is genuine as gonadotroph adenomas may simply be more difficult to diagnose in females. In that elevation of gonadotrophic hormones is normal in postmenopausal females, the contribution of tumoral hypersecretion is often difficult to discern in female patients (Thorner *et al.* 1992). In both sexes, when tumoral hypersecretion of gonadotrophic hormones is demonstrated, FSH levels are most commonly elevated, followed in frequency by elevations of alpha subunit and LH; elevations of the latter are only rarely detected.

Lacking a clinically recognizable hypersecretory state to herald their presence, virtually all gonadotroph adenomas are macroadenomas at presentation. The typical clinical picture is one of a gradually enlarging sellar mass in association with visual failure and hypopituitarism. For the most part, gonadotroph adenomas are well circumscribed lesions having a rather indolent nature; their clinical effects being the result of simple compression rather than gross invasion. In that the rate of gross invasion in these tumors is lower than that of any other macroadenoma (21 per cent) (Scheithauer *et al.* 1986a), postoperative recurrence is infrequent.

Unlike normal gonadotrophs which appear basophilic, neoplastic gonadotrophs lack sufficient numbers of PAS secretory granules, and are therefore rendered chromophobic. Immunopositivity for FSH, LH, and alpha subunit can generally be demonstrated, although it may be faint or focal, particularly in tumors of female patients. Whereas gender related differences in tumor morphology are generally subtle at the light and immunochemical levels, graphic differences between the two sexes are apparent at the ultrastructural level. Tumors arising in male patients have variable ultrastructural features, yet bear little resemblance to the normal gonadotroph. Some "male tumors" are well differentiated, possessing well developed cytoplasmic organelles and a sparse collection of 200–250 nm secretory granules. Others, however, are less differentiated, have few characteristic morphologic features and resemble null cell adenomas. By contrast, the ultrastructure of gonadotroph adenomas occurring in women is both unique and consistent. Such "female tumors" are composed of better differentiated cells, possessing a full complement of cytoplasmic organelles which, overall, resemble those of normal

gonadotrophs. The cytoplasmic hallmark of female tumors is an impressive vesicular dilation of the Golgi complex, aptly termed "honeycomb transformation." Despite these gender-related differences in tumor morphology, the behavior of tumors is similarly indolent in both sexes.

Thyrotroph Adenomas

With fewer than 100 cases reported, TSH secreting adenomas are the least common pituitary tumor type, accounting for only 1 per cent of all pituitary adenomas (Hamilton *et al.* 1970, Hill *et al.* 1982, Saeger and Ludecke 1982, Smallridge *et al.* 1987, Girod *et al.* 1986, Gesundheit *et al.* 1989, McCutcheon *et al.* 1990). Of reported cases, most thyrotroph adenomas have been large aggressive macroadenomas, markedly invasive of surrounding structures. In the majority of instances, the accompanying clinical history is remarkable for some form of thyroid dysfunction. It was once believed that most arose in the context of longstanding primary hypothyroidism, presumably by way of feedback inhibitory loss and induction of thyrotroph hyperplasia and later, adenoma formation. Whereas such a perspective was compatible with earlier experimental studies wherein thryoidectomy induced pituitary thyrotroph adenomas in rodents (Furth *et al.* 1973), careful clinicopathologic correlations of human thyrotroph adenomas have suggested an alternate sequence of events. In fact, in the majority of patients the initial manifestations appear to be those of hyperthyroidism and goitre, events compatible with tumoral TSH hypersecretion. Many such patients were incorrectly believed to be suffering from primary hyperthyroidism and were subjected to some form of thyroid ablation. This served to temporarily ameliorate symptoms, only to be followed later by accelerated tumor growth, optic nerve compression, and/or recurrence of the hyperthyroid state. Only at this point was the pituitary correctly diagnosed as the site of pathology. The invasive nature of these tumors appears to be related to two factors, the first of which is the typical diagnostic delay. A more cogent factor, however, relates to the loss of feedback inhibition. In the same way that end organ ablation contributes to tumor aggressiveness in the context of Nelson's syndrome, similar disinhibiting influences may be operative in the progression of TSH adenomas in the setting of prior thyroidectomy. Fortunately, the routine availability of sensitive TSH assays coupled with the general awareness of thyrotroph adenomas as potential, though rare causes of hyperthyroidism, should now permit a more expeditious diagnosis of the tumor type, perhaps while still in the microadenoma stage. Furthermore, thyrotroph adenomas commonly co-secrete free alpha subunit in excess which may be a helpful diagnostic clue in favor of a pituitary source rather then a primary thyroid cause of hyperthyroidism.

The pathological diagnosis of thyrotroph adenoma can sometimes be problematic, particularly in the absence of a compatible clinical history. Unlike pituitary thyrotrophs which appear strongly basophilic, neoplastic thyrotrophs appear chromophobic as they lack sufficient secretory granules to impart the expected basophilic tinge. TSH immunopositivity, when present, is usually diagnostic, however, the lability of TSH protein may render immunochemical studies inconclusive. By electron microscopy, most thyrotroph adenomas do resemble normal thyrotrophs, but their degree of differentiation can often be quite variable. In the better differentiated tumors, polyhedral shaped cells can be seen bearing elongated cytoplasmic processes in which cytoplasmic microtubules can be seen to accumulate. The cytoplasm contains moderately developed rough endoplasmic reticulum and Golgi complexes. A small (200 nm) and sparse collection of spherical secretory granules assume a characteristic location just below the plasma membrane. Some of the less well differentiated tumors have few characteristic features and closely resemble null cell adenomas, thus electron microscopy may also be inconclusive.

Null Cell Adenomas and Oncocytomas

Approximately one quarter of all pituitary adenomas are unaccompanied by clinical evidence of hormone production, show scant, if any, hormonal immunoreactivities, and are ultrastructurally devoid of specific differentiation attributable to any of the five known anterior pituitary cell types. By definition, such tumors are designated as "null cell adenomas". Adenomas of this class may exist as one of two variants: the pure null cell adenomas and the oncocytomas. The distinction is purely a morphological one and relates to the intracellular accumulation of dilated mitochondria in oncocytomas. Thus, oncocytomas are simply null cell adenomas in which the intracellular mitochondrial content exceeds 10 per cent of the cell volume. This single morphologic distinction aside, null cell adenomas and their oncocytic variants can be considered biologically equivalent tumors, for neither clinical nor prognostic differences exist between the two. In that null cell adenomas and oncocytomas account for 17 per cent and 6 per cent of all pituitary adenomas, respectively, these two lesions collectively represent the most common surgically resected class of pituitary adenomas.

Despite the regularity with which null cell adenomas and oncocytomas are encountered in neurosurgical practice and the fact that their existence has been documented for more than two decades, much uncertainty remains with respect to their causation, cellular origins, and overall biology (Kovacs *et al.* 1990; Asa and Kovacs 1992a). The fact that some of these tumors are morphologically similar to undifferentiated gonadotroph adenomas has

fuelled speculation that null cell adenomas may be neoplastic offshoots of gonadotrophic lineage. The finding that almost 80 per cent of null cell adenomas express glycoprotein hormone genes lends compelling support to this theory (Jameson *et al.* 1987), as do various in vitro studies which document both gonadotropin release and gonadotropin releasing hormone (GnRH) responsiveness by null cell adenomas maintained in tissue culture (Asa *et al.* 1992c). Alternatively, there is preliminary evidence favoring the existence of non-neoplastic null cells scattered within the normal pituitary gland (Kovacs *et al.* 1989). It has been suggested that such "normal" null cells may be transitional, undifferentiated, or precursor cells, ones capable of shifting from a hormonally inactive or resting state to a hormonally active differentiated state. At least one case of a null cell adenoma with plurihormonal differentiation has been documented and points to the potential functional plasticity of null cells. Should non-neoplastic null cells be conclusively validated as genuine cellular elements of the adenohypophysis, one could envision null cell adenomas as neoplastic derivatives of such cells.

Concealed clinically by their endocrinological "silence", null cell adenomas and oncocytomas are slow growing tumors which are usually diagnosed only after they have attained sufficient size to impose mass effects. Most occur in the elderly patient, causing progressive visual loss, hypopituitarism, and headache. It is likely that the majority of these tumors have limited proliferative potential and have undergone years, even decades of covert growth. Whereas slow progressive growth is the rule, a minority of null cell adenomas (5 per cent) have an acute presentation with so rapid a clinical evolution that apoplexy may be suspect. In up to 40 per cent of null cell adenomas and oncocytomas, gross invasion of parasellar structures is evident radiologically and/or intra-operatively (Scheithauer 1986a).

Most null cell adenomas are chromophobic lesions and cannot be distinguished from other sparsely granulated lesions without immunohistochemical studies. In that mitochondria take up acidic stains, oncocytomas often appear acidophilic, particularly if mitochondrial accumulation is marked. Although many null cell adenomas are immunonegative for pituitary hormones, it is not uncommon to see faint immunoreactivity for one or more hormones within isolated or clustered tumor cells. Such meagre immunopositivity usually consists of FSH, LH, and alpha subunit; occasionally a rare GH or PRL immunoreactive cell may be seen. The ultrastructural features of null cell adenomas are characteristically bland, remarkable for an absolute lack of specificity. Tumor cells are small and possess a seemingly desolate cytoplasm in which the secretory apparatus appears poorly developed or vestigial and secretory granules are few and peripherally distributed. With the added feature of mitochondrial accumulation, oncocytomas have a similar ultrastructural appearance.

Plurihormonal Pituitary Adenomas

Whereas the majority of pituitary adenomas are dedicated to the synthesis and secretion of a single hormone, it has become increasingly clear that a number of pituitary adenomas produce two or more hormonal products (Scheithauer *et al.* 1986b, Kovacs *et al.* 1989, Thapar *et al.* 1993b). These "plurihormonal" pituitary adenomas were once considered rare, however recent estimates suggest that that up to 15 per cent of all pituitary adenomas exhibit multihormone processing capability. As defined here, a tumor is designated as plurihormonal if immunopositivity for two or more hormones can be identified within the same tumor cell (monomorphous plurihormonal adenomas), or if the tumor is composed of multiple cell populations, each engaged in the production of a different hormone (plurimorphous plurihormonal adenomas).

Given that there are seven potential secretory products expressed by pituitary tumors (GH, PRL, ACTH, LH, FSH, TSH, and the glycoprotein hormone alpha subunit), the potential combinations of different hormones both in number and in kind are theoretically numerous. In practice, however, there appears to be some predictability to the general pattern of hormone expression amongst these plurihormonal entities, although unusual combinations may also occur. Firstly, plurihormonal tumors occur most commonly in the context of acromegaly, where they constitute 50 per cent of all tumors producing the acromegalic state. These tumors most commonly co-express GH and PRL, and have already been described (mammosomatotroph, mixed GH-PRL, and acidophil stem cells adenomas above). Other commonly seen combinations include GH and TSH; and GH, PRL and TSH. In either of these groups, the alpha subunit may also be co-expressed. Aside from the setting of acromegaly, the other principal class of plurihormonal tumors are those composed of cells resembling glycoprotein hormone producing cells, which express any combination of LH/FSH, alpha subunit, TSH, GH, and occasionally PRL. Less intuitive combinations such as those co-expressing ACTH with other hormonal products may also occur, but are distinctly uncommon.

For unclear reasons, the multiplicity of hormonal products expressed within plurihormonal tumor tissue is not faithfully represented by corresponding elevations in blood hormone levels. The most clinically relevant aspect of plurihormonal tumors pertains to suspicions that plurihormonal tumors may be more aggressive than their monohormonal counterparts. In the case of other endocrine tumors (pancreatic tumors, medullary carcinoma of the thyroid and others), plurihormonal tumors are thought to portend a more malignant course that that of monohormonal versions. Evidence in support of a similar phenomenon in the pituitary remains inconclusive (Kovacs *et al.* 1989). It is known, however, that the overwhelming majority of plurihormonal pituitary adenomas are macroadenomas at presentation, even

in the presence of a hypersecretory syndrome. Furthermore, more than 50 per cent of all plurihormonal pituitary adenomas are grossly invasive at the time of diagnosis Scheithauer *et al.* 1986a, 1986b).

Invasive Adenomas

When sufficiently large, most pituitary adenomas will impose upon adjacent parasellar structures by simple mechanical compression. Despite their well differentiated nature and overall "benign" constitution, a substantial proportion of pituitary adenomas will also be frankly invasive of surrounding dural, osseous, and neural structures. The degree of invasion is often variable, ranging from minute tumor foci permeating adjacent dura, to rank and destructive infiltration of parasellar structures. Although the two are not always easily distinguished, "invasion" implies destructive infiltration whereas "extension" implies directional tumor growth with compression. In general, invasive adenomas exhibit both features. Lateral extension and penetration of the cavernous sinus is probably the most common pattern of gross local invasion. Occasionally, the interstices of the cavernous sinus may become so heavily involved that the carotid artery and cranial nerves transiting therein become ensheathed by tumor. Bony invasion is a regular feature of invasive adenomas and may range from localized infiltration of the sellar floor to extensive destruction of the skull base. Pituitary adenomas routinely extend into the suprasellar region where, in addition to compressing the chiasm, they may so deeply indent the third ventricle that they appear to die within it. Visual disturbance, hypothalamic dysfunction and obstructive hydrocephalus are the typical features of such extensions. As a rule, pituitary adenomas, even invasive ones, tend to displace rather than invade brain substance.

Whereas the aggressive behavior of invasive adenomas generally translates into diminished surgical "cure rates", this aspect of their biology is not faithfully reflected in their histopathological appearance. In fact, invasive adenomas exhibiting extreme local aggressiveness are often deceiving by their relatively innocent histological appearance. The usual morphologic hallmarks of tumor aggressiveness, namely, pleomorphism, nuclear atypia, hemorrhage, increased cellularity and mitotic activity, correlate poorly with a pituitary adenoma's invasive potential, proliferative capacity, tendency for postoperative recurrence, or its overall biological behavior.

As illustrated in Table 2, there is considerable variability in the incidence of invasiveness among different pituitary immunotypes. Moreover, the overall frequency of invasion varies is greatly depending on the criteria used to define the phenomenon. In this regard, radiographic (plain radiographs), intraoperative, and microscopic criteria are the most commonly used to document invasion, and on these criteria 10 per cent, 35 per cent, and 90 per

Table 2. *Size and Frequency of Gross Local Invasion Among the Major Pituitary Tumor Types* (Modified from Scheithauer *et al.*, 1986)

Pituitary tumor type	% Micro-adenoma	% Invasive	% Macro-adenoma	% Invasive	Overall incidence of invasion %
GH cell adenoma	14	0	86	50	50
PRL cell adenoma	33	N/A	67	N/A	52
Mixed GH-PRL cell adenoma	26	0	74	31	31
ACTH cell adenoma (Cushing's disease)	87	8	13	62	15
ACTH cell adenoma (Nelson's syndrome)	30	17	70	64	50
Silent ACTH adenomas	0	0	100	82	82
Gonadotroph adenomas	0	0	100	21	21
Thyrotroph adenomas	0	0	100	75	75
Null cell adenomas	2	N/A	98	N/A	42
Plurihormonal adenomas	25	31	75	59	52

The frequency of microadenomas and macroadenomas, the frequency of invasion among each, and the overall frequency of invasion for all major pituitary tumor types is given. In the case of PRL cell adenomas and null cell adenomas, data is available only for the overall frequency of invasion.

cent of all pituitary adenomas, respectively may be designated as invasive (Scheithauer *et al.* 1986a, Selman *et al.* 1986). Not surprisingly, microscopic evidence of dural invasion increases with tumor size, being present in 66 per cent of microadenomas, 87 per cent of macroadenomas, and in 94 per cent of macroadenomas with suprasellar extension (Selman *et al.* 1986). In that microscopic evidence of dural invasion is so regular a feature in the majority of pituitary adenomas, including the most indolent of microadenomas, it is of little diagnostic use either as an index of biological aggressiveness or as a meaningful index of invasiveness. Accordingly, it has become common practice to designate adenomas as "invasive" on the basis of radiologic or intraoperative evidence of gross invasion instead of the seemingly ubiquitous occurrence of microscopic dural involvement.

Carcinoma of the Pituitary Gland

Despite the regularity with which many pituitary adenomas exhibit aggressive, and seemingly "malignant" local invasiveness, it is intriguing that so

few pituitary tumors actually harbor metastatic potential. In fact, metastasizing pituitary tumors, i.e. pituitary carcinomas, represent an exquisitely rare form of human cancer; fewer than 40 well-documented cases have been described (Mountcastle *et al.* 1989 reviewed in Pernicone and Scheithauer 1993). Pituitary carcinoma is a precisely defined entity, one that includes only those tumors of adenohypophyseal origin with demonstrated craniospinal and/or systemic metastatic dissemination. In contrast to most human epithelial cancers, generic histologic criteria of malignancy (anaplasia, nuclear atypia and pleomorphism, mitotic activity, necrosis, invasiveness) are insufficient to constitute a diagnosis of pituitary carcinoma, for these features may be seen in ordinary pituitary adenomas. Instead, the diagnosis is predicated upon biological behavior and is relatively independent of histology. Metastatic dissemination appears to most commonly involve the cerebrospinal fluid axis, although a variety of extraneural metastatic sites have also been reported, including bone, liver, lymph nodes, lung, kidney and heart.

Pituitary carcinomas primarily affect adults and show a slight female preponderance. Their clinical presentation is surprisingly variable. In some patients the initial clinical course is indistinguishable from that of a benign pituitary adenoma. Local invasion may, or may not be present, and tumor histology may appear entirely benign. A protracted course, often punctuated by multiple local recurrences, is then followed by metastatic dissemination. In many such cases, clear escalation in histologic aggressiveness from primary tumor to metastatic deposit is evident, suggesting that some pituitary carcinomas arise as the result of malignant transformation in a pre-existing benign tumor. Inexplicably, some metastatic deposits retain the benign morphology of the primary tumor. Alternatively, the behavior of some pituitary carcinomas suggests de novo malignancy. Such tumors are biologically malignant from the outset, beginning as locally invasive, cytologically atypical primary tumors which promptly give rise to metastatic dissemination.

Although pituitary carcinomas can be either hormonally active tumors or nonfunctional tumors, the former appear to predominate. Pituitary carcinomas composed of corticotroph (especially in the context of Nelson's syndrome), prolactin cells, and GH cells are the immunotypes most frequently represented. Metastatic deposits generally retain the immunotype of the primary tumor. Because the pituitary is not infrequently a recipient of metastatic carcinomas originating systemically, one must, by careful clinical and pathological examination, exclude the far more common occurrence of a metastasis to the pituitary gland.

The factors which underly the capacity for metastatic dissemination in pituitary carcinoma are obscure, though their mode of spread is more fully understood. Craniospinal dissemination appears to be the result of invasive extension into the subarachnoid space and subsequent dissemination by CSF flow. Intracranial deposits involving brain substance probably develop as the

result of tumor permeation of perivascular (Virchow-Robin) spaces or by venous sinus invasion. Extracranial spread of pituitary carcinomas involves both hematogenous and lymphatic routes. Invasion of the cavernous sinus provides the necessary venous access for transport to the internal jugular vein via the petrosal system. Although the pituitary itself lacks lymphatic drainage, invasion of the tumor into the skull base provides access to a rich lymphatic network, one which in turn mediates systemic dissemination. Death from pituitary carcinoma is invariably the result of mass effects from extensive intracranial disease. To date, relatively few patients have died as the direct consequence of extracranial metastatic disease (Pernicone and Scheithauer *et al.* 1993). In that neither the presence nor the treatment of systemic metastases appears to affect the prognosis of pituitary carcinomas, the frequency of metastases, particularly nonfunctioning ones, is probably under-reported. Thus the true incidence of pituitary carcinoma may be more common than currently believed.

Proliferation Markers and Laboratory Evaluation of Pituitary Tumor Aggressiveness

Given the poor correlation which exists between the histopathology and aggressiveness of pituitary adenomas, the reliable prediction of their clinical behavior has proved to be one of the most inscrutable aspects of pituitary tumor biology. Accordingly, a number of contemporary strategies have been applied to the problem of assessing the proliferative potential of pituitary adenomas. Although many of these are still of research interest only, they are gradually reaching levels of clinical applicability. With ongoing refinements and increasing experience, strategies such as these should, in the foreseeable future, assume increasing importance in reliably predicting the behaviour of any given pituitary adenoma.

Ki-67 is a cell cycle specific nuclear associated antigen of uncertain function whose expression is restricted to proliferating cells in the G1 to M phase of the cell cycle (Gerdes *et al.* 1984). Thus, its immunochemical presence and relative abundance in tumor tissue provides some measure of a tumor's proliferative activity. In one study, invasive adenomas expressed twice the amount of Ki-67 protein as non-invasive adenomas (Knosp *et al.* 1989). In another report, Ki-67 protein was demonstrated in greatest abundance in tumors of Cushing's disease, a finding which the authors interpreted as being compatible with the higher recurrence rates seen in corticotroph tumors (Landolt and Shibata 1991). Although an interesting correlation, any conclusion that the higher surgical failure or postoperative recurrence rates in corticotroph adenomas are the result of enhanced proliferative activity of tumor cells must be interpreted with caution. After all, most corticotroph adenomas are microadenomas, often only a few millimeters in size. More-

over, given their small size, greater technical demands are imposed on the surgeon for definitive intraoperative identification of the tumor and its removal. Accordingly, other issues, likely technical ones, may be more important factors accounting for their higher recurrence rather than the tumors' enhanced proliferative activity alone.

A second proliferation marker which has assumed increasing practical utility in a variety of tumor types is PCNA (proliferating cell nuclear antigen). This nuclear protein is a critical accessory protein of the enzyme DNA polymerase delta (Zuber *et al.* 1989). The latter polymerizes DNA nucleotides essential for polymerization of DNA nucleotides during leading strand DNA replication just prior to cell division. Its nuclear expression is, therefore, a requirement for all replicating cells. PCNA expression was recently studied in a group of pituitary adenomas of all sizes and various immunotypes, including nonrecurrent and recurrent tumors (Hsu *et al.* 1993). Of the 30 recurrent pituitary tumors studied, the percentage of tumor cells expressing PCNA was significantly higher than in those of non-recurrent tumors. Not surprisingly, normal adenohypophyseal tissue contained fewer PCNA positive cells than those of tumorous tissue. The PCNA index, in addition to being highest among recurrent tumors, was also higher in macroadenomas, particularly those exhibiting extrasellar extension. Moreover, among recurrent tumors, a higher PCNA index tended to be accompanied by a shorter disease-free interval. Of further interest was the finding that among recurrent tumors in which tumor tissue from the first and second surgeries were analyzed, the PCNA expression appeared enhanced in recurrent tumor tissue. This observation is compatible with the notion that tumor progression can be viewed as the product of ongoing sublethal genetic damage resulting in clones which have acquired a selective growth advantage.

Recently, histochemical quantification of argyrophil nucleolar organizing regions (AgNORs) in tumor tissue has become another informative proliferation marker for several tumor types. Whereas mean AgNOR counts in some recurrent and invasive pituitary adenomas have been found to be higher than in noninvasive tumors, the correlation has not been consistently observed among all invasive adenomas studied (Stefaneanu *et al.* 1989). This technique, while of some scientific interest, has not proven practically informative in predicting the behaviour of pituitary adenomas. The search for a pituitary specific proliferation marker remains an active area of pursuit. The presence of various antigens and novel proteins has been documented in pituitary tumor tissue such as cytokeratins (Ironside *et al.* 1987), mAB lu-5 (a panepithelial marker) (Kovacs *et al.* 1987), neuron-specific enolase (Asa *et al.* 1988), chromogranin (Lloyd *et al.* 1985), synaptophysin (Stefaneanu *et al.* 1988), galanin (Vrontakis *et al.* 1990) vasoactive-intestinal peptide (Hsu *et al.* 1989), S-100 protein (Marin *et al.* 1992), ubiquitin (Marin *et al.* 1993), and renin (Saint-Andre *et al.*1986). Again, these findings have been

primarily of scientific and/or physiologic interest; none of these markers has proven prognostically or practically informative with respect to pituitary adenoma behavior.

In recent years, several workers have studied pituitary adenomas with flow cytometry. Most studies have shown pituitary adenomas to be diploid, although reports of aneuploidy approach 50 per cent (Mork *et al.* 1980, Anniko *et al.* 1984, Fitzgibbons *et al.* 1988, Joensuu and Klemi 1988). Neither the DNA content nor S-phase fractions, nor aneuploidy in pituitary adenomas correlates well with invasiveness, recurrence, or overall aggressiveness in pituitary adenomas (Joensuu and Klemi 1988). S-phase fractions have also been determined in situ following the in vivo administration of bromodeoxyuridine (BrDU), a thymidine analog (Nagashima *et al.* 1986). The incorporated BrDU in tumor tissue is revealed by immunohistochemistry using anti-BrDU antibody. In that pituitary adenomas have relatively low proliferation rates overall, the S-phase fractions are usually small, generally less than 0.5 per cent. The consistent finding that tumors of Nelson's syndrome have the highest S-phase fractions validates the aggressiveness observed clinically in this group of tumors. The narrow range of observed S-phase fractions in pituitary adenomas overall, however, limits the sensitivity of this technique in distinguishing subtle differences in S-phase fractions between aggressive and non-aggressive pituitary adenoma variants. More promising have been flow cytometric determinations of proliferation associated nuclear antigen p-105. In one report, recurrent diploid tumors demonstrated a significantly increased G2M/G0G1 p-015 fluorescence ratio (Fitzgibbons *et al.* 1988).

The most recent strategy for identifying differences in biological behavior among pituitary adenomas centers on the search for specific genomic alterations which could serve as markers of tumor aggressiveness. The subject of genomic alterations and pituitary tumorigenesis is discussed fully below, however, a few points merit discussion here. Of the genomic alterations screened for among pituitary adenomas and carcinomas, several have been preliminarily correlated with tumor aggressiveness (Fig. 1). To date, activating mutations of the H-*ras* gene have been identified in one invasive prolactinoma, one prolactin producing carcinoma, three ACTH producing carcinomas (Karga *et al.* 1992, reviewed in Prager and Melmed 1993). Given the relatively small number of pituitary tumors exhibiting such mutations, they are unlikely to be common contributors to pituitary tumorigenesis. That their occurrence appears restricted to aggressive carcinomas and invasive adenomas, however, suggests that such mutations occur late in the course of pituitary tumorigenesis and their presence could serve as markers for particularly aggressive tumors. Tumor suppressor gene mutations, specifically those involving the Rb and p53 genes, have also been identified in pituitary tumors, although rarely. Again, their occurrence has been restricted to invasive adenomas and pituitary carcinomas. Mutation of one Rb allele was

detected in one invasive silent corticotroph adenoma and in 4 corticotroph carcinomas (Prager and Melmed 1993). In our laboratory, mutant p53 protein has been detected in a single, yet particularly aggressive prolactin cell carcinoma. Again, mutations of p53 and Rb genes, while uncommon among pituitary tumors overall, do appear to occur in tumors remarkable for aggressive local invasiveness and/or metastasizing capability (Fig. 1).

A final genomic alteration occurring in pituitary adenomas, specifically invasive ones, relates to the protein kinase-C (PKC) family of second messengers. The PKC enzyme family are ubiquitous membrane-bound intracellular kinases whose function is to phosphorylate serine or threonine residues

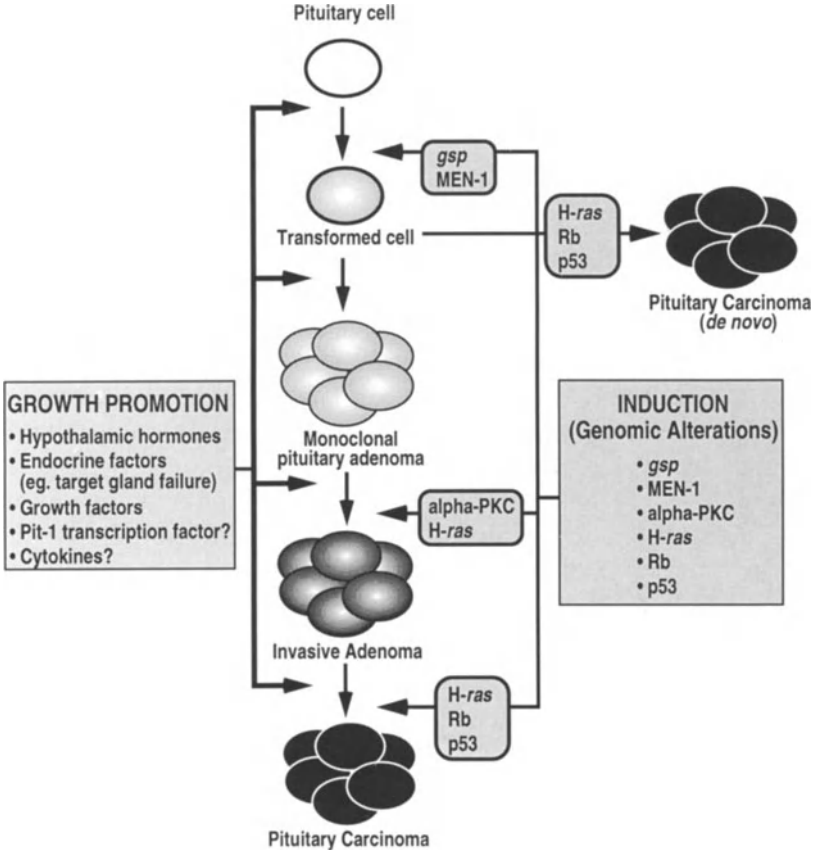


Fig. 1. Illustration of events currently considered important in the genesis and progression of pituitary adenomas. The current two-step model of pituitary tumorigenesis (Melmed 1992), distinguishes initiating events (right side) and growth promotion events (left side). With the exception of *gsp* mutations, which have had substantial study, the importance of other events depicted remains tentative, for they have been the subject of only limited study to date; see text

on important substrate proteins. Such kinase activity regulates a wide variety of fundamental cellular processes, including the transmembrane signalling underlying cell proliferation and differentiation. Altered or aberrant PKC activity has been demonstrated in several human tumors, including pituitary adenomas (reviewed in Gescher 1992). In comparison with normal pituitary tissue, heightened PKC activity and PKC protein expression were demonstrated in both hormonally active and nonfunctioning pituitary adenomas (Alvaro *et al.* 1992). More recently, it has been shown that the specific PKC isoform overexpressed in pituitary adenomas is PKC-alpha. Interestingly, this particular PKC isoform has been favored as one of the isoforms mediating PKC's mitogenic actions. Of further interest was the finding that not only is PKC-alpha overexpressed in pituitary adenomas, the protein is also structurally abnormal (Alvaro *et al.* 1993). Among four invasive adenomas an identical conserved point mutation at position 908 of the PKC-alpha cDNA was identified. The significance of this alteration at the protein level has not been fully characterized, however, it does appear to involve a functionally strategic domain of the enzyme, a region containing the all important calcium binding site. How conformational alterations accompanying such single amino acid substitutions contribute to invasiveness, whether the result of altered calcium binding affinity or other mechanisms, remains to be determined.

Despite the application of the above-mentioned strategies, linkage between the pathological diagnosis of pituitary adenomas and prediction of their biological behavior has yet to reach a practical and prognostically informative level. One important reason undermining progress in this area is the simple fact that pituitary adenomas are, for the most part, low grade neoplasms. Lacking the overtly malignant constitution of the more common high-grade epithelial tumors arising elsewhere, generic proliferation markers informative for the latter are generally of limited utility in pituitary adenomas. Still, such studies of proliferative and invasive potential in pituitary adenomas do provide an insight into this aspect of their biology.

Pathogenesis and Molecular Biology of Pituitary Adenomas

Compatible with existing paradigms of human tumorigenesis, the development of pituitary adenomas appears to be a multicausal, multistep process, one which, in its most abbreviated form, consists of an irreversible tumor initiation phase followed by a tumor progression phase (Melmed 1992). Given the constraints of contemporary knowledge, the specific events necessary to accomplish the process in the pituitary are still only superficially understood. Nonetheless, it is becoming increasingly clear that endocrine factors, hereditary predisposition, and specific somatic mutations may all serve as contributing factors in varying proportions and in varying types of

pituitary adenomas. Before considering the relative roles of these and other pathophysiologic factors in pituitary tumorigenesis, it is critical to acknowledge that transformation in the pituitary is a monoclonal process. This finding is of much conceptual significance and provides the background upon which the other pathophysiologic events must be integrated. Accordingly, we begin this discussion by reviewing current understanding of the clonal origins of pituitary adenomas.

Clonal Origins of Pituitary Adenomas

A fundamental question regarding pituitary tumorigenesis relates to the issue of whether transformation in the pituitary is primarily the product of hypothalamic dysfunction or simply the result of an acquired abnormality intrinsic to an isolated adenohypophyseal cell. The "hypothalamic" hypothesis suggests that pituitary tumors arise as the downstream consequence of excess trophic influences emanating from a dysfunctional hypothalamus. Alternatively, the "pituitary" hypothesis suggests that pituitary adenomas arise as the result of an intrinsic pituitary defect, with neoplastic transformation occurring in relative autonomy from hypothalamic influence. Hypothalamic dysfunction was historically considered an important, if not a necessary component of pituitary tumorigenesis, a view which continues to maintain both experimental and conceptual support. Recent evidence of a clinical, pathologic, and a molecular nature, however, suggests otherwise, providing increasing appeal for tumorigenic mechanisms converging at the level of a single, susceptible, adenohypophyseal cell. That many pituitary adenomas can be successfully "cured" by surgical removal, coupled with the fact that these tumors are rarely accompanied by a zone of peritumoral hyperplasia collectively mitigate in favor of pituitary adenomas arising as the result of an intrinsic pituitary cell defect rather than the result of hypothalamic overstimulation.

Further support for a de novo adenohypophyseal origin for pituitary adenomas was provided by a number of recent reports concerning their clonal composition (Alexander *et al.* 1990, Jacoby *et al.* 1990, Herman *et al.* 1990, Schulte *et al.* 1991, Biller *et al.* 1992). Using the strategy of allelic X-chromosome inactivation analysis which assesses restriction fragment length polymorphisms and differential methylation patterns in X-linked genes, a monoclonal constitution has been confirmed for both functional and nonfunctioning pituitary adenomas. The validation of monoclonality for pituitary tumors has been a conceptually important advance for it establishes pituitary adenomas as monoclonal expansions of a single, somatically mutated and transformed cell. Were generalized hypothalamic overstimulation the dominant initiating event, a population of anterior pituitary cells should simultaneously be affected, giving rise to a population of transformed cells

with a polyclonal tumor being the expected result. Of the pituitary adenomas studied to date, virtually all informative tumors have had a monoclonal composition. One notable exception to this monoclonal scheme, however, involved corticotroph adenomas wherein isolated polyclonal tumors have been identified (Schulte *et al.* 1991). That corticotroph adenomas should, on rare occasion, be exceptions to the rule is not too surprising given that evidence favoring a hypothalamic etiology for this tumor type has been notably stronger than for other pituitary adenomas.

Thus, excluding isolated instances of corticotroph adenoma, pituitary adenomas can generally be regarded as monoclonal tumors derived from a single transformed cell, one in which nonlethal somatic mutation(s) have conferred a selective growth advantage. Whereas such a somatic mutation perspective conforms well to contemporary paradigms of human tumorigenesis, it also tends to minimize the role of hypothalamic influences in pituitary tumor development. Such a tendency may not be fully justified, particularly in view of the abundant clinical and experimental evidence implicating a hypothalamic component to pituitary tumorigenesis (see "endocrine factors", below). Thus, despite the compelling evidence favoring an intrinsic etiology to pituitary tumor development, the pathophysiologic component of hypothalamic dysfunction cannot be entirely ignored and must somehow be integrated in the current monoclonal model of pituitary tumorigenesis.

Recalling that pituitary tumor development is believed to consist of a tumor initiation phase followed by a tumor promotion phase, it is plausible that hypothalamic dysfunction may be an important component of each. Whereas a specific somatic mutation appears to be a necessary step for an adenohypophyseal cell to transform, hypothalamic influences, as mediated by a number of hypothalamic hormones, may modify the cell's susceptibility for such a mutation to occur. When dysregulated, hypothalamic effects on the pituitary may be ones of enhanced stimulation and/or deficient inhibition. Given the heightened proliferative activity of adenohypophyseal cells that would accompany such perturbations, the likelihood of developing transforming mutations would correspondingly increase. Moreover, studies of experimental tumors indicate that, under certain circumstances, a transition from a polyclonal tumor to a monoclonal one may occasionally occur (Woodruff *et al.* 1982). Therefore, pituitary tumors deemed monoclonal on the basis of allelic X-inactivation analysis may indeed have originated as polyclonal proliferations, but during the course of development, all clones except one were competitively eliminated. Should such a phenomenon be operative in the pituitary, hypothalamic dysfunction may prove to have a very genuine role in pituitary tumor initiation after all.

A more persuasive role for hypothalamic dysfunction in pituitary tumorigenesis can be envisioned during the tumor promotion phase of the multistep model of pituitary tumor development. Given that pituitary adenomas fre-

quently express receptors for, and retain responsiveness to hypothalamic hormones, the latter are believed to facilitate the proliferation of transformed cells (Billestrup *et al.* 1986). The net effect of such facilitative activity, whether the result of amplified stimulatory inputs or diminished inhibitory ones, would be tumor progression. Accordingly, aberrant hypothalamic regulation may prove to be an important determinant of various tumor parameters such as growth rate, invasiveness, level of secretory activity and potential for surgical failure and/or postoperative recurrence. That such parameters have yet to be reliably correlated with the presence or absence of any particular genomic mutation further suggests that additional factors, likely hypothalamic ones, may modulate the biological behavior of the transformed adenohypophyseal cell.

Since the initial reports of a monoclonal origin for pituitary adenomas, perspectives of pituitary tumorigenesis have seemingly, yet understandably, been polarized to one specific event in the neoplastic process: the somatic mutation. Admittedly an event mandatory to neoplastic transformation, somatic mutations appear to be but one component of the overall subcellular biology governing pituitary tumorigenesis. Growth factors, hypothalamic hormones, and other regulatory elements, possibly by altering the susceptibility for the occurrence of somatic mutations or later modulating the behavior of the transformed clone, are becoming increasingly recognized as potentially important mediators of tumor development in the pituitary. Thus it is important to recognize that the current model of pituitary tumorigenesis requires the coordinated action of both initiating and promoting events. With this background in mind, the remaining portions of the chapter examine those initiating and promoting events currently considered important to pituitary tumor development.

Pituitary Tumorigenesis: Endocrine Factors

Excluding the relatively few pituitary adenomas arising in the context of a specific predisposing hereditary condition (see below), the overwhelming majority of pituitary adenomas can be considered acquired lesions. Despite exhaustive experimental and epidemiologic study, the development of pituitary tumors has yet to be etiologically and definitively ascribed to any known physical, environmental, or pharmacologic agent. Still, a recurring observation from such studies relates to a possible predisposing, promoting or even inductive effect of altered endocrine states in the development of pituitary tumors. In instances of target gland ablation/failure, such as those occurring in Addison's disease and primary hypothyroidism, the respective frequencies of corticotroph "tumorlettes" and TSH adenomas were higher than those observed in control individuals (Scheithauer *et al.* 1983, Scheithauer *et al.* 1985). Admittedly only a loose correlation, but stronger still, and of greater

practical relevance, is the relationship between the behavior of corticotroph adenomas and thyrotroph adenomas treated with bilateral adrenalectomy and thyroidectomy, respectively. That such tumors tend to be notoriously more aggressive than those having intact pituitary-target gland axes emphasizes the pathophysiological importance of target gland feedback inhibition in modulating the progression of these tumors (Wilson *et al.* 1979).

A final endocrine issue, one repeatedly implicated in the genesis of pituitary adenomas, particularly PRL producing adenomas, concerns the role of estrogens as mediators of transformation and/or neoplastic progression in the pituitary. The tumor-promoting properties of this sex-steroid are transduced by specific estrogen receptors, ones which in response to ligand activation, transform, dimerize and bind to specific DNA addressing sites, thus inducing the transcription of various target genes governing cell proliferation (Barrett 1991). Chronic estrogen administration, though well established as inducing PRL producing tumors in rodents (Cramer and Horning 1936), appears to have a less convincing role in humans. Attempts to implicate oral contraceptive use as an explanation for the high incidence of prolactinomas in premenopausal women has largely been dismissed with case controlled studies (reviewed in Reichlin 1991). Nonetheless, estrogens do alter the morphology and endocrine activity of human adenohypophyseal cells (Scheithauer *et al.* 1989), thus indicating that the anterior pituitary is an important target tissue for estrogen action. That human pituitary adenomas express estrogen receptors was first demonstrated more than a decade ago (Pichon *et al.* 1980). We have since demonstrated the presence of estrogen receptor mRNA in all forms of pituitary adenoma as well as in all cell types of the normal pituitary (Stefaneanu *et al.* 1994). Furthermore, in at least a single instance, one involving a transsexual patient, high dose estrogen therapy has convincingly been correlated with development of a human PRL producing adenoma (Kovacs *et al.* 1994).

Pituitary Adenomas: Cytogenetic Aberrations

The earliest and most graphic evidence in support of the concept that neoplasia represents the successive cellular accumulation of genetic alterations derives from studies depicting the myriad of chromosomal aberrations expressed by tumor cells. Cytogenetic studies of such aberrations have contributed significantly to our understanding of various aspects of tumor biology in a variety of tumor types. In the case of pituitary adenomas, given their low intrinsic mitotic rate and overall benign constitution, metaphase preparations have been difficult to procure and few direct cytogenetic analyses have been successfully performed. Nonetheless, a variety of chromosomal aberrations have been demonstrated in pituitary adenomas. As mentioned previously, flow cytometric studies have demonstrated aneuploidy in up to 50 per cent of

pituitary adenomas. More recently, it has been demonstrated that cytogenetic aberrations are more common among hormonally active pituitary adenomas than in endocrine-inactive ones (Rock *et al.* 1993). Whereas 72 per cent of hormonally active pituitary adenomas (most being of GH and PRL types) exhibited cytogenetic alterations, only 29 per cent of hormonally inactive adenomas deviated from the normal chromosomal complement. Of all cytogenetic alterations, rearrangements involving chromosomes 17 and 19 were most commonly observed, followed in frequency by trisomy of chromosome 7, and other structural abnormalities involving chromosomes 1 and 4. In a recent cytogenetic analysis of a corticotroph adenoma, clonal deletion of 18p was demonstrated (Capra *et al.* 1993).

Given the limited number of cytogenetic analyses performed on pituitary adenomas to date, it is impossible to determine the pathophysiologic significance of chromosomal aberrations so far cataloged. Whether these changes are indeed consistent, nonrandom, and primary alterations which contribute to transformation and/or neoplastic progression in the pituitary remains to be seen. Alternatively, they may simply be random, epigenetic changes reflecting the genetic instability inherent in neoplastic cells, being neither informative nor important to the evolution or progression of pituitary adenomas. Certainly, further studies will be needed to clarify this issue.

Structural Genomic Alterations: Oncogene Activation (v-fos, H-ras, gsp)

Proto-oncogenes are a discrete class of regulatory genes which have a normal and necessary presence in the vertebrate genome. The proteins encoded by these genes subserve a variety of critical cellular functions relating to cell growth, differentiation, and proliferation. Should such genomic elements sustain irreparable yet nonlethal genetic damage, typically as a result of point mutations, deletions, rearrangements, or amplification, the normal gene may be converted into a cellular transformant, or oncogene. The process is referred to as oncogene activation and is generally a tissue-specific phenomenon. That is, the transforming capabilities of oncogenes are restricted to cells which are sensitive to the oncoprotein or dysfunctional gene product encoded by the oncogene. In susceptible cells, the downstream consequence of an activated oncogene is disruption of growth regulation and kinetics, so much so that transformation and uncontrolled cell proliferation ensue.

Although identified in only a minority of pituitary adenomas, oncogene activation is one mechanism of acquiring a transforming somatic mutation within the adenohypophysis. To date, activating mutations of v-*fos*, H-*ras*, and the *gsp* oncogene have been identified in various pituitary adenoma types. Whereas the latter mutation has been consistently observed in a substantial proportion of somatotroph adenomas, the others have been the subject of isolated case reports only.

v-*fos* is a class IV oncogene, one encoding a nuclear oncoprotein having transcriptional action. In an early report of a single prolactinoma, a 10 fold amplification of v-*fos* was demonstrated (U *et al.* 1988). That additional cases harboring similar mutations have not been reported suggests that v-*fos* is not a common transformant in the pituitary.

The *ras* oncogenes were the first nonviral oncogenes to be recognized, and have since been identified in a variety of human tumors. They are actually a family of three structurally similar oncogenes which encode proteins involved in intracellular signal transduction (Class III oncogenes). The proteins encoded by the normal (wild-type) *ras* genes are small monomeric guanine nucleotide (GTP/GDP) binding proteins termed p21 ras. Little is known of the upstream receptors expected to activate *ras*, and even less is known of the downstream targets and second messenger systems thought to be regulated by *ras*. It is known, however, that wild type p21 ras exists in critical equilibrium between an inactive GDP bound state and an active GTP bound state. The transition from active to inactive p21 ras requires a second protein termed GAP (GTP-ase activating protein). Oncogenic mutations of ras are the result of missense mutations causing amino acid substitutions within GTP binding domains. Presumably, oncogenic mutations of *ras* encode a mutant p21 whose conformation properties compromise and/or inhibit GTPase activity, thus shifting the equilibrium in favor of a sustained active state. The positive signal emanating from perpetually activated p21 protein are further transduced downstream, with uncontrolled cell proliferation being the end result. A comprehensive analysis of *ras* mutations involving 19 pituitary adenomas was recently undertaken (Karga *et al.* 1992). In only one instance, a prolactinoma, was a mutation of ras demonstrated; the mutation involved the H-*ras* gene wherein valine was substituted for glycine at codon 12. It is of interest that the prolactinoma harboring this *ras* mutation was unusually aggressive, one remarkable for an early age of onset, multiple recurrences, very high prolactin levels, and unrelenting invasiveness which ultimately proved fatal. A second recent survey of H-*ras* mutations in pituitary carcinomas was recently undertaken (reviewed in Prager and Melmed 1993). Whereas none of the primary pituitary lesions exhibited activating mutations of H-*ras*, the secondary metastatic deposits emanating from these pituitary carcinomas did in fact exhibit mutations of H-*ras*; two were corticotroph carcinomas (codon 12 mutations) and the third was a PRL cell carcinoma (codon 18 mutation). These studies suggest that the occurrence of activating H-*ras* mutations, while uncommon among pituitary adenomas overall, do appear to be associated with a particularly aggressive phenotype and are likely late events in pituitary tumor progression (Fig. 1). Furthermore, the presence of H-*ras* mutations in secondary deposits but not in the primary lesion of pituitary carcinomas is especially intriguing for it suggests that they may play a role in initiating and/or sustaining distant pituitary metastases.

The most consistent and convincing evidence favoring oncogene activation as a transforming mechanism in the pituitary stems from the discovery of the *gsp* oncogene, an oncogene first characterized in GH producing pituitary adenomas (Vallar *et al.* 1987). The signal transduction cascades governing the secretory and proliferative functions of pituitary somatotrophs converge on the adenylate cyclase second messenger system. G-proteins, ones analogous to those described for p21 ras, are essential components of these regulatory cascades. The upstream initiation events and downstream second messenger systems are, however, far better characterized for G-protein-mediated signalling in the somatotroph.

Like those of p21 ras, G-proteins regulating somatotroph function bind GTP. Their capacity to transduce signals from an activated membrane receptor to intracellular effectors requires them to displace bound GDP for GTP, a process which activates the G-protein and initiates the signal to which downstream events are coupled. Termination of receptor stimulation is followed by a coordinated return of the G-protein to its inactive GDP bound state, a process requiring hydrolysis of bound GTP to GDP. Whereas G proteins involved with p21 ras are of monomeric type, those mediating intracellular signalling in the somatotroph are heterotrimeric. The latter designation refers to their composite structure which consists of three distinct subunits (α, β, γ). Both the functionality and specificity of these G-proteins are provided by the alpha subunit, which differs among different members of the G-protein family. The alpha subunit not only contains the activating GTP binding site, but it also has intrinsic GTPase activity. The latter is a critical self-limiting mechanism which serves to hydrolyze bound GTP to GDP, returning the G-protein from its activated GTP bound state to its inactive GDP bound form, and, therefore, terminating its signal to intracellular effectors.

In the normal state, the principal positive regulator for the somatotroph is growth hormone releasing hormone (GHRH), a stimulatory peptide of hypothalamic origin effecting GH secretion and somatotroph proliferation. GHRH binds to specific membrane receptors on the somatotroph surface, its signal being transduced by a stimulatory G protein designated as Gs. Receptor occupancy by GHRH induces a conformational change in the alpha subunit of Gs, causing displacement of bound GDP for GTP. When GTP bound, Gs is subject to a complex dissociative reaction which results in a free (β, γ) dimer and the active alpha subunit-GTP complex. The latter then activates adenylate cyclase which, in turn, elevates intracellular cAMP levels, the second messenger for downstream events inducing somatotroph proliferation and GH secretion. Normally, activation of Gs is a transient event, one in which the active state of Gs is maintained only for the duration of receptor stimulation. Accordingly, termination of the GHRH stimulation is promptly followed by hydrolysis of GTP to GDP, restitution of Gs to its

inactive heterotrimeric form, "turning off" of adenylate cyclase, return of cAMP to basal levels, and termination of signals promoting GH secretion and somatotroph proliferation.

Prompted by their discovery that a subgroup of somatotroph adenomas exhibited high levels of intracellular cAMP and membrane adenylate cyclase activity, the hypothesis that a nontransient, constitutive activation of adenylate cyclase may be the underlying tumorigenic mechanism for this subgroup of GH secreting tumors was introduced (Vallar *et al.* 1987, Landis *et al.* 1989). Moreover, the latter study demonstrated that constitutive activation of Gs could be accomplished by specific mutations involving the alpha chain gene. The alpha chain protein encoded by such mutations exhibited an intrinsic deficiency of GTPase activity, rendering it incapable of self-terminating its activated state. Therefore, such activating mutations stabilize Gs in its active conformation, thus mimicking the effect of persistent GHRH action. By-passing the normal regulatory control provided by GHRH, somatotrophs bearing the mutated alpha chain are conferred an autonomous and unrestrained capacity for GH secretion and cell proliferation, manifesting ultimately as neoplastic transformation. Such activating mutations of the alpha chain gene convert it to an oncogene, now designated as the *gsp* oncogene. Corroborative evidence favoring inactivation of alpha chain GTPase activity as a mechanism to enhance secretory and proliferative functions of pituitary somatotrophs was also provided by elegant experimentation in a transgenic animal model. The cholera toxin, by ADP ribosylation of Arg 201 of the Gs alpha chain, can inhibit intrinsic GTPase activity. Burton *et al.* 1991, prepared a construct in which the cholera toxin gene was inserted into the 5' untranslated end of the GH gene. Mice bearing this transgene, because of irreversible activation of Gs, developed gigantism, somatotroph hyperplasia, and elevated GH levels.

Screening of substantial numbers of somatotroph adenomas has revealed that almost 40 per cent have activating mutations of gsp (Landis *et al.* 1990, Spada *et al.* 1990). In one Japanese report, however, the *gsp* mutations were present in less than 10 per cent of somatotrophs adenomas (Yoshimote *et al.* 1993). In all instances though, the genomic alteration has been a point mutation involving a single base at one of two possible sites within the alpha chain gene. As a consequence, the encoded mutant alpha chain protein has, in all cases, suffered a single amino acid substitution characterized by one of the following: residue Arg 201 to Cys or His, or residue Gln 227 to Arg or Leu. The clinical characteristics of tumors harboring activation mutations of *gsp* do not appear to deviate strikingly from those having the wild-type (normal) alpha chain gene. Whereas age, sex, clinical features, duration of disease, and surgical "cure" rate have been shown to be comparable in both groups, tumors having the *gsp* mutation do tend to be somewhat smaller (Landis *et al.* 1990). Almost 40 per cent of these were microadenomas, as compared to a 15

per cent microadenoma rate in wild type tumors. Although the report of Spada *et al.* found *gsp* positive tumors to have higher basal GH levels, Landis *et al* found their basal GH levels to be lower. In the latter report, *gsp* positive tumors also retained GH suppressibility which, together with their smaller size and lower GH levels suggested an overall more favorable prognosis.

Aside from their occasional presence in thyroid tumors, the occurrence of activating mutations of *gsp* appeared restricted exclusively to pituitary adenomas of somatotrophic type. In an intriguing recent report, however, *gsp* mutations were demonstrated in 2 of 21 endocrinologically inactive pituitary adenomas (Tordjman *et al.* 1993). One of the tumors was strongly immunopositive for LH and FSH, whereas the other was weakly immunoreactive for ACTH. Given that electron microscopy was not performed, the precise tumor type cannot be determined from the report. Nevertheless, each tumor was clinically nonfunctioning and immunonegative for GH. In each instance, a point mutation of the alpha chain gene occurred; in one case the mutation involved substitution of residue Arg 201 to Cys and in the other, residue Gln 227 was substituted by Leu. That activating mutations of *gsp* can occur in adenohypophyseal cells other than somatotrophs suggests that cAMP may mediate cell proliferation in a number of pituitary cell types. Accordingly, *gsp* mutations may represent a more unifying and more common mechanism of pituitary tumorigenesis than previously thought.

The McCune-Albright syndrome is a rare disease characterized by polyostotic fibrous dysplasia, café-au-lait cutaneous pigmentation, and varying endocrine manifestations including sexual precocity, hyperthyroidism, and adrenal hyperlasia. Acromegaly, the result of a GH secreting pituitary adenoma, is occasionally an accompanying feature of the condition (Kovacs *et al.* 1984). Activating mutations of gsp resulting in substitution of Arg 201 by His or Cys have been demonstrated in various tissues of patients with McCune-Albright syndrome (Weinstein *et al.* 1991). That many, but not all tissues of such patients simultaneously exhibit activating mutations of *gsp* indicates that this disorder is the developmental consequence of an early postzygotic *gsp* mutation resulting in mosaicism. Should *gsp* mutations occur in tissues whose proliferation is driven by cAMP (thyroid, adrenal, pituitary), hyperplasia and/or adenoma formation is the result.

Structural Genomic Alterations: Tumor Suppressor Gene Inactivation

When viewed from the perspective of oncogene activation, tumorigenesis can be considered a dominant Mendelian phenomenon wherein only one mutated allele need be expressed to produce the transformed phenotype. Prompted by Knudson's pioneering studies into the genetics of retinoblastoma, it has become increasingly clear that such a perspective is not uniformly valid (reviewed in Levine 1993). By contrast, transformation may, in some

instances, represent the consequence of inactivating mutations of genes which normally exercise inhibitory control over cell proliferation. Accordingly, the concept of tumor suppressor genes arose. From such a perspective, the transformed phenotype can be considered a recessive trait, one requiring the inactivation of both alleles of a tumor suppressor gene. In that *both* alleles of a tumor suppressor gene must be inactivated in susceptible cells before transformation occurs, a "two hit" model of tumor suppressor gene inactivation has been proposed. In the case of hereditary tumor syndromes (e.g. MEN 1, hereditary retinoblastoma, etc.), the first "hit" is inherited as a germline mutation, and the second "hit" occurring as a somatic mutation. In sporadic tumors, two distinct inactivating mutations are needed to incapacitate the tumor suppressor gene.

Of the human tumor suppressor genes so far identified, the retinoblastoma gene (Rb) and the p53 gene are the best characterized. Whereas experimentation in transgenic animals suggest that they may play a role in the development of experimental pituitary tumors, their role in the genesis of human pituitary adenomas appears somewhat limited (Jacks *et al.* 1992, Sumi *et al.* 1993). A third tumor suppressor gene has been implicated in the genesis of human pituitary adenomas occurring in the context of the MEN1 syndrome (Larsson *et al.* 1988).

The Retinoblastoma Tumor Suppressor Gene (Rb)

Functional inactivation of the Rb gene has been linked to the development of a variety of malignant tumors. Transgenic mice engineered in such a way that one of the two germline Rb alleles have been inactivated, develop large, invasive high grade pituitary adenomas (Jacks *et al.* 1992). Such tumors were further shown to have lost the remaining normal Rb allele, thus providing strong evidence in favor of Rb gene inactivation as a mechanism underlying pituitary tumorigenesis. Of twenty mice bearing such heterozygous Rb gene contructs, five developed pituitary adenomas. These tumors were recently studied in our laboratory; all were corticotroph adenomas, immunoreactive for ACTH and of pars intermedia origin. The provocative nature of this report prompted a search for Rb mutations in human pituitary adenomas. In one report, allelic loss of one Rb allele was identified in four pituitary carcinomas and in one invasive corticotroph adenoma; noninvasive adenomas had normal Rb allelic complement (reviewed in Prager and Melmed 1993). In another recent screening of human pituitary adenomas, none of 18 adenomas, including invasive and recurrent ones, exhibited allelic loss of the Rb gene (Cryns *et al.* 1993). Although mutations of Rb are uncommon among pituitary adenomas, their occurrence appears restricted to markedly invasive and or frankly malignant pituitary tumors only (Fig. 1).

The p53 Tumor Suppressor Gene

Located on chromosome 17p13.1, the p53 gene is one of the best characterized human tumor suppressor genes (reviewed in Levine 1993). Moreover, since mutations of the p53 gene represent the most commonly occurring genomic alterations in human cancer, the p53 gene has emerged as the dominant conceptual focus of contemporary cancer research. Although the physiologic functions of normal p53 protein are not precisely known, there is general agreement that it has transcriptional activities, ones which ultimately lead to suppression of cell proliferation and inhibition of oncogene-mediated cell transformation. Whereas the target genes under p53 protein's transcriptional control have yet to be determined, the effects of wild-type p53 activity ultimately converge on the cell cycle, possibly by regulating events which effect passage from late G1 to S phase of the cell cycle. It has been suggested that wild-type p53 may be envisaged as a G1 checkpoint protein, one capable of blocking the passage of DNA damaged cells to the S phase, or somehow effecting DNA repair prior to S phase transfer. Among other repressive functions, p53 protein has also been implicated in the control of programmed cell death (apoptosis). Somatic mutations of the p53 gene are primarily the result of missense mutations, insertions, or deletions with the relative frequency of each alteration varying with the tissue in which the tumor originated. In carcinomas, approximately 80 per cent of mutations are missense mutations which encode a faulty p53 protein. The phenotypes of p53 mutations have three distinct features. Firstly, virtually all mutations are accompanied by a loss of wild-type p53 suppressive function. Secondly, mutant forms of p53 protein are capable of augmenting cell proliferation. Finally, many mutant forms of p53 protein maintain a trans-dominant function, one capable of inactivating the wild-type p53 protein. The reader is referred to a number of recent comprehensive reviews on this subject (Weinberg 1991, Levine 1993, Harris and Hollstein 1993), as the remainder of this section relates specifically to p53 mutations in pituitary adenomas.

Despite the frequency of p53 mutations in human epithelial tumors, they are uncommon among pituitary tumors. In a screening of 22 nonfunctioning and 22 somatotroph adenomas, and 4 pituitary carcinomas, no mutations of the p53 gene were identified (reviewed in Prager and Melmed 1993). Our experience, athough smaller, has been comparable. Although we were unable to demonstrate mutant p53 protein immunochemically in invasive and non-invasive adenomas, its presence was documented in a single prolactin cell tumor, suggestive of a missense p53 mutation in that tumor. Whereas our isolated case of a p53 mutation occurred in a very aggressive and invasive tumor, mutations of the p53 gene are generally considered a pre-invasive event. Thus further study is needed to determine both the precise frequency

of p53 mutations in pituitary adenomas and when in the course of pituitary tumor progression the event occurs.

The MEN 1 Tumor Suppressor Gene

Genetic predisposition for pituitary tumor development is restricted to a single and uncommon condition, the MEN 1 syndrome. This autosomal dominant disorder is characterized by parathyroid hyperplasia/adenomas and tumors of the endocrine pancreas and anterior pituitary. Being a variably penetrant condition, only 25 per cent of MEN 1 patients develop pituitary adenomas; most of these are macroadenomas associated with GH and/or PRL hypersecretion. Approximately 3 per cent of all pituitary adenomas are associated with this condition. The genetic defect of MEN 1 has been isolated to a putative tumor suppressor gene locus on chromosome (11q13) (Larsson *et al.* 1988, Bystrom *et al.* 1990). Susceptible individuals inherit a germline mutation of one of the two 11q13 alleles. Subsequent inactivation of the remaining allele in endocrine tissues is thought to initiate tumor formation. Thus, although the development of MEN 1 is inherited as a dominant trait, the responsible gene behaves in a recessive manner at the cellular level. Tumor suppressor gene loss at 11q13 appeared initially to be a tumorigenic mechanism applicable only to hereditary pituitary adenomas occurring in the context of MEN 1. Since loss of heterozygosity at the 11q13 locus has been demonstrated in at least three apparently sporadic prolactinomas, it is possible that mutation of the MEN 1 may have some role in the development of non-MEN 1 pituitary adenomas as well (Prager and Melmed 1993, Herman *et al.* 1993).

Growth Factors and Pituitary Tumorigenesis

A recurring theme concerning the pathogenesis of pituitary adenomas involves abnormal "physiological" regulation of the pituitary in terms of excess stimulation or deficient inhibition. Growth factors, cytokines, and hypothalamic hormones, given their capacity for autocrine and paracrine stimulation have emerged as likely contributors to the process. Growth factors are regarded as a class of soluble peptides which act by binding to specific cell surface receptors, eliciting a signal which is further transduced to a cellular or nuclear target. Many critical cellular functions such as mitogenesis, angiogenesis, gene transcription, and others are thought to be regulated by such growth factor mediated signal transduction systems.

The normal pituitary gland appears to be an abundant reservoir of growth factors and novel peptides. The pituitary derived growth factors which have been identified on the basis of peptide and or gene expression are listed in Table 3. While it is clear that numerous growth factors reside in the pituitary,

their putative regulatory roles are more obscure. Only for a few of these have preliminary pituitary related functional and regulatory correlates been established. The potential significance of some of the better characterized pituitary related growth factors is reviewed.

Growth hormone releasing hormone (GHRH) is a hypothalamic hormone which is the most important positive regulator of pituitary somatotrophs, stimulating both GH secretion and somatotroph proliferation (Billestrup *et al.* 1986, Vance 1990). Strictly speaking, GHRH is a hormone, but because it shares all the functional properties of a growth factor, its potential role in pituitary tumorigenesis is reviewed here. GHRH acts via a specific receptor located on the somatotroph cell surface. The signal emanating from an activated GHRH receptor is transduced through a classical stimulatory G protein cascade, employing cAMP as the second messenger. Subsequent downstream events are complex, involving activation of a cAMP dependent protein kinase (kinase A) which phosphorylates the cAMP responsive element binding protein (CREB), which in turn transactivates the Pit-1 gene promoter (Bodner and Karin 1987, Castrillo *et al.* 1991). As discussed in some detail below, Pit-1 is transcription factor which transactivates GH gene transcription. The net effect of GHRH stimulation is induction of GH secretion and through analogous, but unclear mechanisms, somatotroph proliferation as well. Several lines of evidence suggest that GHRH hypersecretion may contribute to pituitary tumorigenesis. Firstly, GHRH has been shown to be mitogenic in vitro, where it also induces the expression of c-*fos*, a gene normally activated during stimulated cell proliferation (Billestrup *et al.* 1987).

Table 3. *Pituitary Derived Growth Factors, Based on Protein and/or Gene Expression*

Insulin-like growth factor (I and II)
Epidermal growth factor
Basic fibroblast growth factor
Transforming growth factor-α
Transforming growth factor-β
Thyroid hormone-inducible growth factor
Endothelial cell-stimulating angiogenesis factor
Folliculo-stellate-derived growth factor
Adipocyte growth factor
Chondrocyte growth factor
Vascular permeability factor
Glial growth factor

Secondly, mice transgenic for the human GHRH develop selective hyperplasia of pituitary somatotrophs, and later develop somatotroph and mammosomatotroph adenomas (Asa *et al.* 1990). This experimental data suggests that protracted exposure to GHRH leads to somatotroph hyperplasia which, in some instances, eventually gives way to neoplastic transformation. Whereas hyperplasia of pituitary somatotrophs and clinical acromegaly are the result of GHRH secreting tumors in humans (eg bronchial carcinoids, pancreatic tumors, pheochromocytomas, small cell carcinoma of the lung), somatotroph adenomas rarely develop in the pituitaries of such patients, even after long periods of GHRH exposure. Moreover, as discussed previously, the absence of somatotroph hyperplasia surrounding GH adenomas mitigates against GHRH stimulation alone as the sole mechanism of somatotroph tumorigenesis. Nonetheless, GHRH excess, presumably the consequence of hypothalamic dysfunction, may have a genuine role in somatotroph adenoma development. It is possible the GHRH may function as a promoter, causing proliferation of the transformed cell. Moreover, as the result of its mitogenic activity, GHRH may render cells more prone to activating mutations or increase their susceptibility to the effects of other initiators. A particularly intriguing finding relates to the recent observation that some somatotroph adenomas express GHRH mRNA, raising the possibility that tumor cells may be subject to autocrine stimulation by endogenous tumoral production of GHRH (Ley and Lightman 1992).

Insulin-like growth factor 1 (IGF-1), also known as somatomedin C subserves critical anabolic functions during growth, development, differentiation and tissue repair. Whereas most circulating IGF-1 can be considered hepatic in origin, IGF-1 does appear to ubiquitously present in a variety of human tissues, including the pituitary gland. IGF-1 is the principal mediator of peripheral GH action. In response to elevated levels of GH, the liver produces IGF-1 to mediate the peripheral effects of GH. Accordingly, serum measurements of IGF-1 have become the most sensitive biochemical test for active acromegaly, correlating well with serum GH levels and tumor size (Barkan 1993). Furthermore, normalization of IGF-1 elevations following successful surgical therapy of these tumors is regarded as the best indicator of endocrinologic cure. Available evidence suggests the physiological role of IGF-1 in the pituitary is predominantly an inhibitory one, a finding which contrasts with its better known mitogenic, anabolic, and growth promoting action in other organ systems (LeRoith *et al.* 1992). In the rat, exogenously administered IGF-1 inhibits GH gene transcription, a finding also observed in vitro with human pituitary cell cultures (Yamashita *et al.* 1986, Ezzat and Melmed 1990). The mechanism of such inhibition is unclear, but is believed to be mediated by an incompletely characterized IGF-1 responsive *cis* active element located 500 bases upstream of the GH gene promoter (Prager *et al.* 1989). The extent to which IGF-1 contributes to pituitary tumor development

remains somewhat obscure. In one preliminary report, IGF-1 mRNA was demonstrated to a variable degree in all pituitary tumor types, however, the significance of this finding is uncertain (Thapar *et al.* 1993c).

Epidermal growth factor (EGF) and transforming growth factor alpha (TGFα), will be considered together because of certain similarities. These two growth factors share approximately 30% gene sequence homology and both bind to the epidermal growth factor receptor (EGF-R). This receptor is itself known to be strongly homologous to the *erb* B oncogene product. Both these growth factors have been the subject of considerable study in the context of many human tumors, however only preliminary experimentation has been undertaken in the pituitary. Most of the pituitary related research has been performed on rat pituitary tumor cells lines, and its applicability to human pituitary adenomas is therefore uncertain. Nevertheless there is evidence to suggest that both these growth factors are negative regulators in the pituitary, which leads to the speculation that their functional inactivation may be permissive to the maintenance and/or progression of pituitary adenomas. In the rat, EGF inhibits growth and proliferation of tumerous cell lines by up to 40% (Schonbrunn *et al.* 1980); the inhibitory effects of TGFα in rat cell lines are both more potent and better characterised (Ramsdell 1991). TGFα is cell cycle specific, demonstrating transient inhibition of M phase progression and profound inhibition of G1 cell entry into the S phase. The finding most relevant to human pituitary tumors is that the EGF receptor is present on both the normal rat and human pituitary, however it is absent in the tumorous pituitary (Birman *et al.* 1987). Whether this absence reflects an absolute loss of EGF-R, decreased binding affinity or an altered EGF-R related to *erb B* oncogene activation is unknown. Nevertheless, the potential numbers of functional EGF and TGFα binding sites are effectively reduced. Given the putative inhibitory actions ascribed to TGFα and EGF, this loss of binding and consequently loss of inhibitory input may contribute to deregulated unrestrained cell growth and tumor formation. Further work is required to validate or exclude this theory.

Transforming growth factor beta (TGFβ) has been the subject of a growing body of evidence promoting its role as another pituitary modulator, particularly of gonadotrophic cells. TGFβ is known for its potent inhibitory effects on epithelial cells, both normal and neoplastic (Pietenpol *et al.* 1990). It consists of 2 homo- or heterdimeric peptide motifs all derived from a common precursor molecule. The strongest evidence implicating TGFβ with pituitary hormone growth and regulation derives from its structural and gene sequence homology with the gonadal peptides inhibin and activin (Ying 1988, Roberts *et al.* 1989). The former appears to suppress FSH secretion and the latter is thought to facilitate it. Furthermore, TGFβ, inhibins and activins all share a common membrane receptor. TGFβ functions as a cell cycle specific inhibitor, preventing G1 cell transition into the S phase. Preliminary

impressions of the mechanisms of this inhibition appears somehow to involve the *c-myc* gene product. The hypothesis that functional inactivation of TGFβ may be permissive to pituitary tumorigenesis awaits confirmation.

Basic fibroblastic growth factor (bFGF) is one of the more abundant growth factors identified in the pituitary (Li *et al.* 1992). Despite this relative abundance, functional correlates of bFGF) in the pituitary are largely unknown. In other tumorous and nontumorous tissues, bFGF exhibits potent mitogenic and angiogenic properties, and is considered to be the prinicpal angiogenesis factor in vivo (Gospodarowicz *et al.* 1987). Experimentation with bFGF on clonal cell lines has provided conflicting results, being variably mitogenic, inhibitory, or without any effect on GH3 cells (Mormede and Baird 1988, Black *et al.* 1990, Schweigerer *et al.* 1987). In human pituitary adenomas, bFGF has been shown to stimulate PRL release but appears to have little effect on cell proliferation (Atkin *et al.* 1993). Another member of the fibroblast growth factor family is the gene product of the *hst* gene, which shares considerable sequence homology with bFGF. It has recently been shown that DNA sequences from human prolactinomas containing part of the coding region of the *hst* gene are transforming in NIH 3T3 cell assays (Gonsky *et al.* 1991). Given the abundance of the fibroblast growth factor family in the pituitary, and the preliminary data from these studies, it is possible that this family of growth factors may share some role in the genesis of prolactinomas and other pituitary tumors.

Endothelial cell stimulating angiogenesis factor (ESAF) is a potent mitogen which stimulates microvascular neoangiogenesis, acting specifically on endothelial cells in a host of tumorous and benign pathologic conditions. The relative ESAF content of a variety of benign and malignant intracranial tumors was recently assayed, and correlated with the degree of aggressiveness of the tumor. Three pituitary tumors were included in this study (PRL, GH and FSH secreting tumors), and their ESAF content was found to be elevated to an intermediate degree, at levels between those of malignant gliomas and normal control tissue. Overall, the ESAF content of the various pathologic entities assayed seemed to correlate well with aggressiveness, however due to limited follow-up the prognostic value of this growth factor is unknown.

Growth Factors and Pituitary Neoplasm: Conclusion

From this discussion it should be clear that the number of growth factors putatively implicated in the growth, regulation and transformation of pituitary cells very significantly outnumber the established facts pertaining to their exact biological roles and mechanisms of action. Indeed, the study of growth factors in the pituitary seems to have raised more questions than answers. It appears that growth factors are more likely mediators of tumor

progression rather than of tumor initiation, per se. Further study is clearly required before any definitive role for growth factors in pituitary tumorigenesis can be established.

The Pituitary Specific Transcription Activator: Pit-1

There has been considerable recent interest in the pituitary-specific transcription activator known as Pit-1. Since its initial isolation and characterization, this member of the POU class homeodomain protein family, has been ascribed an important role in the embryogenesis and differentiation of pituitary somatotrophs, lactotrophs, and thyrotrophs (Theill *et al.* 1989, Castrillo *et al.* 1991). The Pit-1 protein contains two domains (POU-specific and POU-homeodomain), both being necessary for its DNA binding and transactivating capabilities. In the case of both the GH and PRL genes, Pit-1 responsive DNA binding sites are located upstream to their respective promoters. Recently, unique Pit-1 binding sites have also been identified on the TSH beta subunit gene.

Whereas there is strong experimental evidence in support of Pit-1's physiologic role in the development, differentiation, and ongoing phenotypic maintenance of somatotrophs, lactotrophs, and thyrotrophs, its role in the development and/or progression of pituitary adenomas remains somewhat conjectural. The fact that somatotroph adenomas frequently co-secrete GH, PRL, and TSH invited early speculation that Pit-1, given its capacity to collectively activate transcription of GH, PRL, and TSH genes, should play some unifying role in the development of adenomas of these secretory types. A number of recent reports have since demonstrated Pit-1 mRNA in pituitary adenomas (Asa *et al.* 1993, Friend *et al.* 1993, Lloyd *et al.* 1993). Furthermore, in the report of Lloyd *et al*, Pit-1 gene expression appeared slightly enhanced in tumor tissue as compared to nontumorous controls. Though more frequently expressed among somatotroph, lactotroph, and thyrotroph adenomas, Pit-1 mRNA has also been identified within corticotroph, gonadotroph, and null cell adenomas as well.

Acknowledgements

This work was supported in part by grants awarded by the Physician Services Incorporation (PSI) Foundation of Ontario, the St. Michael's Hospital Research Society, and the Medical Research Council of Canada (MT-6349). Additional support was provided by the generous donations of Mr. and Mrs. Jarislowsky, Montreal, Canada, and the Lloyd-Carr Harris Foundation, Canada.

References

1. Alexander JM, Biller BMK, Bikkai H, Zervas NT, Arnold A, Klibanski A (1990) Clinically nonfunctioning pituitary tumors are monoclonal in origin. J Clin Invest 86: 336–340

2. Alvaro V, Touraine P, Raisman Vozari R, Bai-Grenier F, Birman P, Joubert (Bression) D (1992) Protein kinase C activity and expression in normal and adenomatous human pituitaries. Int J Cancer 50: 724–730
3. Alvaro V, Levy L, Deburay C, Roche A, Peillon F, Querat B, Joubert D (1993) Invasive human pituitary tumors express a point mutated alpha-protein kinase-C. J Clin Endocrinol Metab 77: 1125–1139
4. Anniko M, Tribukait B, Wersall J (1984) DNA ploidy and cell phase in human pituitary tumors. Cancer 53: 1708–1713
5. Asa SL, Ryan N, Kovacs K, Singer W Matangos PJ (1988) Immunohistochemical localization of neuron-specific enolase in the human hypophysis and pituitary adenomas. Arch Pathol Lab Med 112: 801–804
6. Asa SL, Kovacs K, Stefaneanu L, Horvath E, Billestrup N, Gonzales-Manchon C (1990) Pituitary mammosomatotroph adenomas develop in old mice transgenic for growth hormone-releasing hormone. Proc Soc Exper Biol Med 193: 232–235
7. Asa SL, Kovacs K (1992a) Clinically nonfunctioning human pituitary adenomas. Can J Neurol Sci 19: 228–235
8. Asa SL, Kovacs K (1992b) Pituitary pathology in acromegaly. Endocrin Metab Clin North Am 21: 553–574
9. Asa SL, Cheng Z, Ranyar L, Singer W, Kovacs K, Smyth HS, Muller P (1992c) Human pituitary null cell adenomas and oncocytomas in vitro: effects of adenohypophysiotropic hormone and gonadal steroids on hormone secretion and tumor cell morphology. J Clin Endocrinol Metab 74: 1128–1134
10. Asa SL, Puy LA, Lew AM, Sundmark VC, Elsholtz HP (1993) Cell type-specific expression of the pituitary transcription activator Pit-1 in the human pituitary and pituitary adenomas. J Clin Endocrinol Metab 77: 1275–1280
11. Atkin SL, Landolt AM, Jeffereys RV, Divewr M, Radcliff J, White MC (1993) Basic fibroblastic growth factor stimulated prolactin secretion from human anterior pituitary adenomas without affecting adenoma cell proliferation. J Clin Endocrinol Metab 77: 831–837
12. Barkan AL (1992) Acromegaly. Trends Endocrinol Metab 3: 205–2192
13. Barrett JC (1991) Molecular mechanisms of hormonal carcinogenesis. In: Li JJ, Nandi S, Li SA (eds) Hormonal carcinogenesis. Springer, Berlin Heidelberg New York Tokyo, pp 159–163
14. Biller BMK, Alexander JM, Zervas NT, Hedley-White ET, Arnold A, Klibanski A (1992) Clonal origins of adrenocorticotropin-secreting pituitary tissue in Cushing's disease. J Clin Endocrinol Metab 75: 1303–1309
15. Billestrup N, Swanson LW, Vale W (1986) Growth hormone-releasing factor stimulated proliferation of somatotrophs in vitro. Proc Natl Acad Sci USA 83: 6854–6857
16. Billestrup N, Mitchell RL, Vale W, Varma IM (1987) Growth hormone releasing factor induces c-fos expression in cultured primary pituitary cells. Mol Endocr 1: 300–305
17. Birman P, Michard M, Li Y, Peillon F, Bresion D (1987) Epidermal growth factor-binding sites, present in normal human and rat pituitaries are absent in human 18 pituitary adenomas. J Clin Endocrinol Metab 65: 275–281

18. Black EG, Logan A, Davis JRF, Sheppard MC (1990) Basic fibroblastic growth factor affects DNA synthesis and cell function and activates multiple signalling pathways in rat thyroid FRTL-5 and pituitary GH3 cells. J Endocrinol 127: 39–46
19. Bodner M, Karin (1987) A pituitary-specific trans-acting factor can stimulate transcription from the growth hormone promoter in extracts of non-expressing cells. Cell 50: 267–275
20. Burrow GN, Wortzman G, Rewcastle NB, Holgate RC, Kovacs K (1981) Microadenomas of the pituitary and abnormal sellar tomograms in an unselected autopsy series. N Engl J Med 304: 156–158
21. Burton FH, Hasel KW, Bloom FE, Sutcliff JG (1991) Pituitary hyperplasia and gigantism in mice caused by a cholera toxin transgene. Nature 350: 74–77
22. Bystrom C, Larsson C, Blomberg C, *et al* (1990) Localization of the MEN1 gene to a small region within chromosome 11q13 by deletion mapping tumors. Proc Natl Acad Sci USA 87: 1968–1972
23. Capra E, Rindi G, Pompei Spina M, Scappaticci S (1993) Chromosome abnormalities in a case of pituitary adenoma. Cancer Genet Cytogenet 68: 140–142
24. Castrillo JL, Theill LE, Karin M (1991) Function of the homeodomain protein GHF-1 in pituitary cell proliferation. Science 253: 197–199
25. Cooper PR (1990) Nonoperative management of prolactin-secreting pituitary adenomas. In: Cooper PR (ed) Contemporary diagnosis and management of pituitary adenomas. American Association of Neurological Surgeons, Park Ridge, pp 83–100
26. Cramer W, Horning ES (1936) Experimental production of oestrin of pituitary tumors with hypopituitarism. Lancet 1: 247–249
27. Cryns VL, Alexander JP, Klibanski A, Arnold A (1993) The retinoblastoma gene in human pituitary tumors. J Clin Endocrinol Metab 77: 644–646
28. Ezzat S, Melmed S (1990) The role of growth factors in the pituitary. J Clin Endocrinol Metab 13: 691–698
29. Fitzgibbons PL, Appley AJ, Turner RR, Bishop PC, Parker JW, Breeze RE, Weiss MH, Apuzzo MLJ (1988) Flow cytometric analysis of pituitary tumors: correlations of nuclear antigen p105 and DNA content with clinical behavior. Cancer 62: 1556–1560
30. Friend KE, Chiou YK, Laws ER Jr, Lopes MBS, Shupnik (1993) Pit-1 messenger ribonucleic acid is differentially expressed in human pituitary adenomas. J Clin Endocrinol Metab 77: 1281–1286
31. Furth J, Ueda G, Clifton KH (1973) The pathophysiology of pituitaries an d their tumors: methodological advances. In: Busch H (ed) Methods in cancer research, vol 10. Academic Press, New York, pp 201–277
32. Gerdes J, Lemke H, Baisch H, *et al* (1984) Cell cycle analysis of a cell proliferation-associated human nuclear antigen defined by the monoclonal antibody Ki-67. J Immunol 133: 1470–1715
33. Gescher A (1992) Towards selective pharmacological modulation of protein kinase C-opportunities for the development of novel antineoplastic agents. Br J Cancer 66: 10–19
34. Gesundheit N, Petrick PA, Nissim M, Dahlberg PA, Doppman JL, Emerson

GH, Braverman LF, Oldfield (1989) Thyrotropin-secreting pituitary adenomas. Clinical and biochemical heterogeneity. Case reports and follow-up of nine patients. Ann Intern Med 111: 827–835
35. Gharib SD, Weirman MF, Shupnik MA, Chin WW (1990) Molecular biology of pituitary gonadotropins. Endocr Rev 11: 177–199
36. Girod C, Trouillas J, Claustrat B (1986) The human thyrotropic adenoma: pathologic diagnosis in five cases and critical review of the literature. Semin Diagn Pathol 3: 58–68
37. Gonsky R, Herman V, Melmed S, Fagin J (1991) Transforming DNA sequences present in human prolactin-secreting tumors. Mol Endocrinol 5: 1687–1695
38. Gospodarowicz D, Ferrera N, Schweigerer L, Neufeld G (1987) Structural characterisation and biological functions of fibroblastic growth factor. Endocr Rev 8: 95–111
39. Hamilton CRJ, Adams LC, Maloof F (1970) Hyperthyroidism due to thyrotropin-producing pituitary chromophobe adenoma. N Engl J Med 283: 1077–1080
40. Harris CC, Hollstein M (1993) Clinical implications of the p53 tumor suppressor gene. N Engl J Med 329: 1318–1327
41. Herman V, Drasin NZ, Gonsky R, Melmed S (1993) Molecular screening of pituitary adenomas for gene mutations and rearrangements. J Clin Endocrinol Metab 77: 50–55
42. Herman V, Fagan J, Gonsky R, Kovacs K, Melmed S (1990) J Clin Endocrinol Metab 71: 1427–1433
43. Hill SA, Falko JM, Wilson CB, Hunt WE (1982) Thyrotropin-producing pituitary adenomas. J Neurosurg 57: 515–519
44. Horvath E, Kovacs K (1991) The adenohypophysis. In: Kovacs K, Asa SL (eds) Functional endocrine pathology. Blackwell, Boston, pp 245–281
45. Horvath E, Kovacs K, Killinger DW, Smyth HS, Platts ME, Singer W (1980) Silent corticotroph adenomas of the human pituitary gland: a histologic, immunocytologic and ultrastructural study. Am J Pathol 98: 617–638
46. Horvath E, Kovacs K, Smyth HS, Killinger DW, Schiethauer BW, Randall R, *et al* (1988) A novel type of pituitary adenoma: morphological features and clinical correlations. J Clin Endocrinol Metab 66: 1111–1118
47. Hsu DW, Hakim F, Biller BMK, de La Monte S, Zervas NT, Klibanski A, Hedley-White ET (1993) Significance of proliferating cell nuclear antigen index in predicting pituitary adenoma recurrence. J Neurosurg 78: 753–761
48. Hsu DW, Raskind PN, Hedley-White TE (1989) Vasoactive intestinal peptide in the human pituitary gland and adenomas. Am J Pathol 135: 329–338
49. Ironside IW, Royds JA, Jefferson AA, Timperley WR (1987) Immunlocalization of cytokeratins in the normal and neoplastic human pituitary gland. J Neurol Neurosurg Psychiatry 50: 57–65
50. Jacks T, Fazeli A, Schmitt EM, Bronson RT, Goodell MA, Weinberg RA (1992) Effects of an Rb mutation in the mouse. Nature 359: 295–299
51. Jacoby LB, Hedley-White ET, Pulaski K, Seizinger BR, Martuza RL (1990) Clonal origin of pituitary adenomas. J Neurosurg 73: 1427–1433
52. Jameson JL, Klibanski, Black PM, Zervas NT, Lindell CM, Hsu DW, Ridgeway EC, Habner JF (1987) Glycoprotein hormone genes are expressed in clinically nonfunctioning pituitary adenomas. J Clin Invest 80: 1472–1478

53. Joensuu H, Klemi PJ (1988) DNA aneurploidy in adenomas of endocrine organs. Am J Pathol 132: 145–151
54. Karga HJ, Alexander JM, Hedley-White ET, Klibanski A, Jameson JL (1992) Ras mutations in human pituitary tumors. J Clin Endocrinol Metab 74: 914–919
55. Klibanski A, Zervas N (1991) Diagnosis and management of hormone-secreting pituitary adenomas. N Engl J Med 324: 822–831
56. Knosp E, Kitz K, Perneczky A (1989) Proliferation activity in pituitary adenomas: measurement by monoclonal antibody Ki-67. Neurosurgery 25: 927–930
57. Kovacs K, Horvath E, Thorner MO, *et al* (1984) Mammosomatotroph hyperplasia associated with acromegaly and hyperprolactinemia in a patient with the McCuneAlbright syndrome. Virchows Arch (A) 403: 77–81
58. Kovacs K, Horvath E (1986) Tumors of the pituitary gland. In: Atlas of tumor pathology, Fascicle 21, 2nd Series. Armed Forces Institute of Pathology, Washington, pp 1–269
59. Kovacs K (1988) Pathology of growth hormone excess. Pathol Res Pract 183: 565–568
60. Kovacs K, Horvath E, Asa SL, Stefaneanu L, Sano T (1989) Pituitary cells producing more than one homone. Human pituitary adenomas. Trends Endocr Metab 1: 104–107
61. Kovacs K, Ryan N, Stefaneanu L (1987) Identification of corticotrophs in the human pituitary with mAB lu5, a novel immunocytochemical marker. Pathol Res Pract 182: 775–779
62. Kovacs K, Asa SL, Horvath E, Ryan N, Singer W, Killinger DW, Smyth HS, Scheithauer BW, Ebersold MJ (1990) Null cell adenomas of the pituitary: attempts to resolve their cytogenesis. In: Leschago J, Kameya T (eds) Endocrine pathology update. Field and Wood, New York, pp 17–31
63. Kovacs K, Stefaneanu L, Ezzat S, *et al* (1994) Prolactin producing pituitary adenoma in a male to female transsexual patient following protracted estrogen administration: a morphologic study. Arch Pathol Lab Med 118: 562–565
64. Landis C, Masters SB, Spada A, Pace AM, Bourne HR, Vallar L (1989) GTPase inhibiting mutations activate the alpha chain of Gs and stimulate adenyl cyclase in human pituitary tumors. Nature 340: 692–696
65. Landis CA, Harsh G, Lyons J, Davis RL, McCormick F, Bourne HR (1990) Clinical characteristics of acromegalic patients whose pituitary tumors contain mutant Gs protein. J Clin Endocrinol Metab 71: 1416–1420
66. Landolt AM, Schibata (1991) Growth, cell proliferation, and prognosis of pituitary adenomas. In: Faglia G, Beck-Peccoz P, Ambrosi B, Travagline P, Spada A (eds) Pituitary adenomas: new trends in basic and clinical research. Elsevier, Amsterdam, pp 169–178
67. Larsson C, Skogseid B, oberg K, Nakamura Y, Nordenskjold M (1988) Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma. Nature 332: 85–87
68. LeRoith D, Clemmons D, Nissley P, Rechler MM (1992) Insulin-like growth factors in health and disease. Ann Int Med 116: 854–862
69. Levine AJ (1993) The tumor suppressor genes. Ann Rev Biochem 62: 623–651

70. Ley A, Lightman SL (1992) Growth hormone releasing hormone transcripts in human pituitary adenomas. J Clin Endocrinol Metab 74: 1474-1476
71. Li Y, Koga M, Kasayama S, *et al* (1992) Identification and characterization of high molecular weight forms of basic fibroblastic growth factor in human pituitary adenomas. J Clin Endocrinol Metab 75: 1436–1441
72. Lloyd RV, Jin L, Chandler WF, Horvath E, Stefaneanu L, Kovacs K (1994) Pituitary specific transcription factor messenger RNA expression in adenomatous and nontumorous human pituitary tissues. Lab Invest 69: 570–575
73. Lloyd RV, Wilson BS, Kovacs K, Ryan N (1985) Immunohistochemical localization of chromogranin in human hypophyses and pituitary adenomas. Arch Pathol Lab Med 109: 515–547
74. Marin F, Kovacs K, Stefaneanu L, Horvath E, Cheng Z (1992) S-100 protein immunopositivity in human nontumorous hypophyses and pituitary adenomas. Endocr Pathol 3: 28–38
75. Marin F, Cheng Z, Kovacs K (1993) Ubiquitin immunoreactivity in corticotrophs following glucocorticoid treatment and in pituitary adenomase. Arch Pathol Lab Med 117: 254–258
76. McComb DJ, Ryan N, Horvath E, Kovacs K (1983) Sublinical adenomas of the human pituitary. New light on old problems. Arch Pathol Lab Med 107: 488–491
77. McCutcheon IE, Weintraub BD, Oldfield EH (1990) Surgical treatment of thyrotropin-secreting pituitary adenomas. J Neurosurg 73: 674-683
78. Melmed S (1992) Etiology of pituitary acromegaly. Endocrinol Metab Clin North Am 21: 539–551
79. Melmed S, Braunstein GD, Change RJ, *et al* (1986) Pituitary tumors secreting growth hormone and prolactin. Ann Intern Med 105: 238–253
80. Mork SJ, Laerum OM (1980) Modal DNA content of human intracranial neoplasms studied by flow cytometry. J Neurosurg 53: 198–204
81. Mormede P, Baird A (1988) Estrogens, cyclic adenosine 3',5'-monophosphate and phorbol esters modulate the prolactin response of GH3 cells. J Endocrinol 127: 39–46
82. Mountcastle RB, Roof BS, Mayfield RK, Mordes DB, Sagel J, Biggs PJ, Rawe SE (1989) Case report: pituitary adenocarcinoma in an acromegalic patient. Response to bromocriptine and pituitary testing: a review of the literature on 36 cases of pituitary carcinoma. Am J Med Sci 298: 109–118
83. Nagashima T, Murovic JA, Hoshino T, Wilson CB, DeArmond SJ (1986) The proliferative potential of human pituitary tumors in situ. J Neurosurg 64: 588–593
84. Nyquist P, Laws ER jr, Elliot E (1994) Novel features of tumors that secrete both growth hormone and prolactin in acromegaly. Neurosurgery 35: 179–184
85. Pernicone PJ, Scheithauer BW (1993) Invasive pituitary adenomas and pituitary carcinomas. In: Lloyd RV (ed) Surgical pathology of the pituitary gland. Saunders, Philadelphia, pp 121–136
86. Pichon MF, Bression D, Peillon F, *et al* (1980) Estrogen receptors in human pituitary adenomas. J Clin Endocrinol Metab 51: 897–902
87. Pietenpol JA, Holt JT, Stein RW, Moses HL (1990) Transforming growth factor beta 1 suppression of c-myc gene transcription: role in inhibition of ketatinocyte proliferation. Proc Natl Acad Sci USA 87: 3758–3762

88. Prager D. Melmed S, Fagin J (1989) Feedback regulation of growth hormone gene expression by insulin-like growth factor 1. In: LeRoith D, Raizada MK (eds) Molecular and cellular biology of insulin-like growth factors and their receptors. Plenum, New York, pp 57–68
89. Prager D, Melmed S (1993) Molecular pathology of sporadic pitutiary tumors. Endocr Pathol 4: 175–177
90. Ramsdell JS (1991) Transforming growth factor-α and -β are are potent and effective inhibitors of GH4 pituitary tumor cell proliferation. Endcocrinology 128: 1981–1990
91. Reichlin S (1991) Functional aspects of endocrine neoplasms. In: Kovacs K, Asa SL (eds) Functional endocrine pathology, vol 2. Blackwell, Boston, pp 898–913
92. Roberts V, Meunier H, Vaughan J, Rivier J, Rivier C, Vale W, Sawchenko P (1989) Regulation and regulation of inhibin subunits in pituitary gonadotropes. Endocrinology 124: 552-554
93. Rock JP, Babu VR, Drumheller T, Chason J (1993) Cytogenetic findings in pituitary adenomas: results of a pilot study. Surg Neurol 40: 224-229
94. Saeger W, Ludecke DK (1982) Pituitary adenomas with hyperfunction of TSH: frequency, histological classification, immunocytochemistry and ultrastructure. Virchows Arch 394: 255-267
95. Saint-Andre J-P, Rohmer V, Alhenc-Gelas F, Menard J, Bigorgne J-C, Corvol P (1986) Presence of renin, angiotensinogen and converting enzyme in human lactotroph cells and prolactin adenomas. J Clin Endocr Metab 63: 231–237
96. Scheithauer BW, Kovacs K, Randall RV (1983) The pituitary in untreated Addison's disease: a histologic and immunocytologic study of 18 adenohypophyses. Arch Pathol La Med 107: 484–487
97. Scheithauer BW (1984a) Surgical pathology of the pituitary: the adenomas. Part 1. Pathol Annu 19: 317–374
98. Scheithauer BW (1984b) Surgical pathology of the pituitary: the adenomas. Part 2. Pathol Annu 19: 269–329
99. Scheithauer BW, Kovacs K, Randall RV, Ryan N (1985) Pituitary gland in hypothyroidism. Histologic and immunocytologic study. Arch Pathol Lab Med 109: 499–504
100. Scheithauer BW, Kovacs K, Laws ER Jr, Randall RV (1986a) Pathology of invasive pituitary adenomas with special reference to functional classification. J Neurosurg 65: 733–744
101. Scheithauer BW, Horvath E, Kovacs K, Laws ER, Randall RV, Ryan N (1986b) Plurihormonal pituitary adenomas. Semin Diagn Pathol 6: 69–82
102. Scheithauer BW, Kovacs K, Randall RV, Ryan N (1989) Effects of estrogen on the human pituitary: a clinicopathologic study. Mayo Clin Proc 64: 1077–1084
103. Schonbrunn A, Krasnoff M, Westendorg JM, Tashjian AH (1980) Epidermal growth factor and thyrotropin-releasing hormone act similarly on a clonal pituitary cell strain. Modulation of hormone production and inhibition of cell proliferation. J Cell Biol 85: 786–797
104. Schulte HM, Oldfield EH, Allolio B, Katz DA, Berkman RA, Ali IU (1991) Clonal composition of pituitary adenomas in patients with Cushing's disease:

determination by X-chromosome inactivation analysis. J Clin Endocrinol Metab 73: 1302–1308
105. Schweigerer L, Neufeld G, Gospodarowicz D (1987) Basic fibroblastic growth factor as a growth inhibitor for cultured human tumor cells. J Clin Invest 80: 1516–1520
106. Selman WR, Laws ER, Scheithauer BW, Carpenter SM (1986) The occurrence of dual invasion in pituitary adenomas. J Neurosurg 64: 402–407
107. Smallridge RC (1987) Thyrotropin-secreting pituitary tumors. Endocrinol Metab Clin North Am 16: 765–792
108. Spada A, Arosio M, Bochicchio D, Bassoni N, Vallar L, Bassetti M, Faglia G (1990) Clinical, biochemical and morphological correlates in patients bearing growth hormone secreting with or without constitutively active adenylyl cyclase. J Clin Endocrinol Metab 71: 1421–1426
109. Stefaneanu L, Horvath E, Kovacs K (1989) Argyrophilic organizer region proteins (AgNORs) in adenohypophysial cells and adenomas of the human pituitary. Mod Pathol 2: 192–199
110. Stefaneanu L, Kovacs K, Horvath E, Lloyd RV, Buchfelder M, Fahlbusch R, Smythe H (1994) In situ hybridization of estrogen receptor mRNA in human adenohypophysial cells and pituitary adenomas. J Clin Endocrincol Metab 78: 83–88
111. Sumi T, Stefaneanu L, Kovacs K, Asa SL, Rindi G (1993) Immunohistochemical study of p53 protein in human and animal pituitary tumors. Endocr Pathol 4: 95–99
112. Thapar K, Horvath E, Kovacs K, Muller PJ (1992) Pituitary adenomas: recent advances in classification, histopathology and molecular biology. Diagn Oncol 2: 145–167
113. Thapar K, Kovacs K, Laws E, Muller PJ (1993a) Pituitary adenomas: current concepts in classification, histopathology, and molecular biology. Endocrinologist 3: 39–57
114. Thapar K, Stefaneanu L, Kovacs K, Horvath E, Asa SL (1993b) Plurihormonal pituitary tumors: beyond the one cell-one hormone theory. Endocr Pathol 4: 1–3
115. Thapar K, Kovacs K, Stefaneanu L, Smythe H, Laws ER Jr (1993c) Insulin-like growth factor 1 gene expression in human pituitary adenomas: an in situ hybridization study. Scientific Program 61st Annual Meeting, American Association of Neurological Surgeons, April 1993, Boston, pp 359
116. Theill LE, Castrillo J-L, Wu D, Karin M (1989) Dissection of the functional domains of the pituitary specific transcription factor GHF-1. Nature 342: 945–948
117. Thorner MO, Vance ML, Horvath E, Kovacs K (1992) The anterior pituitary. In: Wilson JD, Foster DW (eds) Williams textbook of endocrinology, 8th ed. Saunders, Philadelphia, pp 221–310
118. Tordjman K, Stern N, Ouaknine G, Yossiphov Y, Razon N, Nordenskjold M, Friedman E (1993) Activating mutations of the Gs alpha gene in nonfunctioning pituitary tumors. J Clin Endocrinol Metab 77: 765–769
119. U SH, Kelly P, Lee WH (1988) Abnormalities of human growth hormone gene and protooncogenes in some human pituitary adenomas. Mol Endocrinol 2: 85–89

120. Vallar L, Spada A, Giannattasio G (1987) Altered Gs and adenylate cyclase activity in human GH secreting pituitary tumors. Nature 330: 566–567
121. Vance ML (1990) Growth hormone releasing hormone. Clin Chem 36: 415–420
122. Vrontakis ME, Sano T, Kovacs K, Friesen HG (1990) Presence of glananin–like immunoreactivity in nontumorous corticotrophs and corticotroph adenomas of the human pituitary. J Clin Endocrinol Metab 70: 747–751
123. Weinberg RA (1991) Tumor suppressor genes. Science 254: 1138–1146
124. Weinstein LS, Shenkar A, Gejman P, Martino MJ, Friedman E, Spiegel AM (1991) Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N Engl J Med 325: 1688–1695
125. Wilson CB, Tyrell JB, Fitzgerald PA, Pitts L (1979) Neurosurgical aspects of Cushing's disease and Nelson's syndrome. In: Tindall GT, Collins WF (eds) Clinical management of pituitary disorders. Raven, New York, pp 99229–99238
126. Woodruff MFA, Ansell JD, Forbes GM, Gordon JC, Burton DI, Micklem HS (1982) Clonal interaction in tumours. Nature 299: 822–824
127. Yamashita S, Weiss M, Melmed S (1986) Insulin-like growth factor 1 regulates growth hormone secretion and messenger ribonucleic acid levels in human pituitary tumors. J Clin Endocrinol Metab 63: 730–734
128. Ying S-L (1988) Inhibins, activins, and follistatins. Gonadal proteins modulating the secretion of follicle-stimulating homone. Endocrin Rev 9: 267–293
129. Yoshimoto K, Iwahana H, Fukuda A, Sano T, Itakura M (1993) Rare mutations of the Gs alpha subunit in human endocrine tumors. Mutation detection by polymerase chain reaction-primer introduced restriction analysis. Cancer 72: 1286–1393
130. Zuber M, Tan EM, Ryoji M (1989) Involvement of proliferating cell nuclear antigen (cyclin) in DNA replication in living cells. Mol Cell Biol 9: 57–66

Biomechanics and Classification of Traumatic Lesions of the Spine

J. P. Chirossel[1], G. Vanneuville[2], J. G. Passagia[1], J. Chazal[2], Ch. Coillard[2], J. J. Favre[1], J. M. Garcier[2], J. Tonetti[1], and M. Guillot[2]

[1] Department of Neurosurgery and Department of Anatomy, J. Fourier University, Grenoble (France), and [2] Department of Anatomy, Auvergne University, Clermont-Ferrand (France)

With 54 Figures

Contents

1. Introduction

There has been a progressive growth of clinical, anatomical, technical and biomechanical knowledge of the spine which has emerged from both specific and collaborative efforts of many investigators. In the same way many distinguished contributors have at various times elaborated the analysis of vertebral trauma and their names appear in the References to this paper.

The first classification of traumatic injuries of the spine was provided by Boehler in 1929[15]. Although highly descriptive, it was already based on the relationship between mechanisms of injury and their resulting lesions. Compression fractures were distinguished from those caused by tension, shearing, or torsion.

In 1931 Watson-Jones[107] re-emphasized the relevance of the distinction between compression and comminutive fractures caused by axial strain and those known as fracture-dislocations involving transverse force (Fig. 1). He was the first to introduce the concept of "instability" resulting from intervertebral tearing injuries.

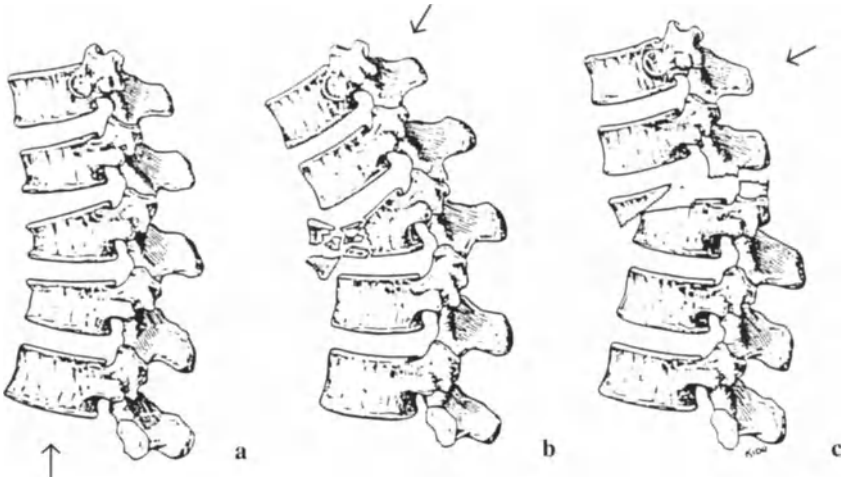


Fig. 1. Watson-Jones classification (1931) (from Watson-Jones[107]). The three types of vertebral body fractures at the dorso-lumbar level are: simple fracture from vertical compression (a); comminutive fracture from acute angulation in flexion (b); fracture-dislocation with anterior displacement and injury to the apophyseal joints (c). In all of these fractures, there may exist lateral displacement, flexion displacements and especially in fractures -dislocations, rotational displacements

In 1963 Holdsworth[51] proposed a classification into 5 groups, which preserved this same relationship between mechanism, lesion and stability. The advantage of this approach was to enable a distinction between stable forms caused by axial loads including the compression and comminutive fractures (which he called the "burst fracture"), and unstable forms such as dislocations, and dislocations by extension or rotation. Using this approach he conceived the idea of two supporting complexes, one being anterior and disco-corporeal, the other posterior and ligamentous. Rupture of the posterior supporting complex would cause instability.

Indeed, it became apparent after Watson-Jones[107] that instability was an essential element of severity in these lesions.

Moreover, in 1948 Chance[25] had emphasized the important role of posterior tearing in a form of unstable fracture associated with a slight anterior compression fracture. In 1949, Nicoll[76] attempted to distinguish acute unstable forms from secondary forms arising from discal or ligamentous injuries.

This attempt to identify anatomical systems or "key" structures involved in stability and whose injury alone would have serious consequences, served for many years as the underlying theme in anatomo-clinical research. Several different concepts emerged from this approach, with varied, often simplistic representations, but nevertheless fruitful and of great didactic value.

In 1958 Decoulx and Rieunau[30] defended the interest of the "posterior wall" concept. Its rupture remained the key element for many years in the diagnosis of spinal injury severity. The posterior wall is understood to include not only that of the vertebral body (posterior plate) but also the posterior segment of the disc covered by the dorsal longitudinal ligament. Viewed in this manner, the posterior wall represents, in fact, a central spinal axis whose essential biomechanical role would be described later.

In 1963 Kelly[57] elaborated Holdsworth's idea of 2 functional complexes, into a figurative and didactic form consisting of 2 columns: one solid, anterior, and the other hollow representing the neural arch (Fig. 2).

In 1970 Roy-Camille[86] once again underlined the importance of the centrospinal structures which he extended to "the middle spinal segment" including the pedicles, isthmus, and zygapophyseal columns.

In 1973 Louis[65–67] described the spinal architecture as an equilibrium of three columns, an anterior corporeo-discal column and two postero-lateral zygapophyseal columns all interconnected by the pedicles and laminae. Moving away from mechanistic diagrams, but remaining just as didactic, he gave real mechanical meaning to the osseous morphology of the vertebral column which reflects the combination of normal equilibrium and physiological stress. He proposed a quantified approach to instability by attributing a coefficient to each of the constituent anatomical elements.

The preceding classifications and essential mechanical concepts were recapitulated by Denis in 1983[32]. Between the anterior and posterior

complexes of Holdsworth and Kelly, he placed a third intermediate entity which in fact corresponds to the central osteo-disco-ligamentous complex of Rieunau's "posterior wall". This approach to injuries and their therapeutic management by reasoning in terms of the mechanical properties specific to each column (Fig. 3) made this classification a widely used model and served as the basis for several other studies.

McAfee in 1983[71] proposed a similar approach in which the effects of the 3 primary forces (compression or axial distraction, and horizontal translation) on the structures of Denis' central column were analyzed.

In 1990 Farcy[36] proposed that for each of the three columns the differential parameter, osseous or ligamentous, of the injury be integrated.

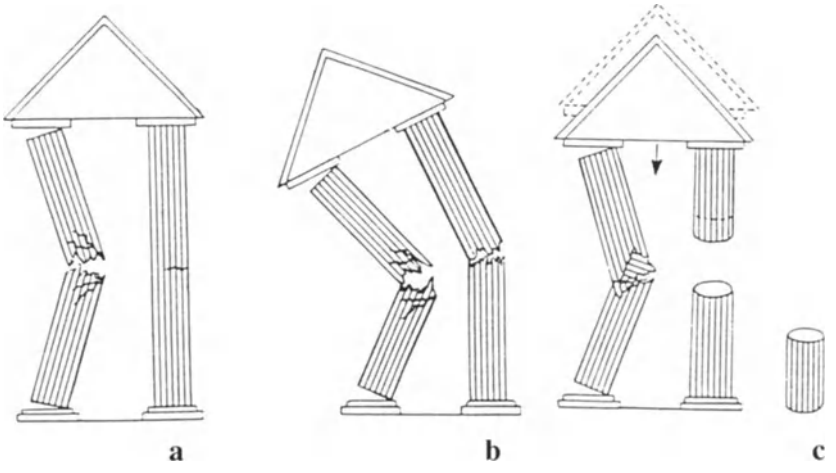


Fig. 2. Kelly's concept of 2 columns (1963) (from Kelly[57]). (a) The two-column concept of the spine as a weight-bearing structure. With residual stability in the posterior column, anterior collapse is incomplete. (b) Loss of posterior column permits pronounced anterior collapse. (c) With laminectomy posteriorly and destruction by trauma anteriorly, no stability remains in the spine

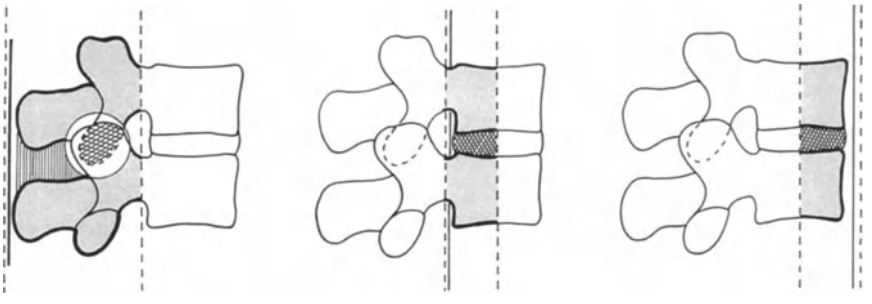


Fig. 3. Denis' concept of 3 columns (1983) (from Denis[32])

Finally in 1993, following several experimental and clinical studies, Argenson[3,4] summarized much of this data in a more simplified manner. Four principal types of injury were proposed with their corresponding dominant mechanical forces and stability criteria. An accent was also placed on the risk of complication secondary to the osseous or ligamentous nature of the central column lesion. The degree of kyphosis and its risk of secondary occurrence were also taken into account.

From the majority of work reported throughout the history of spinal traumatology, there emerges the opposition between fracture-compression entities on the one hand, and fracture-dislocations or luxations on the other. Our classification prolongs this distinction. Indeed the lesions in each one of these groups exhibit a logic which corresponds perfectly with spinal biomechanics. Therefore, we first distinguish predominantly *disco-corporeal* lesions. This group attests to the failure, more or less severe, of the mechanical supporting role assured by the stacked disco-corporeal edifice which is crushed here most often within its ligamentous sheath. The second group includes the transversal, predominantly *disco-ligamentous* lesions of the spinal axis. The torn motion segment is sometimes associated with avulsion of fibrous insertions, thereby threatening intervertebral cohesion. The lesions encountered in this group are usually unstable. A third group of so-called *mixed lesions* combine the different elementary aspects of the preceding forms. Each group is therefore specific and distinguishes itself by its own radiological pattern permitting from the diagnostic stage, and with the aid of data from radio-surgical correlations, prediction of the total extent of osseous and ligamentous involvement, and thus to evaluate its severity by definition not only of the potential neural risk characteristic of each lesion, but also of the precise threat to stability or consolidation.

In the first section, we present the biomechanical data which support our approach to spinal injuries. It is a summary of the work which has accumulated in this field by numerous collaborators, but is essentially drawn from experimental studies in the anatomy laboratory at the University of Clermont-Ferrand (Vanneuville).

2. Experimental Biomechanics

As the dorsal axial element of the trunk, the spinal column is the most essential structure in the static and kinetic functions of the human organism. Solidly anchored it supports the head and upper limbs, and stands on the lower limbs by means of the mobile pelvic girdle. It is surrounded by a rigid thoracic cage and a flexible abdominal cavity.

The vertebral column protects in the spinal canal, the neuro-meningeal elements that it shelters and distributes metamerically and rostro-caudally to all parts of the torso and limbs.

Anatomically, this dorsal, multi-articular edifice composed of bony parts is united by articular, cartilaginous, ligamentous, and muscular elements. Its complex structure results from necessary adaptations to contradictory imperatives of stability, mobility, and protection, and its solutions of compromise induce a certain vulnerability.

Because of man's erect position, the spinal column sustains permanent vertical mechanical strain parallel to its long axis. It is also subjected to variable and divergent forces of compression, distraction, shearing and rotation in three-dimensional space. Any force, stress, or displacement observed in one anatomical plane automatically leads to modifications in the other two planes.

2.1. The Spinal Column: a Composite Material

The spine is constructed from 3 types of material which are themselves composite in nature: bony vertebrae, intervertebral disc, and ligamento-capsular apparatus.

2.1.1. The Vertebrae

2.1.1.1. General Morphology

The basic skeletal component of the mobile spinal column, each vertebra forms an irregular bony ring which surrounds the neural axis (Fig. 4).

In front, the vertebral body increases regularly in volume in the caudal direction. Its upper and lower surfaces are covered by a cartilaginous end-plate serving as intermediary for the insertion of the intervertebral disc.

The vertebral (neural) arch, is a composite of several structures including the pedicles inserted on the lateral edges of the posterior surface of the vertebral body, and the laminae joined medially posteriorly. These structures also increase in volume in the caudal direction.

Different processes are implanted on the neural arch:

– Aligned on each side with the cranial-caudal axis, the cranial and caudal zygapophyses form two bony columns. The progressive change in orientation of the articular facets delineates from top to bottom a veritable spiral passing from a horizontal plane in the upper cervical spine, to a sagittal plane in the lumbar spine (Fig. 4).

– The transverse processes roughly spread outward in a frontal plane, and the posterior and sagittal spinous process are the sites of insertion for muscular and ligamentous tensors.

The cranio-vertebral articulation departs from this fundamental architecture. The atlas and axis constitute the "sub-occipital spine" segment specifi-

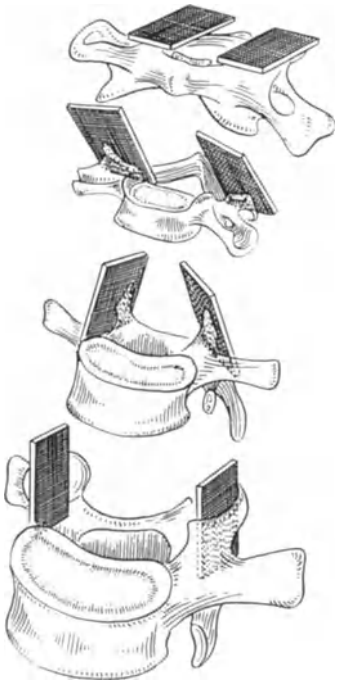


Fig. 4. Vertebral morphology and orientation of the cranial articular facets from the cervical to lumbar level

cally adapted for high mobility of the cephalic extremity, especially in rotation.

In the rest of the mobile spine, the anatomical and functional features of the cervical, dorsal, and lumbar segments are responsible for morphologic differences which have been defined classically[79]. This distinction is especially clear for the middle vertebrae of each group, but in the junctional zones between segments, numerous morphologic convergences are found. These correspond to the transition vertebrae which are distributed variably between individuals. According to Stagnara[94], the transitional vertebra in the dorsolumbar spine varies in position between T9 and L3 with 33% at L1, 22% at T12, and 21% at L2.

2.1.1.2. Structure of Vertebral Bone

The vertebra is a composite mixture of an outer, cortical, compact bone, which encloses and contains the spongy substance. Compact bone forms a thin shell around the vertebral body. It is fine in the ventral and middle regions, and thicker in the juxta-discal regions. In the dorsal region compact bone is especially dense forming the "posterior plate" of the vertebral body

which is somewhat fragile in the center due to the vertebral emissary foramina, from which the venous pedicle emerges from corporeal spongy bone. Compact bone is more abundant in the posterior arch. It forms on the medial aspect of the pedicles and of the laminae, a thick arch which borders the neural canal. The spongy bone which makes up the majority of the vertebral body is generally homogenous in the young subject, heterogenous and lacunar in the elderly subject.

The orientation of spongy trabeculae can be studied on histological slices or on thick slices by radiography, macrophotography, scanning electron microscopy, or by neutron diffraction[6]. Spongy bone architecture is determined by orientation of the trabeculae in the directions of its mechanical stresses (Fig. 5). Vertical and horizontal trabeculae are described in the vertebral body, an arciform system between the two transverse processes crossing the laminae in the neural arch, and vertical trabeculae in the supporting columns of the zygapophyses. A system of oblique trabeculae, crossing the two pedicles, "stretched" between the superior and inferior zygapophyses on one side and the superior and inferior end-plates of the vertebral body on the other side, attests to the functional synergy between the 3 vertebral pillars.

The compact bone is lamellar in structure formed of 3 layers parallel to the superficial plane. The central layer made of Haversian bone is placed between two thin lamellae, one superficial comprised of periosteal bone, and the other deep at the compact/spongy bone interface. The Haversian layer forming the major part of cortical bone orients its trabeculae along the axis of the osteons from which it is constructed.

The Benninghoff method[12] explores this osteonic orientation by determining through "fissure lines" the orientation of the protein network of demineralized bone which is parallel to it (Piekarski).

Using this method, Escande[34] determined the existence of lines orientated in bundles which are constantly found in the vertebral cortical bone (Fig. 6). The corporeo-articular bundles in the cranial and caudal direction combine with their corresponding bundles from adjacent vertebrate to surround the intervertebral foramen. The pediclo-articular or laminar bundles on the medial cortical bone of the neural arch, have a fan-shaped distribution, from

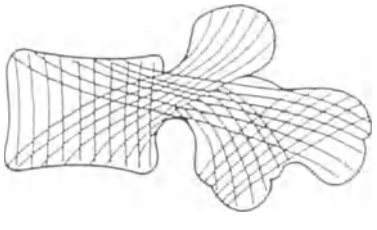


Fig. 5. Orientation of the spongy bone trabeculae

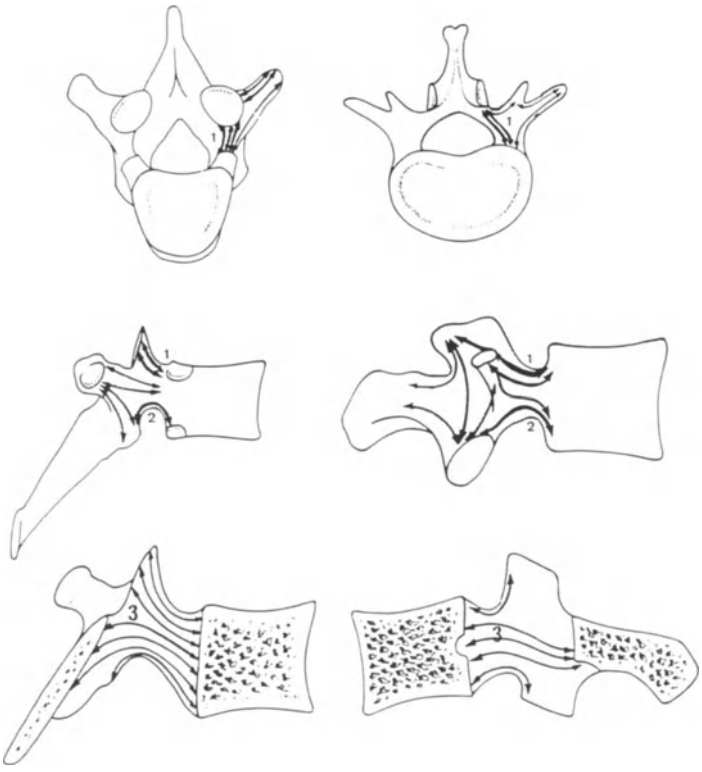


Fig. 6. Osteonic bundles of the cortical bone (from Escande[34]). *1* cranial corporeo-articular bundle, *2* caudal corporeo-articular bundle, *3* medial pediculo-articular or laminar bundle

the implantation of the pedicles in the body towards the articular processes and the laminae.

According to the law of maximal resistance for a minimum of bony tissue, proposed by Roux in 1895 and reformulated by Koch in 1917, the orientation of cortical bone osteons and of spongy bone trabeculae, is determined by the direction of the resultant of chronic stress exerted physiologically in vivo (Piekarski).

The vertebral body appears to have a role both in attenuating shock and in distributing forces. The trabeculae orientated towards the neural arch demonstrate the role of the articular processes. The vertebral body presents a fragile anterior zone situated between two bundles of oblique trabeculae and a solid posterior zone with a high density of compact bone, partly explaining the frequency and the predominance of compression fractures in the anterior part of the vertebral body during trauma.

2.1.1.3. Vertebral Hardness

Bone resistance can be studied in a comparative fashion in all parts of the vertebra by Vickers' microhardness method*[40]. This method used in metallurgy to define the "hardness" (resistance to permanent deformation) of a material sub-divides mechanical behaviours into 3 groups: elasto-plastic (low hardness value), brittle (high hardness value), and intermediate.

A map of vertebral microhardness has been constructed by Fournier (Fig. 7) (Table 1):

Table 1. *Hardness of the Different Constitutive Parts of the Vertebra* (expressed in Vickers units)

Vertebral body:	
– ventral part of the cranial and caudal surfaces	65/70
– lateral part of the cranial and caudal surfaces	65
– dorsal part of the cranial and caudal surfaces	80
– dorso-lateral part of the caudal surface	65
– ventral part of the outer rim (with a variation of 25 in these values)	65
– lateral part of the outer rim	25/40
– dorsal part of the outer rim	80
– spongy bone	15/20
Pedicle:	
– caudal surface	80/85
– medial surface	–
Cranial articular process (ventral surface)	90
Cranial zygapophyseal facet	90
Caudal articular process (dorsal surface)	85
Caudal zygapophyseal facet	90/95
Transverse process:	
– cranial surface	90
– caudal surface	90
– dorsal surface	85
Lateral surface of the lamina	90
Lamina-spinous process junction	90/95
Lateral surface of the spinous process	85

From Fournier[40].

* Or Microdurometry.

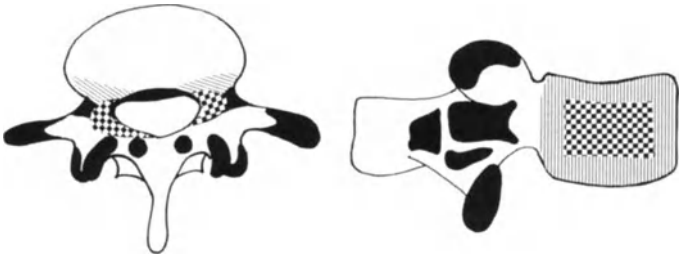


Fig. 7. "Hardness" map of the whole vertebra (from Fournier[40]). Elastoplastic zones, intermediate, brittle

– The neural arch is much harder than the vertebral body, especially at the articular surfaces,

– In the vertebral body, the posterior part of the end-plates is hardest whereas the weakest point is in the center. On the ventral and lateral surfaces hardness is reduced at mid-height.

This vertebral microhardness has been shown by Blaimont to be in close relation with the degree of bone mineralization. If a relationship with resistance in compression is also admitted (Fournier[40]), this method shows that the elasto-plastic vertebral body plays a shock absorbing role while the essential part of static compression is received and transmitted by the dorsal plate of the body and by the vertebral arch.

2.1.2. The Intervertebral Discs

The intervertebral disc is the principal functional element of the articulation joining two adjacent vertebral bodies. Stacked from C2 to S1, the 23 discs represent altogether 20 to 33% of the total height of the spine[111].

2.1.2.1. Each disc forms an entity composed[79] of a central gelatinous nucleus (nucleus pulposus) surrounded by a peripheral fibrous ring (annulus fibrosus) and two cartilaginous end-plates above and below.

The nuclear zone, gelatinous in aspect, is actually composed of a very hydrophilic fibrillar system. By means of its hydrostatic pressure it holds the two adjacent vertebral bodies apart and maintains the intervertebral ligamentous systems in tension.

The annular zone is made up of concentric lamellae containing oblique fibres which are strongly anchored to the adjacent osteo-cartilaginous end-plates, and which are orientated inversely from one layer to the next.

The cartilaginous end-plates are composed of hyaline cartilage.

2.1.2.2. The histo-chemical structure of the annulus and nucleus is, in fact, rather similar which results in a poorly defined transitional zone between the two elements[80].

The proteoglycan content which is responsible for the disc's hydrophilic power (water makes up 85% of the disc's volume) is four times higher in the center than in the periphery.

Histological analysis[106] reveals that collagen fibres constitute 66% of the peripheral portion and only 22% of the intermediate portion. They are very rare in the nuclear region.

Three-dimensional studies of collagen from the annulus show that in the periphery the fibres are more vertical and are inserted on the sub-chondral bone (Sharpey fibres). In the middle part they are oblique, more horizontal, and in continuity with the collagen fibres of the vertebral end-plate. In the center, the fibres have a more random orientation and are not in relation or continuity with the collagen of the annulus or of the cartilaginous end-plates.

2.1.2.3. The behaviour of the various components of the disc has been analyzed by several methods:

– Measurements of intradiscal pressure, in vivo, demonstrate values that vary considerably with changes in posture[75].

– Bortolussi[17] showed, in vitro, that pressure variation is proportional to the force applied toward the center of the nucleus, but that pressure varies according to the point of application of the force.

– Analysis of displacement of the nucleus within the disc, raised as a controversy by Roaf[82], has been studied in vitro by Seroussi[92] who claims that nucleus displacement redistributes the applied stress and increases the structure's resistance.

2.1.3. The Vertebral Ligaments

2.1.3.1. The ligamentous systems are sub-divided into two groups (Fig. 8):

2.1.3.1.1. *The disco-corporeal ligamentous system* includes the anterior and posterior longitudinal ligaments.

The anterior longitudinal ligament forms a continuous fibrous band, which covers the ventral and lateral surfaces of the body and the discs. Made of short fibres stretched from one vertebra to another, and long fibres covering 3 vertebrae, the ligament adheres slightly to the discs and strongly to the vertebral bodies especially at the end-plates. It is thicker in the thoracic spine where the prevertebral muscles are absent.

The posterior longitudinal ligament, a scalloped fibrous band, covers the dorsal surface of the body and the discs within the spinal foramen. It is composed of deep, short fibres, extending between two successive discs and long fibres which cover 3 or 4 vertebrae. Narrow and non-adherent to the middle part of the body, the ligament widens and adheres strongly to the

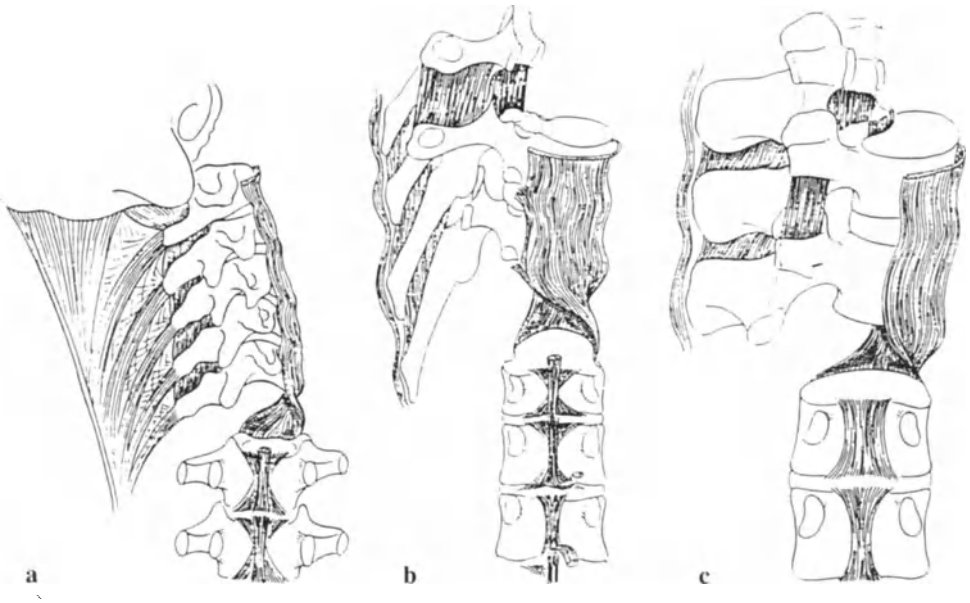


Fig. 8. The intervertebral ligaments. (a) Cervical spine, (b) thoracic spine, (c) lumbar spine

posterior surface of the disc and paradiscal zones on the body extending to the anterior wall of the intervertebral foramen. The ligament is thick in the cervical and thoracic spines, and thinner in the lumbar spine.

In the thoracic region, the 2 longitudinal ligaments exchange fibres with the fibrous covering of the costo-vertebral articulations.

2.1.3.1.2. *The ligaments annexed to the vertebral arch are intersegmental.* They include the ligamentum flavum, interspinous ligament, supra-spinous ligament, inter-transverse ligament, and also the dorso-lumbar fascia as pointed out by Bogduk.

The ligamentum flavum forms two planes laterally, quite thick in the lumbar spine, extending between the lower and upper edges of 2 adjacent laminae. It is rich in elastic fibres (Morris' "elastic syndosmosis"). Reaching outside and in front toward the intervertebral foramen it reinforces the medial portion of the zygapophyseal articular capsules. The two ligamentous sheets are continuous posteriorly with the interspinous ligament.

The interspinous ligament stretches between the inferior and superior edges of adjacent spinous processes, increasing in thickness from the cervical to the lumbar spine, abruptly regressing between L5 and S1. Composed of oblique fibres which spread out like a fan with a posterior base, it facilitates movements of flexion, by widening the space between two spinous processes. Dorsally, it becomes continuous with the supra-spinous ligament which

forms a flattened cord, attached to the summits of the spinous processes and formed of numerous fibres borrowed from neighboring muscles.

The intertransverse ligament is paired and lateral. Absent in the cervical spine, it is constant in the thoracic spine extending between the extremities of the transverse processes where the intertransverse muscles are absent. In the lumbar spine, it is thin, very inconstant, and extends between the mamillary tubercle below and the transverse process above of two adjacent vertebrae.

The thoraco-lumbar fascia forms a dorso-lateral fibrous layer in the posterior lumbar region. It is formed of intercrossed insertion fibres, belonging to the latissimus dorsi, gluteus maximus, and laterally to the lumbo-abdominal muscles. Its posterior topography contributes to its important role as a brake during flexion[16].

2.1.3.2. Histologic Structure

Most of these ligaments are made of tight collagen fibre trusses containing scattered elastic elements. The fibres are pleated[93] giving rise to transversal folds in the fibre trusses.

Except for the ligamentum flavum, the elastic component is not homogenous. It can even be absent in some bundles. In other regions it appears dense in the form of clews especially in zones of confluence between trusses.

During elongation the collagen pleats disappear, the wavy aspect persisting in certain regions only, particularly those which are rich in elastic fibres[18].

2.1.3.3. Ligamentous Behaviour

Orientated along an axis, the ligamentous structures classically respond only to traction forces. They permit physiological mobility, the maintenance of postural attitudes, and limit intervertebral displacements. Their action is often in equilibrium with that of the muscles whose work they spare.

The fibrous structures might also play a role in canalizing the forces as a sheath directing displacements[101]. By the speckle method** it is possible to show the existence of bony structure displacements. These displacements are less important in the disc and their direction is regular when the periosteum and ligaments are present. Removal of the periosteal and ligamentous structures cause displacements in uncontrolled directions.

** In the speckle method, any optically diffusing object illuminated by a laser-type coherent monochromatic beam, presents a very fine granular appearance called speckle. During compression, displacements of the speckle are measured by a double-exposure photographic plate.

2.2. Stability

2.2.1. Vertical Stability: the Supporting Elements and Their Resistance to Compression

2.2.1.1. General Architecture

2.2.1.1.1. Louis' Three Column Concept (Fig. 9)

In the cranio-caudal direction, the weight of the head is transmitted to the axis by two pillars situated in a frontal plane. From this level the vertebral tripod emerges in which the bony segments are stacked to form three columns joined together at each level and through S1, by transverse bridges, the pedicles and the laminae. In the sacrum, forces are transmitted through the two lateral, slightly mobile sacro-iliac joints, and further on through the two hip joints. If the vertebra can be likened to a tripod, then the vertebral column as a whole can be viewed as a structure with three columns: a voluminous ventral corporeo-discal pillar and two dorso-lateral zygapophyseal pillars arranged in a frontal plane[65].

As evidenced by its volume, the anterior column supports the majority of the load. A regular increase in axial forces is observed from the cervical to the lumbar region (according to Vanneuville[100], the Young's modulus doubles from the former to the latter region). In a parallel manner, the "pondero-vertebral index", defined by Delmas[31], which translates the progressive increase in volume of the vertebral segments from the upper to lower spine in

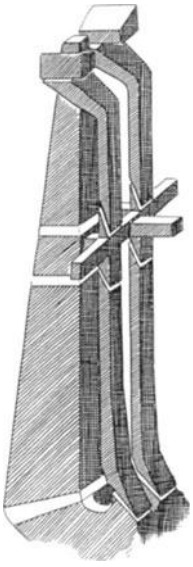


Fig. 9. The 3 supporting columns of the spine (from Louis[65])

proportion to their increasing load constitutes a functional adaptation, whose effect is to diminish the concentration of stress on the lumbar spine (small increase in forces applied per unit of surface area).

2.2.1.1.2. The Sagittal Curves (Fig. 10)

The three spinal supporting columns are not aligned along a vertical axis since three alternate curves (cervical lordosis, dorsal kyphosis, lumbar lordosis) are superposed in the sagittal plane.

According to Euler's law, the presence of curves increases the resistance to axial stress by more than 30% as compared with a rectilinear column[46].

According to Vanneuville[100], the distribution of axial forces within the vertical tripod is different at each spinal level, the force modulus being greater within the postero-lateral pillars, in both lordosis curves, and notably in the lumbar spine where the distribution of forces is practically equal in the anterior and postero-lateral columns emphasizing the important load-supporting role of the posterior inter-zygapophyseal columns.

Fig. 10. The alternate spinal curves

2.2.1.1.3. Osteo-Fibrous Segmentation of the Spinal Axis

This regular alternation of osseous and fibrous segments plays a specific role in the general distribution of load-bearing.

Each bony structure is important in the whole spine at rest, and each vertebral body end-plate is essential, through its orientation, to the equilibrium above it.

Obliquity of the vertebrae harmoniously aligned in the spinal curves, is a mechanical factor in relieving axial stresses that are divided at each vertebra into 2 vectors, a vertical vector in compression, and a horizontal vector in shearing.

The most horizontally orientated vertebrae, the transitional vertebrae and the keystone vertebrae of the curves, are the most exposed to compressive forces. They are often the site of compression fractures.

This role of three mechanically load-supporting columns and that of vertebral end-plate orientation has a direct application in the surgery of spinal trauma. If the conservation and even reconstruction of the three pillars is not solid and correctly orientated, spinal statics will be severely compromised.

2.2.1.2. Elementary Structures and Resistance During Compression

Using direct mechanical methods, White[111] and Vanneuville[100] have studied the displacement of spinal structures undergoing vertical compression.

2.2.1.2.1. The Intervertebral Disc

Subjected to a wide variety of forces and movements the disc tolerates stress that is far greater than that simply due to the weight of the body above it.

The mechanical behaviour of the disc under compression has classically earned it the role of shock-absorber in the transfer of axial forces. If a disc is sliced horizontally the nucleus bulges from the plane of the slice, indicating the existence of internal pressure, linked to its high water concentration. When a compression force is applied to the disc through the end-plate of the upper adjacent vertebra, the nucleus reacts by distributing the force radially to the concentric lamellae of the annulus. Rich in water, and incompressible, the nucleus, in physiological conditions has the essential function of distributing this stress more than of directly bearing the load. The function of load-bearing is assured by the annulus, whose lamellae are successively distended from the center to the periphery. The most central lamellae are considerably deformed while those disposed in the periphery of the annulus are more resistant and deformed only slightly (this behaviour seems to be correlated with the difference in collagen architecture between the central third and peripheral two-thirds of the annulus).

Biomechanical studies of disc resistance to compression employ isolated discs placed between nondeformable plates. The compression forces applied and their consequences on disc displacement can thus be measured:

– The resulting graphs, which are characteristic of visco-elastic structures (Fig. 11), roughly demonstrate an increase in disc rigidity with increasing compressive force, the deformation being increasingly smaller in spite of accentuation of the load. Three phases can be distinguished: (A) Elastic behaviour phase in which the disc remains relatively deformable in response to small loads. (B) Plastic behaviour phase in which the disc becomes increasingly rigid with load augmentation. (C) Brittle behaviour phase in which failure of the material occurs for small increases in load.

From these notions arose that of the "compressive pre-load" emphasized by Janevic[54] who claimed that any compressive force which accentuates disc rigidity causes a considerable reduction in spinal flexibility.

– Among these mechanical responses certain parameters have been studied more extensively. Disc behaviour is not uniform and compression resistance of the anterior elements is greater than that of the posterior elements in segment B of the curve while it is equal in segment A[100]. The disc's resistance properties are essentially due to the annulus. When subjected to compression, the mechanical behaviour of the disc remains identical after removal of the nucleus demonstrating the major if not exclusive role of the annulus in these responses[70]. Furthermore, it has been noted by Farfan[37] that disc rigidity in subjects over 50 years of age is greater than in young subjects.

– Other factors can influence the disc's mechanical responses: An increased speed of load application accentuates rigid behaviour, and consequently diminishes shock-absorbing capacity. While compression of short

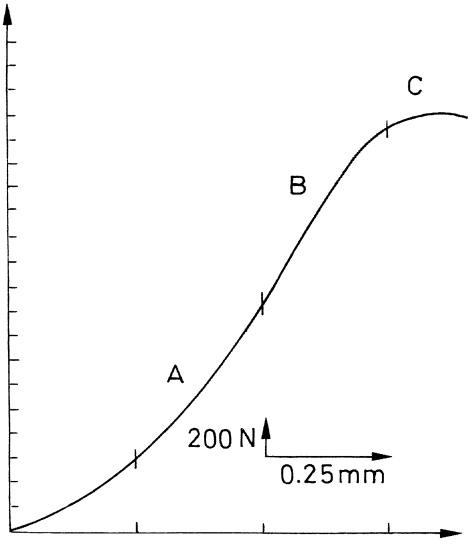


Fig. 11. Curve of whole disc compression (+ standard error). *A* elastic behaviour phase, *B* plastic behaviour phase, *C* brittle behaviour phase

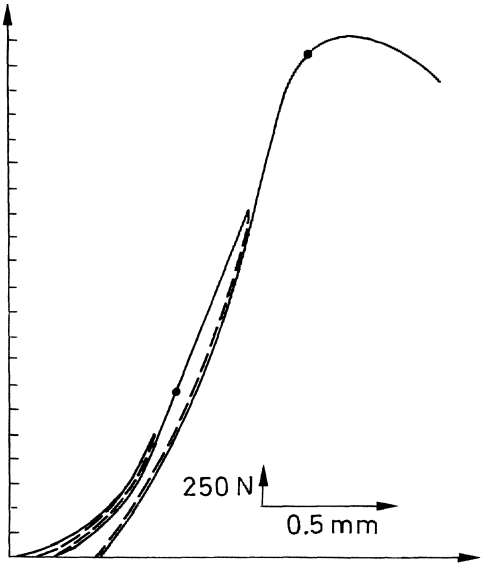


Fig. 12. Measurement of the hysteresis effect during the compression phase of the disc

duration is followed by rapid restitution of the disc's initial height, with however a certain inertia (hysteresis effect) (Fig. 12)[100] under a constant load, the height of the compressed disc stabilizes between 35 and 70 mm (Markolf and Morris)[70]. This notion might explain the reduction in size which has been observed between the morning and evening. Finally during a constantly maintained deformation strain forces have a tendency to diminish with time (load relaxation phenomenon).

The phase of least resistance (failure of material) to high loads is therefore reached more quickly in the case of an abrupt load or when the structure exhibits stiffer behaviour (elderly subject). On the whole, however, the disc's brittle limits are well beyond those of the bony supporting structures (end-plate and vertebral body) for which the brittle phase is more quickly attained. Associated with the radial transfer of forces by the nucleus, there is an initial bulging of the vertebral end-plate which can result in a veritable intra-spongious hernia (Schmorl's nodes)[90].

2.2.1.2.2. The Vertebral Tripod

Biomechanical studies of vertebral bone structures, like those of the disc, are also based on the relationship between the amount of deformation and the applied force[62, 100]

– *Spongy cancellous bone* behaves like a deformable structure during physiological strain in vertical compression, and like a rigid one during

higher forces. As in the graph for the vertebral disc, a terminal phase is noted corresponding to the structure's failure.

Weaver[108] showed, by axial compression of lumbar spongy bone cube samples, that their mechanical properties are the same in all points. Vanneuville *et al.*[100] later demonstrated that spongy bone is more resistant to craniocaudal compression forces than to lateral or ventrodorsal ones (Fig. 13).

– *In the vertebral body* forces are transmitted from one vertebral endplate to another by two structures: cortical and spongy bone. Their relative importance has been quite controversial since according to Evans[35]: the load-supporting part of a vertebral body is the cortical rather than spongy bone, while for Barthley *et al.*[8] and Bell *et al.*[11] resistance to compression is mostly due to spongy bone. In separate studies of cortical and spongy bone Rockoff[84] did not observe a significant difference between these two structures when

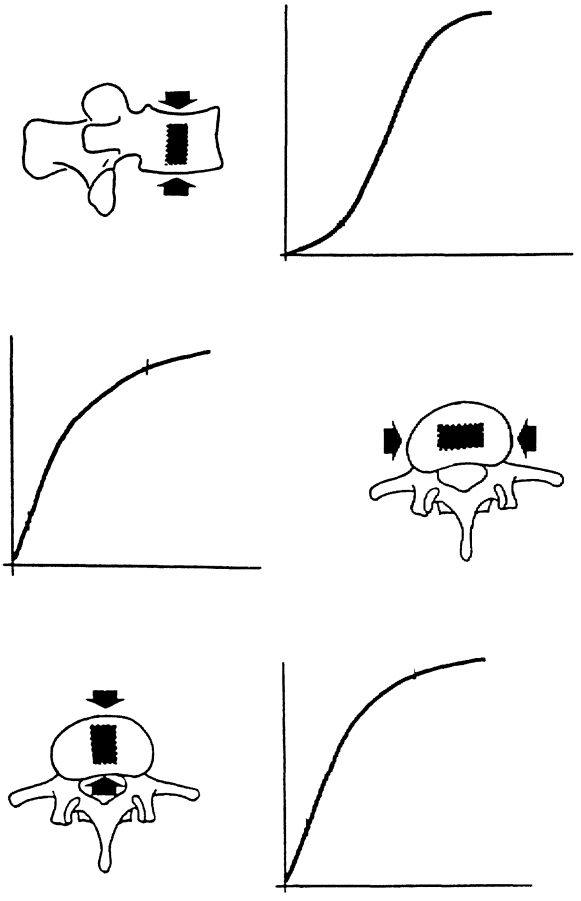


Fig. 13. Graphs of compression of cubic samples of spongy bone in three different axes (vertical – transversal – antero-posterior)

quantifying the relative resistances of compact and spongy bone during compression forces. It appeared to him that the resistance of the two components together is greater than the sum of each element's resistance alone. The physical properties of the two bony constituents is therefore sufficiently different so that they are not simply additive. Vanneuville *et al.*[100] state that the loss of resistance, after removal of the cortical shell is about 33% and that together spongy and compact bone are also more resistant than either constituent by itself. The contribution of spongy bone to vertebral resistance has been evaluated at between 25 and 55%.

Vertebral resistance undergoes rapid decline during the aging process, especially between 20 and 40 years, while after this period it remains relatively stable, in the absence of pathological processes which diminish the bone mass (osteoporosis, osteomalacia). Bell[11] has thus shown that vertebral body resistance is diminished by half when the quantity of bone tissue is reduced by a quarter.

– *Role of the vertebral arch:* numerous methods have been used to study the vertebral arch and especially to determine the loads transferred onto the articular processes. According to Nachemson[75], the vertebral arch and the articular processes play only a minimal role (20%) in the transfer of compression forces. Farfan studying the behaviour of the spine in torsion estimates that 45% of forces are transferred by the zygapophyseal joints. Rolander[85], Weiss[109], Lamy *et al.*[58] studying the force required to rupture the pedicles have obtained a wide range of results which depend on the direction of the force applied and on the techniques of compression and traction.

2.2.1.3. Resistance of the Disco-Vertebral Metameres During Compression

The holographic interferometry method enables the recording and restitution of a light wave in its amplitude and phase. This method has been used by Bleu and Vanneuville[101] to study superficial displacements of the spine during axial compression. A powerful laser emits a continuous beam, of which 90% illuminates the spine and 5% forms the reference wave. Photographic recordings are performed on high resolution emulsions before and after compression. These measurements show that 80 to 90% of displacements are located in the discs, but that bony structures present perceptible plasticity within the vertebral bodies, articular processes, and spinous processes.

Displacements of entire vertebral segments of a spine undergoing vertical compression have also been studied using direct mechanical methods (White and Vanneuville).

– Vanneuville has thus determined the axis along which compression forces are transferred to the interior of the spine and which is located near the posterior plate of the vertebral body ("central axis of torque") (Fig. 14)[100]. The forces transferred below from one vertebra to the next are distributed to

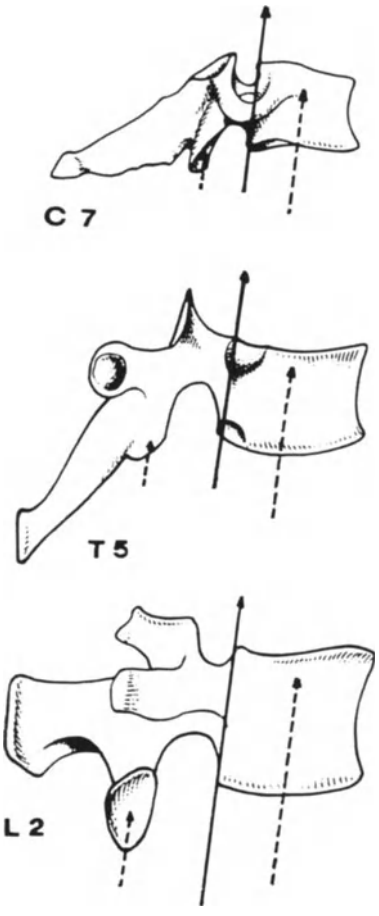


Fig. 14. Lateral view of the vertebra showing the "central axis of torque" (plain line) of the lower adjacent vertebra, and the forces applied to the nucleus and the right zygapophysis (dotted line)

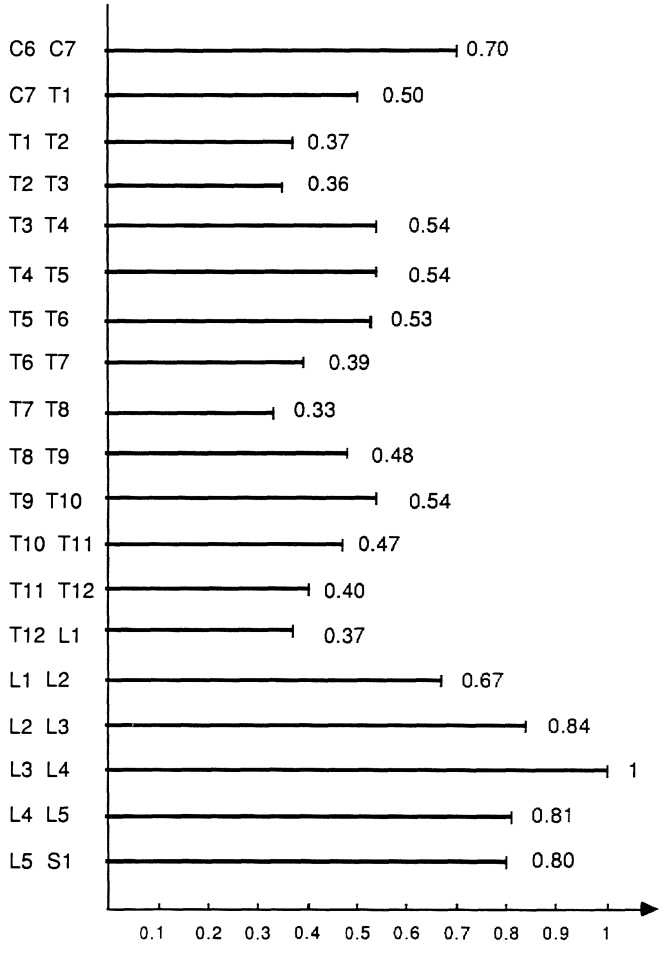
the nucleus and zygapophyseal joints, but differently at each level. It has been shown that major forces are transmitted through the zygapophyseal joints, especially in the lumbar curve summit (Table 2).

– This posterior load-bearing in axial strain has nevertheless been very diversely evaluated. Hakim and King[47] studying lumbar functional units during compression showed that approximately 25% of the load is transferred by the zygapophyseal joints. According to Fiorini and MacCammond[38] 12% of the load tolerated by the torso in 70° of flexion is borne by the zygapophyseal joints. For Adams and Hutton[1,2] the load is negligible in light flexion, but can attain 16% when combining compression and shearing. Miller *et al.*[72] conclude that the loads transmitted by the zygapophyseal joints are not very important when the spine is subjected to compression or flexion-

extension loads, while they can become very important during shearing forces. Finally, Yang and King[113] showed that the loads transferred by the zygapophyseal joints increase with the degree of spinal extension. Excessive loads on the articular processes cause capsular stretching which could be a factor in lower back pain. Furthermore, intervertebral pinching increases the load transmitted by the articular processes.

During a non-physiological axial compression of the disco-vertebral metamere, the vertebral end-plate is first deformed[22], then ruptured[77,82,100–106]. An initial compression of the vertebral body occurs at a force of about 560 Newtons. For higher loads the disc is still more resistant than the vertebral body, which is abruptly fissured by the intra-spongious propulsion of disc

Table 2. *Graph of the Proportion of Forces Transmitted by the Zygapophyses and in the Intervertebral Disc*



material. A second compression is observed at a force of about 720 Newtons which corresponds to crushing of the vertebra after evacuation of its blood content.

2.2.2. Transverse Stability: the Elements of Cohesion and Their Resistance to Tearing

The spinal column is capable of an array of movements which originate in the articular space or motion segment of Schmorl and Junghans[90], composed of three articular structures. The first, anterior, disco-corporeal, and slightly movable, is an amphiarthrosis, devoid of articular cavity, surrounded by ventral and dorsal longitudinal ligaments which form a sheath. The other two are postero-lateral, interzygapophyseal, diarthroses, which possess an articular cavity limited by a synovial membrane, reinforced by a capsule and associated with intersegmental ligaments.

2.2.2.1. The direction and amplitude of movements can define the transverse stability of the spine. Each intervertebral motion segment is capable of only a limited number of movements which are reduced in amplitude, the sum of which constitute the global amplitude of spinal column mobility in the three planes.

When movement possiblities are analyzed separately for the anterior discocorporeal articulation, the disc admits 6 degrees of freedom: flexion-extension, antero-posterior translation, transverse translation, lateral inclination, traction-compression, and rotation. However, this large diversity of movements permitted by the disc is limited by the zygapophyses, to a certain sector of space for each spinal region. The essential role of the zygapophyses is therefore to guide and limit movements so that only three types of intervertebral movement are possible: flexion-extension, lateral inclination, and rotation (Fig. 15).

2.2.2.1.1. Studies performed with the aid of flexion-extension films, have verified that *flexion-extension* can be assimilated to a movement of rotation about a transverse axis ("motor axis"), which projected in the sagittal plane is called "motor center". This center is not located, as some have thought, in the nucleus pulposus, but rather within the vertebral body subjacent to the motion segment. The zygapophyseal interlining and upper surface of the disc form the arc of a circle the center of which is this motor center. Its position is determined by morphologic factors such as obliquity of the articular facets and height of the zygapophyses in relation to the vertebral end-plate, as well as sagittal dimensions of the facets.

The position of this motor center in relation to the motion segment results in an anterior translation effect during flexion. The lower the center the greater is this translation effect. Thus in the interpretation of X-rays one

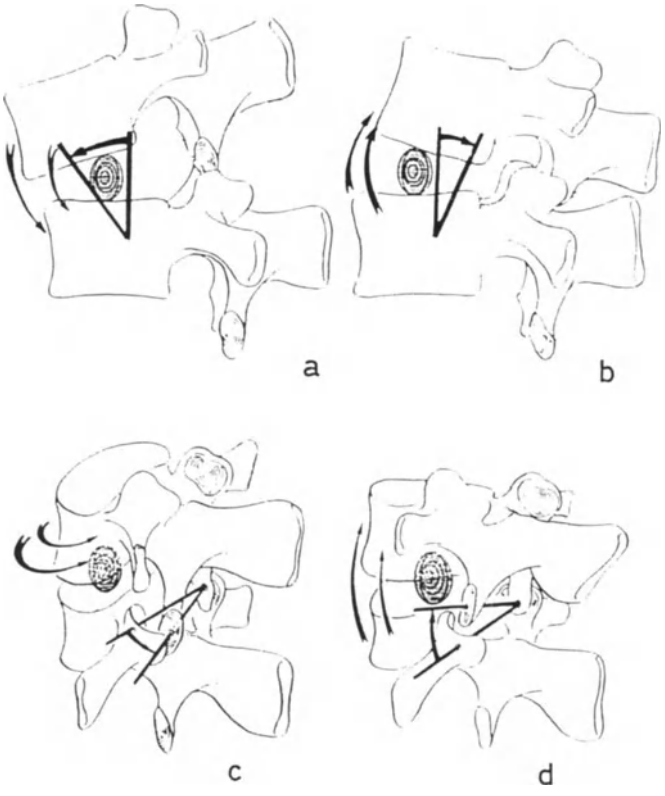


Fig. 15. Mobility of the vertebrae during movements of flexion (a), extension (b), rotation (c), lateral inclination (d)

needs to be familiar with this normal physiological displacement, especially in the cervical spine where the motor center is located at the lower part of the subjacent vertebral body.

2.2.2.1.2. The *movement of lateral inclination* is also assimilable to rotation about an antero-posterior axis. However, in the cervical and dorsal spine, obliquity of the articular facets in the frontal plane will provoke sliding of the superior articular facet down and backward on the side of inclination, and up and forward on the opposite side. There is an obligatory movement of true rotation, called automatic rotation, which is translated on AP films by lateral displacement of the spinous processes. Kapandji[56] has therefore defined an inclination-rotation axis which is perpendicular to the plane of the articular facets. In the lumbar spine, the articular facets are orientated in the sagittal plane, and lateral inclination occurs by rocking between the vertical rails of the superior facets.

2.2.2.1.3. The *movement of rotation* also takes place in a horizontal plane for which the axis of rotation has an anterior location in the cervical and thoracic spine: the articular facets delineate the segment of an ellipse in the cervical spine, and the arc of a circle in the thoracic spine, but the center of each is located in the middle of the vertebral end-plate.

In the lumbar spine the axis of rotation is posterior: the articular facets form a parabolic curve open posteriorly with its center on the spinous process creating a major handicap for rotation because movement amplitude is limited by the disc in front. The morphology of the lumbar zygapophyses constitutes a veritable "anti-rotation system".

Disco-ligamentous lesions from trauma due to shearing are much more frequently encountered in the cervical than in the lumbar spine not only because of the very great mobility of the cervical spine but also because of the limitation of rotation in the lumbar spine.

2.2.2.2. The Elements Limiting Mobility

Integrity of the elements responsible for limiting segmental mobility in the three types of movement studied, is essential to motion segment stability (Fig. 16).

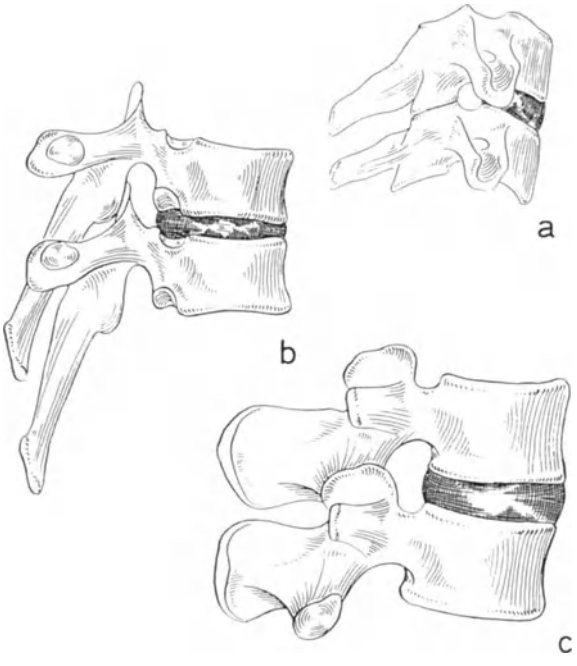


Fig. 16. Elements limiting mobility (posterior zygapophyses (a) – spinous process (b) – vertebral end-plate and disc heights (c))

2.2.2.2.1. The Posterior Abutments

The role of guiding movement is attributed to the zygapophyses because of their morphology. These articular elements constitute abutments during flexion and limit horizontal sliding (antelisthesis) due to their obliquity in the frontal plane. In extension, the tip of the inferior articular process comes to rest on the vertebral isthmus (articular neofacets are encountered here especially in the lumbar spine proportionate with the accentuation of lordosis). In addition to the role in spinal kinetics suggested by the morphology of the articulations, their sometimes different orientation between the right and left sides, and the discordance between the movement center and the center of the disc, all constitute factors of stability opposing movements except for those which occur in privileged planes. Phenomena of osseous plasticity are therefore quite necessary and have been demonstrated using optical methods[100]. These minor modifications in orientation permit the reconciliation of the two imperatives, mobility and stability.

The length and obliquity of the spinous processes are also important, notably in the dorsal spine where movements in extension are limited by this abutment phenomenon. This same role is also encountered in hyperextension and in the lordotic spinal curves.

2.2.2.2.2. The Anterior Limiting Factors

The form of the vertebral body. Orientation of the vertebral body facilitates movement amplitude in the plane which is perpendicular to its largest diameter. In the cervical and lumbar spine the quadrangular body with a large transverse diameter facilitates flexion-extension and limits lateral inclination (especially in the lumbar spine).

The form of the vertebral end-plates. In the cervical region, existence of the unciform processes gives a concave aspect to the upper end-plate in the frontal plane. The lower end-plate is also concave in the sagittal plane.This articular configuration resembles those of a saddle articulation facilitating movements of flexion-extension and lateral inclination.

The height of the disc relative to that of the vertebral body is also important. In the cervical and lumbar spine this height ratio is one-third; in the thoracic spine it is one-sixth. The higher the ratio the greater will be the amplitude of segmental movements.

2.2.2.2.3. *The vertebral environment* also influences segmental mobility notably in the thoracic spine where the costo-vertebral joints limit lateral inclination and axial rotation. Rigidity of the thoracic column due to the presence of the rib cage also limits movements of flexion-extension.

2.2.2.3. The Structures of Intervertebral Cohesion

2.2.2.3.1. The Intervertebral Disc

In axial traction. These studies were conducted on specimens obtained, either by longitudinal sections, or by conserving the vertebral bodies above and below the disc to be stretched (Fig. 17).

Two notions become clear in these studies. The disc tolerates compression better than traction. While the ventral portion of the disc resists compression better, the dorsal portion is more resistant in traction. Furthermore, Galante[43] has shown that in stretching specimens of annulus fibrosus in different directions, maximal resistance is observed when pulling at 15° to the horizontal.

In torsion. These studies were conducted using machines to produce cyclic movements of the superior end-plate at variable angles of rotation. Farfan[37] measured the force required to produce torsion. The resulting curve presents three phases: in the initial phase of 0° to 3°, rotation causes minimal torsion; in the intermediate phase of 3° to 12°, torsion is practically proportional to rotation; and in the final phase of 12° to 20°, torsion increases only slightly. Beyond 20°, the mechanical structures fail. Moreover, he showed that the resistance of a normal disc is 25% greater than that of a degenerated disc. However, Adams *et al.*[1] and Liu *et al.*[63] affirmed that torsion cannot play a role in disc pathology, since the vertebral arch is always damaged before the disc, particularly at the lumbar level.

In shearing. These studies were performed on machines which enable the upper end-plate to effect movements of translation parallel to the lower end-plate. The results show that resistance of the disc to shearing is relatively low in absolute value, but too high to be encountered in pathological circumstances.

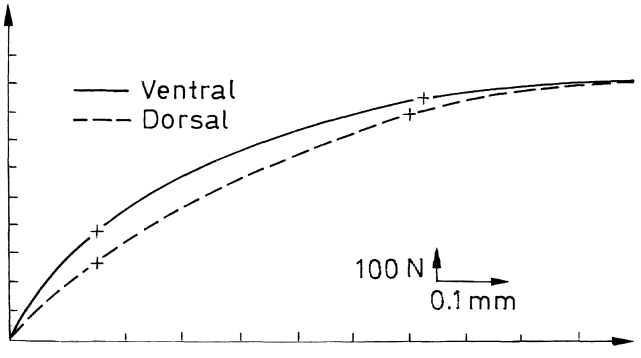


Fig. 17. Ventral and dorsal curves of lumbar disc traction

2.2.2.3.2. The Ligamento-Capsular Apparatus

The ligaments work in a couple with the articular elements to assure horizontal stability of the motion segment by acting as a passive brake. Their arrangement is longitudinal and they work principally in tension.

Both anterior and posterior ligament systems share the work of maintaining intervertebral cohesion.

– The anterior ligament complex, longitudinal and continuous, seems to consolidate the anterior column by forming a ligamentous sheath. The ventral longitudinal ligament as well as the ventral part of the annulus fibrosus classically acts by controlling extension movements. The dorsal longitudinal ligament is particularly well represented in the cervical spine where its integrity is indispensable to the horizontal stability of the motion segment.

– A second functional entity, extending between each set of two vertebrae, assures cohesion of the motion segment posteriorly. The intertransverse ligaments, notably in the thoracic spine, are placed in tension during movements of lateral inclination. The ligamentum flavum, with longitudinal posterior interlaminar fibres, is the only ligament whose characteristics approach those of an elastic body during relaxation. It is highly resistant and its role as a braking system during movements of flexion is coupled with the abutment phenomenon of the zygapophyses. Due to a high elastin content it exhibits a recall response at the end of flexion, which spares muscular energy. Meyer (1873) observed that the ligamentum flavum is in a permanent state of tension in the neutral position (positive resting tone) and is relaxed during extension. The inter- and supra-spinous ligaments are the most posteriorly situated and play a role in the control of flexion movements.

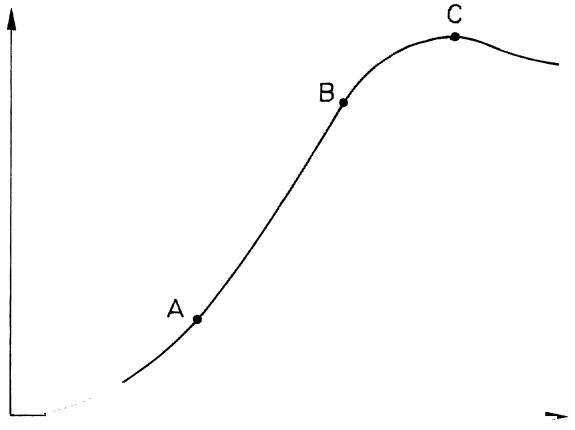


Fig. 18. "Typical graph" of elongation of a ligament (example of tension elongation curve)

– Associated with this ligamentous system is the passive braking system of the dorsal and ventral parts of the annulus fibrosus during movements of flexion-extension (notably in the lumbar spine where their section provokes an increase in mobility by 50%). During rotational movements, all means of intervertebral union participate in the braking role. The collagen fibres which are arranged obliquely in the annulus fibrosus, are especially important in limiting rotation.

Studies of mechanical resistance were performed in traction. However, it is probable that components of compression, torsion, and shearing intervene to produce proprioceptive stimuli during movement. The first results were reported by Nachemson and Evans[74], and by Tkaczuk in 1968[97]. In 1980, Vanneuville *et al.*, followed by Chazal *et al.* in 1984[26], studied all of the spinal ligaments using a traction machine. Graphs of traction versus lengthening (Fig. 18) show an italic S aspect typical of visco-elastic materials for all ligaments. Bourges[18] performed a histological study of ligaments in the 3 segments of the curve: the sinuous aspect of collagen fibres disappears in segment A, elastin fibres rupture in segment B, and the ligament ruptures in segment C.

Each ligamentous structure has its own specific properties but all have the same curve of force versus lengthening (sigmoid aspect), which explains their high capacity of deformation for physiological movements permitting easy mobility. However, their heightened resistance to deformation when physiological amplitudes are exceeded, serves to protect the contents of the spinal canal. Their physical properties, illustrated by the sigmoid curve, are in every way comparable to those of other constituent elements of the spinal column (cancellous bone and disc), with a similar Young's modulus, attesting to their aptitude for deformation. According to Chazal[26], the most resistant ligaments are those which contribute to the formation of the walls of the spinal canal, the dorsal longitudinal ligament and the ligamentum flavum (as well as the intertransverse ligament in the dorsal spine).

The longitudinal ligaments annexed to the vertebral body have an elastic behaviour and lengthening capacity much higher than called upon in these studies which respect physiological possibilities. Their mechanical braking action in extension is limited.

On the contrary, the ligaments of the neural arch, which have a very limited lengthening capacity, are in pre-tension at rest and therefore constitute active brakes to flexion, lateral inclination, and rotation of the spine through early and effective tightening.

By means of this passive braking system, the ligaments contribute to horizontal stability, and also offer resistance when a load is placed on the disc, protecting it against excessive stress (Chazal shows that when the posterior elements are removed, posterior flexion of greater than 15° results in rupture of the disc).

2.2.2.3.3. The Osteo-Cartilaginous Insertions

According to White and Panjabi[111], the rupture of a ligament or of its bony insertion is dependent on the speed of the force responsible: ligament rupture results from abrupt strain, while avulsion of the insertions occurs during more progressive forces.

2.2.3. Global Stability: Elements of Mechanical Strain and Their Controlling Factors

Most biomechanical studies have been carried out using isolated structures or segments containing two or three vertebral metameres. Indeed, diminishing the number of parameters facilitates understanding of equilibrium phenomena. However, the spinal column is a composite and anisotropic structure enclosed within an intricate anatomical complex capable of movement, a reality which cannot be circumvented. Therefore, any elaborated hypothesis is automatically schematic and reductionist.

2.2.3.1. Osto-disco-ligamentous embedding is the mechanical resultant of the characteristics of each element:

Although composite in nature, vertebral material is made up of a visco-elastic continuum whose quality depends on that of the mechanical compromise between its rigid and flexible characteristics. There are some differences in the relative proportion of these two parameters which mechanically mark the osseous or fibrous alternation in spinal segmentation. Any major stress will have a more or less rapid effect, depending on the structure implicated, of increasing rigidity. The material's visco-elastic nature renders it capable of absorbing stress.

The anatomical structure is organized not only to attenuate strain but also to distribute it:

– the vertebra acts along the force lines of its bony trabeculae as a distributor of stress diffusing it to all of its elements.

– the disc also distributes forces radially to the intercrossed fibres of the annulus and to the vertebral end-plates which it deforms.

– the longitudinal ligaments which form a sheath surrounding the disco-corporeal column, appear to play a role in canalizing stress. In their presence, forces remain parallel and homogenously distributed while their removal causes disorganised distribution[101].

Plasticity even of the osteo-discal elements contributes to their geometric fitting. Disco-ligamentous structures sustain 80 to 90% of observed deformations, and the bony structures 10 to 20%. These deformations predominating in the disc also contribute to mechanical anchoring of structures because of opposing orientations of the vertebral tripod's articular surfaces.

All of these mechanical properties of shock absorbance and force distribution constitute an effective adaptation of an anisotropic structure to stress.

Each bony or fibrous structure has its own tolerance threshold for mechanical stress. A heterogenous solidity is thus organized, specific to certain components, and underlining their preponderant role.

In proportion with increasing strain, the risk of rupture is hierarchically distributed even within the same anatomical structure, vertebra, disc, or ligament system.

In the pathology of trauma, lesions follow this same hierarchy, making it possible not only to determine the sequence of ruptures in a vertebra, but also to define the "key structures" by their high resistance such as the posterior plate of the vertebral body or the dorsal longitudinal ligament, structures which have been long considered as the essential elements in spinal stability.

2.2.3.2. Spinal Equilibrium and Stability

Mechanical equilibrium of the spine is closely dependent on factors of vertical and horizontal stability. However, all of these factors are solicited to provide stability depending on particular situations of equilibrium which are themselves affected by posture, movement, and the spinal level in question.

Louis' theory of "bi-orthogonal articular triangulation"[65] further emphasizes this functional synergy within the vertebral tripod. It demonstrates an orthogonal articular system between the articular interlining and the plane of the disc. Depending on the position of the spinal axis with respect to the applied forces, the anterior and posterior articulations share the load differently.

– In the standing position, forces of gravity, coupled with muscular forces result in a compression effect on the intervertebral disc, and a shearing effect on the zygapophyses.

– When lifting a weight, with the trunk in horizontal position, the zygapophyses receive a compression load and the disc a shearing load, in addition to an axial compression effect originating from the muscles.

This theory of bi-orthogonal triangulation, is supported by the often divergent orientation of the zygapophyseal articular surfaces. If this orientation changes gradually throughout the spinal column, as Kapandji[56] had shown, it favours stability to the detriment of mobility which requires the intervention of bone plasticity and ligament laxity in certain planes of movement.

Traumatic forces can specifically involve factors of either vertical or horizontal stability. These factors can also be involved conjointly, associating lesions of load-supporting structures with those assuring the maintenance of intervertebral cohesion.

This possible predominance of traumatic injury to either disco-corporeal or discoligamentous structures, or both together, is the basis of our anatomo-radiological approach to spinal trauma.

2.2.3.3. Active Factors in Regulation

The spine is stable due to its osteo-disco-ligamentous components, but as has been noted by White and Panjabi[111], a simple load of 20 Newtons applied to T1 disrupts equilibrium, thus illustrating the determining role of the spinal musculature.

2.2.3.3.1. The Muscular Apparatus

The muscles act on the spinal column by means of two mechanically opposed groups:

– The extrinsic muscles are situated far from the intervertebral centre of movement. Their contraction determines spatial orientation of the organism by movements of high power and amplitude. These especially include the ham-string, gluteal, abdominal and lumbar muscles, and particularly the psoas major and latissimus dorsi.

– The intrinsic muscles located in the posterior or lateral vertebral grooves include: (i) The long muscles, fairly superficial, bridging several vertebral segments. (ii) The short muscles, deep, pauci- or uni-segmental. During contraction they cause vertebral adjustments to re-establish static and dynamic equilibrium.

The muscular main-stay, particularly in the posterior region of the lumbar spine, renders the column rigid during work, by reinforcing the passive action of the posterior osteo-ligamentous structures[14,17,83].

The muscles play a very important role in spinal stability as has been shown in experiments on weight-lifters[103]. Lifting a load of 1000 Newtons on the shoulders in the squatting position does not produce important radiological modifications in the thoraco-lumbar spinal curves when compared with the resting position. It should simply be noted that in trained subjects, tilting the pelvic girdle at the hip joints renders the sacral end-plate horizontal[104]. Experiments conducted on the effects of carrying back-packs on the back[99], confirm the importance of the spinal musculature in the rigidity of the column, and the fairly small role of mechanisms of passive transfer towards the shoulders (suspenders), or the pelvic girdle.

Biomechanical study of the musculature is complex, even with high performance electro-myography[9] using implantable bipolar electrodes. The muscle models described by Hill[50], Huxley[53], or Goubel[44], which take force and elasticity into account can only be used if positioning is perfectly established, and the directions of the force and muscular momentum are determined.

2.2.3.3.2. Factors of the Spinal Environment

Tissue pressure represents a veritable hydraulic buffer system, because of the adaptability of the arterial and venous systems[39], which probably play an essential role in abrupt loads and "acute" strain[5].

Abdominal pressure contributes to the rigidity of the spine by a mechanism of "inflatable structure"[56]. This pressure is adaptable by muscle contraction of the abdominal wall, perineum, and diaphragm[7,13].

Thoracic pressure is less important in spinal mechanics, because of the relative rigidity of the sterno-costo-chondral complex and the cyclic character of ventilation. However, in the thoracic segment, a part of the vertebral body forces are transferred to the sterno-costo-chondral system[102]. Therefore, if sternotomy is performed in a patient with thoracic kyphosis, this causes abrupt exacerbation of the kyphosis[33].

The resultant of all of these phenomena has been analyzed in different postures, by measuring discal pressure in vivo at the L3–L4 disc[75]. It was shown that the lower lumbar discs tolerate a load of between 90.7 and 120.2 kgs in the standing subject.

2.2.3.3.3. Control Mechanisms

Proprioceptive elements permit multi- and pauci-segmental finely tuned regulation.

Sensory transducers are distributed around the vertebra. Dorsally, the neuromuscular spindles of the paravertebral muscles are connected to the posterior spinal roots in the posterior vertebral notches[59]. Posterolaterally, the zygapophyseal joint capsules are rich in mechanoreceptors[59,100]. Ventrally, where the muscles are few in number, sometimes non-existent in the thoracic spine, capsule-shaped mechanoreceptors are found in the anterior longitudinal ligament[45,69,78].

2.3. Spinomedullary Dynamics

The osteo-ligamentous sheath represented by the spinal canal is deformable in normal mechanical conditions of movement. The requirements of movement are thus naturally and passively sustained by the spinal cord and nerve roots. During non-physiological conditions of excessive amplitudes, the nervous structures can be subjected to strain which exceeds their capacity to adapt. Not only the possible consequence of abnormal demand, excessive strain can also result from structural "borderline conditions" due to pathological alterations or constitutional anomalies.

2.3.1. Behaviour of the Spinal Canal During Movement

2.3.1.1. Transverse Modifications

Each surface of the spinal canal presents a specific behaviour during movement and can be responsible for transverse deformation of the neural axis.

On the ventral surface of the cervical and lumbar spine the discs increase roughly in height from 2 to 8 mm between C2 and S1[65]. Their edges are flat in the young subject, and become rounded and more or less bulging in the adult, especially in the lower lumbar spine. The dorsal canal surface is dihedral, open anteriorly where the laminae alternate with the ligamenta flava. In extension these latter two structures form a cushion, and become equally responsible for the canal stenosis which results in this position. In flexion, on the other hand the diameter of the canal increases by effacement of the discs and ligamenta flava, which are stretched[19,24].

2.3.1.2. Longitudinal Modifications

Movement amplitude is maximal for the whole spine during flexion-extension in the sagittal plane[56].

These highest amplitude movements can serve as references for the analysis of osteo-ligamentous deformation and of possible displacement of the spinal cord and nerve roots. Many authors have studied the vertebral column's movement amplitudes either for each of the 3 segments, or for each of the intervertebral spaces[28,56,73]. Results vary with age, constitution, and physical condition of the subject.

Nevertheless, the lumbar and especially the cervical spine exhibit the highest mobility, while the longer thoracic segment, is almost twice less mobile than either of the other two segments (Table 3). These highly mobile spinal segments contain the cervical and lumbar spinal cord enlargements, and the cauda equina.

The principal consequence of these flexion-extension movements is a modification in the length of the spinal canal. These length variations have

Table 3. *Amplitudes of Spinal Movement*

	Flexion	Extension	Total
Cervical	45°	75°	120°
Thoracic	30°	20°	50°
Lumbar	53°	30°	83°
Total	128°	125°	253°

From Louis[65].

Table 4. *Length Modifications Measured in the Vertebral Canal*

	Flexion	Extension	Total
Cervical	27,5 / 28	–15	43
Thoracic	8,5 / 3	– 3	6
Lumbar	30 / 28	–20	48
Total	59	38	97

From Louis[65].

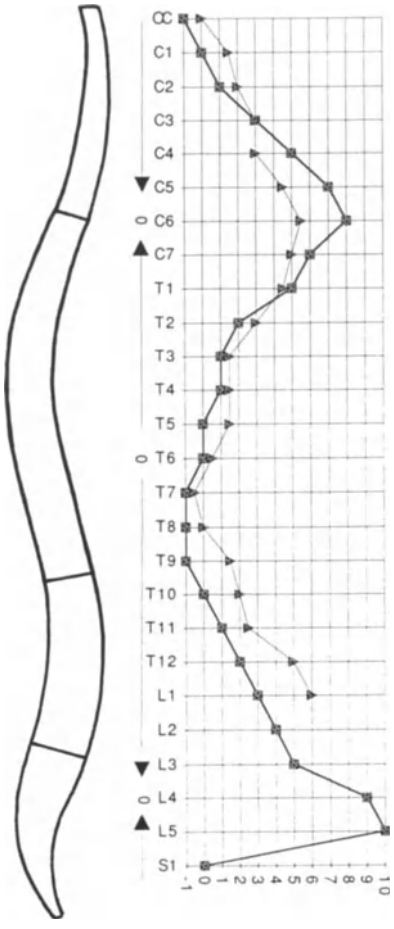


Fig. 19. Vertebro-medullary dynamics (from Louis[64]). ■ Osteo-ligamentous elongation from extension to flexion. ▲ Medullary elongation from extension to flexion

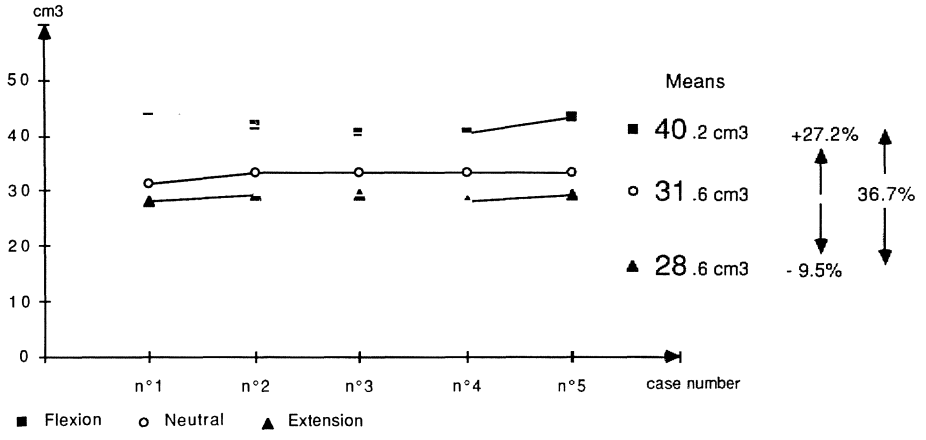
been analyzed by Louis. From extension to maximal flexion, the spinal canal lengthens between 5 and 9.7 cm depending on individual variation (Table 4). These measurements were made during dissection of unfixed cadavers usually of elderly subjects. The dorsal surface of the spinal canal was exposed after resection of the muscles, and articular and ligamentous elements of the posterior arches. Passive movements are dependent on the forces developed. Such non-physiological factors influence the absolute values, but the relative values between each of the segments and vertebral spaces are respected. The results are also in agreement with those from other radiological or clinical measurements in vivo[28,49].

For each of the cervical, thoracic and lumbar spinal segments, movement amplitude is unequally distributed between each of the intervertebral spaces (Fig. 19). Spaces exhibiting the highest mobility are C5–C6 and C6–C7, with 6 to 8 mm of lengthening for each, and L5–S1 with 10 mm of lengthening. The least mobile spaces are located between T5 and T11 which lengthen between 0 and 1 mm.

2.3.1.3. Volumetric Behaviour of the Lumbar Canal

Volume of the lumbar canal is variable according to this segment's position. This has been verified in 5 anatomical preparations of isolated lumbo-sacral columns after removal of the cauda equina. The dura mater which lines the canal is left in place and filled with liquid. Measurement of the relative variations of volume between the extreme positions of flexion extension shows a mean reduction of 36.7% in lumbar canal volume during extension as compared with flexion (Table 5).

Table 5. *Volumetric Variations of the Lumbar Canal During Movement* (measurements in 5 anatomical preparations)



These results accord with the observation that clinical symptoms due to lumbar canal stenosis are improved by the kyphotic posture, and illustrate the quantitative importance of longitudinal and transverse transformations of the spinal canal during movement.

2.3.2. Mechanical Behaviour of the Neural Tissue

The spinal cord is a visco-elastic tissue, exhibiting two adaptive properties in response to mechanical solicitations[20].

The elastic property permits rapid adaptation. It is attributed to the pleated aspect of the connective tissue fibres, as in an accordion, when the medullary tissue is relaxed and the spine is in extension. These same fibres become rectilinear when the spinal cord is stretched and the vertebral column is in flexion.

During extension, the spinal cord and meninges exhibit fine folds on their surface, their diameter is maximal[68], the cauda equina is relaxed and its nerve bundles have a sinuous trajectory. Inversely, during flexion, the spinal cord surface becomes smooth, its diameter decreases, and the bundles of the cauda equina are stretched and rectilinear.

In the pia-mater, fibres are organized in a diamond-shaped trellis-work. The losenges become longer if the spinal cord is stretched, and shorter and more regular if traction ceases. This difference in tissue stress between extension and flexion has been studied by recording pressure variations using intra-medullary transducers. This elastic response is immediate and essentially due to the connective tissue.

The second type of adaptation acts in response to slow phenomena such as compression, and involves tissue modifications in the form of liquid and protein flux. This adaptation increases in importance toward the centre of compression. Flux is directed away from the central zone towards the marginal zones, resulting in a decrease in cell body volumes and in fibre diameters.

Slow localised compression of the spinal cord, even if caused by a blunt surface, can progress towards rupture of the cellular structures in its path, starting in the centro-medullary region and proceeding towards the periphery when the stress persists.

This phenomenon of slow adaptation with deformation of the medullary cylinder is well known in clinical practice during chronic compressive pathologies.

2.3.3. Reciprocal Behaviour

Both myelographic and magnetic resonance imaging show a pre- and retro-medullary "margin of security" in the spinal canal, normally constant in the

neutral, upright position. The spinal cord comes into contact with the convex surface of the canal both during flexion and extension movements[29]. This phenomenon exists spontaneously in the neutral position of the column when there is a tethered cord. In constitutional or acquired stenoses, the "margin of security" surrounding the neural tissue is either diminished or absent. The spinal cord or the cauda equina come in contact with the canal wall in the neutral position. Movements of extension increase protrusions of parietal structures into the canal accentuating wall strain on the contents, as opposed to flexion which relieves wall strain. Traumatic stenoses introduce an additional acute strain factor without the possiblity of nervous system adaptation through its viscous biomechanical component, and any uncontrolled movement can be an aggravating factor.

In order to adapt to variations in spinal canal length, the spinal cord and meninges exhibit properties of elasticity. However, the elongations sustained are not uniformly distributed throughout their entire length, nor do they completely compensate for spinal canal modifications. The entire neuromeningeal structure adapts by more harmoniously distributed stretching: the greatest elongation between two vertebral levels (C6–C7 and L5–S1) corresponds to the most important meningeal and medullary stress (Fig. 19):

– However, for a 50.4 mm elongation of the lumbo-sacral canal, the dura mater varies by only 39.3 mm. The difference of 11 mm is compensated by stretching and cranial ascension of the sacral dura-mater, and stretching and caudal traction of the thoracic dura-mater, with convergence towards the space of greatest mobility, either L5–S1 or L4–L5 depending on the individual. Similarly, in the cervical spine, converging toward C5–C6, the upper cervical and especially thoracic dura-mater behave like a meningeal mobility reserve, while the corresponding osseous structures are practically immobile in flexion-extension. The point of minimal stress is medio-thoracic (T6) where the osteo-neuro-meningeal relationships remain constant. Studies of metameric length variations reveal that the dural segment lengthens by 15% in L1–L2, and by 30% in L5–S1.

– The vertebral column transmits its length and curve variations to the spinal cord, from the occipital foramen where junction with the medulla is stationary[64], to the end of the spinal cord. However, spinal cord movements conform with those of the meninges due to numerous attachments between these two structures, such as the filum terminale, the nerve roots, and the dentate ligaments. During flexion, both structures exhibit the same phenomena of adaptation with maximal stretching of metameres located in the most mobile vertebral segments and converging axial displacements towards these highest amplitude segments. The filum terminale and the cauda equina adapt in the same manner.

Spino-medullary dynamics can be transformed during spinal osteo-synthesis. Using the same methodology as that of Louis, these modifications in

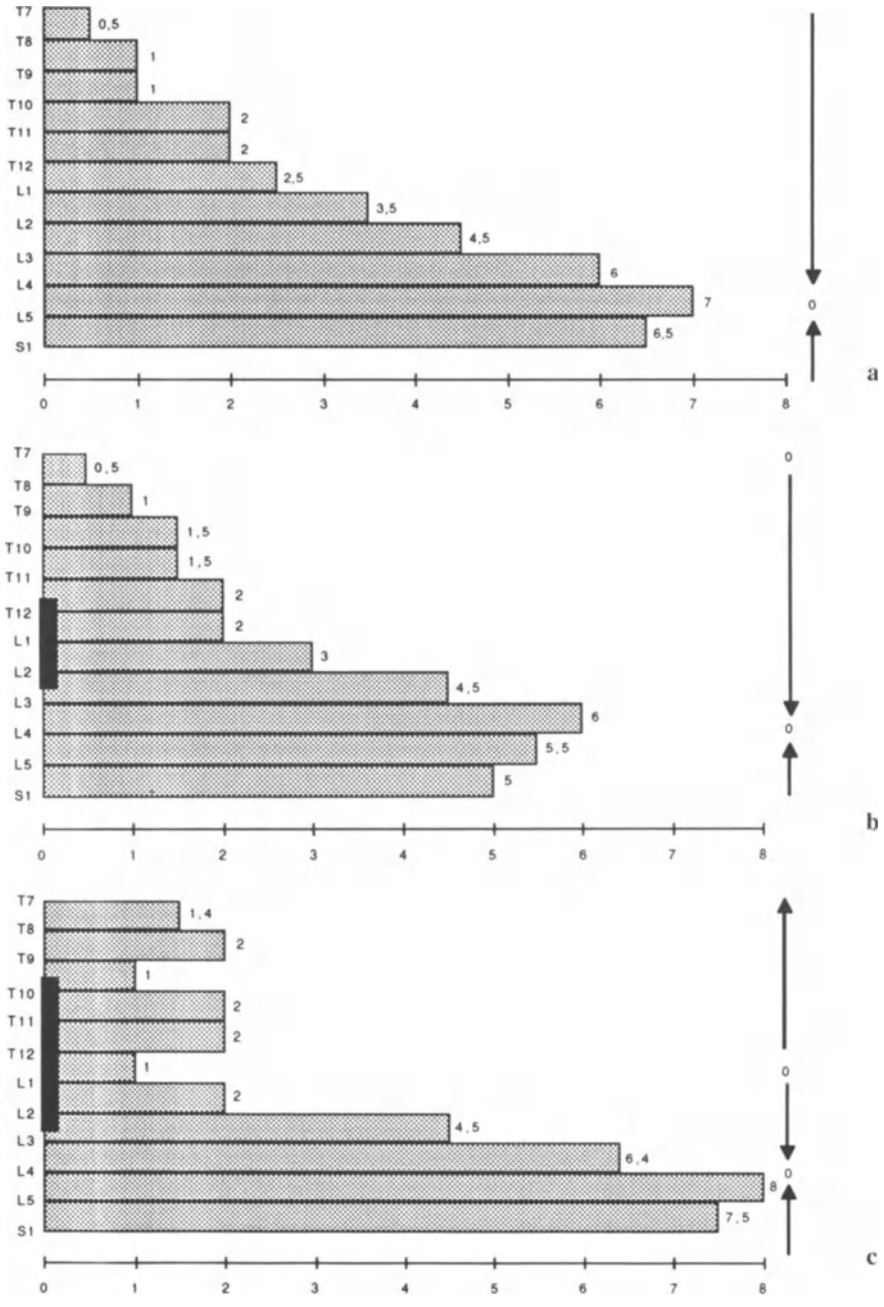


Fig. 20. Neuro-meningeal dynamics. →0← Translation in hyperflexion. ▭ Metameric elongations from hyperextension to hyperflexion. (a) Without vertebral fixation 80° movement amplitude from T7 to S1. (b) With short fixation between T12 and L2 65° movement amplitude. (c) With long fixation between T10 and L2 45° movement amplitude

neuro-meningeal dynamics according to the length of osteo-synthesis were analyzed (Fig. 20):

– fixation by short osteo-synthesis (3 vertebrae) modifies segmental neuro-meningeal stretching only slightly, resulting in the conservation of practically physiological dynamics (Fig. 20b).

– long fixation, however, profoundly disturbs spino-medullary dynamics. Vertebral immobilization in 5 successive levels (Fig. 20c) gives rise to stresses and supra-physiological mobility of the upper and lower spaces adjacent to the immobilization during flexion-extension amplitudes which are almost two times less than normal. The corresponding neuro-meningeal structures undergo the same phenomena. The stationary zone behaves like a slightly mobile segment, equivalent to the thoracic column, and the corresponding neuro-meningeal entity becomes an elongation reserve in order to respond to demands above and below the osteosynthesis with traction forces diverging from the middle of the immobilization.

– Excessive stresses of the spinal cord in upper and lower regions adjacent to osteosynthesis have also been suggested as the cause of adhesion fixation subsequent to arachnoid-epidural scar tissue which can disturb physiological medullary dynamics.

Traumatic spinal cord lesions result, above all, from acute compressive phenomena giving rise to commotion, contusion, or medullary attrition. In

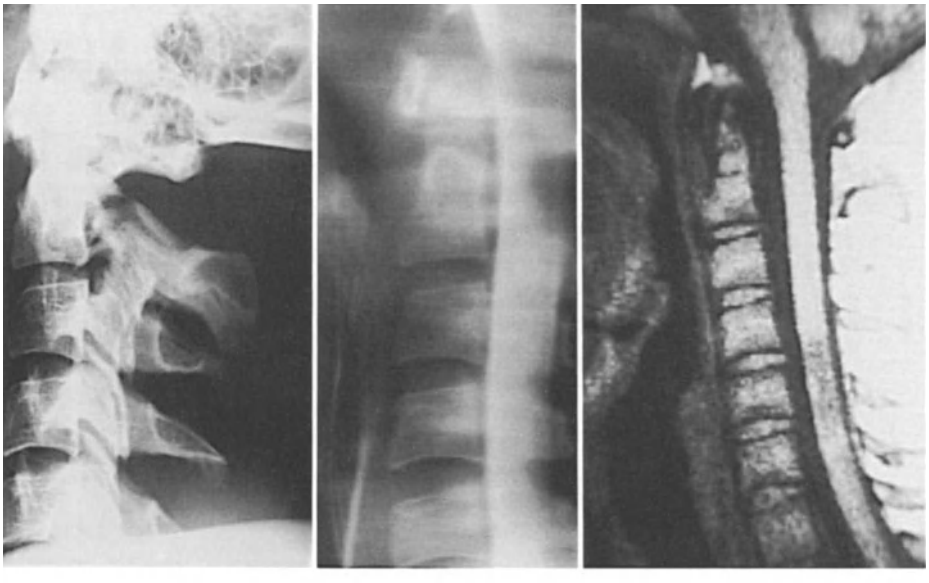


Fig. 21. (a) Bipedicular fracture at C2. (b) Normal myelogram. (c) MRI: intramedullary hypointense signal at C5

clinical practice, however, medullary elongation can also explain certain traumatic quadriplegias. This mechanism is encountered in the child and young adult associated with upper spinal lesions (C2) or even in the absence of lesions of the osteo-ligamentous container. Two demonstrative cases from our experience can be recalled: a child presenting a fracture of the odontoid process with C7-type quadriplegia; and an adult with a bipediculate fracture of C2 and a Brown-Séquard syndrome at C6. In both cases MRI showed intra-medullary signal modifications distant from the vertebral lesions in the lower cervical spinal cord (Fig. 21). This medullary elongation lesion was located at the level of maximal elongation. Sub-occipital bone lesions only attest to the violence of the trauma and spinal elongation. Cases of isolated medullary lesions in C6–C7 without osteo-ligamentous injury have been described previously[96]. It was assumed that trauma had occurred in hyper-extension with shock to the ligamenta flava. The medullary elongation phenomenon would appear to be mechanically more plausible.

This elongation behaviour may also intervene in certain aspects of therapeutic management such as cervical traction which is routinely employed in clinical practice. Breig has shown that cervical traction of 5 kg lengthens the

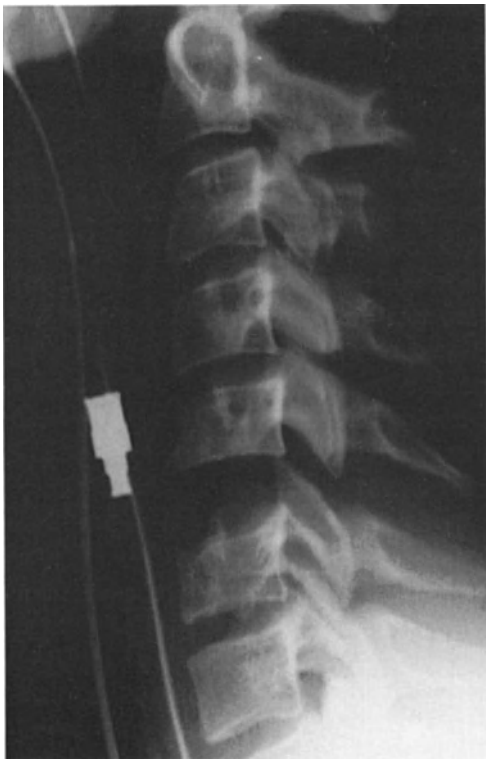


Fig. 22. Inappropriate cervical traction in a severe C5–C6 sprain

cervical canal by 10 mm, and that strain on the edges of a partial medullary wound occurs at 2 kg. Cervical traction which is poorly controlled can therefore result in secondary aggravations (Breig) especially in the case of severe disco-ligamentous lesions in which the involved intervertebral space can become seriously distended (Fig. 22).

3. Anatomo-Radiologic Classification

The following classification of traumatic spinal injuries is inspired by continuous practice in this field over the last 15 years. The case-frequency numbers cited in the text were drawn from a recruitment of 474 cases over a 5-year period between 1987 and 1991. The thoraco-lumbar spine is involved in 233 cases and the inferior cervical spine in 241 cases.

A protocol of lesion analysis more than a general review of case reports is presented for the thoraco-lumbar injuries. Data from previous studies are also included.

Neurological correlations are not considered in the section on the thoraco-lumbar level. Neurological severity at this level is based much more on the

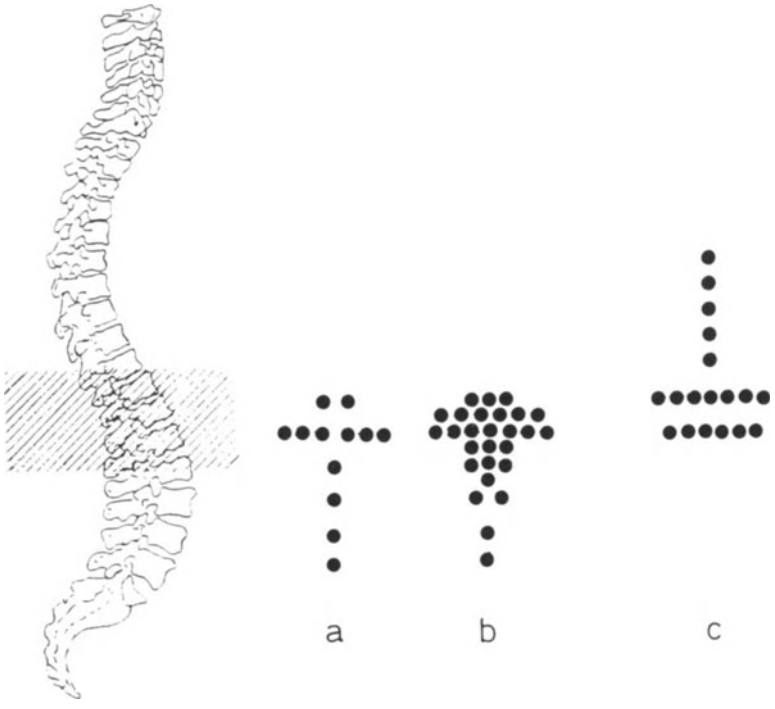


Fig. 23. Distribution of neurological complications in 57 cases of dorso-lumbar spine injuries. (a) No neurological deficit, (b) incomplete neurological syndrome, (c) complete section syndrome

nature of the neural structure involved (spinal cord, or cauda equina roots) than on the character of the vertebral column lesions (Fig. 23). In the cervical spine, however, the severity of neurological involvement can have direct correlation merely with medullary strain. There is a significant correlation between neural complications and the severity of osteo-ligamentous injury which are graded in our classification.

Although the same types of lesion can be found at each level of the spinal column, each spinal segment has its own particular characteristics in response to trauma and should therefore be studied separately. The distribution of different lesion subgroups is in fact highly specific for each vertebral level.

3.1. The Thoraco-Lumbar Spine

At this level the load-supporting role of the vertebral column is strongly emphasized in trauma since disco-corporeal compression type lesions concentrate here (197 out of 233 cases or 84.5%). On the other hand, transverse lesions of the disco-ligamentous type are rare (6%). The model of mixed lesions is that of the Chance fracture[25] first described as a compression-distraction lesion. Generally speaking, these lesions predominate in the 20 to 30 year age group and are on the average twice as frequent in men than in women.

The occurrence of these lesions is concentrated in the transitional thoraco-lumbar spine as has already been very classically described (Fig. 24).

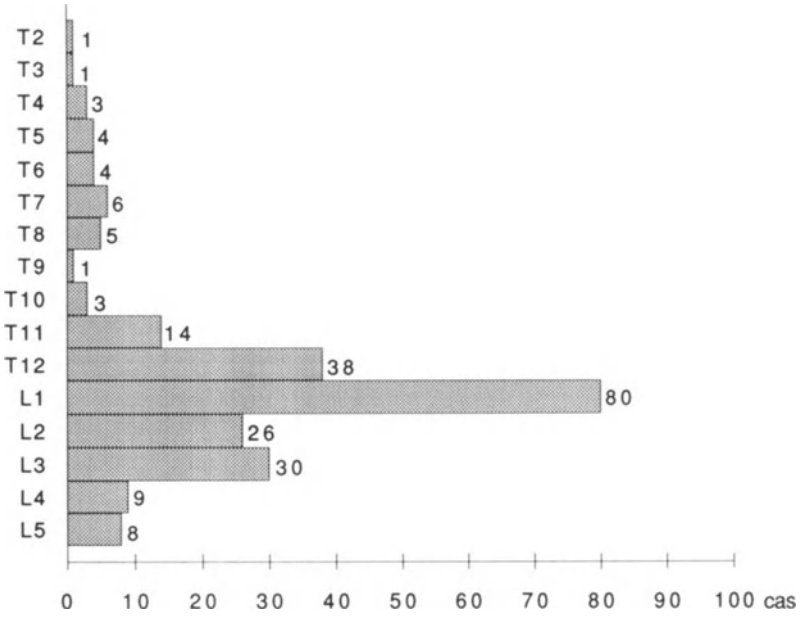


Fig. 24. Distribution of lesions in 233 cases of dorso-lumbar spine injury

3.1.1. Group of Disco-Ligamentous Lesions

The first group is represented by the "disco-ligamentous lesions" individualized by their predominant involvement of the elements of intervertebral union represented by Junghans' motion segment and reuniting the discal, capsulo-ligamentous structures and their osteo-cartilaginous insertions. In this group classically are included the severe sprains, dislocations, and fracture-dislocations. These lesions are rarely encountered at the thoracolumbar level in our series.

Radiological diagnosis bears on the loss of normal anatomical relationships between reciprocal articular surfaces which defines dislocations, or on the osseous avulsions of ligamentous insertions known as fracture-dislocations. This group of bone lesions is represented specifically here by the

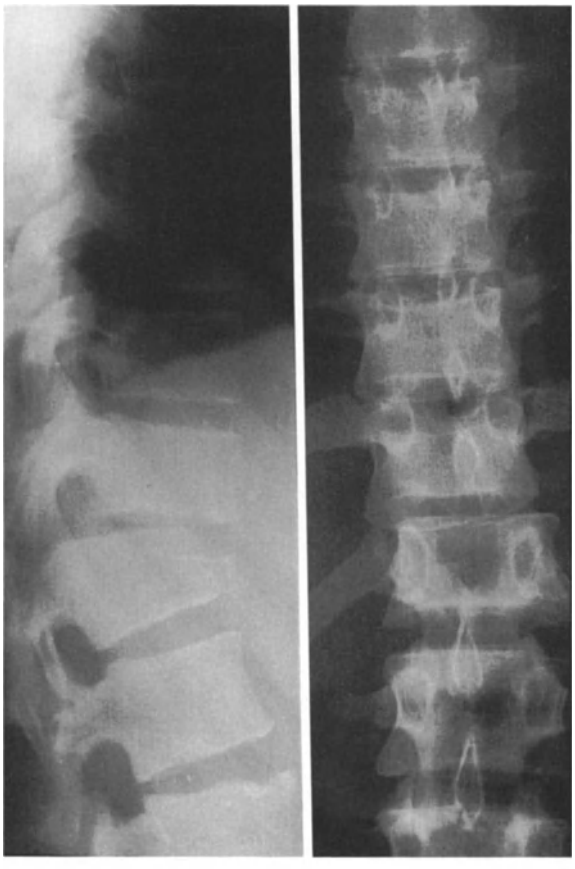


Fig. 25. Fracture-dislocation T11–T12. (a) Lateral view: antelisthesis of T11 – slice fracture of T12 – locked facet. (b) AP incidence: sign of the empty interlaminar space

articular process fractures or by partial bevel corporeal avulsions of the inferior osteo-cartilaginous insertions of the disc which Holdsworth[51] called a "slice fracture" (Fig. 25). These lesions are either strictly anterior, or sometimes lateralized by a rotation mechanism.

Standard X rays generally suffice in the diagnosis of these lesions. Dynamic flexion-extension views are dangerous at the dorso-lumbar level and formally contra-indicated for this group.

– In the lateral view forward slip of the upper adjacent vertebral segment is a revealing sign of the lesion. Anomalies of the articular processes such as sub-luxations, confrontations of the facet tips, locking of the facets, or fractures are usually detected instantly in the lateral view. The "slice fracture" of the vertebral body should be distinguished from a simple anterior marginal fracture or cuneiform compression fracture of the vertebral body: the bevel in fact involves only a middle-sized fraction of the antero-posterior diameter of the vertebral end-plate, and never the whole diameter[67].

– On the frontal view, a major sign for us, rarely absent in this type of lesion, is represented by gaping of the interlaminar space responsible for the image of "empty interlaminar space". Even when other X-ray views are unavailable, the diagnosis can be confirmed by this finding which alone represents the severe character of the lesion. In the same way, a lateral bevel tear of the vertebral end-plates can also confirm the lesion (slice fracture).

Indeed, these simple radiological findings provide evidence of the total rupture of intersegmental fibrous structures. Veritable vertebral transection, the disruption even extends most frequently to the aponeuroses and peri-spinal muscles. Subcutaneous hematoma in the vicinity of the injury is a characteristic clinical sign of this lesion type.

The instability induced by these lesions is severe. It is acute, occurring immediately upon injury, horizontal and menacing to the neuraxis by shearing. It persists even in the long term, due to the poor mechanical holding power of the fibrous scar.

In these lesions, and particularly in the case of articular locking any positioning or manipulation in lordosis is strictly prohibited because of its stenosing action on the spinal canal with resulting neural compression, as can be shown in an anatomical preparation (Fig. 26).

This diagnosis therefore implies transporting the patient in slight kyphosis to the operating table where positioning is undertaken in the same manner.

Ensuring restoration of the spinal canal not only involves surgical reduction of displacements, but also demands that any disc fragments, sometimes detached by avulsion and enucleated into the spinal canal, be carefully sought for and removed. Following reduction of locking facets, lordosis becomes possible and is implicit in final reduction.

Stabilization of this vertebral transection requires osteosynthesis either by screw-fixation of the pedicles, the only fixation technique possible in the case

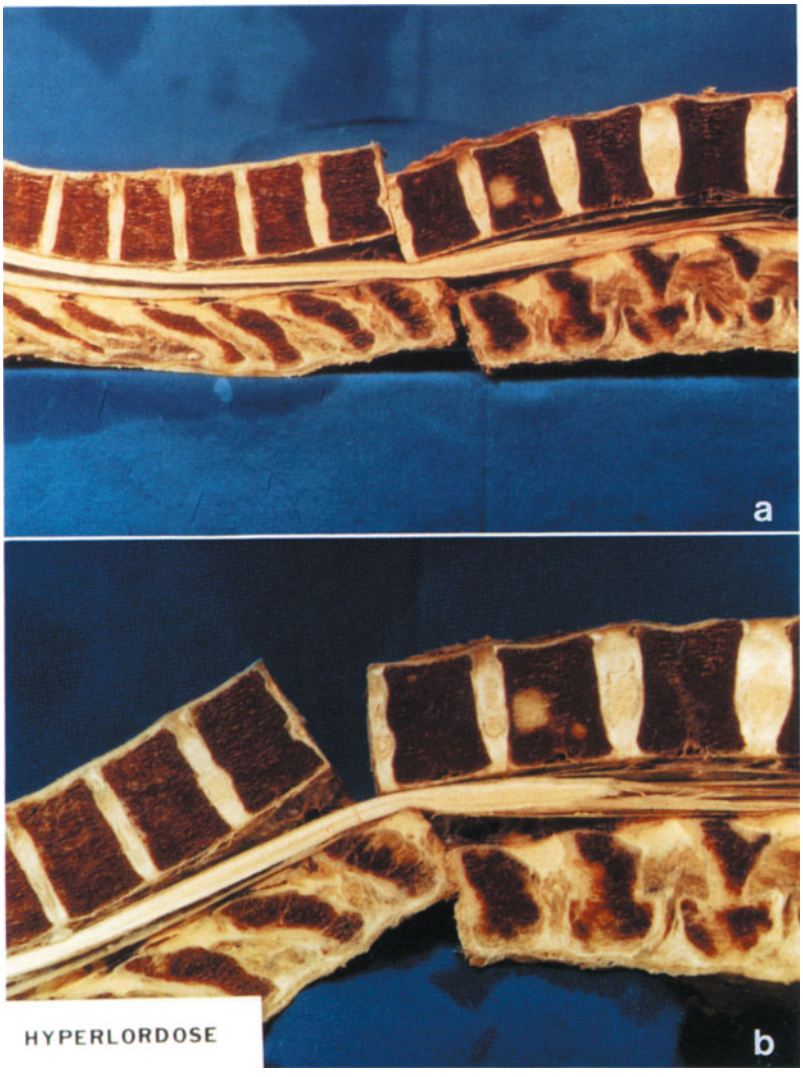


Fig. 26. Anatomical model of luxation with locking facets (T11–T12). (a) Dorsal decubitus. (b) Hyperlordosis manoeuvre

of associated laminectomy, or at best when the vertebral laminae are conserved, by compression fixation using Kempf or Cotrel Dubousset-type preloaded rods over two levels (one single level on either side of the transection).

3.1.2. Group of Disco-Corporeal Lesions

The second group is represented by the "disco-corporeal lesions" characteristic, whatever their degree of severity, by their primary involvement of the

anterior load-supporting column. The classical compression and comminutive fractures ("Burst fracture" of Holdsworth 1963)[51] belong in this group. They result from a violent axial impact, more or less associated with anterior flexion.

Proportionately to the degree of impact it is possible to follow a regular progression of structural damage which ranges from compression to burst fracture of the vertebral body and ends in the collapse of one or both pedicles, the most resistant elements of the vertebra, and always involved last. In general, these lesions are easily analyzed on simple standard X-rays. However, computed tomography (CT) has the advantage of providing more detail.

Compression fracture of the vertebral body occurs initially. It proceeds through three stages of increasing severity (Fig. 27):

1. Compression of the disc first provokes avulsion of the marginal rim in the annular periphery. This is the classical anterior marginal fracture which in fact involves the whole antero-lateral epiphyseal "horse-shoe", as can be

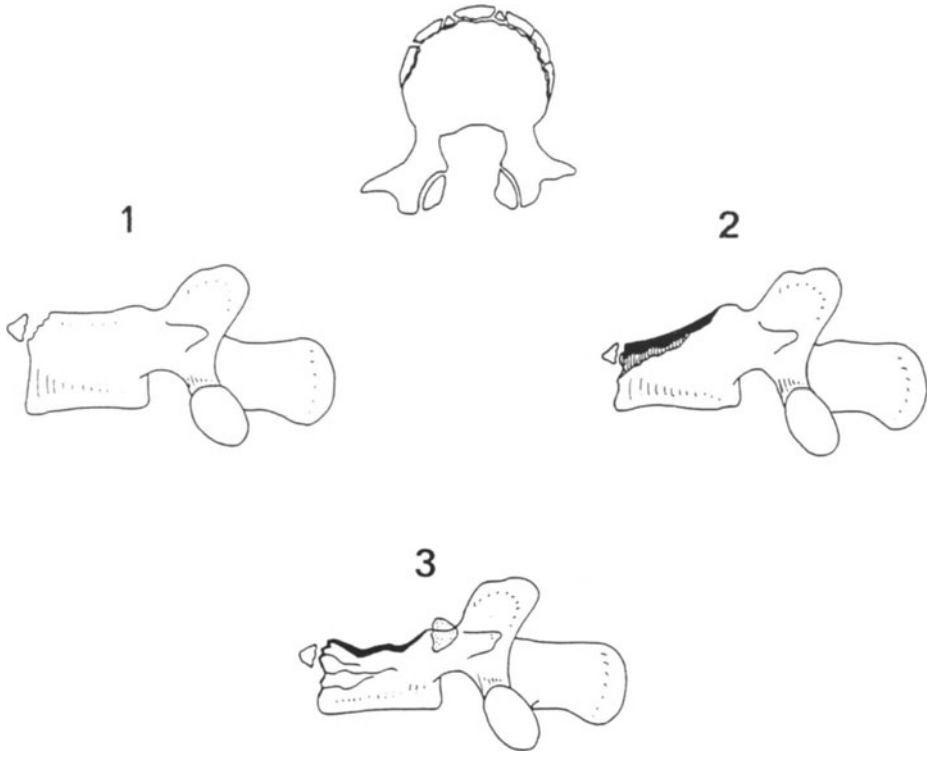


Fig. 27. Disco-corporeal lesions: corporeal compression fracture. Stage *1*: antero-lateral marginal (axial and lateral view). Stage *2*: wedge compression fracture (+ marginal fracture). Stage *3*: interpedicular fragment (+ compression fracture + marginal fracture)

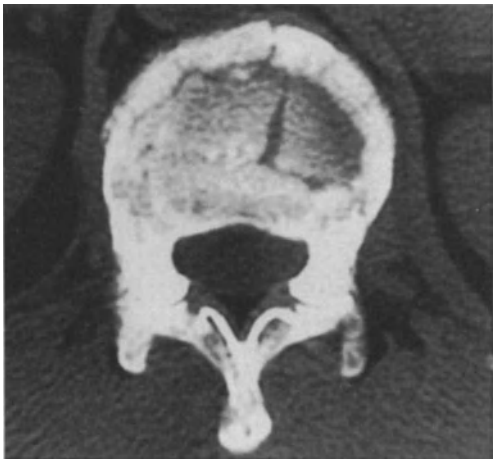


Fig. 28. Antero-lateral marginal fracture in CT

observed in CT (Fig. 28). When isolated, this lesion is fundamentally benign and does not require specific treatment.

2. Collapse of the epiphyseal end-plate occurs next, especially in the anterior part (cuneiform compression fracture), sometimes lateral or even in the centrum (diabolo shaped). It is always associated with the marginal fracture which preceded it. This collapse disturbs vertical alignment, and is more or less tolerable depending on the degree of sagittal or frontal angulation. Estimating the spontaneous outcome toward a permanent degree of angulation must take into account the supplementary loss of angle to be expected after the upper adjacent disc gives way when deprived of its osteo-cartilaginous support.

3. The supplementary degree of end-plate compression is manifested posteriorly at the inter-pediculate rim (Fig. 29). A postero-superior inter-pediculate bone fragment tips backward and protrudes to a greater or lesser degree into the spinal canal[57]. The fragment usually remains sub-ligamentous, in front of the posterior longitudinal ligament (posterior common spinal ligament). Rarely the fragment originates from the postero-inferior edge of the end-plate.

Being only slightly mobile, this fragment usually does not aggravate strictly vertical instability which is already induced by end-plate rocking. However, it represents a neural risk from canal stenosis. Nevertheless, this lesional stability will be absent when rupture of the dorsal longitudinal ligament is associated[112].

The comminutive or burst fracture is provoked by higher impact forces and occurs when all of the preceding lesions have been established. After sinking of the end-plate and tipping of the posterior interpediculate fragment, the nucleus which has already formed an intra-spongious hernia through the

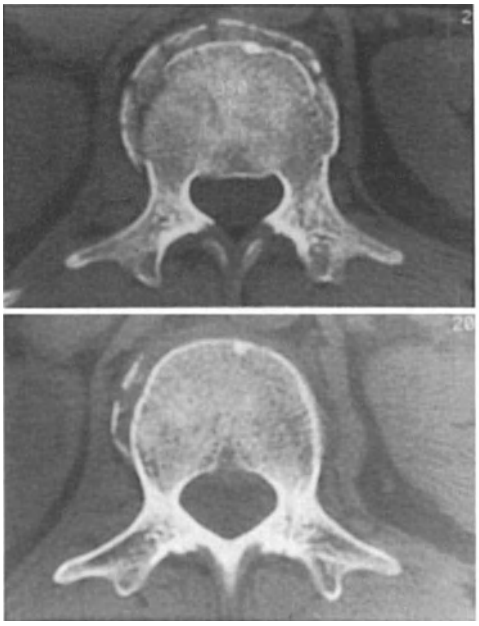


Fig. 29. (a) Posterior interpedicular fragment, (b) without bursting of the vertebral body in CT

end-plate, drives itself like a wedge into the vertebral body and causes it to burst[82]. When in these forms a corporectomy must be performed, the surgeon often finds disc tissue in the sagittal fracture of the spongy core. In a preliminary study of 66 cases of burst fracture we distinguished the following grades of severity (Fig. 30):

1. Simple more or less sagittal fissure limited only to the vertebral body, the lesion can be suspected when a slight widening of the interpediculate distance is observed on the standard AP film ("pre-comminutive form") (4 cases) (Fig. 30a).

2. The burst fracture of the vertebral body next propagates to the neural arch. Initially this lesion exclusively involves the anterior cortical shell, as in a greenstick fracture. The fracture line is well visible on standard frontal X-rays or tomograms, but is not apparent during surgery during exposure of the neural arches (28 cases) (Fig. 30b).

3. The fracture line more often involves both ventral and dorsal cortical layers of the vertebral lamina, or can even extend across the spinous process producing a complete separation of the vertebral ring ("split fracture") (Fig. 30c). The intracorporeal diastasis is variable and easily detected on standard AP X-rays by a widened interpedicular space (when "looking the vertebra straight in the eyes", Roy-Camille) (34 cases) (Fig. 31).

Major displacements can cause veritable "dislocations" of the vertebral

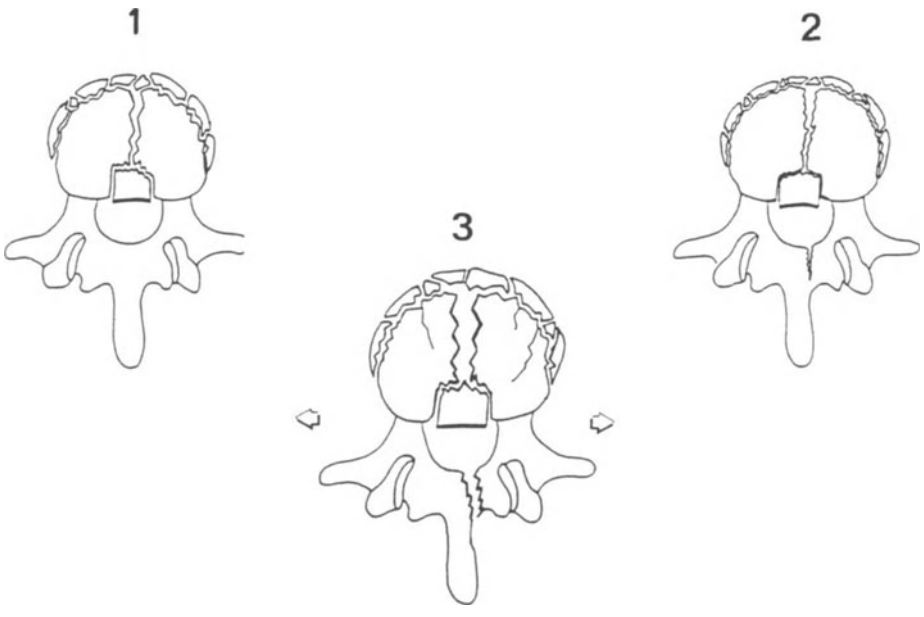


Fig. 30. Disco-corporeal lesions: vertebral bursting. Stage *1*: vertebral body fissure. Stage *2*: bursting of the vertebral body and "greenstick" fracture of the neural arch. Stage *3*: complete bursting of the vertebra ("split fracture")

structure ("unstable burst fracture" of McAfee, 1983)[71], for which standard X-rays or CT can be helpful in recognizing all the preceding elementary lesions which are accumulated, and thus avoid confusion with certain severe fractures of the preceding group involving a large corporeal wedge.

The ultimate degree of severity is represented by *collapse of the posterior plate* of the vertebral body within its zone of highest resistance, at the insertion points of either one or both pedicles (2 cases).

This injury progression is remarkable in its consistency. It enables a methodic analysis of radiographic films, each stage prompting one to look for the sign which corresponds to the lesion of the next higher severity. Each sign of one stage, signifies automatically that all of the components preceding it in that hierarchy are also present.

In these forms, the instability is anterior, and vertical, linked with tipping of the epiphyseal end-plate (Fig. 32) progressively followed by pinching of the space left by the upper adjacent lacerated disc, whose biology was compromised by fracture of its osteo-cartilaginous anchorage. Horizontal instability resulting from the burst fracture is usually minor, but in any case easy to estimate by the importance of inter-fracture diasthesis. Torn ligaments were infrequently encountered and occur in conjunction with major bone damage which is obvious on the X-rays (Fig. 33).

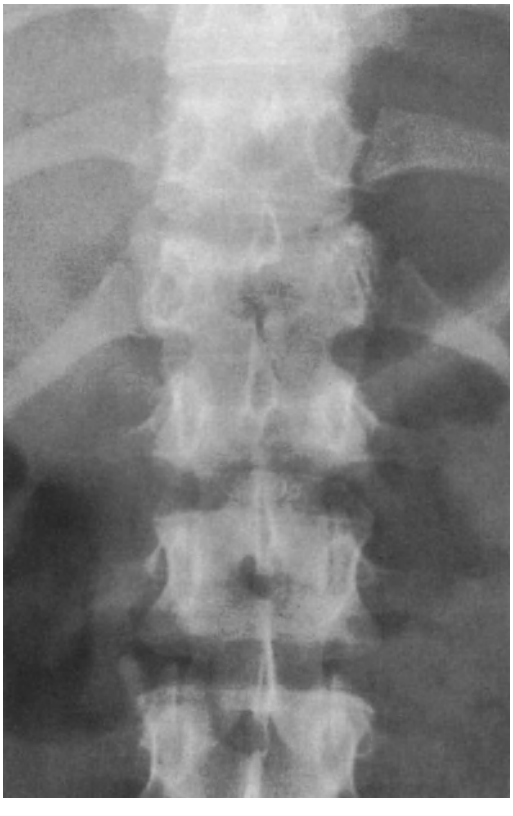


Fig. 31. Standard X-ray (AP incidence): vertebral bursting of T12 is certain: interpediculate widening and median fracture of the neural arch

Development of the neurological risk can be understood in terms of the elementary lesions which develop anteriorly, posteriorly or in the center of the vertebral canal:

– The anterior neural risk represents that of the "saw-horse" formed in front of the neural axis (Fig. 32) and which is the sum of the anterior sagittal angulation and of the detached interpediculate bone fragment protruding posterior to the upper vertebral end-plate. Sagittal tomograms analyze the resulting stenosis with respect to the antero-posterior diameter of the canal. CT provides a more precise evaluation with respect to the canal's cross-sectional surface area (Fig. 34).

– The posterior neural risk depends on the degree of burst fracture extension to the neural arch (Fig. 35) since this extension is often associated with tearing of the underlying meningeal sheath. Nerve root branches can be trapped in these posterior fractures. This ever-present risk imposes a great deal of caution during laminectomy, which begins away from the fracture

Fig. 32. Comminutive fracture of L1 (anatomical slice): – sagittal angulation by corporeal compression fracture, – anterior overriding with posterior interpedicular fragment (high neural risk)

lines so as not to surgically damage these nerve root branches which are lying exposed in the epidural space.

– A "central" neural risk can be added to these lesions by the possible constitution of a compressive arachnoidal cyst[74], common in the dorso-lumbar spine, but whose presence cannot really be correlated with the injury.

Therapeutic management of these forms should concentrate on realigning the vertebral axis by reduction of the corporeal burst fracture. The hyper-lordosis manoeuvre introduced by Boehler[15] is known to be very effective in corporeal reconstruction. Reconstruction of the spinal canal is effected by decompressive laminectomy and/or reduction or resection of the posterior stenosing interpedicular bone fragment. Reduction must be maintained until consolidation (Boehler plaster cast, or osteosynthesis). An anterior surgical approach to resect the bone fragment and perform an interbody bone graft, can be considered.

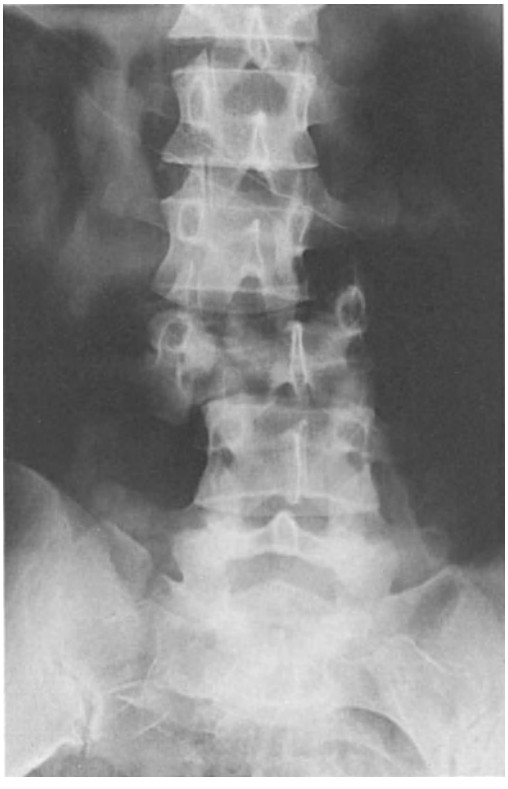


Fig. 33

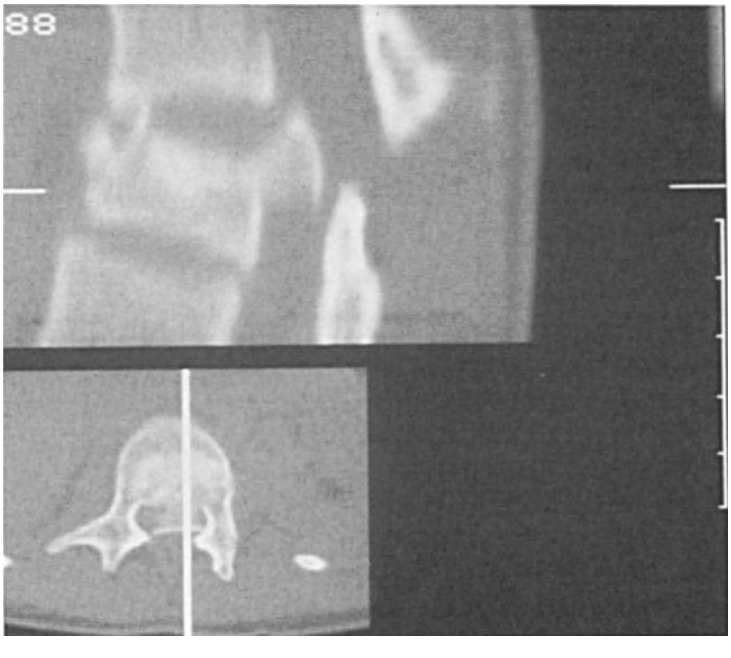


Fig. 34

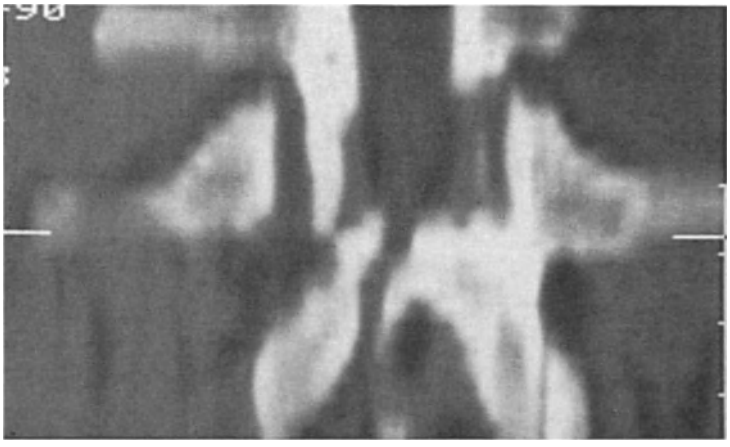


Fig. 35. Comminutive fracture: CT with frontal reconstruction in order to study the neural arch burst fracture

3.1.3. Group of Mixed Lesions

The third group is represented by the "mixed lesions" (22 cases / 9.4%) in which are regrouped both anterior compression lesions of the corporeo-discal column and posterior vertebral transection lesions by distraction[27, 81]. These composite forms present particular characters depending on the level involved:

In the lumbar spine, "the seat-belt fracture", first described by Chance (1948) is the typical mixed form found essentially in the lumbar and dorso-lumbar transitional spine (Fig. 36), associating:

– A compression fracture of the vertebral body, most often moderate, in which there is slight wedging of the vertebral body preceded by antero-lateral marginal fracture of the epiphyseal end-plate. More severe stages of corporeal burst fracture are exceptional in these cases.

– A posterior hemitransection, particular in its transosseous passage in a more or less horizontal plane across the laminae, sometimes the spinous processes, and especially the pedicles. The fracture line exceptionally extends backward through the vertebral body[42].

This posterior vertebral hemisection usually represents the predominant element of the lesion, and is responsible for instability during flexion which opens the posterior fracture line.

Fig. 33. Extreme form of vertebral burst fracture with lateral listhesis (horizontal instability)

Fig. 34. Comminutive fracture: CT with sagittal reconstruction in order to study canal stenosis

While the lateral X-ray very often reveals only the corporeal compression fracture, the frontal view suggests the lesion type by rupture of the cortical bone contours of the pedicle. Bi-orthogonal tomograms provide better detail of the horizontal fracture line through the vertebral arch.

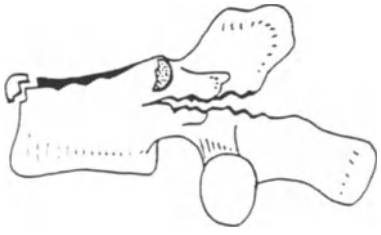


Fig. 36. Chance fracture[25]: Posterior hemitransection (osteo-ligamentous), slight corporeal compression fracture

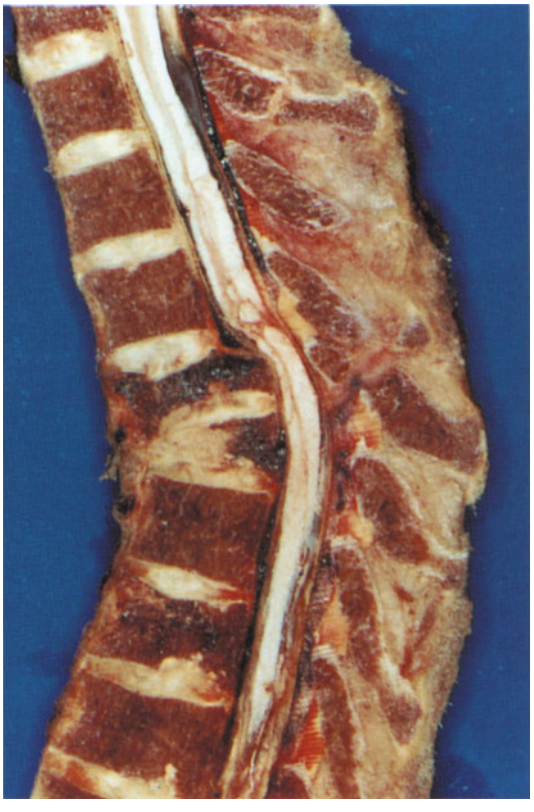


Fig. 37. Mixed lesion in the thoracic spine: compression fracture T4–T5, multi-level fractures of the posterior neural arches, complete medullary attrition

This lesion is only exceptionally menacing to the spinal cord from an interpedicular corporeal bone fragment, and is not usually followed by any neurological complication.

Treatment should aim at reducing the instability in flexion, created by the transection component. As in the disco-ligamentous lesions, a short fixation in compression applied on the posterior arch of the affected vertebra and on the laminae of the upper or lower adjacent vertebra depending on the high or low position of the fracture line, can be considered. This technique is especially indicated in the rare cases of corporeal transection. Fixation in hyperlordosis using a Boehler's plaster cast is most often indicated. The posterior, essentially bony, lesion should consolidate within 3 months in this position of reduction. If wedging of the compression fracture is important, then the same therapeutic principles applied in third degree compression fractures are indicated (hyperlordosis and Roy Camille-type plate-fixation)[89].

In the dorsal spine mixed lesions are the most common. They are characterized by the multiplicity of affected vertebrae, including multiple compression fractures, often severe, and posterior transections involving the isthmus, articular apophyses, and even the transverse processes (Fig. 37).

These lesions are particularly severe and often responsible for permanent spinal cord damage.

3.2. The Inferior Cervical Spine (C3–C7)

At the cervical level, traumatic osteo-ligamentous lesions can be sub-divided into three groups, similar to those described in the dorso-lumbar spine and obeying the same traumatic mechanical conditions.

The particular mobility of the cervical vertebral column characterises its traumatic lesions since affections of the "motion segment" are predominant here. Indeed, the disco-ligamentous injury group (159 cases) represents two-thirds (66%) of our 241 cervical trauma cases, while disco-corporeal lesions (34 cases) are much less frequent (14%). Mixed cervical lesions (48 cases) are typically represented by the "tear-drop" fracture (20%).

– Generally speaking, these lesions occur in the young adult (mean age 30 years; range: 14 to 64 years). With the exception of the tear-drop fracture, they affect two men for every woman.

In our series, the neurological severity of cervical lesions is represented by 99 cases (41%) of quadriplegia (near 16% incomplete and 24% complete). The disco-corporeal lesions and the tear-drop are generally the most severe, with 50% spinal cord involvement as compared to 36% for the whole disco-ligamentous group. Within each group, however, anatomo-radiological analysis of lesion forms permits a grading based on osteoligamentous severity which is confirmed by the frequently parallel graded severity of the neurological risk.

3.2.1. Group of Disco-Ligamentous Lesions

The disco-ligamentous lesions (159 cases) are more or less complete tears of the intervertebral motion segment, which predominate in the transitional levels of physiological mobility, in C5–C6 and C6–C7. There are several varieties: dislocations (72 cases), articular process fractures (58 cases), and severe sprains (29 cases).

Pure dislocations (72 cases): in terms of vertebral dislocation zygapophyseal locking facets is a specific feature.

– It can be unilateral (27 cases) and is detected on oblique 3/4 views by inverse inter-locking (inverse to that which is anatomically normal) between two articular surfaces of the posterior zygapophyses. Unco-corporeal alignment is disrupted. In the lateral view, non-superposition of the unwedged articular facets is represented by Roy Camille's "fool's cap" sign (Fig. 38). During unilateral locking slippage of the body is always less than 50% of the antero-posterior diameter of the end-plate.

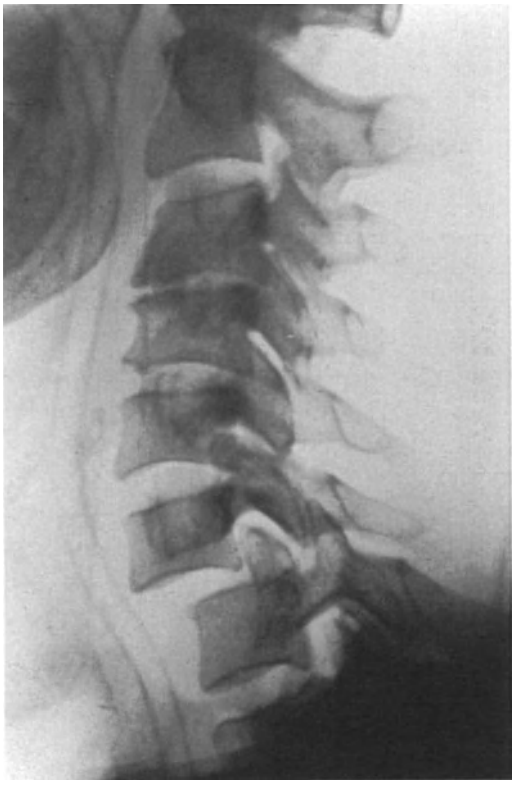


Fig. 38. Pure luxation in C6–C7: Unilateral locked facets (sign of the "fool's cap"), corporeal listhesis < 50%

– It can also be bilateral (23 cases). Once again the oblique 3/4 view shows inverse interlocking of the articular facets and on the lateral view the listhesis is always greater than 50% of the end-plate diameter. The subjacent vertebral body can be the site of an anterior wedge-shaped avulsion of the upper end-plate ("slice fracture") (Fig. 39).

Whether locking is uni- or bilateral, hyperextension in these cases is formally contra-indicated. On the contrary, the neural axis is relieved by slight flexion of the neck.

– Disco-ligamentous tearing may occur without articular sub-luxation (22 cases) (Fig. 40). It is more rarely encountered in dislocation with apposition of the tips of the articular processes. This form is particularly unstable and may progress either to spontaneous reduction with return to the normal anatomical situation or instead to the inversely inter-locked position.

In these three forms disco-ligamentous tearing is always present, severe and complete in bilateral locking facets, partial in unilateral locking, variable in dislocations without locking.

Spinal cord complications are present in half of the cases (36/72 cases) and illustrate gradation of the lesion severity with 74% quadriplegia in bilateral locking forms, 37% in unilateral forms, and 41% in pure dislocations (Table 6).

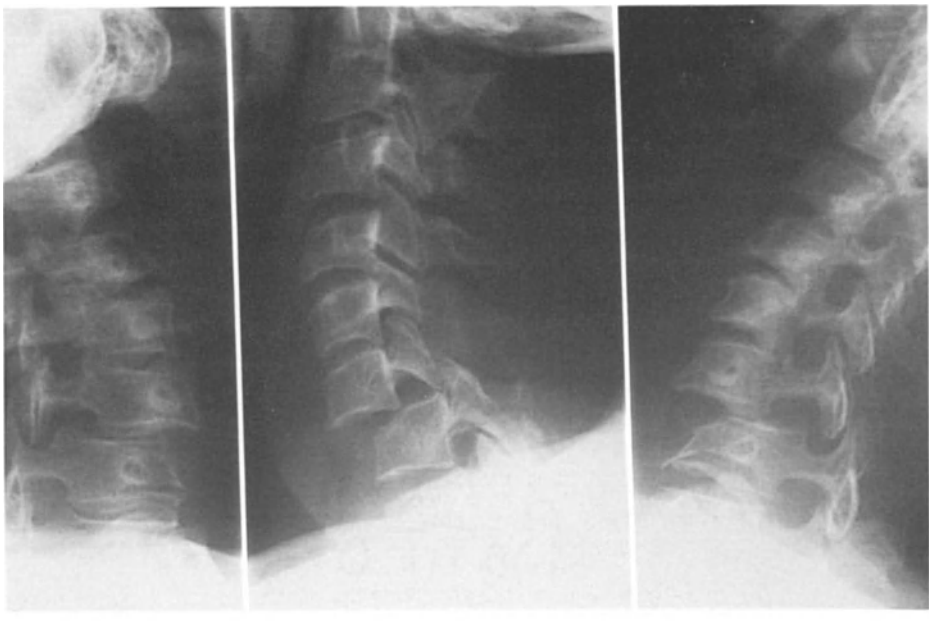


Fig. 39. Fracture-dislocation C6–C7. (a) Bilateral locked facets, (b) "slice fracture" of C7, (c) corporeal listhesis > 50%

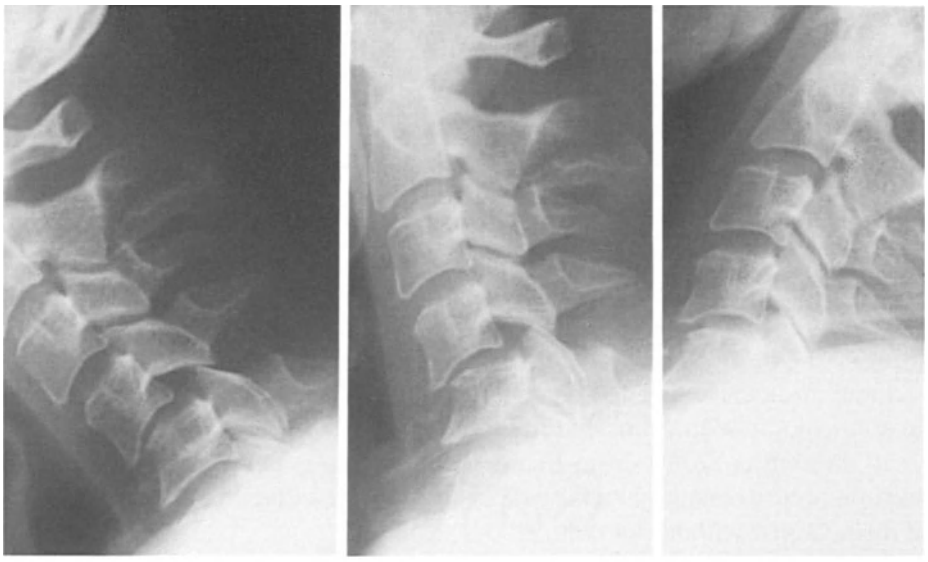
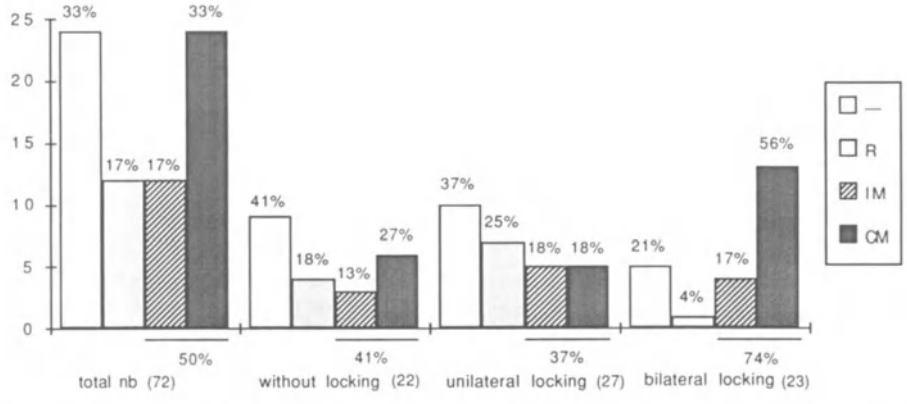


Fig. 40. (a–c) Luxation without locking in C4–C5 (reduction in hyperextension)

Table 6. *Disco-Ligamentous Lesions: Pure Luxations.* Neurological Correlations



— Incomple medullary syndrome, R radicular syndrome, IM incomplete medullary syndrome, CM complete medullary syndrome.

The articular process fractures or fracture-dislocations (58 cases): here again different lesional modalities may be classified by increasing severity. In each one of these forms the oblique 3/4 view is very helpful in revealing the lesion. Tomograms or CT with reconstruction are indispensable to the diagnosis:

1 – Fracture of the upper (Fig. 41) or lower articular facet (6 cases) is associated with a disco-ligamentous lesion of the corresponding intervertebral level, variable in importance, but often benign.

2 – Fracture of the articular block more or less impacted (32 cases) (Fig. 42). Crossing through the body of the articular block this fracture is associated with a disco-ligamentous lesion of either the upper or lower adjacent intervertebral level.

3 – Separation fracture of the articular block (SFAB) (20 cases)[86] (Fig. 43). The block formed by the superior and inferior articular processes is separated from its anterior (pediculo-transverse) and posterior (laminar) attachments by varied fracture lines best demonstrated in CT (Fig. 44).

Once again, the associated disco-ligamentous lesion can either be super- or sub-jacent, or even bifocal.

– The instability of these increasingly severe lesions from the first to the third form sometimes needs verification. In the last two varieties uncertainty as to the level of the disco-ligamentous tear should, in the absence of obvious sub-luxation, be confirmed by flexion-extension films. Locking or impaction at the site of articular fracture is not rare (11/58 cases).

– The neurological risk is ever-increasing in these forms in correspondence with the severity of the osseous lesion. Medullary severity is highest for

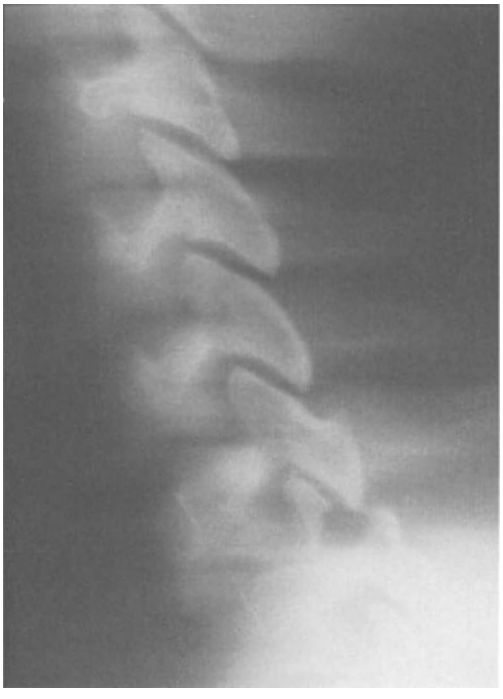


Fig. 41. Fracture of the tip of the superior articular process (sagittal tomogram)

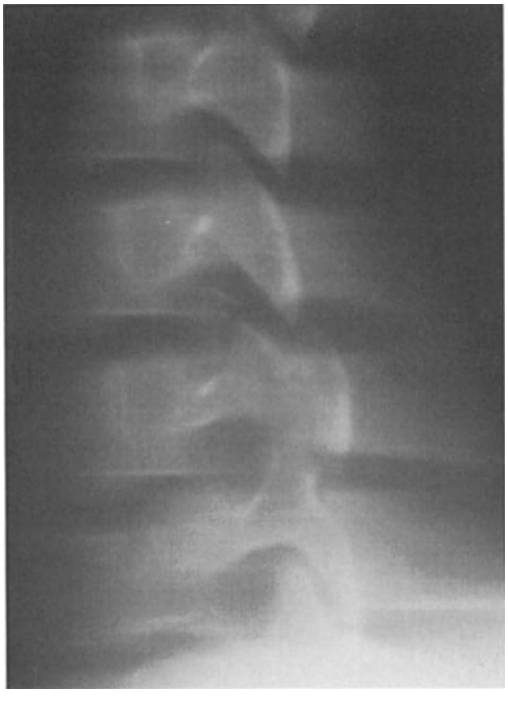


Fig. 42. Impacted fracture of the articular process (sagittal tomogram)

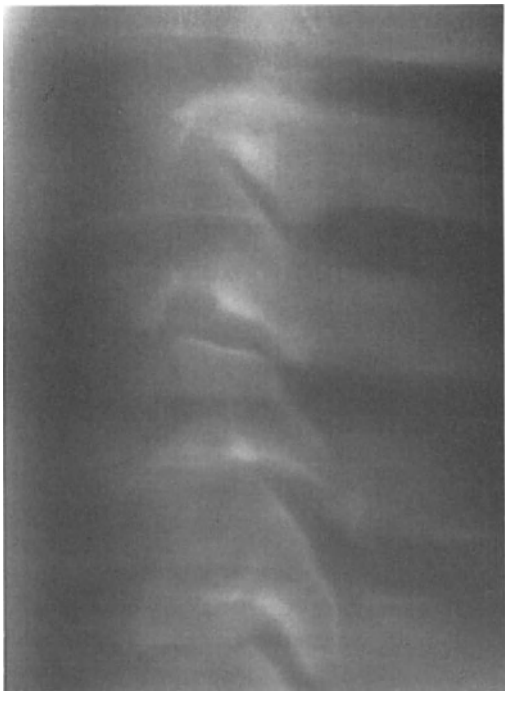


Fig. 43. Separation fracture of the articular block (SFAB) (sagittal tomogram)

the SFAB (40% quadriplegia). For the entire group, however, the important frequency of radicular signs (39%) as well as the generally lesser medullary severity (24% quadriplegia) should be emphasized (Table 7).

Tearing without displacement or fracture defines *the severe sprain* (29 cases). Its diagnosis is difficult in the absence of obvious pinching of the discal space or of loss of parallelism of the posterior articular surfaces (subluxation). Flexion-extension films are valuable in confirming the lesion

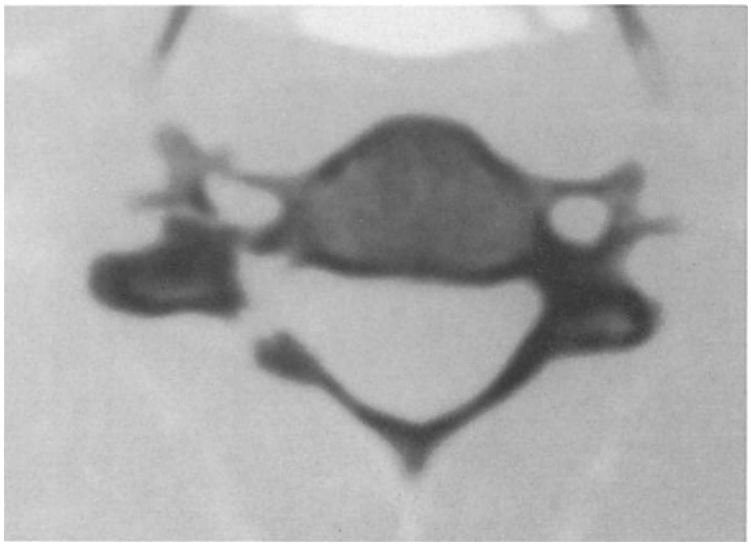
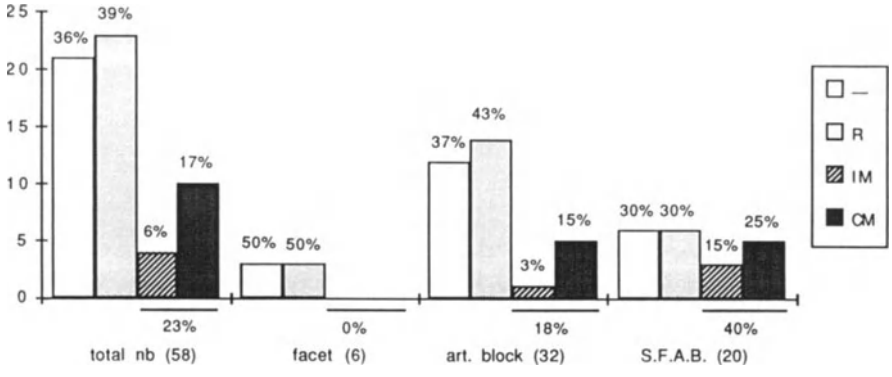


Fig. 44. SFAB by combined pediculate and laminar fracture (CT)

Table 7. *Disco-Ligamentous Lesions: Fracture-Dislocations.* Neurological correlations



SFAB Separation fracture of the articular block.

(Fig. 45) but may also be inconclusive if there is important muscular contracture in the nape of the neck. The films may even be negative and should be repeated later in case of doubt. The importance of disco-ligamentous section is, in fact, variable initially, but has a special tendency to aggravate with passing time. Severe sprain is associated with over one-quarter of spinal cord complications (27%) (Table 8) and again almost 20% are delayed in diagnosis.

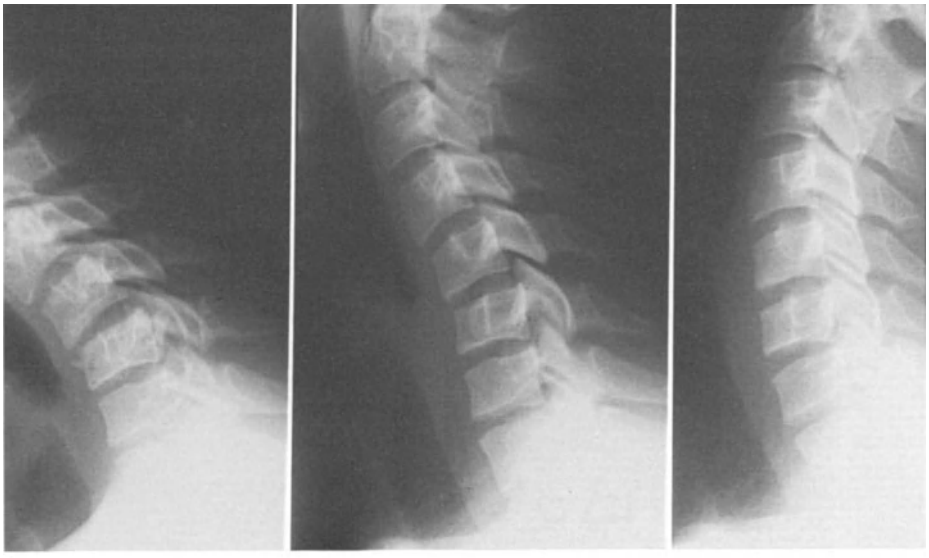
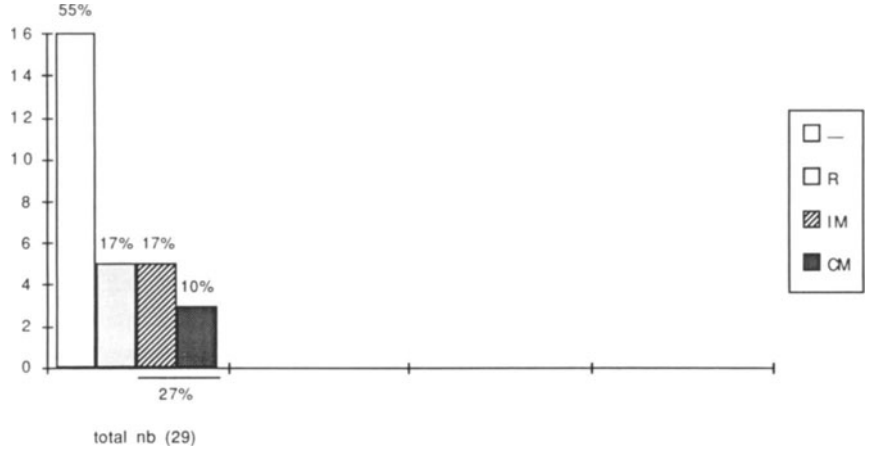


Fig. 45. (a–c) Severe sprain: flexion-extenison X-ray

Table 8. *Disco-Ligamentous Lesions. Severe Sprains.* Neurological correlations



Instability of the entire group of cervical disco-ligamentous injuries, as in the dorso-lumbar level, is typically horizontal, acute and secondary (having a tendency towards aggravation), and in either case permanent. The neurological threat is first radicular, especially in unilateral lesions, but also medullary by a shearing mechanism.

Mono-segmental arthrodesis is indicated in the majority of these forms. The approach and the fixation technique are a matter of experience, however, irreductibility by manual manipulation demands surgical reduction and therefore the posterior approach for the majority of authors. On an anatomically reduced lesion, the anterior approach for segmental fixation with intersomatic graft is a particularly simple and effective solution which also permits checking for the presence of discal frgments often enucleated into the ventral region of the spinal canal.

3.2.2. Group of Disco-Corporeal Lesions

The group of cervical disco-corporeal lesions is poorly represented in our series (34 cases):

The etiology is essentially road (14 cases – 41%) or sports (12 cases – 35%) accidents.

The lesion was isolated in 15 cases and associated in 15 other cases with cranial trauma, evidence of the axial impact transferred to the cervical column. In 6 cases it was associated with a different cervical lesion (1 teardrop and 5 disco-ligamentous lesions). Bifocal disco-corporeal lesions were not an exceptional occurrence (4 cases). These cervical disco-corporeal injuries predominate in the lower levels (20/38 or 52% in C7).

As in the dorso-lumbar level, cervical disco-corporeal lesions also follow a regular progression of increasing severity in terms of osteo-ligamentous damage: initial compression fracture of the vertebral body is followed by burst fracture of the vertebral body. This analogy between cervical and dorso-lumbar lesions is poorly reported in the literature. Nevertheless it is possible to describe the following lesions:

Crush lesions (4 cases of which 2 are bifocal) (Fig. 46) with:

The anterior marginal fracture, less typical than in the lumbar level where it is antero-lateral, is here more often limited to the anterior rim of the end-plate. It should be distinguished by its smaller size from bevel fractures or "slice fractures" encountered in dislocations. Never alone in our series of severe lesions, this form is associated in our cases with corporeal compression fracture. The wedge compression fracture attains the whole antero-posterior diameter of the end-plate. Its size determines the resulting angle of kyphosis and the severity of static disequilibrium. None of the 4 cases (6 lesions) presented a neurological complication (Table 9).

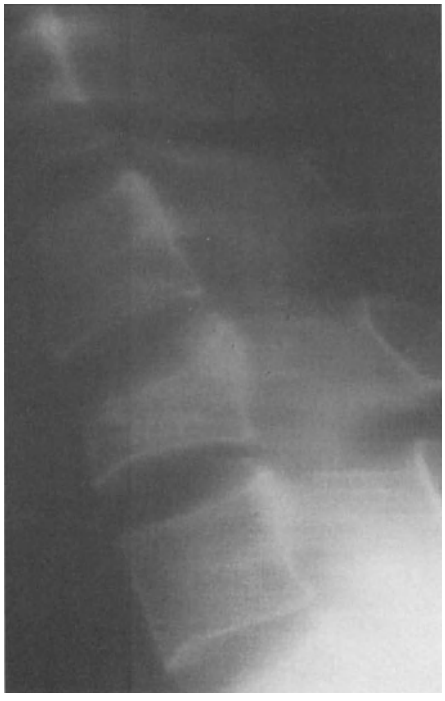
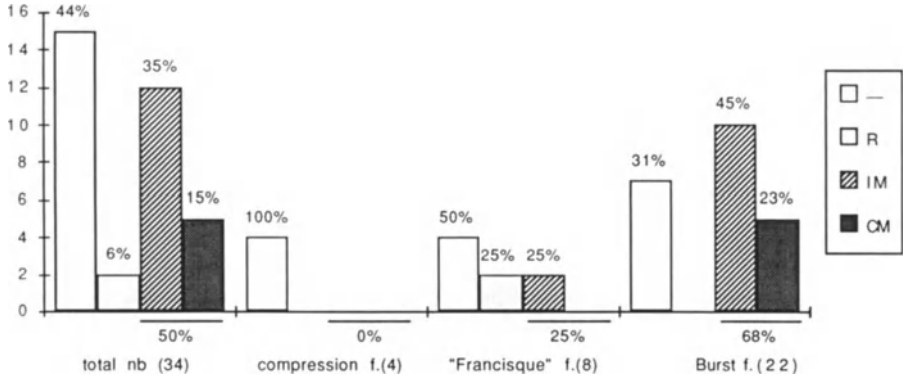


Fig. 46. Cervical disco-corporeal lesion (wedge compression fracture and rough outline of an interpedicular fragment)

Table 9. *Disco-Corporeal Lesions.* Neurological correlations



Burst fracture (22 cases) manifests by a sagittal fracture line in the vertebral body eventually extending to the neural arch. The detached posterior interpedicular fragment is associated and determines the neural risk by acute canal stenosis producing a form very similar to the dorso-lumbar burst fracture (Fig. 47).

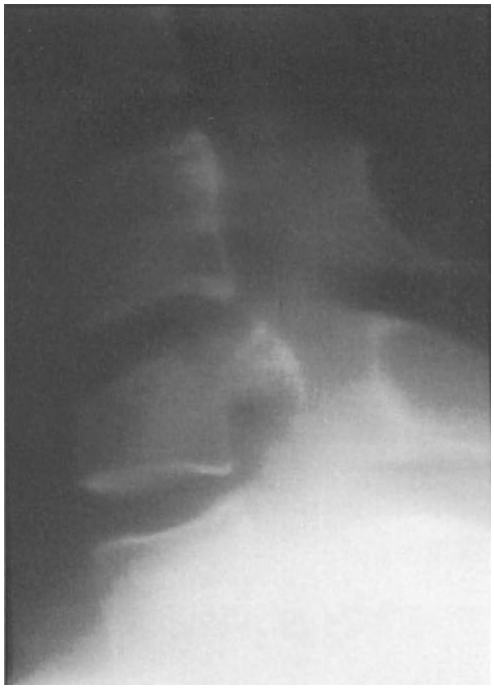


Fig. 47. Cervical disco-corporeal lesion (voluminous interpediculate fragment)

The neurological severity is rather typically correlated with the lesion stage and with canal stenosis (best evaluated by CT) (Fig. 48) with 68% of medullary complications (45% of incomplete and 23% complete quadriplegias).

The transcorporeal fracture line illustrates the role of the disc which drives itself into the vertebral body and bursts it. Nuclear tissue can be found in the fissure at surgery. This sagittal fracture line is also encountered in the tear-drop (group of mixed lesions) but should not cause confusion between the two forms. Compression fracture of the superior end-plate is especially encountered here, while in the "tear-drop" fracture the upper end-plate is intact and the detached antero-inferior fragment of the vertebral body is the identifying feature.

– A third form of vertebral crush-burst fracture is distinguished in the cervical level, which on the lateral X-rays, gives a characteristic image of what we call the "Francisque" fracture by analogy with the double battle-axe of the Frankish warriors. The lesion is formed by a diabolo-shaped compression fracture of the vertebral body with sagittal and eventually frontal burst fracture. The posterior plaque generally appears convex toward the back thereby stenosing the canal (Fig. 49).

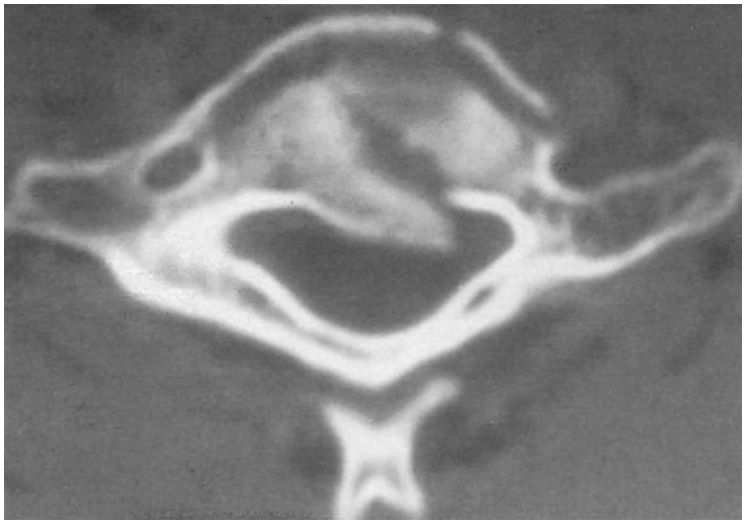


Fig. 48. CT scan of a cervical disco-corporeal lesion

Fig. 49. Cervical disco-corporeal lesion. Sagittal tomogram ("Francisque" fracture)

The neurological severity of this form appeared to us to be intermediate between the compression and burst fractures of which it is only a variant (25% of medullary complications).

These cervical disco-corporeal lesions menace spinal statics in proportion to the importance of sagittal angulation but the ligamentous structures are most often spared which illustrates the stability of these forms, verifiable in flexion-extension studies by fluoroscopy (to be performed only in the certain absence of any neurological deficit).

The severe neurological risk in the whole group (50% of quadriplegias) is well correlated with both lesion stage and canal stenosis (Table 9).

Therapeutic management aims to reconstruct the spinal canal which most often implies corporectomy in order to resect potentially dangerous fragments within the neural canal.

3.2.3. Group of Mixed Lesions

The group of mixed forms which associates corporeal lesions and disco-ligamentous transection is represented here by the tear-drop fracture initially described by Schneider in 1956[91]. This form represents 20% (48 cases) of our cervical traumatic lesions.

Encountered in the young adult (mean age 28 years; range 13–61 years) it affects very specifically 10 men for each woman. Resulting from violent impact, sports accidents (53%) are the most important cause in our series followed by traffic accidents (27%). This is the typical lesion resulting from shallow water diving injuries (10/48 cases), but is also caused by skiing injuries (9 cases) in our series.

The lesion appeared to be isolated in more than half of the cases (26 cases or 54%), but the association of an obvious head injury is also frequent (17 cases or 35%: 12 benign cases or 25%, and 5 critical cases 10%) illustrating the cranial impact which is involved in the mechanism of the injury.

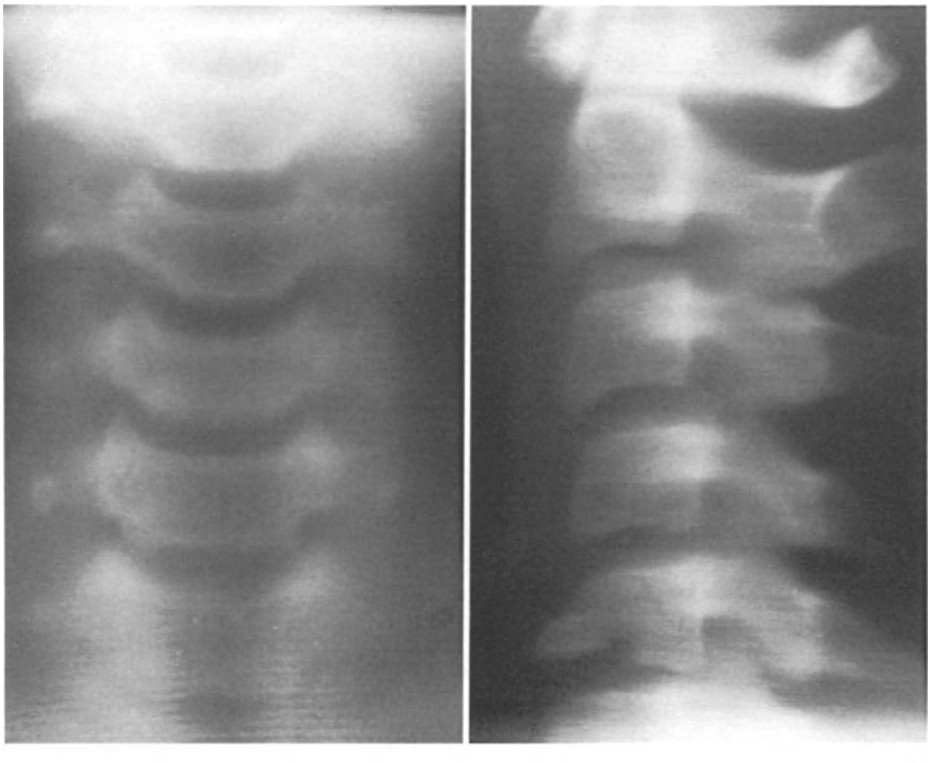
The lesion is significantly more common at C5 (31/48 or 64% of cases), the level representing both the keystone of cervical lordosis and the physiological hinge vertebra in the cervical spine of the young adult.

Defined by the mere presence of an antero-inferior fragment detached from the vertebral body, the so-called tear-drop fracture combines, in fact, diverse associated lesions. Likewise, in spite of a general reputation for neurological severity (50% of quadriplegias in our series), this form includes more or less severe variants. Once again, the severity of the osteo-ligamentous lesions is followed very clearly, by a regular progression in neurological severity.

Forms that can be qualified as *benign* are encountered in 12 cases out of 48. Their existence is rarely reported by authors with the exception of Torg[98] who sites the "isolated fracture".

– The antero-inferior fragment of the vertebral body can, in fact, remain isolated in rare cases (5/12). It alone represents the extent of the lesion, but we believe (as does Torg) that its identity must be established (Fig. 50). The size of the fragment represents a risk to sagittal stability. Because of its tendency to consolidate, this fracture is often treated orthopedically by fixation in lordotic reduction.

– To the antero-inferior fragment can be associated slight retrolisthesis of the postero-inferior corner of the vertebral body (6 cases). The absence of



a b

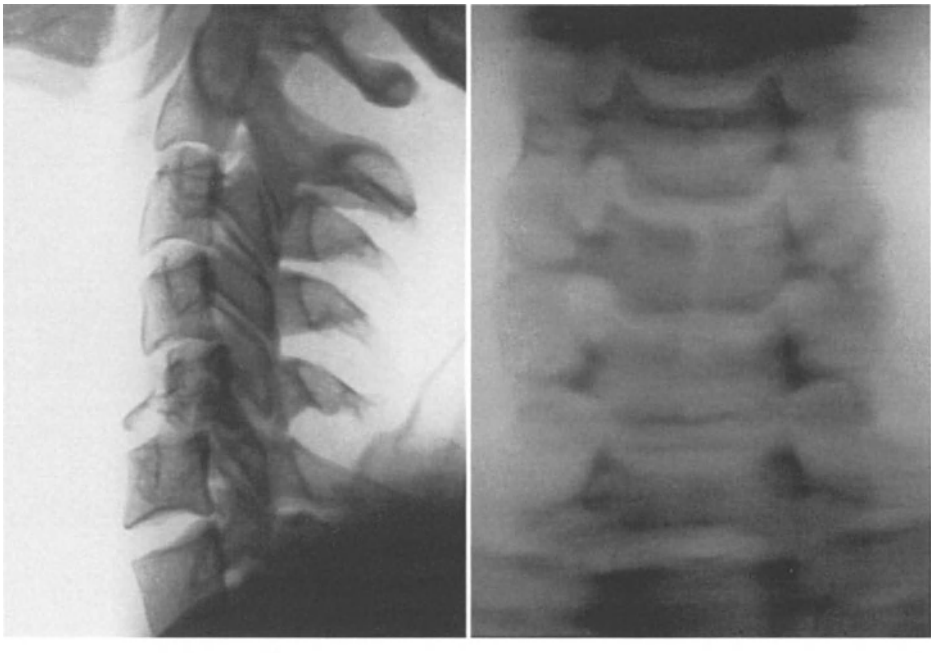
Fig. 50. Tear drop fracture of C5. Benign form without sagittal fissure of the vertebral body (a), nor disco-ligamentous tearing (b)

veritable instability was verified in these cases by flexion-extension studies. This form illustrates (in spite of its neurological benignity) this group's own specific injury progression in which the primary corporeal lesion is followed by the menace of tearing underlying disco-ligamentous structures.

– In one case a sagittal fissure combined with a tear-drop fracture forming a Y-shaped fracture of the vertebral body. It remained isolated without even minor underlying disco-ligamentous involvement. We believe that this form illustrates the corporeal component of the lesion which following antero-inferior fracture can be either "more" corporeal by burst fracture or "more" disco-ligamentous by fibrous rupture, stages which precede the common, complete form described below.

None of these forms was accompanied by neurological deficits, whether radicular or medullary.

The common form encountered in more than half of the cases (26/48 cases or 52%) is severe by its association of the three preceding elementary lesions, antero-inferior fragment of the vertebral body, sagittal burst fracture of the



a b

Fig. 51. Tear drop fracture of C5. Common form: antero-inferior fragment and posterior-inferior retropulsion (a), sagittal burst fracture of the vertebral body (b)

vertebral body (even of the neural arch by a laminar fracture line), and severe underlying disco-ligamentous lesion (Fig. 51). The vertebral body, which is the site of a Y-shaped burst fracture (Fig. 52), is impacted in 2 fragments into the spinal canal through a transverse tear in the disc and dorsal longitudinal ligament (Fig. 53).

The instability of these forms is major and the mode of neural damage highly specific. The slightest cervical flexion impacts the postero-inferior corner of the injured vertebra into the canal, because of primary detachment of the anterior corporeal support base which normally opposes this displacement.

Any flexion in these forms is strictly contraindicated while gentle traction and slight extension tend to realign the posterior wall. Vertebral burst fracture often demands a corporectomy which is also necessary to remove the posterior vertebral plate impacted in the medullary canal.

Medullary complications are frequent here (61%) with two-thirds (42%) producing complete transection (Table 10).

In the forms of major severity (10 cases or 20%) a supplementary disco-ligamentous lesion is associated with the preceding form (aggravated form).

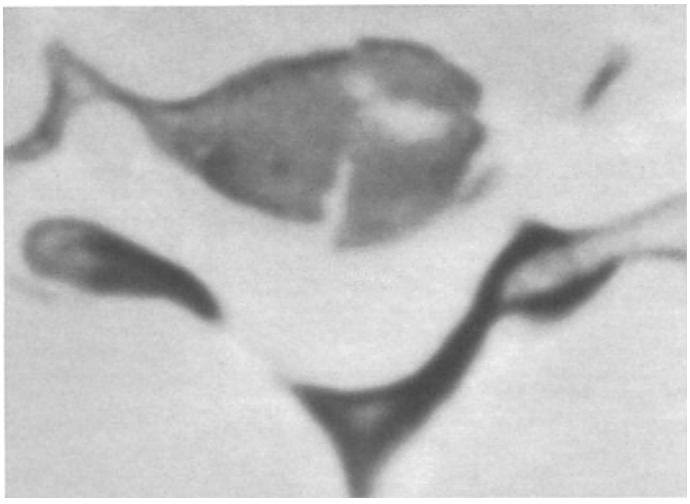


Fig. 52. CT scan: Y fracture of the vertebral body

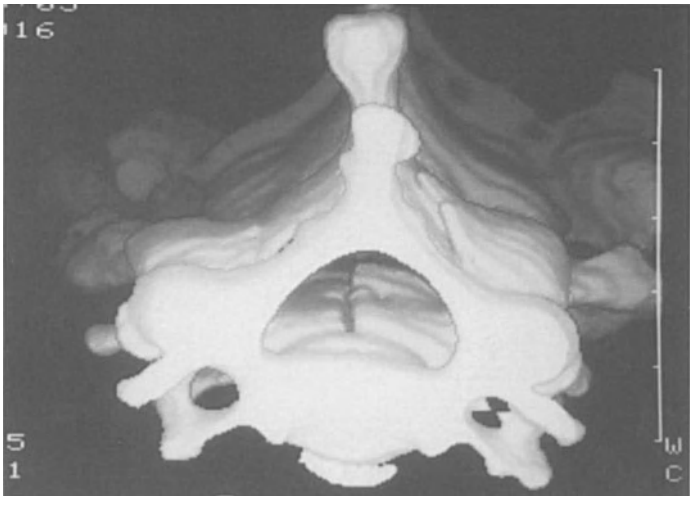


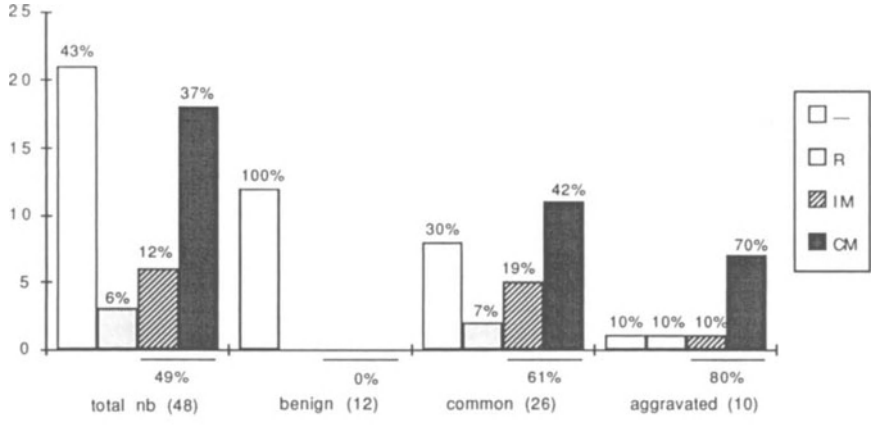
Fig. 53. CT scan (3D reconstruction): impaction into the spinal canal and sagittal fracture of the vertebral body

This additional luxation ends in a veritable incarceration of the burst vertebral body into the spinal canal (Fig. 54).

The medullary severity of these forms is considerable (8 cases or 80%) with almost always complete transection (7/8 cases).

The tear-drop fracture is very diversely interpreted in the literature since it has been confused or assimilated with a crush lesion ("Burst fracture")[10,51,95] or with a lesion of the motion segment[48,86,88].

Table 10. *Mixed Lesions: Tear-Drop Fracture.* Neurological correlations



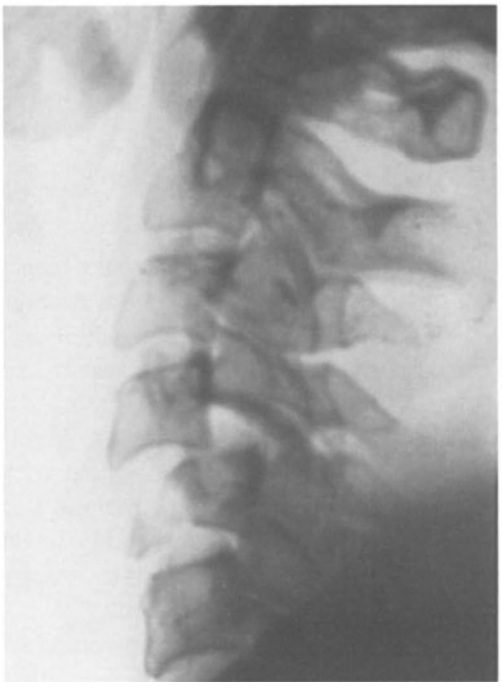


Fig. 54. Tear drop fracture of C5. Major form with incarceration of the vertebral body into the spinal canal by association of a superjacent disco-ligamentous lesion

This diversity in interpretation only emphasizes either the corporeal crush-burst component or that of the disco-ligamentous fibrous tearing, confirming our classification of these lesions. The mixed lesion group associates both components within the framework of a highly specific mechanism

of acute angle flexion-compression load as evoked by shallow water diving accidents and of associated head impacts at the vertex, and also attests the predominance at C5, the keystone of cervical lordosis and physiological hinge in the young adult.

The analysis of elementary lesions and of their combinations seemed to us vital in comprehending the mechanisms involved and interpreting these lesions as affections of a double target, osseous and fibrous.

Our interpretations are in accord with those of Lee[60,61] and Fuentes[41]. Minor forms reflect the primary consequences of the responsible injury mechanism. The common forms aggregate these primary lesions. In the major forms the impact is concluded by violent cervical flexion which causes supplementary luxation and aggravated impaction into the spinal canal.

Therapeutic management reflects the duality of the original lesion and often relies on corporeal resection (indicated in cases of severe comminution of the body and posterior impaction into the canal). The more limited fixation-graft is also sometimes indicated when disco-ligamentous instability predominates. These therapeutic measures can be considered after careful analysis of lesion combinations and the different components of severity.

3.4. The Sub-Occipital Spine

The distinctive anatomy of the first two vertebrae obviously separates their traumatic lesions from the classification applied to the rest of the spine. These lesions can, however, be analyzed in a very similar manner.

The exceptional occipito-atlantoid or atlanto-axial sprains or luxations represent fibrous tearing of the joining structures by spinal transection. Their management implies reduction and bisegmental fixation as for the group of disco-ligamentous lesions in the other two levels. Odontoid fracture represents a trans-osteo-ligamentous equivalent of these forms. The same therapeutic principle is applied recognising the fact that one of the injured elements is osseous (the dens) and is likely to consolidate. In the absence of an important associated ligamentous lesion, permanent atlanto-axial arthrodesis can be avoided.

Bursting of the ring of the atlas defines the Jefferson fracture[55]. Responsible for divergent displacement of the lateral masses, this lesion occurs in response to an impact in axial compression as in the disco-corporeal burst fractures.

Bipedicular fracture of the axis (in fact bi-isthmic mechanically) represents an unstable bony lesion which heals proportionally to the reduction and fixation of the diastasis. One should routinely check for the possible association of tearing in C2–C3, which is in fact an equivalent of the disco-ligamentous transection and should be treated like the same lesions in the inferior cervical spine.

4. Conclusions

By the very nature of the visco-elastic material from which it is made, the spinal column represents a structure of mechanical compromise between rigidity and flexibility.

Each different anatomical part has its own mechanical specificity, resulting in a differential and graded rupture threshold. This mechanical graduation is observed directly in trauma pathology. A regular progression exists in the constitution of lesions of compression (for which constantly observed sequences parallel injury severity), and of disco-ligamentous tearing.

Stability factors can be sub-divided schematically into two entities of vertical and horizontal stability which practically correspond to each of the two lesion categories in our classification: compression lesions predominating in the disco-corporeal column (compression and comminutive fractures) and tearing lesions prevailing in the disco-ligamentous structures (sprain-dislocation and fracture-dislocation). The structural geometry and anisotropy of the spinal column contribute to the complexity. Furthermore, all factors are usually implicated simultaneously and at varying degrees. Traumatic lesions of the mixed variety (compression plus tearing) clearly illustrate the simultaneous action of diverse geometric factors of stability.

This biomechanical approach to both the properties and traumatic lesions of the spinal column is illustrated by our presentation of a series of spinal injuries in a classification which includes both mechanical parameters and characteristic anatomo-radiological lesion entities. This results in an easier diagnostic approach to lesion identification, a precise evaluation of the severity (static or neurological), and an appropriate choice of the therapeutic principles to be applied.

Understanding the mechanical stresses on the neuraxis and its dynamic anatomy permits a more rigorous approach to neurological risks and underlines the importance to be given to postural manoeuvres of mobilization, positioning, or reduction of lesions. These delicate manoeuvres are capable, within a very narrow margin of security, of either relieving strain or seriously compromising neurological status.

5. References

1. Adams MA, Hutton WC (1981) The relevance of torsion to the mechanical derangement of the lumbar spine. Spine 6: 241–247
2. Adams MA, Hutton WC (1983) The mechanical function of the lumbar apophyseal joints. Spine 8: 327–330
3. Argenson C, Boileau P (1993) Classification of thoracolumbar spine fractures. In: Floman Y, Farcy JPC, Argenson C (eds) Thoracolumbar spine fractures. Raven, New York

4. Argenson C, Dintimille H (1977) Lésions traumatiques expérimentales du rachis chez le singe. Rev Chir Orthop 63: 430–431
5. Arnoldi CC (1972) Intervertebral pressures in patients with lumbar pain. A preliminary communication. Acta Orthop Scand 43: 109
6. Bacon GE, Bacon PJ, Griffiths BK (1979) Neutron diffraction studies of lumbar vertebrae. J Anat 28: 277–283
7. Bartelink DL (1957) The role of abdominal pressure in relieving the pressure on the lumbar intervertebral discs. J Bone Joint Surg 39B: 718–725
8. Bartley MH, Arnold JS, Haslam RK, Jee WSS (1966) The relationship of bone strength and bone quantity in health, disease and aging. J Gerontol 21: 517
9. Basmadjian JV (1974) Muscles alive. Their functions revealed by electromyography, 3rd ed. Williams and Wilkins, Baltimore, pp 173–339
10. Beatson TR (1963) Fractures and dislocation of the cervical spine. J Bone Joint Surg 45B: 21
11. Bell GH, Dubar O, Beck JS, Gibb A (1967) Variation in strength of vertebrae with age and their relation to osteoporosis. Calcif Tissue Res 1: 75
12. Benninghoff A (1925) Spaltlinien am Knochen, eine Methode zur Ermittlung der Architektur platter Knochen. Verhandl Anat Gesellsch [Suppl] Anat Anz 60: 189–206
13. Bergmark A (1989) Stability of the lumbar spine. A study in mechanical engineering. Acta Orthop Scand [Suppl] 60: 230
14. Bergoin M (1987) Eléments de biomécanique du rachis scoliotique. In: Poitout D (ed) Biomécanique orthopédique. Masson, Paris
15. Boehler L (1944) Technique de traitement des fractures de la colonne dorsale et lombaire. Masson, Paris, p 149
16. Bogduk N, Macintosh J (1984) The applied anatomy of the thoraco-lumbar fascia. Spine 9: 164–170
17. Bortolussi C, Dosdat JC, Robert H (1979) Approche biomécanique du disque intervertébral lombaire sous différents types de charge par mesure de pression intranucléaire. J Fr Biophys Med Nuc 3: 163–167
18. Bourges M (1980) Approche histologique d'une vertèbre dorsale non décalcifiée, par coupes horizontales de 20 μ. Etude histologique des ligaments inter et supra-épineux au repos et en traction jusqu'à la rupture. Elements de Biomécanique du Rachis, Clermont-Ferrand, Bloc Santé, pp 44–51, pp 168–189
19. Bradford DL, Spurling RD (1945) The intervertebral disc. Thomas, Springfield
20. Breig A (1960) Biomechanics of the central nervous system. Some basic normal and pathological phenomena. Almquist and Wisksall, Stockholm
21. Breig A (1989) Skull traction and cervical cord injury. Springer, Berlin Heidelberg New York Tokyo
22. Brinckmann P, Frobin W, Hierholzer E, Horst M (1983) Deformation of the vertebra endplate under axial loading of the spine. Spine 8: 851–856
23. Chabannes J, Veyre A, Plagner, Janny P, Meyniel G (1974) Le transit isotopique peut-il apporter un argument dans l'indication opératoire des fractures du rachis. Neurochirurgie 20: 205–214
24. Chamberlain WE, Young BR (1939) The diagnosis of intervertebral disc protrusion by intraspinal injection of air: air myelography. JAMA 113: 2022–2024

25. Chance GO (1948) Note on a type of flexion fracture of the spine. Br J Radiol 21: 452–453
26. Chazal J, Tanguy A, Bourges M, Gaurel G, Escande G, Guillot M, Vanneuville G (1985) Biomechanical properties of spinal ligaments and histological study of the supraspinal ligament in traction. J Biomech 18: 167–176
27. Court-Brown CM, Gertzbein SD (1988) Flexion-distraction injuries of the lumbar spine: mechanism of injury and classification. Clin Orthop 227: 52–60
28. De Seze S, Djian A, Abdelmoula M (1951) Etude radiologique de la dynamique cervicale dans le plan sagittal. Rev Rhum Mal Osteoartic 3: 111–116
29. Decker K (1961) La mobilité de la moëlle épinière dans le canal médullaire. Ann Radiol 4: 515–529
30. Decoulx P, Rieunau G (1958) Les fractures du rachis dorso-lombaire sans troubles neurologiques. Rev Chir Orthop 44: 254
31. Delmas A, Pineau H (1969) Signification de la quantité de matériau composant les vertèbres. Acta Anat 556: 139–151
32. Denis F (1983) The three column spine and its significance in the classification of acute thoracolumbar spinal injuries. Spine 8: 817–831
33. Deubelle A (1979) Complication rare des déviations rachidiennes de la neurofibromatose: la compression trachéale directe. Thèse Méd, Clermont-Ferrand, no 44
34. Escande G, Verge-Garret J, Guillot M, Chazal J, Tanguy A (1980) Etude architecturale de la corticale vertébrale (explorée par la méthode de Beninghoff). Eléments de Biomécanique du Rachis, Clermont-Ferrand, Bloc Santé, pp 15–28
35. Evans FG (1957) Stress and strain in bones. Thomas, Springfield
36. Farcy JPC, Weidenbaum M, Glassman SD (1990) Sagittal index in management of thoracolumbar burst fractures. Spine 15: 958–965
37. Farfan HP, Cossette JW, Welis RV, Robertson GN, Kraus H (1970) The effects of torsion on the lumbar intervertebral joints: the role of torsion in the production of disc degeneration. J Bone Joint Surg 52A: 468–497
38. Fiorini GT, Mc Cammond D (1976) Forces on lumbo-vertebral facets. Ann Biomed 4: 354–363
39. Fischer LP, Gonon GP, Carret JP, *et al* (1976) Biomécanique articulaire. Assoc Corporative Etudiants Méd, Lyon
40. Fournier J, Guillot M, Escande G (1980) Microdureté de quelques vertèbres rachidiennes. Eléments de Biomécaniques du Rachis, Clermont-Ferrand, Bloc Santé, pp 69–81
41. Fuentes J-M, Bloncourt J, Vlahovitch B, Castan PH (1983) La tear-drop fracture. Contribution à l'étude du mécanisme et des lésions ostéo-disco-ligamentaires. Neurochirurgie 29: 129–134
42. Fuentes J-M, Bloncourt J, Bourbotte G, Castan PH, Vlahovitch B (1984) La fracture de chance. Neurochirurgie 30: 113–118
43. Galante JO (1967) Tensile properties of the human lumbar annulus fibrosus. Acta Orthop Scand [Suppl 100]
44. Goubel F (1991) Modèles de muscle strié squelettique. Communication: Journée Spécialisée Modèles et Modélisation en biomécanique, Vandœuvre-les-Nancy (INRS), 14 Mars

45. Guillot M, Pionchon H, Pialat J, Bancel B, Galtier B (1988) Etude de l'innervation des ligaments du rachis lombaire chez l'homme. Rev Rhumat 55: 421–423
46. Guillot M, Fournier J, Scheye TH, Escande G, Chazal J, Tanguy A, Vanneuville G (1990) Justification mécanique approchée de la géométrie particulière du rachis humain soumis à contrainte verticale. Bull Assoc Anat 74: 7–8
47. Hakim NS, King AI (1976) Static and dynamic articular facet loads. Proceedings of the twentieth stapp car crash conference: 609–639
48. Harris JH Jr (1978) The radiology of acute cervical spine trauma. Williams and Wilkins, Baltimore
49. Hart FD, Strickland D, Cliffe P (1974) Measurement of spinal mobility. Ann Rheum Dis 33: 136–139
50. Hill DK (1968) Tension due to interaction between the sliding filaments in resting striated muscles, the effect of stimulation. J Physiol 199: 637–684
51. Holdsworth FW (1963) Fractures, dislocations, and fracture-dislocations of the spine. J Bone Joint Surg 45B: 6–20
52. Holdsworth FW (1970) Fractures, dislocations, and fracture-dislocations of the spine. J Bone Joint Surg 52A: 1534–1551
53. Huxley AF (1974) Review lecture muscular contraction. J Physiol 243: 1–43
54. Janevic J, Ashton-Miller JA, Schultz AB (1991) Large compressive preloads decrease motion segment flexibility. J Orthop Res 9: 228–236
55. Jefferson G (1920) Fracture of the atlas vertebra report of 4 cases and review of those previously recorded. Br J Surg 7: 407–422
56. Kapandji IA (1972) Physiologie articulaire: tronc et rachis, Fasc 3. Maloine, Paris, 255 pp
57. Kelly RP, Whitesides TE (1968) Treatment of lumbodorsal fracture-dislocations. Ann Surg 167: 705–717
58. Lamy C, Bazergui A, Kraus H, Farfan HF (1975) The strength of the neural arch and the etiology of spondylolysis. Orthop Clin North Am 6: 215
59. Lazorthes G, Gaubert J (1957) L'innervation des articulations interapophysaires vertébrales. Bull Assoc Anat 95: 488–494
60. Lee CH, Kim KS, Lee FR (1982) Triangular cervical vertebral body fractures: diagnostic significance. AJR 138: 1123-1132
61. Lee CH, Kim KS, Rogers LF (1982) Sagittal fracture of the cervical vertebral body. AJR 139: 55–60
62. Lindahl O (1976) Mechanical properties of dried defatted spongy bone. Acta Orthop Scand 47: 11
63. Liu YK, Goel VK, Dejong A, Njus G, Nishiyama K, Buckwalter J (1981) Torsional fatigue of the lumbar intervertebral joints. Spine 10: 894–900
64. Louis R (1981) Dynamique vertébro-radiculaire et vertébro-médullaire. Anat Clin 3: 1–11
65. Louis R (1982) Chirurgie du rachis. Anatomie chirurgicale et voies d'abord. Springer, Berlin Heidelberg New York
66. Louis R (1983) Surgery of the spine. Springer, Berlin Heidelberg New York Tokyo
67. Louis R, Gouttallier D (1977) Fractures instables du rachis. Symp Rev Chir Orthop 63: 415–481

68. Louis R, Laffont J, Conty CR, Argeme M (1967) Mobilité de la moëlle épinière. Bull Assoc Anat Réunion (Paris-Orsay) 52: 817–827
69. Malinski J (1959) The ontogenic development of nerve terminations in intervertebral disc of man. Histology of intervertebral discs, 11th communication. Acta Anat 38: 96–113
70. Markolf KL, Morris JM (1974) The structural components of the intervertebral disc. J Bone Joint Surg 56A: 675–687
71. McAfee PC, Yuan HA, Lasda NA (1982) The unstable burst fracture. Spine 7: 363–373
72. Miller JAA, Haderspeck KA, Schultz AB (1983) Posterior element loads in lumbar motion segments. Spine 8: 331–337
73. Moll JMH, Wright V (1971) Normal range of spinal mobility. Ann Rheum Dis 30: 381–386
74. Nachemson A, Evans J (1968) Some mechanical properties of the third human lumbar interlaminar ligament. J Biomech 1: 211–220
75. Nachemson A, Morris JM (1964) In vivo measurements of intradiscal pressure discometry: a method for determination of pressure in the lower lumbar discs. J Bone Joint Surg 46A: 1077–1092
76. Nicoll EA (1949) Fractures of the dorsolumbar spine. J Bone Joint Surg 31B: 3, 373–394
77. Perey O (1957) Fracture of the vertebral endplate in the lumbar spine. Acta Orthop Scand 25: 1–101
78. Pionchon H, Tommasi M, Pialat J, *et al* (1986) Etude de l'innervation des ligaments rachidiens à l'étage lombaire. Bull Assoc Anat 70: 63–67
79. Poirier P, Charpy A (1926) Traité d'anatomie humaine. Tome 1: Arthrologie. Masson, Paris
80. Rabischong P, Louis R, Vignaud J (1978) Le disque intervertébral. Anat Clin 1: 55–64
81. Rennie W, Mitchell N (1973) Flexion distraction fractures of the thoracolumbar spine. J Bone Joint Surg 55A: 386–390
82. Roaf FR (1960) A study of the mechanics of spinal injuries. J Bone Joint Surg 42B: 810–821
83. Robert H, Bortolussi C (1984) Evolution "in vitro" de la pression et de la géométrie du disque lombaire en fonction de la stabilité du rachis. J Biophys Med Nucl 8: 243–249
84. Rockoff SD, Sweet E, Bleustein J (1969) The relative contribution of trabecular and cortical bone to the strength of human lumbar vertebrae. Calc Tiss Res 3: 163–175
85. Rolander S (1966) Motion of the lumbar spine with special reference to the stabilizing effect of posterior fusion. Acta Orthop Scand [Suppl 90]: 144 pp
86. Roy-Camille R (1979) Rachis cervical traumatique non neurologique. 1eres journées d'orthopédie de "la Pitié". Masson, Paris
87. Roy-Camille R, Lelievre JF (1975) Pseudarthrose des corps vertébraux du rachis dorsolombaire. Rev Chir Orthop 61: 249–257
88. Roy-Camille R, Louis R, Argenson C, Goutallier O (1977) L'instabilité vertébrale expérimentale dans "Symposium sur les fractures instables du rachis". Rev Chir Orthop 63: 417–475

89. Roy-Camille R, Saillant G (1980) Rachis dorsolombaire traumatique non neurologique. 2èmes Journées d'Orthopédie de la Pitié, Masson, Paris
90. Schmorl G, Junghans H (1956) Clinique et radiologie de la colonne vertébrale normale et pathologique. Doin, Paris
91. Schneider RC, Kahn EA, Arbor A (1956) Chronic neurological sequelae of acute trauma to the spine and spinal cord. J Bone Joint Surg 38A: 985–997
92. Seroussi RE, Krag MH, Muller DL, *et al* (1989) Internal deformations of intact and denucleated human lumbar disc subjected to compression, flexion and extension loads. J Orthop Res 7: 122–131
93. Shah JS, Jayson Ml, Hampson WG (1977) Low tension studies of collagen fibres from ligaments of the human spine. Ann Rheum Dis 36: 139–148
94. Stagnara P, De Mauroy JC, Dran G, Gonon P, Costanzo G, Dimnet J, Pasquet A (1982) Reciprocal angulation of vertebral bodies in a sagittal plane: approach to reference for the evaluation of kyphosis and lordosis. Spine 7: 335–342
95. Stauffer E, Kelly EG (1977) Fracture dislocations of the cervical spine. Instability and recurrent deformity following treatment by anterior interbody fusion. J Bone Joint Surg 59A: 45–48
96. Taylor AR (1951) The mechanism of injury. J Bone Joint Surg 33B: 543–547
97. Tkaczuk H (1968) Tensile properties of human lumbar longitudinal ligaments. Acta Orthop Scand [Suppl] 115: 69 pp
98. Torg JS, Pavlox H, Oneill MJ, Nicols E Jr, Sennett B (1991) The axial load tear drop fracture. A biomechanical clinical and roentgenographic analysis. Am J Sports Med 19: 355–364
99. Vacheron JJ, Poumarat G, Vanneuville G (1993) Forces distribution applied on the spine by a load. Congrès Acaps Caen
100. Vanneuville G, Eescande G, Chazal J, Tanguy A, Bourges M, Verge-Garret J, Deubelle A (1980) Eléments de biomécanique du rachis. 63e Congrès Assoc Anat, Monographie, Clermont-Ferrand, Bloc-Santé
101. Vanneuville G, Tanguy A, Scheye TH, Bleu JP, Gaurel G, Blillet P, Guillot M, Fournier J (1986) Les méthodes optiques dans l'étude des déplacements superficiels des vertèbres lombaires sous charge vertical, premiers résultats et aspects méthodologiques. Bull Assoc Anat 70: 51–57
102. Vanneuville G, Eescande G, Guillot M (1988) Anatomie fonctionnelle de la paroi antéro-latérale du thorax. Cah Kinésithér 134: 57–65
103. Vanneuville G, Poumarat G, Garcier JM, Scheye TH, Campagne D, Coillard Ch (1991) Etude radiographique du rachis lombaire en charge chez l'haltérophile. Bull Assoc Anat 75: 181–186
104. Vanneuville G, Garcier JM, Poumarat G, Guillot M, Chazal J (1992) Mechanisms of orientation of the pelvifemoral base during static loading of the lumbar spine in weight-lifters. Surg Radiol Anat 14: 29–33
105. Vanneuville G, Kyndt TH, Massaux M, Poumarat G, Garcier JM, Guillot M (1994) Etude par interférométrie speckle du rachis lombaire humain sous contraintes de cisaillement et de torsion. Utilisation du système d'analyse Steinbichler. Soc Anat Paris
106. Vanneuville G, Cluzel P, Perissel B, Garcier JM, Massaux M, Gabrillargues J (1994) Le disque intervertébral. Tentative de modélisation en éléments finis. Soc Anat Paris

107. Watson-Jones R (1940) Fractures and other bone and joint injuries. Livingstone, Edinburgh
108. Weaver JK, Chalmers J (1966) Cancellous bone: its strength and changes with aging and an evaluation of some methods for measuring its mineral content. J Bone Joint Surg 48A: 289
109. Weiss EB (1975) Stress at the lumbosacral junction. Orthop Clin North Am 66: 83
110. Whike B (1972) Articular neurology. A Rev Physiotherapy 58: 94–99
111. White AA, Panjabi MM (1978) Clinical biomechanics of the spine. Lippincott, Philadelphia, 533 pp
112. Willen J, Lindahl S, Nordwall A (1985) Unstable thoracolumbar fractures. A comparative clinical study of conservative treatment and Harrington instrumentation. Spine 10: 111–122
113. Yang KH, King AI (1984) Mechanism of facet load transmission as a hypothesis for low-back pain. Spine 9: 557–565

Space-Occupying Lesions of the Sensori-Motor Region

U. EBELING[1] and H.-J. REULEN[2]

[1] Department of Neurosurgery, University of Berne, Berne (Switzerland), and
[2] Department of Neurosurgery, Ludwig Maximilians University, Munich
(Federal Republic of Germany)

With 20 Figures

Contents

Summary

Successful surgery of the sensori-motor region requires precise pre- and intraoperative localization of the sensori-motor region and pyramidal tract. Important aids are the landmarks of cranio-cerebral topography, coronal suture and bregma and the sulcal anatomy of the sensori-motor region, which can be identified in CT or MR images. Due to considerable displacement and distortion of the anatomical structures, elicited by mass lesions, these aids often fail to render reliable support. In this situation, identification of the motor area can be achieved by electrical stimulation of the precentral gyrus in association with the recording of somatosensory evoked potentials of the pre- and postcentral gyrus. The localisation of the "motor mosaics" in relation to the lesion, enable determination of the direction of displacement of the motor strip and the fan of the pyramidal tract. Based on this information the most appropriate route of access to the lesion is selected, either transcortical or transsulcal. Lesion-specific operative techniques as well as location-specific approaches are discussed. With consequent application of these principles the risk of a new persistent motor deficit was as low as 4% . Thus, the indication for surgery in this area can now be set with greater confidence and far more generously than in the past.

Keywords: Sensori-motor region; motor strip; precentral gyrus; surgical anatomy; motor cortex stimulation; motor cortex mapping; somato-sensory evoked potentials.

1. Introduction

Space-occupying lesions involving functionally important brain regions, for instance the sensori-motor region and the speech areas etc., provide a special challenge for neurosurgery. The aim of surgery is to remove the process as radically as possible on the one hand and on the other to preserve neurological function, i.e. to avoid postoperative neurological deficits. Technical advances as for instance microsurgical instrumentation, the operating microscope, ultrasonic aspirator, laser, bipolar coagulation etc., together with modern anaesthesia and the new imaging procedures have reduced mortality to as low as 1–4% and opened entirely new perspectives in neurosurgery. Although the indication for surgery can now be set with greater confidence, we have to continue our search for possibilities to reduce or avoid the risk of additional neurological deficit.

Prerequesites for successful and safe surgery in the sensori-motor area are profound anatomical knowledge of the surgical topography and reliable intraoperative identification of the motor cortex and the pyramidal tract, respectively. The latter has become possible with the intraoperative application of electrophysiological techniques, motor cortex stimulation and cortical recording of SSEP's. We have applied these techniques since 1987 in more than 200 patients with tumours in the sensori-motor area. Simultaneously several anatomical studies of this area were performed.

This review describes our experience with the surgical anatomy of the sensori-motor region, the intraoperative localization of the motor cortex and pyramidal tract as well as the surgical strategies for removal of space-occupying lesions of this region.

2. Surgical Anatomy of the Sensori-Motor Region

2.1. Definition of the Sensori-Motor Region

The term "sensori-motor region" includes the white matter and cortical areas adjacent to the central sulcus (Fig. 1). It borders frontally the precentral gyrus or area 4 (the areas are defined according to Brodman) with adjacent dorsal portions of the frontal gyri (areas 6, 8, 44). Behind it, the postcentral gyrus (areas 1, 2, 3) is limited frontally by the central sulcus. The term "sensori-motor region" also comprises the anterior part of the superior (areas 5, 7) and inferior parietal lobe (areas 39, 40), which abut the postcentral sulcus posteriorly. The medial boundary is formed by the longitudinal fissure, the lateral boundary by the Sylvian fissure.

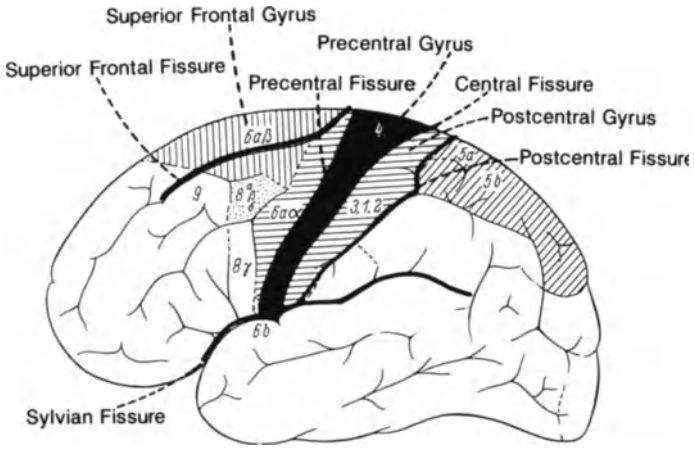


Fig. 1. Lateral view of the sensori-motor cortex with brain areas, modified after Foerster[38]

2.2. *Craniocerebral Topography of the Sensori-Motor Region*

The coronal suture (CS) and the bregma are the two important bony landmarks of the sensori-motor region[1, 22, 23, 52, 55, 96, 97]. Both can be reliably distinguished in lateral x-rays and in CT-images and identified by palpation on the skull. It should be remembered that the distance between the coronal suture and the central sulcus decreases steadily from the midline to the lateral end of the coronal suture[23]. In the midline the distance averages 46–50 mm but amounts only to 33 mm at the lateral end[23]. Since the course of the CS is *highly variable*[23] it can only be employed as a rough landmark of the sensori-motor region[23, 87]. It is, however, useful for outlining the borders of the craniotomy.

2.3. *Anatomy of the Medial Sensori-Motor Region*

"The lateral hemisphere above the lateral fissure is roughly divided into anterior and posterior portions by the central fissure. This fissure begins on the medial surface of the hemisphere and appears on the lateral surface about midway between the frontal and occipital poles. It extends downward and slightly forward toward the lateral fissure, but usually does not quite meet the lateral fissure. This central fissure has bends forward and then backward, the upper and lower genu. Paralleling the central fissure, but lying in front of it, is the so called precentral fissure. In some human brains this is a continuous fissure but more often it is divided into two portions, the superior and inferior precentral part. The convolution between it and the central fissure is the precentral gyrus. Extending forward from the upper part of the precentral

fissure is the superior frontal fissure. The convolution superior to it is the superior frontal gyrus. Posterior to the central fissure and parallel to it lies the postecentral sulcus."[17]

The *junction* of the precentral and superior frontal sulcus constitutes the characteristic *frontal landmark* of the sensori-motor region[22, 66, 76] and is clearly identifiable in 76–88% of all routine CT-scans[22, 52] (Fig. 2) and MRI-images[10, 67]. The junction of the precentral sulcus or central sulcus with the midline is seen in only 12–16%, respectively 44–52% of the cases and thus is less reliable as a landmark[22]. Some average distances and measures of the sensori-motor region are shown in Fig. 3.

Clinical application: The bony and cerebral landmarks on high-quality axial CT- or MR-slices allow exact localization of the lesion and the placement of the craniotomy.

a) The anterior and posterior limits of a tumour can be determined with regard to the CS and its medial and lateral limits with regard to the midline. This enables an exact placement of the craniotomy (Fig. 12).

b) In small lesions without gross displacement and distortion of the sulci and gyri, their exact relation to the central sulcus and the various gyri can be analyzed preoperatively (Fig. 11).

c) In large mass lesions the characteristic configuration (Fig. 2), as seen in the healthy opposite hemisphere, can be transferred to the affected hemisphere.

In many cases this enables a more confident preoperative localization of a lesion in relation to the sensori-motor cortex (Fig. 10).

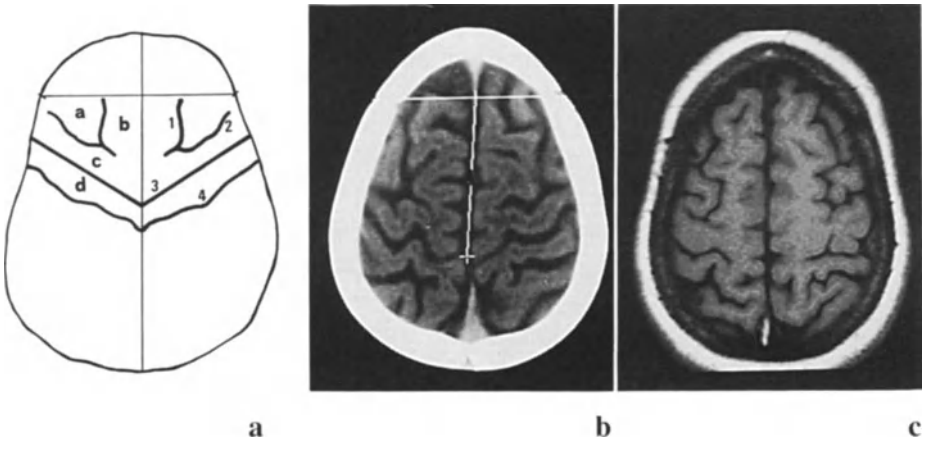


Fig. 2. Top view of the medial sensori-motor cortex with typical fissures and convolutions (a) *a* middle frontal gyrus; *b* superior frontal gyrus; *c* precentral gyrus; *d* postcentral gyrus; *1* superior frontal fissure; *2* precentral fissure; *3* central fissure; *4* postcentral fissure. (b) Axial CT-scan; (c) axial MR-scan

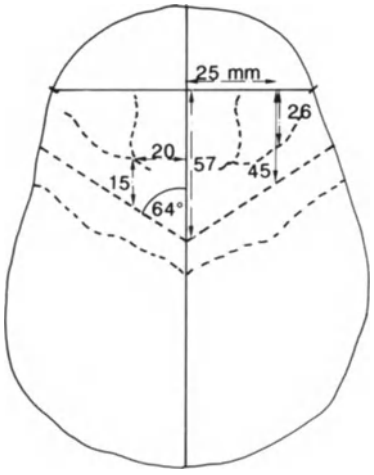


Fig. 3. Top view with important measures and distances as found in the CT[22]. At the midline, the average distance from the coronal suture to the central sulcus is 57 ± 7 mm; 25 mm apart from the midline this distance is only 45 ± 8 mm. In the CT-slice, the distances are measured from the constructed line between the coronal sutures seen on that slice. The angle between the longitudinal fissure and the central sulcus is 64 ± 6°

2.4. Anatomy of the Lateral Sensori-Motor Region (Including Broca's Area)

The inferior frontal gyrus is bordered cranially by the inferior frontal sulcus, dorsally by the inferior precentral sulcus and caudally by the Sylvian fissure. Between the anterior ascending Sylvian branch and the inferior precentral sulcus lies the opercular portion of the frontal operculum (Broca's area of the dominant hemisphere). The primary motor area is situated between the inferior central and precentral sulcus[17, 76].

The lateral precentral fissure constitutes the main landmark for the lateral sensori-motor region (Fig. 4)[25]. The inferior frontal sulcus runs perpendicular to the inferior precentral sulcus to the frontal pole. Anterior and parallel to the inferior precentral sulcus runs the anterior ascending branch of the Sylvian fissure[17, 76]. It is defined by its continuity with the circular (peri-insular) sulcus[18, 33] and divides the dorsal portion of the inferior frontal gyrus.

Three main types of sulcus topography in the lateral sensori-motor region can be distinguished in lateral sagittal MR-images (Fig. 4)[25].

Type 1 is the most frequent type (~ 90%) and characterized by the juxtaposition of the ascending branch of the Sylvian fissure and the inferior precentral sulcus as well as by the presence of a junction between the inferior frontal and inferior precentral sulcus.

Type 2 (5%) corresponds to type 1 except for the absence of a connection between the frontal and precentral sulcus.

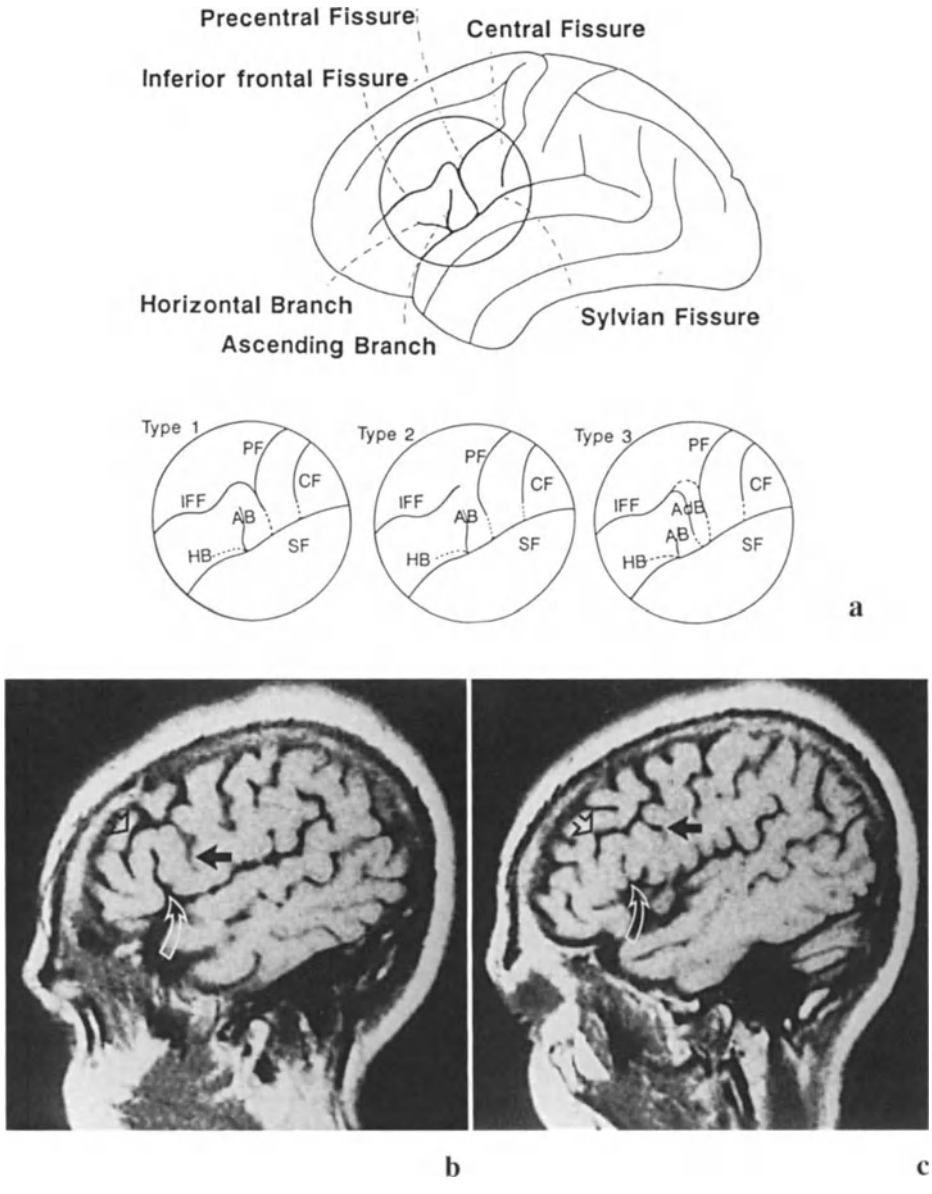


Fig. 4. Sulcal configuration of the lateral sensori-motor region. (a) Illustration of three main types (see text). *PF* precentral fissure; *CF* central fissure; *SF* Sylvian fissure (*HB* horizontal branch; *AB* ascending branch; *AdB* additional ascending branch); *IFF* inferior frontal fissure. (b, c) Lateral sensori-motor region in the MR: inferior frontal fissure (open black arrow) precentral fissure (solid black arrow), ascending Sylvian branch (white arrow)[25]

The characteristic feature of *type 3* (5%) is the presence of an additional sulcus between the ascending ramus of the Sylvian fissure and the precentral sulcus.

2.5. Anatomy and Proportions of the Pyramidal Tract

2.5.1. Anatomy

Functional motor or sensory deficits can be the consequence of both cortical lesions and damage of efferent or afferent fiber bundles. Therefore some important anatomical and topographical data of the pyramidal tract are presented[24, 28].

The pyramidal tract comprises all fibers that run in a longitudinal direction through the medullary pyramid – regardless of their source[14]. The majority of the fibers i.e. 40–60%, originate in the precentral cortex (Brodman area 4)[14,51]. Another 40% are projection fibers originating in the premotor frontal and superior parietal cortex (Brodman areas 5, 6, 7, 8). The remaining 20% originate in the postcentral cortex (Brodman areas 1, 2, 3)[6, 51]. For practical surgical reasons the pyramidal tract is simplified considerabl by reducing its origin to the main source of its fiber (40–60%), namely the primary motor cortex (Brodman area 4) (Fig. 5). These fibers emerge along the entire circumference of the precentral gyrus and converge to the posterior limb of the internal capsule like a fan[6–8, 14, 36, 37, 60, 69, 70, 82, 84].

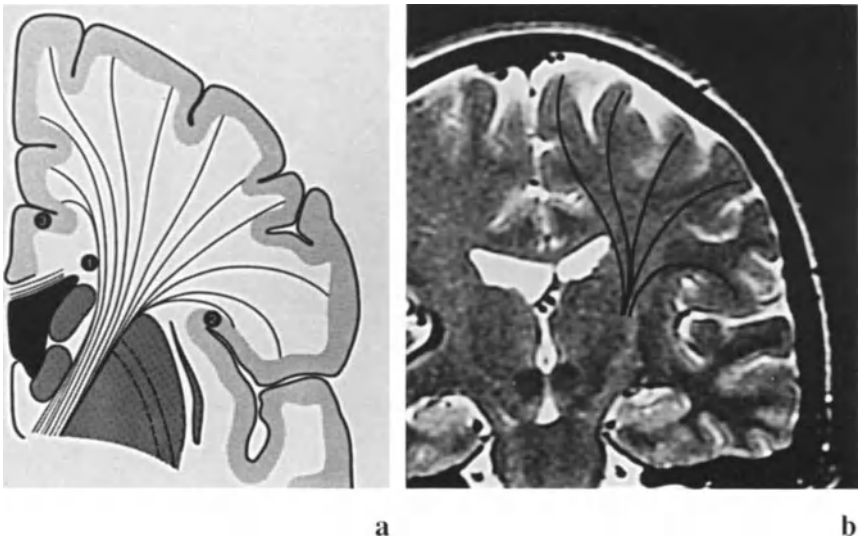


Fig. 5. Coronal view of the pyramidal tract and its landmarks: *1* wall of the lateral ventricle; *2* upper medial circular (periinsular) sulcus; *3* cingular sulcus. (a) Schematic illustration; (b) coronal MR-scan[28]

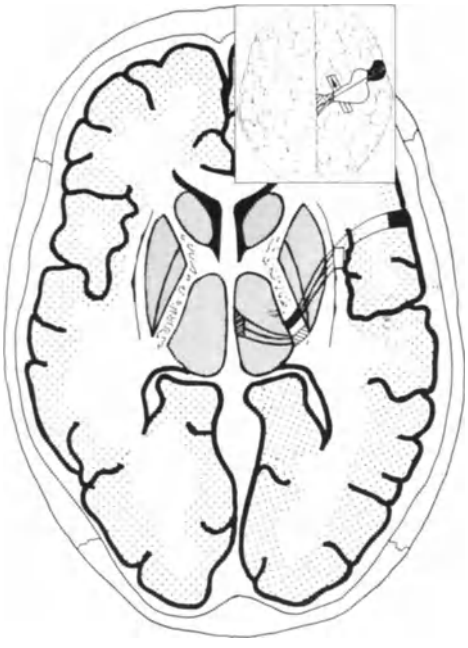
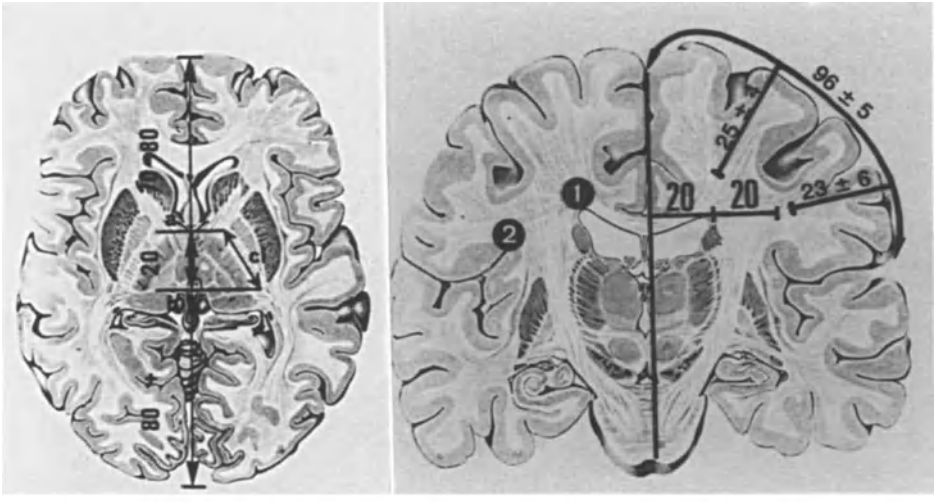


Fig. 6. The axial rotation of the pyramidal tract is shown. In the precentral gyrus the pyramidal tract has a mediolateral, in the internal capsule a lateromedial position. The cortical origin of the different components of the tract and their topography in the posterior limb of the internal capsule is shown (black face; white upper extremity; shaded lower extremity)

The leaf of the pyramidal fan is situated in the subcortical white matter and centrum semiovale, the solid bundle of fibers, constituting the stalk of the fan, in the posterior limb of the internal capsule[7, 82, 95]. There the fibers are arranged in an anterior-posterior direction, depending on their origin (Fig. 6). The fibers of the face are situated anteriorly and the fibers of the foot most occipitally. Situated between both are the fibers of the arm, hand and trunk[34, 45, 68, 85, 98]. The pyramidal tract passes downward through the internal capsule in an oblique fronto-occipital direction[36, 37, 45, 68].

The circumference of the precentral gyrus corresponds to the lateral extent of the leaf of the pyramidal tract. The angle of this leaf to the midline defines the axial orientation of the pyramidal tract in the subcortical white matter[28] and amounts to 62 ± 3° (varying from 55–68°), according to anatomical data[22, 23, 52, 57–59].

The course of the *medial* fibers of the pyramidal fan is determined by the corpus callosum and the lateral ventricle[82]. This can be studied in coronal MR- or CT-images (Fig. 5). The fibers are deflected by the cingulate fissure, the wall of the lateral ventricle and caudate nucleus, before entering the



a b

Fig. 7. Landmarks of the pyramidal tract on the level of the interventricular foramen in axial (a) and coronal (b) view. (a) Line *a* represents the level of the interventricular foramen, line *b* the dorsal limit of the internal capsule's posterior limb. Axial distances from the frontal and occipital poles are given (in mm). *ci* internal capsule. (b) Landmarks of the pyramidal tract and their distances to the midline (in mm) (*1* lateral wall of the lateral ventricle; *2* upper circular (peri-insular) sulcus)[90, 91]. The medial and lateral coronal diameter and circumference of the fan of the pyramidal tract is shown

internal capsule[82]. The external wall of the lateral ventricle usually is located 20 mm from the midline, which can be studied in *coronal* CT- or MR-images ([90], p. 307) (Fig. 7). The most *lateral* fibers of the pyramidal tract have to curve around the medial upper circular (peri-insular) sulcus and the cranial border of the lentiform nucleus[82]. The distance between the lateral wall of the ventricle to the medial limit of the circular (peni-insular) sulcus amounts to only 20 mm (Fig. 7) ([91], p. 159). The pyramidal tract passes this bottleneck before entering the internal capsule.

In axial CT- or MR-studies the knee of the internal capsule can be used as an additional landmark of the pyramidal tract (Fig. 7). The foramen of Monroe may be employed as an indirect landmark, since it is situated roughly on the same level as the knee of the internal capsule. The distances for the localization of the interventricular foramen are shown in Fig. 7.

2.5.2. Proportions

The thickness of the pyramidal tract, measured 1 cm underneath the cortical surface, amounts to about 3 mm, varying from 1 to 5 mm (Table 1)[28]. Thus,

Table 1. *Pyramidal Tract Proportions* (in mm) (n = 30)[a]

Proportions	Mean ± SD	Maximum	Minimum
Thickness in the subcortical white matter:			
lateral	3.2 ± 1.2	5	1
medial	2.8 ± 1.0	6	2
parasagittal	3.3 ± 1.1	6	2
At the entrance of the internal capsule:			
thickness	17.5 ± 2.1	23	14
lateral diameter	7.8 ± 1.6	10	4
Caudal third of the internal capsule:			
thickness	12.1 ± 2.3	16	8
lateral diameter	6.1 ± 1.2	9	4
Breadth of the leaf of the fan:			
lateral	24.9 ± 4.3	31	18
medial	22.8 ± 5.7	31	16
Length of the pyramidal tract:			
precentral gyrus to upper pons	74.0 ± 4.0	82	68

[a] From[28].

the pyramidal tract in the subcortical white matter is a thin and susceptible structure. The mediolateral dimension, however, is considerable in this region (95.9 ± 5.3 mm), corresponding to the lateral circumference of the precentral gyrus. Consequently, the thickness of the pyramidal tract increases when its fibers converge to form the stalk of the fan whereas the lateral diameter decreases in the subcortical course (Table. 1). During their passage through the internal capsule, the pyramidal fibers converge progressively. These results were obtained with the fiber preparation method of Klingler[19, 28, 54, 63].

3. Clinical Syndrome and Neuroradiology of Central Lesions

3.1. Clinical Syndrome

In general central lesions initially present with either epileptic seizures or neurological deficits, rarely both syndromes are combined. Epileptic seizures (focal or generalized) are more common in benign, slowly growing lesions (meningioma, low grade astrocytoma, oligodendroglioma) or vascular malformations (cavernoma, angiomas)[61]. The feature of the seizure (i.e. movement of head, eyes etc.) may yield information of the cortical localisation of

the lesion. Neurological deficits occur in these lesions in a later stage or following a hemorrhage. In addition, a postictal shortlasting motor deficit occasionally may be observed. Neurological deficits as initial symptoms are more common in malignant tumours (glioblastoma, metastasis) and develop early[61]. Therefore anamnestic data of epilepsy are rather suggestive for a benign lesion, neurological deficits for a malignant tumour. In a later stage, both symptoms may be present.

In our material the majority of patients (88%) suffered from neurological deficits. Of the patients with a paresis 69% presented with a hemiparesis, 29% with a monoparesis, in 13% additional speech disturbance and in 10% additional sensory deficit was present. A flaccid paresis was more common than a spastic paresis[31]. The motor deficit is closely correlated with the affected portion of the motor system. A monoparesis usually is the result of a more superficial lesion. In contrast a hemiparesis rather can be expected in more deeply located lesions[31]. Lesions close to the midline, i.e. falx meningioma, usually exhibit a monoparesis of the lower extremity and additional slight paresis of the upper extremity only when the motor fibers of the upper limb are involved by the mass effect or edema. A paresis of the arm or hand is found in lesions affecting the cortex of the convexity. Very lateral lesions, located in the operculum, cause a palsy of the muscles of the face and/or disturbance of the speech, if the dominant hemisphere is involved. In lesions behind the central fissure a sensory deficit or a so-called parietal syndrome may be the major symptom and motor deficits are rare and minor. Signs of a severely raised intracranial pressure today have become rather uncommon and are only seen in patients with rapidly growing malignant tumours or in lesions with acute hemorrhage. Administration of steroids leads to rapid improvement or resolution if the deficits are caused by brain edema and this would indicate a more favourable prognosis with regard to recovery. Vice versa, if no neurological improvement occurs following steroids, damage of the respective structures may be assumed.

3.2. Neuroradiology

Diagnosis is performed with either axial CT- or MR-studies, however, images in a coronal and sagittal plane are necessary in most cases. The angiogram is important to study the feeding arteries and draining veins, the vascularisation of the process as well as the relation of neighbouring vessels to the lesion.

Axial cuts in the CT- or MR-study can depict the topographical relationship between the lesion and the medial, central sulcal pattern and the direction of a possible displacement of the motor system, for instance in a parasagittal lesion (Figs. 10–12). The depth of a lesion, i.e. the involvement

of the pyramidal tract, can be delineated appropriately in coronal planes (Figs. 10, 11, 17). Sagittal imaging is absolutely necessary in lesions involving the lateral central area, because only with this plane, can one study the location of the lesion in relation to the lateral central, precentral and Sylvian fissures (Fig. 4)[25].

In our material the CT-data showed in 68% of the patients a superficial central lesion, i.e. in the cortex or adjacent white matter[31]. In 25% of the patients the lesion was found in the deep white matter and in only 7% the basal ganglia were affected[31]. In 82% the lesions were located in front of the central sulcus, in 11% posterior to it and in 7% in the basal ganglia (Table 2). The etiology of the lesions in our material is given in Table 3.

Table 2. *Location of Central Lesions (n = 100) in Relation to the Central Sulcus*[a]

Location	%
Anterior:	
frontal gyri	11
frontal and precentral gyri	28
precentral gyrus	20
pre- and postcentral gyrus	23
Posterior:	
postcentral gyrus	9
postcentral gyrus and anterior parietal lobe	2
Basal ganglia	7

[a] From[31].

Table 3. *Etiology of Lesion in 100 Patients*[a]

Benign:	
meningiomas	20%
low-grade gliomas	10%
abscesses	4%
cavernous malformations	2%
Malignant:	
glioblastomas	38%
metastases	26%

[a] From[31].

4. Displacement of Anatomical Structures

The distance between the coronal suture and the central or precentral fissure can be measured in CT or MR-images. Bone algorithms are helpful to demonstrate the coronal suture in the CT examination. The distance between the coronal suture and the precentral fissure 2.5 cm apart from the midline in average amounts to 26 mm (maximum and minimum values 7–41 mm); at the lateral end the precentral sulcus may reach the coronal suture[23]. These distances have been recommended as "safety zones" for a corticotomy in this area[90, 91]. However, as these data show, the normal anatomy varies considerably and in addition it may be markedly distorted by space-occupying mass-lesions as well as by edema. In such cases corticotomy may result in undesired damage of the precentral gyrus, even if these "safety zones" are respected during surgery. We therefore have measured the possible displacement of the central structures in a series of 100 patients (in axial CT-studies) as distance between the coronal suture and the visible central sulcus[31].

Frontal lesions may lead to circumscribed dorsal displacement of the sensori-motor area, so that the distance between the coronal suture and the sensori-motor area increases. This posterior displacement of the central sulcus, affected by the tumour, could be as much as 10–40 mm. It is conceivable that the surgeon in such cases, when relying only on the "safety zones" or the normal anatomy of the opposite hemisphere, and in fear of a severe neurological deficit will not attempt a gross total resection of an astrocytoma or a glioblastoma. On the other hand, we have found that parietal tumours may dislocate the sensori-motor area frontally by 5–25 mm so that the distance between the coronal suture and the sensori-motor region is reduced. In these cases, corticotomy may result in unexpected damage of the precentral gyrus and pyramidal tract, although the "safety zones" are respected, if the resection be planned from anteriorly.

Even if attention is paid to these principles, some surprises may occur. In a few cases, after studying and comparing the axial MR of both hemispheres we assumed, for instance, the motor cortex to be displaced to the posterior border of the tumour. To our surprise, motor mapping eventually demonstrated that the motor cortex was displaced in the opposite direction and was intimately neighbouring the anterior border of the tumour. A resection of the tumour, based on our original impression, probably would have led to severe and persisting motor deficit.

5. The Role of Intraoperative Mapping of the Sensori-Motor Cortex

As seen in the previous chapters, the sensori-motor area can often be identified prior to surgery with the aid of a high quality axial CT or MR and the described anatomical landmarks. In many cases, however, normal sulcal

anatomy is considerably distorted by the space occupying lesion and perifocal edema[26, 27, 30, 31, 53]. On the other hand it is a well known experience that during surgery confident localization of this area in the majority of the patients is extremely difficult[26, 27, 30, 53]. In addition, landmarks, distances and "safety zones" are not reliable in case of large tumours due to the considerable displacement of structures.

As a result many attempts have been made to localize motor function intraoperatively. Intraoperative stimulation of the motor cortex has been used frequently, especially for surgical management of epilepsy and also in tumour surgery [9–13, 20, 26, 27, 29, 30, 42–44, 53, 62, 72–75, 78, 80, 86, 99, 100]. Subcortical stimulation of the descending motor pathways has been recommended recently for the same purpose[9, 11].

Several groups use exclusively somatosensory evoked potentials for the identification of the sensory hand area[2–4, 35, 42–44, 53, 93]. Other groups combine somatosensory evoked potentials and direct cortical electrical stimulation of the precentral gyrus[26, 27, 30, 42–44, 53]. We think, that it is preferable to have the combination of both methods at ones disposal although we definitely favour cortical motor cortex stimulation; from our experience with more than 200 patients, it yields more reliable results.

5.1. Technique of Cortical Electrophysiological Mapping

Following opening of the dura, a first attempt should be made to identify the precentral gyrus anatomically. Thereafter the identification of the motor cortex is done by either direct cortical stimulation of the motor cortex or recording of somatosensory evoked potentials or both.

5.1.1. Cortical Electrical Stimulation (MCS)

Cortical electrical stimulation is performed with a bipolar isolated forceps with uninsulated tips (Aesculap, GK 675). The interelectrode distance is 3–5 mm. The stimulation unit of a conventional EMG machine (e.g. Medelec ER 94a; ST 10 Sensor, Nicolet Compact Four, Nicolet Viking II etc.) delivers rectangular pulses of 0.2 ms duration with a repetition rate of 50/s. The stimulation intensity is started at 5 mA and then increased stepwise by 2 mA until a motor reponse of the contralateral face, arm or leg can be observed visually.

The lowest intensity sufficient to elicit a motor response was 5 mA, the mean was 30 mA, the maximum intensity ever used was 50 mA in general anaesthesia. In local anaesthesia the current sufficient to elicit motor responses did not exceed 15 mA. In each patient 5 to 20 different points of the cortex have to be stimulated. Each cortical point that is stimulated is marked with a sterile numbered label. The same stimulation parameters are used for subcor-

tical stimulation, if necessary. Subsequently, photographs of the mapped region can be taken in order to document the findings.

In order to avoid provocation of a seizure, stimulation intensity is increased in stepwise fashion. Stimulation is done at the largest current that does not evoke after-discharge in the sampled area of the cortex. Despite these measures in a few patients a focal seizure occurred, but disappeared within less than 15 seconds or was aborted by administration of 2 mg Clonazepam, i.v. (Rivotril®, Sandoz).

The draping of the patient must allow observation of the face, arm and leg of the affected (contralateral) side. A positive motor response during general anaesthesia consists of a mass movement of the face, flexion, extension or rotation in one of the joints – shoulder, elbow, hand, finger, hip, knee, foot etc. Isolated movements of a single muscle group are rather rare. It is our impression that motor response in local anaesthesia is more specific. A positive motor response can be elicited from the cortex but also sometimes from the subcortical white matter of the tumour bed. This shows the immediate neighbourhood of the descending motor pathway[9, 11, 12, 86]. If stimulation of the motor cortex elicits movements, while stimulation of the subcortical tumour border evokes no response, this can be used as a hint that resection can be continued.

5.1.2. Results of Cortical Motor Stimulation

Sites where stimulation repeatedly evoked motor responses usually were small areas of 1–2 cm^2 and were separated by areas without motor response. The response ceased when the electrode moves to a point a few mm away. The margins of such areas with motor response usually are very sharp, suggesting a graduation between cortex with no role in complex movements to cortex that is essential for it. Wrist flexion, for instance, may be present only close to the central sulcus, while stimulation of the precentral gyrus anterior to this area evoked no response. A common finding is a response-free area between sites for elbow and shoulder movement in the one area and leg movement in the other. This "silent" area may correspond to the area of the trunk.

Although the compilation of all motor responses in 50 patients reveals the classical representation of the homunculus (Fig. 8), we have found considerable inter-individual differences in the localisation of distinct functions, for instance elbow flexion. This may be due to anatomical variances or result from mass displacements.

A motor response was obtained in about 90% of the patients studied. Failure to obtain a motor response may be due to technical problems or may have neurophysiological reasons:

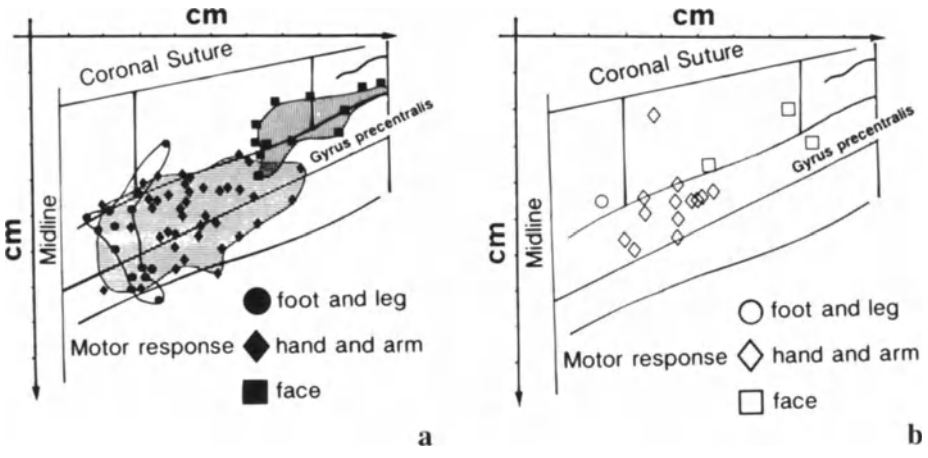


Fig. 8. Cumulative representation of the "motor points" identified by intraoperative stimulation of the motor cortex in patients with precentral (a) and postcentral lesions (b). The central sulcus was constructed with the aid of normal anatomical data[30, 50, 58, 59, 77]

a) The craniotomy may be too small and situated directly above the tumour, i.e. the precentral gyrus is not sufficiently exposed.

b) Failure may arise from inadequate positioning of the patient so that arm and leg are fixed and not fully movable.

c) Despite repeated decurarization motor responses may be absent[12, 42–44, 53, 103]. Either the threshold for stimulation is too high as a consequence of anaesthesia and inadequate decurarization or the electrical excitability of the motor cortex may become exhausted due to prior stimulation or seizure activity[12, 42–44, 53, 103].

d) Marked damage of the motor cortex may also result in inexcitability.

e) Electrical stimulation could not be performed in 2 cases due to severe brain swelling after opening the dura.

It is obvious that in situation b) and e) the recording of cortical sensory evoked potentials, e.g. by stimulation of the median, tibial or trigeminal nerve, may still allow identification of the central fissure under general anaesthesia[2–4, 42-44, 53, 64, 93, 103, 104].

5.1.3. Recording of Somato-Sensory Evoked Potentials

The tibial nerve is stimulated at the ankle, the median nerve at the wrist (rectangular pulses, 10/s, 0.3 ms duration, 30 mA). Recordings were obtained from the cortex using a longitudinal array of four to six electrodes placed in an anteroposterior direction in the presumed hand or leg area. Monopolar (with frontal reference electrode) or bipolar recordings were made with an

analysis time of 50 ms (median) or 100 ms (tibial). Input gain was at about 20 μV/U, filter bandpass ranged from 30 to 600 Hz. One hundred and twenty eight stimuli were averaged[71, 92].

In the pre- and postcentral gyrus, different SSEP of the median nerve can be recorded (Fig. 9)[103]. The characteristic SSEP recorded in the postcentral gyrus is of the N 20–P 30 type, whereas the potential in the precentral gyrus shows a phase reversal of the P 30–N 20 type[103]. Thus, the central sulcus is located between the two electrodes the recordings of which show an inversion of amplitudes of the cortical response.

SSEP-recording allows identification of the transition from sensory to motor cortex in a circumscribed area, mostly the hand field. Identification of the phase reversal in the leg and face field is possible, but less reliable[103]. In some cases we have also observed that the location of the phase reversal did not exactly correspond with the results of motor stimulation. Thus if only one recording is performed a few cm distant from a lesion, a circumscribed displacement of motor function may be missed. In contrast to motor stimulation, further differentiation of the motor fields is not possible with SSEP. The real advantage of motor function mapping in our eyes is that it allows one to determine exactly the "motor mosaics" as well as the "non motor mosaics",

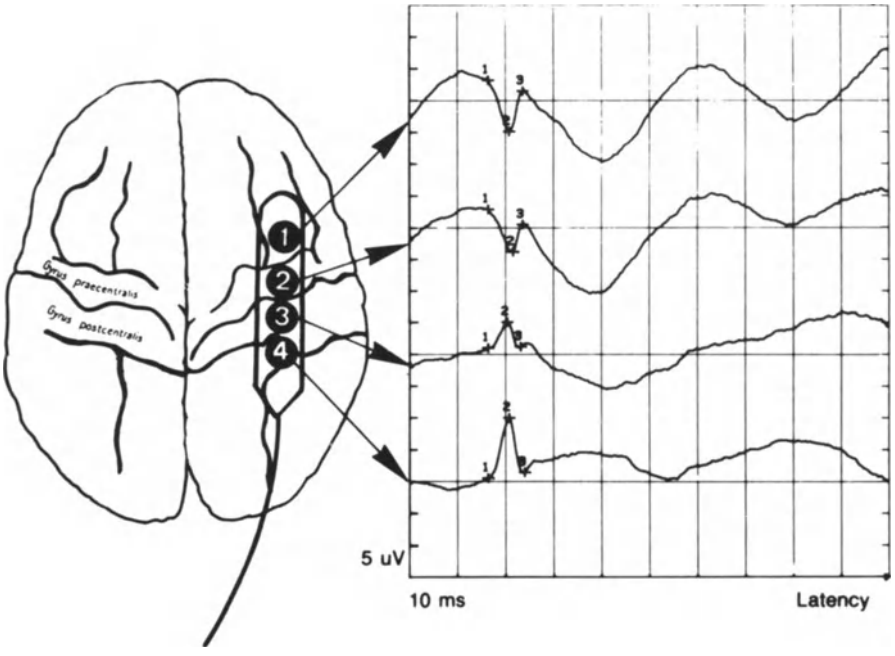


Fig. 9. Diagram demonstrating phase reversal of somatosensory evoked potentials of the median nerve between recording point *2* and *3*. The precentral gyrus shows a potential of the P 20–N 30-type the postcentral gyrus of the N 20–P 30-type. The central sulcus is found between point *2* and *3*[30]

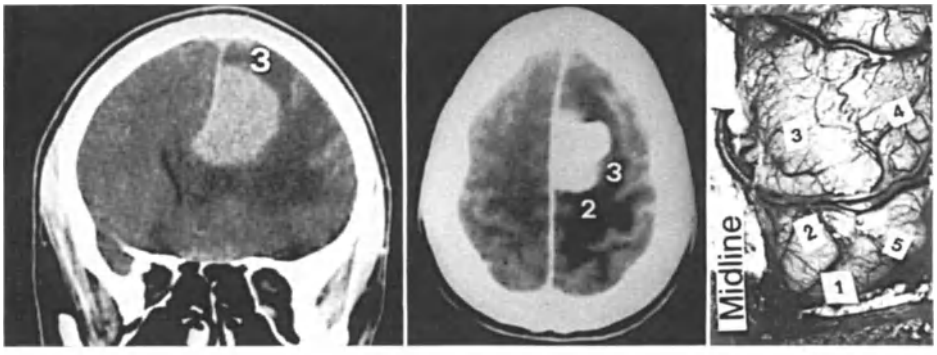


Fig. 10. Axial (a) and coronal (b) CT of a right-sided falx meningioma; *3* superior frontal gyrus; *2* precentral gyrus. Intraoperative photograph (c) demonstrates the deformed precentral gyrus which could be identified by cortical stimulation: point *1* and *2* movement of left leg; point *5* movement of left arm; point *3* and *4* no movement (superior and medial frontal gyrus). The patient had no pre- and postoperative deficits[26]

whether a silent area is present and whether "motor mosaics" intimately border a lesion etc. Therefore we always prefer motor cortex stimulation (MCS) initially. Only in situations where MCS fails for unknown reasons, SSEP-recording may become helpful.

5.2. Examples

5.2.1. Central Falx Meningioma (General Anaesthesia)

Case 1 (Fig. 10): The CT shows a large falx meningioma on the right side underneath the precentral gyrus. The precentral and superior frontal sulcus and precentral gyrus are deformed and shifted posteriorly and laterally. At the cortical surface, anatomical identification of the precentral gyrus was not possible. During cortical stimulation, movement of the left leg was observed at points 1 and 2, and movement of the left arm at point 5 which corresponded to the displaced precentral gyrus. According to these results the tumour was removed totally by a more frontal interhemispherical approach, anterior to the bridging Rolandic vein, which was preserved. Pre- and postoperative neurological examination was normal.

5.2.2. Anaplastic Glioma of the Precentral Gyrus (General Anaesthesia)

Case 2 (Fig. 11): The CT shows a cystic anaplastic astrocytoma (Fig. 11a, b) in the left precentral gyrus. The preoperative examination revealed a severe

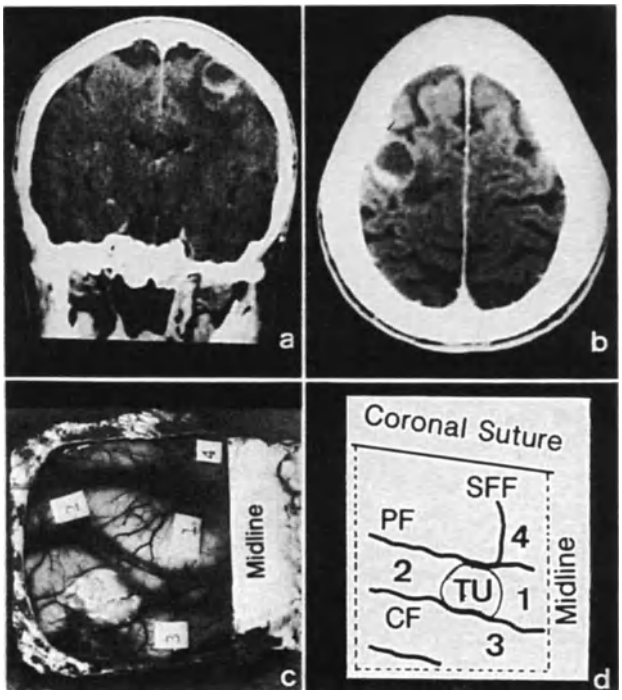


Fig. 11. (a–d) Axial (b) and coronal (a) CT of a cystic tumour (anaplastic astrocytoma) in the left precentral gyrus. Lower illustrations show intraoperative photography (c) and the corresponding drawing (d). Stimulation at points *1* and *2* led to movements of the leg (precentral gyrus), whereas stimulation at point *3* (postcentral gyrus) and *4* (superior frontal gyrus) evoked no motor response. The preoperative paresis of the right upper limb remarkably improved after removal of the tumour[26]

paresis of the right hand. Steroids improved this weakness only partially. Intraoperatively, the precentral gyrus could be identified by the typical sulcal anatomy and cortical stimulation (Fig. 11c, d). Stimulation of points 1 and 2 elicited movements of the right hand, whereas stimulation of points 3 (postcentral gyrus) and 4 (medial frontal gyrus) showed no motor response. After opening the precentral sulcus, the tumour was removed by a trans-sulcal microsurgical approach. The weakness of the right hand recovered within 6 weeks.

5.2.3. Low-Grade Glioma of the Superior Frontal Gyrus (Local Anaesthesia)

Case 3 (Fig. 12): A right handed 34 year old man suffered from focal epileptic seizures, caused by a low grade glioma of the left superior frontal gyrus, adjacent to the precentral gyrus (top). Intraoperatively the motor strip

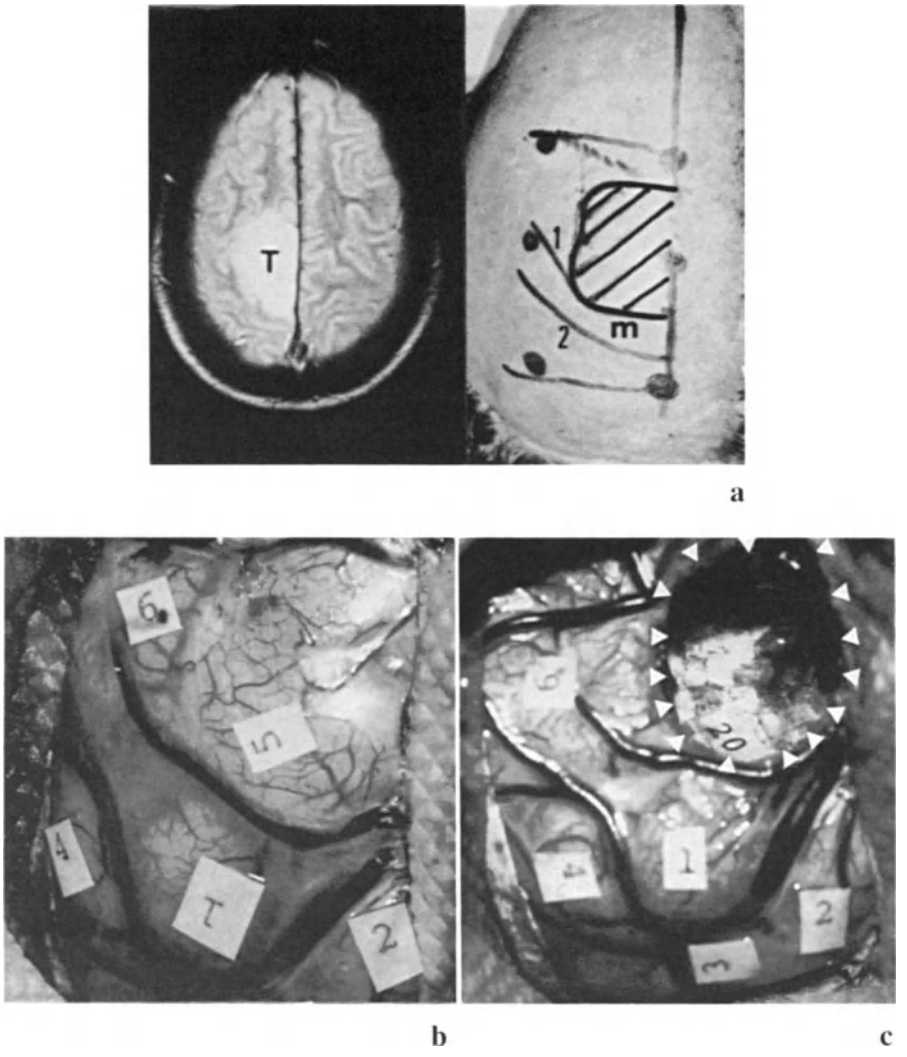
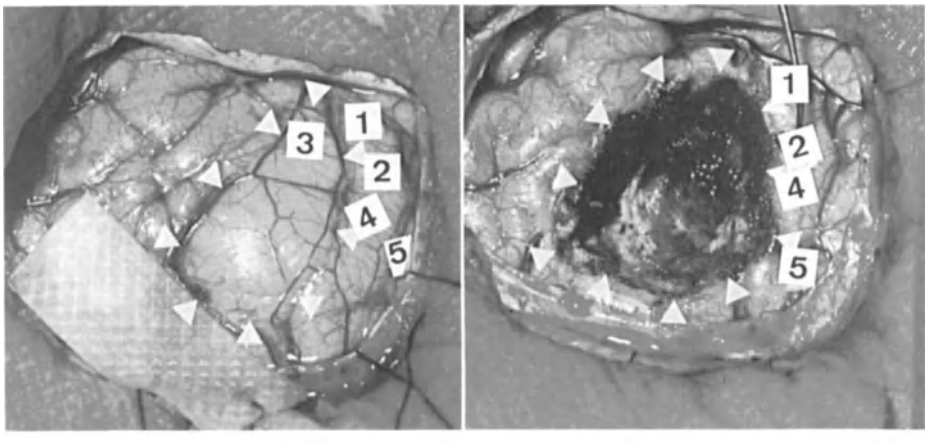


Fig. 12. (a) Left: MR-T2-sequence shows a well delineated low grade astrocytoma in the left superior frontal gyrus (*T*). Right: placement of craniotomy in relation to midline and coronal suture (m motor strip; *1* precentral; *2* central fissure; shaded area tumour). (b) Intraoperative photograph with labelled tickets. *1* movements of hand (motor cortex), *2* no motor response (postcentral gyrus), *4* movement of fingers (motor cortex), *5* no response (superior frontal gyrus, tumour), *6* no response (medial frontal gyrus). (c) Photograph taken after resection of the tumour. White arrows show tumour bed. Point *20* (white matter in tumour bed) indicates site with positive motor response, corresponding to the pyramidal tract. At this area, resection was terminated[30]



a b

Fig. 13. Intraoperative photograph were taken before (a) and after subpial tumour resection (b). The tumour (a) respectively the tumour bed (b) is indicated by white triangles. The precentral gyrus was identified by cortical stimulation (*1, 2* motor response in the left face; *4* motor response of the left hand prior (left) to and after tumour removal (right)[30]

was identified by cortical stimulation (point 1, 2, 4) (center). The resection of the dorsal part of the tumour in the depth of the white matter underneath the precentral fissure probably was incomplete, because at this site (point 20) motor movements of the arm could be elicited by stimulation of the pyramidal tract. After a temporary slight weakness of the lower limb motor function recovered completely. The patient suffered from a malignant recurrent tumour 3 years after surgery.

5.2.4. Low-Grade Glioma of the Operculum (General Anaesthesia)

Case 4 (Fig. 13): Focal seizures in the left face led to the diagnosis of a low grade glioma in the right operculum of a young female teacher. Under general anaesthesia and after identification of the precentral gyrus (point 1, 2, 4) the tumour was resected sharply to the depth of the precentral fissure. After removal the function of the motor cortex was proven intact by repeated positive cortical stimulation (point 1, 2, 4). The postoperative course was uneventful.

5.2.5. Subcortical Central Metastasis (General Anaesthesia)

Case 5 (Fig. 14): The CT shows a deeply located metastasis of a renal-Ca below the right precentral gyrus in the centrum semiovale. The patient suffered a severe hemiparesis. A stereotactic guided craniotomy was performed

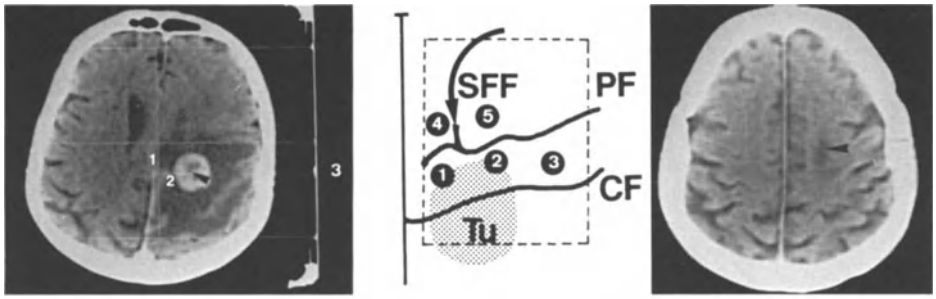


Fig. 14. (a) A metastasis of a renal Ca seated in the white matter below the central sulcus is shown with the stereotactic coordinates (*1* ap; *2* lateral; *3* height) in an axial CT (Leksell frame). (b) Intraoperative situs: *PF* precentral fissure; *CF* central fissure; *SFF* superior frontal fissure; *Tu* tumour (shaded area: not visible at the cortical surface). The broken line outlines the craniotomy. Cortical stimulation showed elevation of left leg at point *1*; flexion of left forearm at point *2*; movement of left hand at point *3* and no motor response at points *4* und *5*. A stereotactic guided persulcal approach through the SFF (black arrow) was chosen to remove the tumour. (c) Postoperative CT 6 weeks after surgery[32]

and the tumour removed by a trans-sulcal approach through the superior frontal fissure (SFF). Cortical stimulation showed motor responses at points 1, 2, 3 (the motor strip) and negative responses at points 4 and 5. The preoperative hemiparesis resolved remarkably after total removal of the tumour.

5.3. Anaesthetic Regimen

Intraoperative mapping of the sensori-motor cortex is usually done under general anaesthesia. It is important to use muscle relaxant only initially and to continue anaesthesia without it.

5.3.1. General Anaesthesia

Intramuscular premedication consists of 0.5 mg atropine, 5–10 mg nicomorphine (Vilan®, Synmedic) and 2.5–5 mg Droperidol (Dehydrobenzperidol®, Jansen). Intravenous induction of anaesthesia is performed with thiopental (4.5 mg/kg) and 1.5 mg/kg suxamethonium-chlorid (Succinolin®, Amuno). A single relaxant dose of 5 mg i.v. Alcuroniumchlorid (Alloferin®, Roche) is given and further anaesthesia is maintained with nitrous oxide 70%, nicomorphine (Vilan®, Synmedic) (150 µg/kg i.v. in repeated doses) and ethrane (0.5–2 volume %). Before commencement of cortical stimulation, the patient is decurarized with atropine (0.02 mg/kg i.v.) and Neostigmin-Methylsulfate (Prostigmin®, Roche) (0.07 mg/kg i.v.). The state of neuromuscular blockade

is controlled by observing motor responses following a train of four electrical stimuli of the median nerve at the wrist[88, 89]. At the end of cortical stimulation, the patient is again relaxed with Alcuroniumchlorid (Alloferin®, Roche)[88, 89]. In lesions of the lateral end of the motor strip, where face and tongue movements are expected as response to cortical stimulation, naso-tracheal intubation should be preferred. In the last cases we maintained general anaesthesia with Alfentanil (Rapifen®, Jansen) and Propofol (Disoprivan®, ICI-Pharma) due to less interference with the neurophysiological procedures.

5.3.2. Local Anaesthesia

Recently a few authors have recommended local anaesthesia, when speech monitoring is necessary in operations near the sensori-motor and speech area of the dominant hemisphere[9, 11, 12, 29, 62, 72, 75, 86]. Stimulation during local anaesthesia, in their opinion also offers the advantage of more reliable results, because there is no severe interference with anesthetic drugs. More importantly surgery in awake patients allows "clinical monitoring" of functions during the procedure by repetitive clinical examinations[9, 11, 12, 29, 62, 72, 86]. On the other hand, in children, in anxious patients, patients with a psychoorganic syndrome, with raised intracranial pressure or with deep seated lesions local anaesthesia is not possible. In general the feasibility, the value and possible advantages of local anaesthesia as a procedure remains to be proven in tumours of the motor area.

Technique: Patients receive a premedication consisting of 0.05–0.1 mg/kg Midazolan (Dormicum®, Roche) and are operated on in a comfortable prone position. The scalp is infiltrated with local anaesthesia (0.375% Bupivacain with Vasopressin). During the skin incision, craniotomy and opening of the dura the patients are sedated with Propofol (Bolus 20 mg, Perfusor: 2.4 mg/kg/h) (Disoprivan®, ICI-Pharma). Analgesia is maintained by intravenous Alfentanil (Rapifen®, Jansen) (repetitive: 1–2 times 3 mcg/kg). After the opening of the dura the sedation is stopped. Following resection of the tumour the patient receives again Propofol (Disoprivan®, ICI-Pharma) and is well sedated.

6. Surgery of Central Lesions

6.1. General Considerations on Localization

Prior to surgery the following questions should be analyzed:

a) Are motor cortex and pyramidal tract affected directly or are they displaced?

b) Does displacement occur in a frontal or occipital direction?

c) Is the lesion located at the cortical surface or subcortically?

If the axial MR or CT scans are carefully studied, the comparison with the normal hemisphere often allows one to determine, whether a lesion is located within, in front of or behind the precentral gyrus. The presumed course of the descending pyramidal tract is then deduced on the basis of the oblique orientation of the precentral gyrus and the position of the lesion within, anterior or posterior to the descending motor pathway. The position of a tumour in relation to the motor cortex offers the most important information, whether the cortex itself or the descending motor pathways are displaced in an anterior or posterior direction or in a medial or lateral direction (Fig. 15). Coronal and sometimes sagittal images may allow one to estimate the

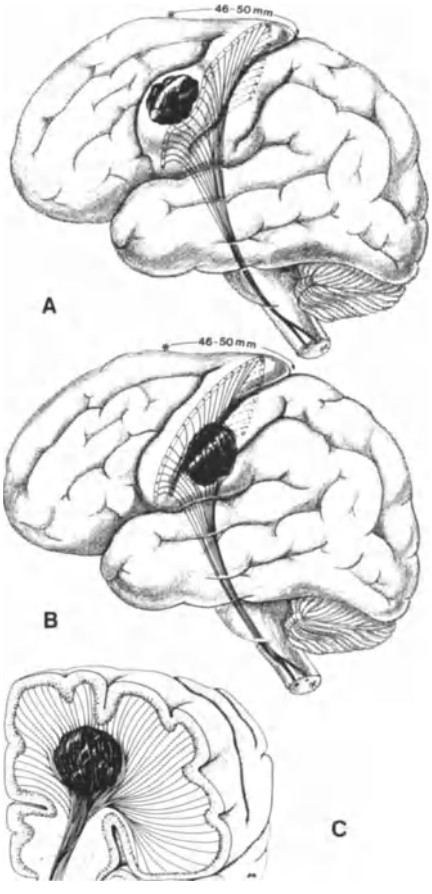


Fig. 15. Displacement of cortex and fibers of the pyramidal tract by tumours. (A) Dorsal displacement of precentral gyrus and pyramidal tract by a superficial lesion located anterior of the motor cortex. (B) Dorsal displacement of subcortical fibers of the pyramidal tract by a deep-seated lesion. (C) Splaying of fibers of the pyramidal tract by a subcortical lesion below the motor cortex

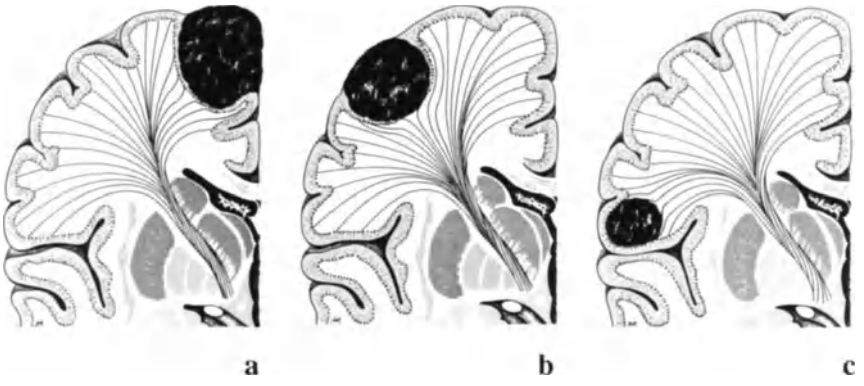


Fig. 16. Different tumour locations with their displacement of the pyramidal tract. (a) Falx meningioma with lateral displacement of the medial portions of the pyramidal tract; (b) convexity meningioma displacing the pyramidal tract downward; (c) cavernoma of the operculum with medial displacement of the lateral portions of the pyramidal tract[28]

direction of the displacement. The neurological deficit in almost all cases supplies additional important information. The observation that steroid medication does not or only partially leads to remission of a paresis may be taken as a hint for direct affection of the fibers of the motor system. Vice versa, the complete or pronounced improvement of weakness under steroids indicates that a paresis is probably the consequence of perifocal edema and/or displacement.

A few examples illustrate this. A typical example is a meningioma, where cortex and descending motor fibers were displaced dorsally (Fig. 10, 15) and ran along the dorsal border of the tumour. Subcortical stimulation during surgery showed the intimate relationship of the descending motor pathways to the dorsal tumour border (Fig. 10). A meningioma of the falx (Fig. 16) displaces the medial portions of the precentral gyrus and pyramidal tract laterally. A convexity meningioma may displace the motor area downward together with the descending motor fibers (Fig. 16). Lateral tumours (Fig. 16) shift the motor system toward the midline. Superficial tumours may displace the precentral gyrus together with the pyramidal tract while deep lesions are likely to shift predominantly the fan of this fiber tract (Fig. 15a, b). In small lesions within the motor gyrus, i.e. a small metastasis or cavernoma, the fibers can be either shifted or splayed around the tumour circumference (Fig. 15c, 17). A considerable part of the circumference of the tumour may be surrounded by motor cortex or fibers of the pyramidal tract (Fig. 15c). It is important to keep in mind that the relationship of the tumour boundary to the thin fan of the pyramidal tract can be very close and even a careful microsurgical dissection may destroy many of the fibers.

6.2. Positioning of the Patient and Drug Regimen

The time spent in planning, positioning the craniotomy and taking care of all the details cannot be overemphasized in avoiding potential complications. The key point in positioning is that the planned area of exposure should be the highest point, taking advantage of gravity and minimal retraction of the brain.

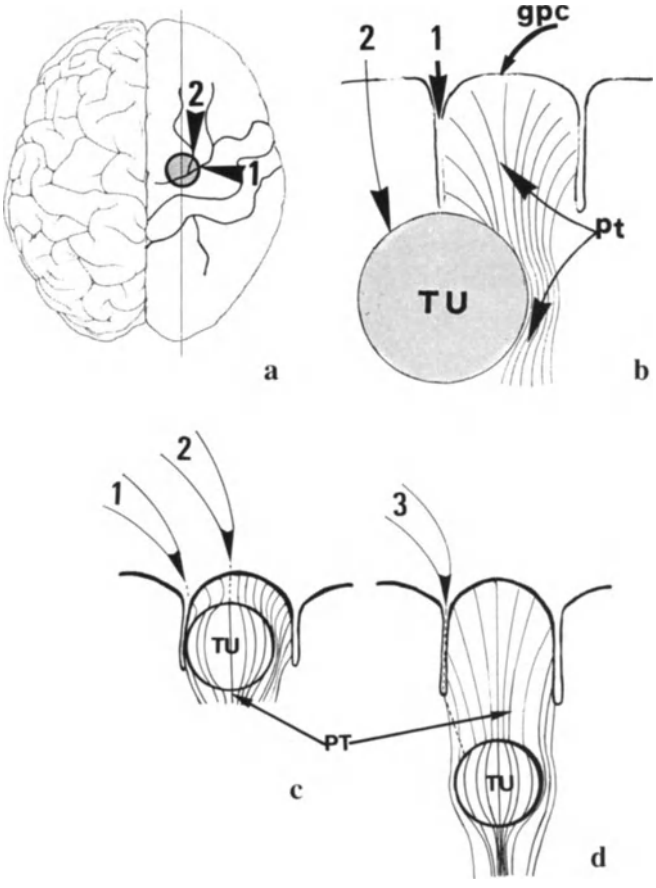


Fig. 17. (a) Schematic drawing of a lesion (shaded area) underneath the precentral (*1*) and superior frontal fissure (*2*). Line a shows a sagittal cut through the lesion and brain (see b–d). (b) The lesion (*Tu*) is shown in relation to the precentral gyrus (*gpc*) and pyramidal tract (*pt*), which is dorsally displaced. The possible persulcal approaches through the precentral (*1*) and superior frontal sulcus (*2*) are shown. (c) A more superficial tumour is shown, where a transcortical approach (*2*) is possible, if the tumour is close to the cortical surface or in a "silent area" of the precentral gyrus (*1*: persulcal approach through the precentral fissure). (d) In a deep seated tumour a persulcal approach (*3*) through the precentral fissure is recommended, offering the shortest and safest route of access to the tumour

The head is slightly elevated and there should not be any undue pressure or traction on the jugular veins. The head and thorax are elevated by 10–30 degrees.

The patient is placed supine in the three pin head holder with the head straight and elevated by about 20–30 degrees and slightly flexed forward for all lesions close to the midline. In convexity or lateral lesions, the head can be turned by 10–40 degrees. In lateral lesions the shoulder is raised with a pad to avoid undue rotation of the head.

If local anaesthesia is used the surgeon has to look very carefully to ensure comfortable positioning of the patient during the procedure. Adequate access for the anaesthetist and neurophysiological team to the patient is mandatory.

Cerebral edema, if present, is usually well controlled with the administration of steroids (dexamethasone or methylprednisolone), beginning 48–72 hours prior to operation. If there is significant edema, it may be wise to give steroids up to 5 days before surgery. A dose of 3×4 mg/day or 4×4 mg/day of dexamethasone is sufficient. All patients receive perioperative antibiotic prophylaxis.

During the craniotomy and exposure of the dura a 20% solution of mannitol is given in a dosage of 1–1.5 g/kg over 20–30 minutes. For seizure prophylaxis phenytoin is used. If the patient is not already loaded with an anticonvulsant, phenytoin is used for seizure prophylaxis intraoperatively. Postoperatively the drug is tapered off within a week, if there were no preoperative seizures, but continued for about 6 months in case of preoperative attacks.

6.3. Placement of Craniotomy

Usually, the lesion is located in the center of the boneflap with a minimum of normal brain exposed. In our situation, the size of the craniotomy is planned in a fashion to expose enough of the sensori-motor cortex to enable cortical stimulation and recording of SSEP. The outlines of the craniotomy are defined as distances to the sagittal and coronal suture, the latter reflecting the primary bony landmarks. The coronal suture almost always can be palpated. If this is not possible, the bregma in the adult is found in a line 13 cm behind the nasion. A craniotomy in the upper medial sensori-motor region extends to the midline, for lateral tumours to the Sylvian fissure. We recommend to outline the borders of the craniotomy, the skin incision and the necessary important structures (midline, coronal suture, bregma, Sylvian fissure, central sulcus etc.) on the skin with a waterproof marker (Figs. 12, 19). The precentral sulcus is localized by its measured distance from the coronal suture or by marks on the skin which are visible on CT- or MR-scan. The recent CT- or MR-Software can localize all axial images on the lateral radiographs so that the margin of the lesion can be roughly outlined. In small

subcortical lesions a stereotactic guided procedure is recommended for exact placement of the craniotomy and route of access.

6.4. General Considerations on Surgical Strategy

Tumours which are *visible at the brain surface* should first be internally decompressed. We prefer the ultrasonic aspirator or a small 3–5 mm electrical loop. With sufficient debulking of the tumour, the use of brain spatulas can mostly be avoided. The surgical microscope allows dissection of the tumour border more confidently and with less injury to surrounding tissue. Following sufficient internal decompression the tumour capsule – if present – can be identified and separated from arachnoid adhesions, arteries and veins. Extirpation is accomplished by gentle traction of the tumour without applying pressure to the cortex or white matter.

As a general principle microsurgical dissection begins at the tumour border *distant* to the motor system. Those portions of the tumour, which are immediately adjacent to the motor cortex and pyramidal tract are removed only at the very end. Here the subcortical resection is adapted to the results of prior cortical and perhaps subcortical stimulation of the descending motor

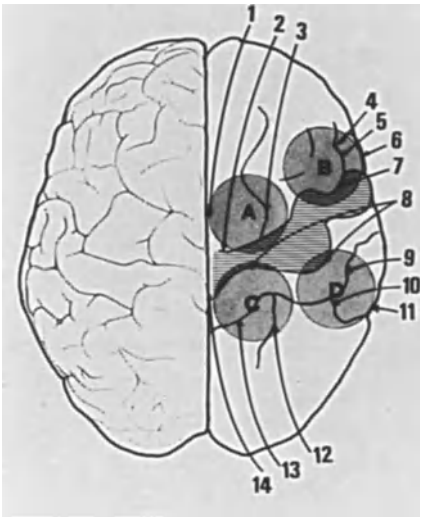


Fig. 18. Possible persulcal approaches: (*A*) medial precentral lesions: *1* interhemispheric fissure; *2* precentral sulcus; *3* superior frontal sulcus. (*B*) lateral, precentral lesions: *4* anterior ascending ramus of the Sylvian fissure; *5* inferior frontal sulcus; *6* stem of the Sylvian fissure; *7* precentral sulcus. (*C*) Medial, postcentral lesions. *8* central sulcus; *12* interparietal sulcus; *13* postcentral sulcus; *14* interhemispheric fissure. (*D*) Lateral, postcentral lesions. *8* central sulcus; *9* postcentral sulcus; *10* posterior ascending ramus of the Sylvian fissure; *11* stem of the Sylvian fissure

pathways[9, 11, 86]. If during progressive resection repeated subcortical stimulation of the resection plane evokes a motor response, fibers of the motor tract must be very close and resection at this plane should be terminated[9, 11].

In *subcortically* and *deep-seated* tumours the principal decision is the choice of the surgical approach, either transcortical or trans-sulcal (Figs. 17, 18). First, the exact location of the lesion in the depths has to be established. Small and deeply situated lesions in our institution are localized by a stereotactic guided craniotomy or the use of ultrasound. Then, the mapping of the motor function is performed. Based on these findings, the shortest and most direct route is selected, where no important cortex is destroyed or the pyramidal tract crossed. Mostly this is possible through a sulcus. Corticotomy should be kept as small as possible and should not be placed in a functionally important cortical area such as the precentral gyrus (except through a silent area!). An approach through functionally less important areas occasionally can be considered, although this requires exact knowledge on the relative importance of the functions of the adjacent areas and their potential for recovery (see chapter 6.6.1).

A persulcal approach is possible and preferable in many, particularly in small lesions, since the distance to the lesion can be shortened[5, 26, 46, 53, 83, 91, 105, 106] (Figs. 17, 18). Generous opening of the sulcus provides sufficient view without excessive compression of the cortical banks of the sulcus or traction on the blood vessels. If two surgical pads are carefully placed into the two ends of the sulcal opening the use of retractor may be avoided. In large tumours due to the risk of damaging the cortical banks and vessels the persulcal approach is less advisable. In these cases a well placed corticotomy in a silent or functionally less important area is safer. With appropriate positioning of the patient and internal decompression of the tumour, retraction of the adjacent cortex may not be necessary at all or can be achieved without exerting great pressure[91] (p. 227).

6.5. Lesion-Specific Operative Techniques

Specific microsurgical techniques have been developed by many groups in the past for the various lesions. In the following a short description is given for the most frequent lesions.

6.5.1 Meningiomas

If the tumour is exposed, removal always starts with extensive internal debulking either with the ultrasonic aspirator, the laser or a small cautery loop, until the shell is thinned out to 4–5 mm only. This has the advantage of minimizing the pressure upon the surrounding tissue. Only after adequate internal debulking has been reached is the arachnoid adhesion between

tumour and adjacent cortex – the arachnoidal ring – opened with microscissors, staying on the tumour capsule. At this time, injection of a small amount of Ringer's solution in the arachnoidal layer between tumour and cortex may facilitate the creation of a dissection plane. If draining cortical veins are adherent to the meningioma, they must be carefully dissected from the tumour capsule. Gentle traction, on the tumour capsule with tumour holding forceps helps to define the tumour-brain interface while working circumferentially with the bipolar forceps or dissector. The separated cortex is protected with moist cottonoids. Small vascular attachments are coagulated and divided. Once internal decompression is achieved, the component of the mass opposite to the motor function should be removed first. Finally the component of the mass adjacent to the "motor mosaics" is approached. This may require higher magnification. Caution must be exercised when the deeper portion of the tumour is reached. Often the cortex is thinned out and the tumour now lies directly on the edematous white matter. The arachnoidal layer mostly is lost. This part of the dissection necessitates particular care. If branches of arteries are adherent, they should be gently separated from the capsule. Once the tumour is removed, sufficient time has to be spent ensuring adequate hemostasis. Jugular compression for 30 s will identify any persisting small open venous vessel.

6.5.2. Low-Grade Astrocytomas

It has been our experience that low-grade astrocytomas presenting on the cortical surface often involve one single gyrus, resulting in a marked gyrus distention, which looks pale and avascular (Figs. 12, 13). This is important, since the bank of the involved gyrus allows a clear cleavage plane between its pia-arachnoidal covering and that of the adjacent sulcus. At the bottom of the sulcus, the astrocytoma expands into the white matter. However, many low-grade astrocytomas, particularly those with a sharp border in the T1 or T2 MR images, continue to have a recognizable boundary.

Our experience so far shows that the tumourous cortex shows no motor function, and there will be no deficit, if the tumour is removed within its limits. The first step, as in most tumours, is the internal debulking. The principle of removal in low-grade astrocytomas is to perform a subpial resection of the tumour along the sulcal borders of the gyrus by using dissector, bipolar forceps and microsuction tip. The critical point is to find and trace the tumour boundary at the depth of the sulcus. An attempt is made to develop a plane of cleavage by observing the different colour and consistency of white matter and astrocytoma. The adjoining white matter is separated by blunt dissection or bipolar coagulation. If small biopsies can be examined histologically in the operation room this may be helpful in finding the tumour border. Bleeding is not a problem as these tumours are relatively

avascular. In general retractors are not necessary and are – if at all – rather used as protector than retractor of the tissue. The use of high power magnification is extremely helpful.

6.5.3. High-Grade Gliomas

The goal in glioma surgery should be an increase in the length and quality of the patient's life by maximal resection of the tumour and minimal disturbance of the surrounding brain. Malignant gliomas can be present on the cortical surface or they can be totally submerged below the cortex. There is no precise margin at the interface of an intrinsic tumour and the surrounding brain. Based on the preoperative estimates of the tumour's size and shape, resection is started in the tumour center (suction, cautery loop, laser, ultrasonic aspirator) and the resection cavity is carefully enlarged until clean white matter is encountered. Most intrinsic tumours are soft enough to be removed easily without traction or pressure. Hemostasis is easily achieved, if normal white matter is reached. The surgeon should be careful not to leave large portions of tumour behind. Unresected tumour is likely to be very troublesome with swelling and bleeding. We therefore avoid mere debulking of the macroscopic part of the tumour, but look for a gross total removal. At the conclusion of the resection irrigation fluid in the tumour bed should be crystal clear.

6.5.4. Metastases

Most metastases are not visible after dural opening and require exact localisation. The approach is chosen according to the result of motor cortex stimulation and the shortest and safest corridor is selected. Metastatic tumours often appear grossly encapsulated and can be easily dissected from the surrounding brain. The tumour surface is coagulated, the tumour is reduced in size and small feeding vessels are identified under the microscope, coagulated and divided. Small cottonoids are used to protect the white matter. With a grasping forceps the tumour may be gently pulled away from the brain and dissected. The final step again is hemostasis and – as a control – a Valsalva manoeuvre. In areas far from the motor pathways, a safety zone of 3–4mm of edematous tissue may be removed.

6.5.5. Cavernomas

In many cases, the malformation extends to within a few millimeters of the pial surface. If it appears at the surface, it is recognizable by either a bulging brown-redish area or by the red-bluish caverns. Cavernomas located deeply or in a buried sulcus are localized either by ultrasound scan if larger than 1 cm or by a stereotactic procedure.

If the lesion is close to the surface the parenchyma is opened with fine forceps over the brown-yellowish discoloured area. If present, a hematoma is removed. The cavernoma is reduced by bipolar coagulation of its multilobulated surface. The border between the cavernoma and the surrounding gliotic brain tissue is usually well defined. This enables one to reduce the lesion and dissect without disturbing the neighbouring tissue. Small feeding vessels, if present, must be identified and coagulated. Small so-called satellite caverns are sometimes found outside the mulberry-like lesion and must be removed carefully. If they are missed they may be the origin of recurrent cavernoma formation. Whether the surrounding yellowish gliotic tissue is responsible for seizures and should also be removed carefully, has not yet been clarified. In about 15–20% of cavernomas a venous malformation may be associated and the approach and removal should be modified to avoid its interruption and the attendant risk of venous infarction.

6.5.6. Abscesses

Abscesses in the sensori-motor cortex currently are treated best by stereotactic puncture, aspiration and drainage [47]. An intracavitary catheter is placed for daily irrigation with antibiotics and external drainage (usually not longer than 24–72 h). The patients receive pre- and postoperatively broad spectrum antibiotic treatment, in combination with low-dose steroids and antiepileptic drugs. The mortalitiy is less than 4% and the risk of additional neurological deficit is very low with this technique[47].

6.6. Location-Specific Operative Approaches

6.6.1. Lesions in the Dorsal Frontal Gyri

Lesions in the dorsal portions of the superior, medial and inferior frontal gyrus – usually low-grade gliomas or rarely meningiomas – are common tumours in most series. They displace the precentral gyrus and pyramidal tract in an occipital direction (Figs. 10, 11, 13). In cases where the sulcal anatomy cannot be clearly identified, it is strongly recommended to adapt tumour resection to the result obtained by electrophysiological stimulation, particularly in tumours adjacent to the precentral fissure (Figs. 11, 13). If the tumour, i.e. a well delineated low grade glioma, is situated directly adjacent to the anatomically and/or electrophysiologically verified precentral gyrus, then resection of the dorsal tumour portions is strictly limited to the visible tumour borders or, if possible, a subpial removal along the cortical bank of the precentral fissure is performed using a small sucker. The bottom of the dorsal superior frontal and precentral fissure should not be crossed dorsally. The oblique course of the precentral gyrus (the 60 degree angle!) and pyramidal tract (Fig. 6) should be kept in mind.

A few words are necessary concerning the functional anatomy of the so-called premotor cortex with regard to a corticotomy or cortical resection. The premotor cortex consists of the supplementary motor area (SMA or area 6aβ) and the premotor cortex (PMC or area 6aα (Fig. 1)[16, 39–41, 86]. The 'frontal eye field' (FEF or area 8) is situated lateral to the SMA and frontal to the PMC. The mastication field (area 6b) is located lateral to the area 6aα and is regarded as segment of the field for the representation of the face in area 4[62]. A number of functions and deficits can be attributed to these regions[14, 16, 39–41, 62, 72, 79, 80, 86]: Lesions of the SMA are characterized by a disintegration and slowing of movements (dysdiadochokinesia) and reduced spontaneous motor actions[39, 94]. Most impressive is the pathological grasp reflex[15, 21] and reduction of spontaneous verbal expression[78, 79, 81]. All these pathological findings resolve completely[16], except slowing of specific movements of both hands[41]. Damage of the PMC causes a transient paresis of the contralateral extremities and inability to initiate and coordinate complex movements[38]. Only a disturbance of discrete finger movements will be the lasting deficit[38]. Similar findings were described by Freund *et al.*, who found a slight paresis of the proximal muscles and a so-called limb-kinetic apraxia, a disintegration of the fluidity of motor actions and complex discrete movements[39–41, 65].

The patients are not handicapped by these deficits, which can only be detected by thorough neurological examination[41].

Lesions of the frontal eye field result in a temporary loss of intended eye movements[16, 48, 49]. A transient disturbed vocalisation can be seen in lesions of the dominant mastication field[16].

After sufficient time, lesions of the SMA result in discrete deficits, whereas lesions of the PMC lead to more severe disorders, such as proximal weakness of the limbs and limb-kinetic apraxia. Damage to the frontal eye field does not result in persisting, grave deficits[16]. Dysarthria, as a consequence of a lesion in the area 6b, of the dominant hemisphere, is usually reversible[62]. Thus, corticotomies in the frontal eye field are the least injurious, because they do not lead to lasting deficits. Preferably, cortical incisions should be placed in the SMA and not in the PMC, because the risk of deficit is smaller.

6.6.2. Lesions of the Precental Gyrus or Pyramidal Tract

Two types of mass lesions can be distinguished: a) the lesion is situated cortically and/or subcortically in the motor system itself (Figs. 11, 14) or b) the motor system is only displaced (Fig. 10). The deeper the lesion is situated in the white matter, the greater are the number of pyramidal fibers involved, and the less favourable will be the outcome. This explains the greater risk for postoperative hemiplegia in patients with deep lesions[28].

In small subcortical lesions usually a trans-sulcal approach is chosen (Figs. 17, 18)[5, 26, 46, 53, 83, 91, 105, 106]. The selection of the sulcus depends on the result of cortical stimulation and the supposed displacement of the descending motor fibers. An approach through the precentral or superior frontal sulcus respectively can be chosen when the tumour is located underneath the precentral sulcus. If the lesion is located within or below the precentral gyrus the smallest number of pyramidal tract fibers are sacrificed when the route through the white matter is as short as possible (Fig. 17).

An approach through the central sulcus is far less favourable, because the dorsal bank of the precentral gyrus contains the densest array of motor neurons[56]. Although we strictly try to avoid corticotomy through the precentral gyrus, in our opinion an exeption is possible, if a lesion is located underneath a "silent" area, a site with no motor response.

a) Our impression is that between the leg and the arm field, there mostly exists an area without visible motor response, probably representing the trunk. We have never observed a motor deficit, if a small corticotomy was performed in this area.

b) Another less likely possibility of a negative response in the motor area may be that a tumour has destroyed the respective portion of the motor system. This, however, should be recognizable by a pre-existing circumscribed motor deficit.

c) A further possibility may be mentioned. We have observed in quite a number of low-grade astrocytomas (WHO-grade II), located within the precentral gyrus and visible at the cortical surface, that motor function could not be evoked over the tumour but rather in the immediate neighbourhood. It seems that the respective function has been either displaced laterally or has migrated to the border. This is a relatively reliable finding, which will be analyzed in detail elsewhere.

6.6.2.1. Medial Precentral Gyrus or Pyramidal Tract

Parasagittal meningiomas and meningiomas of the falx are surrounded laterally by both motor cortex and fibers projecting to the lower extremities, whereas in subcortical tumours mainly the fibers are involved. For removal of deep meningiomas of the falx, the interhemispheric fissure is opened a few cm frontal to the precentral gyrus, paying attention to the bridging veins (Fig. 10). Preservation of the venous tributaries draining the precentral cortex is an important goal. Sacrifice of one of the large tributaries carries a high risk of venous congestion, neurological deficit or seizures. Therefore an angiogram with particular attention to these bridging veins (or a MR-venogram) will demonstrate the most suitable approach and also allow the placement of an appropriately sized bone flap. The tumour is then internally decompressed, the medial portions of the capsule and the attachment removed first,

and finally those portions of the tumour resected that are adjacent to the motor system (Fig. 10). Subcortical tumours are removed gradually in a medial to lateral direction after incision of the cortex bordering the tumour from inside the opened interhemispheric fissure. Paramedian subcortical tumours can be removed after opening the superior frontal sulcus and/or precentral sulcus.

6.6.2.2. Convexity of the Precentral Gyrus and Pyramidal Tract

Typical deficits exhibited by these patients are a paresis of the upper extremity which may be combined with a paresis of the leg, depending on tumour size. The most frequent tumours are menigiomas and low-grade astrocytomas, followed by high grade gliomas and metastases. These lesions represent a special surgical challenge: small tumours may be entirely surrounded by either motor cortex or pyramidal fibers in the white matter (Fig. 17); larger tumours may be partially surrounded by the described structures (Fig. 15). Thus, the risk for a postoperative increase of prior deficits or the induction of new deficits is particularly high. Therefore, extensive and careful internal decompression of the tumour is of considerable importance, so that any pressure on adjacent structures and application of brain retractors can be avoided. Only after extensive internal decompression is the outer border of the lesion attacked following the principles described for the various lesions. High magnification and delicate handling is necessary. If the MCS has yielded information of particular "motor mosaics", then dissection of the tumour border from the adjacent, often edematous and soft white matter in that underlying area should be done with particular attention, keeping in mind that the motor fiber tract is only 3–5 mm thick. Great care is also necessary during the resection of the lower tumour pole. Pyramidal fibers that may be splayed around the tumour, reunite at this point (Fig. 17) and therefore every lesion may lead to severe and persisting hemiplegia.

6.6.2.3. Lateral Precentral Gyrus or Pyramidal Tract

Typically, these patients display isolated paralysis or focal seizures of the muscles of the face and hand. Anatomical landmarks are much less reliable in the lateral precentral gyrus. Often the coronal suture as well as the dimension of the lateral precentral gyrus and frontal operculum cannot be determined accurately (chapter 2.4) and electrophysiological methods therefore are always necessary[29, 62, 72, 75]. In the dominant hemisphere, we remove these lesions under local anaesthesia with concomitant monitoring of speech functions[29]. In the nondominant facial motor cortex tumours are removed by applying the techniques described in the previous chapter. Different sulci situated in the neighbourhood of the lateral precentral gyrus allow some

trans-sulcal approaches (Fig. 18). In general, due to the large extension of hand and face area, deficits recover very well with proper physiotherapy.

6.6.3. Lesions of the Postcentral Gyrus and Anterior Parietal Lobule

Patients typically feature sensory deficits or a parietal lobe syndrome. An accompanying paresis is usually the consequence of motor system displacement or edema and improves within days under steroid medication. The oblique course of the precentral gyrus, from occipito-medial to fronto-lateral, should be taken into consideration during the cortical resection. The motor cortex again is localized by MCS, which allows definition of the anterior limit of resection (Fig. 19). If this is neglected, then extensive cortical resection close to the midline may result in paresis of the lower extremity due to injury of the medial, most occipital portions of the motor cortex.

For transcortical approaches, corticotomy is preferably placed in the postcentral gyrus and not in the superior or inferior parietal lobe. There is evidence that circumscribed lesions of the postcentral gyrus recover more rapidly or are compensated easier[16]. In contrast, lesions of the superior and inferior parietal gyrus, including area 5, may lead to astereognosia and ataxia

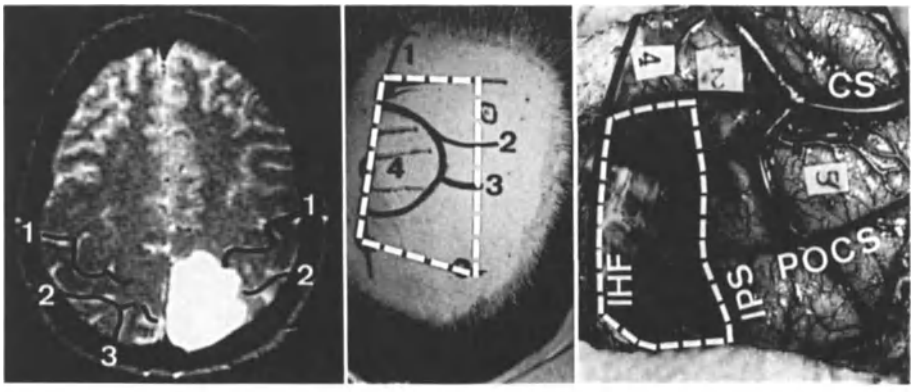


Fig. 19. Example of right-sided postcentral low-grade glioma. (a) Preoperative T2-weighted MR image showing topography relative to the central sulcus (*1*) and postcentral sulcus (*2*); *3* contralateral intraparietel sulcus. (b) The outline of craniotomy (white broken lines) in relation to the tumour (shaded area, *4*) and the midline (*1*), central sulcus (*2*) and postcentral sulcus (*3*) is marked on the skin preoperatively. (c) Intraoperative photograph after subpial tumour resection, guided by cortical mapping. *CS* central sulcus; *POCS* postcentral sulcus; *IPS* intraparietal sulcus; *IHF* interhemispheric fissure. Stimulation at *2* and *4* caused motor responses of the contralateral leg; stimulation at point *5* caused sensory symptoms in the contralateral arm. The resection is marked by the white broken lines

of limb movements, particularly hand movements, that are not easily compensated[16]. In any case, corticotomy should be avoided in the inferior parietal lobe of the dominant hemisphere (areas 39 and 40) due to ensuing neuropsychological deficits (sensory speech, calculating and reading disorders, sensory neglect syndromes). Dependent on tumour localization a number of trans-sulcal routes can be selected, e.g. through the postcentral or interparietal sulcus, the Sylvian fissure and its posterior ascending ramus or the interhemispheric fissure (Fig. 18).

7. Surgical Outcome

In fifty consecutive patients with intraoperative mapping of the sensorimotor cortex prior to lesion removal the result of surgery was carefully examined[30]. The follow-up examination was performed between 6 weeks and 3 months. No patient has died.

The main concern was the comparison of pre- and postoperative neurological deficits. Immediately after surgery in 12 patients a preoperative paresis increased or a new deficit occurred. However, this cleared completely during the postoperative course until the follow-up examination after 6–12 weeks. An example is a female patient with severe preoperative paresis of the leg and foot as well as a slight paresis of the arm who awoke with complete hemiplegia following surgery, persisting for several days, until it recovered to the prior status. In this patient, the precentral gyrus was clearly identified during surgery and consequently preserved. We assume that the trauma of the manipulation of the cortex or pyramidal tract during surgery may cause such transient disturbance. Preoperatively 29 patients (42%) had no neurological deficit (Table 4, Fig. 20) and this number increased until the follow-up examination after 6–12 weeks to 33 (50%). The number of patients exhibiting varying degrees of a paresis decreased from 21 (42%) to 17 (34%). A new, persisting slight hemiparesis occurred in only 2 (4%) patients, both afflicted with a large convexity menigioma in the vicinity of the pre- and postcentral gyrus. In both cases the separation of the tumour boundary from the underlying cortex and adjacent white matter was difficult and small vessels were probably injured.

A further assessment of motor deficits reveals as a general rule; that the chances for a complete recovery become the smaller, the more severe the initial paresis. On the other hand, exceptions are possible and in some patients remarkable improvement my be seen independent of the degree of preoperative paresis. Complete recovery was found in 5 out of 7 patients with slight paresis, but only in 1 out of 8 patients with severe paresis, although in this group 5 patients showed distinct improvement. Even some of the patients with preoperative complete plegia improved to a certain extent, although recovery was never complete (Fig. 20).

Table 4. *Pre- and Postoperative Neurological Findings* (n = 50)[a]

Neurological findings	Pre-operative		Post-operative	
	n	%	n	%
No deficit	21	42.0	25	50.0
Deficit	29	58.0	25	50.0
Dysphasia	1	2.0	0	0.0
Sensory deficit	6	12.0	7	14.0
Paresis:	21	42.0	17	34.0
arm/hand	4	8.0	2	4.0
leg/foot	7	14.0	5	10.0
face	2	4.0	1	2.0
Hemiparesis	8	16.0	9	18.0
Neuropsychological deficit	1	2.0	1	2.0

[a] From[30].

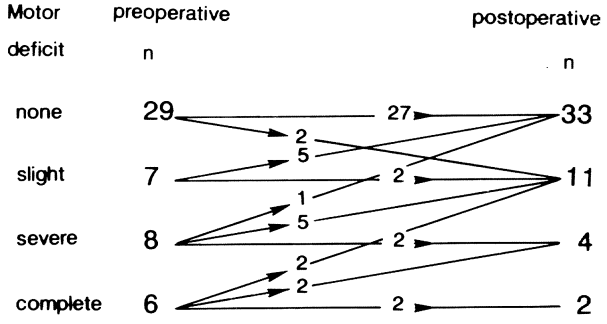


Fig. 20. Comparison of pre- and postoperative motor deficits (n = 50)[30]

The remarkable improvement of motor function witnessed in some cases has also been observed by other groups[43, 53]. In these cases only a relatively small, isolated cortical area was affected by the lesion, smaller than the corresponding cortical representation of this function[43]. This is especially true for the hand and face field, which are proportionately over represented in the cortex[16].

Hypaesthesia was present preoperatively in six patients and remained unchanged during the follow-up period. In one patient a new slight sensory deficit occurred due to an approach through the postcentral gyrus.

The current view is that recovery from a motor deficit is associated with individually different patterns of functional reorganisation. These patterns

certainly are dependent on the site of the lesion, whether cortical or deep, as well as from the lesion size. Although activation of a pre-existing uncrossed ipsilateral motor pathway from the undamaged hemisphere has been reported, the probably more important mechanism in cortical lesions is activation of other systems in the damaged hemisphere. Recruitment of additional (silent?) cortical areas, activation of the supplementary motor area and particularly a lateral spreading or extension of specific motor fields have been described[101, 102]. The latter may play an important role in slowly growing lesions. Finally, recovery may be explained by surviving parts of a motor mosaic or by recovery of fibers, disturbed functionally by pressure, edema etc.

Whatever the mechanism may be, recruitment of additional areas or pathways, recovery of disturbed neurons or fibers, lateral extension of function, compensation by areas with similar function etc., it is important that the motor system has a remarkable potential for functional reorganisation. Despite this capacity, our primary goal is to tailor surgery individually and to avoid additional deficits.

References

1. Ahmadi J, Jong SH, Teal SH, Tsai FY, Zee C, Segall HP (1982) Localization of intracranial lesions utilizing the coronal suture as a landmark on axial computed tomography. Surg Neurol 17: 209–212
2. Allison T (1987) Localization of sensori-motor cortex in neurosurgery by recording of somato-sensory evoked potentials. Yale J Biol Med 60: 143–150
3. Allison T, Mc Carthy G, Wood CC, Darcey TM, Spencer DD, Williamson PD (1989) Human cortical potentials evoked by stimulation of the median nerve. I. Cytoarchitectonic areas generating short-latency activity. J Neurophysiol 62: 694–710
4. Allison T, Mc Carthy G, Wood CC, Williamson PD, Spencer DD (1989) Human cortical potentials evoked by stimulation of the median nerve. II. Cytoarchitectonic areas generating long-latency activity. J Neurophysiol 62: 711–722
5. Apuzzo MLJ (1993) Brain surgery. Complication avoidance and management, vol 1. Churchill Livingstone, New York, pp 379–390
6. Barr LM (1972) The human nervous system. An anatomical viewpoint. Harper, pp 316–330
7. Beevor CE (1890) An experimental investigation into the arrangement of the excitable fibers in the internal capsule of the bonnet monkey. Phil Trans Roy Soc (London) 181 B: 49–88
8. Bennett AH (1885) Case of brachial monoplegia due to lesions of the internal capsule. Brain 8: 78–84
9. Berger MS, Kincaid J, Ojemann GA, Lettich BA (1989) Brain mapping techniques to maximize resection, safety and seizure control in children with brain tumors. Neurosurgery 25: 786–992

10. Berger MS, Wendy A, Ojemann GA (1990) Correlation of motor cortex mapping data with magnetic-resonance imaging. J Neurosurg 72: 383–387
11. Berger MS, Ojemann GA, Lettich E (1990) Neurophysiological monitoring during astrocytoma surgery. Neurosurg Clin North Am 1: 65–80
12. Berger MS, Ghation BS, Haglund MM, Dobbius J, Ojemann GA (1993) Low grade gliomas associated with intractable epilepsy: seizure outcome utilizing electrocorticography during tumor resection. J Neurosurg 79: 62–69
13. Black P, Ronner SF (1987) Cortical mapping for defining the limits of tumor resection. Neurosurg 20: 914–920
14. Brodal A (1969) Neurological anatomy – in relation to clinical medicine, 2nd ed. University Press, New York
15. Bucy PC (ed) (1944) The precentral motor cortex. University of Illinois Press, Urbana
16. Creutzfeld OD (1983) Cortex cerebri. Leistung, strukturelle und funktionelle Organisation der Hirnrinde. Springer, Berlin Heidelberg New York Tokyo
17. Crosby EC, Humphrey T, Lauer EW (1962) Correlative anatomy of the nervous system. McMillan, New York
18. Cunningham DJ (1892) Contribution to the surface anatomy of the cerebral hemispheres. Royal Irish Academy, Dublin
19. Curran EJ (1909) A new association fiber tract in the cerebrum: with remarks on the fiber tract dissection method of studying the brain. J Comp Neurol 19: 645–657
20. Cushing H (1909) A note upon the faradic stimulation of the precentral gyrus in conscious patients. Brain 32: 44–54
21. Denny-Brown D (1965) The cerebral control of movement. University Press, Liverpool
22. Ebeling U, Huber P, Reulen HJ (1986) Localization of the precentral gyrus in the CT and its clinical application. J Neurol 233: 73–76
23. Ebeling U, Rikli D, Huber P, Reulen HJ (1987) The coronal suture. A useful landmark in neurosurgery? Craniocerebral topography between bony landmarks on the skull and the brain. Acta Neurochir (Wien) 89: 130–134
24. Ebeling U, Reulen HJ (1989) Neurosurgical topography of the pyramidal tract. In: Klingler M, Brock M, Frowein RA (eds) Advances in neurosurgery, vol 17. Springer, Berlin Heidelberg New York Tokyo
25. Ebeling U, Steinmetz H, Huang Y, Khan T (1989) Topography and identification of the precentral sulcus in MR-imaging. AJNR 10: 937–942
26. Ebeling U, Schmid UD, Reulen HJ (1990) Tumor surgery within the central motor strip: surgical results with aid of electrical cortical motor cortex stimulation. Acta Neurochir (Wien) 101: 110–117
27. Ebeling U, Schmid UD, Ying Z (1991) Mapping bei Tumorpatienten in der Zentralregion. Schweiz Rundschau Med Prax 47: 1318–1323
28. Ebeling U, Reulen HJ (1992) Subcortical topography and proportions of the pyramidal tract. Acta Neurochir (Wien) 118: 164–171
29. Ebeling U, Seiler RW, Hasdemir MG (1992) Les astrocytomes différenciés (grade II OMS) de la région centrale : portée et limites de la chirurgie. Med Hyg 50: 2488–2493

30. Ebeling U, Schmid UD, Ying Z, Reulen HJ (1992) Safe surgery of lesions near the motor cortex using intraoperative mapping techniques. A report on 50 patients. Acta Neurochir (Wien) 119: 23–28
31. Ebeling U, Huber P (1992) Localization of central lesions by correlation of CT-findings and neurological deficits. Acta Neurochir (Wien) 119: 17–22
32. Ebeling U, Hasdemir MG, Barth A (1993) Stereotaktisch geleitete Mikrochirurgie zerebraler Prozesse. Schweiz Med Wschr 123: 1585–1590
33. Eberstaller O (1890) Das Stirnhirn. Ein Beitrag zur Oberfläche des Gehirnes. Urban und Schwarzenberg, Wien
34. Englander RN (1975) Location of the pyramidal tract in the internal capsule. Anatomic evidence. Neurology (NY) 25: 823–826
35. Firsching R, King N, Börner U, Sanker P (1992) Lesions of the sensorimotor region: somatosensory evoked potentials and ultrasound guided surgery. Acta Neurochir (Wien) 118: 87–90
36. Flechsig P (1881) Zur Anatomie und Entwicklungsgeschichte der Leitungsbahnen im Großhirn. Arch Anat Physiol: 12–75
37. Flechsig P (1887) Ueber Systemerkrankungen im Rückenmark. Arch Heilk 18: 101, 298 ff
38. Foerster O, Bumke O (1936) Handbuch der Neurologie, Bd 6. Springer, Berlin, pp 1–357
39. Freund HJ, Hummelsheim H (1984) Premotor cortex in man: evidence for innervation of proximal limb muscles. Exp Brain Res 53: 479–482
40. Freund HJ, Hummelsheim H (1985) Lesions of premotor cortex in man. Brain 108: 697–734
41. Freund HJ (1988) Abnormalities of motor behavior after cortical lesions in humans. In: Handbook of physiology – the nervous system, vol V, pp 763–810
42. Goldring S (1978) A method of surgical management of focal epilepsy, especially as it relates to children. J Neurosurg 49: 344–356
43. Goldring S, Gregorie E (1984) Surgical management of epilepsy using recordings to localize the seizure focus. J Neurosurg 60: 457–466
44. Gregorie S, Goldring S (1984) Localization of function in the excision of lesions from the sensorimotor region. J Neurosurg 61: 1047–1054
45. Hanaway J, Young RR (1977) Localization of the pyramidal tract in the internal capsule of man. J Neurol Sci 34: 63–70
46. Harky HL, Al-Mefty O, Haines DE, Smith RR (1989) The surgical anatomy of the sulci. Neurosurgery 24: 651–654
47. Hasdemir MG, Ebeling U (1993) Stereotactic guided puncture of cerebral abcesses. Acta Neurochir (Wien) 125: 58–63
48. Holmes G, Horrax G (1981) Disturbance of visual orientation. Br J Ophthalmol 2: 440–468, 506–516
49. Holmes G, Horrax G (1919) Disturbance of spatial orientation and visual attention with loss of stereoscopic vision. Arch Neurol Psychiatry 1: 385–407
50. Horsely V (1892) On the topographical relations of the cranium and the surface of the cerebrum. In: Cunningham CJ (ed) Contribution to the surface anatomy of the cerebral hemispheres. Academy House, Dublin, pp 306–355
51. Jane JA, Yashon D, De Myer D, Bucy PC (1967) The contribution of the precentral gyrus to the pyramidal tract in man. J Neurosurg 26: 244–248

52. Kido DK, LeMay M, Levanswon AW, Benson WE (1980) Computed tomographic localization of the precentral sulcus. Radiology 135: 373–377
53. King RB, Schell GR (1987) Cortical localization and monitoring during cerebral operations. J Neurosurg 67: 210–219
54. Klingler J, Gloor P (1960) The connections of the amygdala and of the anterior temporal cortex in the human brain. J Comp Neurol 115: 333–369
55. Kröenlein RV (1889) Zur craniocerebralen Topographie. Beiträge zur klinischen Chirurgie XXII: 364–370
56. Kwan HC, McKay WA, Murphy BT (1978) Spatial organization of the precentral cortex in awake primates, II. Motor outputs. J Neurophysiol 41: 1120–1121
57. Lang J (1981) Klinische Anatomie des Kopfes. Neurokranium, Orbita, kraniozervikaler Übergang. Springer, Berlin Heidelberg New York
58. Lang J, Belz J (1981) Form und Masse der Gyri und Sulci an der Facies superolateralis und Facies inferior hemispherii. J Hirnforsch 22: 517–533
59. Lang J (1985) Mikroanatomischer Kurs für junge Neurochirurgen. Anatomisches Institut, Universität Würzburg
60. Lassek AM (1954) The pyramidal tract. Its status in medicine. Thomas, Springfield
61. Le Blanc FE, Rasmussen T (1974) Cerebral seizures and brain tumor. In: Vinken PM, Bruyn GW (eds) Handbook of neurology, vol 15. North Holland, Amsterdam, pp 295–301
62. Le Roux PD, Berger MS, Haglund MM, Pilcher WH, Ojemann GA (1991) Resection of intrinsic tumors from nondominant face motor cortex using stimulation mapping: report of two cases. Surg Neurol 36: 44–48
63. Ludwig E, Klingler J (1956) Atlas cerebri humani. Karger, Basel
64. Lüders H, Lesser RP, Hahn J (1983) Cortical somatosensory evoked potentials in response to hand stimulation. J Neurosurg 58: 885–894
65. Luria AR (1966) Higher cortical functions in man. Basic, New York
66. Matsui T, Hirano A (1978) An atlas of the human brain for computerized tomography. Fischer, Stuttgart, Igaku-Shoin, Tokyo
67. Missir O, Dutheil-Desclercs C, Meder JC, Musolino A, Fredy D (1989) Aspect du sillon central en IRM. Central sulcus patterns at MRI. J Neuroradiol 16: 133–144
68. von Monakow C (1915) Zur Anatomie und Physiologie der Pyramidenbahn und der Armregion, nebst Bemerkungen über die sekundäre Degeneration des Fasciculus centroparietalis. Neurol Zbl 34: 217–224
69. Nathan PW, Smith MC (1955) Long descending tract in man. 1st review of present knowledge. Brain 78: 248–303
70. Nathan PW, Smith MC, Deacon P (1990) The corticospinal tracts in man. Course and location of fibers at different segmental levels. Brain 113: 303–324
71. Nuwer MR (1991) Localization of motor cortex with median nerve somatosensory evoked potentials. In: Schramm J, Moller AR (eds) Intraoperative neurophysiologic monitoring in neurosurgery. Springer, Berlin Heidelberg New York Tokyo, pp 63–71
72. Obana WG, Laxer KD, Cogan PH, Walker JA, Davis RL, Barbaro NM (1992) Resection of dominant opercular gliosis in refractory partial epilepsy. Report of two cases. J Neurosurg. 77: 632–639

73. Ojemann GA (1978) Individual variability in cortical localization of language. J Neurosurg 50: 164–169
74. Ojemann GA (1979) Organization for language from perspective of electrical stimulation mapping. Behav Brain Sci 6: 189–220
75. Ojemann GA, Ojemann J, Lettich E, Berger M (1989) Cortical language localization in left, dominant hemisphere. J Neurosurg 71: 316–326
76. Ono M, Kubik S, Abernathy CD (1990) Atlas of the cerebral sulci. Thieme, Stuttgart, pp 36–62
77. Passet J (1882) Über einige Unterschiede des Großhirns nach dem Geschlecht. Archiv für Antropologie (Braunschweig), Bd 14, pp 89–141
78. Penfield W, Boldrey E (1937) Somatic and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain 60: 389–443
79. Penfield W, Welch K (1949) The supplementary motor area in the cerebral cortex of man. Trans Am Neurol Assoc 74: 179–184
80. Penfield W, Rasmussen T (1950) The cerebral cortex of man. McMillan, New York
81. Penfield W (1954) Mechanisms of voluntary movements. Brain 77: 1–17
82. Pfeiffer RA (1934) Myelogenetisch-anatomische Untersuchungen über den zentralen Abschnitt der Taststrahlung, Pyramidenbahn, der Hirnnerven und zusätzlicher motorischer Bahnen. Nov Acta Leop Carol 1: 341–473
83. Pia HW (1986) Microsurgery of glioms. Acta Neurochir 80: 1–11
84. Quensel R (1910) Über den Stabkranz des menschlichen Stirnhirnes. Folia Neurobiol 4: 319–334
85. Ross ED (1980) Localization of the pyramidal tract in the internal capsule by whole brain dissection. Neurology 30: 59–64
86. Rostomily RC, Berger MS, Ojemann GA, Lettich E (1991) Postoperative deficits and functional recovery following removal of tumors involving the dominant hemisphere supplementary motor area. J Neurosurg 75: 62–68
87. Rowland LP, Mettler FA (1948) Relation between the coronal suture and the cerebrum. J Comp Neurol 89: 21–40
88. Schmid U, Sturzenegger M, Ludin HP, Seiler RW, Reulen HJ (1988) Orthodromic (intra/extracranial) neurography of monitor facial nerve function intraoperatively. Technical note. Neurosurgery 22: 945–950
89. Schmid U, Ebeling U, Reulen HJ (1989) Electrophysiological localization of the human sensori-motor cortex. Neurosurgical forum. J Neurosurg 70: 817–818
90. Seeger W (1978) Atlas of topographical anatomy of the brain and the surrounding structures for neurosurgeons, neuroradiologists and neuropathologists. Springer, Wien New York
91. Seeger W (1980) Microsurgery of the brain. Anatomical and technical principles, vol 1. Springer, Wien New York
92. Stöhr M, Dichgans S, Diener HC, Büttner UW (1989) Evozierte Potentiale SEP, VEP, AEP, EKP, MEP, 2nd ed. Springer, Berlin Heidelberg New York Tokyo
93. Suzuki A, Yasmi N (1992) Intraoperative localization of the central sulcus by cortical somato-sensory evoked potentials in brain tumor. Case report. J Neurosurg 76: 867–870

94. Talairach J, Bancaud J(1966) The supplementary motor area in man. Int J Neurol 5: 330–347
95. Talairach J, Szikla G (1967) Atlas of stereotactic anatomy of the telencephalon. Masson and Cie, Paris
96. Taylor EH, Haughton WS (1900) Some recent researches on the topography and convolutions and fissures of the brain. Transactions of the Royal Academy of Medicine in Ireland 18: 511–522
97. Taylor E, Haughton VM, Syverston A, Ho K (1980) Taylor Haughton line revisited. Am J Neuroradiol (Baltimore) 1: 55–56
98. Tredici G, Pizzini G, Bogliun G, Tagliabue M (1982) The site of motor corticospinal fibers in the internal capsule of man. A computerised tomographic study of restricted lesions. J Anat 134: 199–208
99. Uematsu S, Lesser RP, Gordon B (1992) Localization of sensorimotor cortex: the influence of Sherington and Cushing on the modern concept. Neurosurgery 30: 904–913
100. Uematsu S, Lesser RP, Fisher RS, Gordon B, Hara K, Krauss GL, Vining EP, Webber RW (1992) Motor and sensor cortex in humans. Topography studied with chronic subdural stimulation. Neurosurgery 31: 59–72
101. Weiller C, Choller F, Friston KJ, Wise RJS, Frackowiak RSJ (1992) Functional reorganization of the brain in recovery from striatocapsular infarction in man. Ann Neurol 31: 463–472
102. Weiller C, Ramsay SC, Wise RJS, Friston KJ, Frachowiak RJS (1993) Individual patterns on functional reorganization in the human cerebral after capsular infarction. Ann Neurol 33: 181–189
103. Wood CC, Spencer DD, Allison T, McCarthy G, Williams PD, Groff WR (1988) Localization of human sensori-motor cortex during surgery by cortical surface recordings of somatosensory evoked potentials. J Neurosurg 68: 99–111
104. Woolsey CN, Erikson TC, Gibson WE (1979) Localization in somatic sensory and motor areas of human cerebral cortex as determined by direct recording of evoked potentials and electrical stimulation. J Neurosurg 51: 476–506
105. Yasargil MG, Cravens GC, Roth P (1988) Surgical approaches to "inaccessible" brain tumors. Clin Neurosurg 34: 42–110
106. Yasargil MG, von Ammon K, Cavazos E, Doczi T, Reeves JD, Roth P (1992) Tumors of the limbic and paralimbic systems. Acta Neurochir (Wien) 118: 40–52

B. Technical Standards

The Surgery of Cavernomas Both Supra-Tentorial and Infra-Tentorial

J. P. HOUTTEVILLE

Department of Neurosurgery, C.H.U. Caen (France)

With 23 Figures

Contents

History

Intracranial cavernous vascular malformations are variously known as cavernous angiomas, cavernous hemangiomas or, more simply, cavernomas.

The first description of an intracranial cavernoma was given by Virchow in 1863. For over a century, it was considered to be an extremely rare malformation, usually found at autopsy, and exceptionally diagnosed during life. This was reflected in a 1976 review of the literature by Voigt and Yaşargil. Reporting a case of their own, the authors were able to collect and review a total of 164 well-documented cases, published since Virchow's initial description, and for which "a clear description of the histologic appearance of the lesion was available" (Voigt and Yaşargil, 1976). Most were necropsy findings: only 24 had been operated on, with the remaining 140 being diagnosed at autopsy.

In their retrospective study, Voigt and Yaşargil stressed the difficulty of establishing a diagnosis of brain cavernoma during life. Their patient had had four successive cerebral angiograms, following repeated subarachnoid haemorrhage. Findings were all negative. A temporal lesion was eventually demonstrated (and a diagnosis of cavernoma later confirmed by histology)

Table 1. *50 Cavernomas Operated on the Last 20 Years (Personal Series)*

1973 → 1979	1980 → 1987	1988 → 1993
(Isotopes)	(CT scan)	(MRI)
5 cases	16 cases	29 cases

The number of diagnosed cases increased in parallel with the progress of neuroimaging techniques.

after a ^{99}mTc Radionuclide scan was performed. This technique was the first to enable direct visualisation of angiographically occult vascular malformations, among which are cavernomas.

By the end of the 70's and early 80's, with the growing use of computed tomography (CT) scanning, cavernomas were becoming increasingly recognized. Herter *et al.* (1988) were able to find as many cases published over a period of 12 years (166) as Voigt and Yaşargil in the previous 113 years (164).

The CT scan was in turn superseded when high-field MRI allowed the detection of the smallest lesions and demonstrated a typical if not pathognomonic appearance for cavernomas (Rigamonti *et al.* 1987). As illustrated in Table 1, progress in the detection and diagnosis of cavernomas closely parallelled technical progress in neuroradiological imaging.

Cavernoma has thus become a focus of attention in recent years. Several authors became concerned with the natural history of the disorder, generally thought to be benign, and demonstrated that, contrary to previous belief, a cavernoma is not an inert lesion but one which may change with time, with consequent functional and even vital risks to the patient. Such risks are essentially related to haemorrhage (Simard *et al.* 1986) and anatomical localisation (Zimmerman *et al.* 1991). The epileptic potential of cavernomas has also been extensively studied.

The surgical history of cavernomas began in 1890 with Bremer and Carson, who removed a rolandic lesion in a patient with seizures and noted that the operation was nonhaemorrhagic. In 1934, David *et al.* successfully resected a calcified cavernoma of the floor of the fourth ventricle, thus paving the way for the surgery of brainstem cavernomas.

General Features

Incidence – Age – Sex Ratio

From autopsy and MRI series, the reported incidence for intracranial cavernomas varies between 0.39 and 0.53%. In a prospective autopsy series of 4,069 brains, Sarwar and Mc Cormick (1979) identified 16 cavernomas

(incidence: 0.40%). Otten *et al.* (1989) found 131 specimens with histologically verified cavernomas in a series of 24,535 autopsies (incidence: 0.53%). In 118 cases the cavernoma was single, while in 13 cases there were multiple lesions (from 2 to 6). Robinson *et al.* (1991) observed a case incidence of 0.47% in a series of 14,035 MR images performed at the Cleveland Clinic Foundation between 1984 and 1989. From 8,131 MR images done at the North Carolina Baptist Hospital in the period 1986–1989, Del Curling *et al.* (1991) observed a case incidence of 0.39%.

Cavernomas occur at all ages. 25% of cases are observed in children (Herter *et al.* 1988). The sex-distribution is equal (Del Curling *et al.* 1991). However, Giombini and Morello (1978) found a male prevalence of 62.7% in a series of 51 cases. In the experience of Robinson *et al.* (1991), the incidence of haemorrhage was significantly higher in female patients ($p = 0.05$). Several reports mention a higher risk of haemorrhage during pregnancy (Yamasaki *et al.* 1986, Ondra *et al.* 1988, Robinson *et al.* 1991).

Nomenclature

Classification

Of all the classifications of intracranial malformations that have been put forward, we prefer that of Russel and Rubinstein (1989) who categorised cavernomas as vascular hamartomas, together with arteriovenous malformations (AVM), venous malformations, and capillary telangiectases.

Before we detail the pathology of cavernomas, let us mention briefly the main features of the other three types: AVMs are characterised by a mixture of arteries and veins – some of which are arterialised – without an intervening capillary bed. Venous malformations, also called "venous angiomas", consist of anomalous, tortuous or so-called "caput medusae" medullary veins converging towards a large transparenchymal draining vein. Capillary telangiectases are made up of abnormal networks of capillaries, separated by normal brain tissue.

Cavernoma and "Cryptic" Vascular Malformations

In the past cavernomas were sometimes referred to as "cryptic" vascular malformations. Crawford and Russel (1956) suggested using the term for "those small vascular hamartomas which are clinically silent and measure less than 2–3 cm in maximum size", adding: "such malformations may cause intracerebral haemorrhage". The term cryptic, meaning "hidden", should no longer be in use since all vascular hamartomas are now visualised on MRI.

Cavernoma and Angiographically Occult Intracranial Vascular Malformations (AOIVMs)

Two groups of vascular hamartomas were distinguished on the basis of cerebral angiographic findings: those which are opacified by contrast medium, namely typical AVMs and most venous malformations and those which are not, called AOIVMs. The latter include thrombosed AVMs, cavernomas, telangiectases and some venous malformations.

Distribution

In a series of 262 AOIVMs reviewed by Lobato *et al.* (1988), thrombosed AVMs accounted for 43.8%, cavernomas represented 31.2%, while venous angiomas, telangiectases and "unclassified angiomas" accounted for 9.9%, 3.8% and 11.1% respectively.

In their recent retrospective review, Robinson *et al.* (1993b) have re-examined 34 pathological specimens of their own; according to strict histopathological criteria, cavernoma was the most frequently observed lesion (21) while there were only 3 AVMs, 3 venous malformations, 2 capillary malformations and 5 mixed lesions.

Previously, in the experience of Tung *et al.* (1990), 4 of 7 cases, originally regarded as AVMs were reclassified as cavernomas upon further histological study.

Anatomopathophysiology

Negative angiographic findings should not be equated with a complete absence of flow through the lesion.

Cavernomas are angiographically occult for reasons pertaining to their anatomy and haemodynamics: their feeding arteries are too small to visualise at angiography (Brühlmann *et al.* 1985), their walls are devoid of abnormal vessels and the flow through the vascular spaces is low (Little *et al.* 1990).

The persistence of an intracavernomatous flow was demonstrated by using prolonged contrast infusion (Numagushi *et al.* 1979) or by carrying out a second injection series a few minutes after the first one (Huang *et al.* 1984). Under such conditions a capillary blush may appear, representing accumulation – or pooling – of contrast into the vascular spaces of the cavernoma.

So-called *thrombosed AVMs* or *angiographically occult AVMs* in fact represent two distinct types of malformations, depending on the degree of thrombosis (Ebeling *et al.* 1988, Ogilvy *et al.* 1988).

Complete thrombosis may have occurred, usually following repeated haemorrhage. This type is most commonly found in patients who present with epilepsy. In Wharen's series (1982) all but one of seven patients with intractable focal seizures had a completely thrombosed AVM.

Partially thrombosed AVMs still contain abnormal vessels, as may be demonstrated by histological examination. The fact that they go undetected at angiography reflects both the slow flow through such lesions, and the small calibre of their vessels (Ogilvy *et al.* 1988). Partially thrombosed AVMs carry a higher risk of bleeding than completely thrombosed ones.

Finally, partially thrombosed AVMs do not differ greatly from cavernomas in their pathophysiological, clinical and radiological presentation. Distinction between the two therefore seems "of little practical value" to Lobato *et al.* (1988) and is considered "a futile exercise" by Rapacki *et al.* (1990).

An AVM may also be angiographically occult if compressed by a large haematoma. This point was made by Wakai *et al.* (1985) who published 9 such cases, in which a conglomerate of abnormal vessels was found within or adjacent to the haematoma. Histologically there were 8 AVMs and 1 cavernoma.

Venous angiomas should be considered apart. Most authors now regard them as mere venous abnormalities, which are best left alone (Ogilvy *et al.* 1988 b, Rigamonti *et al.* 1988 a). On the other hand, Lobato *et al.* (1988) reported cases of "venous angiomas" which, although not visible at angiography, had caused haemorrhage. In fact these malformations lacked the typical "caput medusae" angiographic appearance and were diagnosed as histological findings from the wall of a cerebral haematoma. It is reasonable to believe with Ogilvy that the structure examined represented the venous component of a true AVM whose arterial component had been obliterated by the haematoma.

*Pathology**

Macroscopic Appearance

Cavernomas vary greatly in size, from 2–3 mm to 2–3 cm in diameter in the case of large, symptomatic lesions. Yet larger forms have been reported (Fig. 16), usually in children or in association with lateral ventricle locations (Ramina *et al.* 1980, Khosla *et al.* 1984, Chadduck *et al.* 1985). In the case of multiple cavernomas, each may be different in size.

Macroscopically, cavernoma has often been likened to a mulberry, dark-red in colour, with a lobulated surface; calcifications and small cysts are commonly seen. The lesion is clearly delineated from the surrounding brain, which usually appears to be stained yellow or brown by old haemorrhage.

Small supplying arteries are not visible to the naked eye and should be searched for with the aid of the operating microscope. In some instances,

---

* With the collaboration of F. Chapon, Neuropathological Department CHU Caen, France.

veins may be found in the vicinity of the cavernoma (cf. section on associated forms).

When sectioned, the gross appearance is comparable to a honeycomb.

Microscopic Appearance

Microscopic descriptions should include the surrounding brain tissue as well as the malformations itself.

Cavernoma

The histological features of cavernoma are usually characteristic (Fig. 1A, B). The lesion is made up of vascular spaces of varying size, lined with a single layer of endothelial cells, and filled with red blood cells. Vascular spaces are separated by collagenous walls of varying thickness; these may indeed be very thin, with a "lace-work" appearance, or very thick in places. Thickening of the wall is due to frequently occurring thrombosis and may result in partial or complete obliteration of the vascular spaces (Fig. 1B). Calcification is often present, especially in the thicker walls. True ossification may be observed in some cases. Unlike capillary telangiectases, there is no intervening normal brain tissue in the cavernomatous area. It must be noted, however, that in some irregularly shaped cavernomas, expansions penetrate the surrounding brain, giving histological sections a confusing appearance, as if normal brain tissue were actually entrapped within the cavernoma itself (Fig. 1A).

The typical pattern of the lesion may be modified in several ways. Elastic fibres may be observed upon microscopic examination of the walls, mostly on the periphery of the lesion (Russel and Rubinstein 1989). In some cases cavernomatous areas are found to coexist with arterioles (Fig. 1C) or veins, suggesting an association with a small AVM. Such an association represents a "mixed or transitional malformation" (Rapacki *et al.* 1990). Scott (1990) insisted on the frequent occurrence of "complex histological appearance with only portions of the lesion containing typical back-to-back cavernous vessels", in a series observed in children. Finally, the typical cavernomatous structure may be almost completely obscured by haemorrhage.

Cavernomas are classically devoid of capsule (Russel and Rubinstein 1989). Some disagree with this concept (Steiger *et al.* 1987, Pozzati *et al.* 1989). In their series, Steiger *et al.* demonstrated that encapsulation is minimal in ruptured cavernomas but prominent in cystic lesions. In the particular case of a giant cystic lesion, the membrane, or capsule, was shown to possess a structure similar to the membranes of chronic subdural haematomas. This feature has been reported by others (Murukami 1990, Scott 1992).

The process of cyst formation itself is controversial. Steiger *et al.* hold the opinion that its source may be an internal haemorrhage. Organisation of a thick capsule is supposed to cause water to be attracted into the cyst by an osmotic effect, similar to that observed in chronic subural haematomas, resulting in gradual enlargement of the cyst. Lechevalier (1989) on the other hand, having observed large cysts in the absence of a thick capsule, believes them to be large cavities containing lysed red blood cells. Finally, according to Ramina *et al.* (1980) and Khosla *et al.* (1984) who observed giant cysts in infants, the early occurrence of these malformations suggests

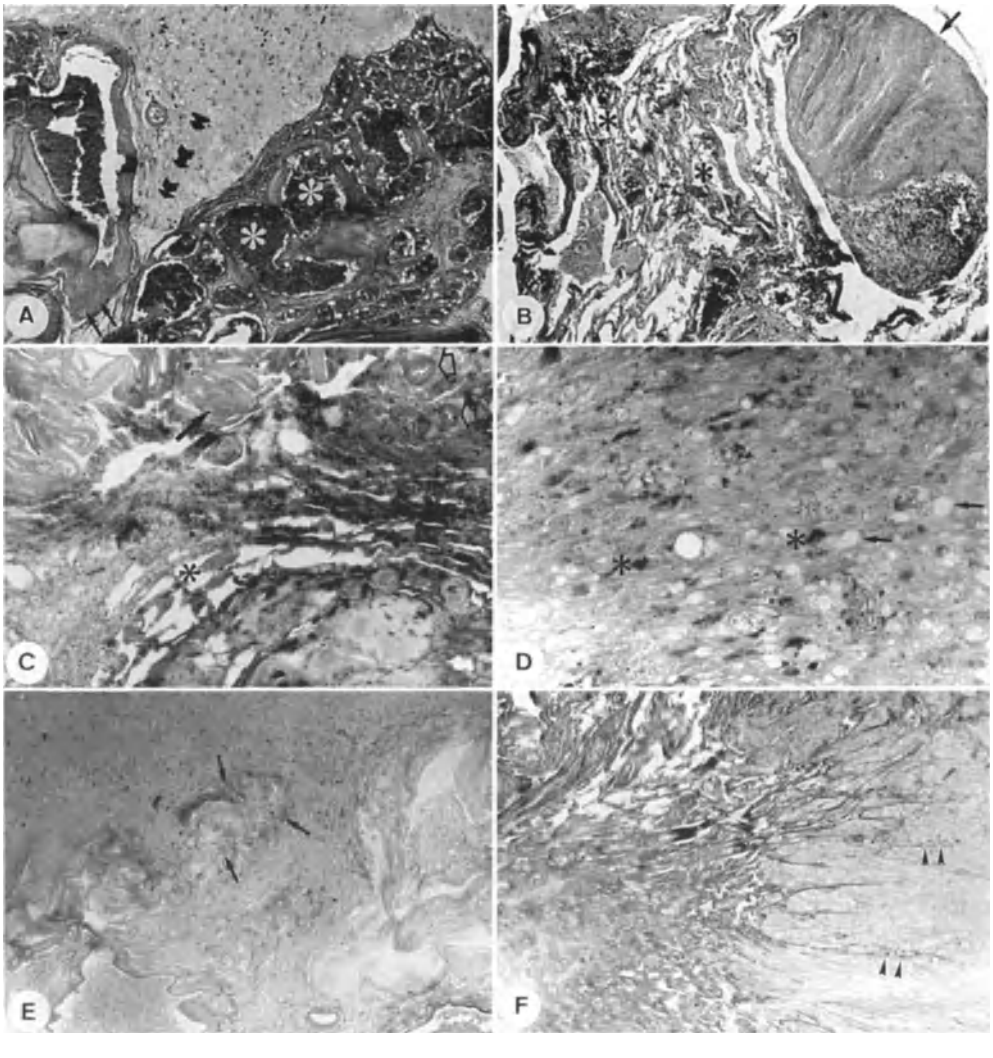


Fig. 1

they may represent complex lesions, associating cavernomatous and cystic components from the onset. In fact cyst formation in cavernomas is probably controlled by mechanisms which vary from case to case. In addition to congenital cysts, the origin of which remains difficult to prove, acquired cysts also exist, as was demonstrated by Pozzati *et al.* (1989). From serial CT scans, such cysts were shown to develop in a matter of weeks or days.

From a surgical viewpoint, the existence of a capsule is an essential factor: by affording clearly defined limits, it makes complete removal possible, even in the case of large lesions, and facilitates surgery: the capsule is seized with forceps and the lesion is gently dissected from the adjacent brain tissue.

Surrounding Brain Tissue

The cavernoma is surrounded by a gliotic rim of varying thickness, in which various features may be observed: necrotic or atrophic areas, hemosiderin (Fig. 1D), calcium and iron deposits. These could play a significant role in the pathogenesis of seizures. Microsatellite malformations, such as small cavernomas, foci of telangiectases, or dysmorphic vessels may also be present (Fig. 1E). In some cases, neuropathological findings include collagen fibres arising from the core of the cavernoma (Fig. 1F), areas of densely proliferating granulation tissue, and partially re-endothelialised haemorrhage, suggesting a possible mechanism for cavernomatous growth (Scott *et al.* 1992).

Fig. 1. Neuropathological features of intracranial cavernomas (personal cases). (A) Case 12. Typical aspect: several thin-walled cavities (white asterisks) containing red blood cells. Some walls are thicker (double black arrows). Brain parenchyma appears to be entrapped between two cavernomatous expansions (large black arrows). Masson Trichrome × 50. (B) Case 9. Loaf-shaped masses representing old, organized thrombosis, with connective strips (arrow) and "lace-work" aspects (black asterisk). Masson Trichrome × 80. (C) Case 36. Mixed complex malformation with lace-work appearance (asterisks), connective loaf-shaped masses (arrow) and small arteries (open arrows). Masson Trichrome × 120. (D) Case 12. Surrounding brain. Haemosiderin deposits (asterisks) and axonal swelling (arrows) Hematein eosin × 120. (E) Case 12. Satellite malformation (atypical hamartoma). Hyalin, thick-walled abnormal vessel in brain tissue surrounding a cavernoma. Masson Trichrome × 30. (F) Case 36. Connective extensions of the lesion penetrating the surrounding brain (arrow heads). Masson Trichrome × 80

*Neuro-Imaging of Cavernomas***

Plain Skull X-Rays

Calcification may be seen on skull X-rays in about 10% of cases, typically as small calcified clusters, but more extensive calcified zones may also be observed (Fig. 2).

Angiography

As previously stated, although a capillary blush may exceptionally be observed, angiographic findings are largely negative (Simard *et al.* 1986, Rigamonti *et al.* 1988, Rapacki *et al.* 1990). In large lesions, an avascular zone may be visualized, sometimes in association with arterial displacement (Numaguchi *et al.* 1977). Finally angiography is most informative in its venous phase, where a venous angioma or a prominent vein may be disclosed near the lesion (see section on "associated forms").

CT-Scan

Although less sensitive than MRI the CT scan has greatly contributed to the detection of cavernomas during life (Savoiardo *et al.* 1983, Ahmadi *et al.* 1985, Simard *et al.* 1986, Sigal *et al.* 1989). Haemorrhage and calcification appear as heterogeneous hyperdense nodules, varying in size, on precontrast scan, with inconstant enhancement after contrast infusion. Typically there is little or no mass effect on the adjacent brain. This feature distinguishes cavernomas from other calcified tumours such as oligodendrogliomas, which in addition usually demonstrate contrast enhancement. If present the cystic part of a cavernoma appears on CT as an isodense or hypodense area of varying size (Fig. 3). The capsule may be visible only after contrast infusion (Steiger *et al.* 1987). In some cases, especially where extensive haemorrhage is present the central lesion may be surrounded by a hypodense rim, due to oedema. Mass effect is frequently observed in such cases.

The typical appearances of a cavernoma may be obscured by extensive haemorrhage. If such a patient is operated on, the surgeon should carefully and thoroughly inspect the operative cavity in search of a cavernoma which can then be removed, if present. If conservative management is considered, surveillance by serial CT scans, or better, MRI studies, should be carried out: the cavernoma which caused the haemorrhage might be disclosed, in which case it should be resected to prevent further haemorrhage (Giombini and Morello 1978, Mazza *et al.* 1989).

** With the collaboration of H. Huet, Neuroradiological Department CHU Caen, France.

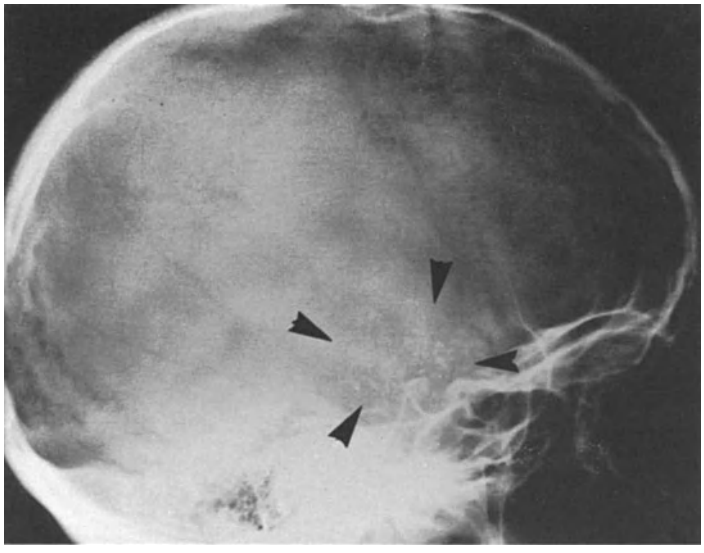


Fig. 2. Case 2. Large, heavily calcified cavernoma of the temporal lobe ("hemangioma calcifians" of Penfield and Ward)

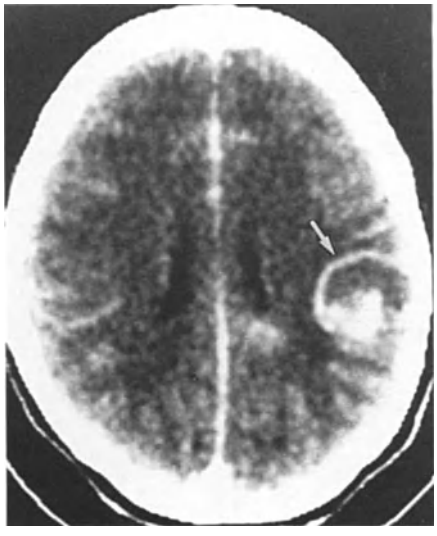


Fig. 3. Case 25. Cystic cavernoma. Postconstrast CT scan: heterogeneous lesion with spontaneously hyperdense area (cavernoma) and isodense area (cyst). Note the thick capsule

It must finally be noted that a cavernoma has been shown to be an active lesion from enlargement and other modifications on serial CT scans well before the advent of MRI (Pozzati *et al.* 1989).

MRI

Since 1985, many authors have emphasized the outstanding value of MR imaging in the positive diagnosis (Fig. 4), operative indications and follow-up of cavernomas.

Typical Appearance (New *et al.* 1986, Rigamonti *et al.* 1987)

On T2-weighted sequences larger lesions appear as a central area of mixed signal intensity (SI), surrounded by a rim of decreased signal intensity corresponding to hemosiderin deposits. Mass effect is absent or only moderate in proportion to the size of the lesion (Fig. 5).

Smaller lesions appear as punctate areas of decreased signal intensity on T2-weighted images (Fig. 7D, E).

Rigamonti *et al.* (1987) compared the sensitivity of CT and MRI in the detection of cavernomas: in 10 patients CT findings were positive in only 7, showing evidence of 14 lesions, while MRI was positive in all 10 cases, demonstrating 27 lesions (using T2-weighted sequences; only 24 were revealed on less sensitive T1-weighted image). The authors insisted that only

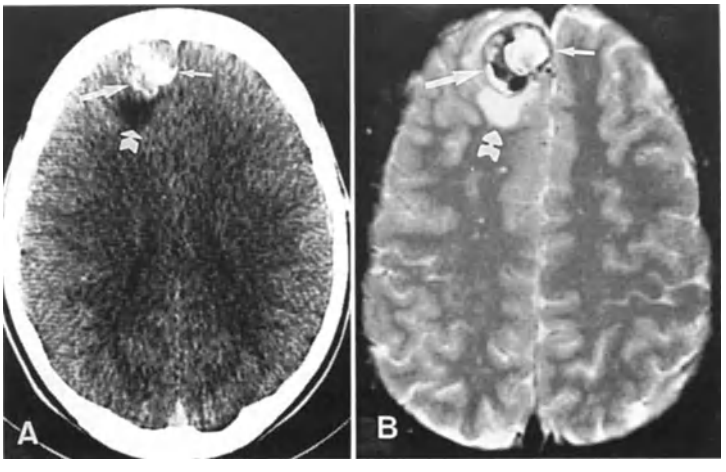


Fig. 4. (A) Case 37. Comparison between CT scan (A) and axial T2-weighted MRI (B) appearances of a frontal cavernoma. Large arrow: lesion itself. Small arrow: intracavernomatous haemorrhage, surrounded by a rim of low signal intensity (haemo-siderin). Thick arrow: surrounding oedema

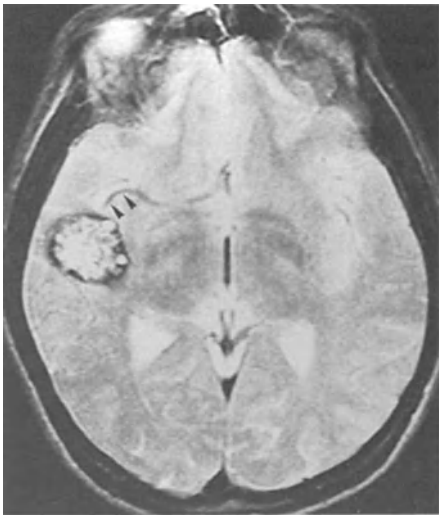


Fig. 5. Case 23. Typical appearance of a temporal cavernoma on axial T2-weighted MRI: central area of mixed signal intensity, surrounded by a rim of low signal intensity. Note the close proximity of the middle cerebral artery (arrowhead), a branch of which was revealed during surgery as being closely related to the lesion

high-field MRI (high-field strength: 1.5 Tesla) should be used in the investigation of cavernomas. They mention the case of a patient in whom 2 lesions had gone undetected at 0.35 T and were later demonstrated using high-field MRI (1.5 T).

Operative Indications

MRI is not only useful in the diagnosis and follow-up of cavernomas, it has also become invaluable in assessing the feasibility of surgery. It allows selection of the most suitable approach, according to precise localisation within various brain structures. This aspect will be detailed in the relevant sections.

Follow-up

Sigal *et al.* (1990) reported a series of 20 patients with 27 lesions followed over a mean period of 18 months. Obvious MRI changes were evidenced in 8 cases, with 4 cases of regression and 4 cases of rebleeding; three new independent lesions were disclosed. Scott (1990) observed very low signals on follow-up MR images of a patient who had undergone partial resection of a brainstem cavernoma 7 years previously; this finding is suggestive of an involutional process or "burning out" of the lesion, initially thought to be

static, and should be confirmed by larger series. In general, further MRI prospective studies are required for better understanding of the natural history of cavernomas.

Cavernoma, a Dynamic Lesion

Modern neuroimaging not only allows the detection of cavernomas during life, but has also greatly contributed to reveal that in the course of time many of these malformations undergo morphological changes, which are responsible for the emergence of neurological symptoms. Clinical signs vary in nature according to the location of the lesion, and in severity as a function of the underlying mechanisms. Haemorrhage is prominent among such mechanisms, which also include extensive calcification, pericavernomatous brain atrophy, enlargement of the cavernomatous matrix, and additional lesions.

Haemorrhage

The main contributory factor to cavernous enlargement is haemorrhage, which also represents a major risk in the course of the disorder. Haemorrhage may occur within the cavernoma, or outside, or both.

Intracavernomatous Haemorrhage (Fig. 15, Fig. 21)

According to Steiger *et al.* (1989), intracavernomatous haemorrhage is caused by wall rupture between adjacent vascular spaces, leading to overall enlargment of the cavernoma. As mentioned earlier, this type of haemorrhage can progress to cyst formation, with pseudotumoural symptoms developing in a matter of weeks (Belloti *et al.* 1985, Nakasu *et al.* 1991) and occasionally days, as reported by Pozzati *et al.* (1989).

Haemorrhage into a cavernoma may result in partial or complete destruction of the malformation, making histological identification difficult.

Extracavernomatous Haemorrhage (Figs. 6 and 14)

Rupture of a peripheral cavity causes extracavernomatous haemorrhage into the adjacent parenchyma or mixed haemorrhage, both extra and intracavernomatous.

This type gives rise to varying clinical symptoms. The haemorrhage generally tends to be self-limiting, since cavernomas are slow-flow, low-pressure malformations (Little *et al.* 1990). The onset is usually less sudden than in the case of a ruptured arteriovenous malformation, with more benign short term consequences. The course is often subacute, then remittent be-

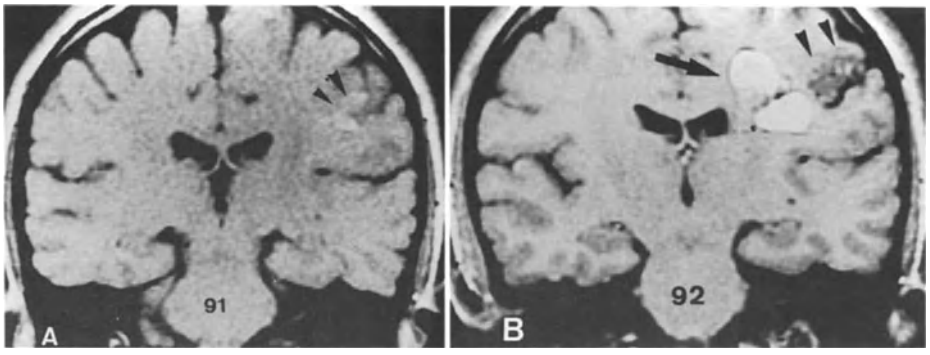


Fig. 6. Illustration of the dynamic character of a cavernoma. (A) Coronal T1-weighted MR image of a left rolandic cavernoma (arrowheads) obtained in 1991 in a 16-year-old patient presenting with right jacksonian seizures. (B) Coronal T1-weighted MR image: same patient one year later, who by then had developed right hemiparesis and dysphasia. A large, recent extra cavernomatous haemorrhage may be seen (large arrow) (by courtesy of Dr. Hôr, Hôspital du Val de Grâce, Paris)

cause of spontaneous resorption of the haemorrhage. However the risk of rebleeding remains significant, with potentially more dramatic clinical expression. As was emphasized by Tung *et al.* "each successive haemorrhage tends to occur at shorter time intervals and each haemorrhage tends to be associated with an increased incidence of permanent neurological deficit". A demonstration of the vital risk associated with haemorrhage originating from a cavernoma was given by Simard *et al.* (1986): in 40 patients with haemorrhagic forms of the disorder, observed since 1960, 11 had been diagnosed at autopsy. Crawford and Russel (1956), Krayenbühl and Sieberman (1965), Mc Cormick and Nofzinger (1966), Giombini and Morello (1978), Becker *et al.* (1979) also reported fatal cases of intracerebral haemorrhage caused by cavernomas. The consequences of an initial or repeated haemorrhage obviously depend on its anatomical localisation, with more serious consequences being associated with eloquent or life-maintaining areas, such as the brainstem. Repeated, small haemorrhage can also produce severe clinical pictures or even cause death, as in the case of a diencephalic cavernoma reported by Mizutani *et al.* (1981).

Calcification

Long before the era of CT and MRI, calcified areas had been shown to enlarge on serial skull X-rays (Savoiardo *et al.* 1983). The increase in size is typically moderate (Fig. 7A, B) but may be considerable in some cases (up to several centimeters in diameter), making surgery increasingly difficult (Galzio *et al.* 1980).

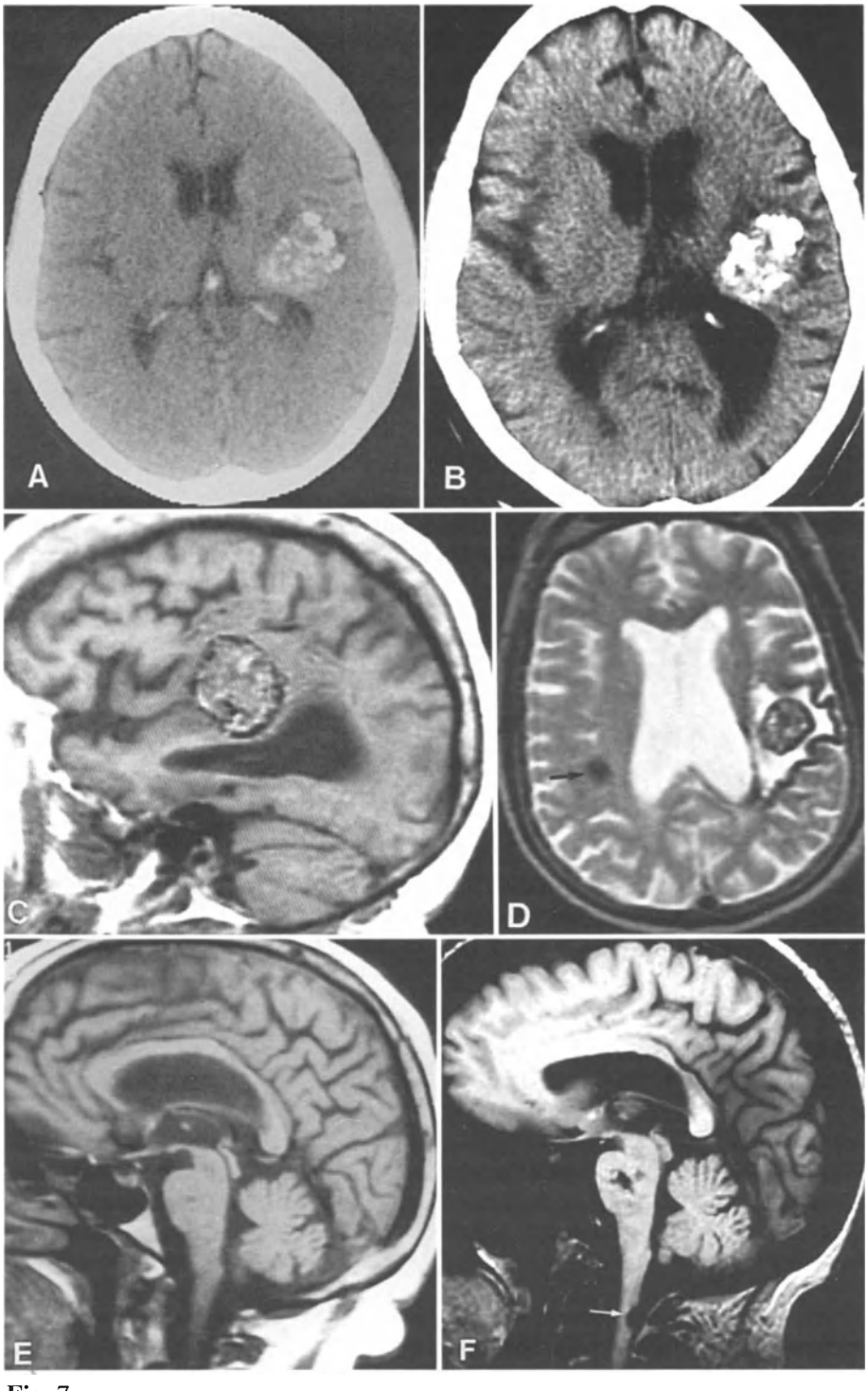


Fig. 7

Such voluminous calcified lesions were termed "hemangiomas calcifians" by Penfield and Ward (1948). According to the authors, these forms were associated with temporal locations (Fig. 2) but they were later found to occur anywhere in the brain (Di Tullio and Stern 1979, Harbauch *et al.* 1984).

Calcified cavernomas account for most epileptic presentations. Haemorrhage is possible, although unlikely (Galzio *et al.* 1980, Simard *et al.* 1986). Very large calcified cavernomas may produce pseudo-tumoural symptoms.

The pathogenesis of calcified forms is not as straightforward as that of the haemorrhagic forms. Recurrent microhaemorrhages have been incriminated, but repeated thrombosis, occurring in extremely low-flow cavernomas appears to be the underlying mechanism.

Pericavernomatous Atrophy

Neuronal depletion in the vicinity of a cavernoma is not an uncommon histological finding. In some cases cortico-subcortical atrophy is visible on neuroradiological studies or at surgery (thus facilitating removal of the lesion in a single mass). We observed cases in which a cavernoma had caused considerable brain atrophy, which contributed to the patient's symptoms (Fig. 7, Fig. 22).

The pathogenesis of such cerebral atrophy is unclear. It could arise as a consequence of the metabolic disturbances (Ryvlin 1991) and reduction of regional blood flow observed in some cavernomas (Houtteville *et al.* 1989 a).

Enlargement of the Cavernomatous Matrix. Additional Lesions

In a few instances, haemorrhage or calcification cannot be incriminated in cavernoma enlargement; the malformation itself appears to increase in size. Several hypotheses have been put forward. Cushing and Bailey (1928)

Fig. 7. Case 24. (A) CT scan done in 1983 in a 52-year-old patient with jacksonian and generalised seizures. (B) CT scan in same patient 5 years later. She then presented with right hemiparesis, hypoaesthesia and intellectual impairment. Calcification is seen to occupy the same area, but appears thicker. Evidence of brain atrophy (enlarged ventricles and sulci) is present. (C) Sagittal T1-weighted image (1988). (D) Axial T2-weighted image (1988) The lesion is surrounded by a large area of high signal intensity, on the periphery of which a rim of low signal intensity may be seen. Note the presence in the opposite hemisphere of a small cavernoma appearing as a homogeneous area of low signal intensity (arrow). (E) Sagittal T1-weighted image. A very small area of low signal intensity is visualised in the pons. (F) One year later a large area of low signal intensity is visible in the pons and a smaller one posteriorly. No evidence of bleeding is present. A new lesion may be seen in the cord (white arrow)

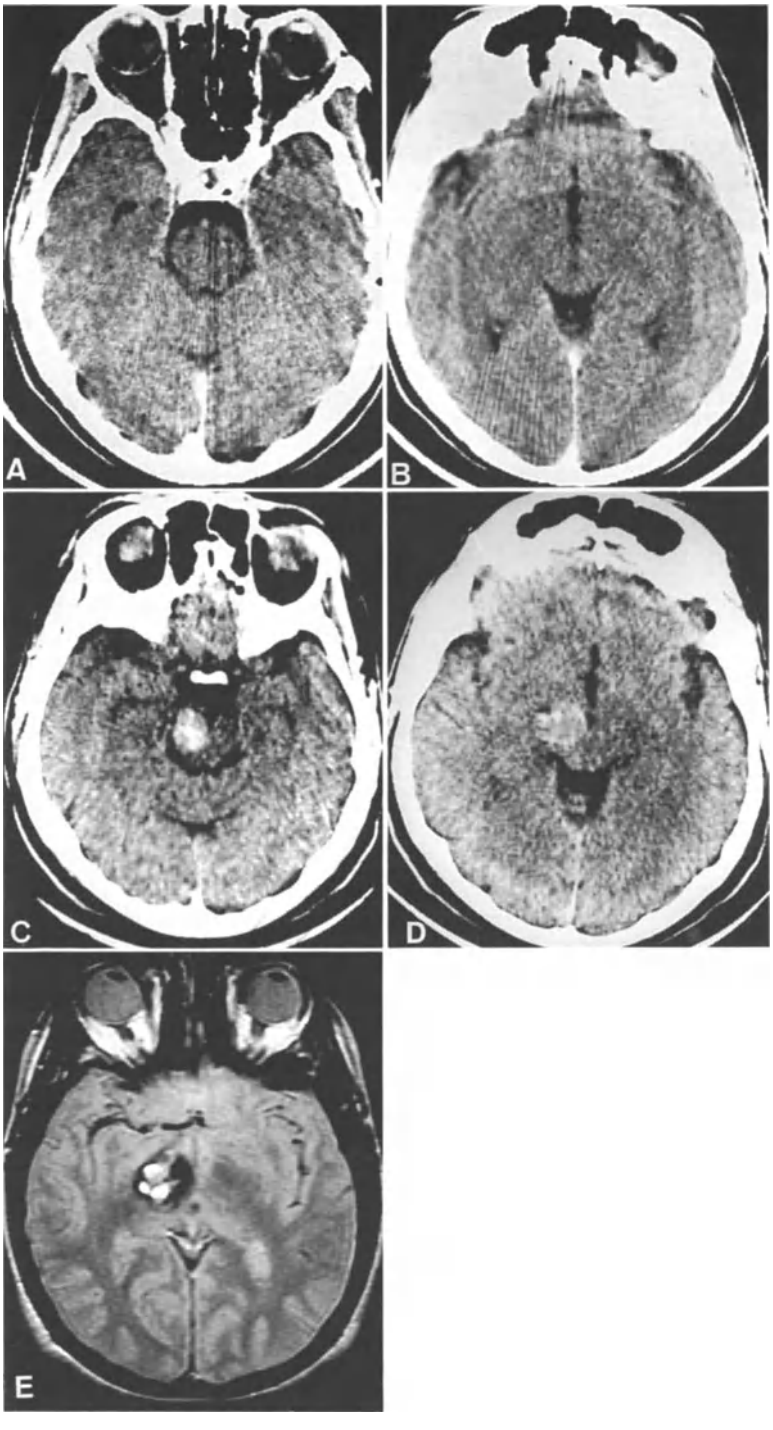


Fig. 8

suggested that a "proliferative blastoma" may be responsible for the growth of "vascular tumours", but made no clear distinction between hemangioblastoma and cavernoma. Rutka *et al.* (1988) hypothesised that "endothelial cell-growth factors" be responsible for the formation of new abnormal vessels, while Scott *et al.* (1992) proposed a process of re-endothelialisation within a haemorrhage. According to Ledoux *et al.* (1991), after Steiger *et al.* (1987), growth occurs as a result of haemorrhage which not only destroys normal parenchyma but also "stimulates connective tissue proliferation with neovascularisation and subsequent enlargement of the lesion".

At present none of these hypotheses has been substantiated, but it is a fact that a cavernomatous "matrix" appears to develop. This view is shared by Zimmerman *et al.* (1991) who use the term "nidus" instead of "matrix".

Also suggestive of a tumour-like growth is the presence of additional lesions in affected patients (Fig. 7E, F), and the detection of cavernomas in patients with previously negative neuroradiological studies (Fig. 8). These facts were noted by Pozzati *et al.* (1989), Zimmerman *et al.* (1991), Sigal *et al.* (1990), Scott *et al.* (1992), and query the congenital origin of some cavernomas.

It can be concluded that cavernomas do not necessarily follow a benign, uneventful course. There is ample evidence that changes occur within these lesions, under the influence of various, interacting factors. Recognition of the dynamic character of these malformations, and growing awareness of the resultant risks to the patient's life and neurologic status, justify the surgical removal of accessible cavernomas.

Associated Forms

Associations of various types of cerebral vascular hamartomas are not uncommonly found upon histological examination of surgical specimens: Vaquero *et al.* (1983), Hayashi *et al.* (1985), Rapacki *et al.* (1990) reported associations of cavernomas with capillary telangiectases.

As previously mentioned, mixed cavernomas have been shown to contain arterioles and venules, suggesting an association with an AVM, only microscopically detectable. The association of a cavernoma with a typical AVM,

Fig. 8. Case 43. "New" cavernoma. (A) CT scan done in 1987 in a 47-year-old woman complaining of transient paresthesia in her left leg (upper brainstem level). (B) Subthalamic level. (C) CT scan done in 1992 in same patient with left hemiplegia, spasticity and hypoesthesia (upper brainstem level). A hyperdense nodule is seen in the right anterior midbrain, extending to the subthalamic region. (D) Subthalamic level. (E) Axial T1-weighted MR image done in 1992 at the subthalamic level (see also Fig. 18)

opacified at angiography, has been described by Hirsch (1981) and by Rapacki *et al.* (1990). More recently, associations of cavernoma with venous malformation have been been reported (Rigamonti *et al.* 1988, Zimmerman *et al.* 1991, Symon *et al.* 1991, Sasaki *et al.* 1991, Miyagi *et al.* 1993). So far, 5 verified cases have been published, based on histological evidence from surgical material (Table 2).

Such an occurrence should be familiar to neurosurgeons because of its considerable surgical implications and calls for several remarks:

1) When neuroradiological studies demonstrate a venous angioma (medullary veins seen to converge towards a parenchymal venous trunk), with evidence of blood effusion nearby, one should remember that venous angi-

Table 2. *Associated Cavernomas and Venous Angiomas Surgically Treated*

Authors	Age/Sex	Symptoms	Lesional site	Treatment	Outcome
Rigamonti *et al.* (1988)	44/F	headache	cerebellar lobe	total excision of C partial excision of VA	per op. cerebellar swelling then good
	11/M	headache	frontal lobe	excision of C alone	good
Zimmerman *et al.* (1991)	36/F	numbness left face tongue	brain stem (medulla)	excision of C alone	good
Sasaki *et al.* (1991)	31/M	dysphasic seizures	temporal lobe	excision of C alone	good
Miyagi *et al.* (1993)	3/F	ICH	lat. ventricle (trigone)	excision of C alone	good

C cavernoma, *VA* venous angioma, *ICH* intra cranial hypertension.

Fig. 9. Supratentorial cavernoma associated with a venous angioma in a 37-year-old woman with episodes of right throbbing hemicrania for 20 years. (A) Precontrast CT scan: small hyperdense area in deep posterior temporal lobe (small arrows). (B) Postcontrast CT scan: visualisation of a large transparenchymal vein (arrowheads). (C) Axial T2-weighted MR image (short TE): appearance of a cavernoma (arrowheads). (D) Typical angiographic appearance of an venous angioma (medullary veins are seen to converge towards a large vein). (E) Postoperative postcontrast CT scan, showing the vein has been left in place (arrowheads). Uneventful postoperative course (by courtesy of Prof. J. D. Born, CHU La Citadelle, Liege, Belgium)

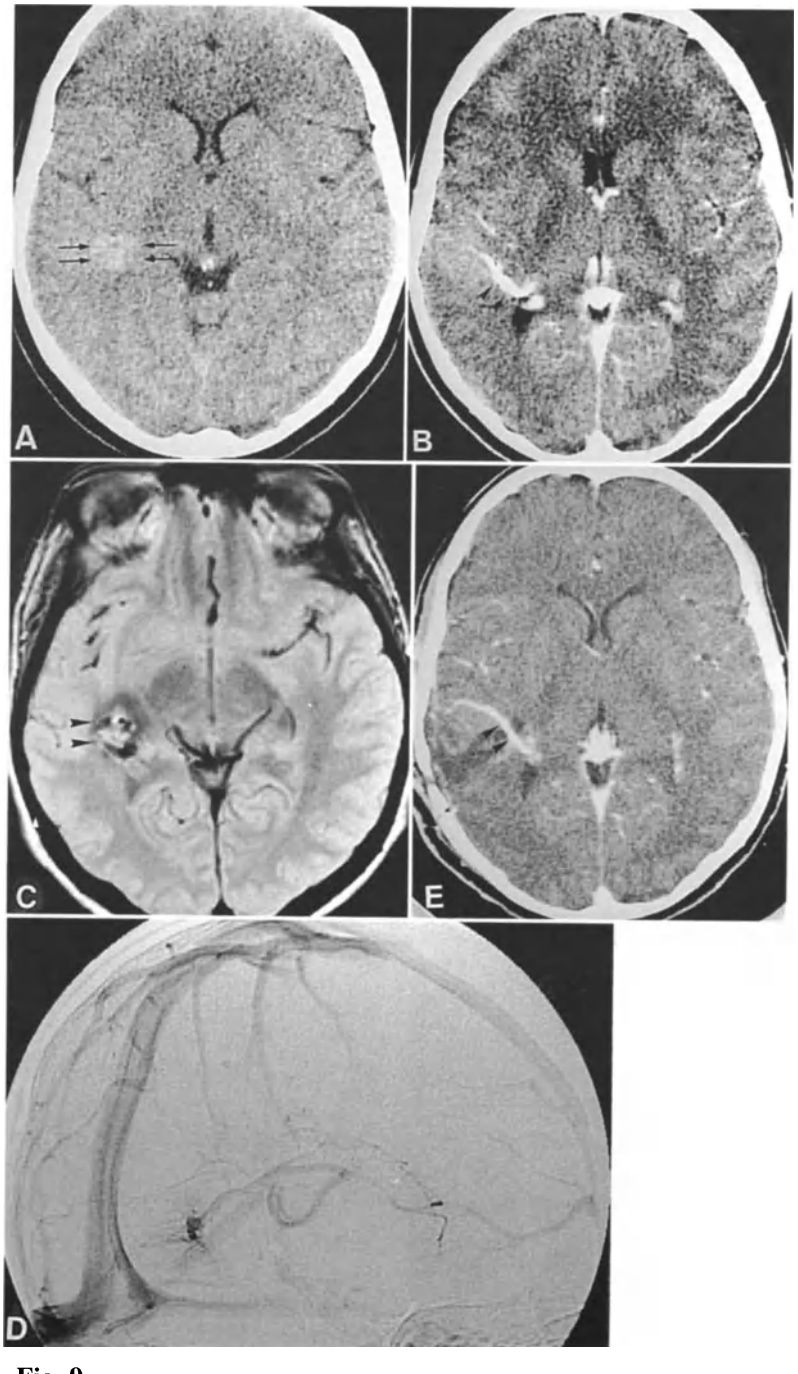


Fig. 9

omas exceptionally cause haemorrhage, and that blood effusion could in fact represent a cavernoma, lacking its typical CT or MRI appearance because of haemorrhage. This has practical consequences: a) any intracerebral haematoma lying near a venous angioma, and requiring evacuation, should be examined histologically b) in future, surgical indications may have to be reconsidered for such haematomas found to occur near venous angiomas, lest a cavernoma should be left in place, and cause rebleeding.

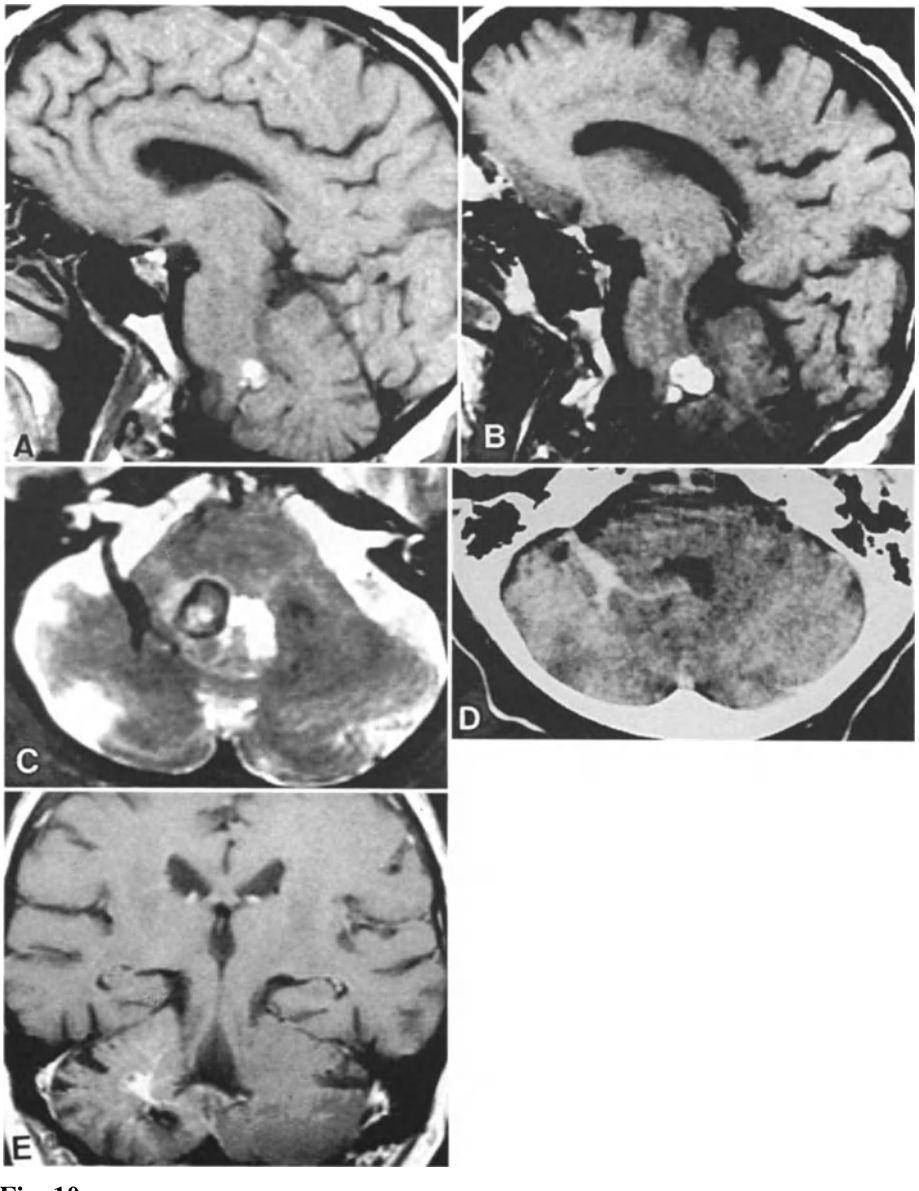


Fig. 10

2) The converse is true: in the presence of radiological findings consistent with a cavernoma, one should be careful not to miss a venous angioma. Typical venous angiomas are easily diagnosed (positive findings on CT scan, MRI and angiography) but less typical forms may occur. The veins near a cavernoma have been shown to perform a double function, draining not only the cavernoma but the surrounding brain tissue as well and should always be spared. Rigamonti *et al.* (1988 a) observed cerebellar swelling (necessitating tonsillar resection) after electrocoagulation of veins adjacent to a cavernoma.

The association of cavernoma and venous malformation are illustrated on Figs. 9 and 10.

Familial and Multiple Forms

Most cavernomas occur in a sporadic fashion, but familial forms of the disorder have been known for a long time. They have been increasingly recognised in recent years with the advent of MRI (Rigamonti *et al.* 1981, Gangemi *et al.* 1990). Some ethnic groups (Mexican-American families for instance) seem to be particularly at risk (Bicknell *et al.* 1978, Rigamonti *et al.* 1988). Inheritance is autosomal dominant, with a high degree of penetrance. In a series of 24 patients who underwent surgery, Rigamonti *et al.* (1988) found 13 patients (54%) belonging to 6 families; 10 were found to harbour multiple cavernomas. Multiple cavernomas were also more common in familial than sporadic forms in the experience of Dobyns *et al.* (50% of cases in a series of familial forms). In our series of 50 patients (Table 3), 9 (18%) were found to be members of 4 families. Among them, 6 patients (66%) had multiple lesions. Among the 41 patients with sporadic forms in our series only 2 (4.8%) had multiple cavernomas.

Fig. 10. Case 31. Infratentorial cavernoma associated with a venous angioma. (A) 10. 06. 89. T1-weighted MR image (sagittal view) showing a small heamatoma of the right angle of the fourth ventricle in a 78-year-old man presenting with sudden vertigo and gait disturbance – no headache. His symptoms resolved completely in 15 days. (B) 15. 07. 89. T1-weighted MR image one month later following recurrence and worsening of the patient's neurologic signs (ataxia): enlargement of the lesion. (C) Associated venous angioma visible on T2 weighted axial MRI scan. (D) Associated venous angioma visible on CT scan. (E) Coronal T1-weighted MR image 6 months after surgery. Complete removal on the cavernoma was carried out, while the venous angioma was left in place. The postoperative course was uneventful; the patient's symptoms were markedly improved

Cavernomas in Children

In 1988, reporting four cases of cavernomas in children, Herter *et al.* noted that 25% of the 166 cases published since 1976 had been diagnosed in patients under the age of eighteen. In 1989, Fortuna *et al.* published 6 cases and reviewed the relevant literature: among the 50 cases available, they observed a peak incidence in the 0–2 year (26.8%) and 13–16 year (35.7%) age-groups. Epilepsy was the most common presentation (45%), other presenting features included haemorrhage (27.3%), intracranial hypertension (16.4%) and neurological deficits (10.9%). Complete surgical removal was achieved in 87% of cases. The death rate was 4.6%. At a mean follow-up of 2.4 years, surgical results were excellent, with only 2.3% of patients suffering worse deficits. Surgery proved also remarkably efficient for epilepsy, with 65% of patients being free of fits and requiring no treatment, and seizures improving or resolving with appropriate medication in the remaining 35%.

In 1992, Scott *et al.* published a series of 19 cavernomas, 18 intracranial and one intramedullary, in patients under 18 years of age. Contrary to Fortuna's findings, neurological deficits were prevalent. The onset was sudden in 14 cases, and progressive in 3. Neuroradiological investigations had been carried out for epilepsy in only 3 patients. 5 patients had a family history of CNS vascular malformations, with multiple forms in 3 cases. 5 patients had multiple cavernomas. Scott emphazised the high frequency of complex histological forms, associating the usual aspect of vascular spaces placed side by side, with areas of proliferative granulation tissue and partially re-endothelialised haemorrhage. Although they reported overall good operative results, with only one case of postoperative deterioration in a brainstem cavernoma, the authors drew attention to the fact that incomplete removal, carried out in 5 patients, led to rebleeding in 2 instances, one year after the initial operation.

Several authors studied cavernoma in the first year of life (Gangemi *et al.* 1989, Nakasu *et al.* 1991). Although general conclusions may not be inferred from such small numbers, several striking features emerge from the series of 16 cases from the literature studied by Nakasu *et al.* An enlarging head and epileptic fits are the usual presenting symptoms. The most common location is the lateral ventricle (5 cases). Large cysts may be present (4 cases), in association with a partially calcified mural nodule, which may not be visible on CT.

Finally, a cavernoma may become symptomatic as early as the neonatal period. Bergeson *et al.* (1992) recently reported a cavernoma presenting as a large frontal haemorrhage in a 2-day-old infant; several members of the family harboured cerebral angiomas, 4 of which had previously been published, including a fatal one, in which death occurred as a result of intracranial haemorrhage.

Natural History

In 1985, Wilkins wrote: "... I do not think that enough untreated cases have been followed in an organized fashion to answer crucial questions about the natural history of the cavernous hemangioma. We do not know whether cavernous angiomas change in size with time, and we do not yet know the approximately yearly risk of a recurrent haemorrhage or of death".

Since then, the development of MR imaging has provided some answers to these questions, allowing indications for surgery to be more clearly defined.

Robinson *et al.* examining 14,065 MR images performed over 5 years at the same institution, discovered 76 lesions with the typical appearance of a cavernoma in 66 patients. 14 underwent surgery, and histology confirmed the diagnosis in all. 86% of patients were followed up over a mean period of 26 months, providing 146 lesion-years of clinical survey. From this series, the estimated yearly risk of haemorrhage was 0.7%, with a significantly higher risk in female patients.

Robinson's conclusion was to recommend surgical treatment in patients who presented with severe haemorrhage and in those with epilepsy unresponsive to medical treatment. Less definite surgical indications are represented by lesions situated within or near eloquent areas, presenting with progressive focal deficits, and by safely accessible lesions in women contemplating pregnancy.

Del Curling *et al.* (1991) analysed 8,138 MR images performed over 4 years at their institution. 32 patients were identified with 76 lesions meeting the MR imaging criteria for cavernomas. The estimated risk of haemorrhage in this population was 0.25% person-year of exposure and the estimated risk of seizure was 1.51% person-year. From these findings the major risk of cavernoma appeared to be epilepsy rather than haemorrhage. The authors recommend that surgical indications should be discussed on an individual basis, with careful assessment of the benefit/risk ratio, before deciding "upon removal of these relatively benign malformations". They also emphazise the need for large prospective studies in order to answer the many unresolved questions about the natural history of cavernomas.

Clinical Presentation

Presenting features are non-specific. The circumstances in which these lesions come to medical attention depend essentially on their location, supra or infratentorial, on their topography and pathological features.

Three modes of presentation have been classically described: epilepsy, haemorrhage and a mass lesion (Simard *et al.* 1986). This classification is not

entirely satisfactory. Surprisingly, marked discrepancies exist in the attribution to the various types of presentation. According to Simard *et al.* (1986), who reviewed 138 cases (126 cases from the literature and 12 of their own), the three modes of presentation were equally represented (about a third each). On the other hand, Vaquero *et al.* (1987), in a smaller personal series (25 cases), found epilepsy to be the most common presenting feature (70%), followed by mass lesion (20%) and haemorrhage (10%). Prior to that, Giombini and Morello (1978), in a series of 51 cases, including 37 cases from literature and 14 personal cases, reviewed the presenting symptoms, and found haemorrhage in 23.5% of cases (with fatal consequences in 3 patients), seizure in 38%, headache in 28% and focal neurological signs in 12%.

These discrepancies may reflect a recruitment bias, owing to the fact that patients entered the series at various stages in the course of the disorder. Simard *et al.* (1986) did mention that 7 out of the 40 patients (17.5%) who presented with haemorrhage had previously had neuroradiological investigations performed for epilepsy.

We personally disagree with the somewhat confusing terms of this classification; epilepsy is a clinical symptom, which may assume various forms, a mass lesion or tumour-like presentation refers to the slowly progressive course followed in some cases and haemorrhage is a pathological term. We would favour a classification based exclusively on clinical findings and suggest the classification of cavernomas into three clinical sub-types: those presenting as epilepsy, those presenting as focal neurologic deficits, and those presenting as headache.

The anatomical constitution of cavernomas is determined by MRI findings, surgical observation and neuropathological data. We agree with Steiger *et al.* (1987) on the need to establish anatomo-clinical correlations.

Haemorrhage, which is the basis of most changes in the course of cavernoma development, deserves a special mention. In our series we classified haemorrhage as: severe (+++), moderate (++), or mild (+), and also noted, whenever possible, whether bleeding was intra- or extra-cavernomatous.

We used the above mentioned method to classify our 50 cavernomas (53 operations) (Table 3).

Table 3. *Summary of 50 Histologically Verified Cases (53 op.)*

Case	Age	Sex	FF	MF	Clinical presentation						Studies performed				Localisation	Type of lesion			Surgery		Outcome		
					Seizures				Focal signs	Other	RN	A°	CT	MRI		Haemor.	Calc.	Other	TR	STR	Follow-up/years	Epilepsy	Other
					GEN	FOC	CH	R															
1	15	F	+	–	+	–	–	–	–	ICH	+	+	–	–	parietal	+++EC	–	–	+	–	20	VG	–
	18	F	–	+	–	–	–	–	+	ICH	+	+	–	–	pons (lateral)	+++EC	–	–	+	–	17	–	no disability
2	14	F	–	–	–	+	+	–	–	–	+	+	–	–	temporal	–	++	TH	+	–	10	G	–
3	48	F	–	–	+	+	–	+	–	HE	+	+	–	–	frontal	–	–	TH	+	–	5	G	–
4	3	M	+	–	–	–	–	–	–	ICH	+	+	–	–	caudate nucleus	+++EC	–	–	+	-	15	–	no disability
5	23	F	+	–	+	–	–	+	–	–	+	+	+	–	frontal	+IC	–	TH	+	–	14	VG	–
6	43	F	–	–	+	+	+	–	–	–	+	+	+	–	rolandic	+	+	–	+	–	13	EXC	–
7	50	M	+	+	+	–	+	–	+	–	+	+	+	–	temporal	++IC	+	–	+	–	4	–	death (brainstem local.)
8	26	F	+	–	+	–	–	+	–	HE	+	+	+	–	parietal	+IC	–	–	+	–	13	G	–
9	20	F	–	–	–	+	–	–	–	–	+	+	+	–	temporal	+++EC	–	–	–	+	13	P	–
	22	F	–	–	–	+	–	–	–	–	–	+	+	–	temporal	++EC	–	–	–	+	–	P	–
10	38	F	–	–	–	–	–	–	VD	–	+	+	+	–	chiasma	+IC	–	M	+	–	13	–	no disability
11	23	M	–	–	+	–	–	+	–	–	+	+	+	–	temporal	+IC	–	–	+	–	11	G	–
12	21	M	–	+	+	–	+	–	–	–	–	+	+	–	frontal	–	+	TH	+	–	10	P	–
13	20	M	+	–	+	+	–	+	–	–	–	+	+	–	temporal	+EC	–	TH	+	–	10	G	–
14	21	M	–	–	–	+	+	–	–	–	+	+	+	–	temporal	–	++	TH	+	–	9	EXC	–
15	38	M	–	–	–	–	–	–	+	HE	+	+	+	–	temporal	++IC	–	–	+	–	8	–	no disability
16	20	F	–	–	+	–	+	–	–	–	+	+	+	–	frontal	–	–	TH	+	–	8	G	–
17	47	M	–	–	–	+	+	–	–	–	–	+	+	–	temporal	–	–	TH	+	–	7	G	–
18	34	M	–	–	+	–	–	+	–	HE	+	+	+	–	frontal	+IC	–	–	+	–	7	EXC	–

Table 3. *Continued*

Case	Age	Sex	FF	MF	Clinical presentation						Studies performed				Locali-	Type of lesion			Surgery		Outcome		
					Seizures				Focal	Other	RN	A°	CT	MRI	sation	Haemor.	Calc.	Other	TR	STR	Follow-up/years	Epi-lepsy	Other
					GEN	FOC	CH	R	signs														
19	19	F	–	–	–	–	–	–	+	ICH	–	+	+	+	pons (floor V4)	++EC	–	–	+	–	6	–	improved
20	19	F	–	–	–	+	–	+	–	–	–	+	+	+	parietal	–	–	TH	+	–	6	VG	–
21	51	F	–	–	+	+	+	–	–	–	+	+	+	+	rolandic	–	–	–	+	–	6	G	–
22	49	M	–	–	+	–	+	–	–	HE	–	–	+	+	temporal	–	–	TH	+	–	6	VG	–
23	32	M	–	–	+	–	–	+	–	–	–	+	+	+	temporal	+IC	–	TH	+	–	5	EXC	–
24	57	F	+	+	+	+	+	–	+	–	–	+	+	+	rolandic	–	++	–	+	–	5	–	stabilized
25	44	M	–	–	–	–	–	–	–	HE	–	+	+	–	temporal	–	–	C	+	–	5	–	no disability
26	30	F	–	–	+	–	–	+	–	–	+	+	+	+	occipital	–	–	–	+	–	5	EXC	–
27	20	F	–	–	+	+	–	+	+	HE	–	+	+	+	rolandic	–	+	TH	+	–	5	VG	no disability
28	15	F	–	+	+	–	–	+	–	HE	–	–	+	+	frontal	–	–	TH	+	–	–	EXC	–
	15	F	–	+	–	–	–	–	+	–	–	–	+	+	cerebellar (lobe)	–	–	TH	+	–	–	–	no disability
29	32	M	–	–	+	+	+	–	–	–	–	–	+	+	parietal	–	–	TH	+	–	4	EXC	–
30	22	F	–	–	–	+	–	+	–	ICH	–	–	+	+	rolandic	++IC	–	TH	+	–	4	G	–
31	78	M	–	–	–	–	–	–	+	–	–	–	+	+	cerebellar	++EC	–	–	+	–	4	–	improved
32	36	M	–	–	+	–	–	+	–	HE	–	–	+	+	temporal	+EC	–	–	+	–	4	EXC	–
33	34	F	–	–	–	+	–	+	–	HE	–	–	+	+	temporal	+EC	–	TH	+	–	4	VG	–
34	19	F	+	+	–	–	–	–	+	ICH	–	+	+	+	thalamic	+++EC	–	–	–	+	4	–	no disability
															temporal-pons				not op.		4	–	asympt.
35	33	M	–	–	–	+	+	–	–	–	–	–	+	+	temporal	–	–	TH	+	–	4	VG	–
36	27	F	–	–	+	+	+	+	–	–	–	–	+	+	temporal	–	+	M	+	–	4	EXC	–
37	17	M	–	–	+	–	–	+	–	–	–	+	+	+	frontal	+EC	–	–	+	–	3	EXC	–
38	62	M	–	–	+	–	+	–	–	–	–	+	+	+	frontal	–	+	C	+	–	3	VG	–

Case	Age	Sex	FF	MF	Clinical presentation						Studies performed				Localisation	Type of lesion			Surgery		Outcome		
					Seizures				Focal signs	Other	RN	A°	CT	MRI		Haemor.	Calc.	Other	TR	STR	Follow-up/years	Epilepsy	Other
					GEN	FOC	CH	R															
39	24	F	+	+	+	–	–	+	–	–	–	+	+	+	temporal	–	–	TH	+	–	1	VG	–
															rolandic	–	–	TH	+	–	–	–	–
40	46	M	–	–	–	–	–	–	+	–	–	–	+	+	midbrain (thal.)	++IC	–	–	+	–	1	–	no disability
41	45	F	–	–	+	+	–	+	–	HE	–	+	+	+	parietal	+IC	–	–	+	–	1	G	–
42	56	M	–	–	–	–	–	–	–	HE	–	+	+	+	parietal	+IC	–	–	+	–	1	–	no disability
43	47	F	–	–	–	–	–	–	+	–	–	–	+	+	rnidbrain (thal.)	++IC	–	TH F	–	+	1	–	improved
44	16	M	–	+	+	–	–	+	–	–	–	–	+	+	frontal	+IC	–	–	+	–	1	VG	–
															rolandic				not op.		–	–	asympt.
45	34	F	–	–	–	–	–	–	+	–	–	–	+	+	cerebellar (vermis)	–	+	TH	+	–	6 m.	–	no disability
46	44	F	–	–	–	+	–	+	–	–	–	–	+	+	temporal	–	–	TH	+	–	6 m.	VG	–
47	41	F	–	–	–	–	–	–	–	ICH	–	+	+	+	frontal	+IC	–	TH	+	–	6 m.	–	no disability
48	34	F	–	–	–	–	–	–	–	ICH	–	+	+	+	caudate nucleus	+++IC	–	–	+	–	6 m.	–	no disability
49	12	M	–	–	–	–	–	–	+	ICH	–	+	+	+	pons	+++IC	–	–	+	–	6 m.	–	no disability
50	11	M	–	–	–	–	–	–	+	HD	–	–	+	+	chiasma	+IC	–	F	+	–	4 m.	–	stabilized

FF familial form, *MF* multiple form, *GEN* generalized, *FOC* focal, *CH* chronic, *R* recent, *ICH* intra-cranial hypertension, *HE* headache, *VD* visual disturbance, *HD* hypothalamic dysfunction, *RN* radionuclide scan, *A°* angiography, *EC* extra cavernomatous, *IC* intra cavernomatous, *EXC* excellent, *VG* very good, *G* good, *TH* thrombosed, *F* fibrosis, *C* cystic, *M* mixed, *TR* total removal, *STR* subtotal removal.

Forms Presenting with Epilepsy

We observed 33 cases*** (66% of all cases; 76.7% of patients with a supra tentorial located cavernoma). All forms of epilepsy may be observed. 17 cases presented with partial seizures, which may have become generalised and were correlated to the site of the cavernoma in 15 instances (cases 2, 3, 6, 13, 14, 17, 20, 21, 27, 29, 33, 35, 36, 41, 46). Among these 2 patients with very large temporal lesions had partial complex seizures associated with partial motor seizures. In 16 patients generalised seizures were present from the onset (cases 1, 5, 8, 11, 12, 16, 18, 22, 23, 26, 28, 32, 37–39, 44).

It must be noted that long standing epilepsy is becoming less frequently observed with the increasing use of MRI, which should be routinely performed in the investigation of epilepsy.

Anatomo-Clinical Correlations

In 14 patients epilepsy was correlated with obvious haemorrhage. In 2 cases, the haemorrhage was severe (cases 1, 9). In 1 case, it was moderate (case 30). A mild haemorrhage was observed in 11 patients (cases 5, 8, 11, 13, 18, 23, 32, 33, 37, 41, 50): only 4 cavernomas were partially thrombosed on histological examination. In 19 patients, haemorrhage was absent (cases 2, 3, 6, 12, 14, 16, 17, 20–22, 26–29, 35, 36, 38, 39, 46), but calcification and thrombosis were frequently observed (9 patients with calcification, 14 with thrombosis).

Postoperative Follow-up

The 33 patients from our series who presented with seizures were reviewed clinically or questioned by telephone in 1993.

– Assessment criteria were as follow: excellent: free of seizures after surgery with no anti-epileptic medication; very good: free of seizures, on antiepileptic medication; good: improved, small number of seizures in spite of treatment; poor: not improved by surgery, frequent seizures.

– Results were: excellent in 10 cases (30,3%); very good in 11 cases (33%); good in 10 cases (30,3%); poor in 2 cases (6%). Almost 2/3 of our patients (63.3%) had an excellent or very fair outcome. Follow-up ranged between 1 and 18 years.

There have been few detailed reports on the results of surgical removal of cavernomas as far as epilepsy is concerned. Simard *et al.* (1986) noted that in 23 patients, 12 (52.17%) were seizure-free one year or more after

*** 2 patients were not considered as an epileptic form. The first one (case 7) had seizures 30 years ago, but was admitted for haemorrhage. The other (case 24) had seizures in the past, but was operated on for progressive hemiplegia reliable to brain atrophy (Fig. 7).

surgery, 2 (8.69%) had persistent seizures and 9 (39.13%) had "a satisfactory course".

In their review of 56 cases from the paediatric literature, Fortuna *et al.* (1989) observed that 65% of patients with epilepsy were free of seizures after surgical removal of their cavernomas. In the remaining 35%, seizures were controlled or reduced in frequency with appropriate treatment.

Finally, interesting results were reported by Robinson *et al.* (1991) who compared two series of patients: the 18 who were not operated on all continued to have seizures in spite of a medical treatment, while 7 out of the 14 patients who underwent surgery (of which 10 with "truly intractable epilepsy") were seizure free after the operation.

The attitude towards epileptogenic cavernomas is still controversial. According to some authors, surgical removal is best limited to the cavernoma itself and the peripheral gliosis, where the latter may be excised without creating further neurological deficits. Others use electrocorticography to identify and resect seizure foci adjacent to the malformation (Buckingham *et al.* 1989, Rougier *et al.* 1989).

Forms with Focal Deficits

We observed 12 cases (24%). All brainstem cavernomas were included in this category; the clinical course was either acute (cases 19, 49), subacute (cases 1, 40, 43) or involved two stages (case 31). Focal signs were also present in our two cases involving the cerebellum (cases 28, 45), and in one involving the thalamus (case 34), as well as in two cases of chiasmal location (cases 10, 50).

Only three cases of supratentorial cavernomas presented with focal neurological deficits (cases 7, 15, 24).

Forms Presenting with Headache

We observed 5 cases (10%). Many patients who present with epilepsy or focal neurologic signs also complain of headache. However, headache may be the only presenting symptom. Two forms should be identified.

– Chronic headache, possibly similar to migraine: we observed two such cases. In one of these (case 25), the cavernoma was shown to be cystic and in the other the lesion mainly consisted of a large cavern (case 42). Both patients were relieved of their symptoms following surgical removal of the lesions.

– Intense headache sudden in onset, suggestive of intracranial hypertension. This presentation may be confused with a subarachnoid haemorrhage with no localising signs. We observed three such cases (case 1: intraparietal haemorrhage, case 4 and 48: haemorrhage located in the caudate nucleus). In all three cases, headache was related to severe haemorrhage (Fig. 15).

Supratentorial Cavernomas

Supratentorial cavernomas account for about 75% of all cases (Voigt and Yaşargil 1976) – 84.9% in our own series (Table 4). They should be studied on the basis of their location, whether deep or superfical. Rare locations will also be considered.

Superficially-Located Cavernomas

Years ago it was demonstrated by neuropathologists that hemispheric cavernomas commonly occur in cortical or subcortical location, which makes them "ideal" surgical lesions, easily accessible and safely removable. This was confirmed by MR imaging, and this modality also demonstrated that some cavernomas, which CT scan findings showed to be deep-seated, were in fact simply "buried" in the depths of a sulcus or fissure. This is illustrated in the following example:

Case 32: 36-year-old man, admitted for generalised seizures and sudden headache. The CT scan revealed a spontaneously hyperdense right posterior temporal lesion, with no mass effect or enhancement on postcontrast scan. The lesion was situated 3 cm deep from the cortex (Fig. 11A). From MRI studies, the lesion was in fact shown to be located cortico-subcortically, in the depths of the sylvian fissure (Fig. 11B, C). At surgery, the cavernoma was exposed by splitting the sylvian fissure, no incision of the temporal parenchyma was required. The postoperative course was uneventful.

Table 4. *Location of Brain Cavernomas, Personal Series (50 Patients, 53 Lesions Operated on)*

Supra tentorial	nb = 45	84.9%
Temporal	17	
Frontal	10	
Parietal	7	
Rolandic	5	
Occipital	1	
Basal ganglia	3	
Chiasma	2	
Infra tentorial	**nb = 8**	**15.1%**
Pons	3	
Cerebellum	3	
Midbrain	2	

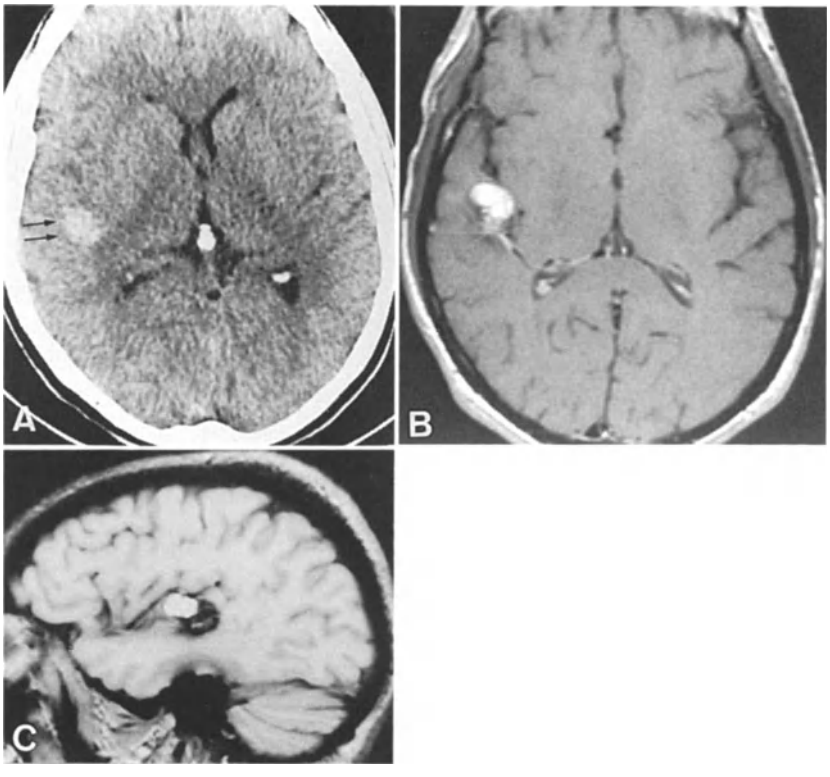


Fig. 11. Case 32. "Buried" cavernoma. (A) CT scan showing the lesion to be situated deep in the right temporal lobe (small arrows). (B) Axial T1-weighted MRI demonstrating the lesion is in fact buried in the sylvian fissure. (C) Sagittal T1-weighted MRI

Operative Techniques

After careful analysis of MR images, we always carry out localising procedures, in order to place the craniectomy exactly over the lesion. For that purpose we use a stereotactic frame, positioned during a CT scan examination.

The applications of stereotaxy have been extended to the surgery of cavernomas. Davis and Kelly (1990) performed stereotactic surgery on 26 angiographically occult vascular malformations. These included 18 AVMs, 6 nonspecific vascular malformations and 2 cavernomas. All patients underwent a stereotactic CT and/or MR scan and a stereotactic and stereoscopic cerebral angiogram preoperatively. No vascular abnormalities were found on any of the angiograms. The necessary surgical equipment involved a console, displaying the imaging studies, and allowing for a target volume to be digitised, and an optimal trajectory selected for the surgical stereotactic approach, which was done through a small trephine craniectomy, under

general anaesthetics. In one case of a lesion located in the rostral midbrain and thalamus, the patient had a poor outcome and died 55 months later without improvement. In 9 patients, minor, transient complications occur. In 3 patients, complete resection could not be achieved by stereotactic techniques. Davis and Kelly conclude their report with this statement: "Stereotactic craniotomy offers significant advantages in the surgical management of angiographically occult vascular malformations".

The key method is careful dissection around the lesion, according to the principles of microsurgery, with adequate exposure of supplying arteries and veins. The surgeon can thus expose and excise any diverticula, if present, or appreciate the exact amount of pericavernous tissue to be resected. These are necessary conditions if the main goal of this surgery, that is complete removal of the cavernoma, is to be attained; failure to do this carries a risk of recurrent haemorrhage, as emphasized by many authors. It is worth noting the analogy with AVMs, which must also be totally resected, to eliminate the risk of further bleeding.

A diagnostic stereotactic biopsy is contra-indicated if MRI findings are consistent with a cavernoma or, more generally, an AOIVM. As pointed out by several authors, this procedure poses a serious risk of haemorrhage. Ahmadi *et al.* (1985) observed two cases of intracranial haemorrhage, one mild and the other massive, in the course of four biopsies.

Once the dura has been exposed, we perform ultrasonic studies on the operative field, to control the reliability of preoperative stereotactic localisation and locate, if necessary, the most superficial area over a subcortical lesion. At this point, there are two possibilities: the cavernoma may be located within the cortex or lie beneath it. A cortical lesion will be immediately visible once the dura has been opened (Fig. 13); it might even be attached to the dura; in which case care should be taken not to exert any traction on the lesion while lifting up the dura. However cavernomas are most commonly subcortical. A yellow-greenish coloration of the overlying brain often indicates the presence of the lesion. Surgical approach requires the use of an operating microscope in all cases and the most direct route should be taken, approaching the lesion at the point where it lies most superficially. To achieve adequate exposure it is often necessary to dissect a sulcus and then retract its edges after a parenchymal incision has been made.

Removal of the lesion in a single mass is often possible in the case of small cavernomas, less than 3 cm in diameter. We used this technique in 26 of our cases. Clear delineation from the surrounding brain tisssue is a constant feature, allowing careful dissection along the plane of the lesion. In the course of the dissection, afferent arterioles should be exposed, gently lifted up, and electrocoagulated one after the other. Neighbouring veins should not be coagulated unless one is certain they drain the cavernoma exclusively. When a large vein is found to result from the union of a vein draining the

cavernoma and a vein draining normal surrounding brain tissue, only the former may be coagulated.

In the course of removing a superficially located cavernoma the surgeon may be faced with the following problems:

– Dissection of the sulcus which would allow the most direct approach may prove difficult because of arachnoidal adhesion or an unusually large number of arterioles. This rarely occurs; in such cases the adjacent cortex has to be incised.

– An arterial branch may appear to be entrapped in the cavernoma and become a problem in the dissection (Fig. 5). We met with this difficulty in 3 cases of temporally located cavernomas (cases 9, 25 and 35). In 2 instances (cases 25 and 35), the entrapped artery could easily be dissected by breaking the cavernoma into fragments. In case 9, however, a voluminous, recurrent cavernoma was found to entrap all the branches of the middle cerebral artery and could not be separated from them; this led to further residue of the lesion. (At the time we did not have a Cerebral Ultrasonic Aspirator (CUSA), which may have been useful in this particular case, although its use near arterial structures is potentially dangerous, as noted by Kudo *et al.* (1989) in the resection of a cavernous sinus cavernoma. The advantage of this technique in difficult cases is discussed below).

– Special care should be taken when dealing with cavernomas located in eloquent zones. The question is open as to whether the quickest route should be taken in such cases, making the incision in the cortex directly overlying the lesion, or more distantly. In all our cases of rolandic location, we have always preferred the more direct approach, since we felt the cortical film over a cavernoma is non-functional, and no aggravation of the deficit occurred postoperatively. In one case (case 27) of a voluminous and relatively deep-seated lesion – shown by ultrasonic scanning to lie 2 cm below the dura – the approach was done following dissection and incision of the retro-rolandic sulcus (Fig. 12B), and the lesion was removed by using the CUSA.

– When it was felt the lesion could not be removed in a single mass, we used the CUSA, which enables the gradual removal of a cavernoma, while exerting no undue retraction of the adjacent brain parenchyma or traction on the lesion itself. Thrombosed or fibrous zones are easily removed with the CUSA; bleeding resulting from rupture of vascular spaces was never felt to be a problem.

This technique proved especially useful with heavily calcified cavernomas, which could not be mobilised. Using the following procedure, we were able to remove an extremely large (5×6 cm in diameter) temporal cavernoma (case 14), adjoining the middle cerebral artery and its branches: following wide exposure of the lesion, the softs parts were gradually aspirated with the CUSA, and the remaining calcified areas were then crushed and removed with a gouge. The lesion was totally resected, and easily freed from surround-

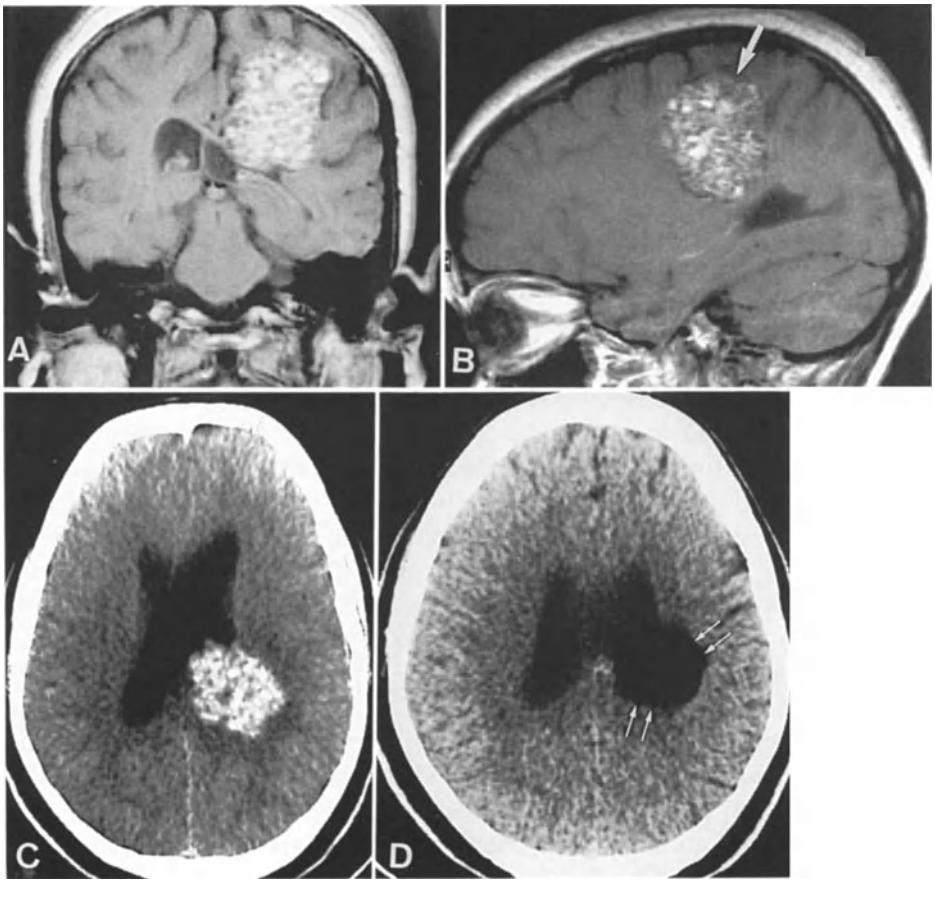


Fig. 12. Case 27. (A) Coronal T1-weighted MRI: large parieto rolandic cavernoma in 19-year-old female patient with progressive paresis of the left leg for 3 years who recently presented right jacksonian seizures. (B) Sagittal T1-weighted MRI, with white arrow showing surgical approach. (C) Pre-operative CT scan. (D) Postoperative CT scan showing the lesion has been completely removed with the use of the CUSA (arrow). Uneventful postoperative course. Full recovery

Fig. 13. Case 7. Peroperative photographs showing the removal of a right temporo occipital cavernoma. (A) The lesion is immediately visible on opening the dura. (B) Dissection at the periphery of the lesion. (C) The lesion is removed in a single mass. (D) Inspection of the operative field. The lateral ventricle is opened and the choroid plexus is exposed (arrowheads). A residual fragment remained (arrow) and was later removed. (E) Appearance and size of lesion

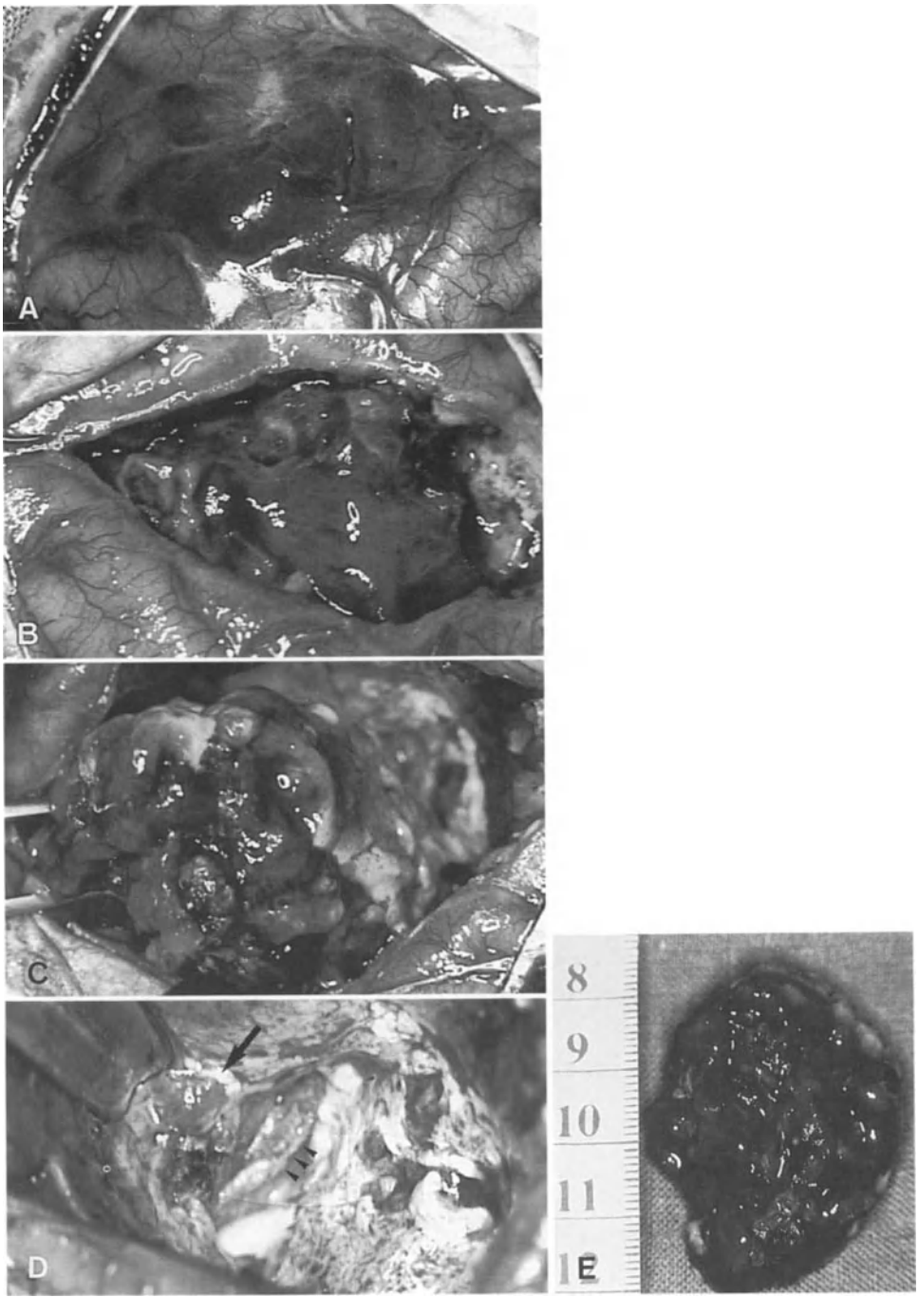


Fig. 13

ing arteries and a large vein running along its inferior aspect, while exerting no undue traction. Again using the CUSA, we carried out complete removal of a large rolandic cavernoma, as shown on Fig. 12D (case 27). This lesion consisted of multiple vascular cavities, some of which contained fluid blood and thrombosed areas, which were easily aspirated by the CUSA on maximum setting. A fibrous framework was then removed, together with small vessels which could be electrocoagulated. In our experience, the use of the CUSA was also helpful in the removal of two deep seated cavernomas of cerebellum [case 28 (Fig. 10) and case 31 (Fig. 23)].

The disadvantage of breaking up a cavernoma lies in the risk, emphasized by many writers, of leaving in place cavernomatous expansions which may cause recurrence (Miller 1961, Giombini 1978, Lavyne *et al.* 1983, Yamasaki *et al.* 1986, Tung *et al.* 1990, Fahlbusch *et al.* 1990, Zimmerman *et al.* 1981, Scott *et al.* 1992). In this type of resection, careful inspection of the walls of the operative cavity is therefore essential, to ensure that no cavernomatous nest is left in place (Fig. 13D).

The attitude towards the surrounding brain tissue obeys the same principles. As mentioned in the chapter on histology, careful histological examination of the parenchyma surrounding a cavernoma sometimes discloses additional, satellite malformations. It is therefore desirable to remove this zone, which may also favour epileptic seizures, being mainly gliotic (Rougier *et al.* 1989). In practice, the extent of pericavernomatous resection depends on the site of the lesion: in a silent zone, extensive resection may safely be carried out, whereas more pericavernomatous tissue should obviously be spared in an eloquent zone. We found the CUSA used at low power most helpful in such cases, allowing gentle aspiration of the pericavernomatous tissue.

Deep-Seated Cavernomas

From a surgical point of view, two types of location ought to be considered: intraventricular and intraparenchymal (basal ganglia, internal capsule).

Intraventricular Cavernomas

They account for 2.5% of all intracranial cavernomas (Voigt and Yaşargil 1976).

Lateral Ventricle Cavernomas (Table 5)

We found 19 well-documented cases of lateral ventricle cavernomas in the literature. In 12 out of 19 cases a mass syndrome was present, with focal neurological deficits or intracranial hypertension. 5 patients had epileptic seizures, either alone (4 patients) or associated with a mass syndrome

Table 5. *18 Patients with Intraventricular (Lateral Ventricle) Cavernomas*

Case	Author	Age/Sex	Clinical presentation			Localisation	Outcome
			Mass lesion	Seizures	Haemorrhage		
1	Merritt (1940)	16 yr/F	–	–	SAH	LLV	NA
2	Arnstein *et al.* (1951)	3 days/M	+	–	–	RLV	died
3	Schneider *et al.* (1958)	33 yr/F	+	+	–	RLV (Ø 10 cm)	hemianopsia
4	Jain (1966)	15 yr/F	+	–	–	LLV (anterior horn)	no deficit
5	Coin *et al.* (1977)	36 yr/F	–	+	–	RLV (trigone)	hemianopsia
6	Numaguchi *et al.* (1977)	43 yr/M	+	–	–	RLV (trigone)	hemianopsia hemiplegia
7	Pau *et al.* (1979)	56 yr/M	+	–	SAH	LLV (temporal horn)	died (no operation)
8	Namba *et al.* (1979)	45 yr/F	+	–	SAH	RLV (body)	no deficit
9	Iwasa *et al.* (1983)	8 days/F	+	–	–	LLV (trigone)	no deficit
10	Chadduck *et al.* (1985)	21 y/F	–	+	–	RLV	hemianopsia
11	Chadduck *et al.* (1985)	29 yr/F	+	–	–	RLV	no deficit
12	Chadduck *et al.* (1985)	4 months/ F	–	+	–	RLV (atrium)	no deficit
13	Simard *et al.* (1986)	22 yr/M	+	–	–	LLV	NA
14	Simard *et al.* (1986)	13 yr/F	+	–	–	LLV	NA
15	Yamasaki *et al.* (1986)	73 yr/M	+	–	–	RLV (trigone)	hemianopsia hemiparesis
16	Tatagiba *et al.* (1991)	33 yr/M	–	–	IVH	LLV (anterior horn)	no deficit
17	Tatagiba *et al.* (1991)	35 yr/M	–	+	–	RLV (posterior horn)	died
18	Tatagiba *et al.* (1991)	24 yr/F	+	–	–	LLV (trigone)	no deficit

SAH subarachnoid haemorrhage, *LLV* left lateral ventricle, *RLV* right lateral ventricle, *IVH* intra ventricular haemorrhage, *NA* not available.

(1 case). In 4 patients the mode of presentation was intracranial haemorrhage (subarachnoid haemorrage in 3, intraventricular haemorrhage in 1), associated with a mass syndrome in 2 cases.

The patients did not differ in age from cavernomas in other locations, except for two neonatal cases (Arstein *et al.* 1951, Iwasa *et al.* 1983).

Until the advent of MRI, no cavernoma in this location was diagnosed as such before surgery. Preoperative diagnoses included intraventricular meningioma, ependymoma, and papilloma of the choroid plexus.

There is no predominating location within the ventricles. In some cases, the cavernoma was reported to be firmly attached to the ventricular wall (Tatagiba *et al.* 1991). This feature is suggestive of a subependymal origin, with subsequent development into the ventricle, where the malformation can reach a considerable size (Schneider and Liss 1958).

The prognosis of lateral ventricle cavernomas is generally poor; 3 patients died, one of them prior to surgery. Residual disabilities are frequent, with hemianopsia ranking first, being observed in 5 (33%) of the survivors. The surgical approach is directly responsible for hemianopsia, in the case of lesions located in the posterior part of the lateral ventricle. A motor deficit was noted in two cases, in association with hemianopsia.

Third Ventricle Cavernomas (Table 6)

This is a rare location. We found only 6 well-documented cases in the literature. In 4 cases, hypothalamic dysfunction was the presenting symptom, associated with loss of vision in 2 cases and memory impairment in one patient. In 3 cases, there were signs of intracranial hypertension, due to hydrocephalus, either alone, in one patient or in association with hypothalamic dysfunction or subarachnoid haemorrhage. An MRI study was performed and a cavernoma subsequently diagnosed in only one patient. The rest were diversely diagnosed as tumours of the optic chiasm, craniopharyngiomas or ectopic germinomas.

Surgical approaches were as follows:

– A sub frontal approach was chosen in one case because a tumour of the optic chiasm was thought to be the diagnosis. This approach was inappropriate. The patient died 3 years later after gradual worsening of his symptoms. At autopsy, a cavernoma was found, with evidence of old and recent haemorrhage, and was shown to occupy the entire anterior half of the third ventricle.

– Transventricular transcortical frontal approaches were used in two instances, the lesion being approached via the foramina of Monro or following interthalamo-trigonal dissection.

– A transventricular transcallosal interhemispheric approach was done in one case.

Table 6. *6 Patients with Cavernomas of the 3rd Ventricle*

Case	Author	Age/Sex	Clinical presentation			Surgical approach	Outcome
			HD	ICH	Other		
1	Mizutani *et al.* (1981)	32 yr/M	+	–	visual disturbance	exploration of optic chiasma	died
2	Pozzati *et al.* (1981)	31 yr/F	–	+	–	frontal transcortical	no deficit
3	Lavyne *et al.* (1983)	48 yr/F	+	–	memory disturbance	frontal transcortical subchoroïdal	3rd ventricle haemorrhage (residual fragment)
4	Harbauch *et al.* (1984)	44 yr/F	–	+	SAH	interhemispheric transcallosal	no deficit
5	Ogawa *et al.* (1990)	40 yr/M	+	–	visual disturbance	interhemisperic translamina terminalis	alive (7 years)
6	Ogawa *et al.* (1990)	16 yr/M	+	+	–	interhemisperic translamina terminalis	alive (6 months)

HD hypothalamic dysfunction, *ICH* intracranial hypertension, *SAH* subarachnoid haemorrhage.

– A bifrontal craniectomy was performed and an interhemispheric approach through the lamina terminalis was used in two cases. With this approach, Ogawa *et al.* (1990) could preserve both olfactory nerves and remove in a single mass each of two large cavernomas, one of which occupied the anterior two-thirds of the third ventricle, as documented by MRI.

Operative results: third ventricle cavernomas are not different from those located elsewhere; in patient 1 no appropriate surgery was carried out and he subsequently died. Patient 2 underwent partial removal of his malformation and later presented several episodes of subarachnoid haemorrhage. The outcome was successful, on the other hand, in the four patients who underwent complete resection.

Cavernomas of the Pineal Region (Table 7)

The seven cases so far reported were all published before the advent of MRI. The mode of presentation was in every respect identical to the usual presen-

Table 7. *7 Cavernomas of the Pineal Region*

Case	Author	Age/Sex	Clinicial presentation			Treatment	Outcome
			ICH	Focal sympt.	Other		
1	Miller (1961)	35 yr/F	+	–	SAH	Torkildsen shunt irradiation partial removal	died 2 years after operation
2	Hubschmann *et al.* (1976)	45 yr/M	–	+	–	ventriculostomy shunt total removal irradiation	good
3	Vaquero *et al.* (1980)	18 yr/F	–	–	HD	total removal	good
4	Vaquero *et al.* (1980)	22 yr/M	+	–	–	VP shunt irradiation total removal	died 15 days after operation
5	Sonntag *et al.* (1981)	4 wk/F	+	+	–	VP shunt total removal	good
6	Occhiogrosso *et al.* (1983)	35 yr/M	+	+	–	VP shunt subtotal removal	mild dysmetria
7	Fukui *et al.* (1983)	22 yr/M	+	+	HD	Torkildsen shunt irradiation total removal	good

ICH intracranial hypertension, *SAH* subarachnoïd haemorrhage, *HD* hypothalamic dysfunction, *VP* ventriculo-peritoneal.

tation for tumours of this region, including intracranial hypertension, vertical gaze palsy, cerebellar signs and hormonal dysfunction. In one case, subarachnoid haemorrhage was the presenting symptom and eventually caused the patient's death, after partial removal of the malformation had been carried out. In the rest a diagnosis of pineal tumour had been made. Four patients had had radiotherapy, without previous histological studies. No reduction in the size of the lesion was noted after this treatment.

Cavernomas of the Basal Ganglia

Because of their deep, intraparenchymous situation within critical regions of the brain, the surgical approach to these malformations remains hazardous, as for other lesions (AVMs, tumours) in the same location.

The incidence of basal ganglia cavernomas is low. Reports on the subject rarely give accurate descriptions of location and surgical approach. An

important distinction should nevertheless be made between thalamic cavernomas and those located in the head of the caudate nucleus, or those located in the lentiform nucleus–internal capsule area.

Thalamic Cavernomas (Table 8)

5 cases have been published so far. In the case published by Simard *et al.* (1986) and previously described by Becker *et al.* (1979), the malformation lay in the posterior part of the thalamus. Surgical approach was through a cortico-sub-cortical incision into the posterior part of the parietal lobe, giving access to the posterior medial portion of the thalamus, which was then directly approached. The post-operative course was remarkable for the persistence of pre-existing hemiparesis and emergence of mild expressive dysphasia.

In the case reported by Vaquero *et al.* (1987), a stereotactic biopsy was initially performed. Four years later, following exacerbation of the patient's hemiparesis and aphasia, a direct surgical approach (the approach is not detailed) was done, and complete resection was carried out. The patient died in the postoperative period.

Table 8. *5 Cavernomas of the Thalamus*

Case	Author	Age/Sex	Clinical presentation	Treatment	Outcome
1	Becker *et al.* (1979)	34 yr/F	hemiparesis hemihypoesthesia/ pain	transcortical (post-parietal lobe) and transventricular approach incision of postero-medial thalamus total removal	worsening then unknown
2	Vaquero *et al.* (1987)	24 yr/F	progressive hemiparesis and dysphasia	stereotactic biopsy radical removal 4 years later	died post-operatively
3	Roda *et al.* (1990)	50 yr/M	hemiplegia aphasia (regression)	interhemispheric transcallosal approach total removal	slight improvement
4	Bertalanffy *et al.* (1991)	5 yr/M	hemiparesis	interhemisperic transcallosal approach	rebleeding (residual fragment)
5	Bertalanffy *et al.* (1991)	30 yr/M	hemiparesis	interhemisperic transcallosal approach	hemiplegia (venous infarction)

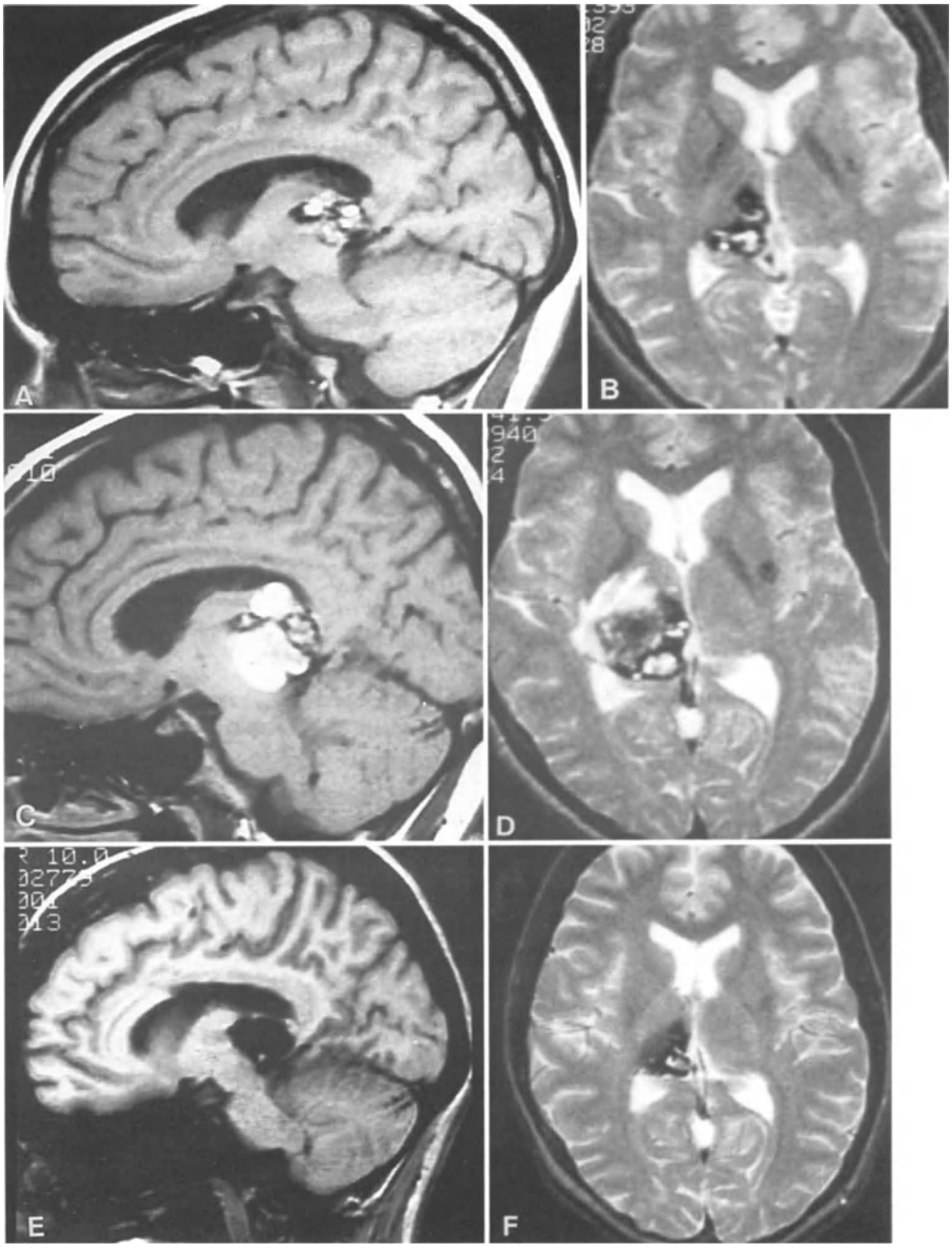


Fig. 14. Case 34. Cavernoma of the right thalamus (see text). (A) Sagittal T1-weighted MRI (1987). (B) Axial T2-weighted MRI (1987). (C) Sagittal T1-weighted MRI (1989). (D) Axial T2-weighted MRI (1989). (E) Sagittal postoperative T1-weighted MRI (1990). (F) Axial postoperative T2-weighted MRI (1990)

In the case published by Roda *et al.* (1990), complete resection of a thalamic cavernoma was carried out through a transcallosal interhemispheric approach, with the patient in a semi-sitting position. At one-year follow-up the patient's hemiparesis and aphasia were markedly improved.

The same approach was used in the two cases published by Bertalanffy *et al.* (1991). The neurological condition of both patients deteriorated in the postoperative period. Aggravation was caused by rebleeding into a residual fragment in one patient, and resulted from venous infarction in the other, following electrocoagulation of large veins near the cavernoma. (This is strongly suggestive of an associated venous angioma).

We operated on a thalamic cavernoma in a 19-year-old girl with a family history of cavernomas (case 34). At the age of seven, she presented a resolving episode of headache. In 1987, screening MRI studies were routinely performed and revealed the existence of three cavernomas, located in the right pulvinar (Fig. 14A, B), the left internal temporal lobe and left pons respectively. She was then free of symptoms and remained so until two years later when she presented with rapidly progressive right hemihypoesthesia and hemiparesis. MRI studies were repeated and showed a large haematoma originating from the thalamic cavernoma (Fig. 14C, D). An interhemispheric transcallosal approach was used, the third ventricle being approached by inter-thalamotrigonal dissection. The right lateral wall of the 3rd ventricle bulged into the cavity of the ventricle, but was not ruptured by the underlying cavernoma. It was incised and the lesion (consisting of recent and old bleeding – was removed without difficulty. However, it was impossible to inspect the whole of the large cavity and determine if the totality of the lesion had been removed. The patient made a remarkably complete recovery: her sensory as well as her motor deficits resolved (follow-up: 4 years). At 6-month follow-up, MRI findings were as follows: on sagittal T1-weighted MR image there was no signal intensity (Fig. 14E); on axial T2-weighted MRI there was a very small area of high signal intensity (Fig. 14F). At 2 year follow-up, MRI findings were unchanged.

In conclusion, thalamic cavernomas are infrequent. They produce severe neurological symptoms (motor and sensory deficits and in some cases aphasia) which may not necessarily resolve after surgery. The surgical approach itself may cause serious sequelae or even death and does not always allow complete removal of the lesion, in spite of the serious risks implied.

Cavernomas of the Caudate Nucleus

We operated on 2 cavernomas located in this area. Both patients presented with intense, sudden headache and on examination showed signs of subarachnoid haemorrhage, resulting from a large haematoma. We observed the first case in 1978 (case 4) and the second in 1993 (case 48).

Case 4: 3 1/2 year-old-boy, with a family history of cavernoma (he was the son of patient no. 4). Presenting features included sudden and severe headache, vomiting and drowsiness, followed 5 days later by meningeal signs. There was no focal deficit

or impairment of consciousness. There was left papilloedema and haemorrhage. The CSF was found to contain RBC. The cerebral angiogram disclosed a right temporoparietal, avascular, space-occupying lesion.

Surgery. A parietooccipital craniectomy was performed. The ventricular cavity was opened (a posterior compartment was formed, as a result of the lesion protruding into the ventricle) and 10 ml of fluid haematoma was evacuated after the lesion was incised. Abnormal vessels (making up the cavernoma) were disclosed and removed in a single mass. These vessels were located in the posterior part of the body of the caudate nucleus.

A mild deficit in the left leg was noted in the post-operative period, and later resolved; at 15-year follow-up, there was no deficit.

Case 48: this 34-year-old right-handed woman (who had given birth to 3 children after 3 problem-free pregnancies) experienced sudden, excrutiating headache, which lasted three days and then resolved. She was referred to our institution following recurrence of her headache and vomiting. She was conscious and had no neurological deficit. The CT scan showed a heterogenous mass located deep in the right frontal lobe (Fig. 15A). On post contrast scan, a well-defined capsule was shown (Fig. 15B). On MRI studies, there was a large heterogeneous spherical lesion occupying the right fronto insular region (Fig. 15C–E). Angiography showed an avascular area in the frontal lobe.

After careful analysis of all relevant findings, we felt the best surgical approach would be a transsylvian approach following a frontopterional craniectomy (Fig. 15C). Peroperative echographic studies were done (Fig. 15F). The cortex overlying the lesion was found to be very thin. It was incised and clots of varying age were evacuated without difficulty. The existence of a capsule was very helpful in achieving complete resection; the lesion finally proved relatively easy to dissect off from the adjacent parenchyma although the walls of the large cavity tended to close in and reduce the size of the operative field. The capsule and clots were sent for histological examination. At the bottom of the cavity, i.e. in the area of the head of the caudate nucleus, a different structure was found and removed, which probably represented the original cavernoma, partially destroyed by haemorrhage. Histologically this structure was made up of vascular spaces of different size and dysmorphic arterioles and veins (mixed cavernoma).

The postoperative course was uneventful. At 4-month follow-up an MRI scan confirmed complete resection, demonstrating a small cavity in the area of the head of the caudate nucleus (Fig. 15G, H).

Fig. 15. Large cavernoma of the head of the right caudate nucleus (see text). (A) Precontrast CT scan. (B) Postcontrast CT scan, showing enhancing capsule (arrowhead). (C) Coronal T1-weight MRI. The inferior part of the lesion is seen to lie in the internal portion of the Sylvian fissure, which will be dissected (arrow). (D) Axial T1-weighted MRI. (E) Sagittal T1-weighted MRI. (F) Peroperative echographic study. (G) Coronal postoperative T1-weighted MRI. (H) Axial postoperative T1-weighted MRI

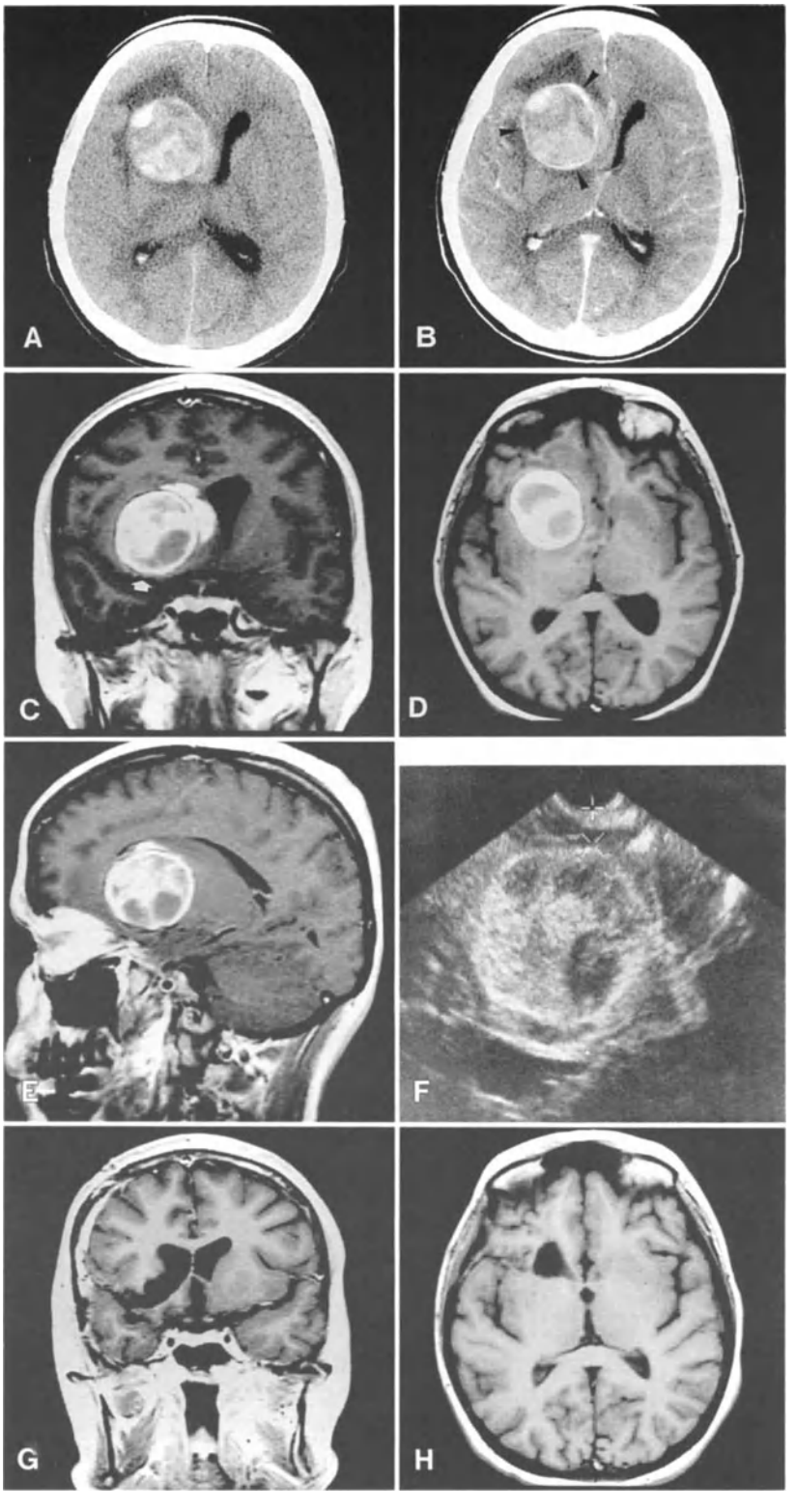


Fig. 15

Cavernoma of the Lentiform Nucleus and Internal Capsule

In their publication, Bertalanffy *et al.* (1991) grouped insular, basal ganglia, thalamic and brainstem cavernomas under the same heading of "deep-seated cavernous angiomas" and emphasized the operative risks involved with basal ganglia cavernomas. They observed complications in all three of their cases and defined the risks as: "damage to lenticulostriate arteries while dissecting through the posterior part of the Sylvian fissure with subsequent ischaemic necrosis in the retrolenticular part of the internal capsule; damage to the internal capsule itself by direct manipulation, and damage to important draining veins".

However, Bertalanffy *et al.* do not give a clear topographic description of their 7 "insular cavernomas", among which they observed only one case of complication attributable to surgery. These so-called "insular cavernomas" seem to have been located in the cortico-subcortical area of the insula and were therefore quite different from those located in the lentiform nucleus itself (Fig. 16).

To us, proper lentiform nucleus cavernomas should not be operated on, at least in patients presenting with minor or non-existent clinical symptoms.

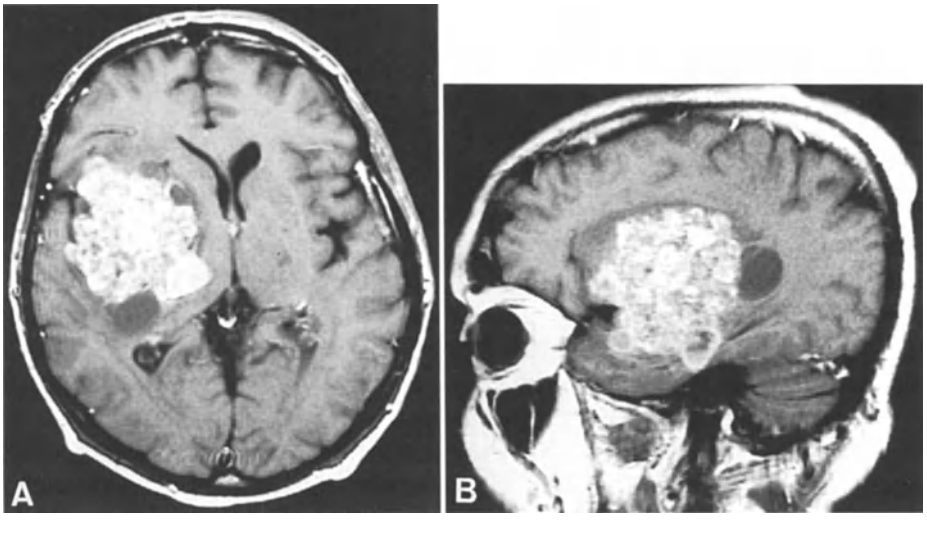


Fig. 16. (A, B) Large insular cavernoma in a 50-year-old patient presenting with left hemiplegia. Complete removal was achieved following dissection of the Sylvian fissure. After surgery, the patient made a complete recovery. This feature suggests the basal ganglia may have been compressed rather than actually involved by the lesion (by courtesy of Prof. J. Brotchi, Hôpital Erasme, Brussells, Belgium)

Cavernomas of the Optic Chiasma

In 1990, reporting on two cases of optic chiasmal cavernomas, Steinberg *et al.* reviewed the literature on AOIVMs in this location. Previously reported cases included 7 cavernomas, 4 "cryptic vascular malformations" and 3 venous angiomas. The authors pointed out that MRI cannot differentiate between these various types, which may in some cases coexist and constitute in the authors' eyes a "pathological continuum".

In addition, Steinberg establishes a link between the 14 verified cases from the literature, and six cases in which evidence of old haemorrhage into an intra-chiasmal cyst made a diagnosis of vascular malformation likely, although histologically unproven. Presenting symptoms typically include progressive or sudden loss of vision ("chiasmal apoplexy") and visual field defects of the chiasmal type. Differential diagnosis includes suprasellar tumours, cysts, and partially or completely thrombosed giant aneurysms. Few cases have been investigated by MRI. In the five which were, this modality proved far more specific than other imaging techniques, showing the typical appearance of a cavernoma, as described for other locations, and demonstrating that the malformation arose from the chiasma itself. The use of CO_2 laser is considered a benefit by Steinberg *et al.* This technique allows for coagulation and vaporizing of the cavernoma with minimal injury to the optic tracts.

Complete removal cannot always be achieved (it has been reported in only 6 cases, including Steinberg's, in which he used the CO_2 laser) but functional vision was preserved in all patients and in some visual acuity and visual fields were found to be subjectively or objectively improved.

An example of cavernoma of the optic chiasma is illustrated on Fig. 17 (personal case 50).

Extra-Axial Cavernomas of the Middle Cerebral Fossa

These are rare, particular forms of the disorder, principally observed in Japanese women (Mori *et al.* 1980, Namba 1983), although a few cases have been published outside Japan (Pasztor *et al.* 1964, Rigamonti *et al.* 1990). In the 23 cases from the literature collected and reviewed by Namba, they always presented as large-sized lesions, occupying the middle cerebral fossa and suprasellar region, and causing bone destruction in the neighbouring structures. Resultant clinical features included optic, oculomotor and trigeminal nerve dysfunction as well as hormonal dysfunction. Symptoms are usually slowly progressive but episodes of exacerbation may be observed, due to sudden haemorrage. Neuroradiological features are those of meningiomas, with intense enhancement on CT and positive angiographic findings, the malformation being supplied by meningeal arteries arising from the

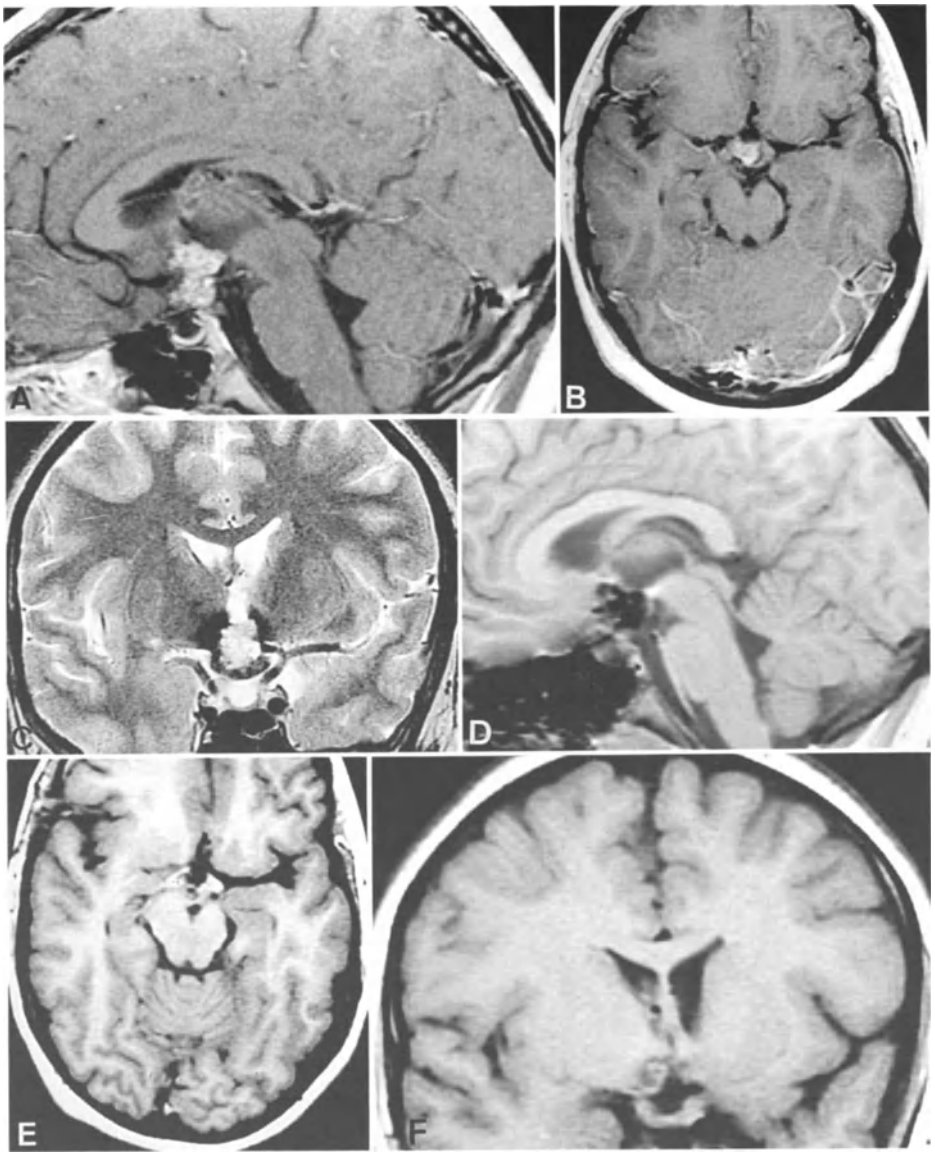


Fig. 17. Case 50. Cavernoma of the optic chiasm extending to the hypothalamus in a 11-year-old child, exhibiting obesity and loss of vision for 6 years. A surgical biopsy (subfrontal approach) was performed at another institution when he was 7, with a diagnosis of craniopharygioma in mind. Histological findings were consistet with a "resorbing haematoma within a vascular malformation". Gradual deterioration of visual function ensued. In 1993 he presented with bitemporal hemianopsia. Complete removal of his cavernoma was carried out using a subfrontal approach and resulted in stabilisation of visual function. Transient diabetes insipidus was noted postoperatively. (A, B) Preoperative sagittal and axial T1-weighted MRI. (C) Preoperative coronal T1-weighted MRI. (D–F) Postoperative T1-weighted MRI

external carotid artery and by the internal carotid artery. These malformations are almost invariably diagnosed as meningiomas before surgery. If surgical intervention takes place, they have been shown to be highly vascularised, extra-dural malformations, probably originating from the cavernous sinus. The use of preoperative radiotherapy has been recommended to reduce the size and vascularity of the lesion (Namba 1983, Shibata and Mori 1987, Rigamonti *et al.* 1990). In the experience of Shibata and Mori, 3 cases were treated by the administration of 3000 rads. In this way, the authors were able to achieve complete surgical removal of one lesion, whereas the initial operation had to be interrupted because of uncontrollable haemorrhage. In the second case, previously deemed inoperable, subtotal resection was carried out following radiotherapy. In the third case, clinical signs resolved and the lesion was significantly reduced in size, so that surgery was no longer necessary. These results suggest that radiotherapy may be a useful adjunctive, if not radical, treatment of extra axial cavernomas and need to be confirmed by further studies.

Cavernomas of the Cavernous Sinus

This was considered an extremely rare location (Rosenblum *et al.* 1986, Sawamura and de Tribolet 1990, Rigamonti *et al.* 1990). However, Meyer *et al.* (1990) recently published six cases of cavernous sinus cavernomas, to which they added one case developed within the petrosal sinus and another located in the torcular.

Although they identify their own cases with the extra-axial cavernomas of the cerebral middle fossa described by Namba, the authors report better operative results, total resection being achieved in 6 out of 8 cases, with no additional deficits.

Meyer *et al.* as well as Momoshima *et al.* (1991), emphasize the value of MRI, especially coronal scans, in the surgical planning. Meyer *et al.* attribute their good results to the fact that the lesion is enclosed within the cavernous sinus. Extradural resection of the lesser wing of the sphenoid and partial resection of the greater wing, affording early exposure of the neurovascular structures within the cavernous sinus, allows for successful removal with negligible morbidity. In one case where subtotal resection was carried out, radiotherapy was administered and had caused a significant reduction in size by one-year follow-up examination.

Prior to Meyer's publication, Harper *et al.* (1982) reported the case of a cavernoma located in the anterior portion of the cavernous sinus, extending to the orbit through the superior orbital fissure and Fehling and Tucker (1988) reported a case located in Meckel's cave. In both cases there was evidence of bone erosion, reflecting the potentially aggressive behaviour of cavernomas.

From a histological view-point, Meyer *et al.* noted the specificity of extra-axial cavernomas. In spite of the structural identity with intra-axial cavernoma, the former never demonstrates old haemorrhage, and, unlike the latter, always appears to be highly vascularised. The authors proposed to term this particular entity "sinus cavernoma".

Sinus cavernomas (developed within a dural sinus) must be differentiated from "dural cavernomas" (Pozzati *et al.* 1988).

Infratentorial Cavernomas

Brainstem Cavernomas

Because of the vital importance, in terms of life and function, of the structures involved, brainstem cavernoma should be considered as a specific entity.

Attempts at surgical treatment were often made in the past, usually in normotensive patients with pontine haematomas. The surgeon would evacuate the clot and a cavernoma or other AOIVM would sometimes be diagnosed incidentally during surgery.

Since MRI allowed preoperative diagnosis and precise, three-dimensional anatomical definition of the lesion, a number of series have been published, reporting planned surgery, the choice of an approach being determined by the exact location of the lesion.

Recent technical progress, such as the surgical laser, or peroperative evoked potentials, have also contributed to improve surgical procedures.

This type of surgery nevertheless remains difficult and potentially hazardous; the indications should be carefully thought-out and discussed on an individual basis.

Clinical Features

The anatomy and neurophysiology of the brainstem account for the clinical presentation; this includes long tract (upper motor neurone, sensory and cerebellar) impairment as well as cranial nerve (the nuclei and initial pathways of which are located in the brainstem) dysfunction. Signs of intracranial hypertension may also be observed, as a result of aqueduct and/or fourth ventricle blockage.

Whenever presenting features point to brainstem involvement, particular attention should be paid to the history: it is generally agreed that brainstem cavernomas tend to follow a remittent course, which could be suggestive of multiple sclerosis before the advent of MRI.

Such a remittent history should not be equated with a benign course, however. In a neurophysiologically vital area, even a small cavernoma can produce considerable injury. Further evidence of this was recently provided

Table 9. *53 Brain Stem Cavernomas Operated on After MRI Studies*

Authors	No. of cases
Yoshimoto *et al.* (1986)	1
Yaşargil (1988)	4
Ondra *et al.* (1988)	1
Seifert *et al.* (1989)	1
Fahlbusch *et al.* (1990)	4
Scott (1990)	2 (children)
Ledoux *et al.* (1991)	2 (children)
Symon *et al.* (1991)	4
Bertalanffy *et al.* (1991)	14
Zimmermann *et al.* (1991)	16 (2 children)
Personal series (1993)	4
Total	53

by Robinson *et al.* (1991), in a study of the natural history of cavernomas; among patients with both supra and infra-tentorial cavernomas, representing a total of 110 year-lesions, morbidity was found to be significantly higher in those with brainstem cavernomas.

In order to provide the reader with valid and up-to-date information on the surgical management of brainstem cavernomas, we shall confine our study to MRI-documented and histologically verified cases. We chose to eliminate a number of cases where no MRI studies were performed or in which histological findings did not support the diagnosis in spite of suggestive MRI appearance (Kashiwagi *et al.* 1990). We have included cases published in literature since 1986. The majority were published after 1991 (Table 9).

Location

Precise knowledge of the site of the lesion is essential to the discussion of surgical indications and selection of the best approach. Localisation is not always restricted to one level (either pons, midbrain or medulla) of the brainstem but rather is predominant in one or the other (Table 10).

Through careful analysis of MR images, the caudal, rostral, ventral or dorsal, lateral or median situation of the lesion can be determined, as well as the area where it lies most superficially, in relation to the surface of the brainstem or the floor of the fourth ventricle; this last point is essential in determining the best approach, to avoid injury to normal brain tissue.

Table 10. *Brain Stem Cavernomas: Localisation (53 Cases)*

Authors	Pons	Midbrain	Pons + midbrain	Medulla	Pons + medulla	Brachium pontis
Yoshimoto	1					
Yaşargil		2				2
Ondra			1			
Seifert	1					
Fahlbusch			2		2	
Scott	1	1				
Ledoux			1			1 (← pons)
Symon	2			2		
Bertalanffy	8	5 (→ insula)				
Zimmerman	4	5 (1 → thalamus)	1	4	1	1 (← pons)
Personal series	2	2 (1 → basal ganglia)				
Total	19	15	5	6	3	5

Zimmerman *et al.* (1991) differ from Davis and Kelly (1990) on the subject. While the latter advocated stereotactic resection of AOIVMs, including those located in the brainstem, Zimmerman wrote: "the straight-line approach does not take advantage of the extra-axial planes of dissection and exposure available with careful microsurgery. This is especially true for cavernous malformations of the brain stem." We agree with this view.

Surgery

Approach (Table 11)

"The most difficult aspect of surgery is adequate exposure for total removal" (Ledoux *et al.* 1991). Contrary to supratentorial cavernomas, the surgical approach to brainstem cavernomas is always difficult. As previously stated, MRI findings are essential in selecting an approach. Depending on cavernoma location, five approaches can be used, either alone or in combination.

Table 11. *Surgical Approaches Used in Brain Stem Cavernomas (53 Cases)*

Authors	Sub-temporal	Suboccipital retro-mastoid	Combined ST + SORM	Suboccipital sub-cerebellar (floor V4)	Sub-occipital supra-cerebellar
Yoshimoto				1	
Yaşargil		2			2
Ondra	1				
Seifert		1			
Fahlbusch	1			2	1
Scott	1			1	
Ledoux				2	
Symon		1		3	
Bertalanffy	1	1		7	5
Zimmerman	3		5	6 (3 + laminectomy C1–C2)	2
Personal series	2			2	
Total	9	5	5	24	10

1) Subtemporal approach (9 cases)

This approach is indicated for anterolateral midbrain and pontomesencephalic cavernomas (Fig. 18). Depending on the exact location of the lesion, it may be necessary to open the tentorium in order to obtain adequate exposure (Ondra *et al.* 1988, Guy *et al.* 1989).

2) Suboccipital supracerebellar approach (10 cases)

This approach has been used in the case of cavernomas located in the posterior part of the midbrain (tectal region), with the patient in a sitting position (Fig. 19).

3) Lateral suboccipital retromastoid approach (5 cases)

This approach is done with a patient in a sitting or park bench position. It is indicated for lesions located in the inferior lateral part of the pons or those

laterally located in the medulla. C1 and C2 laminectomy may be necessary. Yasargil (1988) also proposed using this approach in cavernomas of the brachium conjunctivum. In two cases "the lesions were reached by lifting up the ipsilateral tonsil and dissecting upwards supermedially to the origin of the VII and VIII to the bulbopontine sulcus".

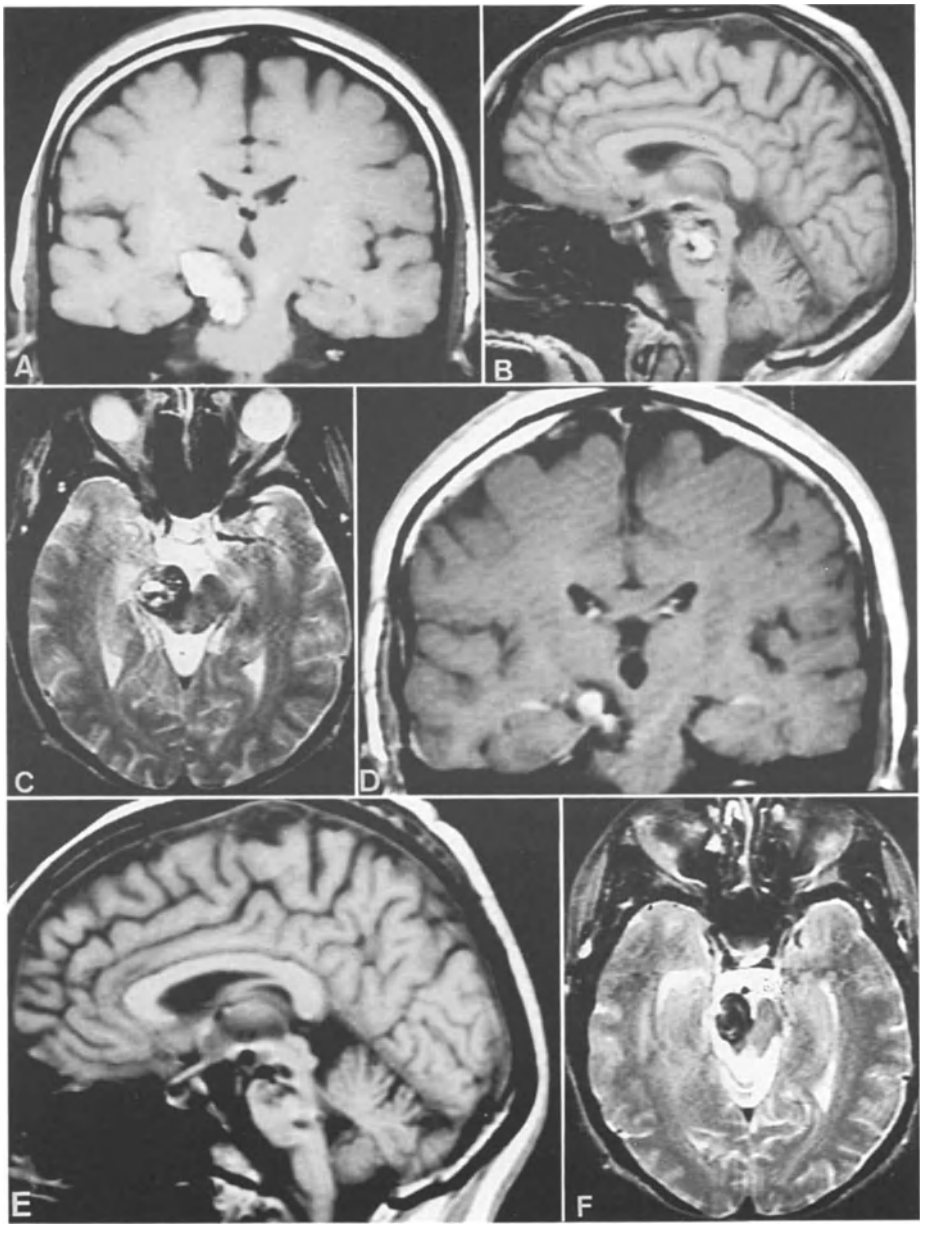


Fig. 18

4) Combined subtemporal and suboccipital retromastoid approach (5 cases)

Zimmerman *et al.* (1991) used the lateral occipital retromastoid approach in combination with the subtemporal approach in 5 cases, in the course of one – or two – stage operations.

5) Suboccipital subcerebellar approach (24 cases)

This approach is the most frequently used (Table 11). In most cases the lesion causes considerable bulging of the floor of the fourth ventricle but the floor remains intact (Fig. 20). Every effort should be taken to approach the lesion at its most superficial portion while taking into account the specific anatomy of the floor of the fourth ventricle and any subsequent risk of injury to cranial nerve nuclei. In other cases the floor is ruptured and should not be incised (Fig. 21).

Surgical Technique

The neurosurgeon's aim, which is to achieve complete removal of the lesion while causing no injury to the normal brain, is almost a contradiction in terms. In addition to an adequate exposure and a good experience with microneurosurgical procedures, a number of technical aids are at present available, namely:

1) ultrasonic localisation (Ondra *et al.* 1988); 2) CO_2 laser (Ondra *et al.* 1988, Seifert and Gaab 1989, Bertalanffy *et al.* 1991); 3) intraoperative electrophysiologic monitoring of brainstem auditory evoked potentials (BAEP) and somatosensory evoked potentials (SSEP) (Ondra *et al.* 1988, Seifert and Gaab 1989, Fahlbusch *et al.* 1990, Bertalanffy *et al.* 1991); 4) monitoring of intracranial pressure through a frontal burr hole (Fahlbusch *et al.* 1990).

Fig. 18. Case 43. Cavernoma of the right anterior midbrain extending to the subthalamic region in a patient with progressive left spastic hemiplegia and hypoesthesia (see Fig. 8). (A) Coronal T1-weighted MRI. (B) Sagittal view. (C) Axial T2-weighted MRI. The operation was carried out via a subtemporal transtentorial approach. The pedoncular portion of the lesion was removed entirely, while the subthalamic portion, appearing completely thrombosed, was left in place. The postoperative course was satisfactory, with stabilisation of the patient's clinical status at 12-month follow-up. (D) Postoperative coronal T1-weighted MRI showing a small area of high signal intensity in the subthalamic area corresponding to the thrombosed part of the lesion. (E) Postoperative sagittal T1-weighted MRI. (F) Postoperative axial T2-weighted MRI

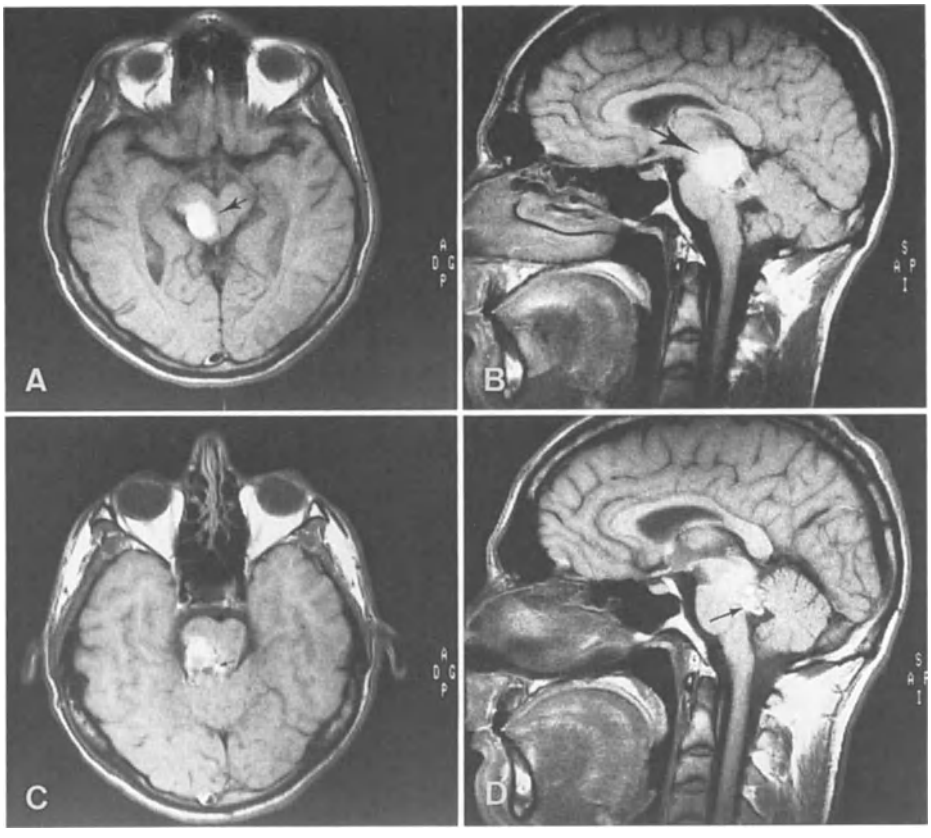


Fig. 19. Sagittal (A, C) and axial (B, D) T1-weighted MRI in a patient with a cavernoma of the right posterior midbrain, operated on in a sitting position via a supracerebellar infratentorial approach (complete removal) (by courtesy of Prof. P. Creissard, CHU Charles Nicolle, Rouen, France)

Apart from these techniques, the authors unanimously recommend that the incision be made parallel to the fibre tracts. This is especially important in the case of cavernomas located in the cerebral peduncles to avoid sectioning the upper motor neurone and spinothalamic tracts. The initial incision should be minimal, no more than 3 to 5 mm in length. (In the case reported by Ondra, the CO_2 laser was used to perform a 0.8 cm ponto-mesencephalotomy). It enables prior evacuation of the fluid hematoma; solid components, made up of the cavernoma itself and possible thrombi, are then gently removed. Yaşargil (1988), in two cases of cavernomas located in the posterior part of the midbrain, for which he used an infratentorial supracerebellar approach, described this phase of the operation in the following terms: "solid components of the cavernoma were removed by introducing a small sponge into the clot cavity and gently stroking the walls with it. Fragments of

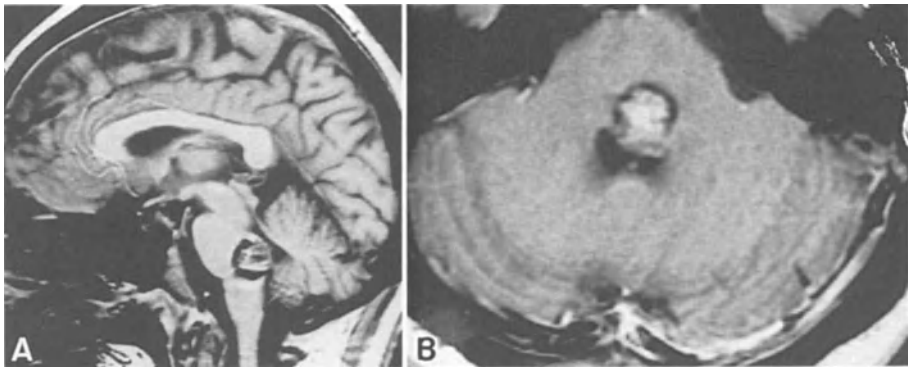


Fig. 20. Case 19. Pons cavernoma protruding into the IVth ventricle. (A) Sagittal T1-weighted MR image. (B) Axial T1-weighted MR image. – 19-year-old patient admitted for intracranial hypertension and VIth and VIIth nerve palsy. She had presented a subarachnoid haemorrhage two years previously, which was not investigated. A suboccipital subcerebellar approach was used; the IVth ventricle was exposed by elevating the vermis. The lesion caused considerable bulging of the left paramedian pontic portion of the floor of the IVth ventricle, but the floor remained intact and had to be incised in order to remove the cavernoma. After surgery the VIth and VIIth nerve palsy incompletely resolved

cavernoma together with small feeding vessels tended to cling to the sponge and could be dissected off and removed".

Another factor to influence technical conditions of the surgical removal of a cavernoma is the delay between the onset of symptoms and surgery (Fahlbusch *et al.* 1990, Bertalanffy 1991).

Fahlbusch *et al.* (1990) consider that relatively early surgery – within 4 to 6 weeks of the haemorrhage – will be made easier by the presence of a haematoma which is still unorganised. Lesser amounts of fibrous and perilesional gliotic tissue will also facilitate surgery. Among the 4 patients with brainstem cavernomas he operated upon, the one who underwent delayed surgery (4 months) experienced an aggravation of his symptoms after surgical removal, which also proved more difficult than in the other three cases.

Scott (1991), although not expressly mentioning the timing of surgery, stressed the difficulties encountered in the surgery of brainstem cavernomas. The innermost parts of the lesion are difficult to distinguish clearly and dissect, being surrounded by gliotic and granulation tissue. According to the author another problem lies in the fact that foci of normal glial tissue are often seen inside the cavernoma itself, which is not perfectly round. Wharen *et al.* (1982) expresses a similar opinion, stating that a number of such malformations are mixed, made of cavernomatous components and telangiectases, interspersed with normal brain tissue.

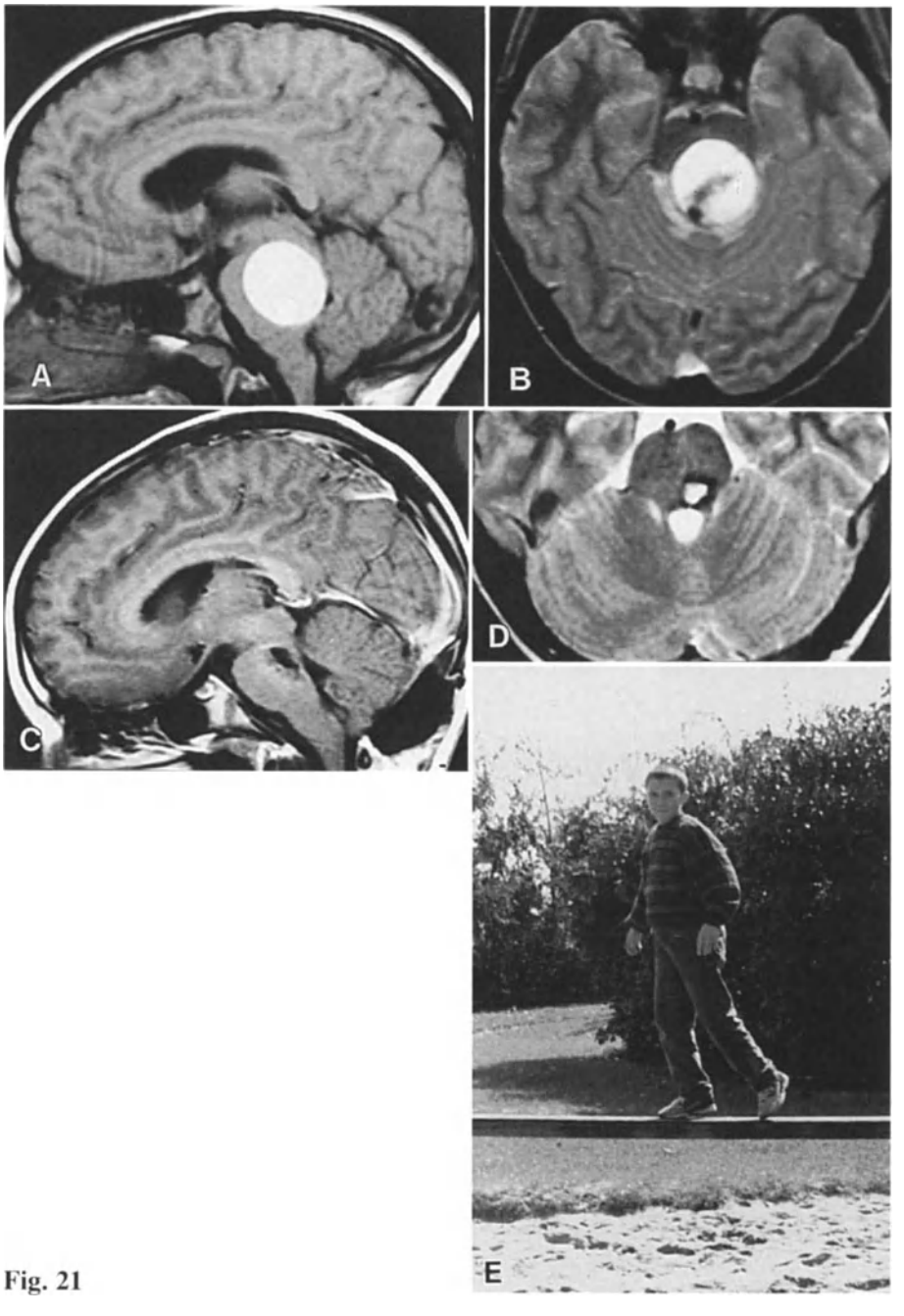


Fig. 21

Finally Scott doubts the capability of laser – which he himself did not use – when applied to the innermost part of the operative cavity, considering how difficult, or even impossible, it is to achieve adequate retraction of its walls.

On the other hand Seifert *et al.* (1989), reporting the case of a right-sided pons cavernoma lying close to the exit zone of the trigeminal nerve, and approached via a retromastoid suboccipital route, found the CO_2 laser ("high focused CO_2 laser beam with a power setting of 3 watts") most helpful to incise the brainstem and vaporise the deeper parts of the lesion, the borders of which proved extremely difficult to dissect. (In this phase of the operation the CO_2 laser was used with the defocused mode and a wattage of 5 to 8 watts). During the vaporising phase, bleeding was insignificant and required no coagulation. The outermost part of the cavernoma had previously been dissected in the usual microsurgical manner, allowing tissue sampling for later neuropathological examination.

The possibility of an associated venous angioma is especially likely in the posterior fossa. It should always be suspected in the case of a brainstem cavernoma and should be carefully ruled out with MRI and vertebrobasilar angiographic studies. The possibility of such an association was noted by Rigamonti *et al.* (1988), Fahlbusch *et al.* (1990), Bertalanffy *et al.* (1991), and Zimmerman *et al.* (1991). In one of Zimmerman's cases, the cavernoma was resected and the venous angioma was left in place.

Surgical Results in Brainstem Cavernomas (Table 12)

Again taking into consideration only those cavernomas documented by MRI and verified histologically (54 cases), good results, i.e. complete resolution

Fig. 21. Case 49. Voluminous pons cavernoma in a 12-year-old boy. Bilateral VIth nerve palsy of sudden onset, followed 15 days later by severe ataxia and right cerebellar signs making writing impossible. Episodes of sudden, excruciating headache. (A) Sagittal T1-weighted MRI: large area of homogeneous high signal intensity in the posterior part of the pons, effacing the ventricular cavity. (B) Axial view. A strip of hyposignal intensity may be seen within the area of high signal intensity. – The patient underwent surgery in May 93 (park bench position; subcerebellar approach). A 10-mm vermian incision was made. At the level of the right upper half of the floor of the fourth ventricle, just above the acoustic radiations the floor was found to be ruptured over a surface of about 10 mm^2, allowing the lesion to be removed without any further incision. Removal of the lesion through this breach was greatly facilitated by the presence of a capsule, giving the surgeon a firm grip on the lesion and affording a cleavage plane which could be followed throughout the operation. The cavity was held open with cottonoids. – (C) Postoperative sagittal MRI scan 4 months later. T1-weighted image. (D) Postoperative MRI scan. T2-weighted image. (E) Full recovery (4 months following surgery)

Table 12. *Operative Results in Brain Stem Cavernomas (53 Cases)*

Authors	No. of cases	Good results	Post-Op. morbidity	Mortality
Yoshimoto	1	1		
Yaşargil	4	4		
Ondra	1	1		
Seifert	1	1		
Fahlbusch	4	4		
Scott	2[a]	1	1	
Ledoux	2[b]	2		
Symon	4	4		
Bertalanffy	14	12	2 1 paradoxal embolism 1 rebleeding from residual fragment	
Zimmerman	16	15[c]		1 (infection shunting at 6 months)
Personal series	4	4		

[a] Subtotal resection in the two cases.
[b] Subtotal resection in a case.
[c] In a case a good result was obtained after a second operation for residual fragment.

or marked improvement of symptoms, were obtained in 92% of cases. A majority of writers stress the fact that a fair outcome was frequently preceded by immediate postoperative aggravation. In the series of Zimmerman *et al.*, one late death taking place six months after surgery, was caused by infection complicating a shunt. In the study by Bertalanffy *et al.*, an extremely poor outcome was the result of peroperative paradoxical embolism. The presence of small foci of residual cavernoma caused rebleeding, 30 months after the initial surgery, in one of Zimmerman's patients. The overall neurologic result was good, however, following a second operation. On the other hand, one of Bertalanffy's patients suffered from rebleeding which produced lesions resulting in a poor outcome. Although the aim of this surgery is to achieve complete resection of the cavernoma, it must be noted that in 2 of Scott's cases, residual cavernomatous fragments had not caused rebleeding at respectively 2 and 4 1/2 year follow-up visits. One of Ledoux's cases was also reported not to have re-bled after partial removal. In the event of an incomplete removal, a postoperative MRI study is warranted in all patients with

surgically treated brainstem cavernomas. If the cavernoma has been totally resected, an area of low signal intensity should be seen. Any residual fragment will appear as a focus of high signal intensity. In the latter case, reintervention is usually preferable, to prevent further bleeding which may occur several years later, but should be discussed on an individual basis.

Conclusion

Analysing the outcome in patients operated on, using the latest technical refinements, it is clear that surgery is the best treatment in the case of brainstem cavernomas. No randomised prospective study is available on the subject, but useful information is provided by the experience of Zimmerman *et al.*: the good results obtained in the patients who underwent surgery were compared with those of 8 cases that were not operated on, due to minor or no clinical symptoms in 7 instances, and occurrence of a venous angioma in one patient. One of the 8 patients later died from massive haemorrhage.

The existence of slowly progressive brainstem cavernomas is beyond doubt, but the natural history of the disorder remains incompletely understood. In the case of a symptomatic brainstem cavernoma, located in such a way as to permit surgical approach while sparing normal brain tissue, there is unanimous agreement on the indication for surgical removal.

Is Radiotherapy Indicated in Intra-Axial Cavernoma?

Some deep-seated cavernomas have been treated initially by radiotherapy in preference to surgery. In a series of 6 pineal cavernomas reported by Fukui *et al.* (1983), 4 patients underwent radiotherapy, without diagnostic histological studies. In all 4 cases radiotherapy proved ineffective and surgical treatment was decided upon. Vaquero *et al.* (1980) reported a similar experience with 2 cases of pineal cavernomas and Ogawa *et al.* (1990) in a case of cavernoma of the third ventricle. Previously, Yoshimoto and Susuki (1986) observed a case of third ventricle cavernoma extending to the hypothalamus which increased in size after being administered 5,000 rads of ^{60}CO radiation. Some brainstem cavernomas have also been treated by radiotherapy, with poor results in the case of a superior cerebellar peduncle lesion treated by stereotactic radiosurgery using the Bragg Peak method (Tung *et al.* 1990). In the experience of Kashiwagi *et al.* (1990), a pontine cavernoma was treated by high energy proton-beam radiotherapy and carefully followed-up for the next two years: gradual clinical deterioration ensued and MR images demonstrated an expanding mass lesion consisting of haematomas of varying age. On the other hand, Yamasaki *et al.* (1986) observed a decrease in the size of 3 brainstem cavernomas on 3-month follow-up CT scans, parallelled by

significant clinical improvement, but no later follow-up findings are given. Giombini and Morello (1978) reported a 12-year remission period in a patient treated by radiotherapy, who later presented with severe haemorrhage. The free interval, according to the authors, was due to spontaneous remission rather than radiotherapy. More recently Kondziolka *et al.* (1990) reported their experience in the treatment of AOIVMs by stereotactic radiosurgery. All lesions were deep-seated and were treated following a second haemorrhage. In 5 cases of relatively large lesions, radiation-related complications occurred. In 4 instances, the malformation was shown to decrease in size, but the authors admitted that no MRI obliteration criteria were present.

Altogether the issue remains controversial. Weil *et al.* (1990) disapprove of the use of stereotactic radiosurgery in this type of malformation and Scott *et al.* (1992) consider this treatment unsuitable for children because of the risk of radiation-induced lesions. We personally feel that radiotherapy, whatever its specifications, is hardly an adequate treatment for this pathology (Steiner, personal communication 1989).

Cerebellum

Intracranial cavernomas are rarely found in the cerebellum, be it in the cerebellar lobes or the vermis (de Tribolet *et al.* 1982). Clinical manifestations do not differ from other locations: in five cases reviewed by Simard *et al.* (1986), 3 cavernomas presented with haemorrhage and 2 as a mass lesion. In Scott's paediatric series (1992), 2 patients out of 19 had a cerebellar cavernoma. Hayashi *et al.* (1985) described a case of vermian cavernoma in a 6-month-old infant; the lesion had reached a considerable size and at histology was found to be mixed, containing cavernomatous components as well as telangiectases. The case observed by Sabatier *et al.* (1989) also occurred in an infant.

We operated on 3 cerebellar cavernomas.

The first one (case 28) (Fig. 22) was located externally at the junction between the left cerebellar lobe and brachium pontis, just behind the cerebellopontine angle. The patient was placed in the lateral park bench position. After the left cerebellar lobe was elevated, branches of the middle cerebellar arteries were dissected from the arachnoid, then gently displaced to the left, exposing the yellow-coloured area overlying the lesion. This was located posteriorly at mid-distance between the VII, VIII and IX, X and XI nerves. An incision was made into the cerebellar cortex overlying the lesion, which was completely removed, using the CUSA at low setting.

Our second case (case 31) (Fig. 10) was located in the right angle of the IVth ventricle, at the junction between the right cerebellar lobe and brachium pontis. It was shown to be associated with a venous malformation. A suboccipital subcerebellar approach was taken, and the floor and right lateral angle of the IVth ventricle were exposed by elevating the vermis. The lesion was immediately visible, consisting of two distinct parts, the cavernoma itself situated in the cerebellar area and a haemato-

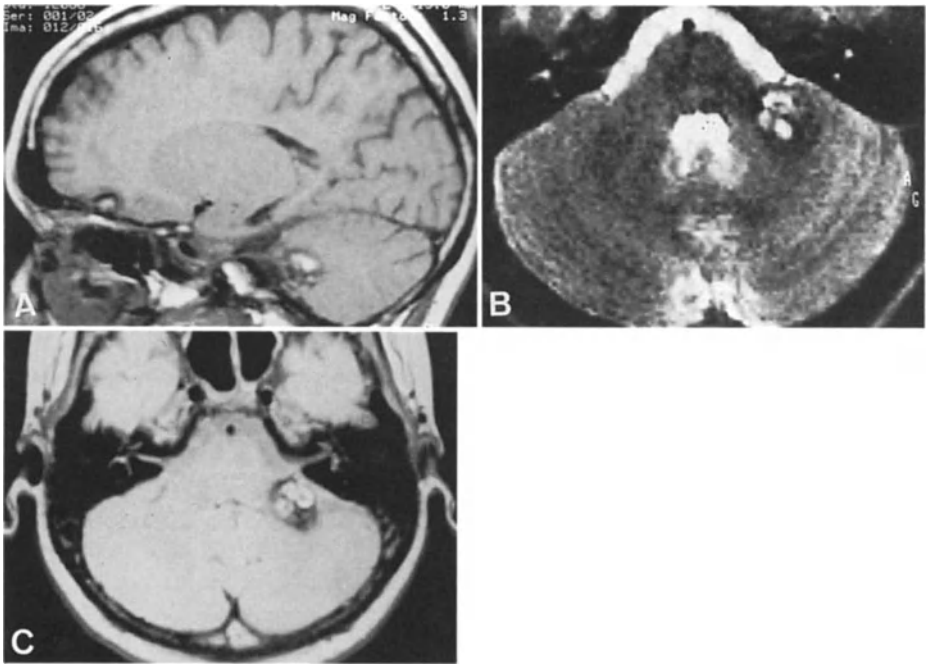


Fig. 22. Case 28. Cerebellar cavernoma. This 15-year-old girl had an MRI scan performed for generalised seizures, which revealed 2 distinct cavernomas, one frontobasal and the other cerebellar [(A) sagittal T1-weighted MR image]. On axial T2 (B) and T1-weighted (C) MRI scans, the cerebellar lesion was shown to be located at the junction between the left cerebellar lobe and brachium pontis, just behind the internal auditory canal

ma extending into the floor of the IVth ventricle. The CUSA proved very useful in removing the lesion completely.

The third cerebellar cavernoma in our series was located in the vermis (case 45) (Fig. 23). Complete resection was achieved through a suboccipital subcerebellar approach.

Extra-Axial Cavernomas of the Posterior Cerebral Fossa

Some authors have mentioned the existence of cavernomas arising from the dura of the tentorium cerebelli (Quattrochi *et al.* 1989). The peroperative diagnosis was that of a meningioma of the cerebellar convexity (Sathi *et al.* 1992). Extra axial cavernomas of the pontocerebellar angle, extending into the internal auditory canal (Sundaresan *et al.* 1976) have also been described, and may easily be confused with an acoustic neuroma: although associated always with peripheral facial paralysis, progresive deafness is the usual mode of presentation.

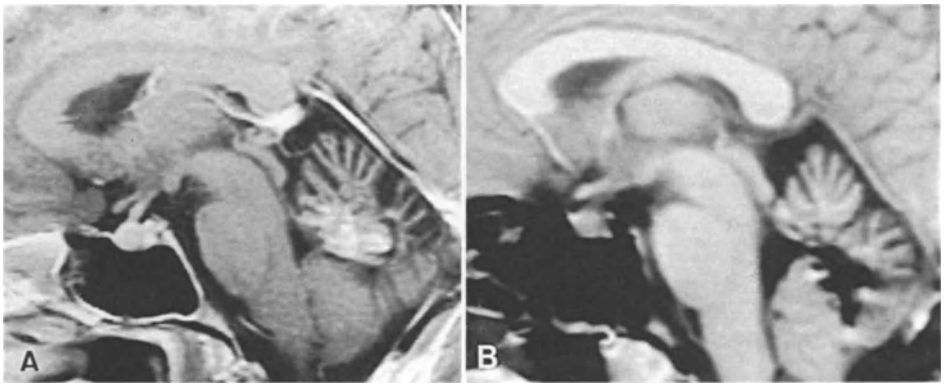


Fig. 23. Case 45. Vermian cavernoma in a 33-year-old woman. At 19 years of age, she presented an episode of unsteadiness and headache which lasted 15 days. Followed by difficulties in keeping her balance when tired. Absence of neurologic signs on examination. She was operated on through a subcerebellar approach. The vermis was incised and the lesion totally removed in a single mass. – (A) Preoperative sagittal T1-weighted MRI. High signal intensity area in the upper vermis, surrounded by a rim of low signal intensity in its posterior inferior part. Atrophic appearance of the overlying vermian cortex. (B) Postoperative sagittal T1-weighted MRI. The vermian cortex appears to be less atrophic than previously. Considerable improvement in gait and balance

Conclusion

Like other angiographically occult intracranial vascular malformations, cavernomas were largely unrecognised until the advent of modern neuroimaging. The CT scan, and to a much greater extent MR imaging disclosed its frequent and ubiquitous occurrence, as well as the existence of multiple forms (usually in association with familial forms), and demonstrated that the vast majority of cavernomas are accessible to surgery. MR imaging has also shown cavernoma to be a dynamic lesion, displaying evidence of intra or extra-lesional, recurrent haemorrhagic changes, with potentially serious consequences to the patient where vital and/or eloquent zones of the brain are concerned. As rebleeding is such a major risk, any cavernoma that has haemorrhaged must be considered as an absolute surgical indication, provided that it can be safely removed without creating any further damage. In other instances, thrombosis (and possibly calcification) is a predominant factor because of the slow flow through the lesion, giving rise to most epileptogenic forms. Here again surgery is indicated, because of the favourable outcome as far as epilepsy is concerned and also to prevent any risk of haemorrhage, which remains a possibility in heavily thrombosed, calcified lesions. Whatever the indication, the neurosurgeon's goal must be the complete removal of

the lesion; this is the only way to eliminate the risk of rebleeding. Whatever the site of the lesion, supra or infra-tentorial, an associated venous malformation should be diagnosed by all available means before surgery, and if present, should always be left in place. There is no alternative to surgery in the case of an intra-axial cavernoma; the efficiency of radiotherapy remains to be proved.

Finally, most authors recommend that an asymptomatic cavernoma, diagnosed incidentally, should not be operated on. The reason behind this attitude lies in our incomplete knowledge to date of the natural history of the disorder, which requires further studies, based on MR imaging, for better understanding.

Acknowledgements

The author wishes to express his thanks to Elisabeth Baranger for translating the manuscript and Sally Turner for correcting it, and also to Lassaad Bsili, Dominique Guernier and Marie-Noëlle Sarraud for their invaluable help in completing this work.

References

1. Ahmadi J, Miller CA, Segall HD, Park SH, Zee CS, Becker RL (1985) CT patterns in histopathologically complex cavernous hemangiomas. AJNR 6: 389–393
2. Arnstein LH, Boldrey E, Naffziger HC (1951) A case report and survey of brain tumors during the neonatal period. J Neurosurg 8: 315–319
3. Becker DH, Townsend JJ, Kramer RA, Newton TH (1979) Occult cerebrovascular malformations. Series of 18 histologically verified cases with negative angiography. Brain 102: 249–287
4. Bellotti C, Medina M, Oliveri G, Barrale S, Ettorre F (1985) Cystic cavernous angiomas of the posterior fossa. J Neurosurg 63: 797–799
5. Bergeson PS, Rekate HL, Tack ED (1992) Cerebral cavernous angiomas in the newborn. Clin Pediatr: 435–437
6. Bertalanffy H, Gilsbach JM, Eggert HR, Seeger W (1991) Microsurgery of deep-seated cavernous angiomas: report of 26 cases. Acta Neurochir (Wien) 108: 91–99
7. Bicknell JM, Carlow TJ, Kornfeld M, Stovring J, Turner P (1978) Familial cavernous angiomas. Arch Neurol 35: 746–749
8. Bremer L, Carson NB (1890) A case of brain tumor (angioma cavernosum) causing spastic paralysis and attacks of tonic spasms. Operation. Am J Med Sci 100: 219–242
9. Brühlmann Y, de Tribolet N, Berney J (1985) Les angiomes caverneux intracérébraux. Neurochirurgie 31: 271–279

10. Buckingham MJ, Crone KR, Ball WS, Berger TS (1989) Management of cerebral cavernous angiomas in children presenting with seizures. Childs Nerv Syst 5: 347–349
11. Chadduck WM, Binet EF, Farrell FW, Araoz CA, Reding DL (1985) Intraventricular cavernous hemangioma: report of three cases and review of the literature. Neurosurgery 16: 189–197
12. Coin CG, Coin JW, Glover MB (1977) Vascular tumors of the choroid plexus: diagnosis by computed tomography. J Comput Assist Tomogr 1: 146–148
13. Crawford JV, Russell DS (1956) Cryptic arteriovenous and venous hamartomas of the brain. J Neurol Neurosurg Psychiatry 19: 1–11
14. Cushing H, Bailey P (1928) Tumors arising from the blood vessels of the brain. Angiomatous malformations and hemangioblastomas. Thomas, Springfield
15. David M, Loisel G, Ramirez C, Brun M (1934) Tumeur angiomateuse et calcifiée insérée sur le plancher du IVe ventricule. Ablation, guérison. Rev Neurol 61: 426
16. Davis DH, Kelly PJ (1990) Stereotactic resection of occult vascular malformations. J Neurosurg 72: 698–702
17. Del Curling O, Kelly DL, Elster AD, Craven TE (1991) An analysis of the natural history of cavernous angiomas. Neurosurgery 75: 702–708
18. de Tribolet N, Kaech D, Perentes E (1982) Cerebellar haematoma due to a cavernous angioma in a child. Acta Neurochir (Wien) 60: 37–43
19. Di Tullio MV, Stern WE (1979) Hemangioma calcifians. Case report of an intraparenchymatous calcified vascular haematoma with epileptogenic potential. J Neurosurg 50: 110–114
20. Dobyns WB, Michels VV, Groover RV, *et al* (1987) Familial cavernous malformations of the central nervous system and retina. Ann Neurol 21: 578–583
21. Ebeling JD, Tranmer BI, Davis KA (1988) Thrombosed arteriovenous malformations: a type of occult vascular malformation. MRI and histopathological correlations. Neurosurgery 23: 605–610
22. Fahlbusch R, Strauss C, Huk W, Röckelein G, Kömpf D, Ruprecht KW (1990) Surgical removal of ponto mesencephalic cavernous hemangiomas. Neurosurgery 26: 449–457
23. Fehlings MG, Tucker WS (1988) Cavernous hemangioma of Meckel's cave. J Neurosurg 68: 645–647
24. Fortuna A, Ferrante L, Acqui M (1989) Cerebral cavernous angioma in children. Childs Nerv Syst 5: 201–207
25. Fukui M, Matsuoka S, Hasuo K, Numaguchi Y, Kitamura K (1983) Cavernous hemangioma of the pineal region. Surg Neurol 20: 209–215
26. Galzio RJ, Zenobii M, Carbonin G, Cristuib-Grizzi IL (1980) Hemangiomas calcifians. Surg Neurol 14: 331–335
27. Gangemi M, Longatti P, Maiuri F, Cinelli G, Carteri A (1989) Cerebral cavernous angiomas in the first year of life. Neurosurgery 25: 465–469

28. Gangemi M, Maiuri F, Donati P, Cinalli G, De Caro M, Sigona L (1990) Cerebral familial cavernous angioma. Neurosurg Res 12: 131–136
29. Giombini S, Morello G (1978) Cavernous angiomas of the brain. Account of 14 personal cases and review of the literature. Acta Neurochir (Wien) 40: 61–82
30. Guy G, Jan M, Guegan Y (1989) Les lésions chirurgicales du tronc cérébral. Neurochirurgie 35 (1): 133
31. Harbauch RE, Roberts DW, Fratkin JD (1984) Hemangioma calcifians. Case report. J Neurosurg 60: 417–419
32. Harper DG, Buck DR, Early CB (1982) Visual loss from cavernous hemangiomas of the middle cranial fossa. Arch Neurol 39: 252–254
33. Hayashi T, Fukui M, Shyojima K, Utsunomiya H, Kawasaki K (1985) Giant cerebellar hemangioma in an infant. Childs Nerv Syst 1: 230–233
34. Herter T, Brandt M, Szüwart U (1988) Cavernous hemangiomas in children. Childs Nerv Syst 4: 123–127
35. Hirsch L (1981) Combined cavernous-arteriovenous malformation. Surg Neurol 16: 135–139
36. Houtteville JP (ed) (1989 a) Les cavernomes intra-crâniens. Neurochirurgie 35: 73–129
37. Houtteville JP, Petit-Taboué MCh, Bouvard G, Derlon JM, Hubert P (1989 b) rCBF studies in intracerebral cavernomas. Congress of Radiosurgery, University of Virginia, Medical Center, Charlottesville (USA). Unpublished data
38. Huang YP, Robbins A, Patel SC, Chaudhary M (1984) Cerebral venous malformation and a new classification of cerebral vascular malformations. In: Kap JP, Schmideck HH (eds) The cerebral venous system and its disorders, Vol XIII. Grune and Stratton, Orlando
39. Hubschmann O, Kasoff S, Doniger D, Llena J, Leeds N (1976) Cavernous hemangioma in the pineal region. Surg Neurol 6: 349–351
40. Iwasa H, Indei I, Sato F (1983) Intraventricular cavernous hemangioma. J Neurosurg 59: 153–157
41. Jain KK (1966) Intraventricular cavernous hemangioma of the lateral ventricle. J Neurosurg 24: 762–764
42. Jain KK, Robertson E (1970) Recurrence of an excised cavernous hemangioma in the opposite cerebral hemisphere. J Neurosurg 33: 453–456
43. Kashiwagi S, Van Loveren HR, Tew JM, Wiot JG, Weil SM, Lukin RA (1990) Diagnosis and treatment of vascular brain stem malformations. J Neurosurg 72: 27–34
44. Khosla VK, Banerjee AK, Mathuriya SN, Mehta S (1984) Giant cystic cavernoma in a child. Case report. J Neurosurg 60: 1297–1299
45. Kondziolka D, Lunsford LD, Coffey RJ, Bissonette DJ, Flickinger JC (1990) Stereotactic radiosurgery of angiographically occult vascular malformations: indications and preliminary experience. Neurosurgery 27: 892–900

46. Krayenbühl H, Siebenman R (1965) Small vascular malformations as a cause of primary intracerebral hemorrhage. J Neurosurg 22: 7–20
47. Kudo T, Veki S, Kobayashi H, Torigoe H, Tadokoro (1989) Experience with the ultrasonic surgical aspirator in a cavernous hemangioma of the cavernous sinus. Neurosurgery 24: 628–631
48. Lavyne MH, Patterson RH (1983) Subchoroidal trans-velum interpositum approach to midthird ventricular tumors. Neurosurgery 12: 86–94
49. Lechevalier B (1989) Etude neuropathologique des cavernomes. Neurochirurgie 35: 78–81
50. Ledoux MS, Aronin PA, Odrezin GT (1991) Surgically treated cavernous angiomas of the brain stem: report of two cases and review of the literature. Surg Neurol 35: 395–399
51. Little JR, Awad IA, Jones SC, Ebrahim ZY (1990) Vascular pressures and cortical blood flow in cavernous angioma of the brain. J Neurosurg 73: 555–559
52. Lobato RD, Perez C, Rivas JJ, Cordobes F (1988) Clinical, radiological and pathological spectrum of angiographically occult intracranial vascular malformations. J Neurosurg 68: 518–531
53. Mc Cormick WF, Nofzinger JD (1966) "Cryptic" vascular malformations of the central nervous system. J Neurosurg 24: 865–875
54. Mazza C, Scienza R, Dalla Bernardin B, Beltramello A, Bontempini L, Da Pian R (1989) Malformations caverneuses cérébrales de l'enfant. Neurochirurgie 35: 106–108
55. Merritt HH (1940) Case records of the Massachusetts General Hospital. J Engl J Med 222: 191–195
56. Meyer FB, Lombardi D, Scheithauer B, Nichols DA (1990) Extra-axial cavernous hemangiomas involving the dural sinuses. J Neurosurg 73: 187–192
57. Miyagi Y, Mannoji H, Akaboshi K, Morioka T, Fukui M (1993) Intraventricular cavernous malformation associated with medullary venous malformation. Neurosurgery 32: 461–464
58. Miller RH (1961) Spontaneous subarachnoid haemorrhage: a presenting symptom of a tumor of the third ventricle. Surg Clin North Am 41: 1043–1048
59. Mizutani T, Goldberg HI, Kerson LA, Murtagh F (1981) Cavernous hemangioma in the diencephalon. Arch Neurol 38: 379–382
60. Momoshima S, Shiga H, Yuasa Y, Higuehi N, Kawase T, Toya S (1991) MR findings in extracerebral cavernous angiomas of the middle cranial fossa: report of two cases and review of the literature. AJNR 12: 756–760
61. Mori K, Handa H, Gi H, Mori K (1980) Cavernomas in the middle fossa. Surg Neurol 14 (1): 21–31
62. Murukami S, Sotsu M, Morooka S, Susuki T (1990) Chronic encapsulated intracerebral hematoma associated with cavernous angioma: a case report. Neurosurgery 26: 700–702
63. Nakasu S, Yoshida M, Nakajima M, Handa J (1991) Cystic cavernous angioma in an infant: CT features. J Comput Assist Tomogr 15 (1): 163–165

64. Namba S, Ishimitsu H, Nakasone S (1979) Cavernous hemangioma of the brain. No Shinkei Geka 7: 277–283
65. Namba S (1983) Extracerebral cavernous hemangioma of the middle cranial fossa. Surg Neurol 19: 379–388
66. New PF, Ojemann RG, Davis KR, Rosen B, Heros R, Kjellberg RN, Adams RD, Richardson EP (1986) MR and CT of occult vascular malformations of the brain. AJNR 6: 771–779
67. Numaguchi Y, Fukui M, Miyake E, Kishikawa T, Ideka J, Matsuura K, Tomonaga M, Kitamura K (1977) Angiographic manifestations of intracerebral cavernous hemangioma. Neuroradiology 14: 113–116
68. Numaguchi Y, Kishikawa T, Fukui M, *et al* (1979) Prolonged injection angiography for diagnosing intracranial cavernous hemangiomas. Radiology 131: 137–138
69. Occhiogrosso M, Carella A, d'Aprile P, Vailati G (1983) Brain-stem hemangioma calcifians. Case report. J Neurosurg 59: 150–152
70. Ogawa A, Katakura R, Moshimoto T (1990) Third ventricle cavernous angioma. Report of two cases. Surg Neurol 34: 414–420
71. Ogilvy CS, Heros RC, Ojeman RG, New PF (1988 a) Angiographically occult arteriovenous malformations. J Neurosurg 69: 350–355
72. Ogilvy CS, Heros RC (1988 b) Angiographically occult intracranial vascular malformations. J Neurosurg 69: 960–962
73. Ogilvy CS, Pakzaban P, Lee JM (1993) Oculomotor nerve cavernous angioma in a patient with Roberts syndrome. Surg Neurol 40: 39–42
74. Ondra SL, Doty JR, Mahla ME, George ED (1988) Surgical excision of a cavernous hemangioma of the rostral brain stem. Case report. Neurosurgery 23: 490–493
75. Otten P, Pizzolato GP, Rilliet B, Berney J (1989) A propos de 131 cas d'angiomes caverneux (cavernomes) du système nerveux central repérés par l'analyse rétrospective de 24,535 autopsies. Neurochirurgie 35: 82–83
76. Pásztor E, Szabo G, Scowik F, Zóltan J (1964) Cavernous hemangioma of the base of the skull. Report of a case treated surgically. J Neurosurg 21: 582–585
77. Pau A, Orunesu G (1979) Vascular malformations of the brain in achondroplasia. Acta Neurochir (Wien) 50: 289–292
78. Penfield W, Ward A (1948) Calcifying epileptogenic lesions. Hemangioma calcifians. Report of a case. Arch Neurol Psych 60: 20–36
79. Pozzati E, Padovani R, Morrone B, Finizio F, Gaist G (1980) Cerebral cavernous angiomas in children. J Neurosurg 53: 826–832
80. Pozzati E, Gaist G, Poppi M, Morrone B, Padovani R (1981) Microsurgical removal of paraventricular cavernous angiomas. Report of two cases. J Neurosurg 55: 308–311
81. Pozzati E, Giuliani G, Ferracini R, Gaist G (1988) Facial nerve palsy secondary to a dural cavernous angioma of the middle cranial fossa eroding the tegmen tympani. Neurosurgery 23: 245–247

82. Pozzati E, Giulani G, Nuzzo G, Poppi M (1989) The growth of cerebral cavernous angiomas. Neurosurgery 25: 92–97
83. Quattrocchi KB, Kissel P, Ellis WG, Frank ED (1989) Cavernous angioma of the tentorium cerebelli. Case report. J Neurosurg 71: 935–937
84. Ramina R, Ingunza W, Vonofakos D (1980) Cystic cerebral cavernous angioma with dense calcification. Case report. J Neurosurg 52: 259–262
85. Rapacki TFX, Brantley MJ, Furlow TW, Geyer CA, Toro VE, George ED (1990) Heterogeneity of cerebral cavernous hemangiomas diagnosed by MR imaging. J Comput Assist Tomogr 14: 18–25
86. Rigamonti D, Drayer B, Johnson P, Hadley M, Zabramski J, Spetzler R (1987) The MRI appearance of cavernous malformations (angiomas). J Neurosurg 67: 518–524
87. Rigamonti D, Spetzler RF (1988 a) The association of venous and cavernous malformations. Report of four cases and discussion of the pathophysiological, diagnostic and therapeutic implications. Acta Neurochir (Wien) 92: 100–105
88. Rigamonti D, Hadley MN, Drayer BP, Johnson PC, Hoenig-Rigamonti K, Knight JT, Spetzler RF (1988 b) Cerebral cavernous malformations. Incidence and familial occurence. N Engl J Med 319: 343–347
89. Rigamonti D, Pappas C, Spetzler RF, Johnson PC (1990) Extracerebral cavernous angiomas of the middle fossa. Neurosurgery 27: 306–310
90. Robinson JR, Awad IA, Little JR (1991) Natural history of the cavernous angioma. J Neurosurg 75: 709–714
91. Robinson JR, Awad IA, Magdinec M, Paranandi L (1993 a) Factors predisposing to clinical disability in patients with cavernous malformations of the brain. Neurosurgery 32: 730–736
92. Robinson JR, Awad IA, Masaryk TJ, Estes ML (1993 b) Pathological heterogeneity of angiographically occult malformations of the brain. Neurosurgery 33: 547–555
93. Roda JM, Alvarez F, Isla A, Blasquez MG (1990) Thalamic cavernous malformation. Case report. J Neurosurg 72: 647–649
94. Rosenblum B, Rothman AS, Lanzieri C, Song S (1986) A cavernous sinus cavernous hemangioma. J Neurosurg 65: 716–718
95. Rougier A, Castel JP, Cohadon F (1989) Les différentes modalités de traitement des cavernomes hémisphériques. Neurochirurgie 35: 115–119
96. Russel DS, Rubinstein LJ (1989) Pathology of tumours of the nervous system, 5th Ed. Arnold, London
97. Rutka JT, Brant-Zawadzki M, Wilson CB, Rosenblum ML (1988) Familial cavernous malformation. Diagnostic potential of magnetic resonance imaging. Surg Neurol 29: 467–474
98. Ryvlin P, Sindou M, Fischer G, Froment JC, Cinotti I, Lebars D, Lavenne F, Mauguiere F (1991) Positron-emission tomography in cavernous angioma with and without partial epilepsy. Epilepsia 32 [Suppl 1]: 41

99. Sabatier J, Gigaud M, Dubois G, Tremoulet M (1989) Cavernome de l'enfant. A propos d'une forme néonatale avec récidive dans l'enfance. Neurochirurgie 35: 109–110
100. Sarwar M, Mc Cormick WF (1979) Intracerebral venous angioma. Case report and review. Arch Neurol 35: 323–326
101. Sasaki O, Tanaka R, Koike T, Koide A, Koizumi T, Ogawa H (1991) Excision of cavernous angioma with preservation of coexisting venous angioma. J Neurosurg 75: 461–469
102. Sathi S, Folkerth R, Madsen JR (1992) Cavernous angioma of the posterior fossa dura mimicking a meningioma: case report and review of literature. Surg Neurol 38: 257–260
103. Savoiardo M, Strada L, Passerini A (1983) Intracranial cavernous hemangiomas: neuroradiologic review of 36 operated cases. AJNR 4: 945–950
104. Sawamura Y, de Tribolet N (1990) Cavernous hemangioma in the cavernous sinus. Case report. Neurosurgery 26: 126–128
105. Schneider RC, Liss L (1958) Cavernous hemangioma of the cerebral hemispheres. J Neurosurg 15: 392–399
106. Scott MR (1990–91) Brain stem cavernous angiomas in children. Pediatr Neurosurg 16: 281–286
107. Scott MR, Barnes P, Kupsky W, Adelman LS (1992) Cavernous angiomas of the central nervous system in children. J Neurosurg 76: 38–46
108. Seifert V, Gaab MR (1989) Laser-assisted microsurgical extirpation of a brainstem cavernoma: case report. Neurosurgery 25: 986–990
109. Shibata S, Mori K (1987) Effect of radiation therapy on extracerebral cavernous hemangioma in the middle fossa. Report of three cases. J Neurosurg 67: 919–922
110. Sigal R, Halimi P, Doyon D, Blais C, Chan KY (1989) Imagerie des cavernomes de l'encéphale. Tomodensitométrie et imagerie par résonance magnétique. Neurochirurgie 35: 89–94
111. Sigal R, Krief O, Houtteville JP, Halimi P, Doyon D, Pariente D (1990) Occult cerebrovascular malformations: follow-up with MR imaging. Radiology 176: 815–819
112. Simard JM, Garcia-Bengochea F, Ballinger WE, Parker-Mickle J, Guisling RG (1986) Cavernous angiomas: a review of 126 collected and 12 new clinical cases. Neurosurgery 18: 162–172
113. Sonntag KH, Waggener JD, Kaplan AM (1981) Surgical removal of a hemangioma of the pineal region in a 4-week infant. Neurosurgery 8: 586–588
114. Steiger HJ, Markwalder TM, Reulen HJ (1987) Clinico pathological relations of cerebral cavernous angiomas: observations in eleven cases. Neurosurgery 21: 879–884
115. Steiger HJ, Markwalder RV, Reulen HJ (1989) Y a-t-il une relation entre manifestation clinique et l'image pathologique des cavernomes cérébraux? Neurochirurgie 35: 84–88

116. Steinberg GK, Marks MP, Shuer LM, Sogg RL, Enzmann DR, Silverberg GD (1990) Occult vascular malformations of the optic chiasm: magnetic resonance imaging diagnosis and surgical laser resection. Neurosurgery 27: 446–470
117. Steiner L (1989) Personal communication
118. Sundaresan N, Eller T, Ciric I (1976) Hemangiomas of the internal anditory canal. Surg Neurol 6: 119–121
119. Symon L, Jackowski A, Bills D (1991) Surgical treatment of pontomedullary cavernomas. Br J Neurosurg 5: 339–347
120. Tatagiba M, Schonmayr R, Samii M (1991) Intraventricular cavernous angioma. A survey. Acta Neurochir (Wien) 110: 140–145
121. Tung H, Giannotta SL, Chandrasoma PT, Zee C (1990) Recurrent intraparenchymal hemorrhages from angiographically occult vascular malformations. J Neurosurg 73: 174–180
122. Vaquero J, Carrilo R, Cabezudo J, Leunda G, Villoria F, Bravo G (1980) Cavernous angiomas of the pineal region. Report of two cases. J Neurosurg 53: 833–835
123. Vaquero J, Leunda G, Martinez R, Bravo G (1983) Cavernomas of the brain. Neurosurgery 12: 208–210
124. Vaquero J, Salazar J, Martinez R (1987) Cavernous angiomas. Neurosurgery 20: 63–64
125. Vaquero J, Salazar J, Martinez R, Martinez P, Bravo G (1987) Cavernomas of the central nervous system: clinical syndromes, CT scan diagnosis, and prognosis after surgical treatment in 25 cases. Acta Neurochir (Wien) 85: 29–33
126. Voigt K, Yasargil MG (1976) Cerebral cavernous hemangiomas or cavernomas. Neurochirurgia 19: 59–68
127. Wakai S, Ueda Y, Inoh S, Nagai M (1985) Angiographically occult angiomas: a report of thirteen cases with analysis of the cases documented in the literature. Neurosurgery 17: 549–556
128. Weil S, Tew JM, Steiner L (1990) Comparison of radiosurgery and microsurgery for treatment of cavernous malformations of the brain stem. J Neurosurg 72: 336 A (abstract)
129. Wharen RE, Scheithauer B, Laws ER (1982) Thrombosed arterio-venous malformations of the brain. An important entity in the differential diagnosis of intractable focal seizure disorders. J Neurosurg 57: 520–526
130. Wilkins RH (1985) Natural history of intracranial vascular malformations: a review. Neurosurgery 16: 421–430
131. Yamasaki T, Handa H,Yamashita J, Paine JT, Tashiro Y, Uno A, Ishikawa M, Asato R (1986) Intracranial and orbital cavernous angiomas. J Neurosurg 64: 197–208
132. Yaşargil MG (1988) Venous, cavernous and occult angiomas. Microsurgery, Vol III B. Thieme, Stuttgart, pp 405–438

133. Yoshimoto T, Suzuki J (1986) Radical surgery on cavernous angioma of the brain stem. Surg Neurol 26: 72–78
134. Zimmerman RS, Spetzler RF, Lee KS, Zabramski JM, Hargraves RW (1991) Cavernous malformations of the brain stem. J Neurosurg 75: 32–39

Surgery for Gliomas and Other Mass Lesions of the Brainstem

A. Bricolo and S. Turazzi

Department of Neurological Surgery, University Hospital of Verona, Verona (Italy)

With 44 partly coloured Figures

Contents

Introduction

In broad outline, the purpose of this chapter is first, to offer a review of past philosophies in the management of brainstem tumours, covering roughly the last half-century; next, to revisit the functional neuroanatomy of the brainstem in relation to modern neurosurgical applications; and finally, to present and discuss specific microsurgical techniques that we have used in 130 cases to date. This latter aspect is still open to much discussion and even controversy as many readers continue to believe that surgery for intra-axial brainstem tumours carries too high a risk and is of doubtful ethical justification. The most stringent opinions hold that the brainstem should be not violated even to obtain biopsy samples or perform partial removal of the tumour.

As recently as 1987, Raimondi expressed a similar attitude, stating that expanding masses within the brainstem should be treated by radiotherapy alone, and that "the mere fact that one can operate on intraparenchymal brainstem tumour and have the child survive is no justification for surgery".

Current views on the role of surgery in the management of brainstem tumours have changed little, despite a number of favourable results reported from different quarters (Hoffman *et al.* 1980, Albright and Schlabassi 1985, Alvisi *et al.* 1985, Epstein and McCleary 1986, Konovalov and Atieh 1988, Bricolo *et al.* 1991, 1993, Pollack *et al.* 1993), these being variously credited to more refined imaging techniques (Bilaniuk *et al.* 1980, Packer *et al.* 1985, Stroink *et al.* 1986, Epstein and Farmer 1993, Ruge 1993), better surgical techniques and equipment (Albright and Schlabassi 1985), and more effective neuroanaesthesia and postoperative intensive care.

Surgery for brainstem tumours has been pioneered by relatively few neurosurgeons and is now being promoted by others, convinced that this delicate and difficult field of surgery can now be approached with increasing confidence.

While we certainly do not intend to promote brainstem surgery as an ordinary or trifling procedure, we do take some pride in adding our own contribution to current literature and thus encouraging the general expectation of promising developments in the treatment of brainstem lesions.

Incidence

The real incidence of brainstem gliomas is not known with the same certainty as that of other tumours of the posterior fossa, since histological diagnosis is all too often wanting for a number of reasons. Many of these patients are not

explored surgically because of a "hopeless" prognosis, and in a good proportion of those actually operated or biopsied, histological diagnosis is not obtained; most of these patients die at home, perhaps after a course of radiotherapy, and no autopsy is done.

Brainstem gliomas have been reported to constitute 9 to 22% of all brain tumours in the pediatric age group (Bailey *et al.* 1939, Bray *et al.* 1958, Lassman and Arjona 1967, Matson 1969, Koos and Miller 1971, Walker 1976). Because of difficulties in making a definite diagnosis, older series reported a lower incidence of brainstem tumours: thus in his 1930 review of Cushing's series, Buckley found only 25 pontine tumours out of 1737 verified tumours of the brain. In 1934, Hare and Wolf reviewed 432 cases of brain tumours in children and found that only 7 such tumours were located in the brainstem. In 1949, Walker and Hopple reported 100 verified brain tumours in children, 12 being pontine gliomas. In their 1954 series of 313 pediatric brain tumours, Ingraham and Matson were able to list 30 brainstem gliomas verified at surgery or autopsy. In 1959, Jackson and Thomson found 24 verified brainstem tumours in a series of 273 intracranial tumours of children. In 1971, Koos and Miller found 47 brainstem (pons and oblongata) tumours diagnosed at surgery or autopsy in a series of 700 brain tumour cases recorded in Vienna.

It is widely recognized that brainstem gliomas are more common in children and adolescents than in adults, though rare in patients under 3 years old. Luse and Teitelbaum (1968) reported one case of congenital pontine glioma where the patient died of respiratory failure at 6 days of age. Autopsy revealed a large malignant glioma of the pons. The youngest patient in Lassiter's series (1971) was 6 months old.

The not uncommon occurrence of these tumours in adult life was emphasized by White (1963): more precisely, he mentioned Gibbs's (1932) report accounting for only 1% of cases in the adult patient group; but then he added that more than one-third of the patients were over age 20 in Henschen's own series of 101 brainstem tumours as well as in his review of previous reports (Buckley 1930, Hare and Wolf 1934, Pilcher 1934, Alpers and Yaskin 1939, Foerster and Gagel 1940). Mean patient ages of 22, 26, and 33 years were reported respectively by Horrax (1927), Barnett and Hyland (1952), and Roth and Elvidge (1960).

History of Management

In 1939, Bailey *et al.* described the treatment of brainstem gliomas as "a pessimistic chapter" in the history of neurosurgery. Traditionally, all tumours involving the brainstem were considered infiltrative with diffuse glial proliferation. In fact, the gross often symmetrical bulge created by the tumour was responsible for terms like "hypertrophy of the pons" (Buckley 1930), "dif-

fuse hypertrophy" (Russell and Rubinstein 1959) and "hypertrophic pons" (Koos and Miller 1971) sometimes applied to this condition. An infiltrative character was attributed to these tumours by pathologists, on the grounds that autopsy revealed the presence of anaplastic foci in most cases, though there is little doubt that the development of anaplastic changes is more often than not a secondary event that accelerates the terminal clinical deterioration of these patients (Russell and Rubinstein 1959). In point of fact the infiltrative growth pattern of these tumours has long been recognized as a major limiting factor in surgical resection (Lassiter *et al.* 1971, Lassman 1974, Villani *et al.* 1975), at the same time corroborating the leading opinion that brainstem gliomas are a homogeneous disease entity not amenable to useful surgery. In 1969, Matson wrote quite didactically that "regardless of specific histology they must all be classified as malignant tumours, since their location in itself renders them inoperable".

For a long time and with only rare exceptions (Sarkari and Bickerstaff 1969) the natural history of these tumours suggested steady progression to death with a mean survival of 4 to 15 months (Bailey *et al.* 1939, Bodian and Lawson 1953, Redmond 1961, Lassman and Arjona 1967, Matson 1969, Golden *et al.* 1972, Villani *et al.* 1975). At the same time, however, reports began to appear of prolonged survivals in the order of 10 years (Lassiter *et al.* 1971, Marsa *et al.* 1973, Sheline 1975) and even up to 20 years or more (Bouchard 1966, Pool 1968, Panitch and Berg 1970, Hoffman *et al.* 1980, Soffer and Sahar 1982). Such prolonged survivals were ascribed to different forms of treatment including cyst aspiration, partial resection of the extra-axial portion of tumour, radiotherapy, or no treatment at all (Bodensteiner *et al.* 1977). Such reports, plus the contributions of CT scanning and MRI, have raised the suspicion of possible misdiagnosis (Matson 1969, Schain and Wilson 1971) and finally led to our understanding that brainstem gliomas are a heterogeneous group of tumours with different prognoses and different treatment possibilities (Edwards and Prados 1987, Pollack *et al.* 1993, Ruge 1993).

The first contributions of surgery in the treatment of brainstem gliomas came from patients managed by radiotherapy and undergoing exploratory surgery for histological confirmation of their diagnosis. In 1954, in their book "Neurosurgery of Infancy and Childhood", Ingraham and Matson stated that surgery was useless since these tumours are not usually associated with CSF blockage and the chance of obtaining a positive biopsy is slight. In 1973, Northfield wrote that when a firm diagnosis is made, operation is not indicated and radiotherapy is usually given. In 1967, Lassman and Arjona stated that they had abandoned exploratory surgery in recent years; and in 1969, Matson confirmed that surgery was avoided whenever satisfactory clinical and ventriculographic studies were at hand. And in 1975, Villani *et al.* found no real usefulness for surgery when they compared the follow-up course of patients treated differently.

The first report ever to express some inclination towards surgery came from Alvisi (1962), describing 5 cases of direct surgery (namely four partial removals and one biopsy) and 5 cases of decompressive surgery of the posterior fossa; this was followed by a more complete series by the same author in 1985.

In 1967, Olivecrona described 26 patients with tumours in the medulla, of which 7 survived for 10 to 25 years after an operation that comprised either partial removal or biopsy and decompression; the tumours in question were "spongioblastomas"; apparently, no radiotherapy was given. The favourable outcome seen in those patients was surprising for the times but is no longer so today, since Epstein and Wisoff (1987), and other authors have emphasized the favourable prognosis of tumours of the cervicomedullary junction and the frequency of low-grade gliomas in that location.

In 1971 Lassiter *et al.* recommended surgical exploration, which they had done in 34 patients to produce evacuation of a significant cyst component in five cases and histological diagnosis in ten. The cystic nature of some brainstem tumours had been described originally by Buckley (1930); it was repeatedly confirmed (Pool 1968, Hoffmann *et al.* 1980, Soffer and Sahar 1982) and found to correlate with benign histology.

Also in 1980, Hoffmann and his associates described a group of "benign" brainstem gliomas that grow exophytically from the floor of the fourth ventricle as amenable to partial surgical resection with long-term survival. In 1986, Epstein and McCleary demonstrated that aggressive surgery could be performed for intrinsic brainstem tumours with acceptably low mortality and morbidity. And in 1987, Epstein and Wisoff described the possibility of removing gliomas of the cervicomedullary junction radically with satisfactory follow-up results. Encouraging results were likewise obtained in resection of low-grade gliomas arising more rostrally in the midbrain (Stroink *et al.* 1987, Vandertop *et al.* 1992). Also, recently favourable results have been reported with radical removal of nodular intrinsic brainstem gliomas (Entzian 1983, Albright and Schlabassi 1985, Konovalov and Atieh 1988, Epstein and Wisoff 1989, Bricolo *et al.* 1991).

The treatment of patients with midbrain tumours continues to represent a challenge, since the efficacy of all treatment modalities must be measured against the natural history of these tumours. Most authors find an almost equal incidence of malignant and benign tumours (Lassman and Arjona 1967, Panitch and Berg 1970, Littman *et al.* 1980, Kim *et al.* 1980, Albright *et al.* 1983). Most of these tumours seem to follow an indolent course, even though at autopsy the majority reveal varying degrees of anaplasia (Littman *et al.* 1980), possibly secondary change acquired during the clinical course. Flexibility in the choice of therapeutic measures is essential, such as clinical and radiological monitoring in patients with apparent benign tumours, to choose the time and type of surgery (or biopsy), as well as of radiotherapy,

when the symptoms appear to progress (Vandertop *et al.* 1992, Pollack *et al.* 1993). Other tumours, however, are characterized by important and progressive clinical symptoms and as such call for immediate treatment with cortisone and prompt decision-making, whether in favour of radiotherapy (Edwards and Prados 1987), tumour biopsy (Baghai *et al.* 1982, Albright *et al.* 1986), or direct aggressive surgery (Epstein and McCleary 1986, Konovalov and Atieh 1988, Bricolo *et al.* 1993). Accruing experience with intra-axial lesions has shown that aggressive surgical resection can be done with minimum morbidity in cases where tumour tissue can be neatly separated from normal structures. Thus, while the role of surgery remains limited in the management of diffusely infiltrating brainstem gliomas, it appears that many patients may benefit from surgical resection of the tumour mass.

Radiotherapy

In the management of brainstem gliomas there is now little room or justification for conservation management – even though isolated patients have been reported to survive for a long time in the absence of treatment (Bodensteiner 1977). Confirmation of the beneficial effects of radiotherapy, was given by Lassman and Arjona (1967), who reported a mean survival time of 15.1 months in patients treated with high-voltage radiation, as opposed to only 4.0 months in patients left untreated.

Radiotherapy without a previous biopsy or histological diagnosis has been the mainstay of treatment for patients harbouring a brainstem glioma; to this day, the procedure represents the best palliative therapy for most of these patients. Because there is usually little difficulty in arriving at a diagnosis by clinical means and modern imaging methods, surgical intervention in quest of tissue diagnosis, cyst evacuation, exophytic lesion removal, and biopsy (Reigel *et al.* 1979, Berger *et al.* 1983) has lost much of its former value. With a firm radiological diagnosis, surgery in the past was usually avoided except for an occasional shunting procedure in a patient with hydrocephalus (Matson 1969, Littman *et al.* 1980).

While irradiation techniques have improved over the years, they remain based on conventional fractional administration. No new approaches to radiotherapy have been produced except for interstitial radiation (Mundinger *et al.* 1991); remarkably, none of the authors has shown interest in stereotactic radiation for these tumours (Ruge 1993).

Practically all workers agree that high dosages are essential, ranging from the 3000 R used by Ingraham and Matson (1954) and Jackson and Thomson (1959) to the 7000–8000 R administered in hyperfractional doses by Edwards *et al.* (1989). Most authors (Abramson *et al.* 1974, Albright 1983, Jenkin *et al.* 1987, Keim *et al.* 1987) have used doses in the region of 5000 R with some latitude in choosing individual dosages according to a

number of factors. The higher dosages of more recent reports are made possible by the concomitant use of steroids, though the literature concerning the therapeutic value of steroid therapy in the management of these tumours remains scant.

Early reports of patients treated only with radiotherapy spoke of none-too-brilliant results albeit with high percentages of prolonged survivals for pathology such as CNS glioma. One example is found in the 1966 paper by Bouchard *et al.*, where approximately one-third (37%) of 71 patients with brainstem glioma died within one year but roughly the same proportion (38%) survived at least five years and 27% were still alive at twenty years. The quality of survival was worthwhile: 81% of survivors past five years were "perfectly well, and all who lived for 15 years or more enjoyed good, useful survival".

Other authors have given good reports: thus Sheline (1975) and Greenberger *et al.* (1977) showed survival in excess of 40% of cases at five years, and several others reported five-year survival rates in the region of 30% (Albright 1983, Arseni and Goldberg 1959, Panitch and Berg 1970, Littman *et al.* 1980); a few, however, reported five-year survivals no better than 20% (Marsa *et al.* 1973, Jenkin *et al.* 1987).

Paradoxically, lower survival figures are shown in more recent reports (Strange and Wohlert 1982, Berger *et al.* 1983, Stroink *et al.* 1986, Jenkin *et al.* 1987): this data reflects the reduced likelihood of misdiagnosis afforded by modern neuroimaging, CSF testing for oligoclonal bands, protein identification, and techniques for virus isolation (Edwards and Prados 1987). This interpretation had been proposed early on by Matson (1969), who concluded his chapter by stating that "should any patient with a clinical diagnosis of a brainstem glioma still be alive as long as 18 months after diagnosis, with or without X-ray treatment, reinvestigation and probably surgical exploration is indicated as some other lesion is probably present". This opinion was shared by Russell and Rubinstein (1959), who stated that follow-up reports of clinical series with incomplete histological data must be viewed with due scepticism.

Most radiologists treat only the involved portion of the brainstem and a narrow margin around it (Mantravadi *et al.* 1982, Halperin 1985, Jenkin *et al.* 1987). Craniospinal irradiation, suggested by Reigel *et al.* (1979) for patients with glioblastoma, is controversial because of the rarity of that tumour in the brainstem and its exceptional dissemination along the subarachnoid pathways (Packer *et al.* 1983).

Early experience with radiation therapy soon revealed the marked variability of responses in treated patients, some showing remission of neurological symptoms in three to six weeks while others improved not at all or deteriorated even before the course of radiotherapy was completed. Bray *et al.* (1958) reported an average survival time of 11.5 months in patients showing improvement with radiotherapy as opposed to less than 5 months in

non-responders. Similar findings were obtained by Lassiter *et al.* (1971), who irradiated all their postoperative brainstem glioma patients. In the 1980 series of Littman *et al.*, none of the patients with a pathological diagnosis of malignancy survived more than 16 months, whereas the remaining patients with well-differentiated gliomas had a five-year survival of 55%. Even though some patients fail to respond to conventional fractional radiotherapy, temporary disease control is achieved in a high percentage of cases (Panitch and Berg 1970, Hara and Takeugi 1977, Littman *et al.* 1980, Halperin 1985, Stroink *et al.* 1986, Eifel *et al.* 1987, Langmoen *et al.* 1991). Adjuvant chemotherapy does not seem to improve the survival of brainstem glioma patients compared to radiotherapy alone (Rosen *et al.* 1974, Fulton *et al.* 1981, Levin *et al.* 1984, Jenkin *et al.* 1987).

Until a few years ago, systematic radiotherapy was given to all brainstem glioma patients without exception, including those treated surgically and those (indeed a sizeable number) for which surgery or biopsy failed to detect tumour tissue; only the more severely ill patients, unable to withstand radiotherapy, were excepted. Whereas Matson (1969) wrote that "to our knowledge, X-ray has never cured a brainstem glioma, and the histology of these lesions is not such as to suggest a favourable response to this treatment", it was only recently that the indications of radiotherapy were reassessed and eligible cases selected (Pollack *et al.* 1993). In particular, the indication for radiotherapy in low-grade gliomas is controversial, with uncertainty as to whether or not radiotherapy should be recommended at all and generally if irradiation should be given at the time of tumour progression (Ruge 1993). In recent series of patients managed surgically, those with "benign" tumours and no evidence of disease progression were not referred for radiotherapy.

The majority of patients receiving a complete course of radiotherapy were thought to benefit from it, sometimes with abatement of papilledema and symptoms of intracranial hypertension. None of these clinical series offers a critical evaluation of the beneficial effects of corticosteroid therapy given concomitantly all through the course of radiotherapy and often continued beyond that.

In conclusion, while brainstem gliomas may not be radiocurable because of their strategic location and the radio-vulnerability of surrounding structures, radiation therapy still plays a major role in their management.

Histology

In terms of their histological aspects, it is by now widely agreed that most brainstem gliomas are astrocytomas that grow pushing apart the adjacent structures widely but do not destroy them. The microscopic appearance is similar to that of a diffuse cerebral or cerebellar astrocytoma with the same tendency to undergo anaplasia (Russell and Rubinstein 1989). Conversely,

glioblastoma is seldom found in the brainstem (Koos and Miller 1971). Both the more recent surgical series, claiming a high percentage of "benign" tumours (Konovalov and Atieh 1988, Pollack *et al.* 1993), and the current views of pathologists refute the former conviction that the biological behaviour of these tumours was generally malignant. Koos and Miller (1971) pointed out that many of these tumours remained unclassified, and explained why they were in fact unclassifiable. Even earlier, in 1954, Ingraham and Matson had suggested that all these tumours should be called "mixed" gliomas since most of them show distinct aspects and areas of glioblastoma multiforme, astrocytoma, and spongioblastoma.

The long-established notion that these tumours were essentially malignant and therefore more amenable to radiotherapy than to surgery reflected at once the near-impossibility of obtaining a histological diagnosis preoperatively and the constant reference to autopsy series report, where secondary and late malignant degeneration was grossly overestimated. More recently, however, the advent of CT scanning and NMR imaging have revealed the focal, nodular, exophytic, and cystic morphological aspects of tumours that are more likely to be very slow-growing lesions such as ganglioglioma, juvenile pilocytic astrocytoma, or mildly anaplastic astrocytoma. Hoffman *et al.* (1980), Stroink *et al.* (1986) and Epstein and Wisoff (1987) suggested that tumour location was an important clue to the involved histopathology. In 1986, Epstein and McCleary found that the more benign forms of astrocytoma occurred mostly at the cervicomedullary junction, just as had been noted earlier by Olivecrona (1967); they regarded these tumours as a continuum of forms occurring in the cervical spinal cord. Benign nodular tumours were reported frequent in the upper brainstem (Stroink *et al.* 1987, Vandertop *et al.* 1992).

The general consensus is that the great majority of tumours affecting the medulla and upper brainstem are benign, whereas pontine gliomas are often infiltrating and malignant (Epstein and McCleary 1986). Still, pontine tumours sometimes present clinically and radiologically like benign superficial tumours exophytic into the fourth ventricle (Hoffman *et al.* 1980, Stroink *et al.* 1986) or into the cerebellopontine angle (Epstein and McCleary 1986, Bricolo *et al.* 1991). Next, the follow-up studies of Alvisi *et al.* (1985), Epstein and McCleary (1986), Bricolo and Turazzi (1987), Stroink *et al.* (1987), and Konovalov and Atieh (1988) have further confirmed the existence of significant correlation between surgical results and tumour histology.

Diagnosis

Before the advent of modern neuroimaging (CTscan and MRI), brainstem tumours were diagnosed by air and contrast X-ray techniques, surgical visualization, or mere clinical evidence; in many cases, however, the description of reported series was completed by necropsy confirmation.

Under the circumstances, stringent diagnostic criteria could not be made, and cases of misdiagnosis were occasionally reported and criticized when unexpectedly long survivals occurred (Matson 1969, Russell and Rubinstein 1959, Edwards and Prados 1987).

Ventricular air studies, if technically satisfactory and in good agreement with the clinical picture, afforded virtually unequivocal diagnosis – even on hindsight. Such studies have represented the most reliable diagnostic instru-

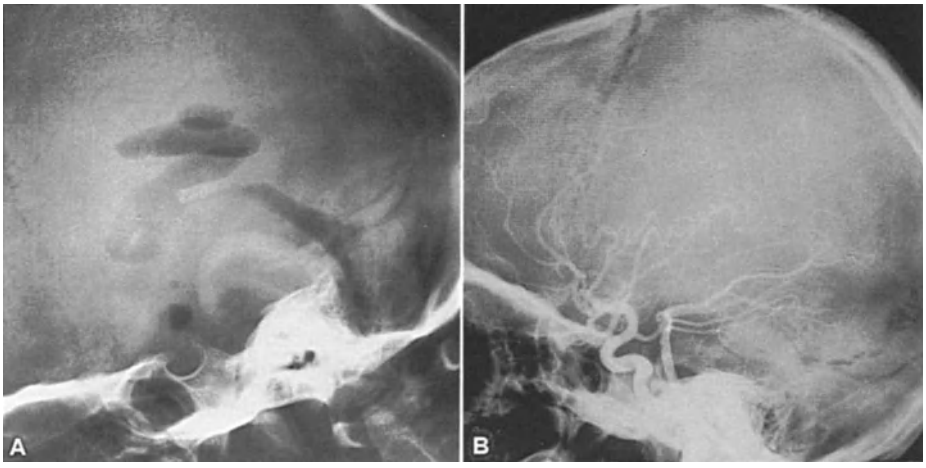


Fig. 1. Lateral views of pneumoencephalography (A) and vertebral angiography (B) showing a typical brainstem enlargement in a 3-year child admitted to our Department in 1973 with diplopia and ataxia. Diagnosis was brainstem glioma; radiotherapy was advised

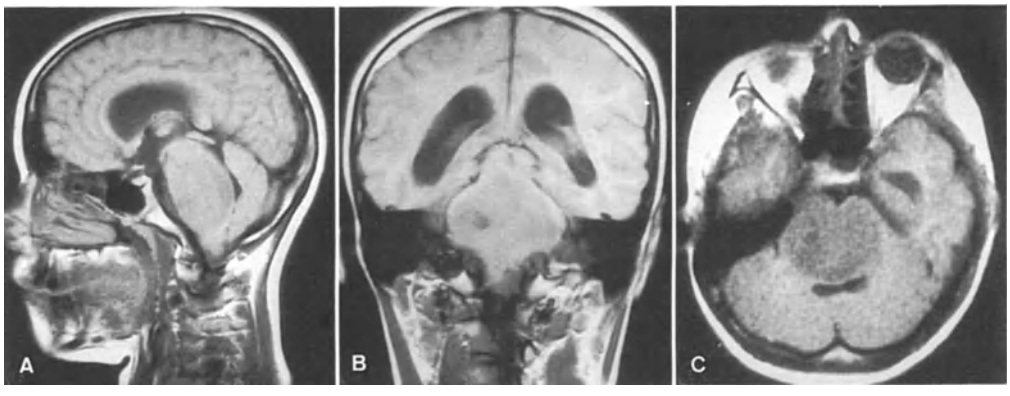


Fig. 2. Sagittal (A), coronal (B) and axial (C) magnetic resonance images demonstrating a diffuse brainstem glioma in a 6-year old girl (1985). A stereotaxic biopsy was performed (fibrillary astrocytoma) followed by brachitherapy

ment for several decades, to the point where surgical exploration was undertaken only when their results were adjudged conclusive.

The more typical pneumoencephalographic finding of brainstem tumour is the posterior and upward displacement of the aqueduct of Sylvius and fourth ventricle ("bowing of the aqueduct") in lateral roentgenograms (Fig. 1A). In the same view, the anterior margin of the fourth ventricle is sharply outlined and the cisterna pontis may be narrowed. The same picture can be produced also by a prepontine tumour; but vertebral angiography will clarify the point, since a brainstem tumour displaces the basilar artery towards the clivus (Fig. 1B). Ventriculography was performed if the patient showed papilledema or symptoms of raised intracranial pressure; if definition with air was inadequate a positive contrast medium was used.

More refined diagnostic tools were developed in time. CT scanning was adopted systematically in the late Seventies and richly illustrated thereafter (Weisberg *et al.* 1978, Bilaniuk *et al.* 1980, Littman *et al.* 1980, Berger *et al.* 1983, Albright *et al.* 1986, Stroink *et al.* 1986); and NMR (Fig. 2) imaging came to the fore in the mid-Eighties (Kucharczyk *et al.* 1985, Packer *et al.* 1985, Epstein and Farmer 1993). The two methods together greatly enhanced the accuracy of evaluation of the tumour characteristics, and yielded valuable indications for differing treatment strategies in individual cases. Further, exploration by the new methods has shown that the incidence of brainstem tumours relative to other tumours of the posterior fossa is significantly higher than formerly believed (Stroink *et al.* 1986); also, new perspectives are opening up in regard to their treatment.

Microsurgical and Functional Correlative Anatomy of the Brainstem

The brainstem (truncus cerebri) may be defined as the part of neuraxis located between the diencephalon and the spinal cord, into which it continues without definite anatomical demarcation. Comprising the midbrain (mesencephalon), pons (metencephalon), and medulla oblongata (myelencephalon), the brainstem is contained almost entirely in the posterior fossa except for a small rostral portion that goes beyond the tentorial incisura and a short tract of medulla oblongata that runs below the foramen magnum (Williams *et al.* 1989). Protected by the clivus and petrous bones, shielded by cranial nerves and arteries of the vertebrobasilar system, and covered by the cerebellum, this small part of the encephalon, only about 6 cm high and 3.7 cm wide at the pons (Lang 1991), presents a highly complex structure both anatomically and functionally. It is crowded by cranial nerve nuclei and by numerous ascending, descending and interconnecting fascicles, bundles and pathways plus the reticular formation, all playing important roles in normal CNS function. Because of its functional importance and difficult surgical access, the brainstem was not explored very much by neurosurgeons in the past.

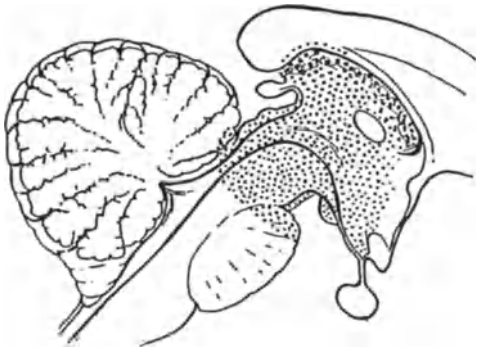


Fig. 3. Diagram of the area "concerned with awareness (consciousness)". (Reproduced from Jefferson and Johnson 1950)

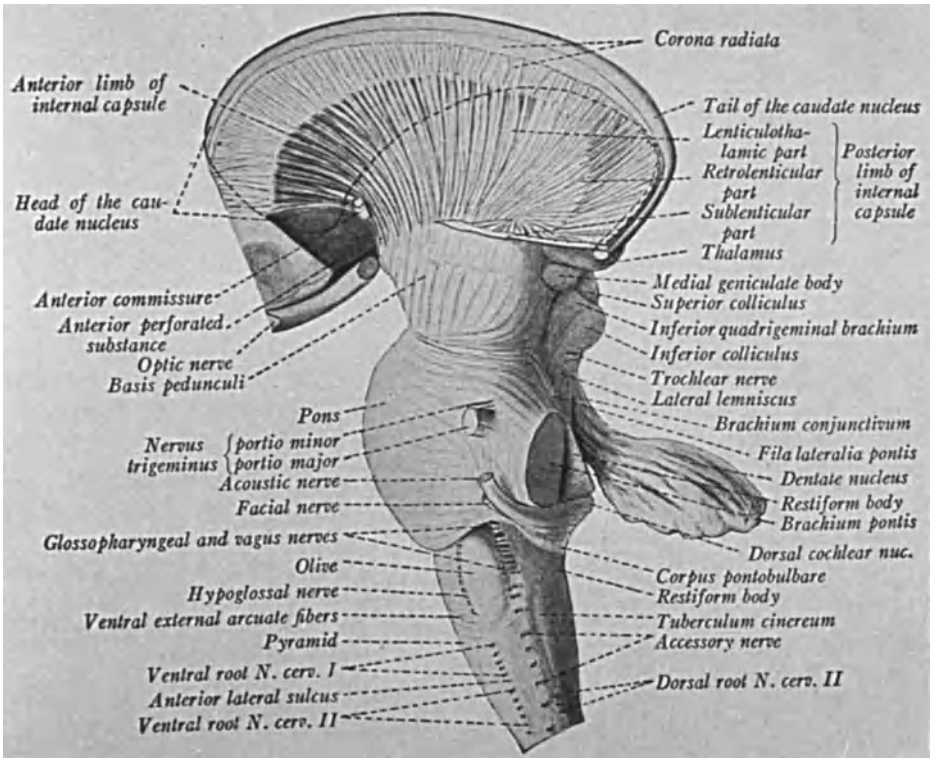


Fig. 4. Lateral view of human brainstem. (Reproduced from Ranson 1935; courtesy of Saunders, Philadelphia)

In this connection as on many other occasions, Cushing was the first to call attention to herniation of the cerebellar tonsils through the foramen magnum and recognize the associated risk of damage to the respiratory, vasomotor, and vagal centers that lie mainly in the closed part of the medulla – the part more likely to be compressed by tonsillar herniation. Cushing held that the logical handling of such an event was the removal of the posterior margin of the foramen magnum and arch of the atlas. For another historic contribution we are indebted to Sir Geoffrey Jefferson (1938), who analyzed his own clinical and pathological data and those of other authors (Le Beau 1938, Van Gehuchten 1937) and identified the mesencephalon as the area of brain more heavily involved in the maintenance of awareness and consciousness, at a time when the loss of consciousness was generally attributed to generalized cortical anemia (Jefferson and Johnson 1950) (Fig. 3).

Operative experience in the matter of brainstem mass lesions is intriguing to review, yet we may easily note (or acknowledge) that the contribution of neurosurgeons in this area has been definitely less extensive than in other CNS applications. The enormous amount of data furnished by experimental neurophysiology and neuroanatomy (Moruzzi and Magoun 1949, Rossi and

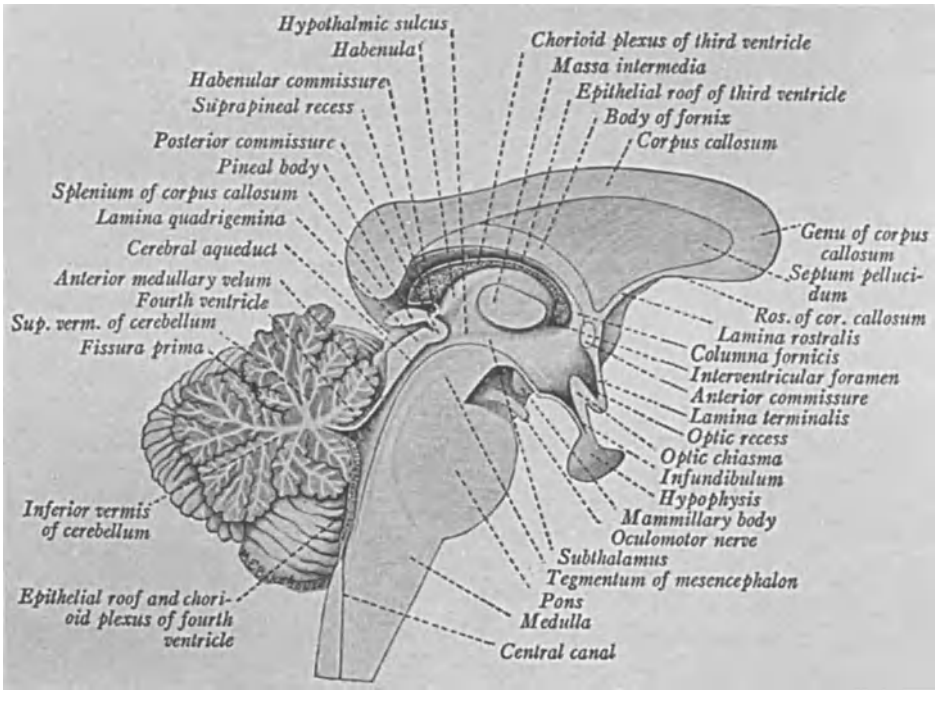


Fig. 5. Median sagittal section through the human brainstem. (Reproduced from Ranson 1935; courtesy of Saunders, Philadelphia)

Zanchetti 1957) has done more to intimidate neurosurgeons away from the brainstem than to entice them to attack it. For a long time, surgical attack on the brainstem was considered forbidden practice or simply "looking for trouble", a brainstem injury being all too often conducive to coma, decerebrate rigidity, apnoea, cardiovascular disorders, and other complications. In more recent times, fortunately, a series of favourable concomitant factors have materially changed this attitude, making the brainstem no longer an inaccessible, inviolable structure.

In this chapter, we shall revisit the external and internal anatomy of the cerebral trunk as is pertinent to surgical manipulation. With due mention of the functions performed by the various structures, we will attempt to outline a map of areas of different functional ranking whereby the surgeon may be guided in his choice of the least dangerous approaches (see Figs. 4–6). From this point of view the brainstem, while a compact and delicate whole, comprises some highly critical places whose damage results inevitably in major neurological failure (Baker 1965, Hodge and Primrose 1993), and others where functional disruption is better tolerated or at any rate not overly disabling.

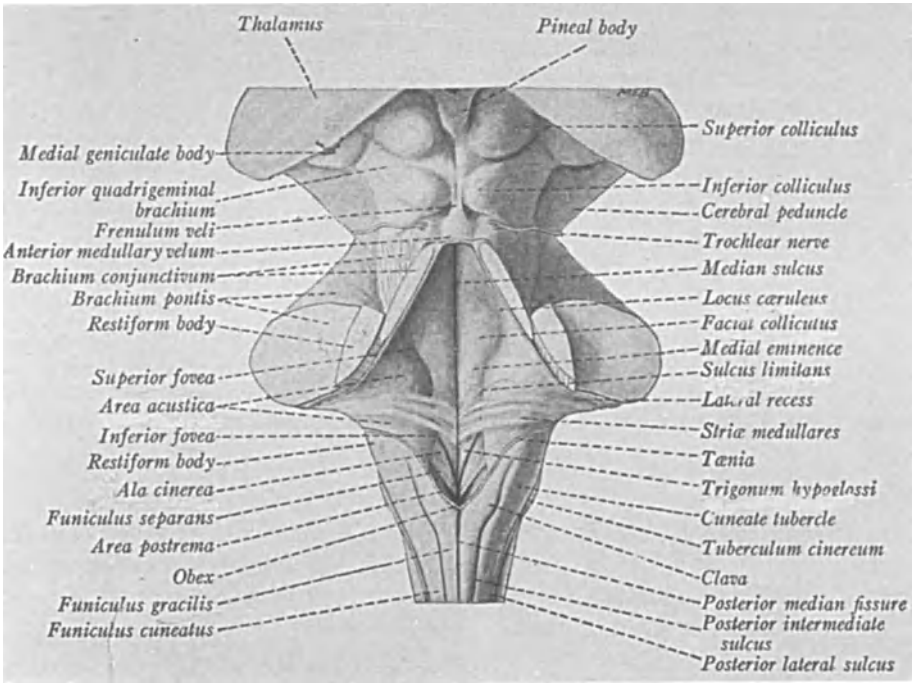


Fig. 6. Dorsal view of human brainstem and the rhomboid fossa, or floor of the fourth ventricle, exposed by removal of the cerebellum. (Reproduced from Ranson 1935; courtesy of Saunders, Philadelphia)

Cranial Nerve Nuclei

The brainstem contains the nuclei of origin and termination of ten of the 12 cranial nerves (from III to XII), altogether some twenty nuclei on each side. The classical studies of Gaskell (1889) and Herrick (1899, 1913), recently reviewed by Nieuwenhuys (1974), reveal that the nuclei in question are essentially arranged in seven longitudinal zones or columns, each being related specifically to functionally distinct fibres (Fig. 7). Whenever a cranial nerve made up of different types of fibres enters the brainstem, its component fibres of each type reach a specific zone or nucleus of their own. Thus the seven different categories of fibres that may occur in cranial nerves match seven different columns in the brainstem, each representing a specific func-

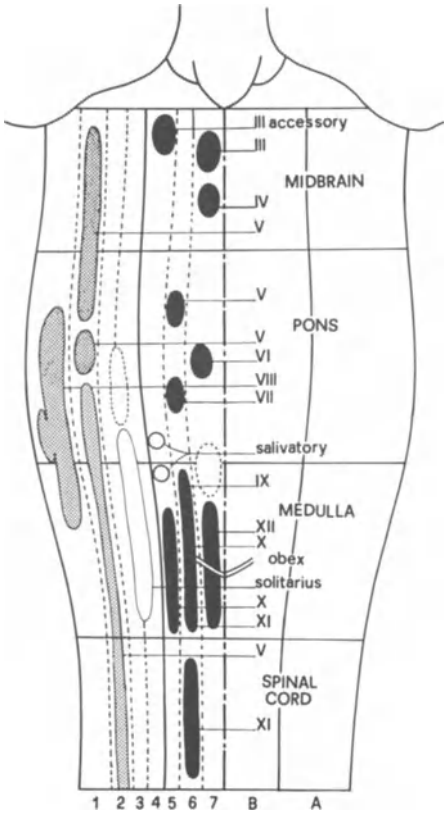


Fig. 7. Schematic line drawing showing the surface projection of the longitudinal organization of the various cell columns forming the cranial nerve nuclei in the mature human brainstem. *1* somatic sensory afferent; *2* general somatic afferent; *3* special visceral afferent; *4* general visceral afferent; *5* general visceral efferent; *6* somatic visceral efferent; *7* general somatic efferent. (Adapted from Nieuwenhuys *et al.* 1988)

tional system; conversely, fibres having the same function tend to be associated together within the brainstem irrespective of the nerves to which they belong. This is exemplified by the fact that all the afferent visceral fibres of the facial, glossopharyngeal and vagus nerves are grouped in the tractus solitarius. At an early stage of its embryologic development, the lateral wall of the neural tube consists of a dorsal or alar and a ventral or basal plate separated by a groove, the sulcus limitans, still visible with the operative microscope on the floor of the fourth ventricle in the adult. The sensory nuclei of cranial nerves develop within the alar plate and the motor nuclei within the basal plate. During development, both plates come to lie in the floor of the fourth ventricle, with the alar plate occupying the more lateral position; and despite these topographical changes the sensory nuclei retain, overall, a lateral position while the motor nuclei are arranged more medially. Thus all nuclei with motor functions (giving rise to visceral or somatic efferent fibres) end up in the more medial columns of the lamina basalis,

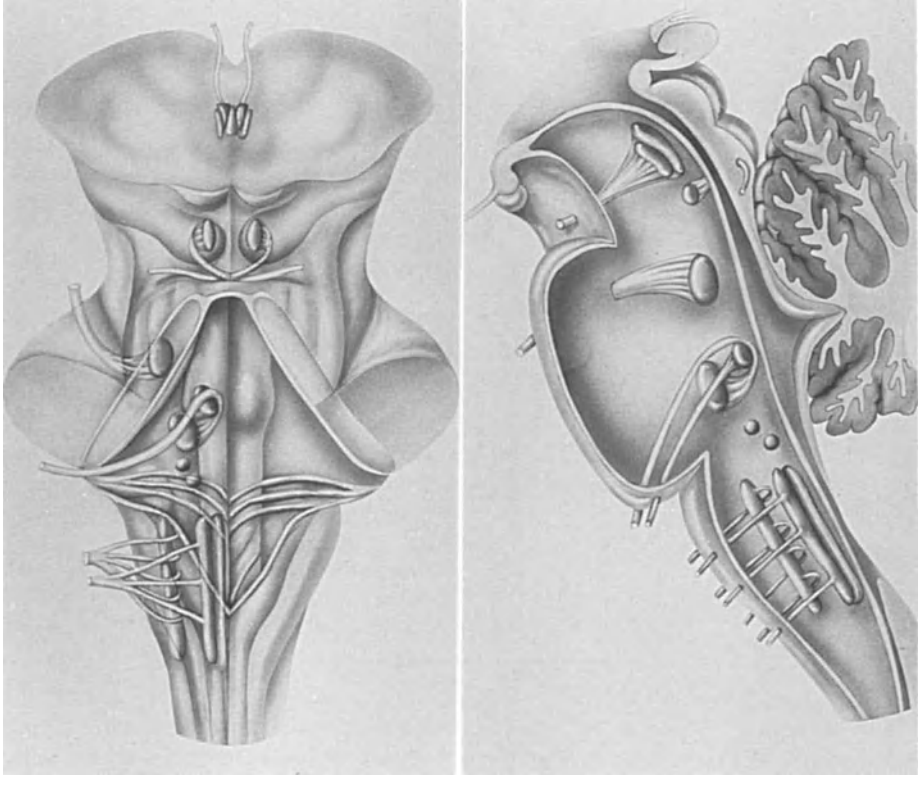


Fig. 8. The locations of the cranial motor nerve nuclei and fibres are schematically shown in three-dimension views on the dorsal aspect and on a sagittal section of the brainstem close to the median plane

whereas those receiving afferent fibres are arranged in the more lateral columns of the lamina alaris. The sulcus limitans marks the separation between these two columns of greatly different functional importance; the medial column being the more dangerous to handle surgically. Very near to the median plane, in an ideal rostral continuation of the anterior horns of the spinal cord, are the nuclei of the III, IV, VI and VII cranial nerves, giving rise to general somatic efferent fibres; and in an adjacent lateral column we find the motor nuclei of the V and VII cranial nerves and the nucleus ambiguus supplying fibres to the IX, X and XI cranial nerves or branchiomotor zone (Nieuwenhuys *et al.* 1988). We may note here that some places in the brainstem are not occupied by important cranial nerve nuclei and may therefore afford comparatively safe entry, as we shall discuss later (Fig. 8).

Arteries

Each part of the brainstem, as shown in Figs. 9 and 10, is characterized by functionally and surgically important arterial relationships (Duvernoy 1978, Lister *et al.* 1982, Martin 1989, Matsushima *et al.* 1992). The superior cerebellar artery (SCA) arises near the apex of the basilar artery and encircles

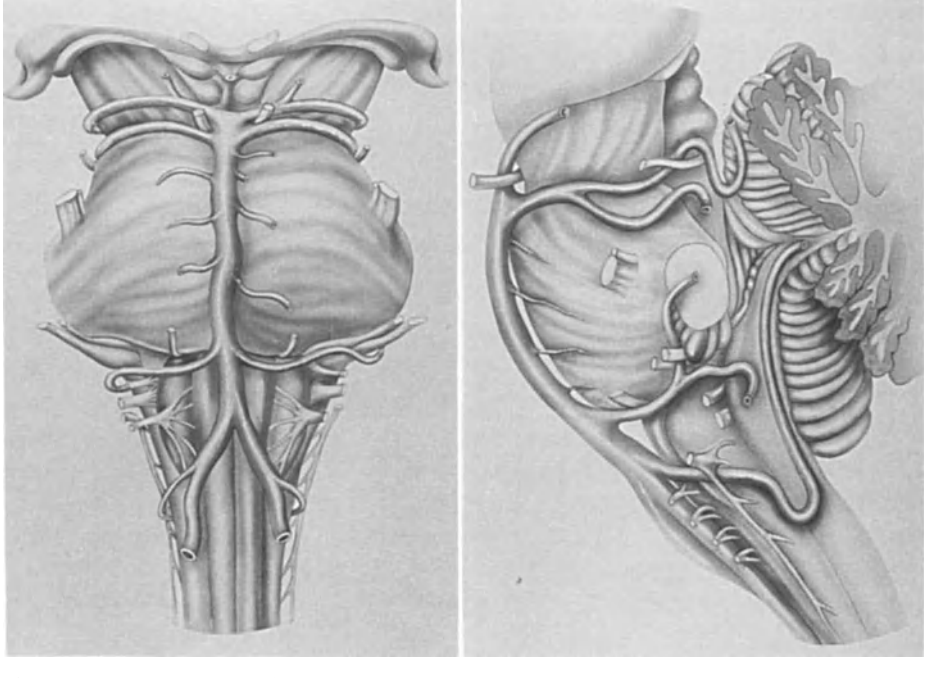


Fig. 9. The vertebrobasilar arterial circulation is schematically illustrated over a view of the lateral and ventral surfaces of the brainstem

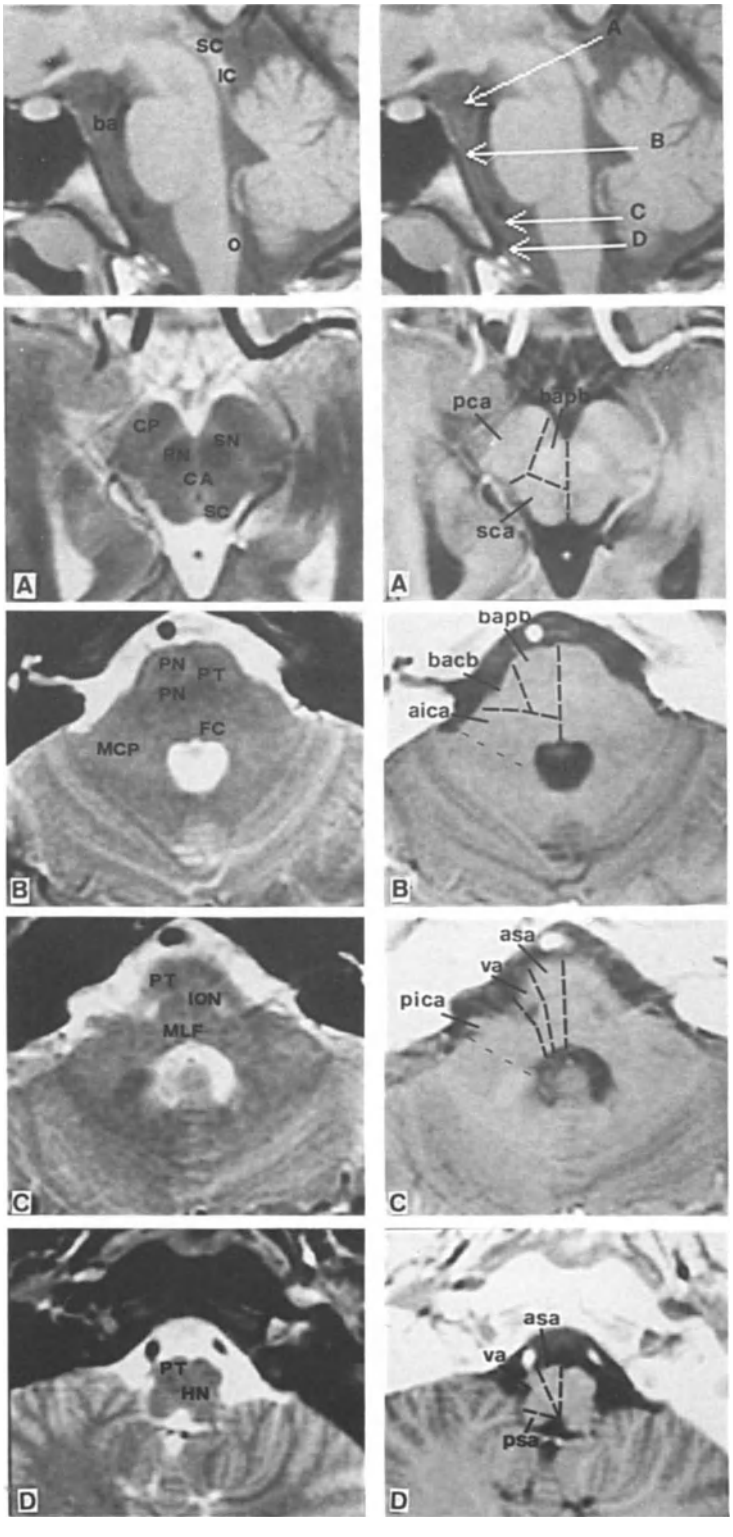

SC
IC
ba
o
A
B
C
D
CP
SN
RN
CA
SC
A
pca
bapb
sca
A
PN
PT
PN
FC
MCP
B
bapb
bacb
aica
B
PT
ION
MLF
C
asa
va
pica
C
PT
HN
D
asa
va
psa
D

Fig. 10

the brainstem near the pontomesencephalic junction, running below the oculomotor and trochlear nerves and above the trigeminus. This artery gives off perforating branches that penetrate the interpeduncular fossa, the cerebral peduncles, and the junctions of the superior and middle cerebellar peduncles and colliculi. Accidental injury to this artery and its occlusion may result in cerebellar ataxia, ipsilateral intention tremor, ipsilateral Horner's syndrome, contralateral loss of pain and temperature sensation, nystagmus, and contralateral hearing disturbance. The anterior inferior cerebellar artery (AICA) originates from the basilar artery and encircles the pons near the abducens, facial and vestibulocochlear nerves; it gives rise to perforating arteries supplying the brainstem and choroid branches serving the lateral segment of the choroid plexus and the cranial nerve related arteries at the lateral recess. Occlusion of the AICA causes a syndrome that reflects essentially the softening of the pons and cerebral peduncles, notably featuring facial and vestibulocochlear nerve palsy. The accidental occlusion of this artery was responsible for grave mortality and morbidity in connection with acoustic nerve tumour removal before the advent of microsurgery (Atkinson 1949).

Last, the posterior inferior cerebellar artery (PICA) arises from the vertebral artery near the inferior olive and passes dorsally around the medulla, where it is intimately related to the rootlets of the hypoglossal, glossopharyngeal, vagus, and accessory nerves. The PICA gives off perforating branches that supply the medulla; its occlusion results in a syndrome of lateral medullary infarction characterized by difficulty in swallowing, ataxia, nystagmus, diplopia, and facial weakness.

Mesencephalon

The midbrain, or mesencephalon, occupies the notch of the tentorium and connects the pons and cerebellum with the forebrain. It consists essentially of

Fig. 10. The wedge-shaped areas supplied by different arteries are schematically illustrated on four normal axial magnetic resonance sections (TR = 2000, TE = 90) through the brainstem. The arrows on the midline sagittal MR scan (TR = 500, TE = 15) of the same patient show the planes of the sections: *A* midbrain; *B* pons; *C* rostral medulla; *D* caudal medulla. *CA* cerebral acqueduct; *CP* cerebral peduncle; *FC* facial colliculus; *HN* hypoglossal nucleus; *IC* inferior colliculus; *ION* inferior olivary nucleus; *MCP* medial cerebellar peduncle; *MLF* medial longitudinal fascicle; *O* obex; *PN* pontine nuclei; *PT* pyramidal tract; *RN* red nucleus; *SC* superior colliculus: *SN* substantia nigra; *asa* anterior spinal artery; *ba* basilar artery; *bacb* basilar artery, circumferential branches; *bapb* basilar artery, penetrating branches; *pica* posterior inferior cerebellar artery; *pca* posterior cerebral artery; *psa* posterior spinal artery; *sca* superior cerebellar artery; *va* vertebral artery. (Courtesy of Dr. Alberto Beltramello, Institute of Radiology, University of Verona)

a dorsal part, the corpora quadrigemina, and a larger ventral portion, the cerebral peduncles, between which is the cerebral aqueduct, connecting the third and fourth ventricles over a length of about 16 mm. In a median position, in the ventral part of the central gray substance that surrounds the aqueduct, we find the nucleus of the oculomotor nerve, from where emerge motor fibres for all the eye muscles except the superior oblique and lateral rectus. Those fibres stream forward through the red nucleus and then emerge along the ventrolateral surface of the basis pedunculi. Caudally, the nucleus of the III cranial nerve continues into that of the trochlear nerve, whose fibres decussate in the anterior medullary velum before they exit on the ventral surface at the lower border of the inferior colliculus. Massive bilateral injury to the core of the midbrain invariably results in a state of coma with fixed eyes and bilateral mydriasis (Plum and Posner 1966, Bricolo 1975).

The ventrolateral aspect of the midbrain consists of the cerebral peduncles and may be approached surgically in several ways such as the trans-sylvian frontopterional, bifrontal through the lamina terminalis, subtemporal, and lateral transpetrous. The peduncles emerge from the cerebral hemispheres and converge as they descend until they meet where they enter the pons, to form the boundaries of the interpeduncular fossa. Here, the posterior perforated substance is traversed by the central branches of the posterior cerebral arteries. The ventral peduncular surfaces are crossed from medial to lateral by the superior cerebellar and posterior cerebral arteries; near the peduncular entry into the hemispheres, the optic tracts run dorsolaterally around them. The fibres of the corticospinal tract occupy only the intermediate three-fifths or so of the peduncle: thus there is a window between the emergence of the oculomotor nerve from the median groove and pyramidal fibres in the peduncle, which affords surgical access to the ventral mesencephalon through the more medial part of the peduncle sparing injury to the motor tract.

This narrow but "fairly safe" entry zone is delimited above by the posterior cerebral artery, below by the superior cerebellar artery, medially by the emergence of the III cranial nerve and basilar artery, and laterally by the pyramidal tract (Figs. 11–13). There is, however, a body of experimental and clinical evidence produced by neurosurgeons who performed sections of the cerebral peduncles in order to relieve abnormal involuntary movements (Bucy 1957, Bucy *et al.* 1961, 1966), revealing the preservation of good or normal motor activity following lesions of the pyramidal tract in that area.

The rostral portion of the midbrain roof (tectum mesencephali) is formed by the lamina quadrigemina (Fig. 6). On its dorsal surface, which is best exposed by the infratentorial supracerebellar approach, we see two pairs of elevations, the colliculi or corpora quadrigemina, each giving rise to a lateral arm or brachium. The superior brachium conveys fibres of the optic tracts from the lateral geniculate body, not only on the same side but also contralat-

erally. The inferior brachium, being the more evident of the two and involved in acoustic function, reaches the medial geniculate body.

The superior colliculi contain important visual reflex centers connected with the optic tracts, visual cortex, and nuclei of the oculomotor nerves (the latter through the medial longitudinal bundle). One of the main functions of the superior colliculus is to take part in the control of orientating responses (combined movements of the eyes, head and body toward external stimuli) and in "foveation", or bringing the image of an object onto the fovea centralis. Injury to the superior colliculi will usually result in paralysis of upward gaze, compounded in more severe instances by paralysis of downward and even horizontal gaze (Alpers 1942, Stein 1987). The visual fields are faithfully represented in the superior colliculus – in lower vertebrates, indeed, that structure receives all the fibres from the optic tracts, and it is only with the growth of the cortex in the phylogenetic ascent of animals that visual perception gradually moves by "encephalization" or "corticalization" to the

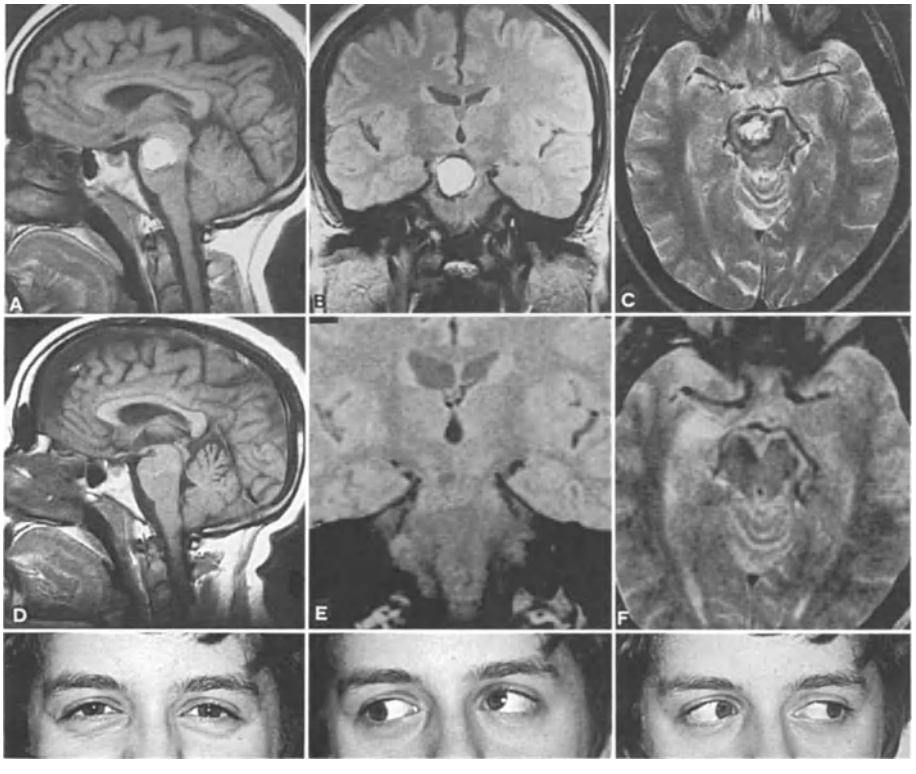


Fig. 11. Cavernoma of the ventral mesencephalo-pontine junction: preoperative (A–C) and one year postoperative (D–F) sagittal, coronal and axial magnetic resonance images. The patient, neurologically intact, has no ocular disturbances

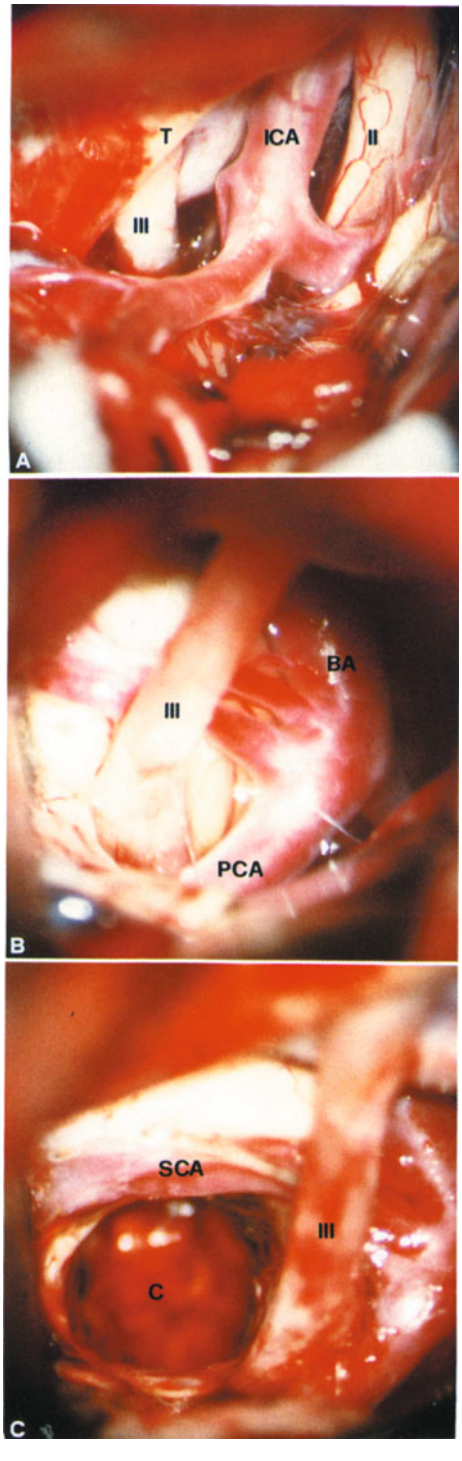


Fig. 12. Intraoperative views of the same patient, as shown in Fig. 11. Fronto-pterional approach (A); by wide opening of the Sylvian fissure the emergence of the left oculo-motor nerve is exposed (B) and the lesion removed (C). *T* tentorium; *ICA* internal carotid artery; *II* optic nerve; *III* oculo-motor nerve; *BA* basilar artery; *PCA* posterior cerebral artery; *SCA* superior cerebellar artery; *C* residual cavity

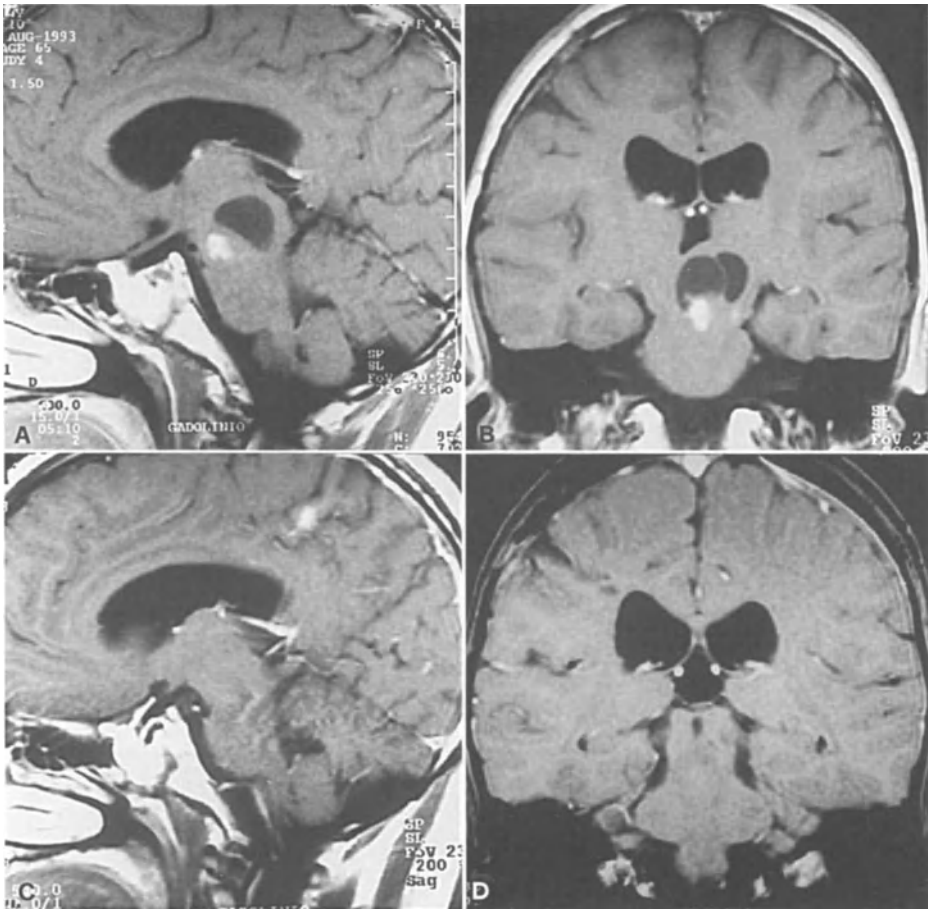


Fig. 13. Benign cystic astrocytoma of the ponto-mesencephalic junction removed via a fronto-pterional trans-sylvian approach. Preoperative (A, B) and postoperative (C, D) contrast-enhanced magnetic resonance images. The preoperative boy's neurological deficits resolved

striate area of the cortex (Brodal 1969). It seems that the superior colliculus may be more than a pure reflex center also in superior mammals, retaining a certain amount of functional dignity in processes of visual perception. Sprague and Meikle (1965) found that cats would neglect stimuli delivered to the contralateral visual field after injury to a superior colliculus. Although we must be wary of transferring experimental animal results to human clinical affairs, we recall the case of a girl in our present series, who underwent removal of a quadrigeminal plate astrocytoma with bilateral damage to the colliculi, and suffered complete blindness for more than one month after surgery, in addition to impaired eye movements (Figs. 14 and 15).

Immediately rostral and ventral to the superior colliculus and dorsal to the cerebral aqueduct at the level of the posterior commissure, we find the so-called pretectal area, which receives the afferent link of the light pupillary reflex from optic nerve fibres via the superior quadrigeminal brachium and sends efferent impulses to the oculomotor nerve via the accessory oculomotor nuclei of the Edinger-Westphal nucleus (Hutchins and Weber 1985). This may explain the bilateral areactive mydriasis presented by many patients after surgery involving the region of the quadrigeminal plate. According to Ranson and Magoun (1933), destruction of the superior colliculus does not abolish the pupillary light reflexes, which however disappear after injury to the pretectal area. At the level of the superior colliculus ventrally to its brachium, most fibres of the spinothalamic and lateral trigeminothalamic tracts are crowded into a small bundle: this was the target area for "mesencephalotomy" (mesencephalic tractotomy), pioneered by Dogliotti (1938) and Walker (1942) for the relief of intractable pain. Interestingly, changes in ocular motility and pupillary reflexes are the more frequent complications of these procedures (Walker 1942, Spiegel 1953, Nashold 1972).

The inferior colliculi are interconnected by commissural fibres and constitute the most important relay station both in ascending and in descending auditory projections. The inferior colliculi, where most fibres from the

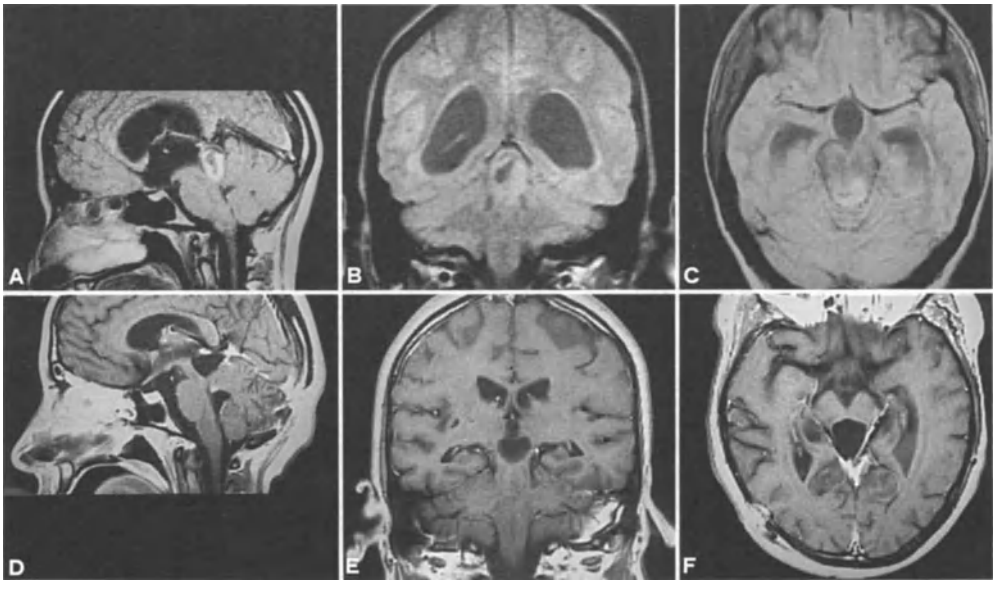


Fig. 14. Oligodendroglioma of the quadrigeminal plate. Contrast-enhanced sagittal (A), coronal (B), and axial (C) magnetic resonance images before and 6 months after surgery (D–F). The tumour was completely removed via a supracerebellar infratentorial approach. A concomitant hydrocephalus was resolved

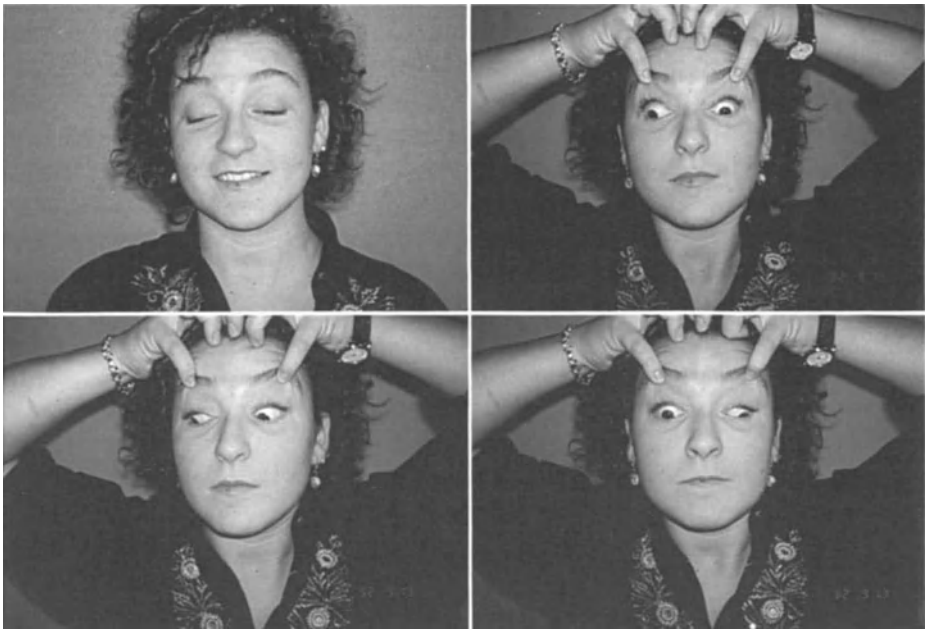


Fig. 15. Same patient as shown in Fig. 14 two years after surgery. She had a disturbed postoperative course initially characterized by unconsciousness and then by blindness, deafness, dilated pupils, severe oculo-motor disorders and psychic disturbances. As the time passed most symptoms cleared but extraocular muscle disorders persisted (Parinaud's syndrome), indicative of a damage of the tectal region

lemniscus lateralis terminate, represent the auditory system in the mesencephalon and play an integrated role in sound discrimination and localization. Fibres passing from the lateral zone of the inferior colliculus to the superior colliculus are important links in the pathway that provides for reflex turning of the eyes and head in response to auditory stimuli (Aitken 1979, Kudo 1981). Severe bilateral injury to the inferior colliculi and (or) inferior quadrigeminal brachium, from where fibres are projected to the medial geniculate body, leads to deafness; unilateral or less severe injury to the same structures results in more or less marked loss of hearing (Figs. 14 and 15).

Pons

The pons, part of the brainstem interposed between the medulla oblongata and the midbrain, consists of two parts differing greatly in structure and function. The dorsal or tegmental part resembles the medulla oblongata, of which it is the direct continuation and likewise a part of the floor of the fourth ventricle. The ventral or basilar portion carries the descending longitudinal

fibres of the pyramidal tract; other than that, it contains structures that are found only at this level. The ventral pons is a recent phylogenetic development and a prominent feature of the brainstem only in mammals endowed with relatively large cerebral and cerebellar hemispheres, forming as it does an important part of conduction pathways between these structures (Ranson 1935). In man the ventral surface of the pons (being the largest component of the brainstem) is markedly convex transversely, less so vertically, and it rests on the clivus and dorsum sellae, with a midline groove accommodating the basilar artery (Fig. 9). The ventral pons is made up of longitudinal fascicles (with the corticospinal tract continuing into the pyramids of the oblongata and the corticopontine fibres ending in the nuclei of the pons) and a transverse band of nerve fibres that aggregate on either side to form a large middle cerebellar peduncle or brachium pontis. Caudally, its border on the medulla oblongata is well demarcated by a transverse ventrolateral sulcus in which run the abducents, facial, and vestibulocochlear nerves. The trigeminal nerve emerges from the lateral aspect of the pons, this exit being generally taken to represent the point of junction of the pons and its brachium (Fig. 4). This area, being easily exposed through the classical retromastoid retrosigmoid approach, was originally recommended for brainstem tumour biopsy by Baghai *et al.* (1982); subsequently, it was considered also as a "safe" entry zone for the removal of certain intra-axial pontine lesions. Like all other brainstem approaches regarded as only moderately dangerous, this one is narrow, consisting only of a tiny window between the emergence of the V, and VII–VIII cranial nerves. Still, a careful angling of the operative microscope and delicate upward displacement of the trigeminus will afford a keyhole through which one can excise intrapontine tumour masses without the risk of added neurological deficits. The brachium pontis as an area of entry to a hemipons can be reached in bloodless fashion also through the paramedian route of the cerebellomedullary fissure (of which more later).

The dorsal or tegmental part of the pons is more complex, comprising as it does a number of structures both crowded together and interconnected: the cochlear nuclei at the restiform body; the trapezoid body and superior olivary nucleus involved in auditory function; the nuclei of the vestibular nerve; the medial longitudinal fasciculus particularly involved in the reflex control of head and eye movements; the medial lemniscus; the motor nucleus of the facial nerve; the nucleus of the abducens nerve, and the nucleus of the trigeminal nerve. The topographical distribution of these structures will be "seen" through the floor of the fourth ventricle, which constitutes the surgical approach to the region.

The posterior surface of the pons, forming the rostral part of the floor of the fourth ventricle, is covered by cerebellum and comprises the brachia conjunctiva (superior cerebellar peduncles) bridged by the anterior medullary velum.

Medulla Oblongata

At its rostral end the cervical spinal cord increases in size and continues without any sharp demarcation into the medulla oblongata; the latter may be said to begin just above the first pair of cervical spinal nerves. The shape of the medulla oblongata is roughly that of a truncated cone about 3 cm long, divided into a closed part containing the central canal and an open part containing the lower half of the fourth ventricle. Like the spinal cord, the medulla shows a number of fairly parallel longitudinal grooves, looking like the direct upward continuation of those which mark the posterior, lateral and anterior funiculi of the spinal cord. This apparent continuity, however, is not so perfect as it looks from the outside, since the tracts of the spinal cord undergo some reorientation as they enter the medulla. The cord tracts howev-

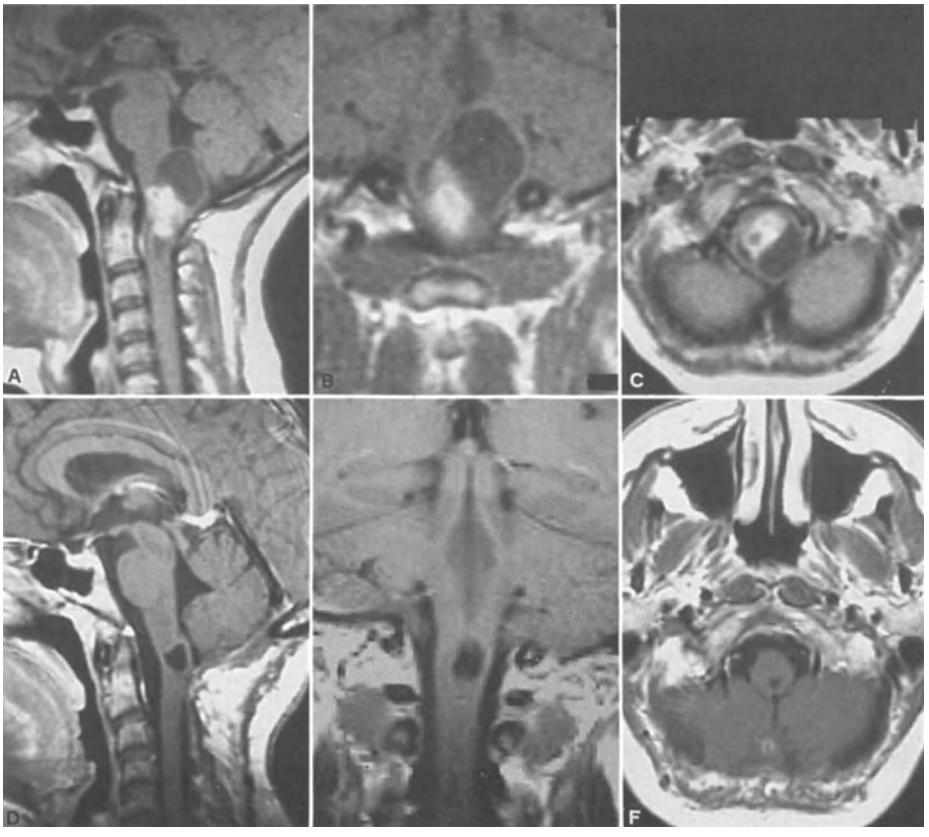


Fig. 16. Sagittal, coronal and axial magnetic resonance images of a patient with a medullary ependymoma before surgery (A–C) and one year later (D–F). The tumour was completely removed and the patient resumed normal life with no neurological deficits

er remain very important reference points to indicate the least damaging entry route for removing intrinsic lesions located therein.

The posterior median sulcus, which continues that of the spinal cord, ends near the middle of the medulla oblongata at the obex, were its lips diverge to mark the inferior triangle of the floor of the fourth ventricle (Fig. 6). The fasciculus gracilis and fasciculus cuneatus flank the posterior median sulcus, running vertical at the beginning but diverging as they reach the lower end of the fourth ventricle, and at the same time enlarging to form elongated eminences, the cuneate tubercle and the clava, produced respectively by the underlying gracile and cuneate nuclei. Injury to this area produces ipsilateral defects of discriminative function, and clinically more important, impairment of motor co-ordination. The resulting ataxia is due to the loss of proprioceptive impulses and is severe: with closed eyes, the patient is unable to

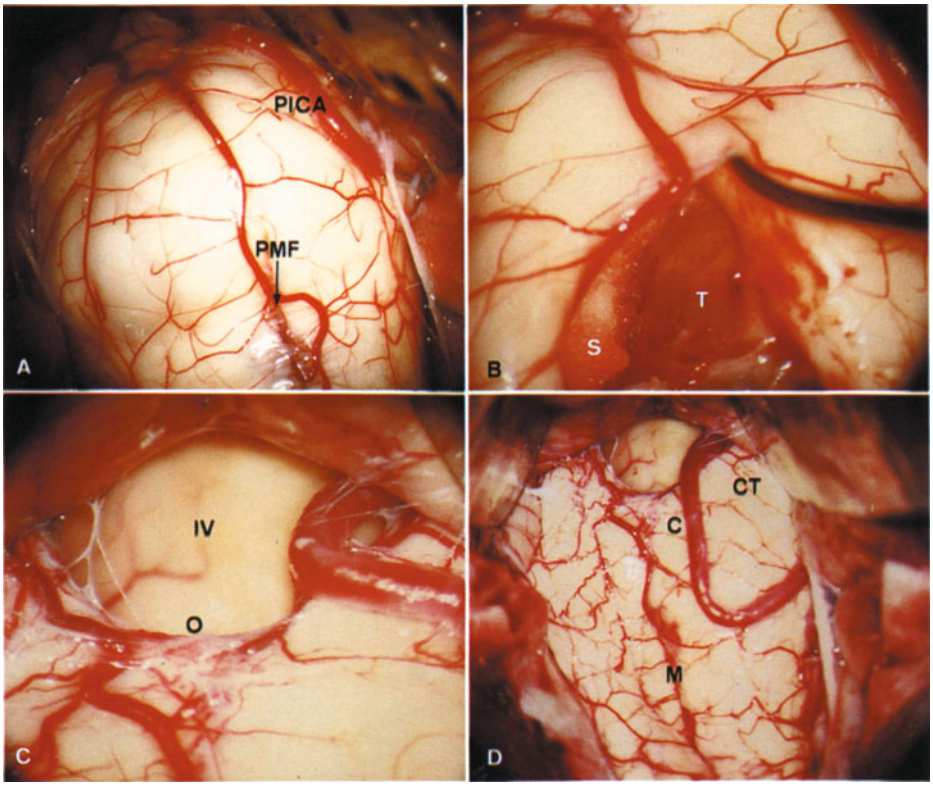


Fig. 17. Intraoperative views of the same patient as shown in Fig. 16. (A) The enlarged medulla at the dura opening; (B) midline mielotomy and tumour dissection; (C) and (D) after complete tumour excision the fouth ventricle is opened and the medulla collapsed. *PICA* Posterior inferior cerebellar artery; *PMF* posterior median fissure; *T* tumour; *S* sponge; *IV* fourth ventricle; *O* obex; *CT* cuneate tubercle; *C* clava; *M* mielotomy

recognize the position in which his joints and limbs are moved. This makes it mandatory to use the median access route, as in tumours of the spinal cord (Figs. 16 and 17). More lateral to the cuneate tubercle, between it and the roots of the accessory nerve, we find a third elevation or bulge, the tuber cinereum. At this point, close to the obex, the spinothalamic tracts of the medulla lie just ventral to the descending spinal trigeminal tract and nucleus. This is the target area used by Sjoquist (1938), Olivecrona (1942), Falconer (1949), Mazars *et al.* (1959), Kunc (1965, 1966), White and Sweet (1969), and Hitchcock (1970) to relieve intractable pain by bulbar and trigeminal tractotomy.

The lateral surface of the medulla features on each side a prominence called the olive. Posterior to it in linear order along the posterolateral sulcus, in continuation of the dorsal spinal nerve root line, there emerge the rootlets of the glossopharyngeal, vagus and accessory nerves. The fewer upper bundles merge together to form the glossopharyngeal nerve, while the more numerous lower bundles fuse to constitute the vagus nerve; both nerves leave the skull through the jugular foramen. The hypoglossal nerve emerges from the lateral sulcus ventral to the olive, between it and the pyramid, with 10–15 slender rootlets soon coalescing to run through the hypoglossal canal in the occipital bone, and cushioned by a plexus of small veins (Rhoton 1979).

The anterior aspect of the medulla oblongata rests on the basilar portion of the occipital bone, the inferior clivus. On either side of its pronounced anterior median fissure there is an elongated eminence, the pyramid, formed by the fibres of the corticospinal tract. At its pontine end the abducens nerve emerges. Just before entering the spinal cord, these fibres cross the median plane, thereby obliterating the median fissure in the caudal part of the medulla oblongata (pyramidal decussation).

Fourth Ventricle

Numerous intrinsic lesions of the brainstem, whether fungating in the cavity or protruding therein, can be reached and removed through the fourth ventricle (Fig. 6). This diamond-shaped cavity is limited ventrally by the pons and medulla, and dorsally by the cerebellum; it continues downward into the central canal of the closed portion of the medulla and communicates with the third ventricle through the cerebral aqueduct, with the cisterna magna through the foramen of Magendie, and laterally with the cerebellopontine angles through the foramina of Luschka. On each side, therefore, the cavity extends into the lateral recesses that surmount the dorsal surface of the restiform bodies, thence to open into the subarachnoid space near the cerebellar flocculus. Protruding as they do from the foramina of Luschka, the flocculus and choroid plexus constitute excellent anatomic reference points during posterolateral brainstem surgery, since these formations are immediately posterior to the emergence of the VII–VIII, IX, and X cranial nerves.

Enlarging the median aperture on the roof of the caudal extremity of the ventricle (the foramen of Magendie) affords the easiest and most bloodless surgical access to the cavity by a standard suboccipital craniectomy.

The ventricular cavity reaches its maximum width (12 mm) in its middle part, where the restiform bodies turn dorsally into the cerebellum; from that level it narrows both upward and downward. The side walls of the ventricle are provided by the brachia conjunctiva, restiform bodies, cuneate tubercles, and clavae. Of the four imaginary angles of the rhomboid fossa, two are lateral and correspond with the lateral recesses, the caudal angle continues into the central canal of the oblongata, and the rostral angle continues into the cerebral aqueduct.

The relationships between the fourth ventricle and the cerebellar surfaces and fissures, through which the ventricle is accessed surgically, are among the more complex in the brain (Matsushima *et al.* 1982). The three deep fissures formed by the embryological folding of the cerebellum over and around the adjacent parts of the mesencephalon, pons, and medulla relate closely with the roof and lateral recess of the fourth ventricle. One is the cerebellomesencephalic fissure, which extends inferiorly between the cerebellum and midbrain and is intimately related to the superior half of the roof. Another is the cerebellopontine fissure, formed by folding of the cerebellum around the sides of the pons and intimately related to the lateral recesses. The third is the cerebellomedullary fissure, which extends superiorly between the cerebellum and medulla and is intimately related to the inferior half of the roof. A major cerebellar artery courses in each fissure: namely the superior cerebellar running within the cerebellomesencephalic fissure; the anterior inferior artery running in the cerebellopontine fissure and being related to it; and the posterior inferior artery running in the cerebellomedullary fissure and being related to it. Each of the fissures communicates with the one adjacent.

The upper or rostral part of the roof of the fourth ventricle is made up of the anterior medullary velum, a small portion of the white substance of the cerebellum. The structure is stretched between the dorsomedial borders of the two brachia conjunctiva and extends from the medullary substance of the cerebellar vermis, where it is surmounted by the lingula, all the way to the lamina quadrigemina. Caudally, the true roof of the cavity is exceedingly thin, as it consists of a single layer of ependymal epithelium supported on the outside by a layer of pia mater, the richly vascular tela choroidea. Suspended from this layer and invaginated into the cavity are vascular tufts covered by epithelium, forming the choroid plexus of the fourth ventricle.

The plexus is T-shaped, the vertical limb on the median plane being double and reaching all the way to the foramen of Magendie; the horizontal arms diverge at a right angle from the top of the vertical limb and run toward the lateral recesses. The best and least vascular route into the fourth ventricle is afforded by the cerebellomedullary fissure, which is covered by the

cerebellar tonsils and by the uvula sandwiched between them. The floor of the cerebellomedullary fissure consists of the tela choroidea, which also makes up the roof of the rostral part of the fourth ventricle and of its lateral recesses (Fig. 5). Particularly with the patient in a semi-sitting position, by spreading and retracting the cerebellar tonsils and keeping the PICAs lateral to the access, one can secure ample exposure of the tela choroidea and cut it off flush with its attachment along the lateral boundaries of the caudal part of the cavity, the tenia of the fourth ventricle, which gathers over the caudal angle to form an ependymal thickening called the obex (Quisling *et al.* 1993). This affords ample access to the floor of the fourth ventricle without splitting the inferior vermis, thereby avoiding any risk of postoperative ataxia (Fig. 18).

The floor of the fourth ventricle, also called rhomboid fossa because of its shape, is formed by the dorsal surface of the pons and the open part of the medulla oblongata; it measures an average 33 mm in height (from the obex to the exit of the trochlear nerve) and 36 mm width in its broadest part in the lateral recess. On its irregularly concave surface the operative microscope often makes it possible to identify some anatomic landmarks that are instrumental in guiding the surgeon in penetration of the brainstem while avoiding or at least minimizing surgical morbidity (Figs. 6 and 19).

Between the cerebral aqueduct and the obex is the median sulcus, which divides the fossa into two symmetrical halves. Identifying this very important groove that marks the midline is important because the groove itself is bordered by the medial longitudinal fascicles whose integrity is essential for

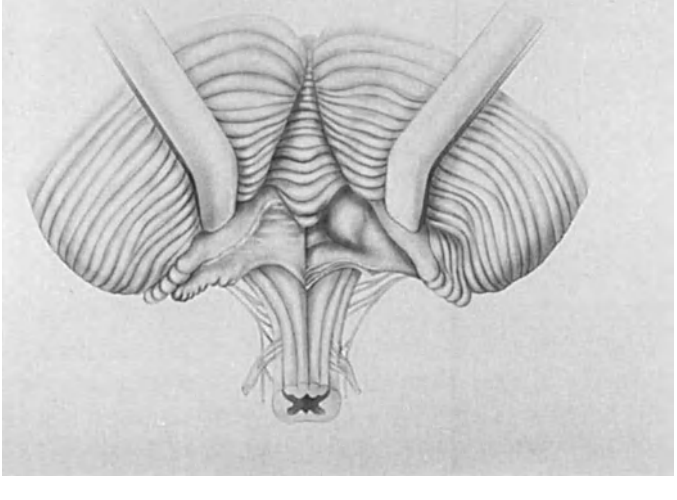


Fig. 18. Exposure of floor of the fourth ventricle via cerebello-medullary fissure

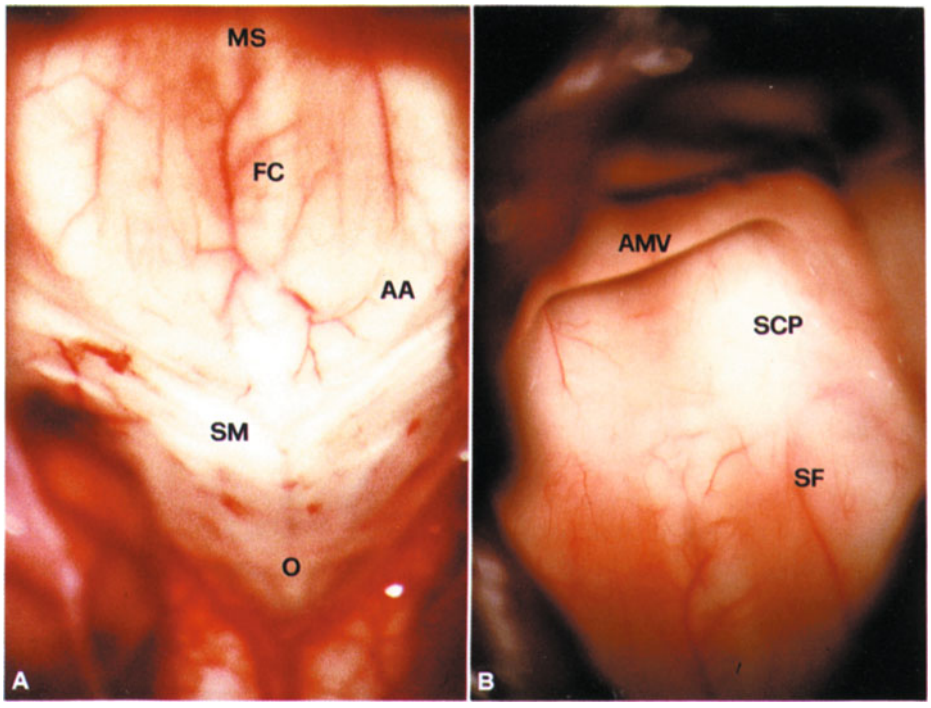


Fig. 19. Intraoperative posterior views (A, B) of the floor of the fourth ventricle: with the patient in semi-sitting position, a complete exposure is achieveable without splitting the vermis. *O* obex; *SM* striae medullares; *MS* median sulcus; *FC* facial colliculus; *AMV* anterior medullary velum; *SCP* superior cerebellar peduncle: *SF* superiore fovea; *AA* area acoustica

the control of conjugate eye movements. Injury to the medial longitudinal fascicles between the abducens and oculomotor nuclei produces the syndrome of internuclear ophthalmoplegia (Fisher 1967). During attempted gaze to the contralateral side, the adducting eye shows paresis due to interruption of the "six-to-three" pathway that innervates the medial rectus motor neurons. It is worth mentioning that oculomotion can be left quite undisturbed by entering the floor of the fourth ventricle through the median sulcus at a point between the abducens nuclei at the facial colliculi and the oculomotor in the midbrain, as long as the two medial longitudinal fasciculi, which have no crossing fibres at that level, are not injured by retraction (Fig. 20). Crossing fibres, instead, are concentrated at the level of the facial colliculi, where a midline incision into the floor of the fourth ventricle would interrupt the axons of the internuclear neurons that cross the midline from the abducens nucleus and then ascend in the contralateral medial longitudinal fascicle to the oculomotor complex. The same penetration would also interrupt the fibres that project from the paramedian pontine reticular formation (PPRF) of

one side to both abducens nuclei. Injury to the PPRF (the "pontine gaze center") causes a horizontal gaze palsy and possibly the total loss of rapid eye movements both horizontal and vertical. Lesions in this area are often associated with paralysis of the facial nerve, whose intra-axial course at this level is closely adjacent to the above mentioned structures. Another important anatomical landmark is the sulcus limitans, a groove found in each half of the floor medial to the prominence of the restiform body. The sulcus limitans represents the line of separation between the parts derived from the alar plate and those originating from the basal plate of the embryonic rhombencephalon (Ranson 1935). Lateral to this sulcus lie the sensory areas of the ventricular floor, including the area acoustica. Medial to the sulcus is a prominent longitudinal elevation known as the medial eminence, which borders the midline and includes the facial colliculus on top of the striae medullares and the underlying trigone of the hypoglossal nerve.

Crossing the intermediate part of the fossa transversely and bulging slightly over it, about 11 mm above the obex, are the striae medullares acousticae (Alphin and William 1944). These are not auditory nerve fibres proper but more probably an aberrant cerebro-pontocerebellar connection. These slim bands of fibres, which wrap the restiform body in the lateral

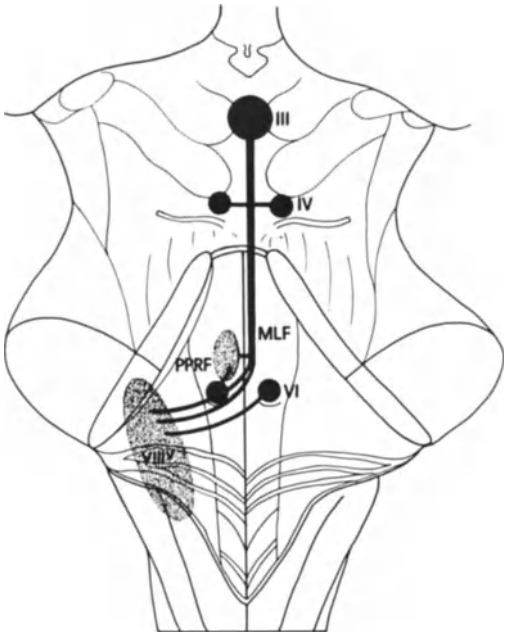


Fig. 20. Schematic summary of the ascending and crossing projections via the medial longitudinal fascicle. *III* oculomotor nuclei, *IV* trochlear nuclei, *MLF* medial longitudinal fascicle, *PPRF* parapontine reticular formation, *VI* abducens nuclei, *VIII* area acoustica

recess and disappear into the median sulcus, roughly mark the imaginary boundary line between the pons and the medulla oblongata (Fig. 6). Unfortunately for the surgeon, this important anatomic landmark is in constant: the striae under discussion are nonexistent in 13% of cases (Lang *et al.* 1991), their numbers varying widely from 0 to 9.

Beneath the striae is the inferior part of the rhomboid fossa, called calamus scriptorius, because of its resemblance to the nib of a quill pen. Within this small concavity, rightly belonging to the medulla oblongata, we can see or imagine three triangles, carefully described by anatomists, and of great functional importance because of the immediately underlying structures: the hypoglossal and vagal triangles and the area cinerea. The two more medial triangles, together looking like the head of an arrow pointed at the obex, make up the trigonum nervi hypoglossi. Immediately below the more medial and elevated part of this triangle lies the nucleus of the hypoglossal nerve. Because the right and left nuclei are very close together, injury to one of them is seldom truly unilateral; the effect of such damage is paralysis and atrophy of the muscles of the ipsilateral half of the tongue, causing difficulty in moving a food bolus within the mouth, dysphagia and dysarthria. Adjacent to the hypoglossal nucleus and medial longitudinal fascicle is the nucleus prepositus hypoglossi, and important pre-oculomotor center that sends fibres to all external eye muscle nuclei both ipsilateral and contralateral (Baker and Berthoz 1975). This may explain some abnormalities of ocular movements that are fairly often associated with median damage to the medulla oblongata over the obex. Caudal and lateral to the hypoglossal triangles are two dark triangular fields, the vagal triangles: the dorsal nucleus of the vagus nerve lies subadjacent to the triangles, its motor fibres being distributed to the nonstriated musculature of the bronchi, heart, oesophagus, and stomach. The nucleus ambiguus, giving rise to efferent fibres for the IX, X, and XI cranial nerves to supply the musculature of the pharynx and larynx, extends through the length of the medulla oblongata in a position only slightly deeper and more lateral to the dorsal nucleus of the vagus adjacent to the spinal nucleus of the trigeminus (Kunc and Marsala 1962). Lesions affecting the vagus and glossopharyngeal nerves or their nuclei result in paralysis of the soft palate with regurgitation into the nose and of the pharyngeal muscles with impaired swallowing and aphonia or dysphonia due to paralysis of the laryngeal muscles; the associated loss of coughing reflexes exposes the patient to the risk of aspiration pneumonia. Acute bilateral lesions may cause severe tachycardia. The third triangular field, lying more laterally, is part of the area acoustica.

Rostral to the striae medullares we find the superior fovea, a shallow depression medial to which rises a round elevation, the facial colliculus, whose inferior border is an average 14 (11.5 to 18.0) mm from the obex (Lang *et al.* 1991). Under cover of this eminence, the fibres of the facial nerve bend

around the abducens nucleus, a spherical mass of gray matter supplying the lateral rectus muscle on each side (Fig. 8). The fibres leaving this nucleus run ventrally toward their exit point from the lower border of the pons near the pyramid of the medulla oblongata. The motor nucleus of the facial nerve, which innervates the platysma and muscles of the face, is located in the tegmental part of the pons, 5 mm below the floor of the fourth ventricle and 6–7 mm from the midline. Its fibres emerge from the dorsal surface of the nucleus and run dorsomedially toward the floor, and become compacted as in a peripheral nerve at a point near the nucleus of the abducens; as they form the genu of the facial nerve, the fibres turn sharply rostrad encircling the nucleus along its medial side beneath the floor of the fourth ventricle and dorsal to the medial longitudinal bundle over some distance (about 5 mm). Next, the facial nerve turns outward and caudad, running close to its own nucleus to make its exit from the side of the caudal border of the pons (Fig. 21). The motor and main sensory nuclei of the trigeminal nerve are just below the floor of the fourth ventricle at its lateral extremity, where the groove between the middle and superior cerebellar peduncles is visible in some cases.

Damage to the area of the facial colliculus invariably causes abducens and facial palsy plus a lateral gaze disturbance. To obviate these severe deficits, especially in patients with formerly intact face and eye motility, one must avoid entering the facial colliculus – which entails identifying it in the first place. Unfortunately this is not always possible, since the rhomboid fossa may be distorted by the intrinsic lesion to the point where even the median sulcus defies detection, while the medullary striae are far too variable to be reliable (Ranson 1935, Lang *et al.* 1991). One possible solution to this problem is direct electrical stimulation of the floor of the fourth ventricle,

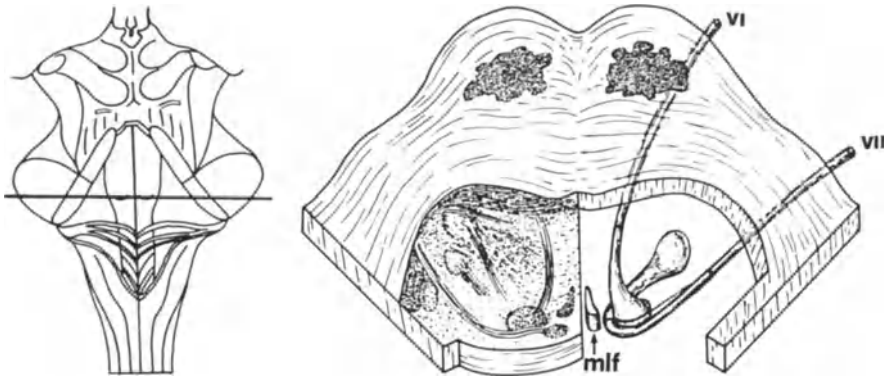


Fig. 21. Three-dimensional schematic cross section throughout the pons showing the location and courses of abducens (*VI*) and facial (*VII*) nerves and medial longitudinal fascicle (*mlf*). Level of section is indicated in inset

which we conduct when necessary with a thin, hand-held monopolar probe and visual observation or electrical recording of any motor response of the facial musculature (Figs. 22–24).

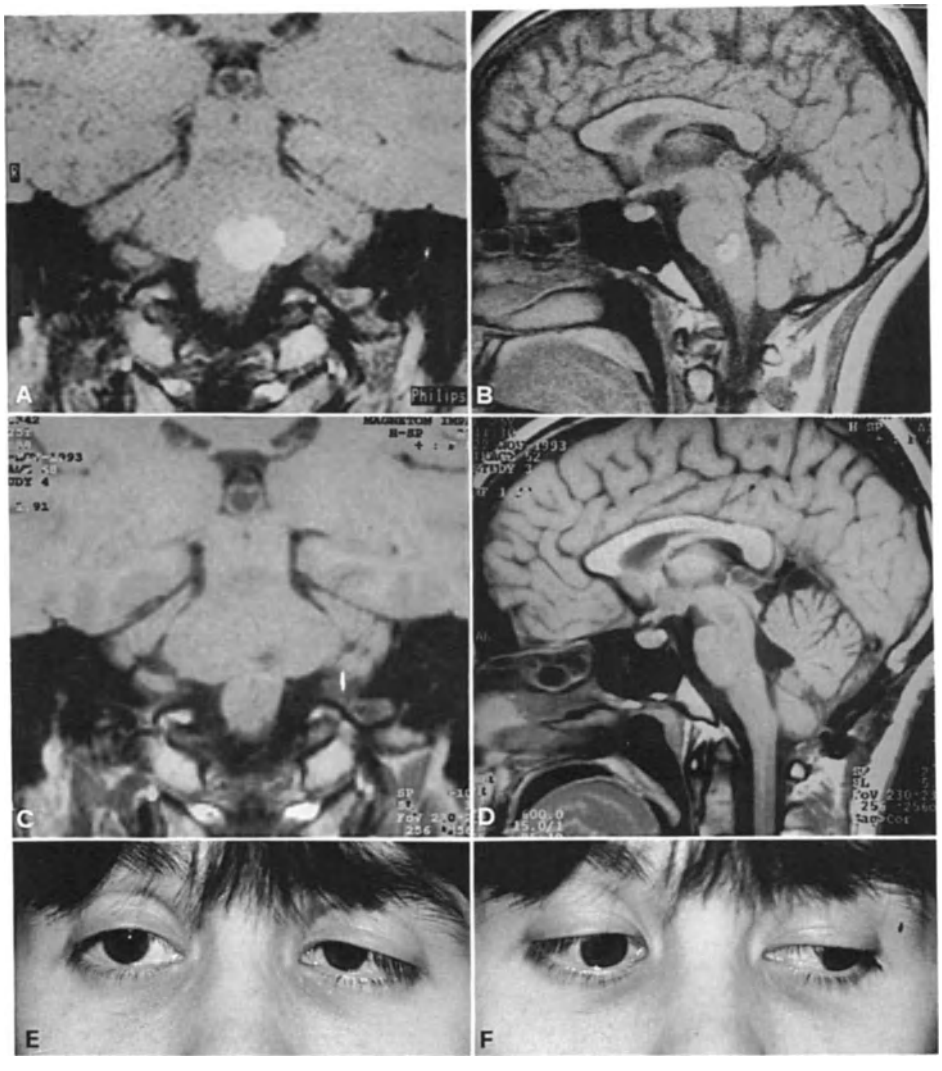


Fig. 22. Preoperative coronal (A) and sagittal (B) magnetic resonance images demonstrating subacute hemorrhage within the pons due to a cavernous malformation. (C) and (D) are the comparable postoperative three years later images showing complete resection of a small cavernoma and hematoma. Eye movements of the patient (E, F) 1 year after surgery documenting the sparing of the facial nerve and medial longitudinal fascicle (no internuclear ophthalmoplegia) and the inability of right eye to fully abduct on right lateral gaze due to damage of abducens nerve of the same side

A more sophisticated and possibly safer method, however, was developed by Strauss *et al.* (1993): this involves the placement in the rhomboid fossa of small silicone strips with embedded electrodes, bipolar stimulation, and bilateral four-channel electromyography from the orbicularis and genioglossal muscles, also affording identification of the hypoglossal nerve triangle.

As recently suggested by Kyoshima *et al.* (1993), access to a hemipons may be gained through the zones above and below the facial colliculus. The suprafacial entry zone is bordered medially by the medial longitudinal fascicle, caudally by the facial nerve and abducens nucleus PPRF, and laterally by the trigeminal motor nucleus and cerebellar peduncles. A longitudinal cut of

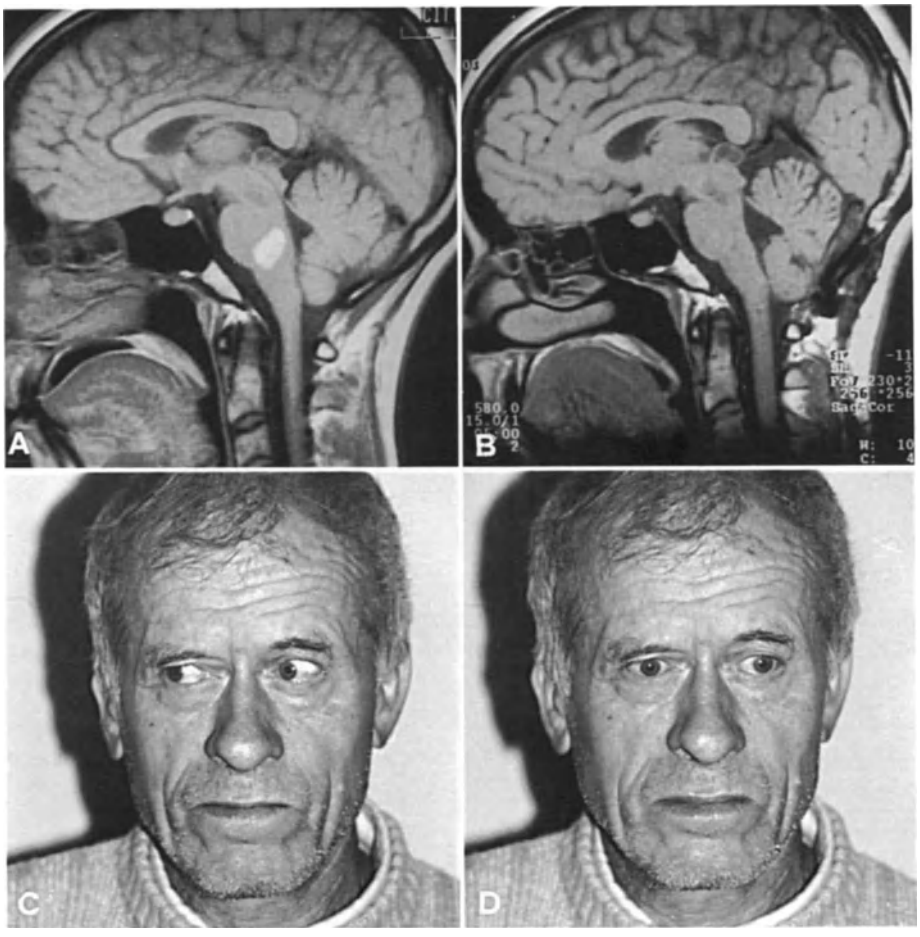


Fig. 23. Sagittal pre- (A) and 4 years postoperative (B) magnetic resonance images of a pontine cavernous malformation. The facial nerve function was preserved and the patient (C and D) showed only a partial lateral gaze palsy with which he adapted very well

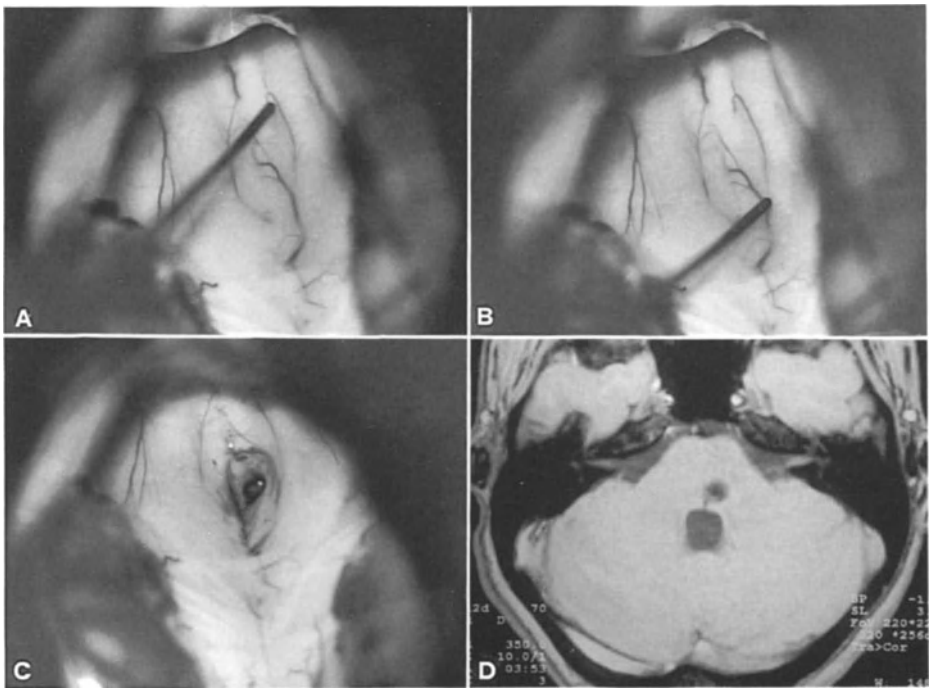


Fig. 24. Intraoperative views of the rhomboid fossa of the same patient, as shown in Fig. 23. The morphology is distorted and the lesion effaced. Direct electrical stimulation allowed localization of the facial colliculus (A) which was displaced more rostrally than expected (B). The infrafacial entry zone was chosen for removal (C). Axial MRI documents the access route and residual cavity (D)

about 1 cm, starting from the superior margin of the colliculus and placed 5 mm away from the median sulcus, will avoid both the intra-axial course of the facial nerve and the medial longitudinal fascicle. If necessary, the access may be enlarged by lateral and (or) superior retraction without damaging any functionally important structures. Conversely the infrafacial entry calls for a longitudinal cut parallel to the above, rising 1 cm from the medullary striae; this approach is narrower then the suprafacial, since its upward enlargement could damage the facial nerve (Fig. 25).

Reticular Formation

In the central part of the brainstem lies the reticular formation, so called by old anatomists because of its net-like appearance resulting from the diffuse aggregation of cells of running in all directions (see Brodal 1969). This is a phylogenetically ancient structure, which was first associated with the maintenance of consciousness by the studies of Moruzzi and Magoun, published

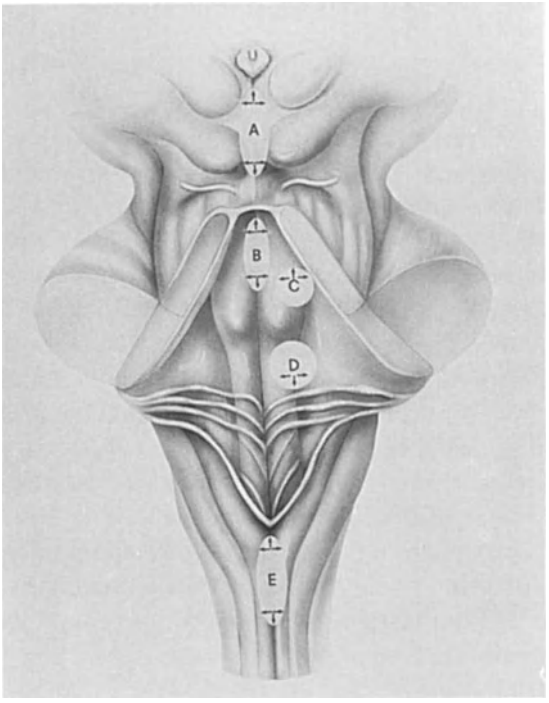


Fig. 25. Relatively safe entry zones into the dorsal brainstem. *A* intercollicular; *B* midline above facial colliculus; *C* suprafacial; *D* infrafacial; *E* midline mielotomy

in 1949. Subsequent studies and anatomo-clinical observations revealed a number of additional functions of the reticular formation, including regulation of the sleep cycle (Oswald 1972), also showing at least in broad outline that the essential components responsible for arousal, hence vigilance and consciousness (the Ascending Reticular Activating System) extended from the lower third of the pons to a rostral level comprising the posterior hypothalamus and thalamic intralaminar nuclei (Rossi 1964, Alemà *et al.* 1966). It takes, however, a fairly extensive and bilateral lesion of the reticular formation to produce coma, the more critical area in that respect seemingly being the midbrain tegmentum (Plum 1972, Bricolo 1975, Durwood *et al.* 1982). It should also be noted that states of stupor and coma seen after such injuries are fairly often reversible, probably because of the richness and plasticity of the reticular formation, whereby the function of cerebral arousal can be resumed after a less than massive lesion (Bricolo 1976). Last, we must bear in mind that lesions that destroy the reticular formation below the lower third of the pons do not pruduce coma (Plum 1972, Turazzi and Bricolo 1977, Burns *et al.* 1980).

Clinical Materials and Methods

Patients

The caseload herein presented totals 137 patients with brainstem tumours, namely 105 gliomas and 32 tumours of a different nature, treated in the Department of Neurosurgery of the University Hospital at Verona (Italy) from 1980, by direct surgery designed for extensive or possibly radical excision of tumour masses. The series extends over the last 13 years, during which the number of operations per year increased steadily (Fig. 26). We numbered in our series such tumours as occupied one or more contiguous parts of the brainstem (the midbrain, pons and medulla oblongata), including those extending from these areas toward the hypothalamus, cerebellar peduncles and cervical spinal cord. We did not include tumours that might have secondary involvement of the rhomboid fossa, such as many ependymomas and medulloblastomas of the fourth ventricle.

All clinical records, neuroimaging studies, detailed descriptions of surgical procedures, and intraoperative photographs were reviewed as well as the documentation of tumour histology, clinical control examinations, and repeat NMR scans made during long-term follow-up.

There were 82 men and 55 women between age 2 and 67 (mean age 31.2); 37 patients (22 males, 15 females) were in the pediatric age group (under 16).

In the great majority of cases, the lesions were diagnosed tentatively or finally as brainstem tumours elsewhere and were referred to our Department for an assessment of operability. Only 6 patients had been irradiated before surgery; 3 had undergone stereotaxic biopsy and radiotherapy, and the 3 others insertion of a ventriculoperitoneal shunt.

Tumour Histology

As can be seen in Table 1, the most common histological diagnosis was glioma (105 cases, or 77% of the total) with a prevalence of "benign" forms (66 cases between low-grade astrocytoma, ependymoma, oligodendroglioma and ganglioglioma as opposed to 39 cases of "malignancy" in the form of anaplastic astrocytoma, oligodendroglioma and glioblastoma). The balance consisted of 18 cases of cavernous malformations and 14 hemangioblastomas, included deliberately in the series to serve as a useful term of comparison with parenchymal tumours proper.

The two types of tumours were distributed differently in the various age groups (Fig. 26), gliomas being more frequent among pediatric patients and those in their thirties, while the so-called vascular tumours were more likely to affect middle-aged patients.

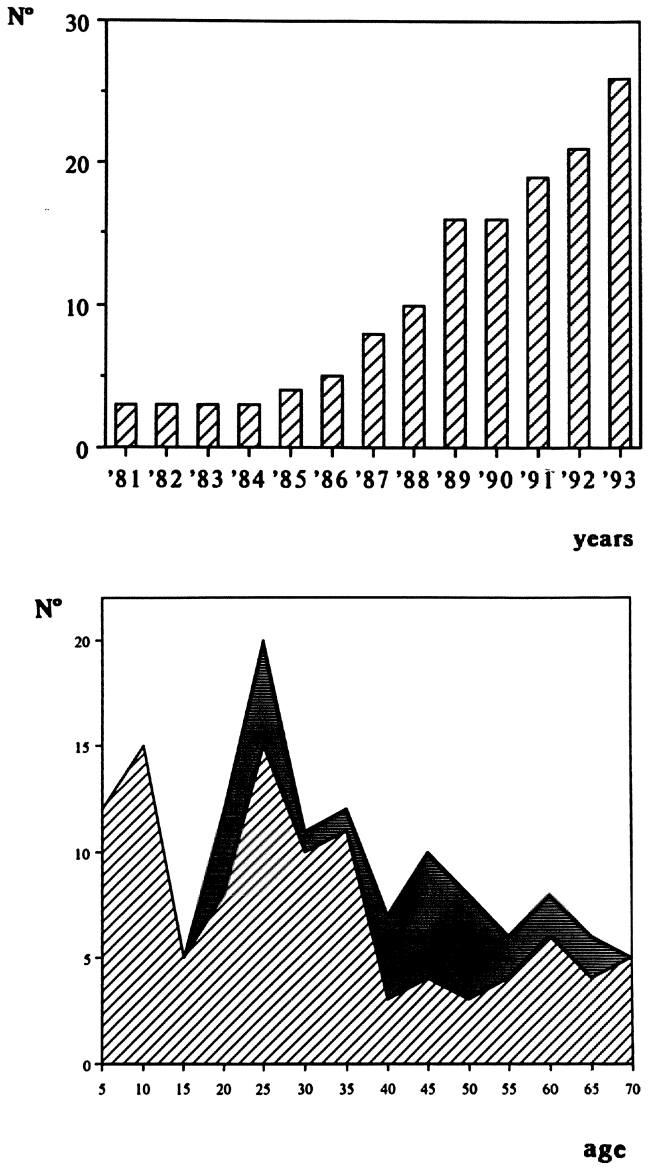


Fig. 26. On the top, the number of brainstem tumours surgically treated by year. On the bottom, gliomas (wide hatching) and vascular tumours (narrow hatching) by age

Clinical Aspects

Most of our patients contributed a history of slow and subtle neurological deterioration not always clearly progressive. Cranial nerve (CN) deficits, headache, ataxia, somatosensory and somatomotor deficits were the more

frequent initial complaints (Table 2). Diagnosis was often delayed because the first presenting symptom was mild and tended to remain stable and isolated for a long time, in addition to being relatively non-specific, as confirmed retrospectively in many cases at the time of history-taking. In our series, a meaningful diagnosis was made at an average 28 months of the onset of symptoms; all but 22 of our patients were symptomatic for more than 2

Table 1. *Pathology of the 137 Brainstem Tumours of the Present Series*

Tumour	No. patients	%
Glioma	105	77
Low-grade	66	48
High-grade	39	28
Vascular	32	23
Cavernoma	18	12
Hemangioblastoma	14	10
Total	137	

Table 2. *First Presenting Symptom and Its Mean Duration in 137 Brainstem Tumour Cases*

Symptoms	No. of patients	Months
Headache	38	42
Diplopia	22	30
Balance disorders	12	20
Arm weakness	9	10
Leg weakness	9	24
Vertigo	9	45
Facial weakness	8	18
Hypoacusia	6	32
Facial dysesthesia	6	112
Torticollis	6	28
Vomiting	4	14
Dysphagia	3	34
Epilepsy	3	52
Hypersomnia	2	2

years before being diagnosed with brainstem tumour. In the last few years, with increased use of NMR scanning and easier access to this examination, there was a tendency toward shorter intervals between onset and diagnosis. The tumours that are usually diagnosed at an earlier stage – within one year of onset – are the glioblastomas and cavernomas, followed by pilocytic and anaplastic astrocytomas, whose history seldom covers more than two years. With the onset, symptoms of "benign" astrocytomas, ependymomas and hemangioblastomas can be traced back to an average time in excess of three years.

Table 3 summarizes the physical signs and symptoms seen at the time of thorough examination shortly before surgery. At that time the clinical picture was dominated by CN deficits, present in fully 75% of our patients, and variously admixed long-tract deficits and ataxia. The single cranial nerve more often affected was the abducens (38% of cases). Compound oculomotor disturbances were however seen in a larger number of patients, namely 82, so that on the whole we can say that more than half the patients (60%) came to surgery with problems of ocular motility. About one-third of the patients presented evident deficits of the lower cranial nerves (IX, X, and XII) with dysphonia and (or) impaired deglutition. Many a patient would present

Table 3. *Clinical Features at the Time of Surgery in This Series*

Signs and symptoms	No. patients	%
CN deficits	103	75
II	3	2
III	23	17
IV	7	5
V	35	26
VI	52	38
VII	32	23
VIII	27	20
IX–X	40	29
XI	17	12
XII	21	15
Ataxia	75	55
Long-tract deficits	61	45
Somatomotor	42	31
Somatosensory	53	39
Headache	66	48
Drowsiness	14	10

deficits involving more than one cranial nerve, the more frequent associations being V–VI–VII–VIII and IX–X–XI. Deficits occurred bilaterally in a number of cases.

The more typical clinical syndrome at the time of surgery was a combination of CN deficits with ataxia and (or) long tract disturbances. Only 8 of our patients underwent surgery in a neurological situation characterized exclusively by CN deficits, and another 34 with ataxia and (or) long-tract deficits only.

Neuroimaging

The first 9 patients of our series were studied only by contrast-enhanced CT scanning; all the others were investigated by NMR imaging, also with paramagnetic contrast medium once this became available. Cerebral angiography was also performed in 45 cases, namely those in which we suspected the presence of a vascular component in the tumour mass. 3 patients examined showed arteriovenous malformations responsible for intra-axial bleeding and were thereupon excluded from this present series.

Table 4. *Neuroimaging Data of the 137 Tumours*

Tumour	No. patients	%
Gliomas	105	
Focal	55	52
Diffuse	34	32
Cervicomedullary	16	15
Prevalent location	137	
Midbrain	36	26
Pons	54	39
Medulla	47	34
Exophytosis from	39	
Midbrain	8	21
Pons	20	51
Medulla	11	28
Exophytosis to	39	
Cerebellopontine angle	11	28
Fourth ventricle	21	54
Others cisterns	7	18
Hydrocephalus	22	16

In order to classify each case in view of surgery, we grouped the presenting tumours as suggested by Epstein and McCleary (1986) into three categories, namely focal, diffuse, and cervico-medullary. In each case the diagnostic procedures employed made it possible to define the prevalent location of tumour in the brainstem and any evident exophytosis. Salient information to emerge from the diagnostic studies is displayed in Table 4.

The more frequent mode of glioma presentation in this series was focal (52% of cases), a mass essentially confined to one part of the brainstem with distorsion and dislocation of neighbouring structures. In 34 cases (32%), the tumour was of the diffuse type, without clear-cut demarcation and with a tendency to cause overall enlargement of affected brainstem segments rather than distorsion of bordering parenchyma. Last, 6 patients (15%) had brainstem tumours growing at the cervico-medullary junction and to various distances into the cervical spinal cord.

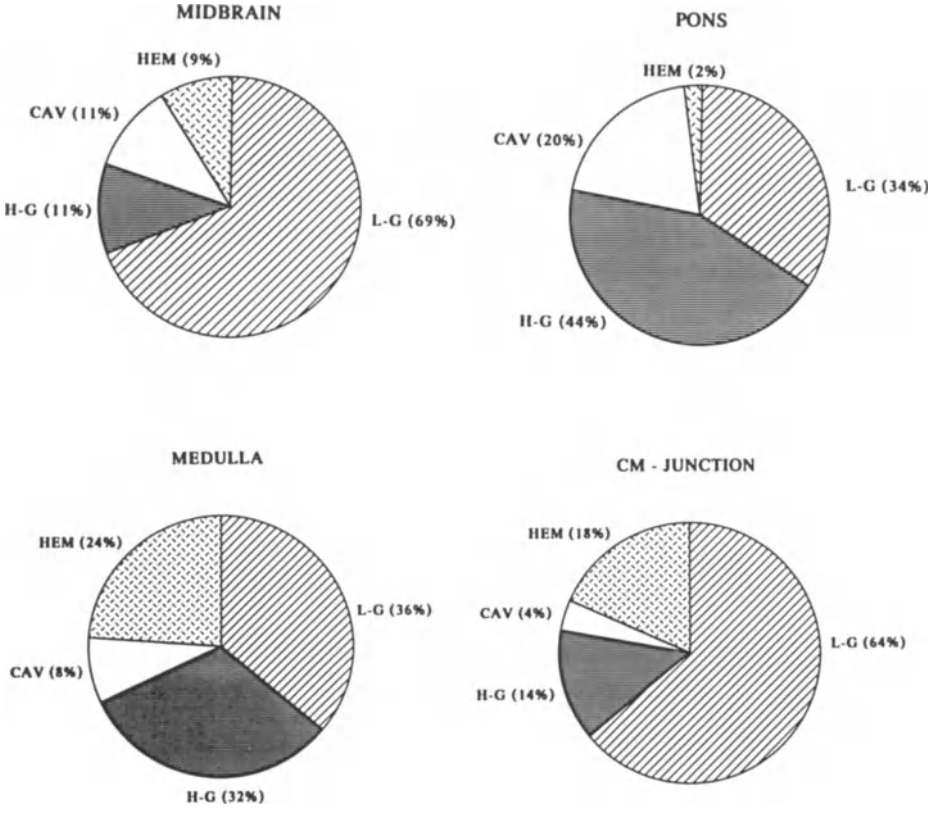


Fig. 27. Pie charts showing the distribution of tumours types in the different parts of the brainstem

Table 5. *Tumour Location and Histology*

Location	No.	Low-grade	%	High-grade	%	Cavern-oma	%	Hemangio-blastoma	%
Midbrain	36	25	70	4	11	4	11	3	8
Pons	54	18	33	24	44	11	20	1	2
Medulla	25	9	36	8	32	2	8	6	24
CM junction	22	14	64	3	14	1	5	4	18
Total	137	66		39		18		14	

The part of the brainstem most often harbouring a tumour was the pons (54 cases, or 39%) followed by the medulla oblongata (34%) and midbrain (26%). In 39 cases (28%), diagnostic procedures were successful in demonstrating tumour exophytosis, this being more often the case with pontine tumours (37%) protruding into the fourth ventricle (54% of all exophytoses).

Our series suggests some kind of relationship between the location of a tumour and its nature (Table 5, Fig. 27). "Benign" gliomas were markedly prevalent in the midbrain and cervico-medullary junction; malignant tumours seemed to prefer the pons and medulla. Vascular tumours are rarer in the midbrain: most cavernomas are found in the pons, while most hemangioblastomas affect the medulla and cervicomedullary junction.

Surgical Technique

The choice of craniotomy and the route to be followed for direct surgical removal of brainstem lesions is based on neuro-anatomoclinical considerations making due allowance for the lesion's placement, and mode of expansion, and likewise for the patient's neurological picture. In essence, the problem is how to reach the tumour mass and remove it without adding new and severe neurological deficits to those already present. Thus the rationale behind these crucial preoperative choices must take into account the ranking of functional aspects relative to surgical injury to one or another tract, nucleus, nerve, or artery in the individual patient.

The excellent multiplanar capabilities of NMR imaging make it possible to locate the tumour mass and its relationship to brainstem structures quite accurately, and so affords valuable guidance in the choice in each case of the surgical approach that will give best exposure with least risk of injuring normal nervous tissue and blood vessels on the way to the lesion and in its vicinity in order to minimize surgical morbidity (Fig. 28).

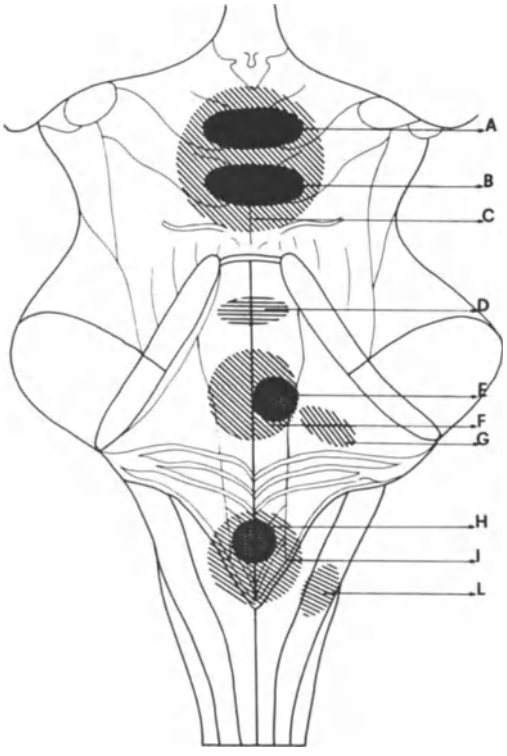


Fig. 28. Outline of the dangerous areas for entering the dorsal brainstem. *A* superior collicula = visual and oculomotor disorders; *B* inferior collicula = auditory disturbances; *C* corpora quadrigemina = as in A and B; *D* medial longitudinal fascicles = internuclear ophthalmoplegia; *E* facial colliculus = facial palsy and internuclear ophthalmoplegia; *F* facial collicula = immobile eyes and bilateral facial palsy; *G* facial nerve = facial palsy; *H* hypoglossus and vagus nerves = dysphagia; *I* calamus scriptorius = dysphagia and cardiorespiratory disturbances; *L* gracilis and cuneate tubercles = ataxia

Surgical Approaches

From the surgeon's point of view and in order to simplify our discussion of the choice of approaches, we may subdivide brainstem lesions into four main groups; namely (a) those located rostral in the posterior fossa, in the midbrain at the tentorial incisura; (b) those protruding into or exophytic in the cerebellopontine angle; (c) those located in the pons and open part of the medulla oblongata close to the floor of the fourth ventricle; and (d) those involving the closed part of the medulla at the cervico-medullary junction. Table 6 specifies the surgical approaches used in this series.

(a) For lesions in the first subgroup we have available a number of routes, final choice being dictated by the exact position of the lesion in the midbrain.

Table 6. *Surgical Approaches Used in This Series*

Craniotomy	Exposure	No. patients
Suboccipital		119
Midline standard	fourth ventricle	54
Midline high	supracerebellar infratentorial	16
Lateral retromastoid standard	cerebellopontine angle	22
Lateral retromastoid high	cerebellomesencephalic fissure	2
Midline low + laminectomy	cerebellomedullary junction	25
Frontotemporal		10
Pterional standard	trans-Sylvian	6
Extended	subtemporal	4
Bifrontal	translamina terminalis	3
Frontal	transventricular transforaminal	3
Occipital	transtentorial	2

If the lesion is dorsal and median in the area of the lamina quadrigemina the best approach – and definitely our favourite – is the *supracerebellar infratentorial route* described first by Krause (1926) and developed in the era of microsurgery by Stein (1971, 1982, 1987), with the patient in a semi-sitting position. The procedure calls for a high bilateral suboccipital craniectomy sparing the foramen magnum but unroofing the transverse sinus and torcular region to give maximum exposure of the superior aspect of the cerebellum by upward retraction of the incised dural flap. Much care must be exercised in placing the patient's head so that the tentorium is aligned as close as possible to the horizontal plane; failing that, it will prove extremely difficult to reach the region in front of the anterior vermis. Division of the bridging veins between the cerebellum and tentorium and of the precentral veins allows the cerebellum to drop under its own weight and relaxes the anterior vermis. A retractor blade is then placed over the cerebellar vermis to keep the distal part of the infratentorial supracerebellar operative corridor widely spread, so that the posterior surface of the tumour can be exposed through the incised arachnoid. Excision of the tumour mass facilitates entry into the third ventricle (Fig. 29) so that CSF flows into the subarachnoid space. This approach can be used successfully also for removing low median lesions in the quadrigeminal region since the anterior vermis can be split and retracted thereby giving adequate access to such lesions as well. For tumours located ventral to the quadrigeminal plate, when the posterior median approach entails the risk of massive damage to the colliculi, a possible alternative could be the *occipital transtentorial approach* originally described by Jamieson

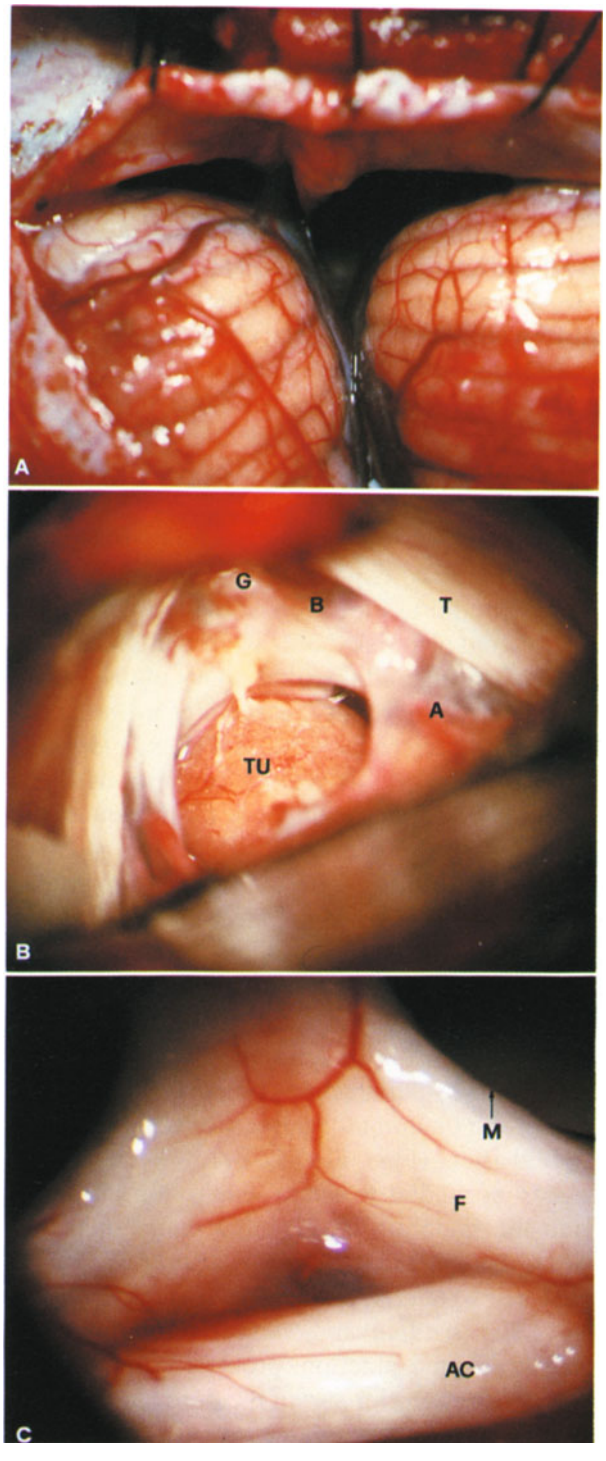


Fig. 29. Intraoperative photographs taken during removal of a quadrigeminal plate astrocytoma via infratentorial supracerebellar approach in sitting slauch position. (A) Initial access between cerebellum and tentorium to the region of the incisura; (B) posterior surface of the tumour; (C) view of the anterior part of the third ventricle chamber after tumour removal. *T* tentorium; *TU* tumour; *A* arachnoid; *G* vein of Galen; *B* basal vein; *M* foramen of Monro; *F* fornix columns; *AC* anterior commissure

(1971) and recommended for the removal of tumours of the posterior part of the third ventricle by Clark (1987), Lapras and Patet (1987), McComb and Apuzzo (1987), Sano (1987), and others. This approach calls for a right occipital craniotomy to expose the transverse sinus, retraction of the occipital lobe, and opening of the tentorium. The main advantage offered by this approach compared to the supracerebellar infratentorial is a reduced risk of injuring the colliculi, since the route affords direct vision into the fissure between the superior vermis, quadrigeminal plate and superior medullary velum. It seems reasonable to believe that the use of this approach in the patient described Figs. 14 and 15 would have spared the corpora quadrigemina and avoided the severe post-operative morbidity that followed.

For the rare dorsal lesions that develop eccentrically on one side towards the surface of the inferior collicular brachium and superior cerebellar peduncle, one may consider both an ipsilateral *subtemporal transtentorial approach* and a high lateral posterior fossa approach utilizing the anatomical pathway of the cerebello-mesencephalic fissure. The former route is accessed through a low mid-temporal craniotomy to expose the incisura and cut the tentorium from medial to lateral; it requires elevation of the temporal lobe. The route is theoretically attractive but also risky, at least in our experience: temporal lobe retraction, however careful, and possible injury to the vein of Labbé with considerable post-operative morbidity, especially in the dominant hemisphere. Thus we prefer a *high lateral suboccipital craniectomy* not requiring temporal lobe retraction, the same as we use for microvascular decompression of the trigeminal nerve in the treatment of tic douloureux.

Lesions of the midbrain located near its ventral surface are accessed surgically through a *pterional trans-Sylvian route* after a frontopterional craniotomy, as developed and extensively applied by Yaşargil *et al.* (1985). Complete opening of the Sylvian fissure allows working in the so-called posterior triangle; with added temporal lobe retraction, one can explore the tentorial edge, third cranial nerve, posterior communicating artery, and interpeduncular cistern. Wider access to the target area can be gained by removing a small portion of the uncus by subarachnoid suction; the anatomical landmark is the emergence of the oculomotor nerve from the midbrain, with above it the posterior cerebral artery (Figs. 11–13). Below the nerve, the superior cerebellar artery runs from medial to lateral encircling the upper brainstem. The entry zone into the midbrain is the small rectangular area outlined medially by the exit of the third cranial nerve, superiorly by the posterior cerebral artery, inferiorly by the superior cerebellar artery, and laterally by the tentorial edge. For median and ventral tumours of the brainstem and (or) mesencephalothalamic junction, protruding into the interpeduncular cistern and bulging in the anterior part of the third ventricle, we advocate a bifrontal craniotomy followed by *subfrontal interhemispheric entry through the lamina terminalis.*

Careful microsurgery enables dissection with preservation of olfactory tract function. Next, the chiasmatic region is widely exposed by interhemispheric dissection (Suzuki *et al.* 1984). Usually the tumour elevates the floor of the third ventricle, so that incision of the lamina terminalis will open both the roof and the floor of the anterior third ventricle to give direct access to the superior and anterior surface of the tumour mass.

For tumours that develop at the mesencephalothalamic level but impinge on the third ventricle from the outside, one may consider an anterior *transcortical or transcallosal transventricular approach.*

(b) Tumours that involve one side of the pons and (or) fungate into the region of the cerebellopontine angle can be reached by a *retrosigmoid route* starting with a retromastoid craniectomy, as used in acoustic neuroma surgery (Figs. 30, 31). A number of intrinsic brainstem gliomas, especially of the diffuse type, seem to originate from the ventral part of the pons and grow more on one side in the direction of the pontocerebellar fibres toward the cerebellar peduncle and cerebellum proper. In such cases, NMR imaging will show the ventral pons deeply grooved by the basilar artery and rotated contralateral to the side of the tumour, the expansion of the involved hemipons, the fourth ventricle reduced and displaced, and the cerebellopontine angle full. With the patient in a semi-sitting position with head rotated toward

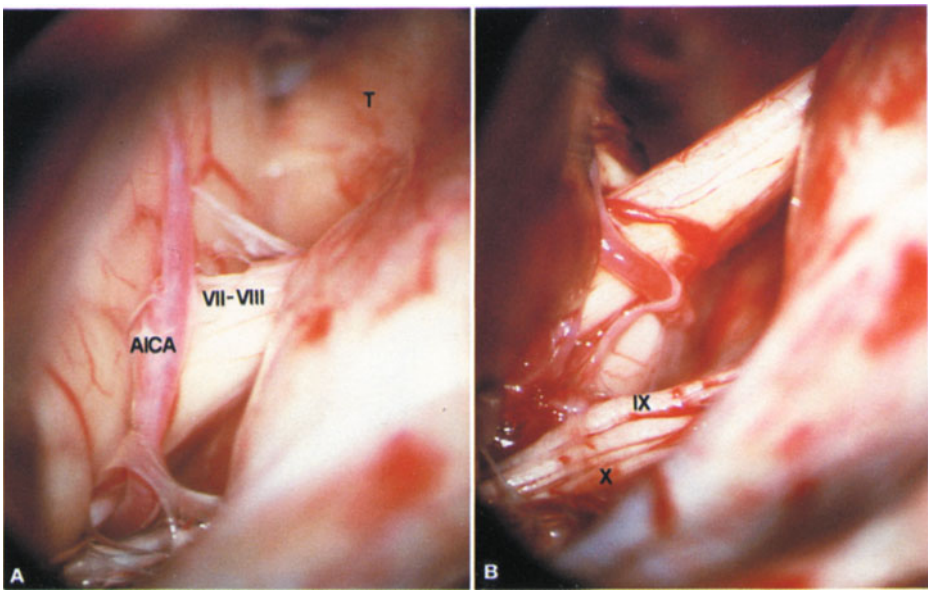


Fig. 30. (A, B) Intraoperative views of a right pontine astrocytoma exophyting into the cerebellopontine angle removed via a standard retromastoid approach in semi-sitting position. *T* tumour; *VII–VIII* facial and vestibulo-cochlear nerves; *AICA* anterior inferior cerebellar artery; *IX* and *X* glossopharyngeal and vagus nerves

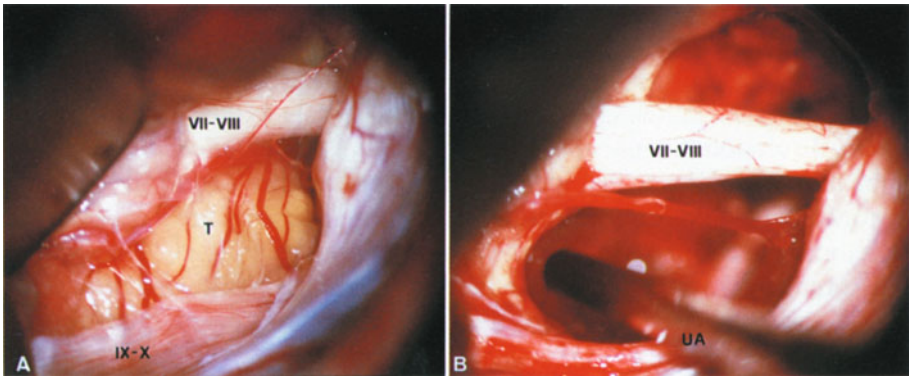


Fig. 31. Intraoperative views of the right cerebellopontine angle during the removal of a huge pontine anaplastic astrocytoma. *T* tumour; *VII–VIII* facial and vestibulocochlear nerves; *IX–X* glossopharyngeal and vagus nerves; *UA* ultrasonic aspirator

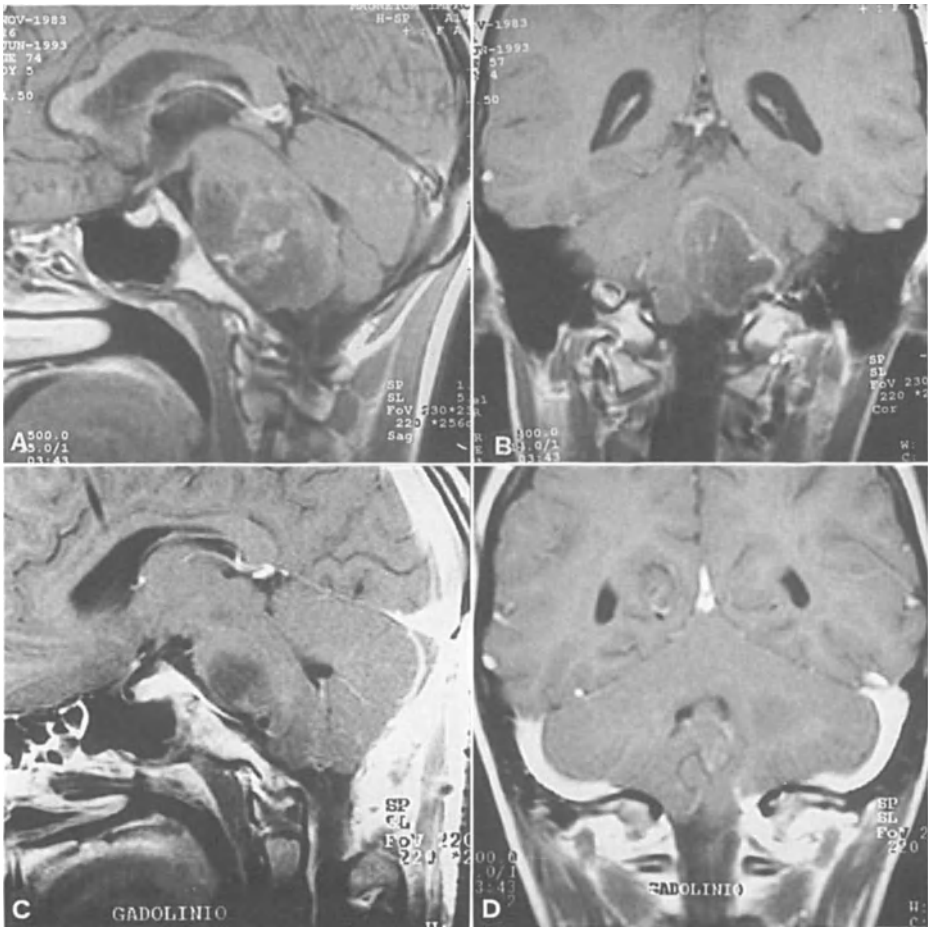


Fig. 32. Pontomedullary malignant astrocytoma. Contrast-enhanced magnetic resonance images before (A and B) and after surgery (C and D)

the side of the lesion, the emergence of the V, and VII–VIII cranial nerves from the brainstem can easily be exposed by opening the cerebellopontine cistern and retracting the cerebellum. Here, as described by Baghai *et al.* (1982) who suggested this approach for brainstem tumour biopsy, the cranial nerves are usually distorted and stretched around the pons.

The standard acoustic approach seems best for removing not only lesions of the lateral pons but also those of the lower lateral midbrain and lateral medulla, and those leaning or protruding into the flocculonodular region (Figs. 32, 33).

(c) For tumours located in the dorsal part of the pons and the open portion of the medulla and protruding into or coming close to the rhomboid fossa, access is by the *trans-fourth-ventricle route* (Figs. 34–38). This classical if not commonplace approach starts with a midline suboccipital craniectomy that includes the foramen magnum and posterior arch of the atlas, followed by splitting of the vermis as recommended by Dandy (1966) and Kempe (1970). This destructive procedure, considered a mandatory step to provide broad access to the fourth ventricle, can be avoided by some technical contrivance to greatly advantage the patient, who will not have to pay the price of new or more severe body truncal ataxia merely for a good approach

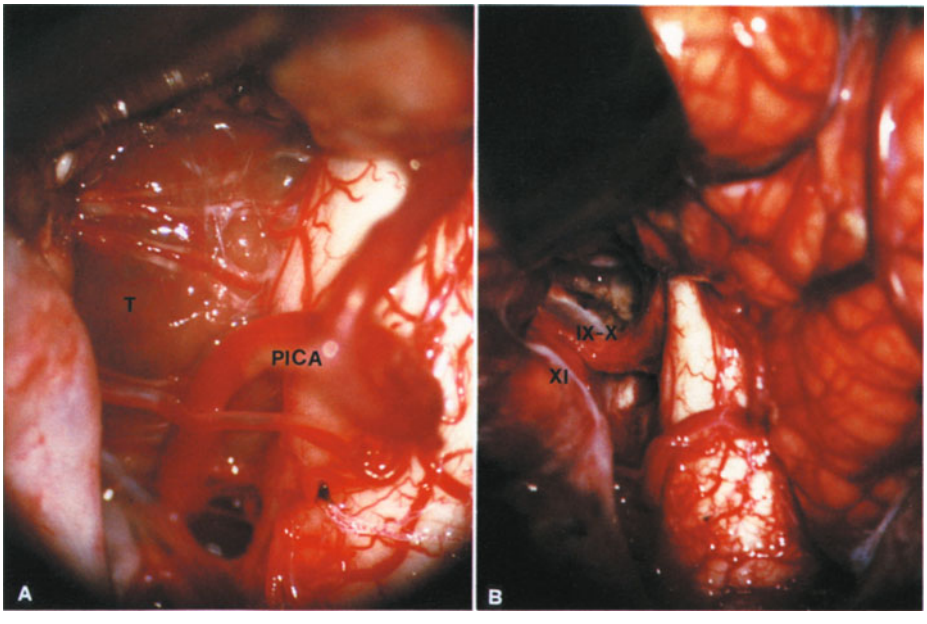


Fig. 33. Intraoperative views of the same patient as shown in Fig. 32. The tumour, almost completely exophyting into the low cerebellopontine angle (A), was removed preserving lower cranial nerves (B). *T* tumour; *PICA* posterior inferior cerebellar artery; *IX-X-XI* glosso-pharyngeal, vagus and accessory nerves

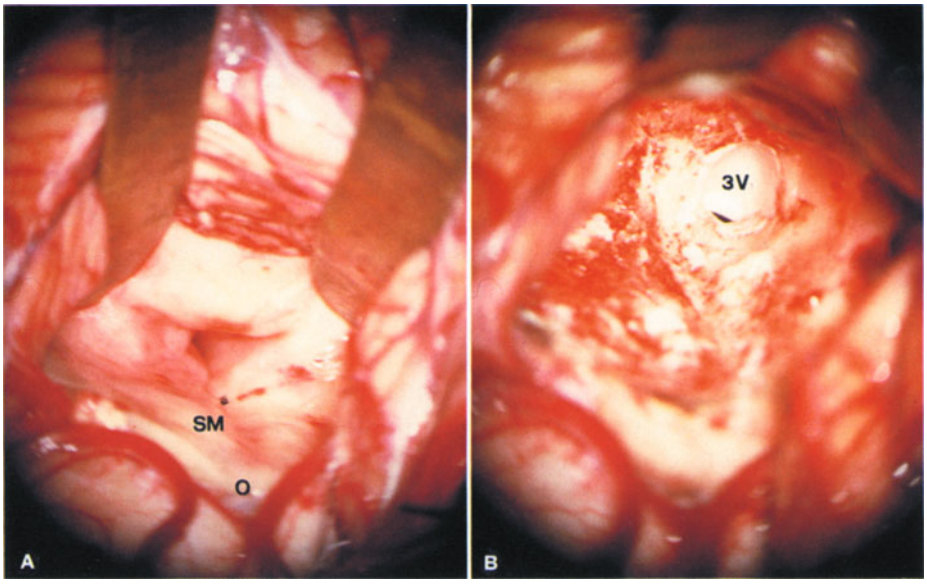


Fig. 34. Pontine diffuse glioma protruding into the fourth ventricle approached (A) and subtotally removed (B) via midline suboccipital craniotomy in semi-sitting position. *O* obex; *SM* striae medullares; *3V* third ventricle

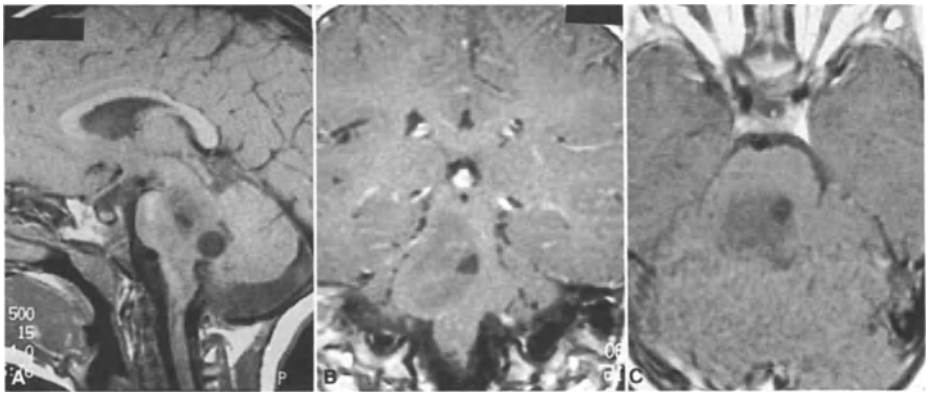


Fig. 35. Large left pontine anaplastic astrocytoma protruding into the fourth ventricle. MR sagittal (A), coronal (B) and axial (C) preoperative images

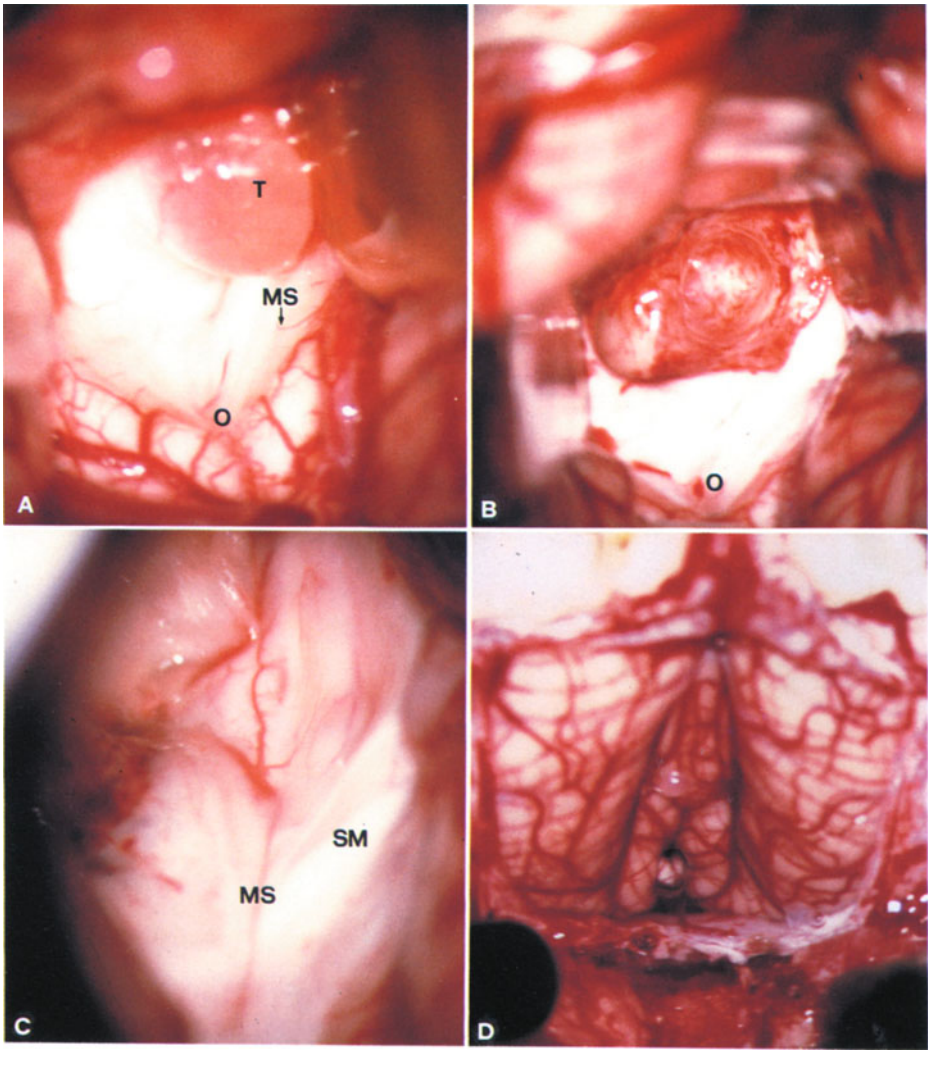


Fig. 36. Intraoperative views of the same patient as shown in Fig. 35. The tumour was approached and subtotally removed via the fourth ventricle by suboccipital craniotomy in semisitting position without splitting the vermis. (A) After opening the dura and cisterna magna, the distorted floor of the fourth ventricle is exposed by distracting the cerebral tonsils and opening the tela choroidea: the tumour is protruding into the rhomboid fossa, occluding the chamber. (B) Tumour removed. (C) Fourth ventricle restored. (D) Cerebellum before the closure. *T* tumour; *MS* median sulcus; *O* obex; *SM* striae medullares

in surgery (Figs. 34, 36, 38). Although Dandy (1966) claimed that opening of the vermis at its center would not cause any functional disturbance, later experience has shown that such lesions as interrupt the cerebellar fibres related to the vestibular system will indeed cause truncal ataxia, a wobbling gait, and head shaking. With the patient in semi-sitting position and the head fairly flexed, wide exposure of the rhomboid fossa can be obtained without sacrificing the vermis through the cerebellomedullary fissure, whose micro-

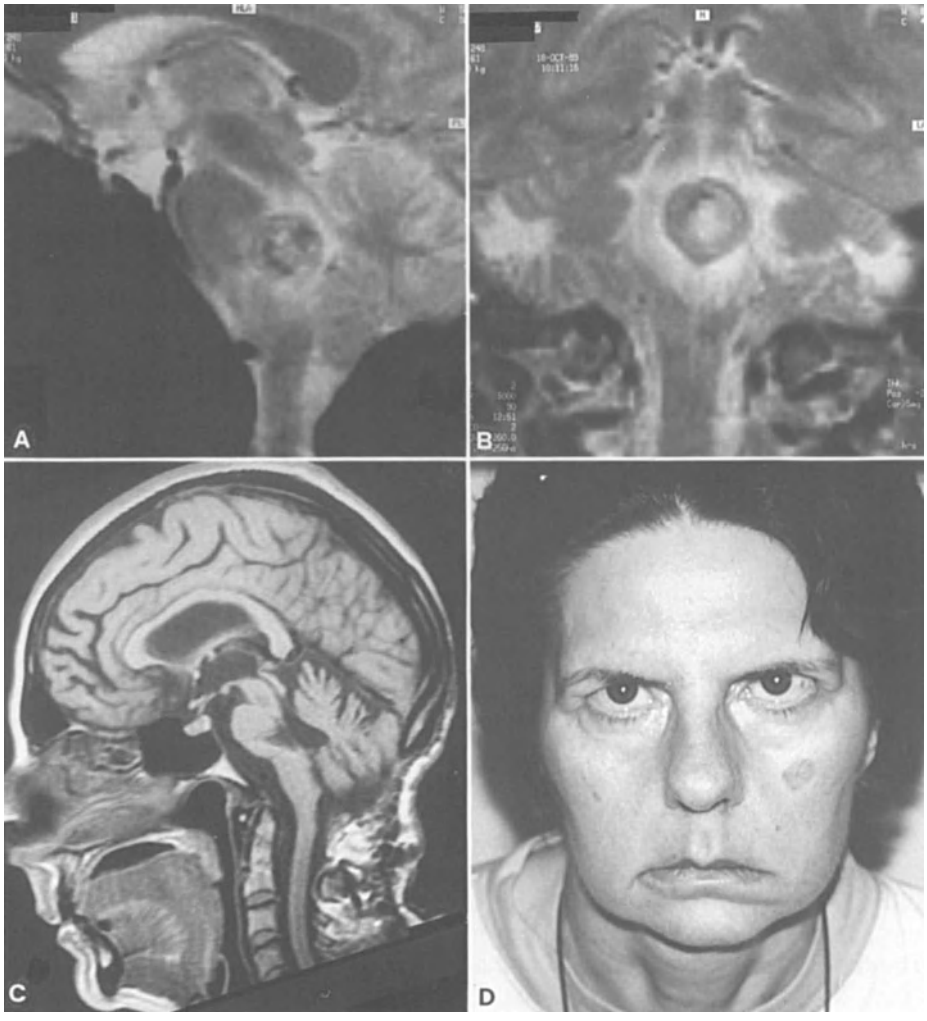


Fig. 37. Sagittal and coronal magnetic resonance images of a patient with pontine focal anaplastic astrocytoma before surgery (A and B) and 4 months later (C). The tumour was completely removed and the patient maintained her preoperative clinical status characterized by bilateral facial palsy and immobile eyes (D)

surgical and NMR anatomy was effectively described by Matsushima *et al.* in a recent paper (1992). By means of elevating and spreading the cerebellar tonsils and displacing the PICAs that run in the fissure itself, one can generously expose the tela choroidea of the roof of the fourth ventricle, cut it at the teniae on both sides, and than fold it back upwardly to expose both lateral recesses if necessary (Fig. 18). The tela choroidea can be incised longitudinally all the way to the anterior medullary velum, to which it is attached along with the choroid plexus. At that point, two strategically positioned self retraining retractors will keep the access open, and suitable angulation of the surgical microscope will yield a complete view of the rhomboid fossa from the obex to the cerebral aqueduct (Fig. 18). This route can be used (or recommended) as well for the removal of tumours of the dorsal midbrain roof that dip into the fourth ventricle, thereby avoiding possible injury to the colliculi.

For tumours farther away from the midline (eg those located in the vestibular area, those exiting from the pontocerebellar angle through the recess, and those growing in the middle cerebellar peduncle), access can be obtained only through the ipsilateral cerebellar fissure (Fig. 39). This creates a posterolateral paratruncal route which affords at once control of the region of the lateral recess and that of the perimedullary area on the same side. Because the anterior wall of the lateral recess is formed by the middle cerebellar peduncle, this route may be proposed for pontine tumours that penetrate the same peduncle.

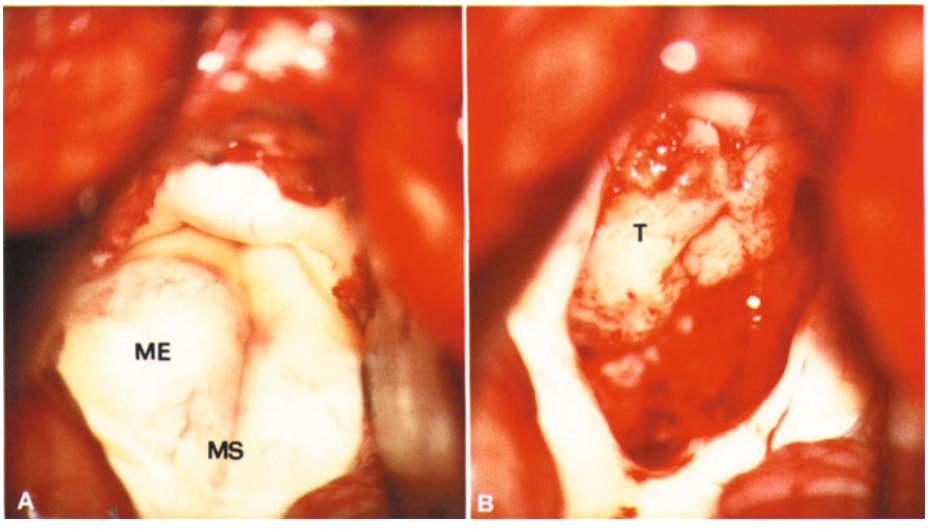


Fig. 38. (A, B) Intraoperative views of the same patient as shown in Fig. 37. *MS* median sulcus; *ME* median eminence and facial colliculus; *T* tumour

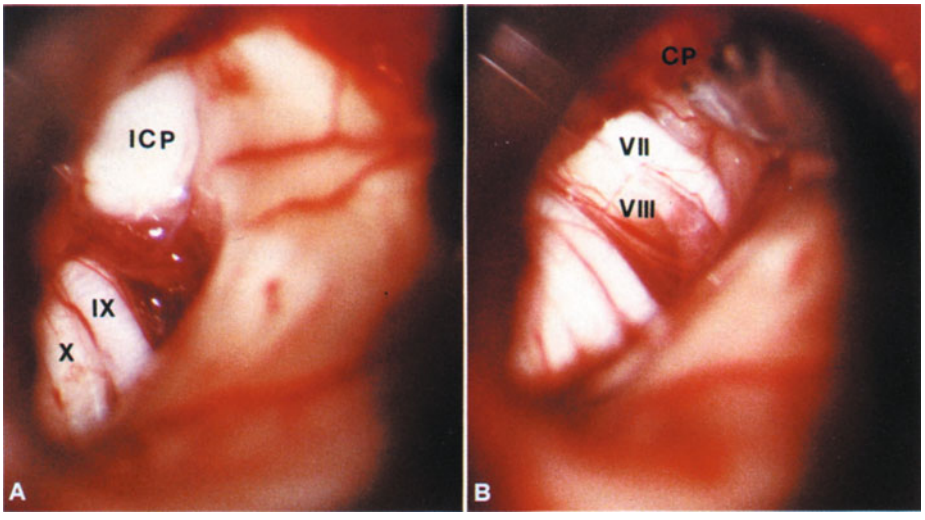


Fig. 39. (A, B) Left lateral recess and foramen of Luschka seen from the fourth ventricle. *ICP* Inferior cerebellar peduncle; *CP* choroid plexus; *IX–X* glossopharyngeal and vagus nerves; *VII–VIII* facial and vestibulo-cochlear nerves

(d) Tumours that develop in the closed part of the medulla and in the cervico-medullary junction are approached through a low midline suboccipital craniectomy, or craniotomy extended to the foramen magnum and posterior arch of the atlas, plus the necessary cervical laminotomy if the lesion grows farther caudad. The laminae are removed en bloc and replaced at the end of the procedure (Fig. 40). The surgical technique of removal is similar to that normally used for removing intrinsic tumours of the spinal cord, the tumour being accessed through a midline myelotomy (Figs. 16 and 17).

General Principles for Tumour Excision

The surgical resection of brainstem tumours calls for the use of meticulous microsurgical techniques, this being necessitated by the delicate nature of the affected structures and by the narrow routes that lead up to the lesions, in turn surrounded by vascular and nervous structures fully as important and delicate (Fig. 41). Whenever a tumour is exophytic or fungating somewhere outside the brainstem (say in the fourth ventricle or the cisterns), its removal begins at such outgrowth; in other words, the tumour itself creates its own entry into the brainstem, where it can be penetrated and removed without any risk to surrounding healthy tissues. Other tumours only bulge from the brainstem surface where they can be faintly seen under the pia or ependyma; here, also, the access route for removal is provided by the tumour itself. Much care,

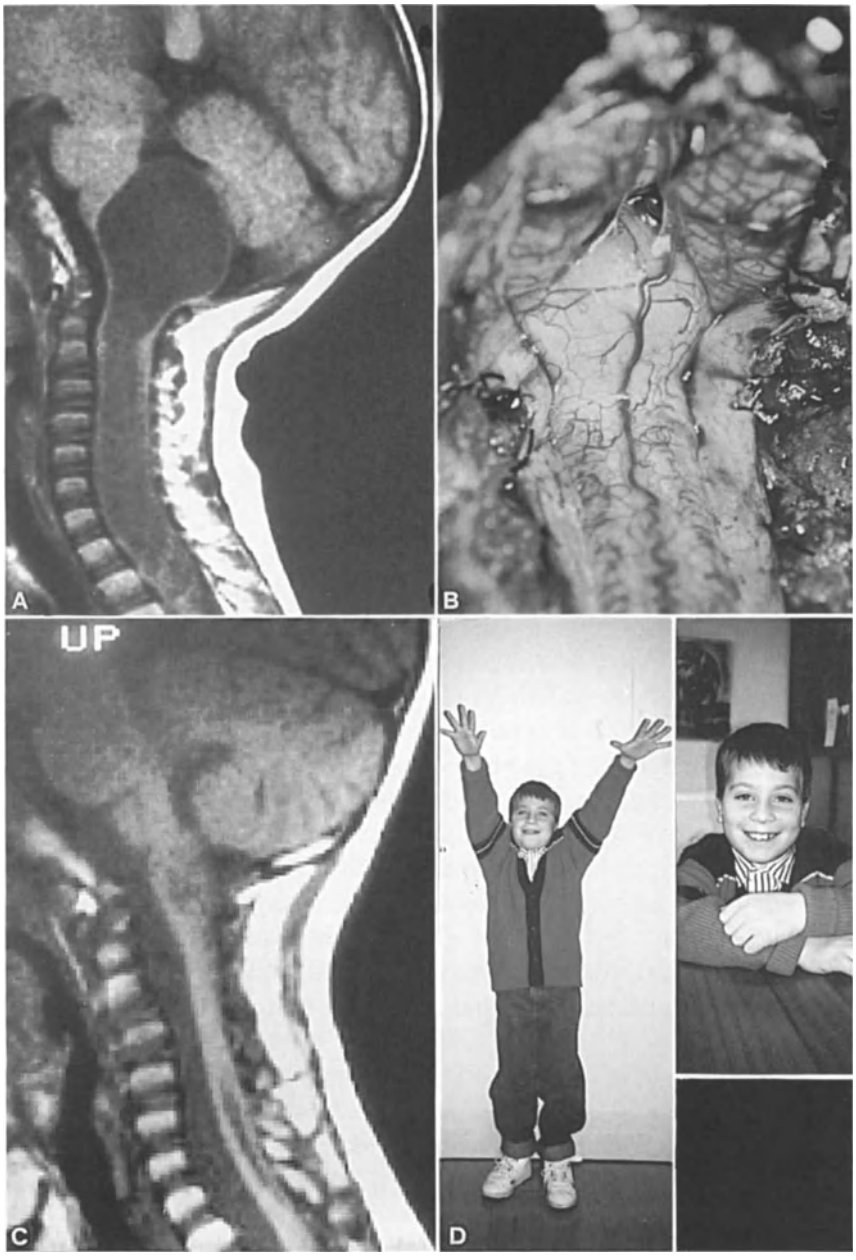


Fig. 40. Sagittal magnetic resonance image (A) in a 18-month child with a cervicomedullary junction astrocytoma admitted to our department in 1986 with severe tetraparesis, torticollis and dysphagia. Operative photograph at opening of the dura after midline low suboccipital craniectomy and cervical laminotomy (B). Three years postoperatively (C) there is a morphological rearrangement with no signs of tumour. The child 7 years after surgery (D) is neurologically intact

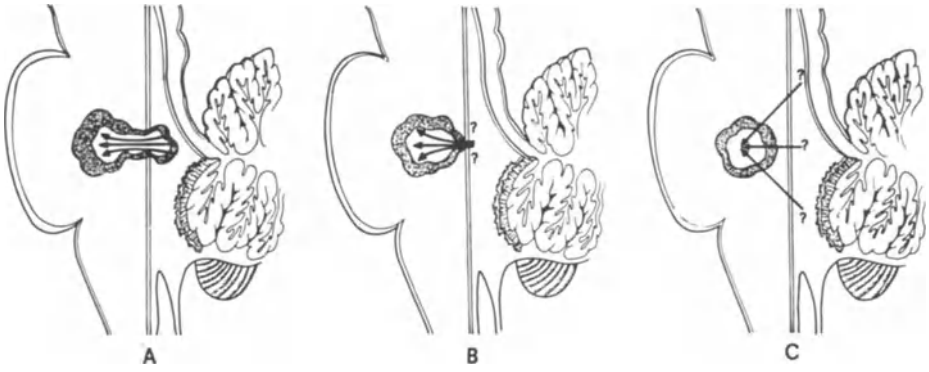


Fig. 41. Schematic drawing shows exophying (A), presenting (B) and pure intrinsic (C) tumour. In removing effaced lesions the choice of the entry route must take into account the functional rank of the structures along the way

however, must be exercised in widening entry points, with all due consideration for the functional ranking of structures around the area where the tumour surfaces, this being vital to the application and direction of retractors. Tumours that have no surface components – the pure intrinsic tumours – require even greater care and thorough understanding of the involved regional anatomy and functions of exposed structures. With a clear mental image of the internal architecture of the brainstem and of the deficits that are likely to be produced by injury to a particular component, the surgeon chooses the entry route most convenient to the patient – not always, alas, the easiest to himself. Delimitation of the entry zone requires accurate orientation based on recognition of the anatomical landmarks described in the preceding section; failing that, or should the anatomy of the rhomboid fossa be gravely distorted by tumour, electrical stimulation may be helpful, and in many centers is now mandatory. Once reached, the glial tumour is removed in small pieces cut with microscissors, by blunt dissection, or by mechanical or ultrasonic aspiration, always remaining inside the tumour and never yielding to the temptation of removing the tumour en bloc. Looking for cleavage from the beginning implies retraction of healthy tissues, which may seem or feel light but is really quite traumatic to the small, richly microvascular structures involved, hence conducive to "unexpected" postoperative deficits.

Ultrasonic aspiration must be used with utmost care at the lowest effective intensity and suction rate – so far, we have been unable to find a sufficiently small and finely balanced handpiece such as this type of surgery would require. The instrument must be angled so that its destructive action is constantly aimed at the inside of the tumour mass, if injury to surrounding healthy structures is to be avoided. At any rate, we keep debulking rigorously confined to the inside of the tumour and stop whenever boundaries with

normal tissues become poorly defined. This rule is followed all the more strictly when debulking goes close to highly critical structures. All through the debulking stage we collect enough specimens of tumour material to afford immediate and definitive histological examination. Immediate information about the type and degree of malignancy is of value in suggesting a greater or lesser need to strive for radical excision.

Surgical strategy is somewhat different for cavernomas. In the brainstem as elsewhere, these vascular tumours are sharply delineated masses, dark blue with small ochre spots being the evidence of past hemorrhages (Zimmermann *et al.* 1991, Anson and Spetzler 1993). In most cases, limiting scar tissue is found to surround the tumour mass (Yoshimoto and Suzuki 1986), so that the lesion can be removed en bloc without undue injury to neighbouring brainstem structures. Cavernous malformations are gently squeezed and shrunk by bipolar coagulation, their surface being delicately dissected from the surrounding gliotic tissue.

Radical surgical excision is the aim, since any remnants of cavernoma tissue would inevitably grow back and bleed again. Obviously, extreme care must be devoted to perfect hemostasis of the residual cavity.

Hemangioblastomas of the brainstem, unlike those located elsewhere, are almost never associated with cyst formation that would greatly facilitate their excision. As a rule, these are solid tumours firmly wedged in nervous structures and of course richly vascular (Resche *et al.* 1993). Here the target, unfortunately, is en-bloc removal as a single piece, since its vasculature is totally devoid of contractile elements and any attempt at piecemeal removal would invite inordinate, sometimes disastrous bleeding; in fact, bipolar coagulation would open up new blood vessels instead of closing old ones. The squeezing procedure, so serviceable for reducing the size of cavernomas, will usually start a hemorrhage instead. Thus we must very delicately dissect the outer surface of the tumour from the surrounding nervous tissue and coagulate afferent blood vessels as we go. This requires a certain amount of brainstem retraction, which must obviously be kept down to an absolute minimum.*

Results

Extent of Tumour Removal

As we said before, the goal of operation is to remove as much tumour as possible while trying not to add new neurological deficits to the existing picture. Table 7 displays the degrees of tumour removal achieved in the various types of neoplastic disease included in our series.

---

* A useful point to remember is that the haemangioblastoma is a sponge, and retraction of the tumour itself is not only haemostatic, but less traumatic to the surrounding brainstem. – Editor

Table 7. *Extent of Surgical Removal Related to Tumour Subgroups and Histology*

Tumour type	No.	Total	%	Subtotal	%	Partial	%
Total series	137	92	67	33	24	12	9
Focal	82	72	88	10	12	–	–
Diffuse	34	2	6	22	65	10	29
Cervicomedullary	21	18	86	1	5	2	9
All gliomas	105	62	59	31	30	12	11
Low-grade	66	54	82	10	15	2	3
High-grade	39	8	21	21	54	10	26
All vascular	32	30	94	2	6	–	–
Cavernoma	18	17	94	1	6	–	–
Hemangioblastoma	14	13	93	1	6	–	–

"Complete" tumour excision, so adjudged at operation by the surgeon and expressing his conviction to have reached healthy tissue all around the tumour mass, was achieved in 92 of 137 patients, or 67% of our cases. Tumour removal was adjudged subtotal, ie. accounting for not less than 80% of the original mass, in 33 patients (24% of the series). In the other 12 patients (9% of cases), removal was rated only "partial", with the greater part of the tumour remaining where it was. In nearly all cases, the surgeon's immediate judgment on the extent of removal was confirmed by repeat neuroimaging over the first few months after surgery.

The observed degrees of tumour removal were in some ways related to the tumour's neuroradiological presentation and histological nature. The highest percentages of total gross removal were elicited in the focal (88%) and cervico-medullary (86%) subgroups; in contrast, the same degree of removal was achieved in only 2 of 34 patients (6%) with neuroradiological pictures of the diffuse type. Thus the preoperative NMR appearance of a brainstem tumour is a very important factor in determining the extent of removal to be achieved at least in the majority of our cases. What makes total removal difficult and in fact not recommended, is mainly the lack of tumour demarcation from healthy neighboring tissues; indeed, when such feature is compounded by tight wedging of the tumour between critical structures, no further excision should be attempted. We must recognize that in our own experience, occasional disregard of this principle may have contributed to an avoidable increase of operative morbidity.

Other complicating factors are the anatomical narrowness and unfavourable angling of the access route, and also the onset of cardiovascular disorders during the dissection of brainstem tumours. Sometimes, such un-

favourable factors are variously associated together, obviously creating the conditions for partial removal at best.

Because of their parenchymal nature, glial tumours are those which make it most difficult to achieve complete removal, obtained in only 59% of our cases, much less than the 94% rate (all patients but two) afforded by the so-called vascular tumours, namely cavernomas and hemangioblastomas. Even among gliomas, however, low grade tumours were completely removed in 54 of 66 patients, or 82% of our cases, bringing the result in terms of surgical removability close to that of non-parenchymal brainstem tumours. Conversely, subtotal and partial removals (80%) were in the same order of frequency for malignant gliomas.

On the whole we can say that a focal low-grade glioma of the brainstem presents itself to the surgeon as a lesion inherently amenable to radical or seemingly total removal.

Postoperative Course and Complications

We must first acknowledge that it would be unrealistic to expect a patient emerging from the operating theatre after surgery for a brainstem tumour to be in better shape than at entry – the opposite is indeed the rule, as illustrated in Table 8.

In this present series we had no intraoperative mortality, and two deaths occurred in the early postoperative period as follows: one patient with a huge

Table 8. *Early and 1-Month Postoperative Clinical Status*

Complications	First week		1 Month	
	No. patients	%	No. patients	%
Death	2	1	5	4
Stupor	6	4	3	2
Coma	10	7	–	–
New CN deficit	32	23	14	10
New sensorymotor deficit	29	21	8	6
Ataxia	?			
Mechanical ventilation	31	23	–	–
Tracheostomy	7	5	2	1
Severe dysphagia	16	12	4	3
Repeat surgery	3	2	6	4
CSF shunt	17	12	7	5

medullary hemangioblastoma, removed subtotally because of intraoperative cardiac disorders and other technical difficulties, died three days postoperatively from brainstem failure after repeat surgery done to remove a blood clot from the original tumour site; and another died five days after surgery from cardiopulmonary complications after partial removal of a diffuse malignant glioma of the cervico-medullary junction.

In nearly all cases, the patient is clinically and neurologically worse off after surgery than before, and therefore needs constant, meticulous assistance. Immediately after surgery, all patients were nursed in our neurosurgical intensive care unit, where they remained for periods ranging from one day to four weeks: 16 patients failed to regain consciousness after surgery; 6 remained stuporous; and 10 in a comatose state for various lengths of time. In addition to the two patients who died shortly after surgery (see above), two others died two to three weeks after surgery from cardiopulmonary complications without ever regaining consciousness, and still another patient died after return to the ward and regaining both consciousness and independence. The cause was a sudden major respiratory failure followed by irreversible cardiocirculatory collapse. The patient was harbouring a huge medullopontine cavernoma that was removed radically. Of the other 12 patients that failed to waken after surgery, 9 regained full consciousness gradually and 3 remained in stupor for more than one month. All three had been operated on for lesions in the tectal part of the midbrain; and in all three, impaired consciousness was associated with ocular movement disorders.

Aside from impaired consciousness, what contributes most to postoperative neurological deterioration is the onset of new cranial nerve deficits or the aggravation of pre-existing ones (not shown in the table). Thus important oculomotor disorders, facial palsy, impaired mastication and deglutition, and somatic motor and sensory deficits combine to make the early postoperative course fairly unrewarding. From the point of view of intensive care the most dangerous disorders are palsies of the lower cranial nerves causing severe dysphagia, in turn calling for careful attention to prevent aspiration pneumonia. Fortunately, many of our patients initially showing this kind of deterioration improved somewhat within the first month after surgery, with materially reduced morbidity of this type at four weeks.

Outcome

Most of our patients remained in close contact with our Department, and were monitored without undue difficulty, both from the clinical point of view and in terms of repeat neuroimaging from time to time. In December 1993 (mean follow-up time 3.5 years postoperative, we completed our review of the whole series. By that time another 18 patients were reported dead in addition to the five succumbing in the first month, bringing the overall

mortality up to 18%. All new deaths, occurring between 4 and 28 months after surgery, were the direct or indirect consequence of tumour regrowth and progression. Three of these patients underwent repeat surgery; the others were rated unable to withstand further operation; 7 had received radiotherapy. The cumulative survival rate for the 105 patients treated surgically for brainstem gliomas was 68% at two years and 65% at three years, both rates being very significantly higher ($p < 0.0001$) for patients with low-grade glioma (95% at three years) than for those with malignant glioma (22% at three years), the latter showing a mean survival of 9.5 months (Fig. 42).

Surviving patients usually showed progressive neurological improvement after the first month; also as a result of physical rehabilitation therapy, with restoration of transiently lost cranial nerve functions. Many cranial nerve deficits and oculomotor disorders resolved characteristically within 8 months of surgery. Ataxia and long tract dysfunction also improved substantially in time, so that most patients were able to resume practically normal activities.

In order to better assess our results, we regrouped our patients into three outcome categories: the results were rated good if patient was improved relative to preoperative conditions, or if patient continued self-sufficient and able to cope with his or her previous occupations; fair if patient was unchanged and self-sufficient but not able to resume previous activities; and poor if patient was still disabled and needing assistance. Table 9 displays these data arranged by type of pathology. Overall, outcome was much better in the subgroups of patients harbouring low-grade gliomas and cavernomas.

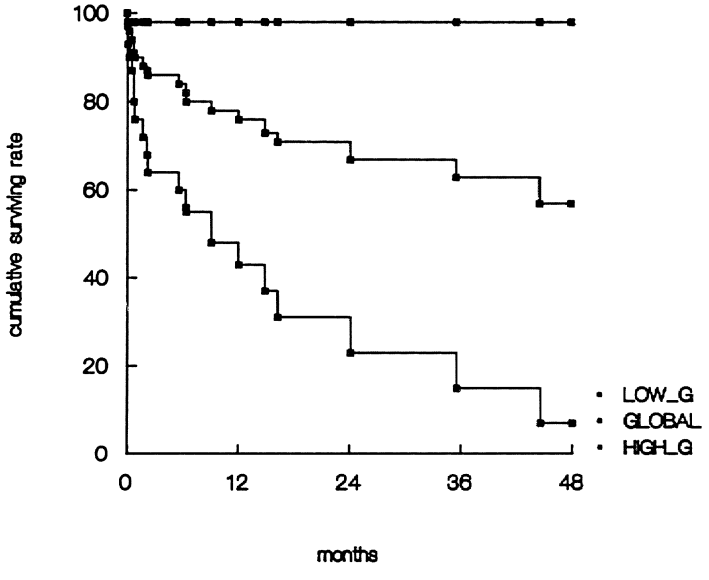


Fig. 42. Cumulative survival rate for the 105 brainstem gliomas of the present series

Table 9. *Outcome Related to Histopathology in the Present Series (As of December 1993 – Mean Follow-up: 3.5 years)*

Tumour	No.	Good	%	Fair	%	Poor	%	Death	%
Gliomas	105	63	60	15	14	7	7	20	19
Low-grade	66	54	82	9	14	3	5	–	–
High-grade	39	9	23	6	15	4	10	20	51
Vascular	32	24	75	4	12	1	3	3	9
Cavernoma	18	16	89	2	11	–	–	–	–
Hemangio-blastoma	14	8	57	2	14	1	7	3	21
Total	137	87	63	19	14	8	6	23	18

Table 10. *Magnetic Resonance Imaging in Surviving Patients (As of October 1993 – Mean Follow-up: 3.4 years)*

Tumour type	No.	No tumour	Residual	Regrowth
Low-grade glioma	58	50	6	2
High-grade glioma	14	5	3	6
Cavernoma	14	13	1	–
Hemangioblastoma	8	6	1	1
Total	94[a]	74 (78%)	11 (12%)	9 (10%)

[a] 20 patients lost to MRI recheck.

For 94 of 114 surviving patients in the whole series, we obtained recheck NMR imaging documents, as listed and graded in Table 10. In 78% of these cases, NMR scans revealed no evidence of tumour; indeed, it was rewarding to see how in the majority of cases the brainstem had resumed an entirely normal morphology.

Discussion

The management of brainstem tumours, especially gliomas, remains controversial. These tumours, long considered beyond the reach of direct ablative surgery, are still looked upon with a good deal of perplexity by neurosurgeons, who find themselves hesitating between the classical conservative therapeutic attitude and the new possibilities offered by today's diagnostic tools and surgical equipment.

Earlier on, intrinsic tumours of the brainstem were thought to constitute a homogeneous nosologic category not amenable to direct surgical manipulation and therefore treated empirically and blind by radiation therapy. The results being on the whole disappointing. More recently, the direct surgical attack on these lesions has been branded by some as a useless endeavour, plainly "looking for trouble". At best, surgical methods are credited with some marginal value in terms of emptying cyst formations, removal of exophytic components or collecting enough tissue to make a firm histologic diagnosis. In point of fact, several voices have been heard to challenge the real value of histological diagnosis obtained stereotaxically, now that new and non-invasive diagnostic methods have been made generally available and prove more richly contributory as time goes by: CT scanning, NMR imaging, and digital subtraction angiography. Even the real effectiveness of irradiation and chemotherapy in modifying the behaviour of these lesions is challenged from some quarters.

The main reason offered to justify operative nihilism in brainstem tumours was the high mortality and morbidity traditionally associated with direct surgical attack on this delicate part of the central nervous system. Yet if we take a closer look at the problem we discover that there is little evidence to show that direct brainstem surgery invites disaster, and one begins to suspect that a taboo-like fear was what really kept the surgeon away from this area. The literature of the last two decades has contributed increasingly numerous reports of patients with intrinsic lesions of the brainstem treated successfully by surgery: thus, in particular, the by now rich series of hematomas alone or associated with vascular malformations and tumours treated directly, show not only the feasibility but indeed the advantages of such treatment (Kempe 1964, Pouyanne *et al.* 1967, Koos *et al.* 1969, Obrador *et al.* 1970, Murphy 1972, Martini 1971, Arseni and Stanciu 1973, Scott *et al.* 1973, Chou *et al.* 1975, Becker and Silverberg 1978, Humphreys 1978, Doczi and Thomas 1979, Pau *et al.* 1979, Sano and Ochiai 1980, Vaquero *et al.* 1980, Pak *et al.* 1981, O'Laoire *et al.* 1982, Sano 1983, Umansky *et al.* 1983, Nakamura *et al.* 1985, Russell *et al.* 1986, Sanford and Smith 1986, Kashiwagi *et al.* 1990, Konovalov *et al.* 1990, Weil and Tew, 1990, Fahlbusch *et al.* 1990, Fahlbusch and Strauss 1991, Symon *et al.* 1991). In addition, a number of isolated patient reports and small series of intrinsic brainstem pathology cases afford further proof of the feasibility of this type of surgery (Myers *et al.* 1961, Ishii and Rapin 1971, Archer *et al.* 1972, Weaver and Coulon 1979, Hacker and Fox 1980, Entzian 1983, Jooma *et al.* 1985, Tomita 1986, Pendl and Vorkapic 1988, Hefez *et al.* 1990, Obana and Wilson 1991, Jelsma *et al.* 1993). For our part, we do not accept the premise that brainstem gliomas are by their own nature and location "untouchable" tumours to be treated only conservatively. Partly in the light of our own growing experience and partly encouraged by reports from other quarters

(Hoffmann *et al.* 1980, Epstein and McCleary 1986, Stroink *et al.* 1986, 1987, Epstein and Wisoff 1987, Konovalov and Atieh 1988, Guy *et al.* 1989, Epstein and Farmer 1993, Pollack 1993), we have approached the problem with a more aggressive attitude based on accurate preoperative definition of the tumour.

A number of peculiarities must be considered in assessing a brainstem tumour, the first being its location, since this is what makes resection difficult in many cases. Compared to gliomas of the cerebral hemispheres, those located in the brainstem can be accessed and exposed only through very narrow approaches, so that even a lesion of not more than 1 cm in so small a structure may confront the surgeon with insuperable technical obstacles to resection. Surgery performed so close to highly critical structures with apparently minimal tissue damage may invite major postoperative complications. NMR imaging has greatly increased our ability to identify and describe a brainstem glioma. NMR findings are highly diagnostic and most valuable since they will not only tell a glial lesion from anything else but also, in the majority of cases, a focal from a diffuse glioma. Thus it has become increasingly evident that brainstem tumours, formerly thrown in the same basket merely because they affect vital and highly functional areas, actually differ in terms of their imaging presentation, this being related to different histopathologic and clinical characteristics; and this, in turn, makes it possible to choose the therapeutic strategy most likely to help in the individual case.

With precise imaging on hand, plus the availability of advanced microsurgical techniques, and the support of adequate postoperative intensive care to cope with transitory failures of vital functions, one may nowadays feel confident and justified in scheduling for surgery such patients as appear amenable to and likely to benefit from it.

In our case-load, the results of surgery may be considered satisfactory in terms of the extent of removal and clinical outcome in focal tumours and those of the cervico-medullary junction; not so in those appearing diffuse by NMR imaging. Glial tumours of the focal persuasion are for the most part low-grade and amenable to total or subtotal removal, followed by an essentially benign biological behaviour. Most patients of this description survived with a degree of neurological disability compatible with a normal style of life; in such cases, as noted before, recheck NMR scans usually revealed complete freedom from tumour tissue. Thus ablative surgery seems to be of definite value when neuroimaging suggests a focal, noninvasive tumour formation. Such tumours can indeed be removed completely or nearly so with acceptably low mortality and morbidity – our own experience confirms that these tumours usually displace normal brainstem structures without invading them, so that once penetrated and debulked, the reduced tumour mass can be excised without undue destruction or damage to neighbouring nerve pathways.

One problem still open to discussion and definitely demanding added experience is that of glial tumours of the so-called diffuse type, which seem to enlarge rather than distort brainstem structures. Most of our cases of this type were anaplastic tumours not amenable to generous removal; the overall outcome was not gratifying when measured against the magnitude of surgical endeavour. Yet in a minority of cases the treatment was fairly rewarding – to the point where we begin to suspect that an unfavourable preoperative NMR scan may not be so trustworthy after all. While one could hardly recommend direct surgery for regular diffuse gliomas that enlarge the whole brainstem (once labelled brainstem hypertrophy), the same surgery affords the only opportunity to assess the chances of identifying and removing tumour tissue without damaging neural structures. The idea that accurate selection of patients for surgery is the crucial aspect in the case of diffuse glioma may lose some of its cogency if the intended surgery is associated with a relatively low risk; be that as it may, experience in this area stands in need of enrichment.

The important message that seems to emerge from our own work and that of other groups that have tackled the problem of treating brainstem tumours more or less by the same philosophy is that a distinct if not yet clearly defined group of brainstem gliomas can be treated surgically just like gliomas elsewhere in the central nervous system. This consideration justifies continuing efforts over the coming years toward the amplification of our knowledge in this field, such as can only stem from the intense study of patients presenting with a brainstem tumour designed to augment our understanding of how the tumour grows and what other factors may influence its prognosis. To that end, it is clearly necessary for many surgeons to renounce their nihilist attitude and enter this field, at least as a first step, with extended therapeutic trials.

Concluding Remarks

In the general atmosphere of impotence that surrounds brainstem tumours, some innovations have emerged that may soon promote a more rational and constructive approach to the management of these lesions. To begin with, it is by now a recognized fact that brainstem tumours no longer represent a homogeneous nosologic group amenable only to nonspecific treatment; instead, these tumours differ in their clinical, histopathological and MRI patterns and it is essential that they be regarded as distinct entities. By now, we know for sure that the growth of brainstem gliomas is infiltrative and proliferative only in a minority of cases. In brainstem glioma the expanding mass usually dislocates neighbouring nervous structures without invading them; also, the tumour itself tends to move as it grows toward the surface of the brainstem, thus facilitating its surgical approach and removal (Figs. 43, 44). Modern neuroimaging techniques afford the clear-cut discrimination of

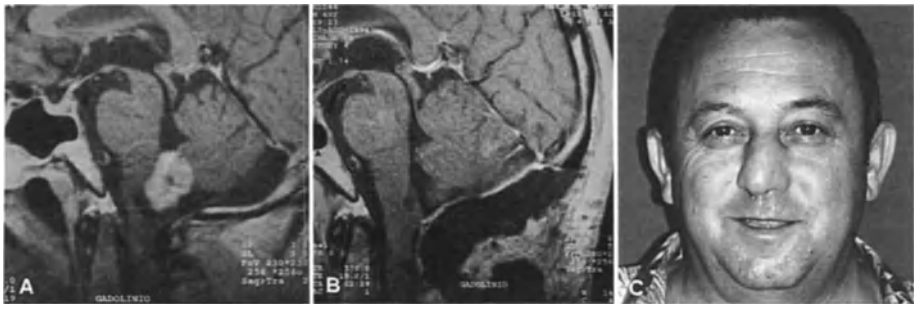


Fig. 43. (A) Preoperative magnetic resonance image of a medullary astrocytoma exophiting into the IV ventricle. (B) Postoperative image demonstrating the total removal. (C) The patient one week after surgery at discharge

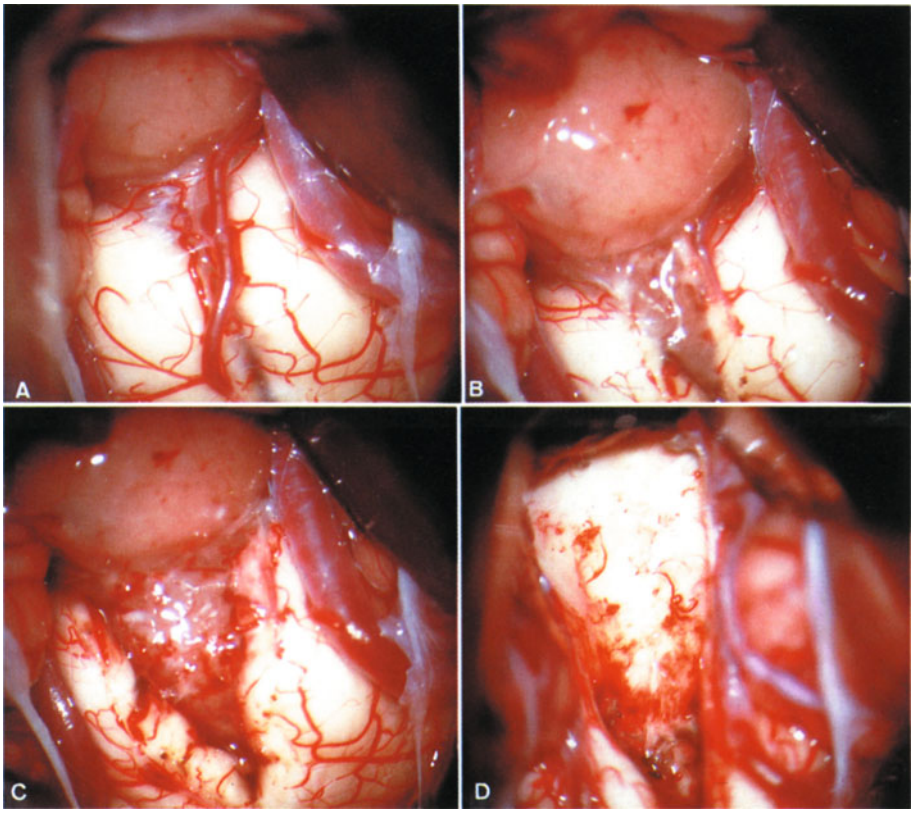


Fig. 44. Intraoperative photographs of the same patient as shown in Fig. 43. (A) The hood of the tumour protruding at the obex; (B) and (C) the exposure of the tumour by opening the posterior median fissure; (D) the lower rhomboid fossa after total removal

different tumour types and hence the choice of best surgical strategy in the individual case. The experience accrued over recent years shows that the brainstem can be violated with acceptably low risk by careful microsurgery. Within such a picture, a more aggressive direct surgical policy proves effective in securing the complete removal of many brainstem tumours with major clinical improvement, prolonged survival, and even permanent cures. So, while there may be some way to go before we can claim that the overall prognosis of brainstem tumours should no longer be viewed with pessimism, we do conclude that direct surgery gives every evidence of constituting a valid, worthwhile form of treatment for many such tumours.

Acknowledgements

We wish to thank the nursing and rehabilitation staff of our Neurosurgical Intensive Care Unit for their contribution to patient management. We are grateful to Mrs Francesca Zambonini for her precision in typing the manuscript and references, and to Mrs Cristina Bertolin for her expertise in assembling clinical records and other documents.

This work was supported in part by the N. H. Marastoni Foundation for Neurosurgery in Verona (Italy).

References

1. Abramson N, Raben M, Cavanaugh PJ (1974) Brain tumours in children: analysis of 136 cases. Radiology 112: 669–672
2. Aitken L (1979) The auditory midbrain. Trends Neurosci 2: 308–310
3. Albright AL, Price RA, Guthkelch AN (1983) Brain stem gliomas of children. A clinicopathological study. Cancer 52: 2313–2319
4. Albright AL, Schlabassi RJ (1985) Use of the cavitron ultrasonic aspirator and evoked potentials for treatment of thalamic and brainstem tumours in children. Neurosurgery 17: 564–568
5. Albright AL, Guthkelch AN, Packer RJ, *et al* (1986) Prognostic factors in pediatric brain-stem gliomas. J Neurosurg 65: 751–755
6. Alemà G, Perria L, Rosadini G, Rossi GF, Zattoni J (1966) Functional inactivation of human brain stem related to the level of consciousness. J Neurosurg 24: 629–639
7. Alpers BJ (1942) Partial paralysis of upward gaze. Confin Neurol (Basel) 5: 1–12
8. Alpers BJ, Yaskin GC (1939) Gliomas of the pons. Arch Neurol Psychiat 41: 435–459
9. Alphin TH, William TB (1944) The course of the striae medullares in the human brain. J Comp Neurol 80: 65–68
10. Alvisi C (1962) Considerazioni sul trattamento chirurgico dei gliomi bulbopontini. Min Neurochir 6: 5–7
11. Alvisi C, Cerisoli M, Maccheroni ME (1985) Long-term results of surgically treated brainstem gliomas. Acta Neurochir (Wien) 76: 12–17

12. Anson JA, Spetzler RF (1993) Surgical resection of intramedullary spinal cord cavernous malformations. J Neurosurg 78: 446–451
13. Archer CR, Roberson GH, Taveras JN (1972) Posterior medullary hemangioblastoma. Radiology 103: 323–328
14. Arseni C, Goldberg M (1959) Psychic disturbances in infiltrative gliomata of the brain stem. Acta Neurochir (Wien) 7: 292–300
15. Arseni C, Stanciu M (1973) Primary haematomas of the brain stem. Acta Neurochir (Wien) 28: 323–330
16. Atkinson WJ (1949) The anterior inferior cerebellar artery. J Neurol Neurosurg Psychiatry 12: 137–151
17. Atlas SW, Grossman RI, Savino PJ, *et al* (1987) Internuclear ophthalmoplegia: MR-anatomic correlation. AJNR 8: 243–247
18. Baghai P, Vries JK, Bechtel PC (1982) Retromastoid approach for biopsy of brain stem tumours. Neurosurgery 10: 574–579
19. Bailey P, Buchanan DN, Bucy PC (1939) Intracranial tumours of infancy and versity childhood. University Press, Chicago, pp 188–241
20. Baker GS (1965) Physiologic abnormalities encountered after removal of brain tumours from the floor of the fourth ventricle. J Neurosurg 23: 338–343
21. Baker R, Berthoz A (1975) Is the prepositus hypoglossi nucleus the source of another vestibulocular pathway? Brain Res 86: 121–127
22. Barnett HJ, Hyland HH (1952) Tumours involving the brainstem. Quart J Med 21: 265–284
23. Becker DH, Silverberg GD (1978) Successful evacuation of an acute pontine hematoma. Surg Neurol 10: 263–265
24. Berger MS, Edwards MSB, La Masters D, *et al* (1983) Pediatric brain stem tumours: radiographic, pathological and clinical correlations. J Neurosurg 12: 298–302
25. Bilaniuk LT, Zimmerman RA, Littman P, Gallo E, Rorke LB, Bruce DA, Schut L (1980) Computed tomography of brain stem gliomas in children. Radiology 134: 89–95
26. Bodensteiner J, Bell WE, Hart MN (1977) 13-year survival of a child with an untreated brainstem glioma. Letter. J Pediatr 90: 842–843
27. Bodian M, Lawson D (1953) The intracranial neoplastic diseases of childhood. Br J Surg 40: 368–392
28. Bouchard J (1966) Radiation therapy of tumours and disease of the nervous system. Lea and Febiger, Philadelphia, pp 119–135
29. Bray PF, Carter S, Taveras JM (1958) Brainstem tumours in children. Neurology 8: 17
30. Bricolo A (1975) Neurosurgical exploration and neurological pathology as a means for investigating human sleep semiology and mechanisms. In: Lairy GC, Salzarulo P (eds) Experimental study of human sleep: methodological problems. Elsevier, Amsterdam, pp 51–82
31. Bricolo A (1976) Prolonged post-traumatic coma. In: Vinken PJ, Bruyn GW (eds) Handbook of clinical neurology. Injuries of the brain and skull, part II. North-Holland, Amsterdam, pp 699–755
32. Bricolo A, Turazzi S (1987) Esperienza nella chirurgia dei gliomi del tronco cerebrale. In: Attualità in neurochirurgia. Monduzzi, Bologna, pp 45–50

33. Bricolo A, Turazzi S, Cristofori L, *et al* (1991) Direct surgery for brainstem tumours. Acta Neurochir (Wien) [Suppl] 53: 148–158
34. Bricolo A, Turazzi S, Christofori L, Talacchi A, Berlucchi S (1993) Surgical treatment of brainstem tumours: experience in 75 patients. Abstract, AANS 61st Annual Meeting, Boston, April 24–29
35. Brodal A (1969) Neurological anatomy in relation to clinical medicine, 2nd Ed. Oxford University Press, New York, p 807
36. Buckley RC (1930) Pontine gliomas: a pathologic study and classification of twenty-five cases. Arch Pathol Lab Med 9: 779–819
37. Bucy PC (1957) Is there a pyramidal tract? Brain 80: 376–392
38. Bucy PC, Keplinger JE (1961) Section of the cerebral peduncles. Arch Neurol 5: 132–139
39. Bucy PC, Ladpli R, Ehrlich A (1966) Destruction of the pyramidal tract in the monkey. The effects of bilateral section of the cerebral peduncles. J Neurosurg 25: 1–20
40. Burns J, Lisak R, Schut L, *et al* (1980) Recovery following brainstem hemorrhage. Ann Neurol 7: 183–184
41. Chou SN, Erickson DL, Ortiz-Suarez HJ (1975) Surgical treatment of vascular lesions in the brain stem. J Neurosurg 42: 23–31
42. Clark WK (1987) Occipital transtentorial approach. In: Apuzzo MLJ (ed) Surgery of the third ventricle. Williams and Wilkins, Los Angeles, pp 591–610
43. Dandy WE (1966) The brain. Prior, Hagerstown, pp 452–458
44. Doczi T, Thomas DGT (1979) Successful removal of an intrapontine haematoma. J Neurol Neurosurgy Psychiatry 42: 1058–1061
45. Dogliotti M (1938) First surgical section in man of lemniscus lateralis. Curr Res Anesth Analg 17: 143
46. Durwood QJ, Barnett HJM, Barr HWK (1982) Presentation and management of mesencephalic hematoma. Report of two cases. J Neurosurg 56: 123–127
47. Duvernoy HM (1978) Human brainstem vessels. Springer, Berlin Heidelberg New York
48. Edwards MSB, Prados M (1987) Current management of brainstem gliomas. Pediatr Neurosci 13: 309–315
49. Edwards MSB, Wara WM, Urtasun RC, Prados M, Levin Va, Funton D, Wilson CB, Hannigan J, Silver P (1989) Hyperfractionated radiation therapy for brainstem glioma: a phase I–II trial. J Neurosurg 70: 691–700
50. Eifel PJ, Cassady JR, Belli JA (1987) Radiation therapy of tumours of the brainstem and midbrain in children: experience of the joint center for radiation therapy and childrens's hospital medical center (1971–1981). Int J Radiat Oncol Biol Phys 13: 847–852
51. Entzian W (1983) Removal of intraponto-mesencephalic spongioblastoma. Neurosurg Rev 6: 67–70
52. Epstein F, McCleary EL (1986) Intrinsic brain-stem tumours of childhood: surgical indications. J Neurosurg 64: 11–15
53. Epstein F, Wisoff J (1987) Intra-axial tumours of the cervicomedullary junction. J Neurosurg 67: 483–487
54. Epstein FJ, Wisoff JH (1989) Brainstem tumours in childhood: surgical indications. In: McLaurin RL, Schut L, Venes JL, *et al* (eds) Pediatric neurosurgery.

Surgery of the developing nervous system, 2nd Ed. Saunders, Philadelphia, pp 357–365
55. Epstein F, Farmer JP (1993) Brain-stem glioma growth patterns. J Neurosurg 78: 408–412
56. Fahlbusch SC, Strauss C, Huk W, Rockelein G, Kompf D, Ruprecht RW (1990) Surgical removal of pontomesencephalic cavernous hemangiomas. Neurosurger 26: 449–457
57. Fahlbusch R, Strauss C (1991) Zur chirurgischen Bedeutung von cavernösen Hämangiomen des Hirnstammes. Zentralbl Neurochir 52: 25–32
58. Falconer MA (1949) Intramedullary trigeminal tractotomy and its place in the treatment of facial pain. J Neurol Neurosurg Psychiatry 12: 297–311
59. Fisher CM (1967) Some neuro-ophthalmological observations. J Neurol Neurosurg Psychiatry 30: 383–392
60. Foerster O, Gagel O (1940) Die encephalen Tumoren der Oblongata, Pons und des Mesencephalons. Ztschr Ges Neurol Psychiat 168: 295–331
61. Fulton DS, Levin VA, Wara WM (1981) Chemotherapy of pediatric brainstem tumour. J Neurosurg 54: 721–725
62. Gaskell WH (1889) On the relation between the structure, function, distribution and origin of the cranial nerves; together with a theory of the origin of the nervous system of vertebrata. J Physiol 10: 153–211
63. Gibbs FA (1932) Frequency with which tumours in various parts of the brain produce certain symptoms. Arch Neurol Psychiat 28: 969–989
64. Golden GS, Ghatak NR, Hirano A, French JH (1972) Malignant glioma of the brain stem: a clinicopathological analysis of 13 cases. J Neurol Neurosurg Psychiatry 35: 732–738
65. Greenberger JS, Cassady JR, Levene MB (1977) Radiation therapy of thalamic, midbrain and brain stem gliomas. Radiology 1222: 463–468
66. Guy G, Jan M, Guegan Y (1989) Les lésions chirurgicales du tronc cérébral. Neurochirurgie 35 [Suppl 1]: 1–33
67. Hacker RJ, Fox JI (1980) Surgical treatment of brain stem carcinoma: case report. Neurosurgery 6: 430–432
68. Halperin EC (1985) Pediatric brain stem tumours: patterns of treatment failure and their implications for radiotherapy. Int Radiat Oncol Biol Phys 11: 1293–1298
69. Hara M, Takeuchi K (1977) A temporal study of survival of patients with pontine gliomas. J Neurol 216: 189–196
70. Hare CC, Wolf A (1934) Intramedullary tumours of the brain stem. Arch Neurol Psychiat 32: 1230–1252
71. Hefez DS, Zinreich SH, Long DM (1990) Surgical resection of intrinsic brainstem lesions: an overview. Neurosurgery 27: 789–799
72. Henschen F (1955) Tomoren des Zentalnervensystems und seiner Hüllen, III G, Tumoren der Brücke. In: Lubarsch O, Henke F, Rossle R (eds) Handbuch der speziellen pathologischen Anatomie und Histologie. Springer, Berlin Göttingen Heidelberg, pp 743–749
73. Herrick CJ (1899) The cranial and first spinal nerves of menidia. J Comp Neurol ix: 153–455
74. Herrick CJ (1913) Anatomy of the brain. In: The reference handbook of the medical sciences, Vol 2. Wood, New York, pp 274–342

75. Hitchcock ER (1970) Stereotactic trigeminal tractotomy. Ann Clin Res 2: 131–135
76. Hodge CJ, Primrose D (1993) Infratentorial procedures: physiological considerations: In: Apuzzo MLJ (ed) Brain Surgery. Churchill, Livingstone New York, pp 1569–1590
77. Hoffmann HJ, Becker L, Craven MA (1980) A clinically and pathologically distinct group of benign brain stem gliomas. Neurosurgery 7: 243–248
78. Horrax G (1927) Differential diagnosis of tumours primarily pineal and primarily pontine. Arch Neurol Psychiat 17: 179–192
79. Humphreys RP (1978) Computerized tomographic definition of mesencephalic hematoma with evacuation through peduncolotomy. Case report. J Neurosurg 49: 749–772
80. Hutchins B, Weber JT (1985) The pretectal complex of the monkey: a reinvestigation of the morphology and retinal terminations. J Comp Neurol 232: 425–442
81. Ingraham FD, Matson DD (1954) Neurosurgery of infancy and childhood. Thomas, Springfield, p 259
82. Ishii N, Rapin I (1971) Cystic astrocytoma of the brain stem. Neuropaediatrie 3: 217–229
83. Jackson IJ, Thomson RK (1959) Pediatric neurosurgery. Thomas, Springfield
84. Jamieson KG (1971) Excision of pineal tumours. J Neurosurg 35: 50–553
85. Jefferson G (1938) Tentorial pressure cone. Arch Neurol Psychiat 40: 857–876
86. Jefferson G, Johnson RT (1950) The cause of loss of consciousness in posterior fossa compressions. Folia Psychiat Neurol Neurochir Neerlandica 53: 306–319
87. Jelsma RK, Jelsma LF, Johnson GS (1993) Surgical removal of brainstem astrocytomas and hemangioblastomas: report of three cases and review. Surg Neurol 39: 494–510
88. Jenkin RDT, Boesel C, Ertel I, Evans A, Hittle R, Ortega J, Sposto R, Wara W, Wilson CB, Anderson J, Leikin S, Hammond D (1987) Brain tumours in childhood: a prospective randomized trial of irradiation with and without ajuvant CCNU, VCR, and prednisone. A report of the children's cancer study group. J Neurosurg 66: 227–233
89. Jooma R, Torrens MJ, Bradshow J, Brownell B (1985) Subependymomas of the fourth ventricle. Surgical treatment in 12 cases. J Neurosurg 62: 508–512
90. Kashiwagi S, Van Loveren HA, Tew JM Jr, Wiot JG, Weil SM, Lukin RA (1990) Diagnosis and treatment of vascular brainstem malformations. J Neurosurg 72: 27–34
91. Keim H, Potthof PC, Schmidt K, Schiebusch M, Neiss A, Trott KR (1987) Survival and quality of life after continuous accelerated radiotherapy of glioblastomas. Radiother Oncol 9: 21–26
92. Kempe LG (1964) Surgical removal of an intramedullary haematoma simulating Wallenberg's syndrome. J Neurol Neurosurg Psychiatry 27: 78–80
93. Kempe LG (1970) Operative neurosurgery, Vol 2. Springer, Berlin Heidelberg New York, pp 14–17
94. Kim TH, Chi HW, Pollan S, Hazel JH, Webster JH (1980) Radiotherapy of primary brain stem tumours. Int J Radiat Oncol Biol Phys 6: 51–57

95. Konovalov A, Atieh J (1988) The surgical treatment of primary brain stem tumours. In: Schmideck HH, Sweet WH (eds) Operative neurosurgical techniques, 2nd Ed. Grune and Stratton, New York, pp 709–737
96. Konovalov A, Spallone A, Makhmudov UB, Kukhlajeva JA, Orezova VI (1990) Surgical management of hematomas of the brain stem. J Neurosurg 73: 181–186
97. Koos WT, Sunder-Plassmann M, Salah S (1969) Successful removal of a large intrapontine hematoma. Case report. J Neurosurg 31: 690–694
98. Koos WT, Miller MH (1971) Intracranial tumours of infants and children. Thieme, Stuttgart, pp 346–350
99. Krause F (1926) Operative Freilegung der Vierhugen, nebst Beobachtungen über Hirndruck und Dekompression. Zentralbl Chir 53: 2812–2819
100. Kucharczyk W, Brandt-Zawadzki M, Sobel D, Edwards MSB, Kelly W, Norman D, Newton TH (1985) Central nervous system tumours in children: detection by magnetic resonance imaging. Radiology 155: 131–136
101. Kudo M (1981) Projections o the nuclei of the lateral lemniscus in the cat: an autoradiographic study. Brain Res 221: 57–69
102. Kunc Z (1965) Treatment of essential neuralgia of the 9th nerve by selective tractotomy. J Neurosurg 23: 494–500
103. Kunc Z (1966) Significance of fresh anatomic data on spinal trigeminal tract for possibility of selective tractotomies. In: Knighton RS, Dumke PR (eds) Little Brown, Boston, pp 351–363
104. Kunc Z, Marsala J (1962) La localisation et la terminaison des voies afférentes des nerfs IX et X dans le bulbe. Acta Neurochir (Wien) 19: 512–522
105. Kyoshima K, Kobayashi S, Gibo H, Kuroyanagi T (1993) A study of safe entry zones via the floor of the fourth ventricle for brain-stem lesions. J Neurosurg 78: 987–993
106. Lang J (1991) Clinical anatomy of the posterior cranial fossa and its foramina. Thieme, Stuttgart
107. Lang J Jr, Ohmachi N, Lang J Sr (1991) Anatomical landmarks of the rhomboid fossa (floor of the 4th ventricle), its length and its width. Acta Neurochir (Wien) 113: 84–90
108. Langmoen IA, Lundar T, Storm-Mathisen I, *et al* (1991) Management of pediatric pontine gliomas. Childs Nerv Syst 7: 13–15
109. Lapras C, Patet JD (1987) Controversies, techniques and strategies for pineal tumour surgery. In: Apuzzo MLJ (ed) Surgery of the third ventricle. Williams and Wilkins, Los Angeles, pp 649–662
110. Lassiter KRL, Alexander E Jr, Davis CH Jr, Kelly DL Jr (1971) Surgical treatment of brain stem gliomas. J Neurosurg 34: 719–725
111. Lassman LP (1974) Tumours of the pons and medulla oblongata. In: Vinken PJ, Bruyn GW (eds) Handbook of clinical neurology, vol 17. North Holland, Amsterdam, pp 693–706
112. Lassman LP, Arjona VE (1967) Pontine gliomas of childhood. Lancet I: 913–915
113. Le Beau J (1938) L'oedème du cerveau. Son rôle dans l'evolution des tumeurs et des abcés intra-craniens. Thèse de Paris, 233 pp
114. Levin VA, Edwards MSB, Wara WM, *et al* (1984) 5-Flurouracil and 1 (2-chloroethil)3cyclohexyllnitrosourea (CCNU) followed by hydroxyurea, miso-

nidazole, and irradiation for brain stem gliomas: a pilot study of the Brain Tumour Research Center and the Children's Cancer Group. Neurosurgery 14: 679–681
115. Lindheimer JH, Barrows HS (1962) Recurrent pontine hemorrhage incident to venous angioma of the pons: report of a case. Bull LA Neurol Soc 27: 128–133
116. Lister JR, Rhoton AL Jr, Matsushima T, Peace D (1982) Microsurgical anatomy of the posterior inferior cerebellar artery. Neurosurgery 10: 179–199
117. Littman P, Jarret P, Bilaniuk L, *et al* (1980) Pediatric brain stem gliomas. Cancer 45: 2787–2792
118. Luse SA, Teitelbaum S (1968) Congenital glioma of brain stem. Arch Neurol (Chic) 18: 196–201
119. Mantravadi RV, Phatak R, Bellur S, Liebner EJ, Haas R (1982) Brain stem gliomas: an autopsy study of 25 cases. Cancer 49: 1294–1296
120. Marsa GW, Probert JC, Rubinstein LC, Bagshaw MA (1973) Radiation therapy in the treatment of childhood astrocytic gliomas. Cancer 32: 646–654
121. Martin JH (1989) Neuroanatomy, text and atlas. Elsevier, New York
122. Martini PM (1971) L'hématome bulbotubérantiel opérable. Acta Neurol Belg 71: 261–268
123. Matson DD (1969) Neurosurgery of infancy and childhood, 2nd Ed. Thomas, Springfield, pp 469–477
124. Matsushima T, Rhoton AL Jr, Lenkey C (1982) Microsurgery of the fourth ventricle. Part I: Microsurgical anatomy. Neurosurgery 11: 631–667
125. Matsushima T, Fukui M, Inoue T, Natori Y, Baba T, Fujii K (1992) Microsurgical and magnetic resonance imaging anatomy of the cerebellomedullary fissure and its application during fourth ventricle surgery. Neurosurgery 30: 325
126. Mazars G, Pansini A, Chiarelli J (1959) Coagulation du faisceau spinothalamique et du faisceau quintothalamique par stereotaxie. Rev Neurol (Paris) 100: 516
127. McComb JG, Apuzzo MLJ (1987) Posterior intrahemispheric retrocallosal and transcallosal approaches. In: Apuzzo MLJ (ed) Surgery of the third ventricle. Williams and Wilkins, Los Angeles, pp 611–641
128. Milhorat TH (1975) Pontine glioma (letter to editor). JAMA 32: 595–596
129. Moruzzi G, Magoun HW (1949) Brain stem reticular formation and activation of the EEG. Electroenceph Clin Neurophysiol 1: 455–473
130. Mundinger F, Kraus DF, Krauss JK, Birg W (1991) Long-term outcome of 89 low-grade brainstem gliomas after interstitial radiation therapy. J Neurosurg 75: 740–746
131. Murphy MG(1972) Successful evacuation of acute pontine hematoma. Case report. J Neurosurg 37: 224–225
132. Myers J, Scott M, Silverstein A (1961) A cystic hemangioblastoma of pons. J Neurosurg 18: 694–697
133. Nakamura N, Sekino H, Yaguchi Y, Fuse T (1985) Successful total extirpation of hemangioblastoma originating in the medulla oblongata. Surg Neurol 24: 87–94
134. Nashold BS Jr (1972) Defects of ocular motility after stereotactic midbrain lesions in man. Arch Ophthal (Chic) 88: 245–256

135. Nieuwenhuys R (1974) Topological analysis of the brain stem: a general introduction. J Comp Neurol 156: 255–276
136. Nieuwenhuys R, Voogd J, Van Huijzen Chr (1988) The human central nervous system. A synopsis and atlas, 3rd Ed. Springer, Berlin Heidelberg New York Tokyo
137. Northield DWC (1973) The surgery of central nervous system. Blackwell, London
138. Obana WG, Wilson CB (1991) Epidermoid cysts of the brainstem. J Neurosurg 74: 123–128
139. Obrador S, Dierssen G, Ordoriz BJ (1970) Surgical evacuation of a pontine-medullary hematoma. Case report. J Neurosurg 33: 82–84
140. O'Laoire SA, Crockard HA, Thomas DGT, *et al* (1982) Brainstem hematoma. A report of six surgically treated cases. J Neurosurg 56: 222–227
141. Olivecrona H (1942) Tractotomy for relief of trigeminal neuralgia. Arch Neurol Psychiat (Chic) 47: 544–564
142. Olivecrona H (1967) Handbuch der Neurochirurgie, Band 4, Teil 4. Springer, Berlin Heidelberg
143. Oswald I (1972) Sleep. In: Critchley M, O'Leary JL, Jennett B (eds) Scientific foundation of neurology. Heinemann, London, pp 190–193
144. Packer RJ, Allen J, Nielsen S, Petito C, Deck M, Jereb B (1983) Pontine glioma: clinical manifestations of meningeal gliomatosis. Ann Neurol 14: 177–182
145. Packer RJ, Zimmermann RA, Leurson T, *et al* (1985) Nuclear magnetic resonance in the evaluation of brain stem gliomas of childhood. Neurology 35: 397–401
146. Pak H, Patel SC, Malik GM, *et al* (1981) Successful evacuation of a pontine hematoma secondary to rupture of a venous angioma. Surg Neurol 15: 164–167
147. Panitch HS, Berg BO (1970) Brain stem tumours of childhood and adolescence. Am J Dis Child 119: 465–472
148. Pau A, Viale ES, Turtas S (1979) Surgical removal of a pontine hematoma associated with a cryptic angioma. Case report. Acta Neurochir (Wien) 50: 299–303
149. Pendl G, Vorkapic P (1988) Microsourgery of midbrain lesions. Acta Neurochir (Wien) [Suppl] 42: 130–136
150. Pilcher C (1934) Spongioblastoma polare of the pons. Arch Neurol Psychiat 32: 1210–1229
151. Plum F (1972) Organic disturbances of consciousness. In: Critchley M, O'Leary JL, Jennett B (eds) Scientific foundation of neurology. Heinemann, London, pp 193–201
152. Plum F, Posner JB (1966) The diagnosis of stupor and coma. Blackwell, Oxford
153. Pollack IF, Hoffmann HJ, Humphreys RP, Becker L (1993) The long-term outcome after surgical treatment of dorsally exophytic brainstem gliomas. J Neurosurg 78: 859–863
154. Pool JL (1968) Gliomas in the region of the brain stem. J Neurosurg 29: 164–167
155. Pouyanne H, Got M, Julien J, *et al* (1967) Deux cases d'hématomes intra-protubérantiels opérés. Etude critique. Neurochirurgie 13: 738–742

156. Quisling RG, Quisling SG, Mickle JP (1993) Obex/nucleus gracilis position: its role as a marker for the cervicomedullary junction. Pediatr Neurosurg 19: 143–150
157. Raimondi AJ (1987) Pediatric neurosurgery. Theoretical principles. Art of surgical techniques. Springer, Berlin Heidelberg New York Tokyo
158. Ranson SW (1935) The anatomy of the nervous system, 5th Ed. Saunders, Philadelphia
159. Ranson SW, Magoun HW (1933) The central path of the pupillo constriction reflex in response to light. Arch Neurol Psychiat (Chic) 30: 1193–1202
160. Redmond JS Jr (1961) The roentgen therapy of pontine gliomas. Am J Roentg 88: 644–648
161. Reigel DH, Scarff TB, Woodford JE (1979) Biopsy of pediatric brain stem tumours. Childs Brain 5: 329–340
162. Resche F, Moisan JP, Mantoura J, *et al* (1993) Haemangioblastoma, haemangioblastomatosis, and von Hippel-Lindau disease. In: Symon L *et al* (eds) Advances and technical standards in neurosurgery, Vol 21. Springer, Wien New York, pp 197–304
163. Rhoton AL Jr (1979) Microsurgical anatomy of the posterior fossa cranial nerves. Clin Neurosurg 26: 398–462
164. Rosen G, Ghavimi F, Vanucci R, Deck M, Tan C, Murphy ML (1974) Pontine glioma: high-dose methotrexate and leucovorin rescue. JAMA 230: 149–1152
165. Rossi GF (1964) A hypothesis on the neural basis of consciousness. Acta Neurochir (Wien) 12: 187–197
166. Rossi GF, Zanchetti A (1957) The brain stem reticular formation. Arch Ital Biol 95: 199–435
167. Roth JC, Edvidge AR (1960) Glioblastoma multiforme: a clinical survey. J Neurosurg 17: 736–750
168. Ruge JA (1993) Mid-brain tumours in children. Crit Rev Neurosurg 3: 66–71
169. Russell B, Rengachary SS, McGregor D (1986) Primary pontine hematoma presenting as a cerebello-pontine angle mass. Neurosurgery 19: 129–133
170. Russell DS, Rubinstein LJ (1959) Pathology of tumours of the nervous system. Edward Arnold, London
171. Russell DS, Rubinstein LJ (1989) Pathology of tumours of the nervous system, 5th Ed. Williams and Wilkins, Baltimore, pp 149–152
172. Sanford RA, Smith RA (1986) Hemangioblastoma of the cervicomedullary junction. J Neurosurg 64: 317–321
173. Sano K (1983) Spontaneous brain stem hematoma. Neurosurg Rev 8: 71–77
174. Sano K (1987) Pineal region and posterior third ventricular tumours: a surgical overview. In: Appuzzo MLJ (ed) Surgery of the third ventricle. William and Wilkins, Los Angeles, pp 663–683
175. Sano K, Ochiai C (1980) Brain stem haematomas. Clinical aspects with reference to indications for treatment. In: Pia HW, Langmaid C, Zierski J (eds) Spontaneous intracerebral haematomas. Advances in diagnosis and therapy. Springer, Berlin Heidelberg New York, pp 366–371
176. Sarkari NBS, Bickerstaff ER (1969) Relapses and remissions in brain stem tumours. BMJ 2: 21–23

177. Schain RJ, Wilson G (1971) Brain-stem encephalitis with radiographic evidence of medullary enlargement. Neurology 21: 537–539
178. Scott BB, Seeger JF, Schneider RC (1973) Successful evacuation of a pontine hematoma secondary to rupture of a pathologically diagnosed "cryptic" vascular malformation. Case report. J Neurosurg 39: 104–108
179. Sheline GE (1975) Radiation therapy of tumours of the central nervous system in childhood. Cancer 35: 957–964
180. Sjöquist O (1938) Studies on the pain conduction in the trigeminal nerve. Acta Psychiat Scand [Suppl] 17: 1–139
181. Soffer D, Sahar A (1982) Cystic glioma of the brain stem with prolonged survival. Neurosurgery 10: 499–502
182. Spague JM, Meickle TH (1965) The role of the superior colliculus in visually guided behavior. Exp Neurol 11: 115–146
183. Spiegel EA (1953) Mesencephalotomy in treatment of intractable facial pain. Arch Neurol Psychiat 69: 1–13
184. Stein BM (1971) The infratentorial supracerebellar approach to pineal lesions. J Neurosurg 35: 197–202
185. Stein BM (1982) Supracerebellar approach for pineal neoplasms. In: Schmidek H, Sweet W (eds) Operative neurosurgical techniques, Vol 1. Grune and Stratton, New York, pp 599–607
186. Stein BM (1987) Infratentorial supracerebellar approach. In: Apuzzo MLJ (ed) Surgery of the third ventricle. Williams and Wilkins, Los Angeles, pp 570–590
187. Strange P, Wohlert L (1982) Primary brain stem tumours. Acta Neurochir (Wien) 62: 219–232
188. Strauss C, Romstöck J, Nimski C, Fahlbusch R (1993) Intraoperative indentification of motor areas of the rhomboid fossa using direct stimulation. J Neurosurg 79: 393–399
189. Stroink AR, Hoffman HJ, Hedrick EB, Humphreys RP (1986) Diagnosis and management of pediatric brain-stem gliomas. J Neurosurg 65: 745–750
190. Stroink AR, Hoffman HJ, Hendrick EB, *et al* (1987) Transependymal benign dorsally exophytic brain stem gliomas of childhood: diagnosis and treatment recommendations. Neurosurgery 20: 439–444
191. Suzuki J, Katakura R, Mori T (1984) Interhemispheric approach through the lamina terminalis to tumours of the anterior part of the third ventricle. Surg Neurol 22: 157–163
192. Symon L, Jackowski A, Bills D (1991) Surgical treatment of pontomedullary cavernomas. Br J Neurosurg 5: 339–347
193. Tomita T (1986) Surgical management of cerebellar peduncle lesions in children. Neurosurgery 18: 568–575
194. Turazzi S, Bricolo A (1977) Acute pontine syndromes following head injury. Lancet 2: 62–64
195. Umansky F, Toledo E, Cohen M, *et al* (1983) Successful removal of an acute brain stem hematoma in a young child. Childs Brain 10: 350–354
196. Vandertop WP, Hoffman HJ, Drake JM, Humphreys RP, Rutka JT, Armstrong DC, Becker LE (1992) Focal midbrain tumours in children. Neurosurgery 31: 186–194

197. VanGehuchten P (1937) Le mécanisme de la mort dans certains cas de tumeurs cérébrales. L'Encéphale 2: 113–127
198. Vaquero J, Areitio E, Leunda G, *et al* (1980) Hematoma of the pons. Surg Neurol 14: 115–118
199. Villani R, Gaini SM, Tomei G (1975) Follow up study of brain stem tumours in children. Childs Brain 1: 126–135
200. Walker AE (1942) Relief of pain by mesencephalic tractotomy. Arch Neurol Psychiat 48: 865–883
201. Weaver EN Jr, Coulon RA Jr (1979) Excision of a brainstem epidermoid cyst: case report. J Neurosurg 51: 254–257
202. Weil SM, Tew JM Jr (1990) Surgical management of brain stem vascular malformations. Acta Neurochir (Wien) 105: 14–23
203. Weisberg LA, Nice C, Katz M (1978) Cerebral computed tomography: A text-atlas. Saunders, Philadelphia, pp 123–127
204. White HH (1963) Brain stem tumours occurring in adults. Neurology (Minn) 13: 292–300
205. White JC, Sweet WH (1969) Pain and the neurosurgeon. A forty-year experience. Thomas, Springfield
206. Williams PL *et al* (1989) Gray's anatomy, 37th Ed. Churchill, Edinburgh Livingstone
207. Yasargil MG, Teddy PJ, Roth P (1985) Selective amygdalo hippocampectomy. Operative anatomy and surgical technique. In: Symon L *et al* (eds) Advances and technical standards in neurosurgery, Vol 12. Springer, Wien New York, pp 93–123
208. Yoshimoto T, Suzuki J (1986) Radical surgery on cavernous angioma of the brainstem. Surg Neurol 26: 72–78
209. Zimmermann RS, Spetzler RF, Lee SK, *et al* (1991) Cavernous malformations of the brain stem. J Neurosurg 75: 32–39

Hearing Preservation in Acoustic Tumour Surgery

M. Samii and C.Matthies

Department of Neurosurgery, Nordstadt Hospital, Hannover
(Federal Republic of Germany)

With 7 Figures

Contents

Summary

900 acoustic neurinomas were removed by the suboccipital approach at Nordstadt Neurosurgical Department from 1978 to 1992 by the same surgeon (M. S.). While 247 patients were deaf on the involved side before surgery, there were 653 patients ears with some preoperative hearing. Preservation of

the cochlear nerve was always attempted, and the overall-rate of hearing preservation was 38% (249 of 653), regardless of pre- and postoperative quality of hearing or of tumour sizes. In small tumour sizes below 3 cm of diameter preservation rate was 51%, in large tumours above 3 cm of diameter it was 22%. A classification system of hearing quality was made up considering pure tone audiometric hearing losses (PTA HL) at 1 to 3 kHz, and individual maximum speech discrimination scores. The usefulness of the preserved hearing is further evaluated considering the quality of hearing in the contralateral ear, and by application of other classification schemes. Presentation of the surgical strategies and their refinements by personal experience provide the base for discussion questioning whether and how further progress may still be anticipated.

Keywords: Acoustic neuroma; audiometry; brainstem evoked response audiometry; BERA monitoring; (speech) discrimination score; hearing preservation; suboccipital approach.

Introduction

Acoustic neurinomas have remained a challenge to neurosurgeons throughout all decades of this century; and though they are more and more reliably handled with regard to diagnosis as well as to treatment, they are still not mastered.

The least understood phenomenon is the lack of correlation of tumour characteristics and hearing quality, i.e. the presence of nearly normal hearing in some large tumours (Figs. 6 and 7) and the presence of deafness or very poor hearing in even tiny intrameatal processes (Fig. 1)[5]. With the introduction of microsurgical techniques complete tumour removal with integrity of the brainstem and with precise anatomical nerve preservation has become possible in an increasing percentage of cases. Though this was a breakthrough for reduction of mortality and morbidity[57, 80], the cochlear nerve remained a problem[26, 39], and in many cases showed no postoperative function despite presumed anatomical integrity[83].

As soon as mortality rates were reduced to a minimum and functional facial nerve preservation overtook the 50% margin, the battle, however, drifted over to another topic, the surgical approaches.

Discussions on opportunities of hearing preservation were either neglected or cut off by certain beliefs such as "hearing preservation is not necessary in case of a contralateral functioning ear"[85], "hearing preservation is not worthwhile because the possibly preservable hearing is so bad that it is not useful", "only in a very few cases is an attempt of hearing preservation possible and worthwhile, but for these few cases the costs for equipment and personal are by far too high for the society", statistics are presented that make the argument of "hearing preservation" by suboccipital surgery academic[38].

With time an increasing number of authors believed in the possibility of hearing preservation and proved it by their own data[5, 7, 18, 19, 30, 44, 52, 54, 56, 57, 69, 73–76, 79, 80, 83]. A few surgeons believed that the attempt to preserve hearing was useful in each case[11, 22] and that each functionally preserved cochlear nerve might be useful now or later in a patient's life or with further technological development. A very few followed the principle that not only microsurgery, but functional microsurgery was the topic of the decade, because only further progress in general in our field was to be achieved by operating in a functional way, understanding and respecting the neuronal physiology. This philosophy implies that the surgeon has to be prepared to continuously prove which techniques and operative steps still measure up to his goals and which need to be changed and improved, with the aid of other positioning, instrumentation, technology, specialists.

The evaluation of 900 cases of acoustic neurinomas operated by one neurosurgeon offers the opportunity to delineate the development over a period of 15 years.

Material and Methods

900 acoustic neurinomas were removed by the suboccipital approach in 864 patients. There were eight deaths within the first postoperative month, due to aspiration pneumonia in 3 cases, pulmonary embolism in 2 cases and brainstem dysfunction and cerebellopontine hemorrhage in 2 cases. 74 patients had evident Neurofibromatosis-2 (NF-2) with bilateral acoustic neurinomas. 790 patients were free of any NF-2 features, and were treated for unilateral tumours.

Tumour Removal

In the semi-sitting position[59, 60, 87] with the patient's head tilted and rotated by 30° to the involved side, suboccipital craniectomy is performed exposing the borders of the transverse and sigmoid sinuses. After a laterally convex dural incision and CSF drainage by opening of the cerebello-medullary cistern the cerebellum is gently retracted and the posterior wall of the internal auditory canal (IAC), possibly a part of the tumour and the brainstem become visible. After removal of the dura from the posterior aspect of the IAC and opening of the canal by the use of decreasing sizes of diamond drills the intrameatal tumour extension is exposed; the posterior and lateral semicircular canals as well as the jugular bulb are respected, and the distance to the fundus is intermittently measured by platelet shaped knives of 2 mm diameter. Depending on tumour consistency, partial tumour mobilization inside the IAC is followed by extrameatal intracapsular tumour reduction with either the platelet-shaped knife or the CUSA, thereby, continuously decreasing compression

of surrounding neural and vascular structures. Thanks to continuous saline irrigation by the "third hand", the neurosurgical assistant, precise bimanual nerve preparation is possible and cautery is reduced to a minimum and left up to the end of surgery only for the final arrest of minor bleeding that has not stopped spontaneously in the meantime; hereby, maximum safety to brainstem and nerve vascular supply is guaranteed. Early coagulation of tumour capsule vessels branching from nerve feeding vessels especially is prohibited and induction of vasospasm is prevented. As soon as the tumour mass is mostly removed and the relation between tumour border and neural structures is relaxed, final preparation of neural structures and total freeing of tumour residua is performed by strictly gripping purely the arachnoid sheeth with the forceps and by limiting over-stretching in one direction[30]. The most tight junction between tumour and nerve-vessel-bundle, just before their entrance into the IAC, is prepared at the very end; here, sharp dissection might become necessary in order to prevent over-stretching of the facial nerve; its integrity is tested by continuous facial electromyography and by electrical stimulation at the end. Palpation with the platelet-shaped knife at the fundus, and, in very few cases, where drilling is very limited by the labyrinthine structures[29], testing with a micro-mirror ensures completeness of intrameatal tumour removal. After jugular venous compression performed by the anaesthesiologist in order to make any open or torn veins visible for final haemostasis, any opened mastoid cells at the IAC are carefully closed, to prevent an intradural CSF otorhinological fistula, by a little bone wax and by a piece of muscle fixed by fibrin glue. A last careful inspection of the cerebellopontine angle and the removal of the retractor are followed by continuous water-tight dural closure.

In 884 cases tumour removal was complete; in 16 cases deliberate subtotal removal was performed, with the goal of brainstem decompression in 3 elderly disabled patients and bilaterally in one NF-2 patient, for the sake of cochlear nerve decompression for preservation of hearing in 11 cases of NF-2. By opening the internal auditory canal and tumor reduction as long as brainstem auditory evoked potentials were satisfying, hearing was preserved in 8 of these 11 cases and has stayed stable with regard to hearing quality in their last hearing ear for up to 5 years now. Intraoperative BAEP and immediate postoperative hearing were lost in two patients; in one patient BAEP and hearing were preserved, but lost 2 weeks after the operation and this same patient needed re-operation because of tumour regrowth five months later.

Recurrences in non-NF-2 patients occurred in 2 cases; one patient with a large brainstem compressing hemorrhagic tumour and preoperative facial paralysis showed a recurrence of the same size and type within one year, was reoperated and has stayed free of any further recurrence for 18 months; one patient noticed deterioration and final loss of her initially preserved hearing

4 years postoperatively and was reoperated for a recurrence of 25 mm. Recurrence rates and management in NF-2 will be discussed in detail elsewhere.

Tumour sizes were measured considering intra- and extrameatal tumour extension; large tumours were above 30 × 20 mm, small tumours measured up to 30 × 20 mm. Tumour extension was described as follows: class T1 purely intrameatal, T2 intra-extrameatal, T3a filling the cerebellopontine cistern, T3b reaching the brainstem, T4a compressing the brainstem, T4b severely dislocating the brainstem and compressing the fourth ventricle.

Hearing tests were performed before surgery and one to two weeks postoperatively in each case; long-term controls are to be reported elsewhere. In 44% these tests were performed at the ENT Department of Hannover Medical School, in 40% at the ENT Department of Nordstadt Hospital, Teaching Hospital of Hannover Medical School, and in 16% these tests were performed in peripheral hospitals or ENT practices. Tests consisted of pure tone audiogram in all cases and of speech discrimination tests in 76% of cases; because of many patients from foreign non-German speaking countries, these patients could not be tested for speech discrimination; 50% of patients with some postoperative hearing preservation had their speech discrimination tested.

The currently used classification system of our department is outlined on Table 1; the audiometric classification (Table 1a) system goes in steps of 30 dB, functional deafness is defined as PTA HL > 90 dB; the average PTA HL is calculated as the mean of air conduction data at 1 kH, 1.5 kHz, 2 kHz

Table 1a. *Audiometric Hearing Classification*

A1	good hearing	0–30 dB hearing loss
A2	fair hearing	31–60 dB hearing loss
A3	bad hearing	61–90 dB hearing loss
A4	functional deafness	91–120 dB hearing loss
A5	deafness	> 120 dB hearing loss

Table 1b. *Classification of Speech Discrimination*

D1	normal discrimination	100–95%
D2	good discrimination	90–70%
D3	fair discrimination	65–40%
D4	bad discrimination	35–5%
D5	lost discrimination	0%

and 3 kHz. Each patient's best speech discrimination score is taken for classification of speech discrimination (Table 1 b).

Further evaluation of the same data was performed with classification criteria used by Gardner, by Shelton and House, by the Mayo Clinic and by British colleagues.

Results

Evaluation by Nordstadt Classification System

Among 900 tumours operated upon, 247 involved ears (27%) were functionally deaf (A4, A5) preoperatively. Of 653 tumours with preoperative PTA HL up to 90 dB (A1, A2, A3) in 249 (38%) some hearing was preserved postoperatively (A1, A2, A3). Table 2 a gives the postoperative preservation rates within each preoperative hearing class.

Table 2 b and c demonstrate the results of small and large tumour sizes separately. Out of 414 small tumours below 30 mm size, there were only

Table 2 a. *Pre- and Postoperative Hearing Function in 900 Acoustic Neurinoma Resections According to Nordstadt Classification System*

Pre-op hearing		Preserved hearing Cl. A1–3 n = 249	Post-op hearing Class A1 n = 37	Post-op hearing Class A2 n = 98	Post-op hearing Class A3 n = 114	Post-op Class A4 n = 37	Post-op Class A5 n = 614
Pre-op Class A1 0–30 dB	n = 196 22% of 900	110 56% 44%	33 17% 89%	47 24% 48%	30 15% 26%	3 2% 8%	83 42% 14%
Pre-op Class A2 31–60 dB	n = 248 27% of 900	84 33% 34%	3 1% 8%	42 17% 43%	39 15% 34%	12 5% 32%	152 62% 25%
Pre-op Class A3 61–90 dB	n = 209 23% of 900	50 24% 20%	1 1% 3%	9 4% 9%	40 19% 35%	14 7% 38%	145 69% 24%
Pre-op Class A4 91–120 dB	n = 24 3% of 900	2 8% 1%	–	–	2 8% 2%	5 21% 14%	17 71% 2%
Pre-op Class A5 > 120 dB	n = 223 25% of 900	3 1% 1%	–	–	3 1% 3%	3 1% 8%	217 98% 35%

62 cases (15%) with preoperative deafness as compared to 185 (38%) preoperatively deaf ears out of 486 large tumor cases.

In large tumours hearing was preserved in 66 out of 301 cases (22%); only in 9 cases (3%) postoperative hearing was good (A1, PTA HL up to 30 dB); however, when referring to those with preoperatively good hearing, 39% within this class had hearing preserved, 9% with good, 16% with fair and 14% with bad PTA HL. Preservation rate within preoperative class A2 was 18%, within class A3 it was 13%.

In small tumours hearing was preserved in 183 out of 352 cases (52%). Preservation rate was best within the best preoperative hearing class (A1), 67%; here 22% belonged postoperatively to the same class, 29% were A2 and 16% were A3. In case of preoperative fair hearing A2 preservation rate was 51%, with 2% of improvement to class A1. In preoperative class A3 preservation rate was 34 %, with even 6 cases (6%) improving to one class higher A2 and 1 case (1%) improving to two classes higher A1.

Table 2b. *Pre- and Postoperative Hearing Function in 414 Small Acoustic Neurinomas < 30 mm*

Pre-op hearing		Preserved hearing Cl. A1–3 n = 183	Post-op hearing Class A1 n = 29	Post-op hearing Class A2 n = 75	Post-op hearing Class A3 n = 79	Post-op Class A4 n = 19	Post-op Class A5 n = 212
Pre-op Class A1 0–30 dB	n = 116 28% of 414	79 67% 43%	26 22% 90%	34 29% 45%	19 16% 24%	2 2% 11%	35 31% 17%
Pre-op Class A2 31–60 dB	n = 126 30% of 414	63 51% 34.5%	2 2% 7%	35 28% 47%	26 21% 33%	4 3% 21%	59 46% 28%
Pre-op Class A3 61–90 dB	n = 110 27% of 414	37 34% 60%	1 1% 3%	6 6% 8%	30 27% 38%	9 8% 47%	64 58% 30%
Pre-op Class A4 91–120 dB	n = 11 3% of 414	1 9% 0.5%	–	–	1 9% 1%	2 18% 11%	8 73% 4%
Pre-op Class A5 > 120 dB	n = 51 12% of 414	3 6% 2%	–	–	3 6% 4%	2 4% 10%	46 90% 21%

Preservation in 179 of 352 neurinomas with preoperative hearing (51%). Recovery in 4 of 62 neurinomas with preoperative deafness (6%).

Table 2c. *Pre- and Postoperative Hearing Function in 486 Large Acoustic Neurinomas > 30 mm*

Pre-op hearing		Preserved hearing Cl. A1–3 n = 66	Post–op hearing Class A1 n = 8	Post–op hearing Class A2 n = 23	Post–op hearig Class A3 n = 35	Post–op hearing Class A4 n = 18	Post–op hearing Class A5 n = 402
Class A1 48 60%	n = 80	31 39%	7 9%	13 16%	11 14%	1 1%	
0–30 dB	16% of 486	47%	88%	57%	31%	5.5%	12%
Class A2 93 75%	n = 122	21 18%	1 1%	7 7%	13 10%	8 7%	
31–60 dB	24% of 486	32%	12%	30%	37%	44%	23%
Class A3 81 82%	n = 99	13 13%	–	3 3%	10 10%	5 5%	
61–90 dB	20% of 486	20%		13%	29%	28%	20%
Class A4 9 69%	n = 13	1 8%	–	–	1 8%	3 23%	
91–120 dB	3% of 486	1%			3%	17%	2%
Class A5 171 99.5%	n = 172	–	–	–	–	1 0.5%	
> 120 dB	36% of 486					5.5%	43%

Preservation in 65 of 301 neurinomas with preoperative hearing (22%). Recovery in 1 of 185 neurinomas with preoperative deafness (0.5%).

Table 3. *Hearing Preservation Depending on Tumour Extension*

Tumor extension grade	Intrameatal 1	Intra-extrameatal 2	Filling the CPA cistern 3A, 3B	Compressing the brainstem 4A, 4B
Pre-op hearing rate	86%	83%	77%	59%
Post-op preservation rate	47%	53%	42%	18%
	A1 16%	A1 7%	A1 5%	A1 2%
	A2 21%	A2 26%	A2 14%	A2 5%
	A3 10%	A3 20%	A3 23%	A3 11%

Table 4a. *Postoperative Speech Discrimination*

Post-op discrimination	Post-op hearing			Preserved discrimination
	Class A1	Class A2	Class A3	
	37	96	114	246
Class unknown	11	39	57	107
Class known	26	57	56	139
Class D1 100–95%	18	14	3	35 25%
Class D2 90–70%	8	31	7	46 33%
Class D3 65–40%	–	7	23	30 22%
Class D4 35–5%	–	5	16	21 15%
Class D5 < 5%	–	–	7	7 5%

Table 4b. *Postoperative Pure Tone Audiometry and Speech Discrimination Score in 131 Cases with Hearing Preservation.* Evaluated out of 249 with hearing preservation

Post-op audiometry	Post-op SDS				
	100–95% Class D1	90–70% Class D2	65–40% Class D3	35–5% Class D4	0% Class D5
Class A1 0–30 dB	18	8	–	–	–
Class A2 31–60 dB	6	31	7	5	–
Class A3 61–90 dB	3	7	23	16	7

Table 3 shows the results split according to tumour extension and degree of compression or dislocation of structures. Evaluation of this parameter in 760 cases showed 3% belonging to grade 1, 19% to grade 2, 41% to grade 3 and 38% to grade 4. Hearing preservation rate is reduced with increasing tumour extension, with an over-proportionately severe decrease in grade 4, i.e. in brainstem dislocation, to as little as 18% preservation.

Table 4 demonstrates postoperative speech discriminations scores; those were tested only in 75% of the whole group and 131 of 249 cases (53%) with hearing preservation. Of these 131 tested cases 103 (79%) had SDS of 40 to 100%.

Evaluation Based on Gardner's, Shelton's and House' Criteria

Of 37 patients with PTA HL of 0 to 30 dB, 26 of these had SDS of 70 to 100% fitting into Gardner's grade 1.

Gardner grade 2: 52 patients had PTA HL of 31 to 50 dB, 2 had SDS of 50 to 69%, but 28 patients had SDS of 50 to 100%.

159 patients had PTA HL of 51 to 90 dB, 29 had SDS of 5 to 49%, but 81 had SDS of 5 to 100%. 37 patients had PTA HL of 91 to 120 dB, 32 had SDS of 1 to 5%.

612 patients had PTA HL above 120 dB.

So, most of the evaluated patients had better SDS than expected by Gardner's classification system (Table 5a, b).

Table 5a. *Evaluation by Gardner's Criteria*

Post-op hearing				
Grade 1 0–30 dB 100–70%	Grade 2 31–50 dB 69–50%	Grade 3 51–90 dB 49–5%	Grade 4 91–120 dB 4–1%	Grade 5 > 120 dB 0%
26	2	29	32	612

Table 5b. *Evaluation by Extended Gardner's Criteria*

Preserved hearing	Post-op hearing					
	Grade 1 0–30dB 100–70%	Grade 2 31–50dB 100–50%	Grade 3 51–90dB 100–5%	Grade 4 91–120dB 100–1%	Grade 5 > 120dB 0%	Functional deafness
135	26	28	81	32	612	644

The Interear Difference

Among 249 patients with postoperative hearing preservation 42 had an interear difference of 0 to 30 dB. 28 had an interear difference of 31 to 40 dB. 24 had an interear difference of 41 to 50 dB.

Examples

Figures 1 and 2 illustrate two cases of preoperative bad hearing that, by the majority of authors would be regarded as non-serviceable and non-useful to be preserved. The first case presents a 48-year-old female with bad hearing and predominant vestibular disturbances due to an intrameatal tumour; after complete tumour resection with functional preservation of cochlear, facial and partial vestibular nerves, she made a good recovery with continuous improvement of gait and hearing. The second case of a small tumour in a 49-year-old man is a further example of improvement postoperatively.

Figure 3 demonstrates a typical example of the generally accepted situation for hearing preservation attempts in a 51-year-old female with small acoustic neurinoma, good pre- and postoperative PTA hearing and good speech discrimination.

Figure 4 shows a case that would be regarded as worth trying hearing preservation by some and as useless by others: The 45-year-old female had a small acoustic neurinoma and only fair pre- and postoperative hearing, but showed considerable improvement within 1 year after surgery to good hearing function.

Figure 5 illustrates a case many would not regard as useful or as possible for hearing preservation because of tumour size and hearing function. The 45-year-old female with medium-sized neurinoma and poor preoperative hearing has good postoperative hearing, due to improvement of PTA and of SDS.

Figures 6 and 7 demonstrate hearing preservation of good quality in two cases of large tumours. In Fig. 6 the 58-year-old female with a large left sided neurinoma (50 × 40 mm) has good hearing before and still 3 years after tumour removal. In Fig. 7 the 23-year-old male with Neurofibromatosis II and contralateral deafness has a large right sided neurinoma with good hearing before and still 3.5 years after surgery.

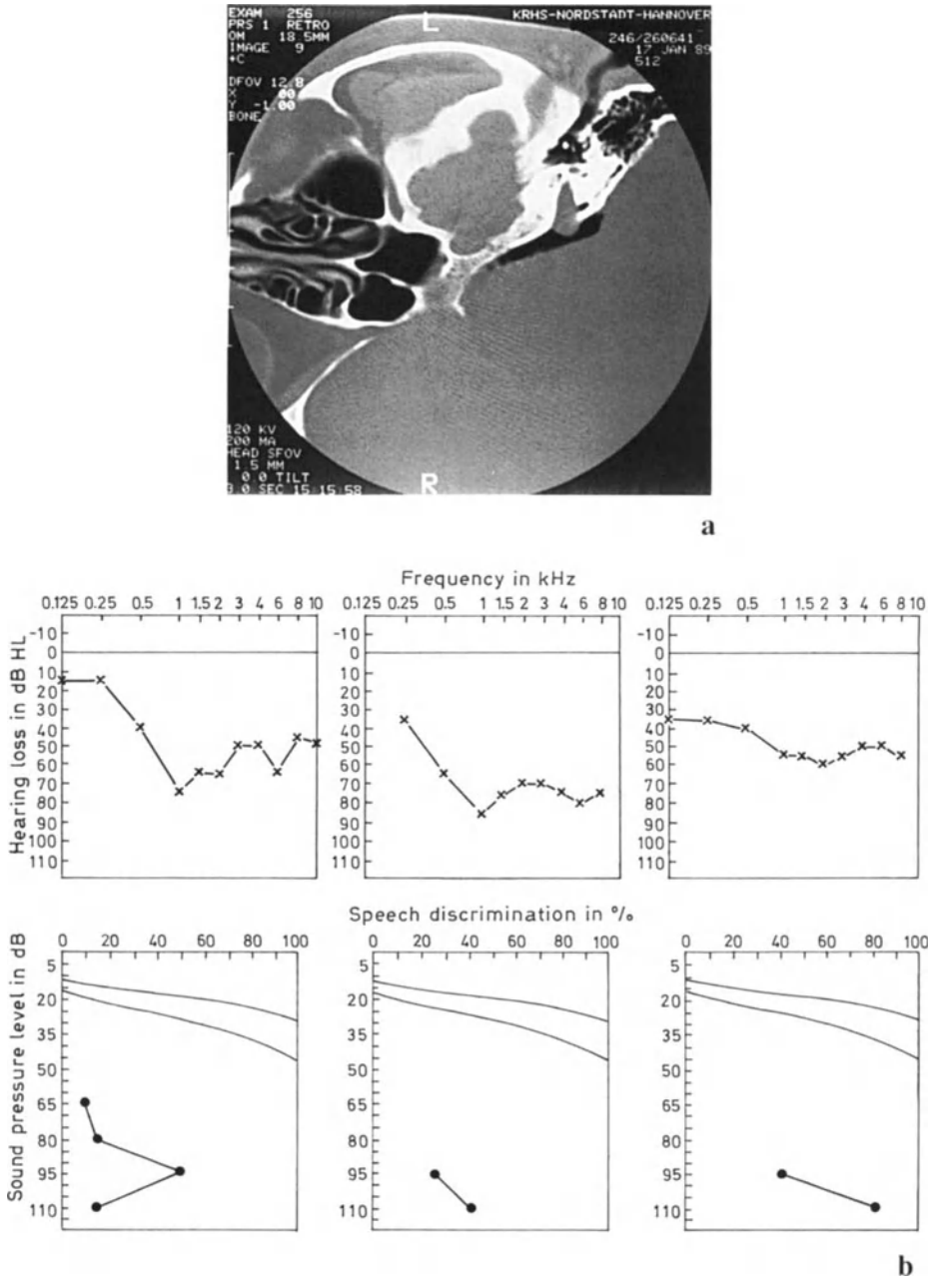


Fig. 1. (a) A case of poor hearing despite only small intrameatal tumour and with improvement after surgery. 48-year-old female with intrameatal neurinoma, severe vestibular disturbances, poor hearing before and immediately after surgery, improvement of PTA and SDS within 2 years after surgery. (b) Left: preoperative, middle: immediately postoperative, right: 2 years postoperative

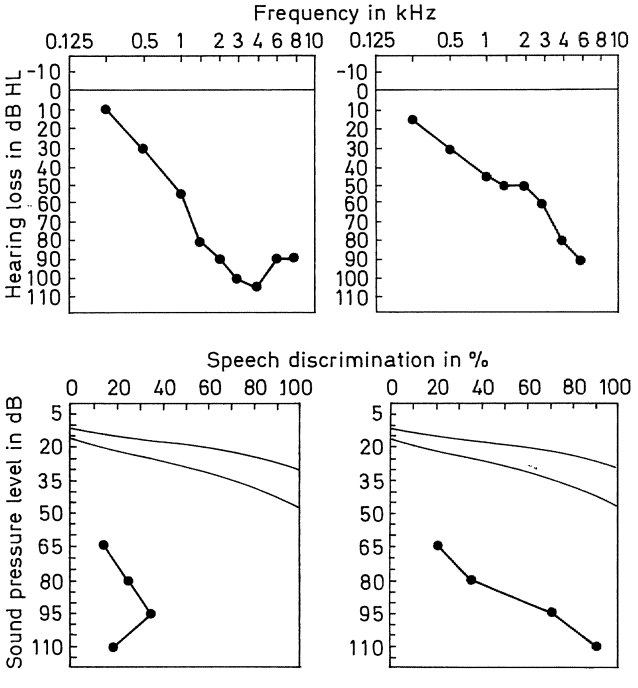


Fig. 2. A case of a small tumour with bad hearing that would be defined as non-serviceable and non-useful to be preserved by the majority of authors. 49-year-old male with small intra-extrameatal neurinoma, with poor preoperative (left) and fair postoperative hearing, improvement of PTA and SDS 2 years after surgery (right)

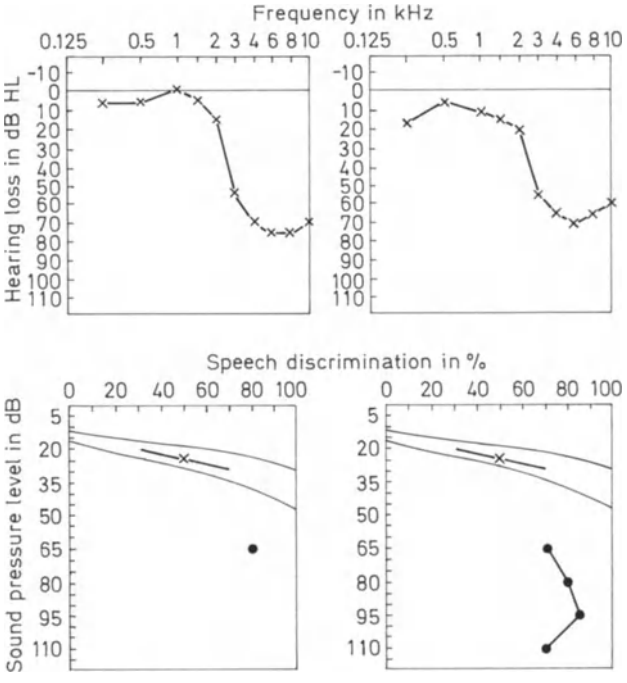


Fig. 3. 51-year-old female with small acoustic neurinoma, good pre- and postoperative hearing, good speech discrimination. Left: preoperative, right: postoperative

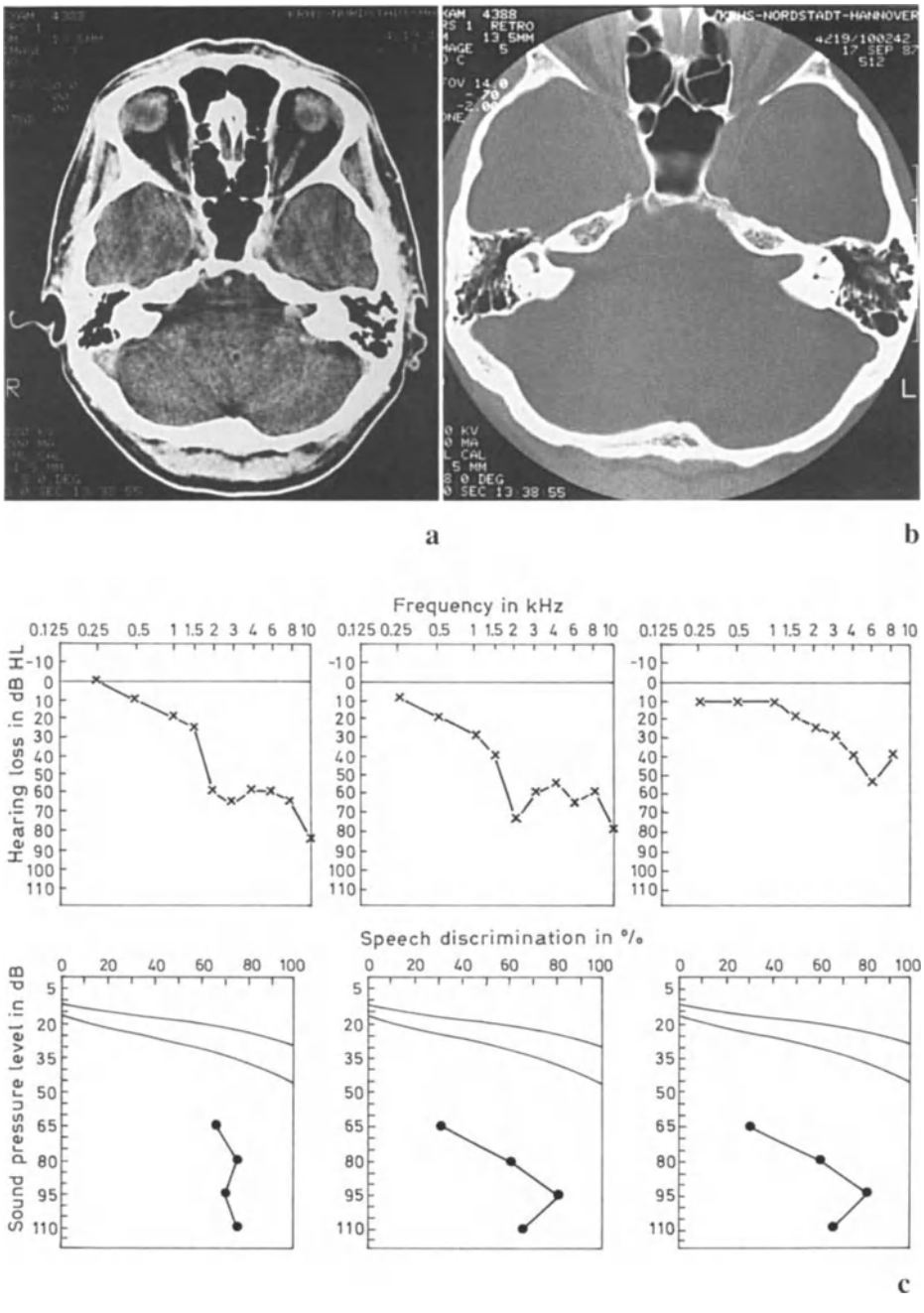


Fig. 4. (a, b) 45-year-old female, small acoustic neurinoma, fair pre- and postoperative hearing, improvement within 1 year after surgery to good hearing function. (c) Left: preoperative, middle: immediately postoperative, right: 1 year postoperative

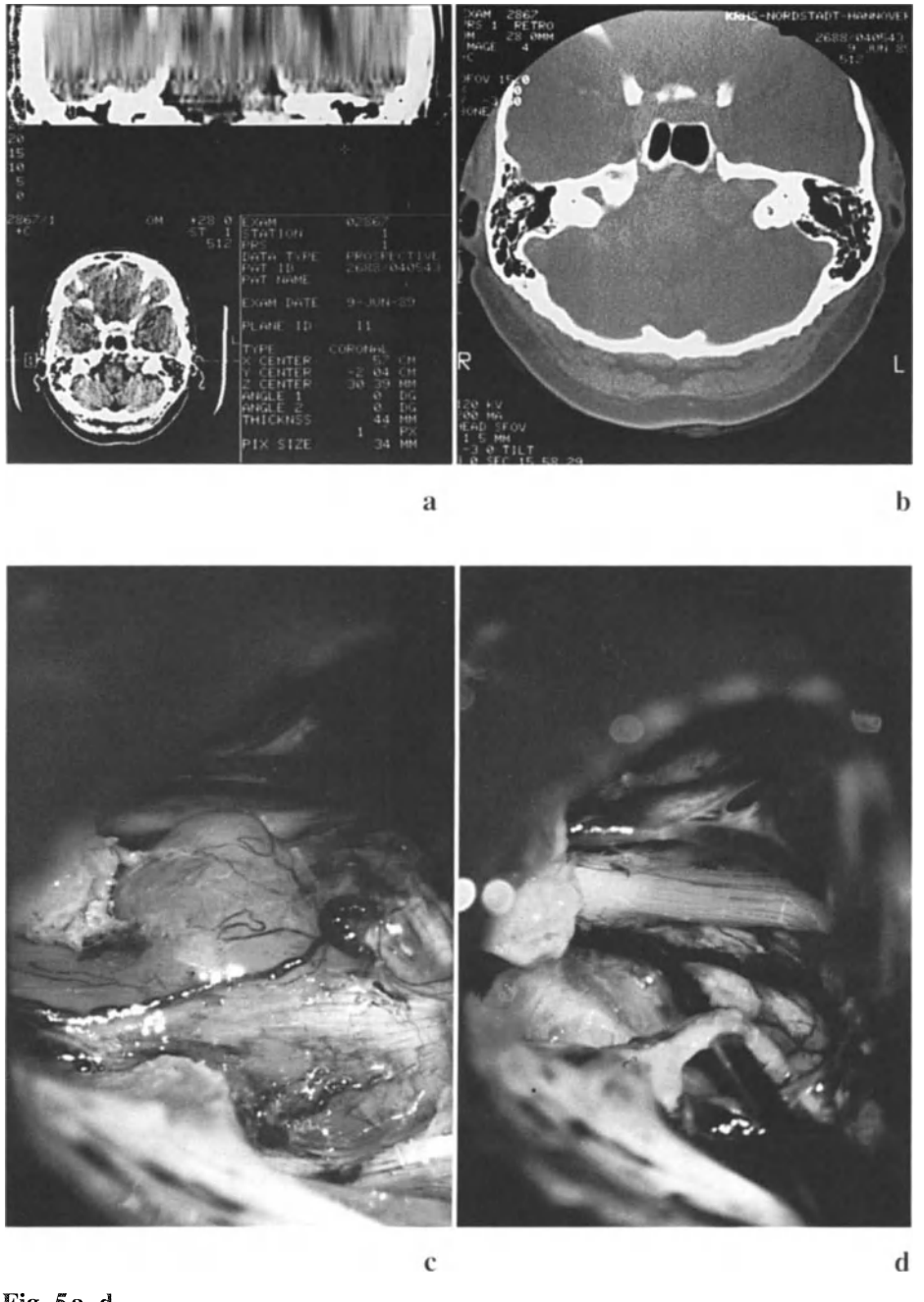


Fig. 5a–d

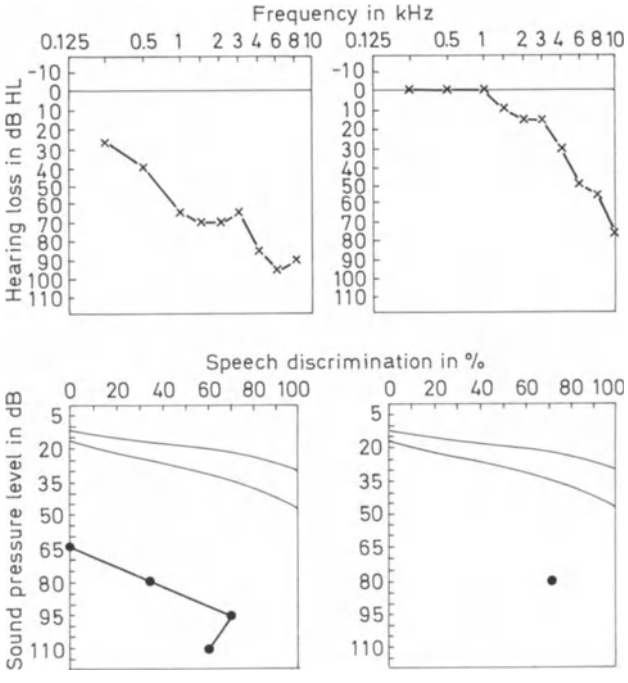
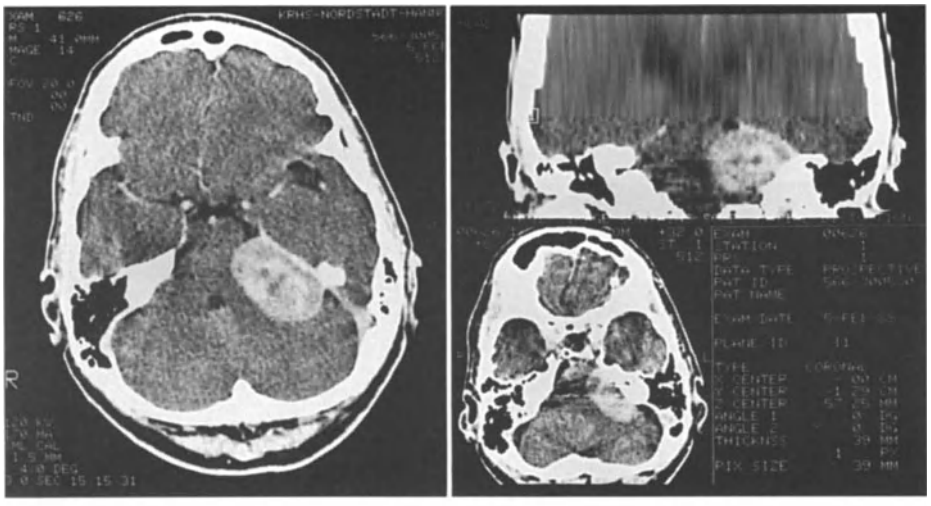
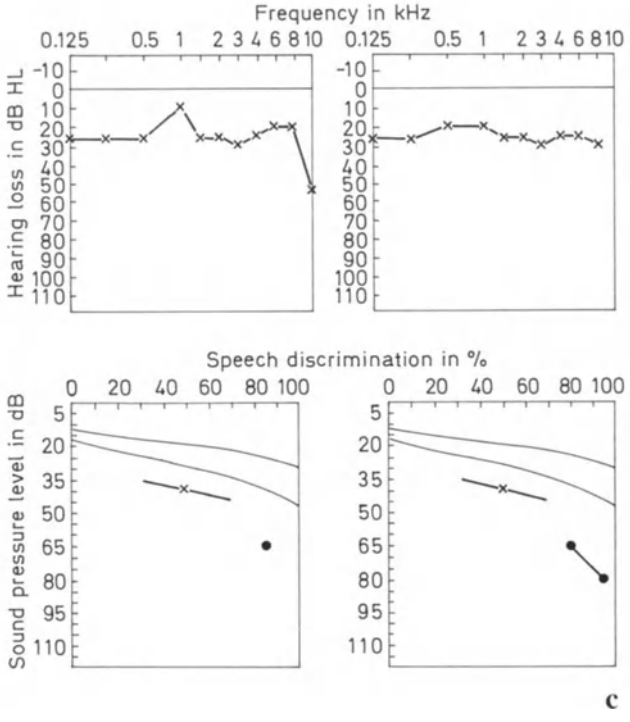


Fig. 5e

Fig. 5. (a–d) A case many would not regard as useful or as possible for hearing preservation. 45-year-old female with medium-sized neurinoma, poor preoperative and good postoperative hearing, improvement of PTA and of SDS. (e) Left: preoperative, right: postoperative



a b



c

Fig. 6. (a, b) 58-year-old female with large left sided neurinoma (50 × 40 mm), good hearing before and 3 years after tumour removal. (c) Left: preoperative, right: 3 years postoperative

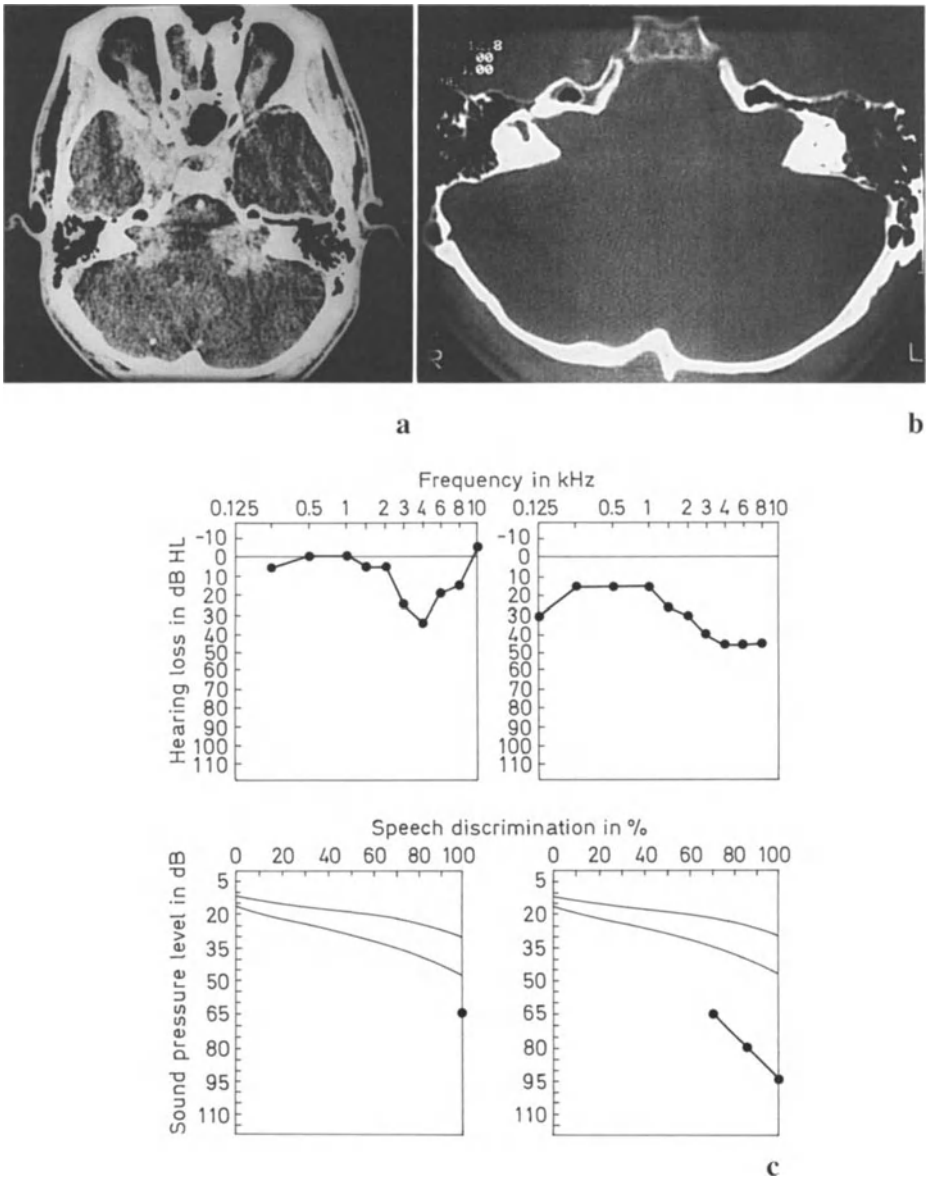


Fig. 7. (a, b) A case of neurofibromatosis II and contralateral deafness. 23-year-old male with large right sided neurinoma, good hearing before and still 3.5 years after surgery. (c) Left: preoperative, right: postoperative

Discussion

After two decades of discussion about the "chances and risks of hearing preservation", to date, discussion can be cut short on some of the former topics of controversy:

Completeness of Resection

Some authors question the "feasability"[62] of total tumour removal and hearing preservation because of histological findings of tumorous nerve infiltrations[10, 13, 48, 49]. Some[40] completely reject the principle of hearing preservation surgery in "favour of total tumor removal" because, by their immunohistochemical study (monoclonal mouse antibodies to human neurofilaments), "the cochlear nerve-tumour interface showed no clear cleavage in those cases in which macroscopically visible adherences between the cochlear nerve and the tumour were present"; 60% of specimens in one study showed tumoral invasion of the cochlear nerve.

Such infiltrations or tumorous nerve changes are sometimes visible in NF-2, and these findings might be fundamentally different intraindividually in either side of an NF-2 patient. However, the minor incidence of recurrences in our series illustrates that by total microsurgical removal as it is performed in our patients relevant tumour rests evidently were not left behind for the sake of hearing preservation.

Moreover, in the majority of cases the so-called acoustic neurinoma is a vestibular schwannoma originating from the vestibular nerve and only compressing the cochlear nerve. In patients with good hearing the intraoperative situation is usually characterized by easy separation between the cochlear nerve and the tumour.

Deliberate subtotal tumour removal should only be performed in rare cases of life rescuing decompressive surgery (3 cases = 0.3% in our material) or in the case of a special agreement with a patient in whom a tumorous cochlear nerve is anticipated (13 cases = 1.4% in our material); several successful cases have been reported on partial tumour removal[32, 43] or on decompressive surgery by opening the internal auditory canal[15]; these procedures can only be carried out by somebody with great experience in hearing preserving surgery, because otherwise, due to the extreme vulnerability of the cochlear nerve, hearing is most likely to be lost despite incomplete tumour removal.

The attitude of removing the tumour "immuno-histologically" completely would imply sometimes resection of a macroscopically intact cochlear nerve; that nerve, according to our and others'[6] experiences never shows any tumour recurrences and, in increasing numbers, will function well for decades.

Radiotherapy Instead of or Prior to Acoustic Neurinoma Surgery

Gamma Knife Therapy

Lunsford and Linskey[36,37] achieved so-called "tumour control in 96% of patients during an average follow-up of 1.7 years; tumour shrinkage occurred in 23% of patients". These statements are of course a matter of discussion because a constant tumour size over 1.7 years in acoustic neurinomas is an unreliable result; growth studies performed by MRI over several years suppose 1 to 4 mm growth per year and several cases have been encountered of spontaneous cessation and later reoccurrence of tumour growth[86]; separation of the effect of radiotherapy and the growth rate of the patient's tumour remains uncertain. Useful hearing preservation rates were 50% at 6 months and 30% 1 year after treatment. Probably, vascular scarring developing over time may be the reason for this severe late deterioration.

Linear Accelerator

Darrouzet[9] reported that out of 8 patients with good hearing on the irradiated side (50 to 60 Gy by linear accelerator), 3 maintained identical thresholds, but 5 secondarily developed total deafness. Maire 1992, using a 9 MV linear accelerator and a mean total dose of 5140 cGy (180 cGy/fraction), advocates radiotherapy in patients in bad general condition with large neurinomas and in NF-2 cases.

While radiosurgery may be a correct indication in rare cases inoperable because of other medical reasons[50], it is apparently *no alternative* if hearing preservation is required, and especially we believe, at present, it cannot be recommended in NF-2 patients' last ears because delayed hearing deterioration is too frequent and too severe after radiotherapy.

Timing

In our experience the chances for hearing preservation are far better in the case of short duration of symptoms. "Some surgeons advocate the premicrosurgical philosophy of observation rather than removal in order not to disturb intact functions". Shelton[67] also believes that their results of 67% hearing preservation and near normal facial function in 97% of cases at one year postoperatively in tumours up to 5 mm in size by the middle fossa approach speak in favour of early surgical removal.

Surgical Approaches

The argument that the middle fossa or posterior fossa approaches, the only routes enabling hearing preservation (with few exceptions)[41], are more dangerous to the patient or especially to the facial nerve than the translabyrin-

thine route is no longer looked upon as serious[8, 18, 39, 47]. In general, the approach a surgeon is best familiar with will be the least risky to the patient. The suboccipital route gives the best survey and access to the brainstem and its vascular supply[55], therefore, in a micro-neurosurgeon's hands it is the safest and most suitable, enabling him, in a single procedure, to remove tumours of any size and any extension, including supratentorial or jugular foramen or foramen magnum extensions (as they occur quite frequently in NF-2), and to preserve cranial nerves and brainstem structures as well as their vascular supply, and to reconstruct the facial nerve which, of course, is also possible in translabyrinthine surgery[4].

House[25] was the first to use the middle fossa approach for hearing preservation. Very good postoperative preservation rates are reported by his group, such as 35% preservation within 10 dB of the preoperative speech reception threshold and within 15% of the preoperative speech discrimination. Shelton[63] reported the results of 106 middle fossa acoustic tumor removals over a 25-year period with measurable postoperative hearing in 59% of cases. House[27] judged best candidates those with tumours less than 5 mm extrameatal size and preoperative PTA HL up to 30 dB and SDS of 70 to 100%; in 31% to 59% hearing can be preserved by the middle fossa approach[88].

Sanna[61] reported better results by the middle fossa approach than by the suboccipital route; preservation rate was higher (50 versus 29%) and 20% serviceable hearing quality only by the former approach.

However, it was also House who reserved the middle fossa approach (and hearing preservation) for a long time for purely intrameatal tumours. Wigand *et al.*[89] have demonstrated tumour removals up to a size of 30 mm by the enlarged middle cranial fossa approach in a large study of 190 patients. All the other authors reporting on the extended middle fossa approach remove tumours up to 20 mm, and agree that hearing preservation in tumours larger than 15 to 20 mm extrameatal size is best attempted by the suboccipital approach[7,17]. Reported preservation rates by the extended middle fossa approach range from 31% to 50% [31] to 59%[88]; however, above 20 or even 30 mm size, preservation rates with many authors drop virtually to 0%; besides, preservation rates were usually calculations from 10 to 20% selected cases of all those operated upon.

Some authors use either approach depending on tumour sizes and/or hearing quality as for instance Glasscock[19] who reported 35% successful hearing preservation in unilateral and even 44% preservation in bilateral cases. Others who often have to remove large tumours and who often try to preserve hearing, have abandoned more and more the translabyrinthine approach and mostly use the retrosigmoid approach, because they regard it as safe, giving good survey and access[3, 5, 7, 8, 14, 30, 73]; the effect of continuous training for hearing preservation should not be underestimated.

For the suboccipital/retromastoid approach hearing preservation rates of

11%[14], 12%[21], 16%[78], 18%[11], 23%[77], 32%[1,47], 36%[53], 37%[70], 43%[14], 35% to 44%[19], 52%[82], 65%[32], 82%[20,72] are reported.The highest preservation rates were achieved under highly selected conditions and very small tumour sizes up to 10 or 15 mm.

Others have proven, some time ago, that hearing preservation is achievable[79,80] also in large tumours by the suboccipital approach.

In summary, preservation rates are very similar with either approach[2], however accessible tumour size is limited in the middle fossa approach.

Most of the reports contain results of selected attempts of hearing preservation (i.e. out of a clinical group of one or several hundred patients, groups of 20 to 50 patients with specific criteria were selected), and selection usually implies dropping difficult cases, although, as demonstrated here, the struggle for hearing preservation or even hearing improvement in case of poor preoperative hearing and in large tumours can be successful. If we only considered preoperative hearing classes A1 and A2, hearing preservation rate would be 194 of 446 (43%) in any tumour size.

Criteria for Useful Hearing Quality

Hinton *et al.*[24] see an "important difference between hearing preservation which pleases the surgeon and that which will be appreciated by the patient" and believe that only in 1 to 10% patients might fulfill criteria of useful hearing such as a SDS of 50% or more and PTA difference of up to 30 dB and a tumour size < 2 cm.

Silverstein[71] (130 cases in 17 years) advocates attempting hearing preservation "under 65 years of age and by the retrosigmoid approach in tumours 1.5 cm or less if pure-tone average is less than 30 dB and the SDS is greater than 70%". This refers to Silverstein's classification from 1986 where Class I, i.e. a good hearing result was specified as PTA 0 to 30 dB and 70 to 100% discrimination; to Class II belonged those with 35 to 60 dB PTA and 65 to 50% discrimination, to Class III, non-serviceable hearing, those with PTA 65 to 75 dB and 25 to 45% discrimination, and to Class IV, poor hearing, those with PTA 80 to 100 dB and 0, to 20% discrimination.

Rowed[58] classified serviceable hearing as SRT less than 50 db and SDS greater than 60%. Nadol[45] defines useful hearing as at least 70 dB speech reception threshold or SDS of at least 15%.

As long as there is so little agreement about useful hearing quality, the only way of making one's own results more understandable is by applying different criteria on the same material. However, if such classification criteria are used to exclude patients from hearing preservation surgery, this attitude neglects the fact that improvement of speech discrimination or also PTA ([66,84]) is sometimes possible after surgery as illustrated in some examples (Figs. 1, 2, 4, and 5).

Chances of Hearing Preservation

In 1988 Gardner[16] reviewed the current literature and re-evaluated cases by a classification system similar to Silverstein's. The total number of cases under review was 621, with 221 reported successes. Cases limited to those having a unilateral acoustic neuroma, with valid supportive audiometry, were 394, with 131 successes (33%). There were five cases of hearing preservation with unilateral acoustic neuromas 3 cm or larger.

Almost all the authors agree that preservation is more likely in smaller tumours with good preoperative hearing[6, 12, 14, 22, 23, 68, 73] and in early operations[18, 20, 21, 51], although Shelton[64] did not find any influence of preoperative hearing on chances of hearing preservation and McKenna[42] did not find any strong correlation between preoperative tumour size or hearing and chances of hearing preservation. The majority of authors report on attempts of hearing preservation in tumours up to 20 mm[28, 47]. Agreement exists about the necessity of training; therefore some advocate attempting hearing preservation in any case[12]. Kveton[33, 34] doubts the usefulness of BAEP monitoring because of higher incidences of preservation without than with monitoring; direct eighth nerve monitoring might be more reliable.

Silverstein[69] used direct eighth nerve monitoring and found it reliable and useful; hearing preservation was 54% in tumours below 15 mm. Symon[81] monitored the electrocochleogram (ECochG) of 24 patients with good preoperative hearing, using a transtympanic electrode, during acoustic neuroma excision. While 7 patients retained some hearing, two patients had normal ECochG waveforms at the end of operation but were nevertheless deaf. Thus, there is not an invariable correlation between immediate preservation of the ECochG and hearing. As expected, tumour size was important in hearing preservation. Five of seven patients with tumours less than 1.5 cm in diameter retained some hearing after operation, whereas 15 of 17 patients with tumours greater than 1.5 cm in diameter were deaf.

Thomsen *et al.*[85] reported on an analysis of 72 patients with tumours smaller than 2 cm among a group of 300 cases and concluded that only a maximum of 5% of the patients, using the broadest criteria, could be candidates for hearing-conserving surgery. They further argued that "In all these patients the contralateral ear had hearing within normal limits (PTA 0–20 dB and SDS 95–100%). Since preservation of hearing would be achieved in only half of those subjected to suboccipital removal and since the hearing retained in patients with successful operations generally is poorer than the preoperative level, the number of patients obtaining serviceable hearing is so modest that preservation of hearing cannot be considered a valid argument in favour of suboccipital tumour removal. From a statistical point of view the risk of losing hearing in the opposite ear after tumour removal is negligible."

In our material, 172 cases had preoperative PTA HL of 0 to 40 dB and SDS of 61 to 100%, i.e. 19% were candidates by Thomsen's criteria. And as all that are involved in the treatment of acoustic neurinomas work on earlier detection at smaller tumour stages and with better preoperative auditory function, everybody should be prepared for the attempt to preserve hearing.

Closing Remarks

Finally, there are several words to be said about the classification systems. As demonstrated by our material the broadly used criteria by Shelton/House[65] or Gardner[16] did not ideally fit with reality with regard to SDS: Postoperatively most of our patients had better SDS than expected by the classification system. So the upper limits of SDS classes must be left open or a change to another (better) classification should be considered, if SDS class is better than PTA class; a change according to Jannetta's system appears useful. Furthermore, as in some patients SDS improve, postoperatively, there is also sense in attempting hearing preservation, with preoperative bad SDS[52].

The criteria of inter-ear difference appears quite sensible for estimating the ability to communicate binaurally/stereophonically. However, for social communication also a larger inter-ear difference can still be of great use. Many patients report that they suffer a lot when being approached by somebody from their deaf side whom they cannot notice. To these patients we usually suggest a cross head microphone mounted on their spectacles, if they wear any. However, the ability to hear such an approaching or even to understand some words (40% or more) just monaurally on the operated side is much appreciated by the patient[52], even if not by the audiologist.

As pointed out in the last table (Table 6), considerable progress in preservation rates has been achieved; the two factors we believe to have contributed to this are increasing surgical experience and its conscious and unconscious refinement by the companionship of neurophysiological monitoring. Surgical experience is not simply based on large case numbers but is generated by the continuous struggle for a mode of preservational functional surgery, i.e. the trial to preserve the nerves in function whatever tests

Table 6. *Improvement of Hearing Preservation Rates*

	Jan 78–Sept 86 cases #1 – #300	Oct 86–Feb 90 cases #301 – #600	Feb 90–Dec 92 cases #601 – #900
Pre-op hearing	66%	75%	80%
Large tumors	62%	52%	50%
Post-op hearing	25%	40%	46%

have said about the quality of function, and to look and to consider one's own impression of the neural structures intraoperatively and the neurophysiological feedback. Neurophysiologal monitoring, if performed by the right team, is a mechanism for feedback training, with positive and negative conditioning which thereby induces a new process of understanding of neuronal physiology and refines the microsurgical technique. The persistent limitations in speed of information and in reliability of motoring will be counteracted by further technological devices, such as laser-Doppler measurements[35].

It is important that the conviction of the possibility of hearing preservation in increasing rates is conveyed to medical colleagues in general[46] because they will usually be the first contacted by the patient and on their awareness the individual management, early specific diagnosis and treatment or delay, will depend.

References

1. Baldwin DL, King TT, Morrison AW (1990) Hearing conservation in acoustic neuroma surgery via the posterior fossa. J Laryngol Otol 104 (6): 463–467
2. Belal A Jr, Linthicum FH, House WP (1982) Acoustic tumour surgery with preservation of hearing. A histopathological report. Am J Otol 4: 9–16
3. Bentivoglio P, Cheesman AD, Symon L (1988) Surgical management of acoustic neuromas during the last five years. Part II: Results for facial and cochlear nerve function. Surg Neurol 29: 205–209
4. Brackmann DE, Green JD (1992) Translabyrinthine approach for acoustic tumor removal. Otolaryngol Clin North Am 25 (2): 311–329
5. Cohen NL (1979) Acoustic neuroma surgery with emphasis on preservation of hearing. Laryngoscope 89: 886–896
6. Cohen NL, Ransohoff J (1984) Hearing preservation – posterior fossa approach. Otolaryngol Head Neck Surg 92 (2): 176–183
7. Cohen NL, Hammerschlag P, Berg H, Ransohoff J (1986) Acoustic neuroma surgery: an eclectic approach with emphasis on preservation of hearing. Ann Otol Rhinol Laryngol 95: 21–27
8. Cohen NL (1992) Retrosigmoid approach for acoustic tumor removal. Otolaryngol Clin North Am 25 (2): 295–310
9. Darrouzet V, Maire JP, Flocquet A, Guerin J, Bebear JP (1990) Irradiation of neurinoma. Why? How? First results. (L'irradiation des neurinomes. Pourquoi? Comment? Premiers resultats.) Rev Laryngol Otol Rhinol Bord 111 (3): 211–215
10. Eckermeier L, Pirsig W, Mueller D (1979) Histopathology of 30 non-operated acoustic schwannomas. Arch Otorhinolaryngol 222: 1–9
11. Fischer G, Morgon A, Fischer C, Bret Ph, Massini B, Kzaiz M, Charlot M (1987) Total removal of acoustic neuromas. Facial nerve and hearing preservation. Exérèse complète des neurinomes de l'acoustique. Préservation du nerf facial et de l'audition. Neurochirurgie 33: 169–183

12. Fischer G, Fischer C, Remond J (1992) Hearing preservation in acoustic neurinoma surgery. Comment. J Neurosurg 76 (6): 897–900; J Neurosurg 76 (6): 910–917
13. Forton G, Moeneclaey L, Declau F, Marquet J (1989) The involvement of the cochlear nerve in neurinomas of the eighth cranial nerve. Arch Otorhinolaryngol 246: 156–160
14. Frerebeau P, Benezech J, Uziel A, Coubes P, Segnarbieux F, Malonga M (1987) Hearing preservation after acoustic neurinoma operation. Neurosurgery 21 (2): 197–200
15. Gadre AK, Kwartler JA, Brackmann DE, House WF, Hitselberger WE (1990) Middle fossa decompression of the internal auditory canal in acoustic neuroma surgery: a therapeutic alternative. Laryngoscope 100: 948–952
16. Gardner G, Robertson JH (1988) Hearing preservation in unilateral acoustic neuroma surgery. Ann Otol Rhinol Laryngol 97 (1): 55–66
17. Giannotta SL (1992) Translabyrinthine approach for removal of medium and large tumors of the cerebellopontine angle. Clin Neurosurg 38: 589–602
18. Glasscock ME III, Kveton JF, Jackson CG, Levine SC, McKennan KX (1986) A systematic approach to the surgical management of acoustic neuromas. Laryngoscope 96: 1088–1094
19. Glasscock ME III, Hays JW, Minor LB, Haynes DS, Carrasco VN (1993) Preservation of hearing in surgery for acoustic neuromas. J Neurosurg 78: 864–870
20. Haines SJ, Levine SC (1993) Intracanalicular acoustic neuroma: early surgery for preservation of hearing. J Neurosurg 79: 515–520
21. Harner SG, Laws ER Jr, Onofrio BM (1984) Hearing preservation after removal of acoustic neurinoma. Laryngoscope 94 (11): 1431–1434
22. Harner SG, Beatty CW, Ebersold MJ (1990) Rterosigmoid removal of acoustic neuroma: experience 1978–1988. Otolaryngol Head Neck Surg 103: 40–45
23. Helms J (1992) Hearing preservation in acoustic neurinoma surgery. Otolaryngol Pol 46 (6): 533–537
24. Hinton AE, Ramsden RT, Lye RH, Dutton JE (1992) Criteria for hearing preservation in acoustic schwannoma surgery: the concept of useful hearing. J Laryngol Otol 106: 500–503
25. House WF (1964) Transtemporal bone microsurgical removal of acoustic neuromas. Report of cases. Arch Otolaryngol 80: 667
26. House WF, Hitselberger WE (1985) The neurootologist's view of the surgical management of acoustic neuromas. Clin Neurosurg 32: 214–222
27. House WF, Shelton C (1992) Middle fossa approach for acoustic tumor removal. Otolaryngol Clin North Am 25 (2): 347–359
28. Hughes GB, Sismanis A, Glasscock ME III, Hays JW, Jackson CG (1982) Management of bilateral acoustic tumors. Laryngoscope 92 (12): 1351–1359
29. Jacob U, Gerhardt HJ, Staudt J, Dilba V (1990) Chirurgische Anatomie der Pars petrosa und der Fossa cranii posterior unter dem Aspekt der Hörerhaltung bei der Operation von Akustikusneurinomen. (Surgical anatomy of the petrous canal and posterior cranial fossa in relation to hearing preservation in surgery of acoustic neuroma). HNO 38 (3): 83–91

30. Jannetta PJ, Moller AR, Moller MB (1984) Technique of hearing preservation in small acoustic neuromas. Ann Surg 200: 513–522
31. Kanzaki J, Ogawa K, Shiobara R, Toya S (1989) Hearing preservation in acoustic neuroma surgery and postoperative audiological findings. Acta Otolaryngol Stockh 107 (5–6): 474–478
32. Kemink JL, La Rouere MJ, Kileny PR, Telian SA, Hoff JT (1990) Hearing preservation following suboccipital removal of acoustic neuromas. Laryngoscope 100: 597–602
33. Kveton JF (1990) Delayed spontaneous return of hearing after acoustic tumor surgery evidence for cochlear nerve conduction block. Laryngoscope 100: 473–476
34. Kveton JF (1990) The efficacy of brainstem auditory evoked potentials in acoustic tumor surgery. Laryngoscope 100 (11): 1171–1173
35. Levine RA, Bu-Saba N, Brown MC (1993) Laser-Doppler measurements and electrocochleography during ischemia of the guinea pig cochlea: implications for hearing preservation in acoustic neuroma surgery. Ann Otol Rhinol Laryngol 102 (2): 127–136
36. Linskey ME, Lunsford LD, Flickinger JC, Kondziolka D (1992) Stereotactic radiosurgery for acoustic tumors. Neurosurg Clin North Am 3 (1): 191–205
37. Lunsford LD, Linskey ME (1992) Stereotactic radiosurgery in the treatment of patients with acoustic tumors. Otolaryngol Clin North Am 25 (2): 471–491
38. Maddox HE (1977) The lateral approach to acoustic tumors. Laryngoscope 87 (9): 1572–1578
39. Maniglia AJ, Fenstermaker RA, Ratcheson RA (1989) Preservation of hearing in the surgical removal of cerebellopontine angle tumors. Otolaryngol Clin North Am 22 (1): 211–232
40. Marquet JF, Forton GE, Offeciers FE, Moeneclaey LL (1990) The solitary schwannoma of the eighth cranial nerve. An immunohistochemical study of the cochlear nerve-tumor interface. Arch Otolaryngol Head Neck Surg 116 (9): 1023–1025
41. McElveen JT Jr, Wilkins RH, Erwin AC, Wolford RD (1991) Modifying the translabyrinthine approach to preserve hearing during acoustic tumour surgery. J Laryngol Otol 105 (1): 34–37
42. McKenna MJ, Halpin C, Ojemann RG, Nadol JB Jr, Montgomery WW, Levine RA, Carlisle E, Martuza R (1992) Long-term hearing results in patients after surgical removal of acoustic tumors with hearing preservation. Am J Otol 13 (2): 134–136
43. Miyamoto RT, Roos KL, Campbell RL Worth RM (1991) Contemporary management of neurofibromatosis. Ann Otol Rhinol Laryngol 100(1): 38–43
44. Montgomery WW (1978) Bilateral acoustic neurinomas. A case report. Ann Otol Rhinol Laryngol 87 (1): 135–137
45. Nadol JB Jr, Chiong CM, Ojemann RG, McKenna MJ, Martuza RL, Montgomery WW, Levine RA, Ronner SF, Glynn RJ (1992) Preservation of hearing and facial nerve function in resection of acoustic neuroma. Laryngoscope 102 (10): 1153–1158
46. Nadol JB (1993) Review article. Medical progress: hearing loss. N Engl J Med 329 (15): 1092–1102

47. Nedzelski JM, Tator CH (1984) Hearing preservation: a realistic goal in surgical removal of cerebellopontine angle tumors. J Otolaryngol 13 (6): 355–360
48. Neely JG (1984) Is it possible to totally resect an acoustic tumor and conserve hearing. Otolaryngol Head Neck Surg 92: 162–167
49. Neely JG (1985) Hearing conservation surgery for acoustic tumors – a clinical-pathologic correlative study. Am J Otol [Suppl]: 143–146
50. Nehls DG, Spetzler RF, Shetter AG, Sonntag VKH (1985) Application of new technology in the treatment of cerebellopontine angle tumors. Clin Neurosurg 32: 223–241
51. Ogawa K, Kanzaki J, Ogawa S, Tsuchihashi N, Ikeda S (1991) Progression of hearing loss in acoustic neuromas. Acta Otolaryngol [Suppl] (Stockh) 487: 133–137
52. Ojemann RG, Levine RA, Montgomery WM, McGaffigan P (1984) Use of intraoperative auditory evoked potentials to preserve hearing in unilateral acoustic neuroma removal. J Neurosurg 61: 938–948
53. Palva T, Troupp H, Jauhiainen T (1985) Hearing preservation in acoustic neurinoma surgery. Acta Otolaryngol Stockh 99 (1–2): 1–7
54. Rand R, Kurze T (1968) Case reports and technical notes: preservation of vestibular, cochlear and facial nerves during microsurgical removal of acoustic tumours. J Neurosurg 28: 158
55. Rhoton AL Jr (1974) Microsurgery of the internal acoustic meatus. Surg Neurol 2: 311–318
56. Rhoton A (1976) Microsurgical removal of acoustic neuromas. Surg Neurol 6: 211
57. Rosenberg RA, Cohen NL, Ransohoff J (1987) Long-term hearing preservation after acoustic neuroma surgery. Otolaryngol Head Neck Surg 97: 270–274
58. Rowed DW, Nedzelski JM, Cashman MZ, Stanton S, Harrison RV (1988) Cochlear nerve monitoring during cerebellopontine angle operations. Can J Neurol Sci 15 (1): 68–72
59. Samii M, Turel KE, Penkert G (1985) Management of seventh and eighth nerve involvement by cerebelloponline angle tumors. Clin Neurosurg 32: 242–272
60. Samii M (1989) Tumors of the internal auditory canal and cerebellopontine angle. I. Acoustic neuroma. In: Samii M, Draf W (eds) Surgery of the skull base. An interdisciplinary approach. Springer, Berlin Heidelberg New York Tokyo, pp 377–395
61. Sanna M, Zini C, Mazzoni A, Gandolfi A, Pareschi R, Pasanisi E, Gamoletti R (1987) Hearing preservation in acoustic neuroma surgery. Middle fossa versus suboccipital approach. Am J Otol 8 (6): 500–506
62. Schessel DA. Nedzelski JM, Kassel EE, Rowed DW (1992) Recurrence rates of acoustic neuroma in hearing preservation surgery. Am J Otol 13 (3): 233–235
63. Shelton C, Brackmann DE, House WF, Hitselberger (1989a) Middle fossa acoustic tumor surgery: results in 106 cases. Laryngoscope 99: 405–408
64. Shelton C, Brackmann DE, House WF, Hitselberger WE (1989b) Acoustic tumor surgery. Prognostic factors in hearing conversation. Arch Otolaryngol Head Neck Surg 115 (10): 1213–1216

65. Shelton C, Hitselberger WE, House WF, Brackmann DE (1990) Hearing preservation after acoustic tumor removal: long-term results. Laryngoscope 100: 115–119
66. Shelton C, House WF (1990c) Hearing improvement after acoustic tumor removal. Otolaryngol Head Neck Surg 103 (6): 963–965
67. Shelton C, Hitselberger WE (1991) The treatment of small acoustic tumors: now or later? Laryngoscope 101 (9): 925–928
68. Shelton C (1992) Hearing preservation in acoustic tumor surgery. Otolaryngol Clin North Am 25 (3): 609–621
69. Silverstein H, McDaniel AB, Norrell H (1985) Hearing preservation after acoustic neuroma surgery using intraoperative direct eighth cranial nerve monitoring. Am J Otol [Suppl]: 99–106
70. Silverstein H, McDaniel A, Norrell H, Haberkamp T (1986) Hearing preservation after acoustic neuroma surgery with intraooerative direct eighth cranial nerve monitoring: Part II. A classification of results. Otolaryngol Head Neck Surg 95 (3): 285–291
71. Silverstein H, Rosenberg SI, Flanzer JM, Wanamaker HH, Seidman MD (1993) An algorithm for the management of acoustic neuromas regarding age, hearin, tumor size, and symptoms. Otolaryngol Head Neck Surg 108 (1): 1–10
72. Slavit DH, Hamer SG, Harper CM Jr, Beatty CW (1991) Auditory monitoring during acoustic neuroma removal. Arch Otolaryngol Head Neck Surg 117 (10): 1153–1157
73. Smith MF, Clancy TP, Lang JS (1977) Conservation of hearing in acoustic neurilemmoma excision. Trans Am Acad Ophthalmol Otolaryngol 84: 704–709
74. Smith MFW, Lagger RL (1984) Hearing conservation in acoustic neurilemmoma surgery via the retrosigmoid approach. Otolaryngol Head Neck Surg 92: 168–175
75. Sterkers JM, Hamann IKIE (1979) The retrosigmoid approach: a possibility to preserve hearing function in operations of acoustic neuroma. Arch Otolaryngol 223: 463
76. Sterkers JM (1982) Preservation de l'audition dans la chirurgie du neurinome de l'acoustique par la voie d'abord retrosigmoid (80 cas). Rev Laryngol 103: 21
77. Sterkers JM, Desgeorges M, Sterkers O, Corlieu P, Viala P (1986) Chirurgie du neurinome de l'acoustique et autres tumeurs du conduit auditif interne et de l'angle ponto-cerebelleux. A propos de 602 cas. (Surgery of acoustic neuroma and other tumors of the internal auditory canal and cerebellopontile angle. Apropos of 602 cases). Ann Otolaryngol Chir Cervicofac 103: 487–492
78. Strauss C, Fahlbusch R, Berg M, Haid T (1989) Funktionserhaltende Mikrochirurgie bei der suboccipitalen Entfernung großer Akustikusneurinome. (Function-saving microsurgery in suboccipital removal of large acoustic neuromas). HNO 37 (7): 281–286
79. Sugita K, Kobayashi S, Mutsuga N, Suzuki Y, Mizutani T, Shibuya M, Kageyama N, Tanahashi T (1979) Microsurgery for acoustic neurinoma – lateral position and preservation of facial and cochlear nerves. Neurol Med Cir 19: 637–641

80. Sugita K, Kobayashi S (1982) Technical instrumental improvements in the surgical treatment of acoustic neurinomas. J Neurosurg 57: 747–752
81. Symon L, Sabin HI, Bentivoglio P, Cheesman AD, Prasher D, Barratt H (1988) Intraoperative monitoring of the electrocochleogram and the preservation of hearing during acoustic neuroma excision. Acta Neurochir Wien [Suppl] 42: 27–30
82. Symon L, Bordi L, Compton JS, Sabin IH, Sayin E (1989) Acoustic neuroma: a review of 392 cases. Br J Neurosurg 3: 343–348
83. Tator CH, Nedze1ski JM (1985) Preservation of hearing inpatients undergoing excision of acoustic neuromas and other cerebellopontine angle tumors. J Neurosurg 63: 168–174
84. Telian SA, Kemink JL, Kileny P (1988) Hearing recovery following suboccipital excision of acoustic neuroma. Arch Otolaryngol Head Neck Surg 114 (1): 85–87
85. Thomsen J, Tos M, Harmsen A (1989/90) Acoustic neuroma surgery: results of translabyrinthine tumour removal in 300 patients. Discussion of choice of approach in relation to overall results and possibi1ity of hearing preservation (see comments) CM: Comment in: Br J Neurosurg 3 (6): 741–743. Comment in: Br J Neurosurg 4 (4): 356. Br J Neurosurg 3 (3): 349–360
86. Valvassori GE, Guzman M (1989) Growth rate of acoustic neuromas. Am J Otol 10: 174–176
87. Von Gösseln HH, Samii M, Bini W (1991) The lounging position for posterior fossa surgery: anesthesiological considerations regarding air embolism. Childs Nerv Syst 7: 368–374
88. Wade PJ, House W (1984) Hearing preservation in patients with acoustic neuromas via the middle fossa approach. Otolaryngol Head Neck Surg 92 (2): 184–193
89. Wigand ME, Haid T, Berg M (1989) The enlarged middle cranial fossa approach for surgery of the temporal bone and of the cerebellopontine angle. Arch Otorhinolaryngol 246 (5): 299–302

Subject Index

Advances and Technical Standards in Neurosurgery

Edited by L. Symon (Editor-in-Chief), L. Calliauw, F. Cohadon, J. Lobo Antunes, F. Loew, H. Nornes, E. Pásztor, J.D. Pickard, A.J. Strong, M.G. Yasargil

Volume 21

1994. 69 partly coloured figures. XIII, 286 pages.
Cloth DM 228,–, öS 1596,–, approx. US $ 149.00
ISBN 3-211-82482-0

Contents:

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

Edited by L. Symon (Editor-in-chief), L. Calliauw, F. Cohadon, J. Lobo Antunes, F. Loew, H. Nornes, E. Pásztor, J.D. Pickard, A.J. Strong, M.G. Yasargil

Volume 20

1993. 97 figures. XIII, 308 pages.
Cloth DM 240,–, öS 1680,–, US $ 160.00
ISBN 3-211-82383-2

Contents:

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

Springer-Verlag and the Environment

WE AT SPRINGER-VERLAG FIRMLY BELIEVE THAT AN international science publisher has a special obligation to the environment, and our corporate policies consistently reflect this conviction.

WE ALSO EXPECT OUR BUSINESS PARTNERS – PRINTERS, paper mills, packaging manufacturers, etc. – to commit themselves to using environmentally friendly materials and production processes.

THE PAPER IN THIS BOOK IS MADE FROM NO-CHLORINE pulp and is acid free, in conformance with international standards for paper permanency.